The Fifth Arkadi M. Rywlin
International Pathology Slide Seminar
Symposium in Anatomic Pathology
14–16 June 2012 in Stockholm · Sweden

- Programme
- General information
- Cases
Welcome to the 5th International AMR Slide Seminar!

The 5th Arkadi M. Rywlin (AMR) slide seminar in anatomic pathology will be held at the Swedish Society of Medicine in Stockholm, Sweden.

The AMR is a non-profit organization created in 1991 to promote and advance exchange of ideas among academic and clinical pathologists throughout the world in a spirit of cooperation and collegiality.

The format of the symposium will be an extended slide seminar.

A total of 73 selected cases will be presented and discussed by the faculty.

The symposium will focus mainly on diagnostic problems and controversies in surgical pathology utilizing a case study format and will be of interest to general surgical pathologists and trainees in pathology.

Course Directors
Saul Suster, M.D. and Göran Elmberger, M.D., PhD
CONTENTS

Programme ................................................................. 5

Participating faculty .................................................... 8

The Arkadi M. Rywlin, M.D. International Pathology Slide Seminar ........ 9

General Information ......................................................... 11

Cases ................................................................. 21

Who was Berzelius? ............................................................. 193

Brief history of the SSM ............................................. 194

Presentation of the SSM .................................................. 195

History of the building .................................................. 196
Thursday, 14 June 2012

07.30–7.40  Welcome addresses
Peter Friberg, the Swedish Society of Medicine
Göran Elmberger, M.D., PhD, Introduction to the symposium

07.40–8.00  Short History of the AMR Club. Saul Suster, M.D.

**MORNING SESSION – Thoracic Pathology:**

**Chairs:** T. Colby and T. Krausz

08.00–08.15  Case 1 – Placental transmogrification of lung (Colby)
08.15–08.30  Case 2 – Multifocal epithelioid hemangioendothelioma of lung (Krausz)
08.30–08.45  Case 3 – Rhodococcus equi infection of lung (Colby)
08.45–09.00  Case 4 – BAC-like invasive adenocarcinoma of lung (Marchevsky)
09.00–09.15  Case 5 – Sarcomatoid malignant mesothelioma (Krausz)
09.15–09.30  Case 6 – Follicular bronchiolitis due to exposure in popcorn factory (Marchevsky)

09.30–10.00  Coffee Break

10.00–10.15  Case 7 – Mature teratoma of thymus with colloid carcinoma (Marchevsky)
10.15–10.30  Case 8 – Pseudosarcomatous “metaplastic” thymoma (Suster)
10.30–10.45  Case 9 – IgG4 sclerosing lung disease (Colby)
10.45–11.00  Case 10 – Basaloid carcinoma of thymus (Falconieri)
11.00–11.15  Case 11 – Collision tumor of lung (met. LMS + prostate CA) (Suster)
11.15–11.30  Case 12 – Synovial sarcoma of pleura (Falconieri)
11.30–11.45  Case 13 – Primary cribriform adenocarcinoma of lung (Suster)
11.45–12.00  Case 14 – Angiosarcoma in lung masquerading as DAH (Elmberger)

12.00–13.30  LUNCH

**AFTERNOON SESSION – Bone and Soft Tissue Pathology:**

**Chairs:** M. Miettinen and K. Cooper

13.30–13.45  Case 15 – Sclerosing epithelioid fibrosarcoma (Cooper)
13.45–14.00  Case 16 – Myxoinflammatory fibroblastic sarcoma (Cooper)
14.00–14.15  Case 17 – Pelvic chordoma (Unni)
14.15–14.30  Case 18 – Leiomyosarcoma of bone (Unni)
14.30–14.45  Case 19 – Composite hemangioendothelioma (Mentzel)
14.45–15.00  Case 20 – Malignant transformation in dermatofibroma (Mentzel)
15.00–15.15  Case 21 – Familial tumoral calcinosis (Miettinen)
15.15–15.30  Case 22 – Desmoplastic small round cell tumor of peritoneum (Krausz)

15.30–16.00  Coffee Break
Please note! There will be no time to change clothes. Choose clothes suitable for the whole day, umbrella depending on the weather, and a jacket for the evening! Informal dress is almost always applicable in Sweden.

**Friday, 15 June 2012**

**MORNING SESSION: Genitourinary Pathology and Miscellaneous:**

Chairs: J. Epstein and I. Damjanov

- **08.00–08.15** Case 31 – STUMP of prostate (Epstein)
- **08.15–08.30** Case 32 – Nested carcinoma of urinary bladder (Epstein)
- **08.30–08.45** Case 33 – Acquired cystic disease-related renal cell carcinoma (Adsay)
- **08.45–09.00** Case 34 – Malignant epithelioid renal angiomyolipoma (Damjanov)
- **09.00–09.15** Case 35 – Medullary carcinoma of kidney (Epstein)
- **09.15–09.30** Case 36 – Muscious and tubular spindle cell renal cell carcinoma (Damjanov)

**09.30–10.00** Coffee Break

- **10.00–10.15** Case 37 – Sarcomatoid carcinoma of adrenal (Fedeli)
- **10.15–10.30** Case 38 – Epithelioid angiosarcoma of adrenal (Fedeli)
- **10.30–10.45** Case 39 – Lymphangiomatosis of spleen (Bisceglia)
- **10.45–11.00** Case 40 – Hodgkin lymphoma complicating small lymphocytic lymphoma (Ben-Dor)
- **11.00–11.15** Case 41 – Renal hemangioblastoma mimicking renal cell carcinoma (Bacchi)
- **11.15–11.30** Case 42 – ALK+ diffuse large B-cell lymphoma (Bacchi)
- **11.30–11.45** Case 43 – Medullary sponge kidney with arterial fibromuscular dysplasia (Bisceglia)
- **11.45–12.00** Case 44 – Paraganglioma of the carotid body (Familial form with SDHD mutation) (Sobrinho-Simoes)

**12.00–13.30** LUNCH

**AFTERNOON SESSION: Gynecologic and Breast Pathology:**

Chairs: E. Silva and M. Fukunaga

- **13.30–13.45** Case 45 – High-grade ovarian carcinoma (Silva)
- **13.45–14.00** Case 46 – Minimal deviation adenocarcinoma of endometrium (Silva)
- **14.00–14.15** Case 47 – Leiomyomatosis peritonealis disseminata (Bisceglia)
- **14.15–14.30** Case 48 – Malignant breast adenomyoepithelioma (Bleiweiss)
- **14.30–14.45** Case 49 – Mixed invasive mucinous and micropapillary CA of breast (Bleiweiss)
- **14.45–15.00** Case 50 – Phyllodes tumor of breast with liposarcoma (Ben-Dor)
- **15.00–15.15** Case 51 – IgG4 sclerosing disease of breast (Bacchi)
- **15.15–15.30** Case 52 – Acinic cell carcinoma of breast (Lamovec)
15.30–16.00  Coffee Break

16.00–16.15  Case 53 – Adenocarcinoma of endocervix (Silva)
16.15–16.30  Case 54 – Hypercalcemic small cell carcinoma of ovary (Fukunaga)
16.30–16.45  Case 55 – Wolffian tumor of broad ligament (Fukunaga)
16.45–17.00  Case 56 – Omental metastasis of ovarian CA in pt. with breast CA (Bleiweiss)
17.00–17.15  Case 57 – Early complete mole (Fukunaga)
17.15–17.30  Case 58 – Rosai-Dorfman disease of breast (Damjanov)
17.30–17.45  Case 59 – Metastatic melanoma to breast mimicking carcinoma (Falconieri)
17.45–18.00  Case 60 – Pancreatic type solid/papillary tumor of ovary (Fedeli)

18.30  Symposium dinner and cruise to Vaxholmskastell (www.kastellet.com)

Saturday, 16 June 2012

MORNING SESSION: Gastrointestinal and Head & Neck Pathology:

Chairs: V. Adsay and E. Montgomery

08.00–08.15  Case 61 – Pancreatic neuroendocrine tumor (Adsay)
08.15–08.30  Case 62 – Pancreatic acinar cell carcinoma mimicking NET (Adsay)
08.30–08.45  Case 63 – Pancreatic oncocyctic neuroendocrine carcinoma (Ben-Dor)
08.45–09.00  Case 64 – Metastatic GIST to the meninges (Cooper)
09.00–09.15  Case 65 – Plexiform fibromyxoma of stomach (Miettinen)
09.15–09.30  Case 66 – Succinate dehydrogenase-deficient GIST (Miettinen)

09.30–10.00  Coffee Break

10.00–10.15  Case 67 – Histoplasmosis in Crohn’s disease (Montgomery)
10.15–10.30  Case 68 – Familial polyposis coli (Montgomery)
10.30–10.45  Case 69 – Plasmablastic lymphoma of oral cavity (Wakely)
10.45–11.00  Case 70 – Sclerosing mucoepidermoid carcinoma of thyroid (Lamovec)
11.00–11.15  Case 71 – Hürthle cell (oncocytic) variant of follicular carcinoma (Sobrinho-Simoes)
11.15–11.30  Case 72 – Cribriform papillary thyroid carcinoma (Lamovec)
11.30–11.45  Case 73 – Primary small cell carcinoma of the thyroid with PNET features (Sobrinho-Simoes)

12.00  Conclusion
PARTICIPATING FACULTY

Volkan Adsay, M.D.
Professor and Director of Anatomic Pathology
Emory University School of Medicine
Atlanta, GA, USA

Carlos Bacchi, M.D.
Director, Pathology Consultants
Botucatu, Brazil

David Ben-Dor, M.D.
Head, Department of Pathology
Barzilai Medical Center, Ashkelon, Israel

Michele Bisceglia, M.D.
Director of Anatomic Pathology
Ospedale Casa Sollievo della Sofferenza
San Giovanni Rotondo, Italy

Ira Bleiweiss, M.D.
Professor and Director of Anatomic Pathology
The Mount Sinai Medical Center
New York, N.Y., USA

Kum Cooper, M.D.
Professor of Pathology
The Vermont University Medical Center,
Burlington, VT, USA

Thomas Colby, M.D.
Professor and Chairman
Department of Pathology
The Mayo Clinic, Scottsdale, AZ, USA

Ivan Damjanov, M.D.
Professor of Pathology
University of Kansas, Kansas City, KS, USA

Göran Elmberger MD, PhD
Medical Director
Department of Pathology
Karolinska University Hospital
Stockholm, Sweden

Jonathan Epstein, M.D.
Professor and Director of Anatomic Pathology
The Johns Hopkins University Hospital
Baltimore, MD, USA

Giovanni Falconieri, M.D.
Division of Anatomic Pathology
"S. Maria della Misericordia"
General Hospital
Udine, Italy

Franco Fedeli, M.D.
Head, Department of Pathology
Anatomia Patologica, Ospedale S.Andrea, La Spezia, Italy

Masaharu Fukunaga, M.D.
Head, Department of Pathology
Jikei University School of Medicine
The Daisan Hospital, Komae, Japan

Thomas Krausz, M.D.
Professor and Director of Anatomic Pathology
The University of Chicago, Chicago, IL, USA

Janez Lamovec, M.D.
Professor of Pathology
The Institute of Oncology,
Ljubljana, Slovenia

Alberto Marchevsky, M.D.
Professor of Pathology
Cedars-Sinai Medical Center
Los Angeles, CA, USA

Thomas Mentzel, M.D.
Dermatopathology Bodensee
Friedrichshafen, Germany

Markku Miettinen, M.D.
Department of Pathology
National Institutes of Health,
Bethesda, USA

Elizabeth Montgomery, M.D.
Professor of Pathology
The Johns Hopkins University Hospital
Baltimore, MD, USA

Fredrik Petersson, M.D, PhD
Associate Professor
National University of Singapore
Department of Pathology
Singapore

Elvio Silva, M.D.
Professor of Pathology
MD Anderson Cancer Center
Houston, TX, USA

Manuel Sobrino-Simões MD, PhD
Professor of Pathology
Pathology Department
Hospital de São João,
Oporto, Portugal

Saul Suster, M.D.
Professor of Pathology
The Medical College of Wisconsin
Milwaukee, WI, USA

Krishnan K Unni, M.D.
Professor of Pathology
Medical College of Wisconsin
Milwaukee, WI, USA

Paul Wakely, M.D.
Professor of Pathology
The Ohio State University
Columbus, OH, USA

Eduardo Zambrano, M.D.
Director of Anatomic Pathology
Medical College of Wisconsin
Milwaukee, WI, USA
The Arkadi M. Rywlin, M.D. International Pathology Slide Seminar

The Arkadi M. Rywlin (AMR) International Pathology Slide Seminar was started in 1990 by Dr. Saul Suster at the Mount Sinai Medical Center of Greater Miami in Miami Beach, Florida (USA), to honor the memory of his mentor, Prof. Arkadi M. Rywlin (1923–1987). The AMR Seminar started as an informal exchange of interesting or problem cases amongst colleagues whose purpose was to share their experience with other members in a collegial environment. The opening sentence of the letter inaugurating the Seminar read: “The purpose of the Club is to carry out an active exchange of interesting, unusual, or challenging cases in diagnostic pathology on a regular basis among its members. This exercise is meant to be conducted in a non-competitive and friendly spirit, with a view towards sharing and broadening our knowledge and experience in the different aspects of anatomic pathology”. The club started with 9 founding members, and currently counts with 45 members, with more than 65 pathologists having belonged to the Club since its inception. More than 1,000 cases have been circulated in the club during its 20 years of existence. More than 25 collaborative publications have been generated based on cases circulated in the Club, and selected cases have been regularly published in “Advances in Anatomic Pathology” since 2001. In 2002, thanks to the generous support of Dr. Michele Bisceglia and his institution, “Casa Solievo della Soferanza” in San Giovani Rotondo, Italy, the first Arkadi M. Rywlin International Pathology Slide Seminar Symposium in Anatomic Pathology was organized. This meeting was followed by other highly successful international meetings in Brisbane, Australia (2004), Srní, the Czech Republic (2005), Mexico City, Mexico (2008), Istanbul, Turkey (2010), and the present one in Stockholm. Future meetings are planned for Tel-Aviv, Israel (2013), Tokyo, Japan (2014), and a half-day program at the International Academy of Pathology (IAP) Meeting to be held this year in October in South Africa.

The slide seminars are conducted through the mail. Approximately 3–4 exchanges take place each year. A complete set of glass slides for distribution to all the members is submitted by the contributing pathologists on the cases of their choice, accompanied by a written description of the case, including clinical history, histologic findings, results of ancillary techniques, diagnosis, discussion with review of the literature, pertinent references, and questions posed to the other members of the club in reference to the case being circulated. This material is centrally collated and redistributed to all the members, and their comments and responses are transferred to a single document which is posted on the official AMR Club website (http://www.amr-seminar.org). Plans are underway to scan the slides from past seminars using virtual slide imaging technology to incorporate them into the website. Pertinent clinical pictures, imaging studies, and results of special techniques such as electron microscopy and molecular studies, are also uploaded in the website along with each case. Dr. Juan Rosai, one of the initial members of the club, has also asked for approval to scan all past AMR Slide Seminar cases to include in the “Juan Rosai Collection of Surgical Pathology Seminars” sponsored by USCAP and Aperio and that will be featured in the United States and Canadian Academy of Pathology website.

The person after whom the seminar is named, Arkadi M. Rywlin, M.D., was the Chairman of Pathology at the Mount Sinai Medical Center of Greater Miami, Miami Beach, Florida and Professor of Pathology at the University of Miami School of Medicine from 1962 until his untimely death in 1987. Professor Rywlin graduated medical school at the University of Geneva and took his initial training in Pathology under Professor Rutishauser. He immigrated to the United States in 1953 and resumed his training in Pathology at the University
of Chicago under Prof. Otto Saphir. He transferred to Miami in 1962 where he was to head the Department of Pathology and Laboratory Medicine at Mount Sinai Medical Center for 25 years. Prof. Rywlin was a classically trained pathologist who quickly became widely recognized as one of the preeminent hematopathologists of his generation. He single-authored the first book devoted to bone marrow pathology (Histopathology of the Bone Marrow, Little, Brown, Co, Boston, 1976), and contributed extensively to the literature on diseases of the bone marrow. His paper describing a simple technique for the preparation of bone marrow smears and sections (Am J Clin Pathol 53:389–393, 1970) rapidly became the standard of practice for obtaining bone marrow samples and the favored technique in the United States. Prof. Rywlin, however, was also a superb general pathologist and was able to offer an educated opinion on most areas in pathology. As Dr. A. Bernard Ackerman, his most prominent disciple, commented years later, "Arkadi rarely ever missed a diagnosis, and when he missed it was only by an inch, never by a mile…". Dr. Ackerman, in his preface to his famous tome on “Histologic Diagnosis of Inflammatory Skin Disorders” dedicated his book “…to Arkadi M. Rywlin, mentor in the science of pathology and in the art of life; wise, generous and loyal friend”. Prof. Rywlin was an outstanding educator and trained dozens of residents and fellows; his approach was straightforward and logical and stimulated his trainees to exercise critical judgment when approaching problems in pathology. The Club was founded to honor the memory of this giant of pathology and to advance the spirit of critical thinking that characterized what was known to all those who had the privilege to train under him as “Rywlinian”.

Saul Suster, M.D.
GENERAL INFORMATION

When & Where
June 14–16, 2012 at the Swedish Society of Medicine (SSM), Klara Östra Kyrkogata 10 in Stockholm

Lunch, coffee / tea and refreshments
will be served on the on-site Restaurant on second floor.

Social program
Thursday June 14, at 6.30 p.m.
Reception at the City Hall hosted by a member of the Presidency of the City Council and co-hosted by Stockholm's County Council. Address: Hantvergargatan 1 in Stockholm.

The City Hall of Stockholm is one of the most beautiful and well known buildings in the world and the most exclusive ballroom in Stockholm, frequently used for the yearly Nobel Banquet.

The City of Stockholm is governed from the City Hall. Around 200 politicians and civil servants have their offices here.

The Mayor of Stockholm is Mr. Sten Nordin. The City’s political organisation also comprises eight governing Vice Mayors who are full-time politicians and appointed by the City Council.

101 councillors are appointed following general elections held at the same time as the parliamentary and county council elections.

The City Hall of Stockholm is one of the best known buildings in Sweden. It holds the most exclusive ballroom in Stockholm, hosting the yearly Nobel Banquet.

How to get there? We will arrange for a joint walk from the Swedish Society of Medicine at 6.10 p.m. It takes approx 10 minutes to walk to the City Hall at Hantverkgargatan 1.

Please note that there will be no time to change clothes. Choose clothes suitable for the whole day and evening, umbrella depending on the weather and a jacket for the evening! Informal dress is almost always applicable in Sweden.
Friday June 15, at 6.30 p.m.
Cruise to Vaxholms kastell from Nybroviken at 6.30 p.m.
BBQ-buffet at the Exercishuset & Borggården at Kastellet

The cruise from Nybroviken/Stockholm to Vaxholm takes approx 45-60 minutes.

How to get there? We will arrange for a joint walk from the Swedish Society of Medicine at 6.10 p.m. It takes approx 10 minutes to walk to Nybroviken and Strandvägen quay.

Please note that there will be no time to change clothes. Choose clothes suitable for the whole day and evening, umbrella depending on the weather and a jacket for the evening! Informal dress is almost always applicable in Sweden.

How to get back to central Stockholm?
We have estimated to leave Vaxholm kastell at 11 p.m. with taxi-boats (approx 5 minutes). From Vaxholm we have arranged for bus-transportation to the Clarion Hotel (approx 45 minutes) at the Östra Järnvägsgatan 35 in Stockholm.
THE SYMPOSIUM HAS BEEN MADE POSSIBLE THROUGH EDUCATIONAL GRANTS FROM

MAIN SPONSOR FOR THE MEETING:

ROCHE

QIAGEN AB

BOEHRINGER INGELHEIM AB

HISTOLAB PRODUCTS AB

ELI LILLY SWEDEN AB

LEICA MICROSYSTEMS AB
Skräddarsydd behandling

– Rätt läkemedel till rätt patient

Skräddarsydd behandling innebär att vi kan hitta de patienter som har störst nytta av ett visst läkemedel. Genom att i tester undersöka hur den enskilde patientens sjukdom ser ut på gen- eller molekylnivå, kan vi hitta de patienter som bäst kan tänkas svara på en viss behandling; Rätt läkemedel till rätt patient.

Roche har en ledande position inom skräddarsydd behandling

Inom Roche finns en del i företaget som utvecklar diagnostiska tester och en del som tar fram nya och bättre läkemedel. Som ett av världens ledande läkemedelsföretag har Roche unika möjligheter att kunna leverera skräddarsydda behandlingar, inte minst genom att vi inom Roche kan kombinera diagnostik och läkemedel.

När det gäller bröstcancer, hudcancer, lungcancer och hepatit har vi redan tester och läkemedel som gör att vi kan ge rätt läkemedel till rätt patient.

I mer än 160 pågående projekt samarbetar diagnostik- och läkemedelsdivisionen inom Roche för att hitta ännu flera skräddarsydda behandlingar.
Roche

We Innovate Healthcare
Personalized healthcare promises better treatments at lower costs to healthcare providers. As the market and technology leader, QIAGEN delivers:

- Dependable assays for companion diagnostic development
- Advanced mutation-detection technologies, including real-time PCR and Pyrosequencing®
- Partnership with leading pharmaceutical companies

For more information about the global leader in molecular detection technologies, call QIAGEN today or visit www.qiagen.com.
Fullt Automatiserad Dubbelfärgning i 1-Steg

Mångfaldiga dina möjligheter med NYA Leica ChromoPlex™ 1 Dubbelfärgningskit för BOND

- Två kromogener i en och samma detektionskit
- För användning med kommersiella och självvaliderade antikroppscocktailar
- Överlägsen metod, jämfört med sekventiella dubbelfärgningar
- Genererar skarp, tydlig och bakgrundsfri rödbrun färgning

Kontakta din lokala återförsäljare för en skräddarsydd Totalt IHC & ISH-lösning idag.

Vår Totala Histologi lösning hjälper dig att uppnå bättre arbetsflöde, befrämjar säkerställd diagnostik och levererar det som är av värde – bättre patientvård.

www.leica-microsystems.com
Onco.10. 22087S

TesTa aLL icke småcellig Lungcancer för egfr-muT aTioner.
iressa ger mer än 70% objecTive response raTe för egfrm + paTienTer.


AstraZeneca AB, 151 85 Södertälje, tel: 08-553 260 00.
A new generation of digital slide scanners from 3D Histech

Pannoramic 250 Flash belongs to the new generation of digital slide scanners and is the latest addition to the Pannoramic family. Pannoramic 250 Flash offers award-winning* image quality in both bright-field and fluorescent scanning with an automatic camera changer, 250 slides capacity and a new refined scanning technique with two times faster scanning than earlier models. 1 cm² is scanned in 40 seconds (40x) respectively 20 seconds (20x).

* Pannoramic 150 SCAN digital slide scanner won "Quality Scan" in Berlin, May 2010.

3D Histech also offers:
- Teleconsultation
- Automated Image Analysis
- Remote Slide Access
- Workflow Management
- Tissue Micro Arrayer Systems
- Advanced Diagnostic Tools
- Fluorescent Slide Analysis

New products from pfm medical facilitates your work in the laboratory!

pfm Cassette Trimming System CTS 500 is used to remove excess wax from the sides of the cassette after embedding. This simplifies and speeds up the preparation of the cassette before insertion in the microtome.

Easy to use; hold the side of the cassette against the hot surface and the wax melts away immediately.

pfm Mobile Cooling System MCS 400 is a quiet and easy-to-place complement to all the other cooling systems at the laboratory.

Up to 20 blocks are easily cooled down below room temperature right next to the sectioning workstation, avoiding the need for alternative cooling methods such as with ice cubes.

CONTACT US TO FIND OUT MORE!

CUSTOMER SERVICE: +46 (0)31-709 30 30
mail@histolab.se  www.histolab.se
### Cases

#### 14 June - Morning Session - Thoracic Pathology:

<table>
<thead>
<tr>
<th>Case</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>Placental transmogrification of lung (Colby)</td>
<td>22</td>
</tr>
<tr>
<td>Case 2</td>
<td>Multifocal epithelioid hemangioendothelioma of lung (Krausz)</td>
<td>24</td>
</tr>
<tr>
<td>Case 3</td>
<td>Rhodococcus equi infection of lung (Colby)</td>
<td>27</td>
</tr>
<tr>
<td>Case 4</td>
<td>BAC-like invasive adenocarcinoma of lung (Marchevsky)</td>
<td>30</td>
</tr>
<tr>
<td>Case 5</td>
<td>Sarcomatoid malignant mesothelioma (Krausz)</td>
<td>32</td>
</tr>
<tr>
<td>Case 6</td>
<td>Follicular bronchiolitis due to exposure in popcorn factory (Marchevsky)</td>
<td>36</td>
</tr>
<tr>
<td>Case 7</td>
<td>Mature teratoma of thymus with colloid carcinoma (Marchevsky)</td>
<td>38</td>
</tr>
<tr>
<td>Case 8</td>
<td>Pseudosarcomatous “metaplastic” thymoma (Suster)</td>
<td>40</td>
</tr>
<tr>
<td>Case 9</td>
<td>IgG4 sclerosing lung disease (Colby)</td>
<td>42</td>
</tr>
<tr>
<td>Case 10</td>
<td>Basaloid carcinoma of thymus (Falconieri)</td>
<td>46</td>
</tr>
<tr>
<td>Case 11</td>
<td>Collision tumor of lung (met. LMS + prostate CA) (Suster)</td>
<td>48</td>
</tr>
<tr>
<td>Case 12</td>
<td>Synovial sarcoma of pleura (Falconieri)</td>
<td>50</td>
</tr>
<tr>
<td>Case 13</td>
<td>Primary cribriform adenocarcinoma of lung (Suster)</td>
<td>52</td>
</tr>
<tr>
<td>Case 14</td>
<td>Angiosarcoma in lung masquerading as DAH (Elmberger)</td>
<td>54</td>
</tr>
</tbody>
</table>

#### Afternoon Session - Bone and Soft Tissue Pathology:

<table>
<thead>
<tr>
<th>Case</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 15</td>
<td>Sclerosing epithelioid fibrosarcoma (Cooper)</td>
<td>60</td>
</tr>
<tr>
<td>Case 16</td>
<td>Myxoinflammatory fibroblastic sarcoma (Cooper)</td>
<td>62</td>
</tr>
<tr>
<td>Case 17</td>
<td>Pelvic chordoma (Unni)</td>
<td>65</td>
</tr>
<tr>
<td>Case 18</td>
<td>Leimyosarcoma of bone (Unni)</td>
<td>67</td>
</tr>
<tr>
<td>Case 19</td>
<td>Composite hemangioendothelioma (Mentzel)</td>
<td>69</td>
</tr>
<tr>
<td>Case 20</td>
<td>Malignant transformation in dermatofibroma (Mentzel)</td>
<td>71</td>
</tr>
<tr>
<td>Case 21</td>
<td>Familial tumoral calcinosis (Miettinen)</td>
<td>73</td>
</tr>
<tr>
<td>Case 22</td>
<td>Desmoplastic small round cell tumor of peritoneum (Krausz)</td>
<td>74</td>
</tr>
<tr>
<td>Case 23</td>
<td>Low-grade fibromyxoid sarcoma (Montgomery)</td>
<td>76</td>
</tr>
<tr>
<td>Case 24</td>
<td>Post-radiation epithelioid angiosarcoma of skin (Zambrano)</td>
<td>78</td>
</tr>
<tr>
<td>Case 25</td>
<td>Adamantinoma of bone (Wakeley)</td>
<td>81</td>
</tr>
<tr>
<td>Case 26</td>
<td>Mesenchymal chondrosarcoma (Wakeley)</td>
<td>83</td>
</tr>
<tr>
<td>Case 27</td>
<td>Intracranial Epstein Barr virus-associated smooth muscle tumor (Petersson)</td>
<td>86</td>
</tr>
<tr>
<td>Case 28</td>
<td>Extraneural soft tissue perineurioma (Zambrano)</td>
<td>94</td>
</tr>
<tr>
<td>Case 29</td>
<td>Desmoplastic fibroma of mandible (Zambrano)</td>
<td>97</td>
</tr>
<tr>
<td>Case 30</td>
<td>Spindle cell cutaneous lymphoma (Mentzel)</td>
<td>100</td>
</tr>
</tbody>
</table>

#### June 15 - Morning Session: Genitourinary Pathology and Miscellaneous:

<table>
<thead>
<tr>
<th>Case</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 31</td>
<td>STUMP of prostate (Epstein)</td>
<td>101</td>
</tr>
<tr>
<td>Case 32</td>
<td>Nested carcinoma of urinary bladder (Epstein)</td>
<td>103</td>
</tr>
<tr>
<td>Case 33</td>
<td>Acquired cystic disease-related renal cell carcinoma (Adsay)</td>
<td>106</td>
</tr>
<tr>
<td>Case 34</td>
<td>Malignant epithelioid renal angiomylipoma (Damjanov)</td>
<td>108</td>
</tr>
<tr>
<td>Case 35</td>
<td>Medullary carcinoma of kidney (Epstein)</td>
<td>109</td>
</tr>
<tr>
<td>Case 36</td>
<td>Mucinous and tubular spindle cell renal cell carcinoma (Damjanov)</td>
<td>110</td>
</tr>
<tr>
<td>Case 37</td>
<td>Sarcomatoid carcinoma of adrenal (Fedeli)</td>
<td>112</td>
</tr>
<tr>
<td>Case 38</td>
<td>Epithelioid angiosarcoma of adrenal (Fedeli)</td>
<td>115</td>
</tr>
<tr>
<td>Case 39</td>
<td>Lymphangiomatosis of spleen (Bisceglia)</td>
<td>117</td>
</tr>
<tr>
<td>Case 40</td>
<td>Hodgkin lymphoma complicating small lymphocytic lymphoma (Ben-Dor)</td>
<td>121</td>
</tr>
<tr>
<td>Case 41</td>
<td>Renal hemangioblastoma mimicking renal cell carcinoma (Bacchi)</td>
<td>125</td>
</tr>
<tr>
<td>Case 42</td>
<td>ALK+ diffuse large B-cell lymphoma (Bacchi)</td>
<td>127</td>
</tr>
<tr>
<td>Case 43</td>
<td>Medullary sponge kidney with arterial fibromuscular dysplasia (Bisceglia)</td>
<td>129</td>
</tr>
<tr>
<td>Case 44</td>
<td>Paraganglioma of the carotid body (Familial form with SDHD mutation) (Sobrinho-Simoes)</td>
<td>133</td>
</tr>
</tbody>
</table>
### 15 June · Afternoon Session: Gynecologic and Breast Pathology:

<table>
<thead>
<tr>
<th>Case</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>High-grade ovarian carcinoma (Silva)</td>
<td>135</td>
</tr>
<tr>
<td>46</td>
<td>Minimal deviation adenocarcinoma of endometrium (Silva)</td>
<td>136</td>
</tr>
<tr>
<td>47</td>
<td>Leiomyomatosis peritonealis disseminata (Bisceglia)</td>
<td>137</td>
</tr>
<tr>
<td>48</td>
<td>Malignant breast adenomyoepithelioma (Bleiweiss)</td>
<td>141</td>
</tr>
<tr>
<td>49</td>
<td>Mixed invasive mucinous and micropapillary CA of breast (Bleiweiss)</td>
<td>143</td>
</tr>
<tr>
<td>50</td>
<td>Phyllodes tumor of breast with liposarcoma (Ben-Dor)</td>
<td>144</td>
</tr>
<tr>
<td>51</td>
<td>IgG4 sclerosing disease of breast (Bacchi)</td>
<td>147</td>
</tr>
<tr>
<td>52</td>
<td>Acinic cell carcinoma of breast (Lamovec)</td>
<td>149</td>
</tr>
<tr>
<td>53</td>
<td>Adenocarcinoma of endocervix (Silva)</td>
<td>151</td>
</tr>
<tr>
<td>54</td>
<td>Hypercalcemic small cell carcinoma of ovary (Fukunaga)</td>
<td>152</td>
</tr>
<tr>
<td>55</td>
<td>Wolffian tumor of broad ligament (Fukunaga)</td>
<td>154</td>
</tr>
<tr>
<td>56</td>
<td>Omental metastasis of ovarian CA in pt. with breast CA (Bleiweiss)</td>
<td>155</td>
</tr>
<tr>
<td>57</td>
<td>Early complete mole (Fukunaga)</td>
<td>156</td>
</tr>
<tr>
<td>58</td>
<td>Rosai-Dorfman disease of breast (Damjanov)</td>
<td>157</td>
</tr>
<tr>
<td>59</td>
<td>Metastatic melanoma to breast mimicking carcinoma (Falconieri)</td>
<td>158</td>
</tr>
<tr>
<td>60</td>
<td>Pancreatic type solid/papillary tumor of ovary (Fedeli)</td>
<td>160</td>
</tr>
</tbody>
</table>

### 16 June · Morning Session: Gastrointestinal and Head & Neck Pathology:

<table>
<thead>
<tr>
<th>Case</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>61</td>
<td>Pancreatic neuroendocrine tumor (Adsay)</td>
<td>162</td>
</tr>
<tr>
<td>62</td>
<td>Pancreatic acinar cell carcinoma mimicking NET (Adsay)</td>
<td>165</td>
</tr>
<tr>
<td>63</td>
<td>Pancreatic oncocytoic neuroendocrine carcinoma (Ben-Dor)</td>
<td>167</td>
</tr>
<tr>
<td>64</td>
<td>Metastatic GIST to the meninges (Cooper)</td>
<td>171</td>
</tr>
<tr>
<td>65</td>
<td>Plexiform fibromyxoma of stomach (Miettinen)</td>
<td>173</td>
</tr>
<tr>
<td>66</td>
<td>Succinate dehydrogenase-deficient GIST (Miettinen)</td>
<td>174</td>
</tr>
<tr>
<td>67</td>
<td>Histoplasmosis in Crohn's disease (Montgomery)</td>
<td>177</td>
</tr>
<tr>
<td>68</td>
<td>Familial polyposis coli (Montgomery)</td>
<td>180</td>
</tr>
<tr>
<td>69</td>
<td>Plasmablastic lymphoma of oral cavity (Wakely)</td>
<td>183</td>
</tr>
<tr>
<td>70</td>
<td>Sclerosing mucopidermoid carcinoma of thyroid (Lamovec)</td>
<td>185</td>
</tr>
<tr>
<td>71</td>
<td>Hürthle cell (oncocytic) variant of follicular carcinoma (Sobrinho-Simoes)</td>
<td>187</td>
</tr>
<tr>
<td>72</td>
<td>Cribriform papillary thyroid carcinoma (Lamovec)</td>
<td>189</td>
</tr>
<tr>
<td>73</td>
<td>Primary small cell carcinoma of the thyroid with PNET features (Sobrinho-Simoes)</td>
<td>191</td>
</tr>
</tbody>
</table>
Case 1

Thomas Colby, M.D., The Mayo Clinic, Scottsdale, AZ, USA

Case History:
A 45-year-old man presented with tension pneumothorax. A bullous lesion was identified radiologically and the thoracic surgeon removed a large bulla that involved the right upper and middle lobes. Sections are shown from the upper lobe.

Histologic Findings
The histology clearly shows that there is no normal lung tissue. There are papillary-like structures that bear some resemblance to placental villi. These have associated histiocytic reaction in the edematous stroma and patchy chronic inflammation. The outer epithelial lining is by TTF+ CK+ epithelial cells. Some of the papillary structures have central vessels and there are some vacuolated spaces in the stroma. There are some calcifications present within some of the papillary structures.

Diagnosis:
Placental transmogrification of the lung (giant bullous emphysema/placentoid bullous lesion of the lung).

Discussion
This lesion represents a pathologic curiosity. Some would consider it just a variant of emphysema or, in particular, a variant of bullous emphysema but the clinical features in some of the cases are sufficiently distinctive that I think that it should be recognized as an entity in its own right. Clinically these patients present as though they have a large bulla and in contrast to the more common smaller bulla associated with COPD, the lesions may be relatively localized radiologically and the patients tend to be younger (middle age) without sex predilection. The symptoms are those of an air-filled mass lesion and include dyspnea, chest pain, and recurrent pneumothoraces. Some patients are asymptomatic. Less than 20 cases are reported in the literature. The lesion has been seen in severe smoking-related emphysema.

Grossly the specimen appears to be a large collapsed bulla and while they may merge with the adjacent lung parenchyma they also may be sharply demarcated. They may have a somewhat spongy or cystic appearance, depending on the size of the spaces and the extent of the placental villous-like change. Some contain gelatinous material and some have a vesicular or grape-like appearance. The lesions are usually lobar but may affect more than one lobe or the entire lung.

Histologically there is bullous emphysematous change that appears to be panacinar with spaces containing structures resembling hydropic villi from a placenta. The cores of the villi contain vessels and stroma cells, lymphocytes, plasma cells, and histiocytes and occasionally bundles of smooth muscle. Some of the villi become sclerotic or calcified. Lymphoid aggregates may be present. In some cases fat and chondroid metaplasia is present and a relationship to fibrochondromatous hamartoma has been suggested. The villi are lined by type 2 cells.

One case reported had histologic features of placental transmogrification but had presented as a solitary nodule radiologically. The lesion has been reported in Swyer-James syndrome.

The differential diagnosis includes other causes of large cystic lesions such as cystic neoplasms, cavernous vascular lesions, and otherwise uncomplicated large bullae. Surgical resection is the treatment of choice and is considered curative.

REFERENCES


**Case 2**

Thomas Krausz, M.D., The University of Chicago, Chicago, IL, USA

**Clinical History:** 20-year-old female presented with dyspnea. CT showed features suggestive of interstitial lung disease. Video-assisted thoracoscopic with wedge biopsies of right upper, middle and lower lobes were performed (biopsies from all sites showed similar histologic features). Representative section of lower lobe biopsy submitted for the seminar.

**Pathology:**
During gross examination scattered small rubbery, tan nodules (1 – 6 mm in diameter) were seen on the cut surfaces the pulmonary wedge biopsies. Frozen section was read as “malignant neoplasm” defer to permanent for classification.

Histologically there are multiple neoplastic nodules of polygonal/epithelioid cells distributed in subpleural, perivascular/intravascular and peribronchiolar locations with striking interstitial as well as intraalveolar spread.

The infiltrating tumor nodules vary in shape, cellularity and amount of myxohyaline stromal matrix. Most of the neoplastic cells exhibit an epithelioid phenotype with abundant amphophilic cytoplasm and rather bland round vesicular nuclei containing small, solitary nucleoli. The cytoplasm of most tumor cells is homogenous but cytoplasmic vacuole, occasionally containing red blood cell, can be observed in rare cells. In places, where the stroma is densely fibrotic, there is some spindling of the tumors cells. Moderate nuclear pleomorphism can be observed only focally and mitotic figures are infrequent (< 1 mitosis/10HPFs).

**Immunohistochemical study:** Virtually all the tumor cells express strong membranous immunoreactivity for endothelial marker CD31 and nuclear staining for FLI-1. Other endothelial markers (CD34, Factor VIII and D2-40) are positive only focally. The tumor cells are negative for epithelial markers (CAM5.2, CK7, AE1/AE3, EMA) and melanocytic markers (HMB45, MelanA, Mitf1 and S100). There is extensive, strong immunoreactivity for Vimentin and histiocytic markers (CD68, CD163) and muscle markers (SMA, MSA, desmin) are negative.

**Diagnosis:** Multifocal epithelioid hemangioendothelioma of the lung

**Comments:** Epithelioid vascular tumors encompass a broad histologic spectrum, including epithelioid hemangioma, a benign tumor; epithelioid hemangioendothelioma (EHE), a low-grade malignant tumor; and epithelioid angiosarcomas (EA), a high-grade malignant tumor. Vascular differentiation in EHE and EA is difficult to recognize histologically, because the neoplastic cells do not form morphologically apparent vascular channels, but instead are characterized by a nested or cored proliferation of neoplastic epithelioid cells which in cases of EHE are embedded within a proteoglycan-rich myxohyaline stroma. The endothelial lineage of differentiation can be confirmed by immunoreactivity for endothelial markers or by specific ultrastructural features. The histologic differential diagnosis of EHE and EA include carcinoma, melanoma, histiocytic neoplasms and some sarcomas exhibiting epithelioid phenotype (e.g. epithelioid sarcoma).

Primary vasoformative neoplasms of the lung are rare; therefore, the clinical and radiological features are often mistaken for other, more common pathologic processes until their neoplastic vasoformative/endothelial nature is established by histologic examination. The best recognized benign vascular tumors of the lung include hemangioma and lymphangiomma while the malignant ones are epithelioid hemangioendothelioma, angiosarcoma and Kaposi’s sarcoma. The diagnosis of a primary malignant vascular/endothelial neoplasm requires exclusion of metastasis from extrapulmonary sites. Pulmonary epithelioid hemangioendothelioma was first described as “intravascular bronchioloalveolar tumor” by Dail and Liebow in 1975, suggesting that this tumor was of epithelial origin. Subsequently electron microscopic studies have proven the endothelial differentiation of this tumor. Following the description of a similar tumor under the term of “epithelioid hemangioendothelioma” in the soft tissue by Weiss and Enzinger in 1982 it has been realized that these tumors were essentially morphologically identical and the term “epithelioid hemangioendothelioma” has since been used to designate these neoplasms regardless of their location. To date, more than 100 pulmonary cases have been described. Primary epithelioid hemangioendotheliomas of serous membranes, most frequently of the pleura, have also been recognized. Pulmonary epithelioid hemangioendothelioma virtually always presents as a multifocal disease with multiple...
discrete nodules measuring less than 2 cm in diameter. Close association with various vascular structures and focal intraalveolar growth is typical. The tumor nodules often have a relatively hypocellular center surrounded by a rim of more cellular tissue. There is a combination of nested to trabecular growth pattern typically associated with a myxohyaline matrix. Attenuated strands of tumor cells may also be seen. Typical examples of EHE are composed of rather bland epithelioid cells but focal spindling may be present. The frequency of intracytoplasmic lumina, sometimes containing erythrocytes, varies from case to case. In contrast to EA, most cases of EHE show neither significant nuclear pleomorphism nor brisk mitotic activity.

Distinguishing EHE from EA is important in view of the marked differences in disease progression and prognosis. Historically, especially in cases of EHE occurring in soft tissue, increased mitotic activity, nuclear pleomorphism and tumor necrosis were found to be prognostically important. In some of these “malignant” examples of EHE the histologic features overlap with those of EA. The recently described disease-defining gene fusion WWTR1-CAMTA1 (t(1;3)(p36.3;q25) in epithelioid hemangioendotheliomas as a constant aberration independent of anatomic sites (bone, soft tissue, liver, lung) is a useful diagnostic marker (FISH or RT-PCR analysis) in differentiating EHE not only from epithelioid hemangioendotheliomas and epithelioid angiosarcomas but also from its mimics.

Clinically pulmonary EHE mostly occurs in younger individuals with a median age of 36 years at diagnosis. It is much more frequent in females (80%). Patients are often asymptomatic or present with cough, dyspnea or pleuritic chest pain. Rarely there is hemoptysis and pleural effusion. Radiologically, EHE is characterized by multiple small nodular lesions affecting both lungs and mimicking granulomatous or interstitial lung disease. Interestingly, rare cases have been seen with concurrent bronchioloalveolar carcinoma.

Pulmonary EHE is regarded as a low-grade malignant neoplasm with a protracted clinical course and non-aggressive behavior but metastatic potential. Life expectancy ranges from 1 to 20 years with a 5-year survival rate of 60%. Deyrup et al. (2008) correlated tumor size (> 3cm) and more than three mitotic figures per high-power field with reduced 5-year survival in EHE (59% vs 100%) in cases of EHE of soft tissue. Interestingly, Makhlouf et al. (1999) found that mitotic count and nuclear atypia did not affect outcome in cases of EHE of the liver. The applicability of these data for cases of pulmonary EHE requires further studies. Clinical factors of poor prognosis include extensive intrapulmonary and pleural spread with hemorrhagic pleural effusion. Lau K et al (2011) proposed a novel staging system with prognostic value for EHE: pleural effusion or other signs of uncontained tumor growth, hemoptyisis, and osseous involvement of more than two bones implies worse survival than does localized and discrete tumors, regardless of number of organs involved. Partial regression have been described in rare cases, but most patients eventually die of respiratory failure due to extensive replacement of the lung parenchyma by tumor. Surgical excision is the treatment of choice if the disease is limited. Lung transplantation may be considered in cases of aggressive growth. Neither chemotherapy nor radiotherapy has proven to be effective in the treatment of EHE, although antiangiogenic therapy has been successful in rare case.

REFERENCES

- Okamura K et al. A case of pulmonary epithelioid hemangioendothelioma surviving 10 years without
435.

• Ye B et al. Multiple organ metastases of pulmonary
epithelioid hemangioendothelioma and a review of the

• Lau K et al. Clinical patterns and outcome in epithelioid
hemangioendothelioma with or without pulmonary
involvement. Insights from an internet registry in the

• Lin BT et al. Malignant vascular tumors of the serous
membranes mimicking mesothelioma: a report of 14

• Weissferdt A, Moran CA. Primary vascular tumors of the

• Errani C et al. A novel WWTR1-CAMTA1 gene
fusion is a consistent abnormality in epithelioid
hemangioendothelioma of different anatomic sites.

• Tanas MR et al. Identification of a disease-defining gene
fusion in epithelioid hemangioendothelioma. Sci Transl
Case 3

Thomas Colby, M.D., The Mayo Clinic, Scottsdale, AZ, USA

Case History: A 45-year-old HIV-positive man had multiple nodular lesions in the left upper and lower lobes of the lungs and biopsies were taken.

Histologic Findings
The sections show necrotic nodules in the lung that are sharply circumscribed. They are composed of sheets of eosinophilic histiocytes and regions of necrosis with neutrophils. Many of the histiocytes have eosinophilic cytoplasm and contain eosinophilic globules. Some of the globules are calcified and form classic Michaelis-Gutmann bodies. Within the areas of necrosis one can see bacteria. Gram stains confirm the presence of Gram+ bacteria. PAS stains show large numbers of PAS positive lysosomes in the histiocytes. Von Kossa stain shows calcification in the Michaelis Gutmann bodies.

Diagnosis: Rhodococcus equi infection of the lung (culture proven) in the setting of HIV with morphologic features of pulmonary malakoplakia.

Discussion
While malakoplakia is defined on the basis of distinctive histiocytes (Von Hansemann’s cells) with lamellar calcific inclusions (Michaelis-Gutmann bodies) and not by the specific causal bacteria, the majority of cases of pulmonary malakoplakia in the lung occur in the setting of Rhodococcus equi infection, particularly in the setting of a HIV/AIDS.

Malakoplakia was first recognized in the bladder and approximately 75% of cases affect that site. Many other sites of involvement have been described, including other sites in the GU tract, of the GI tract, the soft tissue, skin, brain, bone, lungs, conjunctiva, ear, mastoid, et al. In some patients multiple sites are affected.

Pathogenetically, malakoplakia is thought to represent defective macrophage processing of organisms which accumulate as a phagolysosomes, some of which calcify to form classic Michaelis-Gutmann bodies. The profusion of lysosomes causes the distinctive eosinophilic appearance of the histiocytes which are seen to best advantage with PASd stains.

Malakoplakia of the lung is histologically distinctive and can be readily diagnosed in small biopsies, including fine needle aspirations based on the distinctive cytology of the cells, the presence of Michaelis-Gutmann bodies, and the frequent presence associated bacteria.

The differential includes other lesions with large numbers of histiocytes although careful inspection generally shows the distinctive features in malakoplakia which separate it from Whipple’s Disease, histiocyte-rich mycobacterial and fungal infections in immunosuppressed patients, non-specific granulomatous inflammation, storage diseases, drug reactions (e.g. amiodarone reaction), and other lesions with increased histiocytes in the lung.

Rhodococcus equi is best known in veterinary medicine as a cause of chronic cavitary pneumonia, ulcerative enteritis, and supplicative lymphadenitis in foals. Human infection has been described since the late 1960s, and most recent cases in the lung have been associated with AIDS.

Rhodococcus equi (formerly Corynebacterium equi) is a Gram positive coccobacillus with some variation in morphology depending on solid culture media (coccoid forms most common) and liquid culture media (long rods or short filaments). The organisms may be acid fast but this is inconstant. R. equi can be cultured in ordinary media with aerobic incubation at 37°C. R. equi is gelatinase positive, catalase positive, nonfermentive, oxidase negative, and often urease positive. PCR-based assays are available to provide a specific and sensitive means to detect the virulent strains of R. equi in tracheal aspirates of foals and these techniques are more rapid than routine cultures (Takai ref). R. equi is ubiquitous and found in the soil as well as in the guts of herbivores. In one study, soil from all 19 horse farms sampled was positive for the organism.

Pulmonary involvement is the most common manifestation of Rhodococcus equi infection in humans. It typically is associated with cough, fever, and localized infiltrate(s) or mass lesions that may cavitate. Tracheal and endobronchial involvement has been described. The process may invade adjacent structures in the chest wall or mediastinum. Pleural effusions may be present. Not all cases are associated with malakoplakia. Histologic studies suggest that early on there is acute inflammation and necrosis and over time histiocytes accumulate,
eventually becoming sheet-like, and some develop the classical Michaelis-Gutmann bodies.

REFERENCES


Case 4

Alberto M. Marchevsky, M.D., Cedars-Sinai Medical Center, Los Angeles, CA, USA

Clinical History:
The patient is a 79-year old woman with a previous medical history of hypertension, vertigo and various orthopedic surgeries and a 16 pack year history of cigarette smoking. She had quit smoking in 1980. In June 2010 she was found to have a mass density in the left lung on routine chest X-ray. PET/CT scan showed enlarged mediastinal lymph nodes and a 2.0 cm subpleural mass in the left lower lobe of the lung. PET showed uptake in mediastinal lymph nodes and the lung mass with no extrathoracic metastases. She underwent mediastinoscopy with frozen sections that yielded negative lymph nodes. A left VATS was then performed, with left lower lobe wedge biopsy, frozen section and completion lobectomy.

Pathology description:
Wedge biopsy showed an ill-circumscribed, gray-tan, soft tumor measuring 2.0 x 2.0 x 1.2 cm. Completion lobectomy showed no residual tumor. Hilar, subcarinal, aortic pulmonary window, paraaortic and peribronchial lymph nodes were negative for tumor. Pathology slides of the wedge lung biopsy showed a mucinous neoplasm with prominent lepidic growth features and focal areas of presumed stromal invasion that are difficult to identify and measure with certainty. The tumor cells exhibited cytokeratin 7 immunoreactivity. Immunostains for cytokeratin 20, TTF-1 and Napsin A were negative. The completion lobectomy specimen showed no residual tumor.

Diagnosis: Mucinous adenocarcinoma of the lung
Frozen section of the lesion was diagnosed in 2010 as bronchioloalveolar carcinoma, mucinous type. Permanent sections of the tumor were diagnosed as bronchioloalveolar carcinoma, mucinous type with focal areas of stromal invasion that are difficult to identify and measure with certainty. The tumor cells exhibited cytokeratin 7 immunoreactivity. Immunostains for cytokeratin 20, TTF-1 and Napsin A were negative. The completion lobectomy specimen showed no residual tumor.

Discussion:
This case is presented to elicit discussion about how best to assess the presence of stromal invasion in cases of pulmonary adenocarcinoma in-situ, mucinous type. In our institution we are routinely asked to distinguish adenocarcinoma in-situ/minimally invasive adenocarcinoma from invasive adenocarcinomas of the lung. Tumors in the first group are usually treated with VATS wedge resection, unless there are technical issues such as tumor location or others that require a VATS lobectomy. Invasive adenocarcinomas are treated with lobectomy. Histopathological criteria of invasion include stromal reaction in the form of recent fibrosis, and infiltration of tumor cells into the stroma. The diagnosis of stromal invasion can be difficult, particularly in mucinous neoplasms. We have seen only rare instances of “classical” mucinous adenocarcinoma in-situ of the lung presenting as small neoplasms composed of mucin secreting cells that line thin alveoli that exhibit no significant fibrosis or inflammation. More often mucinous adenocarcinomas of the lung grow in a lepidic growth pattern with preservation of the underlying lung architecture but the alveoli underlying the tumor cells are frequently fibrotic and inflamed. Are these tumors adenocarcinomas in-situ? How do we measure the extent of invasion in these lesions? What is the prognosis of these patients? To my knowledge, these issues are not thoroughly discussed in the literature and there is limited evidence regarding the significance of histopathological features.

REFERENCES


Case 5

Thomas Krausz, M.D., The University of Chicago, Chicago, IL, USA

Clinical History: 69-year-old male with right pleural thickening and recurrent pleural effusion who undergoes right thoracotomy and pleurectomy.

Additional history: Previous closed pleural biopsy performed at an outside hospital was diagnosed as “pleural fibrosis, no tumor” and repeat biopsy as “atypical fibrous mesothelial lesion, malignant mesothelioma can not be excluded”

Pathology: Frozen section specimen (intraoperative consultation) during thoracotomy was read as “fibrous pleural plaque with focal atypia, defer to permanent”. Right pleurectomy specimen received as multiple, white-tan, rubbery, flat tissue fragments (largest fragment measured 15 x 11 cm with maximal thickness of 0.7 cm), aggregate weight 270 gm. The submitted sections for the seminar were cut from two different paraffin blocks, both showing similar features. There is marked fibrous hypovascular thickening of the pleura with variable cellularity. Foci of abrupt transition from hyalinized to more cellular areas composed of bland spindle cells are present. Architecturally storiform regions alternate with “patternless” foci as well as horizontally aligned collagenous fascicles. Sections derived from one of the blocks also show a focus of epithelioid cells, which comprise less than 1% of the whole tumor. The fibrotic process extends into the adipose tissue of the chest wall. In other blocks (not submitted) there are hyaline plaques, focally calcified, characterized by relatively acellular collagen arranged in “basket weave” fashion. Immunohistochemical studies showed that most of the spindle cells are positive for keratin CAM5.2, which also highlighted keratin positive spindle cells in the adipose tissue. Keratin 5/6 gave negative result. Other mesothelial markers (WT-1, calretinin, D2-40) were only focally positive.

Diagnosis: Desmoplastic sarcomatoid malignant mesothelioma of the right pleura

Comments: The pleural biopsies preceding the pleurectomy were not conclusive and the frozen section diagnosis during thoracotomy was also deferred for permanent sections. These events reflect the diagnostic challenge posed by desmoplastic mesothelioma. The submitted H&E sections exhibit several but not all the typical features of sarcomatoid desmoplastic malignant mesothelioma. The focal presence of horizontally orientated fascicles of spindle cells merging with areas of hyaline plaque may cause differential diagnostic dilemma. Invasion of adipose tissue by keratin positive spindle cells in this clinicopathologic setting is conclusive for the diagnosis of desmoplastic malignant mesothelioma. Primary tumors of the pleura are rare overall, and diffuse malignant mesothelioma is the most common of these neoplasms. WHO classifies malignant mesothelioma into epithelial, sarcomatoid, and biphasic types, each of which can be subdivided further. This classification has implications for both diagnosis and prognosis. Prognosis is poor for all malignant mesotheliomas, but sarcomatoid malignant mesotheliomas have a particularly poor response to treatment, with a median survival of 6 months. Histologic diagnosis of sarcomatoid malignant mesothelioma, especially of desmoplastic malignant mesothelioma, can be more problematic than for epithelioid or biphasic malignant mesothelioma, because of histologic similarity with benign fibrous pleurisy, and with non-mesothelial tumors (various sarcomas and sarcomatoid carcinomas), and because of restricted/inconsistent expression of mesothelial markers on immunohistochemistry. The correct diagnosis is very important because of the different prognostic and therapeutic implications of other disorders that mimic sarcomatoid mesothelioma (e.g. desmoplastic mesothelioma vs. fibrous pleurisy; sarcomatoid mesothelioma vs. synovial sarcoma). Sarcomatoid mesotheliomas can be subclassified as ordinary/conventional, desmoplastic, lymphohistiocytoid, and heterologous sarcomatoid mesotheliomas. One of the largest clinicopathologic studies (Klebe S et al, 2010) identified 326 cases of sarcomatoid mesotheliomas among 2000 consecutive malignant mesotheliomas (16%) with a median age of 70 years (range 41 – 94 years). Most tumors were pleural (319; 98%), and 7 were peritoneal (2%). Some desmoplastic features were identified in 110 cases (34%), and 70 (21%) were classified as desmoplastic. Rare subtypes included two cases of lymphohistiocytoid type (< 1%) and eight heterologous mesotheliomas (2%). Immunoreactivity for cytokeratins was observed in 261/280 cases (93%) and for calretinin in 31%. Pleural plaques were present in 79% of cases for which information was available, and asbestosis was
This discussion will focus on desmoplastic malignant mesotheliomas (for comprehensive differential diagnosis of sarcomatoid mesothelioma see reference Travis WD, 2010). Desmoplastic mesothelioma is defined by at least 50% of the tumor showing typical collagenous stroma with paucicellular atypical invasive mesothelial proliferation. Tumors with >10% but <50% desmoplastic features are classified as sarcomatoid mesotheliomas with focal desmoplastic features.

The main differential diagnosis of desmoplastic malignant mesothelioma is benign fibrous pleurisy. Both are paucicellular lesions in which most of the thickened pleura is composed of dense collagenous tissue, although each may have more cellular areas. The histologic diagnosis of desmoplastic malignant mesothelioma can be reliably made when the paucicellular fibrotic lesion exhibits storiform arrangement or the “patternless pattern” of Stout together with one or more of the following four criteria: 1) invasion, 2) bland necrosis, 3) frankly sarcomatous foci, and 4) distant metastasis (see references below for detailed description of each criterion). Fibrous pleurisy exhibits “zonation” with highest cellularity immediately beneath effusion and increased fibrosis away from effusion. In contrast to desmoplastic malignant mesothelioma, fibrous pleurisy is richly vascular with capillaries arranged perpendicularly to the pleural surface. Also, fibrous pleurisy does not show keratin positive pleural cells invading adipose tissue, muscle or lung parenchyma. It is important to remember that keratin positivity in serous membranes does not distinguish between benign reactive mesothelial process and malignant mesothelioma. Any active benign or malignant mesothelial proliferation is keratin positive if stained with a broad-spectrum anti-keratin and keratin immunoreactivity is seen in both epithelioid and spindle mesothelial cells. However, keratin immunostaining is still useful for assessment of the distribution of lesional mesothelial cells, including the neoplastic mesothelial cells invading adipose tissue, muscle or lung in cases of malignant mesothelioma.

A diagnostic pitfall: to diagnose desmoplastic malignant mesothelioma by confusing the “fake fat” phenomenon in organizing pleuritis with invasion of real adipose tissue by keratin positive mesothelial cells. The keratin positive mesothelial cells are oriented horizontally in the former and vertically in the latter, which should help one to avoid misinterpreting this phenomenon.

A variety of methods have been attempted in an effort to distinguish between reactive and malignant mesothelial lesions, however, in practice such distinction depends more on morphologic expertise than any foolproof ancillary tests like expression of EMA, telomerase, GLUT-1 and IMP3 in mesothelioma and desmin in reactive mesothelial cells.

However, there is emerging data that homozygous deletion of 9p21 locus harboring gene CDKN2A (p16) in up to 74% of malignant mesotheliomas has both diagnostic and prognostic value. Demonstration of CDKN2A (p16) deletion by FISH is particularly useful diagnostically in separating benign from malignant mesothelial proliferations of serous fluids and small biopsy specimens. Application of this assay certainly improves the accuracy of diagnosis of malignant mesotheliomas especially in sarcomatoid since there is homozygous deletion in almost 100% of sarcomatoid as compared to 70% in epithelioid mesotheliomas. Cases with CDKN2A deletion usually also have loss of p16 protein expression. According to some studies loss of p16 immunoreactivity has the same prognostic significance as homozygous deletion of p16, while other studies showed about 23% discrepancy between FISH and immunohistochemistry. Loss of p16 immunoreexpression in the absence of 9p21 deletion may be the result of point mutation or methylation. Best survival was observed in patients where the tumor showed p16 immunoreactivity and lack of p16 deletion. MTAP resides in the same gene cluster of 9p21 region and is co-deleted in the majority of CDKN2A (p16) deleted cases. CDKN2A and MTAP deletions in peritoneal mesotheliomas are correlated with loss of p16 protein expression and poor survival. However, it is important to keep in mind that deletion of 9p21 has been documented in a variety of human cancers; therefore it is not helpful in differentiating malignant mesotheliomas from non-mesothelial neoplasms involving serous membranes.

The molecular basis of the broad histologic spectrum of malignant mesotheliomas can partly be explained on the biologic potential of mesothelial cells. Mesothelial cells share characteristics of both epithelial and mesenchymal cells. Epithelial characteristics include polygonal shape, presence of cytokeratin intermediate filaments (cytokeratin 6, 8, 18, and 19), tight junctions, expressions of cadherins and the ability to secrete basement membrane. They also exhibit mesenchymal characteristics such as presence of vimentin, desmin and upon stimulation, alpha smooth muscle actin. Accordingly the mesothelial cells have the ability to change their phenotype (from polygonal to spindle) comparable to changes seen during embryonic development in the form of epithelial-to-mesenchymal transition (EMT). This observation has implications for our understanding not only of repair but also of
the morphologically diverse phenotypes (epithelioid, biphasic, sarcomatoid) of malignant mesothelioma. Interestingly, after several passages in culture, mesothelial cells loose their epithelioid, polygonal phenotype, cytokeratin expression and adopt a spindled, fibroblast-like phenotype. Incubation of mesothelial cells with the wound repair and pro-fibrotic mediator transforming growth factor-β1 (TGF-β1) induced EMT in mesothelial cells and upregulated smooth muscle actin and type I collagen expression, consistent with myofibroblastic differentiation. The data indicate that the mesothelium is a likely source of fibrogenic cells during serosal inflammation/fibrosis and wound healing and may play important roles in the formation of serosal adhesions. Mesothelial cells also undergo EMT during continuous ambulatory peritoneal dialysis with the induction of the transcription factor Snail and a dramatic down-regulation of E-cadherin and cytokeratins. The epithelial-to-mesenchymal transition, initially recognized as an essential mechanism for embryonic development, is nowadays regarded as a key player in additional physiologic and pathologic processes such as wound healing and tumor progression including metastasis. EMT is a complex genetic program, which implies the acquisition of migratory phenotype with the loss of cadherin-mediated cell-cell adhesion and apical-basal polarity. This causes the normal epithelial and mesothelial cells to dissociate from their neighbors and migrate. Several transcription factors have been described as key inducers of EMT, including members of the Snail superfamily (Snail1 and Snail2), the basic helix-loop-helix family (bHLH), and the two zinc-finger E-box-binding homeobox factors (ZEB1 and ZEB2). There are a number of well-described signaling pathways that control the expression of Snail factors, but the regulation of the expression of bHLH and ZEB factors is less well known. However non-coding RNAs (microRNAs) especially the miR-200 family are emerging as central players in gene expression regulation through the targeting of the mRNAs of the cadherin repressors ZEB1 and ZEB2. Given the lack of any universally accepted treatment for mesothelioma, the short life expectancy and the need for definitive diagnosis in order to support claims for compensation, the responsibility of the pathologist is onerous. The correlation between clinical history, radiographic and pathologic findings is a must for correct diagnosis. As the diagnosis of mesothelioma during life is often based on limited histological material, a multimodal diagnostic approach using routine and special stains, along with immunohistochemistry, molecular testing and sometimes electron microscopy is recommended. Guidelines for pathologic diagnosis of malignant mesothelioma have been published by the Mesothelioma International Interest Group (Husain et al, 2009), for the management of pleural malignant mesothelioma by the European Respiratory Society and European Society of Surgeons Task Force (Scherpereel et al, 2010) and for peritoneal mesothelioma the guidelines reviewed by Chua et al 2009. Pathologists play an important role in the diagnosis and management of malignant mesothelioma.

REFERENCES


• Krasinskas AM et al. CDKNA2 and MTAP deletions in peritoneal mesotheliomas are correlated with loss of p16 protein expression and poor survival. Modern Pathol 2010; 23:531–538.


• Ikeda K et al. Diagnostic usefulness of EMA, IMP3, and GLUT-1 for the immunocytochemical distinction of malignant cells from reactive mesothelial cells in effusion cytology using cytospin preparations. Diagn Cytopathol 2011; 39:395–401.


Case 6

Alberto M. Marchevsky, M.D., Cedars-Sinai Medical Center, Los Angeles, CA, USA

**Clinical History:** The patient is a 40-year old man with a previous medical history of childhood asthma, gastroesophageal reflux disease (GERD) with incompetent lower esophageal sphincter, alleged myocardial infarct secondary to anesthetic throat spray and opiate abuse and dependence. He worked in a popcorn factory and was exposed to flavoring chemicals for approximately 6 months. During that time period he developed progressive shortness of breath. He was evaluated at another hospital and underwent a wedge lung biopsy 3 years prior to admission to our hospital. The biopsy was diagnosed as obliterative bronchiolitis with necrotic granulomas secondary to Histoplasmosis and is not currently available for review. The patient was treated or bronchiolitis obliterans but did not respond to medical treatment. He developed increasing exertional dyspnea and was referred to our hospital. Physical examination showed signs of pulmonary hyperinflation with no clubbing. Chest X-ray was normal. Chest CT scan without contrast showed diffuse hyperinflation with bronchiectatic changes in the upper and lower lobes, and focal parenchymal and pleural scarring possible related to prior open lung biopsy. Pulmonary function tests showed a FVC= 54% of predicted, FEV-1=19% of predicted, total lung capacity= 108% of predicted, DLCO= 32% of predicted. Barium swallow with esophagogram showed positional reflux to the level of the thoracic inlet, a sliding hiatal hernia, and normal esophageal motility. He underwent a bilateral sequential lung transplant.

**Pathology description:** Grossly, the explanted lungs were overinflated with bilateral cylindrical bronchiectases in the upper and lower lobes.

Microscopically, the lungs showed bronchiectases, chronic follicular bronchiolitis, focal obliterative bronchiolitis and peribronchial areas of endogenous lipid pneumonia with focally prominent cholesterol granulomas. Peribronchial lymph nodes showed old necrotizing granulomas with structures suggestive on GMS stains of spores of Histoplasma sp, although the possibility of calciospherites could not be entirely excluded. Cultures were negative.

**Diagnosis:** “Popcorn lung disease”

We issued a descriptive diagnosis of bronchiectases, follicular bronchiolitis, and lipid pneumonia. Possible associations with chronic hypersensitivity pneumonitis (extrinsic allergic alveolitis), GERD, and/or changes secondary to diacetyl exposure were discussed. Later on I was unexpectedly subpoenaed for a deposition by the patient’s lawyer and learned that he had been a worker in a popcorn factory.

**Discussion:** The case probably represents an example of so-called “popcorn lung disease1-10. The syndrome was first identified in 2000 when the Missouri Department of Health and Senior Services identified cases of bronchiolitis obliterans in former workers of a microwave popcorn plant in Jasper Missouri. The National Institute of Occupational Safety and Health issued an alert in 2004 and additional patients were reported of respiratory problems related to diacetyl-containing flavorings used in butter-flavored microwave popcorn. Patients develop cough, wheezing, and worsening shortness of breath. Some individuals develop systemic symptoms with fever, night sweats and weight loss. In contrast with cases of hypersensitivity pneumonitis, the symptoms do not improve when the workers go home at the end of the day or on weekends or on vacation. The clinical differential diagnosis includes asthma, chronic bronchitis, emphysema, pneumonia and others. Spirometry shows fixed airways obstruction with decrease in FEV1 and increase lung volume that does not improve with asthma medications. Diffusing Capacity of the lung (DLCO) is usually normal. High-resolution CT scan shows areas of heterogenous air trapping on the expiratory view, haziness and thickened airway walls. Lung biopsy is reported to show obliterative bronchiolitis. However, according to a recent Center for Disease Control and Prevention (CDC) report “open lung biopsy appears to be insensitive because of the patchiness of the pathologic abnormality and the ease with which the diagnosis has been initially missed even by experienced chest pathologists”. A few cases of presumed obliterative bronchiolitis have also been described in heavy users of butter-flavored microwave popcorn. To my knowledge, the pathologic features of this syndrome are not all that well characterized and only a small number of case reports or small case series have described pathologic findings of obliterative bronchiolitis. Our patient exhibits pathologic findings that are different from those seen in biopsies with either bronchiolitis obliterans associated with cryptogenic organizing pneumonia (COP) or oblite-
rative pneumonitis (OB) seen in chronic rejection, exposure to ammonia and other toxins. In particular, the biopsy shows numerous foamy macrophages centered around chronically inflamed and scarred airways that are more prominent than those seen in cases of endogenous lipoid pneumonia secondary to obliterative bronchiolitis or other conditions.

REFERENCES


Case 7

Alberto M. Marchevsky, M.D., Cedars-Sinai Medical Center, Los Angeles, CA, USA

Clinical History:
The patient is a 22-year old woman who developed migraines, back discomfort and right chest pain that radiated down her arm. Symptoms were intermittent and she did not experience shortness of breath, difficulty swallowing or other problems. Chest X-ray showed mediastinal widening. Chest CT showed a 4.8 cm anterior mediastinal mass with solid areas, foci of low-density indicating fluid formation and clusters of calcification. The lesion appeared inseparable from the right upper lobe of the lung and was not associated with the thyroid or other mediastinal structures. Mediastinal lymph nodes were unremarkable. The patient underwent right VATS resection. Intraoperatively the mass was not adherent to the lung and was very close to the right phrenic nerve, without infiltrating it. The tumor was completely excised. Postoperatively the patient was referred to an oncologist who referred the case for discussion at our weekly GU tumor board. As the patient had a rare neoplasm that had been completely resected and there was no clinical evidence for residual or metastatic disease it was recommended that he should be observed without administration of adjuvant chemotherapy. The patient is currently tumor free approximately 7 months after surgery.

Pathology description:
The tumor measured 4.5 cm in largest dimension, was well encapsulated and showed solid, soft gray areas and cystic areas with grumous white content.

Microscopically it was composed of an admixture of mature tissues, including squamous epithelium, enteric and respiratory epithelium, cartilage and neural tissue. In addition there were areas of an infiltrating moderately differentiated mucin secreting, “colloid” adenocarcinoma. No transcapsular invasion by the carcinoma was seen. Resection margin was free of tumor.

Diagnosis: Mature thymic teratoma of the mediastinum with mucin secreting “colloid” adenocarcinoma

Discussion:
This is a very rare case of a woman with mature teratoma of the thymus associated with mucin secreting “colloid” carcinoma. Teratomas and other germ cell tumors are unusual mediastinal tumors that usually arise in the thymus and occur almost exclusively in male patients 1-14. For example in the largest series of patients with primary term cell tumors of the mediastinum by Moran and Suster only 2 of 322 patients were women9. In this cohort, patients ranged in age from 1 to 79 years of age with a mean age of 40 y.o. All types of germ cell tumors were represented with mature and immature teratomas, teratomas with additional germ cell components, including seminomas, yolk sac tumors, embryonal carcinomas and choriocarcinomas and teratomas with non-germ cell epithelial or mesenchymal components. The classification of germ cell tumors of the mediastinum shown in table I was proposed. An adenocarcinoma or squamous cell carcinoma was seen in only 4 of the 322 tumors.

Interestingly, mucinous epithelial neoplasms have been described in patients with ovarian mature teratomas. For example, McKenney and associates reported 42 patients with mucinous epithelial tumors arising in association with mature ovarian teratomas15, 16. The patient’s ages ranged from 17 to 66 years old, with a mean age of 39 y.o. Mucinous tumors included mucinous cystadenoma, mucinous epithelial neoplasm of low malignant potential, intraepithelial carcinoma and 5 patients with invasive mucinous carcinomas. Pseudomyxoma ovarii was described in 55% of the 42 patients; none had an appendiceal lesion. Vang an associates described another cohort of 44 ovarian mucinous tumors associated with a mature cystic teratoma17. They included 6 mucinous carcinomas. Mucinous neoplasms expressed variable immunophenotype and while most lesions exhibited CK7-/CK20+/CDX2+/villin+ immunophenotype others such as CK7+/CK20- were observed. It was hypothesized that neoplasms having CK7 expression with or without CK20 expression were derived from upper gastrointestinal tract or sinonasal-type teratomatous elements while those with CK20, CDX2 and/or villin immunoreactivity were derived from intestinal type tissues.
Table I

Classification of Germ Cell Tumors of the Mediastinum
Moran and Suster, Cancer 1997

Teratomatous tumors
- Mature teratoma
- Immature teratoma
  - Teratomas with additional malignant components
    - Type I: with another germ cell tumor component
    - Type II: with non-germ cell tumor epithelial component
      (squamous cell carcinoma, adenocarcinoma, other)
    - Type III: with a malignant mesenchymal component
      (rhabdomyosarcoma, chondrosarcoma, other)
    - Type IV: with any combination of the above

Nonteratomatous tumor
- Seminomas
- Yolk sac tumors
- Embryonal carcinomas
- Choriocarcinomas
- Combined nonteratomatous tumors

REFERENCES

Case 8

Saul Suster, M.D., The Medical College of Wisconsin, Milwaukee, WI, USA

Clinical History:
A 59 year old man was seen for symptoms of shortness of breath and chest pain. A CT scan of the chest shows a large anterior mediastinal mass. The patient had a history of smoking and hypertension, but no evidence or past history of tumor elsewhere. A core needle biopsy of the mass was undertaken, which showed atypical cells consistent with malignancy. The patient underwent median thoracotomy with a complete surgical excision.

Pathologic Findings:
The surgical specimen consisted of a well-circumscribed and completely encapsulated firm mass measuring 12 x 10 x 9.5 cm. The outer surface was smooth and glistening. Cut section showed a gray-white, homogenous rubbery tissue without any areas of hemorrhage or necrosis. Histologic sections showed a biphasic tumor composed of sheets and islands of round to polygonal tumor cells with large nuclei and abundant eosinophilic cytoplasm, surrounded by sheets of spindle cells. The islands of large, round to polygonal tumor cells displayed sharp cell borders with a distinctive cohesive appearance. In some areas, the nuclei appeared more atypical, with bizarre nuclear forms, enlargement of nuclei and nuclear pleomorphism. Some cells displayed prominent intranuclear cytoplasmic inclusions. Rare mitotic figures were identified. Stromal calcifications could also be seen in a few areas. The spindle cell component showed a uniform proliferation of bland-appearing fibroblastic or myofibroblastic cells, with elongated nuclei devoid of mitotic activity and surrounded by a scant rim of amphophilic cytoplasm. In some areas, the spindle cell population adopted a prominent storiform pattern of growth. There were no areas of hemorrhage or necrosis.

Special Studies:
Electron microscopy showed well-developed intercellular junctions attached to tonofilaments in the large, epithelioid and polygonal cells, and abundant intracytoplasmic intermediate filaments without cell junctions in the stromal spindle cells.

Diagnosis:
Thymoma with pseudosarcomatous stroma (“metaplastic thymoma”).

Discussion:
This tumor was first described in 19971 in a study of 6 patients who presented with large, well-circumscribed anterior mediastinal masses without any history of tumor elsewhere. Interestingly, despite the good circumscription and complete encapsulation, the tumors were initially considered malignant and some of them were diagnosed as thymic carcinosarcoma. In the original study, the tumors showed evidence of epithelial differentiation in the epithelioid component, and the stromal, spindle cell component showed features of fibroblastic or myofibroblastic differentiation. It was noted that a few of the spindle cells in the stroma also displayed mild focal positivity for EMA. All patients were treated by simple, complete surgical excision. The follow-up in those patients showed that none recurred or metastasized over a period of up to 12 years. A subsequent study was published 2 years later by Yoneda et al,2 who reported 5 cases of an identical tumor which they interpreted as a low-grade variant of thymic carcinoma showing “mesenchymal metaplasia” of the tumor cells. Despite the fact that the spindle “metaplastic” component was acknowledged as being histologically bland, and that the clinical follow-up of their patients demonstrated a benign course without evidence of recurrences or metastases, the authors postulated that this represented a malignant neoplasm equivalent to thymic carcinoma. The latest edition of the WHO book on Pathology and Genetics of Tumors of the Lung, Pleura, Thymus and Heart3 has introduced the term “metaplastic thymoma” for this condition.

Thymoma with pseudosarcomatous stroma is a rare form of thymoma that occurs mostly in middle aged adults (mean age: 50 years) with a male predilection. The tumors are most often asymptomatic and found incidentally on routine radiographic examination. None
of the cases reported so far has shown an association with myasthenia gravis. The tumors are characterized by sharp circumscription and encapsulation and measure between 5-16 cm in greatest dimension. The most striking characteristic is the biphasic morphology, which may lead to a misdiagnosis of carcinosarcoma or sarcomatoid (spindle cell) carcinoma. Attention to the cytologic features of the spindle cell stromal component will be necessary for proper diagnosis. Despite the high cellularity and storiform pattern, the spindle cells in the stroma have the appearance of benign fibroblastic or myofibroblastic cells and are devoid of cytologic atypia, nuclear pleomorphism or mitotic activity. The epithelioid component bears a striking resemblance to atypical thymoma (WHO type B3), and the cells may range from round, to oval to polygonal. The majority of the cases reported so far have behaved in a benign fashion without recurrences or metastases; however, one report in an infiltrative tumor claimed the patient suffered a local recurrence.

REFERENCES


3. Travis WD, Brambilla E, Muller-Hermelink HK et al. WHO Classification of Tumors. Pathology and Genetics of Tumors of the Lung, Pleura, Thymus and Heart, IARC, Lyon, 2004.


**Case History:** A 54-Year-Old Woman Presented with Drooping of Her Eyelid. An orbital mass was identified and resected and a diagnosis of orbital pseudotumor was made. Two years later, at age 56, she developed symptoms of “bronchitis” and CT showed a 6 cm diameter right lower lobe mass that was PET scan positive. Because of suspected carcinoma she underwent right lower lobectomy. Three months after the lobectomy (no additional treatment had been given) she presented with dyspnea and recurrent eye symptoms; she showed transient response to prednisone, but over the next few months she developed chest pain, fever, and weight loss. There were new infiltrates on CT scan. Her serum IgG4 levels were normal. She was begun on bortezomib therapy for 16 weeks with a symptomatic response and documented response on the CT scan. She remains asymptomatic and unchanged 18 months later.

**Histologic Findings**
The orbital pseudotumor showed a mixed lymphoid infiltrate with bands of fibrosis surrounding some lymphoid follicles. There were numerous plasma cells. Some venous infiltration by the lymphoid infiltrate was noted. Greater than 25 IgG4 positive plasma cells were present in many high power fields. Gene rearrangements studies done retrospectively on the orbital pseudotumor were negative for a clonal process.

The sections of lung showed a dense mixed lymphoplasmacytic infiltrate including lymphoid follicles following lymphatic grouts with cuffing and invasion of bronchovascular structures and veins, as well as bronchioles. The infiltrate was mixed and rich in plasma cells and included eosinophils. Greater than 25 IgG4 positive plasma cells per high power field were present. CD3, CD20, kappa and lambda did not show any of the features suggestive of lymphoproliferative disease.

**Diagnosis**
IgG4 related disease involving lung and orbit.

**Discussion**
IgG4 related disease is a recently described entity, first recognized in the pancreas and initially named autoimmune pancreatitis. As it became apparent that extrapancreatic disease was not uncommon, the designation of IgG4 related disease (or similar synonym) has been preferred. In a recent large collective study from Japan primary manifestations were found in the following regions:

- Head and neck – 23 cases
- Thoracic – 16 (lung/pleura – 15, breast – 1)
- Liver/pancreas – 27
- Retroperitoneal – 13
- Systemic – 35 (with multiple sites involved)

The list of affected sites by IgG4 disease is increasing: pancreas, biliary tract, liver, salivary gland, orbit, lung, kidney, prostate, breast, aortic, pituitary, retroperitoneum, trachea, bone marrow, lymph node, stomach, brain, mesentery, thyroid, mediastinum, pleura, and others.

In the pancreas there are five key features that include the distinctive histology (lymphoplasmacytic sclerosing pancreatitis, obliterative phlebitis, increased IgG4 positive plasma cells), sausage-shaped enlargement on imaging, elevated serum IgG4 levels, involvement of extra pancreatic sites, and response to steroid therapy.

At present IgG4 disease is considered the syndrome of unknown etiology; it tends to affect the middle-aged elderly, much more commonly men. Symptoms relate to the sites involved and there is often a lack of fever or constitutional symptoms. IgG4 serum elevation appear to correlate with the number of sites involved and the levels may decrease with steroid therapy, although an absent of elevated IgG4, as in the case presented, does not exclude the condition.

IgG4 positive cells may be seen in a variety of conditions and thus some effort of quantitation is important. There are two ways that have been used to quantitate IgG4 positive plasma cells: 1) the total number per high power field (in the regions where the highest numbers are present) and cutoffs used have been: > 25/ hpf., >30, and >50 and 2), determining the percentage of IgG4 positive cells among all IgG positive cells and this has been important in lymph nodes where large numbers of IgG4 positive cells are frequently present. In lymph nodes a percentage of IgG4 positive cells greater than 40% of the total IgG positive cells is considered significant. While elevated numbers of IgG4 positive plasma cells, by either method above, is compatible with IgG4-related
IgG4 related disease may present in a variety of patterns in the lung including solitary nodule, regional consolidation, multiple nodules/infiltrates, and diffuse interstitial lung disease. The distinctive histologic features of IgG4 disease in the lung are infiltrates along lymphatic routes with a mixed lymphoid population including lymphoid follicles, sclerosis, plasma cells, lymphocytes, and occasionally eosinophils. There is infiltration of veins and arteries and airways. There is an absence of necrosis and studies for clonality are negative.

The previous diagnoses for IgG4 related disease in the lung are many and varied, from inflammatory myofibroblastic tumor/plasma cell granuloma/lymphomatoid pseudotumor to lymphomatoid granulomatosis to Rosai-Dorfman disease to non-specific interstitial pneumonitis.

The differential diagnosis for IgG4 disease in the lung, at least as currently reflected in the diverse spectrum of cases that have been reported, is quite broad and clearly there are cases that remain undiagnosed because they are descriptively diagnosed as an inflammatory process. The possibility of IgG4 related sclerotic disease should thus be considered in the following scenarios: suspected lymphoma in the lung but clonality cannot be proven, inflammatory masses with sclerosis that do not fit well into some other entity, and lymphoid proliferations that show vascular infiltration without necrosis or classic features of vasculitis.

REFERENCES


Bronchus in lung

Vein in lung

IgG4 stain lung

IgG4 stain orbit
Case 10

Giovanni Falconieri, M.D., "S. Maria della Misericordia", General Hospital Udine, Italy

Case history: A 37-year-old man was admitted to the hospital complaining of shortness of breath. Instrumental investigations revealed a mass of the anterior mediastinum. Thoracotomy and mass resection were carried out.

Pathologic features: The tumor measured 6 x 5 x 3 cm and was described by the surgeon as locally infiltrating. It was firm and homogeneous on the cut surface. Histologic examination of H&E-stained sections revealed ribbons and festoons of epithelioid cells with peripheral palisading of basal nuclei. Artifactual retraction of the basal cell layers from the surrounding stroma revealed distinctive clefting within the proliferation. Attempts at cyst formation were recognized focally. Tumor cells were strongly positive for keratins, p63, and, focally, for CD56 and synaptophysin.

Diagnosis: Basaloid carcinoma of the thymus (BCT).

Comment: Thymic carcinomas are usually aggressive tumors that may exhibit a broad phenotypic spectrum. In contrast to thymomas, they are not associated with history of myasthenia gravis and lack such gross and microscopic features of thymic organotypic differentiation as lobulation, septi, and perivascular spaces. In addition, they exhibit a remarkable histologic heterogeneity and, with few exceptions, are microscopically similar to carcinoma arising in other organs. Since immunohistochemical stains cannot confirm a specific diagnosis, the morphologic diagnosis of thymic carcinoma remains an elusive one and requires careful clinicopathologic correlation. BCT is rare, with fewer than 30 cases documented in the literature. It has no predilection for gender or age, although patients in the sixth decade of life are more frequently affected. BCT usually presents as a large but well-circumscribed mass. Cyst formation is a characteristic feature here as well as in several other primary malignant tumors of the thymus. Although BCT may seem to be a low-grade disease, distant metastases have been reported in about one third of cases.

Histologically BCT looks rather monotonous, with ribbons of tumor cells that appear to be basaloid and also dark blue cells. A common feature is nuclear overlapping and varied palisading of the nuclei at the periphery. Mitotic figures are frequent. Cystic spaces resembling multilocular cysts may be recognized microscopically; however, they are lined by neoplastic cells and are therefore not true cystic spaces, which are presumed to be acquired lesions of the thymus gland secondary to inflammation. Cyst formation is a common feature of thymic lesions, hence its gross and microscopic documentation can provide useful clues to the primary diagnosis. Another pattern seen in BCT features nesting tumor cells rather than tumor cells in ribbons; a radial arrangement around perivascular spaces has also been described. Sarcomatoid, squamous, or glandular differentiation has been described in some cases. Other uncommon features that can help to identify the thymic origin of the lesion include the presence of myoid cells or a transition of BCT to areas of thymoma, usually of the spindle cell type.

In cases where clues unique to thymic tumors are not immediately recognized, one must proceed clinically by first ruling out metastasis from a primary tumor in another visceral location, especially the lung and upper aerodigestive tract. BCT is characteristically immunoreactive for keratins, p53, and p63. Positivity for CD117 has been reported in more than half of such cases. On the other hand, CD5 was reported in a few. The proliferative index ranges from less than 2% to 15%.

Recently BCT has been reappraised in a series of 12 cases reported by Brown and colleagues, who also provide a review of 29 similar published cases. An analysis of these data suggests that, contrary to previous belief, BCT pursues an unfavorable course in most patients, with frequent tumor-related deaths.

SUGGESTED REFERENCES


Case 11

Saul Suster, M.D., Medical College of Wisconsin, Milwaukee, WI, USA

Clinical History:
A 78 year old man was seen for a large mass in the right lower lobe of lung. The patient had been admitted through the emergency room for hemoptysis and shortness of breath. The patient had a history of arteriosclerotic heart disease, diabetes, and had been recently diagnosed with a Gleason grade-3 prostate carcinoma, which was found on core biopsy done for elevated serum PSA. CT scan showed a homogeneous, well-circumscribed mass almost entirely occupying the right lower lobe. The patient was scheduled for surgery for excision of the mass.

Pathologic Findings:
The resected specimen showed a single, well-circumscribed intraparenchymatous mass that measured 6 x 6 x 6 cm. The mass abutted the pleural surface but did not infiltrate the pleura. The cut section showed a tan-white homogeneous surface with central areas containing friable tissue. Histologic examination revealed a biphasic cellular proliferation composed of fascicles of pleomorphic and atypical spindle cells admixed with small islands and microscopic foci of an atypical glandular proliferation. The spindle cell proliferation showed fascicles that intersected at right angles, and were composed of a highly pleomorphic population of cells with oval, hyperchromatic nuclei and abundant eosinophilic cytoplasm admixed with scattered larger, pleomorphic tumor cells showing bizarre, multilobated nuclei and abnormal mitotic figures. Areas showing stromal hyalinization with keloidal collagen deposition were also present. In a few sections, foci of benign-appearing osteoclast-type multinucleated cells were also seen. The glandular component was characterized by small islands of cohesive epithelial cells displaying a striking cribriform pattern. The cells lining the cribriform spaces showed large nuclei with prominent eosinophilic nucleoli and occasional scattered mitotic figures, and were surrounded by an ample rim of eosinophilic cytoplasm. The tumor was unencapsulated but sharply demarcated from the surrounding pulmonary parenchyma.

Immunohistochemical studies showed strong positive staining of the epithelial component with cytokeratin AE1/AE3 and CAM5.2, and negative staining for CK7 and CK20. Stains for beta-catenin, chromogranin, synaptophysin, TTF1 and napsin-A were also negative. A stain for PSA and PSAP showed strong cytoplasmic positivity of the tumor cells in the epithelial component. The stromal (spindle and pleomorphic) component showed strong cytoplasmic positivity for vimentin, SMA, and weak staining for SMMS, but was negative for cytokeratins, S-100 protein, bcl-2, CD99, desmin, myogenin, and CD34.

Diagnosis: Collision tumor: metastatic leiomyosarcoma plus prostate adenocarcinoma.

Comment:
This tumor presented a challenge for diagnosis because of the lack of an adequate history from the start. Because the patient had his medical care at an outside institution, it took several days to obtain his chart and speak with his previous physicians to get a complete picture of his clinical history. The patient had a history of a soft tissue sarcoma of the thigh removed 12 years previously, which had been diagnosed at another institution as a moderately-differentiated leiomyosarcoma. More recently he had a biopsy of the prostate for elevated PSA which showed a low-grade (Gleason grade 3) prostate adenocarcinoma. At the time we reviewed the lung tumor we were unaware of this history and were under the impression that this represented a primary lung tumor.

The morphologic differential diagnosis for this tumor included a pulmonary carcinosarcoma and a biphasic pulmonary blastoma. Carcinosarcoma is defined as a biphasic tumor that contains within the same tumor mass two well-defined and histogenetically dissimilar components: a carcinomatous component and a frank sarcomatous component. They are distinguished from sarcomatoid carcinoma in that the spindle cell, sarcomatoid component in the latter shows features of epithelial differentiation by immunohistochemistry or electron microscopy, whereas in carcinosarcoma, the spindle cell elements represent a true sarcoma. The present case qualified for a diagnosis of carcinosarcoma based on the distinct staining pattern of the two malignant components. Biphasic pulmonary blastoma is another rare lung tumor characterized by the admixture of glandular components with an atypical spindle cell proliferation. The glandular elements in pulmo-
nary blastoma are characterized by complex cribiform glandular structures that can be very similar to those observed in our case. Characteristically, an accumulation of round, basaloid cells are seen at the base of the glands (so-called “morules”). The epithelial cells in pulmonary blastomas, however, are known to stain with beta-catenin and TTF1, both of which were negative in our tumor, thus ruling out this diagnosis.

Finally, the possibility of entrapped or aberrant epithelial elements in a primary sarcoma of the lung is another more remote possibility.3 Aberrant epithelial differentiation in sarcoma has been rarely described in some types of soft tissue sarcoma, such as malignant peripheral nerve sheath tumor (“glandular malignant schwannoma”), angiosarcoma, and malignant mesenchymoma. Distinguishing a primary sarcoma from a metastasis from a distal primary soft tissue tumor is nearly impossible in the absence of a detailed clinical history. Also, late or distant metastases of sarcomas to the lung can often display features that differ from those seen in the primary tumor.4,5 In the present case, the unlikely scenario of a collision metastasis from 2 unrelated neoplasms to the same site occurred complicating the diagnosis and raising alternative diagnostic possibilities.

REFERENCES


Case History
A 39 year-old was admitted to the hospital complaining of shortness of breath, chest pain and general discomfort. Instrumental investigations including revealed a pleural mass. Thoracotomy and mass resection was carried out.

Pathologic features. The tumor measured 7 x 4 x 3 cm and was soft with a slightly lobulated external surface. On cut section it had a fish-flesh appearance and was homogeneously yellowish with occasional grey streaks. Histologic examination of HE stained sections revealed a cellular tumor featuring relatively monotonous elements and haphazardly arranged in swirling fascicles. Other patterns which could be recognized included herringbone, palisading or hemangiopericytic. The ground substance was scant. Tumor cell nuclei were spindle with tapered end, frequent mitotic figures, usually small nucleoli. The cytoplasm was lightly eosinophilic. Immunohistochemistry was positive for bcl2, CD34, CD99, calponin, and vimentin; on the other hand CD31, Keratins, calretinin, desmin, S100 protein, actins, c-kit were negative. A Fish assay revealed a t(x:18) chromosomal translocation.

Diagnosis: Monophasic, spindle cell synovial sarcoma of pleura.

Comment. Synovial sarcoma (SS) is a tumor of questionable histogenesis, with disputed parental cell. As with other soft tissue tumors with no normal counterpart, such as the Ewing family neoplasms, alveolar soft part sarcoma, epithelioid sarcoma or clear cell sarcoma, it may probably reflect the genetic aberration that engendered a unique phenotype. SS is a relatively common neoplasm especially in young adult patients, yet is considered the most frequent intrathoracic sarcoma where it has been described in the pleura, lung and mediastinum. Although microscopically identical to synovial sarcoma arising in the limb soft tissues, mediastinal lesions may be confused with many, intrathoracic spindle-cell lesions. Pleural synovial sarcoma appear to occur in younger patients although the age at presentation may be broad (mean 35 years). Most common symptoms include chest pain and dyspnea. A pleural based mass and effusions are the most common radiographic findings. Grossly, these tumors appear as soft, tan, well circumscribed mass. Focal hemorrhage and necrosis are common. Of interest, a sizable minority of these cases may have cystic changes or may have focal calcifications enabling their recognition on radiologic investigations. Pleural SS pursues an aggressive course, with nearly half patients accounting for tumor related death. Microscopically, synovial sarcoma of the pleura may be either biphasic or monophasic. Biphasic tumors features gland-like spaces admixed with spindle, fibroblast-like cells; occasionally, the glandular structures may include pseudopapillary structures or intraluminal amorphous material. Monophasic spindle-cell tumors are more frequent. They are composed of cellular tumor arranged in whorls or fascicles. The ground substance may be inconspicuous. Tumor cells have tapered-end nuclei and a moderate amount of stainable cytoplasm. Mitotic figures are usually present. Unusual microscopic features have been reported in a small but definite subset of cases, including verocay bodies, rosette formation, adenomatoid or papillary changes, rhabdoid features, osteoid or myoid changes. Extensive myxoid tumors have been also reported in some series. In addition, synovial sarcoma may be associated with a poorly differentiated morphology featuring large epithelioid or small cell variants, or high-grade spindle cells. Synovial sarcoma is often associated with the t(x:18) translocation product. Immunohistochemistry is often positive for keratins (especially keratins 7 and 19) and EMA; however expression of epithelial markers may be focal or absent, especially in spindle cell lesions, and testing on sections from different tumor samples may be needed to find just some focal reactivity. Bcl2, calponin and CD99 are very often detected in synovial sarcoma. Scattered S100 protein positive cells may be detected up to one third of cases. CD34 and Fli-1 may show erratic positivity as well. In essence, although the use of several antibodies may be of some value in the differential diagnosis, there is no “magic bullet” and the results of immunohistochemistry should be always cautiously interpreted in the appropriate clinical and pathologic context. Because of the broad morphologic spectrum and its non-specific immunohistochemical profile, thoracic monophasic spindle cell SS may be confused with other malignancies such as sarcomatoid carcinoma, spindle-cell mesothelioma, melanoma, and other spindle-cell sarcomas including malignant PNST. Positivity for calretinin has been also observed occasionally in syno-
vial sarcoma, indicating thus that positive immunohistochemical results should be interpreted carefully and always in the proper clinical context. Metastatic spindle cell carcinoma is most often associated with a primary tumor in the lung. In addition it is diffusely keratin positive, in contrast to the inconsistent immunoreaction usually seen in synovial sarcoma, either patchy positive or even negative. Spindle cell mesothelioma may be often difficult to distinguish from spindle cell synovial sarcoma: the differential diagnosis is further compounded by the fact that any tumor that invades and grows within the pleura may then virtually encase the lung in a neoplastic rind, hence closely mimicking mesothelioma. A clinically oriented approach is often critical in these situations: in fact, mesothelioma occurs in older individuals who may have history of asbestos exposure, whereas synovial sarcoma tends to affect younger patients. A microscopic clue to mesothelioma may be of diagnostic help in poorly differentiated cases of synovial sarcoma, yet a negative test does not exclude the diagnosis as long as 1/3 of cases do not show chromosomal translocation.

SUGGESTED REFERENCES


Case 13

Saul Suster, M.D., The Medical College of Wisconsin, Milwaukee, WI, USA

Clinical History:
A 56 year old man with no previous significant clinical history was seen for persistent cough and weight loss. A CT scan of the chest revealed a mass in the right lower lobe of lung. At thoracotomy, a 5.0 x 4.5 x 4.0 cm well-circumscribed, tan-gray subpleural mass was present. The pleura overlying the tumor showed and area of puckering and granularity. The tumor did not involve the bronchial or vascular structures and was 3 cm. away from the nearest surgical resection margin.

Pathologic Findings:
Histologic examination revealed a glandular proliferation with a striking cribriform growth pattern. There were well-circumscribed nests and islands of tumor cells displaying punched-out spaces that were lined by atypical polygonal cells with large, vesicular nuclei and prominent eosinophilic nucleoli and surrounded by abundant eosinophilic cytoplasm. In some areas, the tumor cells adopted a focal papillary or micropapillary configuration. The cells in these areas displayed round to oval nuclei, and some of them showed clearing of the nuclear chromatin and longitudinal nuclear grooves reminiscent of papillary thyroid carcinoma. Numerous scattered psammoma bodies were also seen distributed at the base of the glands. Foci of lymphatic invasion were also noted. The tumor was seen to focally infiltrate the pleura.

Immunohistochemical stains showed strong positivity of the tumor cells for CK7, TTF1 and napsin-A, and were negative for CK20, CDX2, thyroglobulin, PSA, PSAP, and a mucicarmine stain. Molecular studies for EGFR and KRAS were negative, but the tumor showed an ALK/EML4 fusion by FISH using a break-apart probe specific for the ALK locus.

Diagnosis: Primary cribriform adenocarcinoma of lung.

Discussion:
Cribriform architecture is not a characteristic pattern in lung adenocarcinoma and tumors displaying this unusual growth pattern are not included in the WHO classification of lung tumors. In the literature, cribriform adenocarcinomas of the lung, when mentioned, are grouped within the acinar subtype and, according to the actual recommendations by the IASLC/ATS/ERS, there is not sufficient data to separate them from other subtypes. Because of their rarity, the presence of a predominant or exclusive cribriform growth pattern in a lung tumor of an adult or elderly patient generally raises the diagnostic possibility of a metastasis. In the present case, the initial diagnosis involved a metastasis from the prostate, gastrointestinal tract and thyroid. Metastases from prostate carcinoma to the lung often display a cribriform pattern of growth and can be solitary. PSA and PSAP negative staining help to rule out this possibility. Metastases from colon adenocarcinoma can have a prominent cribriform pattern; however, they are most often arranged in a “garland” pattern with small cribriform spaces distributed along the periphery of large cystic areas containing abundant “dirty” necrosis. The cells in intestinal type adenocarcinomas also tend to be columnar and contain cytoplasmic mucin. Metastases of papillary thyroid carcinoma (PTC) to the lung can be observed late in the course of the disease, and there is a “morular-cribriform” variant of PTC that is characterized by prominent cribriform growth pattern similar to that observed in the present case. The presence of focal areas displaying a papillary growth lined by cells showing clearing of the nuclear chromatin, longitudinal grooves, and psammoma bodies also heightened the similarity with PTC in this instance. However, negative staining for thyroglobulin, as well as subsequent physical and ultrasound examination failed to disclose evidence of a tumor in the thyroid in this patient.

We recently presented a study at USCAP of 15 cases of primary cribriform adenocarcinomas of the lung that were confused for a variety of metastatic tumors from other organs. Primary lung tumors with a cribriform architecture resembling colorectal carcinomas have been described recently by Inamura et al. and others. The tumors can have either a pulmonary or an enteric immunophenotype. However, what is less known is that other tumors other than colorectal adenocarcinomas showing a prominent cribriform growth pattern are also capable of metastasizing to the lung and can arise from diverse sites such as the gallbladder, paranasal sinuses, urinary bladder, breast, prostate, pancreas, salivary glands, thyroid, sweat glands, stomach, ovary, uterus and endocervix. Awareness that there also exist primary cribriform lung adenocarcinomas that can display
similar features is, therefore, of importance for correct diagnosis.
Some studies have suggested that lung tumors harboring the ALK translocation may be more frequent in cases displaying a cribriform architecture. Only one of 6 cases tested in our study displayed the ALK translocation, indicating that cribriform architecture may not be a reliable morphologic marker for selecting patients for ALK testing.

REFERENCES


Clinical history:
55-year-old male with 6-months history of progressive anemia, hemoptyses and liver failure. CT reveals multiple nodules partly necrotic in the liver and progressive diffuse bilateral pulmonary infiltrates. Radiologists suspected liver metastases and hepatopulmonary syndrome. Liver core biopsies x 3 and laparoscopic liver wedge resection were signed out as inflammatory liver disease NOS. Therefore, patient underwent evaluation for liver transplantation. Open/VATS lung biopsy was performed from RLL with clinical diagnoses of hepatopulmonary syndrome or ILD? Preliminary diagnosis from other pathologist was diffuse alveolar hemorrhage syndrome probably due to idiopathic hemosiderosis with a differential diagnosis of ILD consistent with atypical UIP. I received case as consultant with limited access to previous history and radiology.

Pathological findings:
Sections from VATS biopsy showed multiple nodular areas of different characteristics with a background of normal lung tissue. The nodular infiltrates had a vaguely lymphangitic pattern of distribution thus preferentially located in the pleural-subpleural-septal-peribronchiolar areas.
In some areas fresh hemorrhage without much reaction could be seen. Iron stains from these areas did however show a slight increase in hemosiderin containing macrophages confirming true hemorrhage.
I other areas the hemosiderin content in intraalveolar macrophages was much higher and clearly visible as coarse pigment grains even in routine HE stains. Here interstitial reactions in form of collagenous fibrosis and elastosis were seen as well as fibroblast-focus like changes and a prominent organizing pneumonia pattern (OP/BOOP). No honeycombing reorganizing fibrosis was however detected.

Bronchi and bronchioli were generally unremarkable.
Pulmonary arterioles were prominent with medial and intimal asymmetrical cellular hyperplasia. Some vessels showed signs of obliteration and recanalization. The pulmonary capillary bed in association with nodular changes was markedly prominent.
Pleura itself was generally normal but subpleural fibro-elastic change was pronounced in association with small vessel proliferation.

The dominating impression was that of a diffuse alveolar hemorrhage (DAH) with superimposed organizing pneumonia pattern (OP/BOOP).
Only on a closer look searching for possible underlying etiological clues slightly cellular areas with atypical spindle cells were noted in areas of increased interstitial fibrosis around bronchioles and subpleural.

Special studies:
In short vascular immunohistochemical markers such as CD31, CD34, WT-1, fVIII, Fli-1, Claudin5 and ERG all were more or less positive. Thrombomodulin, Actin, VEGF, HHV8, p63, TTF1 and all cytokeratins were negative. p53 staining lit these cells up - “like a Christmas tree” - to paraphrase my old friend and mentor Sonny Johansson - showing affected areas with a clear lymphangitic distribution pattern in every single section. In p53 stain a spindled atypical cell form with occasional angioformative clusters could be discerned. p21 completely negative indicating a probable p53 mutation. The atypical cells further revealed a high proliferative index around 30 % - in Ki-67 stain.

Preliminary diagnosis: Diffuse alveolar hemorrhage (DAH) with organizing pneumonia (BOOP) secondary to angiosarcoma.

Further review of previous liver biopsies:
Since the pattern of distribution in the lung was lymphangitic rather than a dominating nodule and radiology showed diffuse bilateral pulmonary infiltrates I suspected a metastatic angiosarcoma. Previous abdominal CT scan indicated multinodular tumor in liver and I therefore reviewed previous liver biopsies. On second look and on performing vascular markers the presence of a probably primary hepatic angiosarcoma could be confirmed. Multinodular presentation of primary liver AS is quite common.

Follow-up:
Patient died of progressive liver failure 3 months after presentation. On autopsy no additional manifestations of AS could be detected and since the whole liver was found to be infiltrated with multinodular hemorrhagic AS and pulmonary infiltrates were a rather minor component a primary liver AS was confirmed.
Final diagnosis: Diffuse alveolar hemorrhage (DAH) with organizing pneumonia (BOOP) secondary to lung metastases of an occult primary liver angiosarcoma - metastatic angiosarcoma in the lung masquerading as DAH.

Discussion:
DAH
Bleeding from the lung originates from the bronchial vessels, the pulmonary vessels, or the microcirculation of the lung. Bleeding of bronchial origin is usually a result of bronchiectasis or endobronchial malignancy. Pulmonary hemorrhage originating from the small, medium, and large pulmonary vessels is most commonly due to systemic vasculitis, which can also involve the microcirculation. Vasculitides involving the microvasculature is known as pulmonary capillaritis. Diffuse alveolar hemorrhage (DAH) is a clinicopathologic syndrome describing the accumulation of intraalveolar RBCs originating from the alveolar capillaries. All causes of DAH have the common denominator of an injury to the alveolar microcirculation. Diffuse alveolar hemorrhage (DAH) is a life-threatening disorder characterized clinically by the presence of hemoptysis, falling hematocrit, diffuse pulmonary infiltrates and hypoxemic respiratory failure. Hemothysis is the usual presenting symptom, however it is not always present, even when hemorrhage is severe enough to be life threatening. Patients with alveolar hemorrhage present with complaints of cough, dyspnoea, and hemothysis. Chest x-ray will reveal patchy alveolar infiltrates which may start in a focal, unilateral pattern and become more diffuse with time. While a CT scan will confirm the alveolar nature and extent of the process, it adds little to the diagnosis over a chest film. Bleeding into the alveolar spaces is the main characteristic of diffuse alveolar hemorrhage (DAH) and is due to disruption of the alveolar-capillary basement membrane. While the differential diagnosis is broad, the majority of cases of DAH are caused by pulmonary-renal syndromes, connective tissue disorders and drugs. A surgical lung biopsy may be required to elucidate the underlying histology in cases with negative serology and not being a part of a systemic disease. Alveolar hemorrhage must be distinguished from other causes of red blood cell accumulation in the alveolar space, most notably surgical trauma at the time of biopsy. True alveolar hemorrhage often demonstrates intra-alveolar fibrin and hemosiderin in the alveolar walls and hemosiderin-laden alveolar macrophages. Hemosiderin, a product of haemoglobin degradation, appears at least 48 hours after bleeding and is helpful in distinguishing DAH from surgical trauma. There also may be areas of mild interstitial thickening and occasional associated organizing pneumonia or diffuse alveolar damage.

Capillaritis is the most common accompanying histopathological condition in DAH, especially in cases caused by vasculitis or collagen vascular disease. While a lung biopsy can be very useful in confirming DAH it usually can not pinpoint the actual etiology for bleeding. Ideally the lung biopsy should be received fresh in the laboratory and a small part of it be subjected to immunofluorescence studies of the same kind we use for medical kidney biopsies or skin biopsies for bullous diseases. In most reviews of DAH underlying malignancy is either not mentioned or listed only as an remote possibility. Still those cases can be subjected to a definitive histopathological diagnosis if considered at microscopy.

Table 2. Causes of Diffuse Alveolar Hemorrhage

<table>
<thead>
<tr>
<th>With Pulmonary Capillaritis</th>
<th>Without Pulmonary Capillaritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wegener's granulomatosis</td>
<td>Angiosarcoma as cause of pulmonary hemorrhage</td>
</tr>
<tr>
<td>Microscopic polyangiitis</td>
<td>Angiosarcoma is a rare malignant tumor of endothelial derivation that accounts for &lt;1%of all sarcomas. It can arise at any region of the body; skin and soft tissue are the most common sites involved. Other well-recognized sites, such as, the breast, liver, lung, spleen, bone, heart, central nervous system, gastrointestinal tract, adrenal gland, ovary, prostate, vagina, maxillary sinus and areas of previous irradiation have also been described. Angiosarcomas, regardless of their sites of origin, are particularly likely to metastasize to the lung. Other frequent</td>
</tr>
<tr>
<td>Isolated pulmonary capillaritis</td>
<td>Angiosarcoma as cause of pulmonary hemorrhage</td>
</tr>
<tr>
<td>Connective tissue diseases</td>
<td>Pulmonary capillaritis hemangiomatosis</td>
</tr>
<tr>
<td>Primary antiphospholipid syndrome</td>
<td>Lymphangiolelomyomatosis/tuberous sclerosis</td>
</tr>
<tr>
<td>Mixed cryoglobulinemia</td>
<td>Human immunodeficiency virus infection</td>
</tr>
<tr>
<td>Behcet's syndrome</td>
<td>Neoplasms (eg. metastatic angiosarcoma, choriocardinoma)</td>
</tr>
<tr>
<td>Henoch-Schönlein purpura</td>
<td>From Colby et al (reference 6)</td>
</tr>
<tr>
<td>Goodpasture's syndrome</td>
<td>Angiosarcoma as cause of pulmonary hemorrhage</td>
</tr>
<tr>
<td>Pauci-immune glomerulonephritis</td>
<td>Angiosarcoma is a rare malignant tumor of endothelial derivation that accounts for &lt;1%of all sarcomas. It can arise at any region of the body; skin and soft tissue are the most common sites involved. Other well-recognized sites, such as, the breast, liver, lung, spleen, bone, heart, central nervous system, gastrointestinal tract, adrenal gland, ovary, prostate, vagina, maxillary sinus and areas of previous irradiation have also been described. Angiosarcomas, regardless of their sites of origin, are particularly likely to metastasize to the lung. Other frequent</td>
</tr>
<tr>
<td>Immune complex-associated glomerulonephritis</td>
<td>Angiosarcoma as cause of pulmonary hemorrhage</td>
</tr>
<tr>
<td>Drug induced</td>
<td>From Colby et al (reference 6)</td>
</tr>
<tr>
<td>Acute lung allograft rejection</td>
<td>Angiosarcoma as cause of pulmonary hemorrhage</td>
</tr>
<tr>
<td>Pulmonary Capillaritis</td>
<td>Angiosarcoma as cause of pulmonary hemorrhage</td>
</tr>
<tr>
<td>Idiopathic pulmonary hemosiderosis</td>
<td>Angiosarcoma as cause of pulmonary hemorrhage</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Angiosarcoma as cause of pulmonary hemorrhage</td>
</tr>
<tr>
<td>Goodpasture's syndrome</td>
<td>Angiosarcoma as cause of pulmonary hemorrhage</td>
</tr>
<tr>
<td>Diffuse alveolar damage</td>
<td>Angiosarcoma as cause of pulmonary hemorrhage</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>Angiosarcoma as cause of pulmonary hemorrhage</td>
</tr>
<tr>
<td>Trimellitic anhydride</td>
<td>Angiosarcoma as cause of pulmonary hemorrhage</td>
</tr>
<tr>
<td>Mitral stenosis</td>
<td>Angiosarcoma as cause of pulmonary hemorrhage</td>
</tr>
<tr>
<td>Coagulation disorders</td>
<td>Angiosarcoma as cause of pulmonary hemorrhage</td>
</tr>
<tr>
<td>Pulmonary veno-occlusive disease</td>
<td>Angiosarcoma as cause of pulmonary hemorrhage</td>
</tr>
<tr>
<td>Pulmonary capillaritis hemangiomatosis</td>
<td>Angiosarcoma as cause of pulmonary hemorrhage</td>
</tr>
<tr>
<td>Lymphangiolelomyomatosis/tuberous sclerosis</td>
<td>Angiosarcoma as cause of pulmonary hemorrhage</td>
</tr>
<tr>
<td>Human immunodeficiency virus infection</td>
<td>Angiosarcoma as cause of pulmonary hemorrhage</td>
</tr>
<tr>
<td>Neoplasms (eg. metastatic angiosarcoma, choriocardinoma)</td>
<td>Angiosarcoma as cause of pulmonary hemorrhage</td>
</tr>
</tbody>
</table>
Pulmonary angiosarcomas are usually secondary tumors, and only slightly more than 20 primary cases have been described so far. If an angiosarcoma presents in the lung, it most likely represents a metastasis from a primary tumor of the pulmonary arteries, the heart or a distant site. Primary pulmonary angiosarcomas and metastatic angiosarcomas in the lung have similar symptomatology and radiological features. The most common presenting symptom of pulmonary angiosarcoma is haemoptysis, while relatively few cases present with spontaneous pneumothorax, pneumomediastinum or pulmonary haemorrhage (DAH) or secondary symptoms as anemia. The alarming symptoms or the reactive tissue response can mask the underlying malignancy and make diagnosis difficult. Primary pulmonary angiosarcomas can be uninnodal involving one vessel or airway or multifocal with ill-defined, soft, red-violet nodules in the lungs and pleura. Metastatic pulmonary angiosarcoma exhibits a variety of radiographic appearances. The common CT manifestations of metastatic angiosarcoma are multiple solid nodular lesions and multiple thin-walled cysts that are often accompanied by haemorrhagic change. The size of the lesion may vary from a small nodule to a large mass invading the mediastinum or the chest wall. Bilateral nodules are uncalcified and indistinguishable from those seen in other metastatic malignant neoplasms on chest radiographs.

The histologic findings are ill-defined nodules admixed with a distinctly lymphangitic pattern in distribution involving bronchovascular bundles, interlobular septa, and visceral pleura. A background of acute and chronic pulmonary hemorrhage is a prominent feature. Features of primary angiosarcoma of the lung are similar to angiosarcomas at other sites with atypical endothelial cells forming variably sized vascular channels and occasional solid spindle or epithelioid cell nodules. Most angiosarcomas form distinct vascular channels, albeit of irregular size and shape. Moreover, the vascular channels of the tumor often communicate with each other. These vascular channels are also immature and easily dissecting. Indeed, extensive regional invasion and disseminated disease are frequently identified at the time of initial presentation. Angiosarcoma is histologically divided into two categories, namely classical and epithelioid variants. Angiosarcomas of epithelioid subtype usually are cytokeratin positive. In those cases there is a significant risk of miscalling them as carcinomas. Among the various immunohistochemical markers used for detecting endothelial phenotype are factor VIII-related antigen, CD31, CD34, Fli-1, ERG, claudin-5 and WT-1. Actin can be useful to detect partially preserved pericyte layer. Collagen type IV and laminin highlights surrounding basement-like material. HHV-8 and p24 can be used in detecting HIV related forms. The prognosis is poor with all patients dying within months of the initial presentation.

Differential diagnosis of pulmonary angiosarcoma
Differential diagnosis between pulmonary angiosarcomas and other masses, especially lung carcinoma and a variety of vascular lesions with epithelioid endothelial cells, is not possible without biopsy. The distinction between benign and malignant vascular lesions can be quite challenging, even on histopathological studies, and requires immunohistochemical analysis in most patients. Other malignant tumors that enter the differential diagnosis of pulmonary angiosarcoma are hemangiendothelioma and pseudoangiosarcomatous carcinoma.

Hepatic angiosarcoma
In the present case a primary hepatic angiosarcoma was finally detected after review of radiographs, earlier liver biopsies and finally confirmed at autopsy. Vascular tumors of the liver in adult patients include cavernous hemangioma, a common benign tumor; epithelioid hemangioendothelioma, a rare, usually low-grade malignant tumor; and angiosarcoma, a rare and very aggressive tumor. All these primary mesenchymal tumors develop on a normal liver and may also affect other organs. A definitive diagnosis of epithelioid hemangioendothelioma and angiosarcoma requires histopathological examination. Although primary hepatic angiosarcoma (HA) is rare and accounts for only 2% of primary hepatic tumor, it is the most common malignant mesenchymal tumor of the liver. The lack of specific symptoms and radiological findings leads to the delay of diagnosis resulting in the poor prognosis. HAS usually develops in the sixth and seventh decades of life, and is more frequent in males than in females (ratio 3:1). Two-thirds of patients have symptoms and signs mimicking chronic liver disease. Occasionally, abdominal pain is intense and may be the first symptom. In 15% of patients, the initial complaint is an acute spontaneous hemoperitoneum secondary to the rupture of a nodule on the surface of the liver. In other patients, clinical manifestations are related to the presence of pulmonary or skeletal metastases. At diagnosis, metastases are common. Fifty percent of patients develop metastases before death. HA is often a multicentric, more rarely solitary tumor.
made of large red, hemorrhagic masses, varying in size. Elongated or round tumoral endothelial cells exhibited severe nuclear atypia and frequent mitoses and grew along dilated sinusoids, separated by surviving atrophic or hyperplastic hepatocytes. The well-differentiated tumors consist of irregular anastomosing, blood-filled vascular channels that are lined by variably atypical endothelial cells. The less-differentiated tumors may show solid strands and sheets, resembling carcinoma or lymphoma. Changes such as thrombosis, infarction, and hematopoiesis can occur. Positivity of endothelial markers is a clue for diagnosis.

Hepatopulmonary syndrome
Hepatopulmonary syndrome (HPS) is a clinical three-some composed of liver disease, intrapulmonary vascular dilatation (IPVD) and arterial gas abnormalities. Its occurrence has been described in up to 32% of cirrhotic candidates for liver transplantation. It also affects non-cirrhotic patients with portal hypertension. Its pathogenesis is not well defined, but an association of factors such as imbalance in the endothelin receptor response, pulmonary microvascular remodelling and genetic predisposition is thought to lead to IPVD. Diagnosis is based on imaging methods that identify these dilatations, such as contrast echocardiography or perfusion scintigraphy with 99mTc, as well as analysis of arterial gases to identify elevated alveolar-arterial differences in O2 or hypoxemia.

Conclusions:
• DAH is an uncommon presenting manifestation of angiosarcoma
• Primary or metastatic angiosarcoma should be included in the differential diagnosis of DAH
• In the setting of DAH with OP without obvious cause one needs a high index of suspicion for detecting an underlying angiosarcoma
• AS can consist of very subtle tumor infiltrates against dominating reactive background
• Interpretation in context with complete clinical & radiological findings
• Always review any biopsies taken before even in absence of “positive” diagnoses

REFERENCES
14. Lara AR, Schwarz ML. Diffuse alveolar hemorrhage. 

15. Newsome BR, Morales JE. Diffuse alveolar hemorrhage. 

diagnosis of diffuse pulmonary haemorrhage]. 

17. Rai S, Barthwal M, Bhattacharya P, Bhargava S, Pethe 
M. Metastatic angiosarcoma presenting as diffuse alveolar 
CT lung

CT liver

CT liver
Case 15

Kumarasen Cooper, M.D., The Vermont University Medical Center, Burlington, VT

Clinical History
A 47-year-old man presented to his primary care physician with a 1 year history of a painless, slowly enlarging mass in the left upper arm. Physical exam revealed a large, firm, fixed mass concerning for sarcoma.

Radiologic Imaging
Magnetic resonance imaging (MRI) of the arm showed a 10 cm well-defined mass embedded within the posterior aspect of the left deltoid, consistent with sarcoma. Multiple small foci of hypodensity were concerning for necrosis and calcification.

Computed Tomography (CT) scan of chest was performed to assess for metastatic disease, revealing multiple bilateral pulmonary nodules. The nodules were smooth to slightly lobulated and were present in all lobes of both lungs. The largest nodule measured approximately 1 cm in diameter and was located in the lateral segment of the middle lobe.

Gross Specimen
The mass was ovoid and appeared well-circumscribed, measuring 11.5 x 7.5 x 6.0 cm. The cut surface of the mass was extremely firm, with a tan-white, whorled pattern and a few scattered areas of hemorrhage. No necrosis was appreciated grossly.

Microscopic Examination
The tumor was composed of small epithelioid cells with distinct cell borders, arranged in cords, strands, and occasional alveolar patterns. The cells contained eosinophilic cytoplasm and round to oval, slightly irregular nuclei with stippled chromatin and occasional indistinct nucleoli. The tumor cells were embedded in an intervening dense, eosinophilic collagenous stroma. Centrally, zones of sclerotic collagen with rare intervening tumor cells were evident, and appeared consistent with ischemic degeneration. The mitotic count ranged from as low as 5 to as high as 11 mitoses per 10 high powered fields. Multiple areas of lymphovascular invasion were identified, and despite the gross appearance of circumscription, multiple areas of tumor cells surrounding and invading adjacent skeletal muscle were found. Immunohistochemical staining showed strong, diffuse positivity for vimentin and Bcl-2. The tumor was otherwise negative for keratins, CD34, EMA, and S-100.

The pulmonary nodules were also biopsied and diagnosed as metastatic sarcoma.

Diagnosis
Sclerosing epithelioid fibrosarcoma
- Grade 2 (French Federation of Cancer Centers, Sarcoma Group (FNCLCC))
- AJCC: pT2b, pNx, pM1

Treatment and follow-up
Following wide excision of the tumor with negative margins, the patient was treated with Doxil followed by second-line Temodar for his pulmonary metastases. Despite treatment, the patient’s metastases continued to increase in size and number, with new metastatic disease subsequently identified in the liver, ribs, and left clavicle. He was offered further chemotherapy with gemcitabine, but chose to discontinue chemotherapy and is currently exploring naturopathic treatment. At his last oncology visit, he continued to feel well despite increasing metastatic burden, and is currently asymptomatic from his metastases.

Discussion
Herein is presented a case of sclerosing epithelioid fibrosarcoma, a rare form of low grade sarcoma. Both the architecture (growth in nests, cords, and sheets) and epithelioid cytology can prompt an incorrect diagnosis of poorly differentiated carcinoma or sclerosing lymphoma. However, this tumor is consistently negative for keratins and leukocyte common antigen by immunohistochemistry. Accurate diagnosis and grading of this tumor is critical, because despite its banal cytomorphic appearance, it has been shown to behave in a moderately aggressive pattern. It is prone to local recurrence as well as distant metastases, and multiple case series have demonstrated greater than 50% tumor-related mortality.

Potential relationship between Sclerosing Epithelioid Fibrosarcoma and Low Grade Fibromyxoid Sarcoma

The FUS (FUsed in Sarcoma) gene is involved in transcription activation, and has been shown to fuse with, and strongly activate multiple transcription factors in various human diseases. The fusion of FUS to transcription factors CREB3L2 [t(7;16)] and CREB3L1
[t(11;16)] is known to occur in 95% of low grade fibro-myxoid sarcomas. Until recently, these fusions were thought to be specific markers for LGFMS; however, in 2007, Guilou et al. demonstrated that 4 of 7 sclerosing epithelioid fibrosarcomas harbored FUS-CREB3L2 rearrangements. This suggests that although LGFMS and SEF are clinically distinct tumors, they may be genetically related, and in fact may represent opposite ends of a single “fibrosing fibrosarcoma spectrum.”

Several groups have since studied this potential relationship, with varying results:

- Wang, et al (2011): 3/3 SEFs with LGFMS-like areas demonstrated t(7;16), but only 1/16 of pure SEFs demonstrated t(7;16).
- Rekhi, et al (2011): 1 SEF with LGFMS-like areas demonstrated t(7;16), 1 pure SEF did not demonstrate t(7;16).

Conclusions

1. The architectural and cytomorphological features of sclerosing epithelioid fibrosarcoma can lead to misdiagnosis as poorly differentiated carcinoma or sclerosing lymphoma. The variable EMA positivity of sclerosing epithelioid fibrosarcomas can potentiate this confusion. However, SEF is consistently negative for keratins and lymphoid markers, hence immunohistochemistry is critical in making the correct diagnosis.
2. Both SEF and LGFMS have been shown to harbor FUS gene rearrangements.
3. Sclerosing epithelioid fibrosarcoma may be related to low grade fibromyxoid sarcoma, with the two tumors representing opposite ends of the same disease spectrum.
4. Differentiation between SEF and LGFMS is critical as SEF is clearly more aggressive and the diagnosis conveys a worse prognosis.
   a. LGFMS is a relatively indolent disease with a protracted clinical course and lower risk of local recurrence and distant metastasis (~10% and ~5% risk, respectively).
   b. SEF follows a more aggressive clinical course and is prone to local recurrence and especially distant metastasis (~50% and up to 85% risk, respectively).

REFERENCES

Case 16

Kumarasen Cooper, M.D., The Vermont University Medical Center, Burlington, VT

Clinical History:
A 33 year old female presented with 2-3 month history of an enlarging non-traumatic soft tissue mass on the right foot. She did not have any pain nor symptoms other than difficulty wearing shoes. She was able to continue to bear weight and remain physically active. Physical examination revealed a palpable, superficial, firm, non-mobile soft tissue mass approximately 3 cm in size overlying the first metatarsal on the dorsum of the right foot.

Imaging:
AP, lateral and oblique right foot X-rays revealed a soft tissue mass on the dorsum of the foot without evidence of soft tissue mineralization nor adjacent bony or periosteal changes. MRI of the foot showed evidence of a superficial, well delineated soft tissue mass in the dorsal subcutaneous tissues at the level of the midfoot. The mass appeared intimately associated with the extensor hallucis longus tendon and measured approximately 3.5 cm in length by 2.8 cm in width x 0.9 cm in height. The radiological differential diagnosis included giant cell tumor of tendon sheath and a neurogenic tumor with no support of a cyst, lipomatous nor vascular tumor. Staging studies were performed including a PET CT and a thin cut chest CT, both revealing no evidence of metastatic disease.

Pathological Findings:
The tumor was received as multiple red-yellow to white firm fibrous soft tissue fragments measuring 3.9 x 2.3 x 2.1 cm. The cut surfaces were tan-yellow and focally gelatinous. Microscopically, this tumor is characterized by nodules of myxoid tissue surrounded by cellular to hyalinized stroma, variable inflammatory cells and large atypical cells with prominent nucleoli. On low power, the regional variation between myxohyaline areas and cellular granulation tissue-like areas with inflammation is notable. The bizarre atypical cells are interspersed throughout non-myxoid stroma and the paucicellular myxoid tissue. The appearance of the bizarre-shaped nuclei spans the spectrum from ganglion-like cells to Reed-Sternberg-like cells to cells mimicking lipoblasts. The ganglion-like cells have a large, vesicular, irregularly shaped nucleus and a huge nucleolus. The cytoplasm is prominent and spindled forms are also present. The bi-nucleated forms of these cells resemble Reed-Sternberg cells. The multivacuolated lipoblast-like cells are found in the myxoid areas and feature hyperchromatic, enlarged, sometimes indented nuclei in addition to cytoplasmic vacuoles. Occasional scattered multinucleated giant cells are identified. The stroma outside the myxoid nodules alternates between cellular and hyalinized areas. Within the myxoid nodules the cells vary from being spindled to epithelioid with mild to moderate nuclear atypia (except for the bizarre cells). The hyalinized areas are prominent and contain only a few tumor cells with thick-walled vessels. Mitoses, including atypical forms, are present but difficult to find.

The inflammatory cells are most prominent in the non-myxoid cellular areas and complete the histologic picture. The composition is that of lymphocytes, plasma cells, polymorphonuclear leukocytes (especially within the myxoid areas), and eosinophils. Occasionally the intense inflammation may partially obscure the large atypical cells. In summary, the essential criteria for a diagnosis of IMHT is the location on distal extremities, myxoid nodules scattered about hyalinized to cellular stroma, large bizarre ganglion-like cells or lipoblast-like cells and a mixed inflammatory cell infiltrate.

Follow up:
Patient has had continued surveillance MRI and clinical examinations. As of one year later, there has been no evidence of recurrence nor metastatic disease.

Discussion:
Inflammatory myxohyaline tumor of distal extremities is a neoplasm of low malignant potential. It is characterized by large ganglion-like cells, myxoid nodules and a stroma that varies from being cellular to hyalinized, with associated inflammation.

This tumor was first published in 1998 with the appearance of three simultaneous reports comprising significant numbers of patients. The descriptive labels used by these authors were remarkably similar: "Inflammatory myxohyaline tumor of distal extremities" (Weiss), "Acral myxoinflammatory fibroblastic sarcoma" (Kind...
A total of 75 cases have been reported to date. The age of patients has ranged from childhood to the ninth decade. The majority are in the fifth and sixth decades. These tumors affect the sexes equally. Almost all tumors occurred in the hands/fingers (two-thirds), feet/toes, ankle/wrists, whilst a few involved the arms/lower legs. Significantly, no tumors developed on the trunk, head/neck, or within body cavities. Patients present with a history of a slowly growing painless mass, most often in the subcutaneous tissue. The lesions ranged in size from 1 to 8 cm (median, 3 to 4 cm). They frequently infiltrate the subcutaneous tissue. The lesions were also demonstrated in a few cases. The atypical cells are present, they are usually cytokeratin negative in the neoplastic cells. A single case report with cytogenetic analysis showed t(1;10)(p22;q24) in addition to the loss of chromosomes 3 and 13. More recently both t(1;10) and amplification of 3p11-12 has been described in IMHT and hemosiderotic fibrolipomatous tumor (Hallor, 2009).

**Immunohistochemistry:**
Immunohistologic examination of a total of 35 cases from both series demonstrated vimentin positivity in all atypical cells. A variable number of atypical cells was also immunopositive for CD68 and CD34. Weak, focal smooth muscle actin and keratin immunopositivity were also demonstrated in a few cases. The inflammatory infiltrate comprised a mixture of both B and T cells, especially the latter. The S-100, HMB-45 and epithelial membrane antigen were negative in the neoplastic cells.

**Differential Diagnosis:**
- Tenosynovitis may be considered, especially when the heavy inflammatory infiltrate obscures the large atypical cells and when the tumor growth involves the synovial lining of a tendon sheath. The finding of the bizarre cells should avoid this error.
- Inflammatory myofibroblastic tumor (IMT) (inflammatory pseudotumor) enters the differential diagnosis due to the presence of a spindle cell component and the inflammation in IMHT. However, the bizarre cells of IMHT are not present in IMT. Further, IMT practically never occurs in the distal extremities.
- Ganglion cysts and juxta-articular myxomas do not contain the large atypical cells found in IMHT. Further, juxta-articular myxomas involve larger joints and do not exhibit the increased focal cellularity of IMHT.
- Proliferative fasciitis is also characterized by ganglion-like cells. However, the ganglion-like cells of IMHT are much more atypical than those of proliferative fasciitis, which also lacks marked inflammation.
- Neural tumors with enlarged nuclei and myxoid stroma are S-100 positive; whilst the cells in IMHT are negative.
- Myxoid liposarcoma enters the differential diagnosis as a result of the lipoblast-like cells. However, myxoid liposarcoma does not feature the large atypical nuclei and never occurs in the distal extremities. The characteristic plexiform vasculature and signet ring lipoblasts are not features of IMHT.
- Pleomorphic liposarcoma is rare in acral locations and the large multivacuolated cells in IMHT are not true lipoblasts.
- Extraskeletal myxoid chondrosarcoma is not characterized by the marked inflammation, fibrosis and cellular atypia of IMHT.
- Atypical lipomatos tumors contain atypical cells but primarily comprise adult fat.
- Epithelioid sarcoma can have significant inflammation, contain scattered atypical polygonal and spindle-shaped cells and often originates in the superficial tissue of the distal extremities. However, the majority of the cells in epithelioid sarcoma are round cells with eosinophilic cytoplasm. When large atypical cells are present, they are usually cytokeratin positive, whilst similar cells are cytokeratin negative in IMHT. Even when positive in the latter, it is focal and weak.
- Myxofibrosarcoma (myxoid MFH) on purely histologic evidence is fraught with difficulty. However, the clinical presentation on the distal extremity, paucity of mitotic figures, ganglion-like or Reed-Sternberg-like cells, and marked inflammation are useful features to recognize IMHT.
Treatment and Prognosis:
The recurrence rate in the follow-up of the patients in the two published series of IMHT was 22% and 67% respectively. Some of the recurrences were multiple and aggressive enough to warrant amputation. In one patient, the recurrence extended up the arm. Recurrences may also occur more than a decade after the initial excision. The efficacy of post-operative radiation is difficult to assess given the prolonged course of many of these tumors. Although spread to a regional lymph node has been documented in one case, distant metastases has not been reported to date. Hence, IMHT appears to have a recurring potential but its metastatic capacity (to date) is very low. In the Kindblom series, 31 percent persisted with disease, 64 percent were alive without disease, and 5 percent were dead of other causes. No patient had died of IMHT at the last follow-up.

REFERENCES


**Case 17**

**K. Krishnan Unni, M.D., Medical College of Wisconsin, Milwaukee, WI, USA**

**Clinical History:**
A 72 year old woman with no significant previous history was seen for back pain. CT scan showed a large, 10 cm. heterogeneously enhancing lytic mass in the distal sacrum, extending into the perisacral space and abutting on the rectum. Dorsally the mass extended through the sacrum into the subcutaneous region, and involved the paravertebral muscles on the left side. A fine needle aspiration showed blood-stained mucoid material with atypical cells characterized by abundant bubbly cytoplasm. An en-block, partial resection of the sacrum was undertaken.

**Pathologic Findings:**
The surgical specimen consisted of a 970 gm. portion of bone, skeletal muscle, soft tissue and skin that measured 18.5 x 18 x 8.5 cm. Upon sectioning, there was an 18 x 9 x 7.5 cm tan gray to white, ill-defined, rubbery and gelatinous mass with focal areas of hemorrhage that extended to the inferior and deep margins of the specimen. Histologic examination showed a lobulated cellular proliferation separated by fibrous bands. The lobules were composed of sheets and cords of tumor cells displaying small to medium-sized nuclei with mild to moderate nuclear atypia. The tumor cells were characterized by abundant pale, vacuolated cytoplasm with a bubbly appearance (so-called “physaliphorous cells”). Some of the cells contained large cytoplasmic vacuoles filled with mucin. The tumor cells were arranged in cords or strands of tumor cells. Singly scattered atypical cells could also be identified floating in a mucinous stroma. Few mitotic figures were identified. The background stroma showed abundant deposition of myxoid material.

Immunohistochemical studies showed positivity of the tumor cells for cytokeratin, EMA and S-100 protein. There was also focal positivity for polyclonal CEA; stains for MOC31 and CD10 were negative. Fresh tissue submitted for karyotype showed chromosomal aberrations, including loss of chromosomes 3, 4 and 13.

**Diagnosis:** Chordoma of sacrum.

**Discussion:**
Chordomas are tumors believed to be derived from notochordal rests which account for 1-3% of all malignant bone tumors. The tumors have a tendency to originate in the axial skeleton along the midline. About 60% of cases occur in the sacrococcygeal region, and 30% occur in the base of the skull. Other locations include the cervical spine and the thoracolumbar region.

Tumors arising from the lower spine are characterized by pain in the lower back and constipation, which is usually the result of obstruction by secondary compression by tumor. The tumors in sacral location have a tendency to spread into the presacral area and can be identified by palpation on rectal examination. Symptoms related to compression of nerve roots are also common. The tumors often infiltrate into the surrounding soft tissue. Radiologically they typically present as solitary, central lytic structures causing destruction of bone and showing evidence of extension and destruction into adjacent soft tissue. Bone destruction is the radiologic hallmark of chordoma. About half of the patients may exhibit focal areas of calcification within the lesion.

Histologically, chordoma is characterized by cells with abundant bubbly cytoplasm (so-called “physaliphorous cells”). Because of its notochordal, neural derivation, the cells exhibit strong nuclear positivity for S-100 protein, while coexpressing epithelial markers, including cytokeratins and EMA. The most compelling evidence for the notochordal origin of these tumors was the discovery of a gene duplication in the transcription factor T gene (brachyury) in familiar cases. Array comparative genomic hybridization studies have shown unique duplications in the 6q27 region in tumor samples from patients with familial chordoma. This duplicated region, which contains only the brachyury gene, has also been found to be uniquely overexpressed in almost all sporadic chordomas but is not present in other bone and cartilaginous tumors.

A monoclonal antibody has now been developed to brachyury (SC 20109 Santa Cruz, CA, USA) that can be applied on formalin-fixed paraffin-embedded tissues. Chordomas are characterized by strong nuclear positivity, a feature not observed in other cartilaginous tumors. This antibody can come in handy in cases of distant metises of chordoma, which can occur to lung, lymph node and skin in advanced cases. They may also be of help in clival and spheno-occipital location in which the tumor can adopt a chondroid appearance and closely resemble a cartilaginous neoplasm. In rare
instances (<5% of cases), chordoma can also be associated with a high-grade sarcoma (so-called “dedifferentiated chordoma”); demonstration of brachyury positivity in the better differentiated components of the tumor may be of aid in establishing a correct diagnosis.

REFERENCES

Case 18

K. Krishnan Unni, M.D., Medical College of Wisconsin, Milwaukee, WI, USA

Clinical History:
A 48 year old woman was seen for pain in her left leg. An X-ray showed a lytic lesion involving the epimetadiaphysis of the tibia. There was cortical destruction of the proximal tibia with extension into soft tissue; no matrix production could be identified. A below the knee left leg amputation was carried out.

Pathologic Findings:
The resected specimen showed a large soft tissue mass located between the tibia and the fibula extending from the cortex of the tibia into the adjacent soft tissue. Cut section of the tibia showed a tan-pink and glistening tumor involving the medullary canal that measured 7 cm in greatest diameter and destroyed the cortex. Histologic examination showed a fascicular spindle cell proliferation with variable cellularity. The spindle cells were arranged in fascicles that focally were cut at right angles, but areas showing whorls and storiform appearance could also be identified. The tumor cells showed elongated nuclei with prominent chromatin pattern and eosinophilic nucleoli. The tumor cells displayed abundant, finely fibrillary cytoplasm. Nuclear pleomorphism was evident and scattered mitoses could be identified. There was no evidence of bone or cartilaginous matrix production.

Immunohistochemical stains showed strong positivity of the tumor cells for vimentin, smooth muscle actin, calponin and smooth muscle myosin. There was focal positivity for H-caldesmon, but negative staining for desmin. Stains for S-100 protein, CD34, bcl-2, CD99, myogenin, cytokeratins and EMA were negative. A MIB-1 stain showed strong nuclear positivity in > 25% of the tumor cells.

Diagnosis: Primary leiomyosarcoma of bone.

Discussion:
Primary leiomyosarcoma of bone is a rare condition, with only a few short series reported in the literature.1-3 The tumors can occur over a wide age range (9-87 years), with a median age of 47 years. Review of the literature reveals a slight male predilection. The most common presenting symptom is pain, followed by pathologic fracture. The majority of the tumors reported in the literature occur in long bones of the lower extremities.

The most common location is in the metaphysis of long bones; however, many show extension into the epiphysis or the diaphysis.

The radiologic differential diagnosis for these lesions can be quite challenging. In about 20% of cases, areas of calcification are seen that may lead to a mistaken diagnosis of osteosarcoma4. A lytic lesion with destruction of the cortex and without evidence of matrix production is the most frequent and consistent radiologic finding in these tumors. In cases of tumors with adjacent soft tissue involvement, the possibility of a primary soft tissue sarcoma with secondary infiltration of bone has to be considered. Some consider the tumor a primary soft tissue sarcoma with secondary bone involvement when the bulk of the lesion is located outside of the bone. It has been proposed that >70% of the tumor must be intraosseous for the lesion to qualify as a primary leiomyosarcoma of bone.5

Histologically, leiomyosarcoma of bone can show the classical appearance of their soft tissue counterparts, although rare epithelioid and myxoid variants of intraosseous leiomyosarcoma have also been described.1 The main differential diagnosis is with osteosarcoma, from which they differ significantly due to the absence of osteoid production. Distinguishing a low-grade leiomyosarcoma from intraosseous leiomyoma is also of importance because of the differences in prognosis.5 Total absence of mitotic activity is required for a diagnosis of intraosseous leiomyoma. Other spindle cell sarcomas of bone that can enter in the differential diagnosis include fibrosarcoma, solitary fibrous tumor, mesenchymal chondrosarcoma, and pleomorphic high grade sarcoma (MFH). Use of immunohistochemical stains will facilitate this differential diagnosis due to the strong expression of smooth muscle-associated markers in leiomyosarcoma. A metastasis of leiomyosarcoma from another site must always be excluded by means of a careful clinical history. Metastasis from a sarcomatoid carcinoma can be excluded by use of immunohistochemical stains for epithelial markers.

Surgical excision with clear margins is the optimal treatment for these tumors. The tumors appear to be radioresistant and do not respond to chemotherapeutic agents. Intraosseous leiomyosarcoma is, in general, a
tumor associated with aggressive behavior. In the series by Antonescu et al, no differences in clinical behavior could be observed between the histologically low grade and high grade tumors. Distant metastases, particularly to the lung, are a common occurrence.

REFERENCES


Case 19

Thomas Mentzel, M.D., Dermatopathology Bodensee, Friedrichshafen, Germany

Clinical History:
A 66-year-old female patient developed a 5.5 cm measuring neoplasm on the left chest wall. Clinically, a close relationship to the artery subclavia and the plexus brachialis has been reported, and grossly, a nodular neoplasm with a thin pseudocapsule has been described.

Pathological Findings:
Histologically, an infiltrating, heterogeneous vascular neoplasm is seen. In addition to lobular areas showing features of sclerosing haemangioma, infiltrating vascular structures lined by enlarged endothelial tumour cells with enlarged vesicular nuclei are seen. These vascular structures resemble features of retiform haemangiendoendothelioma, and focally, intravascular, dabsceoid endothelial proliferations are noted. In one block neoplastic cells with cytoplasmic vacuoles are set in a myxohyaline stroma resembling morphological features of epithelioid haemangiendoendothelioma. The endothelial tumour cells stain positively for CD31 and ERG, and Ki-67 antibodies reveal areas with an increased proliferative activity.

Diagnosis: Composite haemangiendoendothelioma

Comments:
The term haemangiendoendothelioma, first coined more than 100 years ago by F.B. Mallory, has been used for a number of vascular neoplasms that show a considerable variation in their morphological appearance and more importantly, in their biological behaviour, ranging from benign to malignant, angiosarcomatous neoplasms. Therefore the use of the term haemangiendoendothelioma without further specification is confusing and should be eschewed. Benign lesions include spindle cell haemangiendoendothelioma, that has been renamed spindle cell haemangioma. On the other hand epithelioid haemangiendoendothelioma represents a malignant vascular neoplasm that has a better prognosis than rare epithelioid angiosarcoma, but metastasized in 20 to 30% of cases, and approximately 15% of the affected patients died of disease. Kaposiform haemangiendoendothelioma (KHE) and papillary intralymphatic angioendoendothelioma (PILA) represent locally aggressive vascular neoplasms with an increased risk for local recurrence but without metastatic potential. The prognosis of patients with KHE and PILA is related mainly to the size, depth, anatomic site and extent of the lesion. Retiform haemangiendoendothelioma, rare polymorphous haemangiendoendothelioma, the recently described pseudomyogenic haemangiendoendothelioma, and composite haemangiendoendothelioma are locally aggressive, rarely metastasizing vascular neoplasms with an increased rate of local recurrences. Composite haemangiendoendothelioma occurs predominantly in adults, and only one congenital neoplasm has been reported. The majority of reported neoplasms arose in dermis and subcutis of the distal extremities. Clinically, composite haemangiendoendothelioma represents a low-grade malignant vascular neoplasm and is characterized by a locally aggressive and an increased rate of local recurrences, whereas metastases are rare but may occur. The histological hallmark of composite haemangiendoendothelioma is the irregular admixture of epithelioid and retiform haemangiendoendothelioma-like tumour areas with angiosarcomatous areas and areas of benign and malformative vascular changes. However, despite the presence of focal angiosarcomatous areas composite haemangiendoendothelioma has a much better clinical prognosis than ordinary angiosarcoma of skin and soft tissues.

LITERATURE


Case 20

Thomas Mentzel, M.D., Dermatopathology Bodensee, Friedrichshafen, Germany

Clinical History:
A 39-year-old male patient presented in 2000 with an ulcerated dermal neoplasm arising on the left buttock. Grossly, a 9.0 x 6.5 x 2.8 measuring skin specimen has been described, and histologically, a cellular spindle cell neoplasm of the dermis with focal infiltration of the subcutis was reported. The diagnosis of an ulcerated dermatofibroma with no evidence of malignancy was made. In 2009 the patient reported a slowly growing recurrence, that showed a rapid enlargement within 3 weeks in 2011. The local recurrence measured 12 x 6.5 x 3 cm and was marginally excised and a wide reexcision with tumour free margins was later performed. The local recurrence represents the seminar material.

Pathological Findings:
Histologically, a dermosubcutaneous specimen with a partly hyperplastic and elevated, focal ulcerated epidermis was received. The cellular dermal neoplasm showed variable morphological changes. Focally areas resembling ordinary, cellular and aneurysmal dermatofibroma were seen. In these areas plump spindled and histiocyte-like cells were arranged in mainly storiform partly also fascicular structures and tumour cells contained enlarged nuclei with irregular nuclear borders and nucleoli. Focally foamy cells and haemosiderin deposits were noted. In addition, areas composed of atypical spindled tumour cells containing enlarged and hyperchromatic nuclei and scattered multinucleated tumor giant cells which were arranged in fascicles or in cellular sheaths were present. In these areas an increased proliferative activity (10-12 mitoses in 10 high-power fields) and areas of tumour necrosis were noted. Immunhistochromically, a focal expression of alpha-smooth muscle actin was detected. A wide reexcision was performed and there is no sign of recurrence at 8 months.

Diagnosis: "Malignant" dermatofibroma

Comments:
Dermatofibroma (fibrous histiocytoma) represents a frequent benign mesenchymal neoplasm of the skin, whereas it occurs only rarely in subcutaneous and deep soft tissues. Over the years several morphological variants have been described, and their knowledge is important for the differential diagnosis to more aggressive neoplasms. These variants include epithelioid dermotofibroma, palisading dermatofibroma, atrophic dermatofibroma, ossifying dermatofibroma, dermatofibroma with osteoclast-like giant cells, lipidized “ankle-type” dermatofibroma, cholesterotic dermatofibroma. Clinically important, cellular dermatofibroma, aneurysmal dermatofibroma, atypical dermatofibroma as well as dermatofibromas arising on the face and in subcutaneous and deep soft tissues have an increased risk for local recurrence (up to 20%) in striking contrast to conventional dermatofibromas, that only rarely recur, even if incompletely or marginally excised. During the last years a few examples of cellular, aneurysmal, atypical dermatofibroma as well as of dermatofibromas arising on the face and in deep soft tissues have been reported that metastasized to lymph nodes and the lungs and even caused death of patients in some instances. Morphologically, the primary and the metastatic neoplasms showed classical features of the mentioned variants of dermatofibroma, and so far no predictive mophological features have been identified to separate classical benign dermatofibroma from rare metastasizing dermatofibroma. Very rarely, cases of dermatofibroma may show an obvious malignant transformation into fibroblastic/myofibroblastic sarcomas of the skin composed of atypical pleomorphic tumour cells with increased proliferative activity and even tumour necrosis and these neoplasms are characterized by an adverse clinical outcome.

LITERATURE


• Guillou L, Gebhard S, Salmeron M, Coindre JM. Metastasizing fibrous histiocytoma of the skin: a clinicopathologic


Case 21

Markku Miettinen, M.D., National Institutes of Health, Bethesda, USA

**History:** 30 year male. A 2 cm presacral subcutaneous mass was removed.

**Diagnosis:** Familial tumoral calcinosis. Histologically there are multiple cystic spaces containing fine granular and larger flaky calcified deposits. There is a mild osteoclastic giant cell reaction surrounding the calcified material. The overlying skin is ulcerated. The patient had massive multifocal subcutaneous calcifications in the chest wall, shoulder and hip.

**Discussion**

Familial tumoral calcinosis is usually a disease inherited in an autosomal recessive pattern, with occurrence of homozygous loss of function mutations in genes regulating calcium metabolism, resulting in defective regulatory proteins. The disease has an early onset with involvement already in the childhood. The patients usually develop soft tissue calcifications that can be multifocal and complicated with ulceration and infections. The calcifications have predilection to periarticular sites, and trauma may enhance their development. When large, the calcifications show radiologically multiple, calcifying, fluid level containing cysts. Bone changes, such as hyperostosis can also be present. The patients in familial tumoral calcinosis can be hyperphosphatemic or normophosphatemic, but they are generally not hypercalcemic, except in cases linked with specific mutation types (KL mutations). In some forms of disease, multifocal visceral and arterial calcifications also occur. In hyperphosphatemic forms, mutations have been most commonly detected in GALNT3 gene (encoding for UDP-N-acetyl-alpha-D-galactosamine: polypeptide N-acetylgalactosaminyltransferase 3), FGF23 gene (encoding fibroblast growth factor 23), and KL (Klotho = Coronary artery disease, susceptibility to, which is a co-receptor to FGF23). In normophosphatemic forms, mutations have been detected in SAMD9 gene encoding for a protein of unknown function. There is some evidence that mutation type and site can modify disease phenotype.

Far more common than familial tumoral calcinosis is one associated with end stage renal disease associated with parathyroid hyperplasia and hypercalcemia. These calcifications are also often periarticular. Tumoral calcinosis-like lesions occur in tenosynovial tissues in distal extremities as small nodules. They are usually idiopathic but sometimes linked with rheumatoid disease. These manifest histologically as small nodules in fingers and hands and contain microscopic calcific spherules and focal giant cell reaction.

**REFERENCES**


Case 22

Thomas Krausz, M.D., The University of Chicago, Chicago, IL, USA

**Clinical History:** 40-year-old male presented with abdominal pain. Colonoscopic biopsy from ascending colon suggested poorly differentiated neuroendocrine carcinoma. Right hemicolectomy and partial omentectomy was performed for ascending colon and omental mass.

**Pathology:** The colonoscopy was performed at an outside institution. The colonoscopic biopsy showed a few loose clusters of discohesive, polygonal tumor cells with moderate amount of eosinophilic cytoplasm. The nuclei were rounded with stippled chromatin pattern. Immunohistochemical study resulted in focal Cam5.2, synaptophysin and CD56 immunoreactivity, but no staining for CDX2, cytokeratin 7, 20, WT1, calretinin, S100, Melan A. The features were regarded as suggestive of a poorly differentiated neuroendocrine carcinoma. Right hemicolectomy specimen showed a circumscribed, firm mass, 12 x 10 x 7.7 cm, involving the mesocolon and the colonic wall and abutting the mucosa. The mucosa of the ascending colon was smooth with the exception of a 2 cm nodular area corresponding the underlying extrinsic tumor mass. The histologic slide submitted for the seminar is from this region. The cut surface of the mass was whitish yellow with areas of hemorrhage and necrosis. A portion of the mass was submitted for frozen section and read as: “poorly differentiated malignant tumor, defer for permanent”. Partial omentectomy specimen contained a 3cm, firm mass with whitish cut surface. The tumor is located in the mesocolon and adjacent wall of the colon, with focal invasion into the overlying mucosa. The tumor cells are arranged in both cohesive and discohesive nests of varying size as well as focally anastomosing broad ribbons and cords. These structures are surrounded by a prominent desmoplastic stroma. The neoplastic cells are, for the most part, round or oval with scant eosinophilic cytoplasm and round hyperchromatic nuclei containing inconspicuous nucleoli. In places, the tumor cells exhibit striking rhabdoid features with paranuclear intracytoplasmic hyaline inclusions indenting the nucleus. Intranuclear cytoplasmic inclusions are frequent. Some foci show nuclear pleomorphism and multinucleated tumor giant cells. Mitotic activity: 12 mitoses/10HPFs. Areas of tumor necrosis is present. A battery of immunohistochemical tests was performed and showed the tumor cells to be reactive with markers associated with epithelial (Cam.5.2, AE1/AE3, EMA), mesenchymal (vimentin), myogenic (desmin) and partial neural differentiation (NSE, CD56). Keratins, vimentin and desmin had a striking paranuclear dot-like pattern corresponding to the paranuclear hyaline intracytoplasmic inclusions on H&E. WT1 N-terminus antibody showed cytoplasmic, while Carboxy terminus antibody nuclear immunoreactivity. Some tumor cells showed positivity for CD99. No immunoreactivity was observed with the following antibodies: INI-1, FLI-1, chromogranin, synaptophysin, SMA, MSA, Myogenin, CK7, CK20, CK5/6, CDX2, calretinin, S100, HMB45, Melan A, CD117 and DOG-1. Molecular cytogenetic studies (FISH) were positive for rearrangement of the EWSR1 region at 22q12 in 94% of the interphase cells analyzed from a representative paraffin embedded tissue section. RT-PCR showed that EWSR1 fusion partner is WT1, corresponding to t(11;22)(p13;q12) translocation.

**Diagnosis:** Desmoplastic Small Round Cell Tumor involving ascending colon, peritoneum and omentum

**Comments:** Desmoplastic small round cell tumor (DSRCT) is a rare, highly aggressive neoplasm occurring usually in young males (M:F = 4:1), mostly between ages 15 – 35 years. It most frequently involves the abdominal and pelvic peritoneum without an identifiable visceral site of origin. DSRCT may occur rarely in extra-abdominal locations (pleura, paratesticular region, ovary, kidney, pancreas, parotid,, sinonasal region, CNS, bone extremities and cervicovaginal region) as well as in adults. DSRCT is characterized by nests and cords of small round or oval cells separated by prominent desmoplastic stroma, a polyphenotypic immunoprofile and the characteristic t(11;22)(p13;q12) translocation, which results in the fusion of the EWSR1 gene on 22q12 and the WT1 gene on 11p13. WT1 is a Wilms’ tumor suppressor gene that encodes a zinc-finger-type transcription factor which normally represses promoters that control expression of growth factors such as PDGFA. The EWSR1-WT1 fusion protein appears to induce expression of PDGFA, which is not only a potent mitogen but also a chemoattractant for fibroblasts and endothelial cells; a likely explanation for the commonly seen desmoplasia and rich stromal vascularity in this tumor.
Rare examples of DSRCT have variant translocation like EWS-ERG or EWS-FLI1 which usually seen in Ewing/PNET neoplasms. The differential diagnosis of DSRCT includes other small round cell tumors, ES/PNET, poorly differentiated carcinoma, small cell carcinoma, Merkel cell carcinoma, small cell malignant mesothelioma, alveolar rhabdomyosarcoma, neuroblastoma, Wilms tumor, ovarian small cell carcinoma with hypercalcemia, and lymphoma. The immunoreactivity for epithelial, mesenchymal, and neural antigens, especially the paranuclear dot-like pattern of desmin, is very helpful to solve the differential diagnostic dilemma. However, the morphologic spectrum of DSRCT has expanded significantly since its original description: cases showing larger cells, glands, rosettes, “zellballen” pattern, vacuolated cells, cystic degeneration pleomorphic variant and even tumors without desmoplasia, hence the definitive diagnosis of DSRCT usually requires immunohistochemical and molecular genetic testing.

The exact nature of DSRCT is still uncertain. Immunohistochemical studies characteristically show polyphenotypic differentiation. Even though the vast majority of DSRCTs occurs on peritoneal surfaces, there is no evidence of mesothelial differentiation. DSRCT is a highly aggressive neoplasm with poor prognosis. Currently there is no highly effective treatment for DSRCT. Extensive tumor debulking followed by systemic chemotherapy is the most frequently employed treatment. Rare cases showed significant response to PDGFR inhibitor therapy.

This case was selected for the seminar not only because of the characteristic histologic and immunohistochemical features but also to illustrate the difficulty to arrive to a definitive diagnosis on the colonoscopic biopsy and on frozen section. This particular example also illustrates the broad morphologic spectrum of this entity.

**REFERENCES**


- Tison V. Intracranial desmoplastic small-cell tumor.


Case 23

Elizabeth Montgomery, M.D.
The Johns Hopkins University Hospital, Baltimore, MD, USA

Clinical history
This 7 cm tumor of the deep soft tissues of the thigh was enucleated by a surgeon and described as a “cyst”.

Diagnosis
Low-grade fibromyxoid sarcoma

Low-grade fibromyxoid Sarcoma and Hyalinizing Spindle cell tumor with Giant Rosettes
Low-grade fibromyxoid sarcoma is a tumor composed of bland, fibroblast-like cells with a swirling, whorled, vaguely storiform pattern in a fibrous and focally myxoid stroma, occasionally with plexiform vasculature. These first reports highlighted their deceptive resemblance to fibromatoses(1). These tumors have little mitotic activity and minimal nuclear pleomorphism (since it is a translocation-associated sarcoma it has uniform cells) (2-3). This lesion recurs, but many cases also metastasize (e.g. to lung). This tumor is not quite equivalent to low-grade examples of myxofibrosarcoma, since the latter occur in older patients, are more pleomorphic and less fibrous, and seldom metastasize when superficial. Ultrastructural reports have shown fibroblastic differentiation and this tumor is regarded as a low grade variant of fibrosarcoma. Hyalinizing spindle cell tumor with giant rosettes(4) is an entity within a spectrum with low-grade fibromyxoid sarcoma (5). These tumors have infiltrative borders microscopically and are composed of bland spindled cells situated in a hyalinized to myxoid stroma, often with “cracking” artefact in the collagen. Characteristic were scattered large rosette-like structures often merge with serpiginous areas of dense hyalinization. The rosettes consist of a central collagen core surrounded by a rim of rounded cells morphologically and immunophenotypically different from the cells of the spindled stroma. These cells express a number of antigens, including S100 protein, neuron-specific enolase, and Leu 22, in contrast to the stroma, which usually lacks these antigens.

An identical characteristic translocation is found in both low-grade fibromyxoid sarcoma and hyalinizing spindle cell tumor with rosettes; t(7;16)(q33;p11)(6) fuses the FUS gene (also called TLS) to CREB3L2 (also called BBF2H7)(7). MUC4 labeling has been reported as a characteristic feature of low-grade fibromyxoid sarcoma(8) although it can also be encountered in ossifying fibromyxoid tumor (9).

Sclerosing Epithelioid Fibrosarcoma
Sclerosing epithelioid fibrosarcoma(10) can mimic metastatic carcinoma, particularly lobular carcinoma of the breast. These lesions affect primarily the deep musculature of adults without gender predilection, usually involving the lower limbs and limb girdles. Most are large. These lesions display a white grey cut surface characterized microscopically by a uniform population of small slightly angulated rounded cells with scant cytoplasm arranged in nests, cords, and sometimes in an “Indian file” array. There is a background of dense sclerosis, minimal inflammation and sometimes zones of cartilage and mineralization. Mitotic activity is scant. Patchy epithelial membrane antigen (EMA), S100 protein, as well as patchy keratin have all been reported in these lesions, which display ultrastructural features of fibroblasts(11). Since the histologic differential diagnosis is with carcinoma, the keratin and EMA can pose diagnostic problems if attention is not paid to the patchy pattern of the reactivity. These tumors can behave quite aggressively. In the earlier series, 53% of patients had persistent disease or local recurrence and 43% had metastases. Eighty six per cent of patients in the more recent series had metastases and over half of the reported patients had died of disease during the follow-up period.

Although the story is incompletely developed, sclerosing epithelioid fibrosarcoma can be tentatively considered as a high-grade form of low-grade fibromyxoid sarcoma as the two tumors share genetic alterations and sclerosing-epithelioid-like zones can be encountered in low-grade fibromyxoid sarcomas(12-15).

REFERENCES


The patient is a 56 year-old-woman with clinical history of invasive ductal carcinoma of the left breast, status post neoadjuvant chemotherapy and partial mastectomy with postoperative radiation therapy in 2003. Eight years later, the patient developed bilateral breast lesions with positive uptake on PET/CT, clinically suspicious for recurrence/metastasis from prior left breast carcinoma. The patient underwent bilateral core biopsies followed by bilateral mastectomies.

Grossly, the left breast weighed 1,865 gm, measured 30.0 x 26.5 x 12.0 cm, and contained a 22.0 x 10.0 x 9.0 cm firm, purple-red ill-defined mass with an extensively hemorrhagic appearance, present predominantly within the inferior portion of the specimen with a few satellite areas present within the superior half of the breast ranging from 1.0 to 2.5 cm in greatest dimension. The right breast weighed 1,202 gm and measured 25.0 x 19.0 x 5.0 cm, containing a 4.5 x 3.5 x 3.5 cm ill-defined, purple-brown, firm area present in the upper outer quadrant. Histologically, the ill-defined hemorrhagic areas consisted of an invasive, poorly differentiated malignant tumor composed of anastomotic slit-like spaces lined by enlarged cells containing, hyperchromatic, pleomorphic nuclei with prominent nucleoli. Frequent cellular areas with an epithelioid appearance, characterized by round to polygonal cells with abundant eosinophilic cytoplasm were noted. Immunohistochemical stains showed the tumor cells to be strongly positive for CD31, CD34, and vimentin and negative for cytokeratin AE1/AE3.

**Diagnosis:** Post-radiation epithelioid angiosarcoma

**Discussion:** Angiosarcoma accounts for only 1 to 2% of all soft tissue sarcomas, and develops from the endothelial lining of blood vessels in any organ, but most frequently in the breast, liver, bones and skeletal muscle. Angiosarcoma may present in different clinical settings, the most common being as a sporadic tumor, occurring typically in the scalp or face of an elderly patient. The second most common scenario is angiosarcoma secondary to chronic, long-standing lymphedema, usually in the setting of radical mastectomy with total lymphadenectomy for the treatment of breast cancer (Stewart-Treves syndrome). With modern approach to the treatment of early breast cancer, radical mastectomy with total lymphadenectomy has been traded for breast conserving surgery with sentinel lymph node biopsy and radiotherapy. This change in management has probably resulted in a decreased incidence of lymphedema-associated angiosarcoma, but at the same time it has coincided with more frequent reports of the third most common presentation: radiation-associated angiosarcoma. This last form can also occur as a complication of radiation therapy given for various benign and malignant diseases other than breast carcinoma. Strobbe et al have estimated that the incidence of angiosarcoma in previously irradiated breasts is 0.16%, in contrast with primary breast angiosarcoma, which accounts for less than 0.01% of all breast neoplasms. The cumulative incidence of post-radiation angiosarcoma has been reported to be of 0.9 per 1000 cases during 15 years, making it a rare, but important complication of breast cancer treatment. The risk, however, is not believed to outweigh the benefit of radiation therapy administration.

Most sporadic angiosarcomas occur in patients with no history of breast cancer, and are deep-seated neoplasms that arise from the breast parenchyma, with a hemorrhagic, sponge-like or microcystic appearance. Post-radiation angiosarcoma, on the other hand, tends to be cutaneous and multifocal, with very few cases affecting the parenchyma of the breast itself. It usually appears as a bruise-like, erythematous area that can ulcerate or become nodular, often with edema and small satellite lesions adjacent to the main tumor. Most patients come to the office complaining of a rash, and its appearance often gives the impression of an inflammatory breast carcinoma or infectious mastitis. Histopathologically, it is characterized by a continuum spectrum that ranges from a well-differentiated angiomatous pattern that mimics benign vascular lesions to a poorly-differentiated infiltrative solid pattern, with marked cytologic atypia. Most of the time, areas showing an admixture of different grades of differentiation can be seen within a single tumor. A well-differentiated pattern consists of irregular interanastomosing channels lined by endothelial cells that grow infiltrating and dissecting pre-existing dermal collagen fibers and forming intraluminal papillary structures. In some cases, cytologic features can be misleadingly benign; however, significant cytological atypia as well as endothelial multilayering are usually present. As angiosarcoma becomes less differentiated, endothelial multilayering is more pronounced, often
forming areas of solid tumor growth. In moderately-differentiated angiosarcoma, most of the tumor is still composed of a well-differentiated pattern, however additional foci of papillary formations are seen, with mitotic figures and cytologic atypia being more easily identified. Foci of solid and spindle cell proliferation, areas of necrosis and hemorrhage (‘blood lakes’) may be observed. Poorly-differentiated angiosarcoma may contain areas of well- or intermediate-grade pattern, especially at the periphery, but endothelial cells are severely atypical. Papillary formations, areas of necrosis, ‘blood lakes’ and endothelial tufting are prominent, with solid and spindle cell areas devoid of vascular formations. Many times, immunohistochemistry is the only definite way to make the correct diagnosis. Antibodies that recognize endothelial cell markers are used, such as CD31, CD34, Factor VIII and Fli-1. CD31 is the most sensitive and specific marker, although it is not always the cleanest. CD34 and factor VIII are expressed in most angiosarcomas, but not so much in the poorly differentiated type. It is also important to take into account that cytokeratin may be occasionally positive in epithelioid areas; however, this is usually focal. If an overly limited panel of antibodies is used, especially in a small biopsy specimen, poorly-differentiated angiosarcoma can be misdiagnosed as carcinoma.

Recently, some authors have described the appearance of what they have termed atypical vascular lesions (AVL) within skin that was previously irradiated. These lesions are not frankly malignant, and present as small, circumscribed papules. Histologically, however, they have some features that overlap with well-differentiated cutaneous angiosarcoma. Although they have been reported to have a benign course, there are only limited reports, with not enough follow-up data, and evidence of occasional progression to frank angiosarcoma exists. The relationship of AVL with radiation-associated cutaneous angiosarcoma is still unclear, but it has been proposed that these may not be separate entities, but rather they could represent a morphologic continuum, in which AVL could be the earliest manifestation of post-radiation vascular proliferative lesions. Well-differentiated cutaneous angiosarcoma shares morphologic features with AVLs, and significant overlap exists. Many times, it is very difficult to differentiate one from the other, but usually AVLs appear relatively circumscribed and confined to the dermis, without infiltrating subcutaneous tissue. In AVLs, there is no significant atypia or multilayering of endothelial cells, and they don’t have areas of necrosis or ‘blood lakes’. At the present time, there are no absolute diagnostic parameters or criteria to differentiate between the two. This, along with the finding of AVL-like areas present in focal regions within frank cutaneous angiosarcomas, further support the hypothesis that both AVLs and cutaneous angiosarcomas are part of the same disease process. On occasion, several biopsies may be necessary to establish an unequivocal diagnosis of suspicious lesions. In individual cases, it may also result impossible to morphologically separate AVL from acquired progressive lymphangioma or hobnail hemangioma without the assistance of detailed clinical information.

Prognosis for any type of angiosarcoma is very poor (worse than for breast carcinoma), with most patients dying from the disease. Aggressive management of frank angiosarcoma is usually recommended, with wide excision or mastectomy and careful clinical follow-up. Chemotherapy (especially with anthracyclines, ifosfamide or taxanes) and radiation therapy are usually reserved for palliation of advanced disease. For radiation-associated angiosarcoma, re-irradiation is felt to be associated with increased side-effects, and has been usually avoided. However, a high rate of local control, disease-free and overall survival were noted recently using hyperfractionated and accelerated radiotherapy with or without subsequent surgery. For AVL, there are no accepted standardized recommendations. It is advisable to be cautious, since their clinical behavior is poorly characterized, but seems to be unpredictable. In general, complete excision with negative margins and careful pathological evaluation is advisable to exclude a possible focus of angiosarcoma. Patients should be carefully followed clinically, and any new or recurrent lesions within the previously irradiated area should be re-biopsied.

REFERENCES


Case 25

Paul E. Wakely, Jr., M.D., The Ohio State University, Columbus, OH, USA

History:
A 51-year-old woman presented with a 2 year history of increasing pain in her left distal tibia that was particularly intolerable at night. She has a bony prominence over the area. Eleven years earlier a biopsy performed in this same area was diagnosed as “atypical hyperchromatic cells and fibrous stroma”. The surgeon interpreted this result as probable fibrous dysplasia, and since she was relatively asymptomatic nothing was done during this interval (over a decade) until recently. Plain X-rays demonstrated a loose and expansile lesion in her distal tibia that expanded the cortex and also involved the medullary cavity. An MRI demonstrated no lesions elsewhere. She underwent biopsy and subsequent radical resection.

Pathology:
Grossly, a 9.0 cm long segment of tibia revealed on cut surface a 5.3 x 2.5 x 2.4 cm. pale tan, firm mass involving the diaphyseal portion of the medullary canal and cortex. The mass elevated the periosteum, but did not grossly penetrate it. Microscopically, a proliferation of cells in nests, cords, and tubules (resembling glandular spaces) with basloid epithelial features haphazardly infiltrated marrow spaces within a fibrous stroma, and showed formation of immature woven bone. No foci of fibrous dysplasia were present. Focally, neoplastic cells showed a spindle cell pattern. Monomorphic tumor cell nuclei were rounded, moderately chromatic with evenly dispersed fine chromatin, infrequent micronucleoli, and few mitoses. Immunostaining results: cytokeratin AE1/3, p63, vimentin, and EMA positive

Diagnosis:
Adamantinoma, left tibia, classic type.

Comment:
Adamantinoma, a rare low grade malignancy of bone, typical peaks in patients from their teenage years up to their late 30’s, but a wide age range from early childhood to elderly individuals exists. Male to female ratio is nearly the same. Symptoms are non-specific; there may be pain and swelling typically of very long duration. Although other bones have been reported with adamantinoma, the tibia and fibula are the only two bones routinely affected with the former involved in 85–90% of cases. These neoplasms also are reported in pretribial soft tissues. Adamantinoma synchronously occurs in both tibia and fibula in as much as 50% of cases. About 70% of cases involve the mid-shaft of the tibia, with a typical plain X-ray finding of sharply circumscribed lucent zones with sclerotic borders within the cortex. Multifocal radiolucencies are common producing a "soap bubble" appearance. Rarely, this tumor is within the medullary cavity. Clinical onset is characteristically insidious and patients often tolerate symptoms for many years (as in this case) prior to seeking medical attention.

The gross appearance of adamantinoma is a non-specific grey-white mass sometimes with small cysts. Four principal epithelial patterns of the classic type include: basloid, tubular, spindle cell, and squamoid histologic variants with the 1st two patterns being most common. Osteofibrous dysplasia-like stroma is often intermingled with the epithelial component; those examples dominated by this dysplasia are termed differentiated (regressing) type and are almost exclusive to patients < 20 years of age. The basloid variant has epithelial cells in solid nests showing distinctive peripheral palisading. The tubular pattern contains cell columns and mimics glandular neoplasia. Mitoses are minimal regardless of histologic subtype. Immunostaining is positive for pan-keratin markers, and vimentin, but unlike other bone or soft tissue neoplasms with epithelial markers, it lack cytokeratin 8 and 18. The squamous pattern/variant of adamantinoma can be frightening, and may even demonstrate keratin pearl formation thus leading to an incorrect diagnosis of metastatic squamous carcinoma. Spindle cell adamantinomas may be mistaken for sarcomas, particularly synovial sarcoma.

The relationship to adamantinoma to osteofibrous dysplasia remains unclear. Some see it as a regressing or differentiated phenomenon; while others postulate that it is a precursor lesion to adamantinoma development. Complete en-bloc resection is necessary to prevent local recurrence of adamantinoma which can be as high as 31%. Neither radiation nor chemotherapy is effective for this neoplasm. Local recurrence usually occurs 5–15 years after diagnosis, but has been reported as late as 3 years afterwards. Metastatic rates – primarily to lungs or nearby lymph nodes – are quoted to be from 12% to 30%, and can appear even after a long disease free interval of over 10 years. There is no correlation between behavior and histopathology.
REFERENCES


Case 26

Paul E. Wakely, Jr., M.D., The Ohio State University, Columbus, OH, USA

History: A 28 y/o man presented with a 4 month history of low back pain, leg weakness, and numbness. MRI showed a lesion involving the posterior aspect of L5 with diffuse homogenous enhancement measuring 2.3 x 2.1 x 2.6 cm, with extension into the anterior epidural space. Clinical diagnosis was metastatic carcinoma from an unknown primary.

Pathology: Grossly, 3.5 x 2.5 x 2 cm. tan to gray-white, firm tumor with focal hemorrhage was found on cut section. Sheets of malignant small round cells infiltrated the marrow cavity. Cells had round-to-oval finely granular nuclei and meager cytoplasm. Mitoses were easily found. Most slides had foci where capillaries were dilated producing a hemangiopericytomatous vascular pattern. Small rounded areas of primitive nodular chondroid differentiation, some more obvious than others, were recognizable; these foci blended almost imperceptibly with the malignant small cells, but in a few foci they were distinct. No foci of true hyaline cartilage with lacunar cells are present. IHC showed weak reactivity of small cells with CD99; stains for S-100, CD45, chromogranin, synaptophysin, myoglobin, SMMS, smooth muscle actin (SMA), desmin, and CK AE1/AE3 were negative. EM showed primitive cells set focally in a fibrillar matrix consistent with chondroid differentiation. The cytoplasm contained a paucity of organelles with occasional glycogen and RER.

Diagnosis: Mesenchymal chondrosarcoma, bone

Discussion: Mesenchymal chondrosarcoma (MCS) described by Lichtenstein and Bernstein, is a malignant tumor characterized by a dimorphic pattern of highly undifferentiated small round cells and islands of chondroid matrix. It is considered a rare form of chondrosarcoma (ChS) (about 2% of cases) affecting adolescents and young adults. A wide age range extends from 5-74 yrs. Gender distribution is roughly equal. Patients complain of pain & occasional swelling, but can be asymptomatic for > 1 year. MCS occurs both in bone (skeletal type) and soft tissues (extraskeletal type). Skeletal MCS tends to involve the jaw, ribs, ilium and vertebrae, and less frequently, pelvic bones, femur, other long tubular bones and rarely the phalanges. One third of MCS are extraskeletal, and primarily involve head and neck. Radiological features are non-specific. Since MCS may display mineralized matrix and stippled densities, it can sometimes be confused radiologically for ChS. Cortical destruction with associated soft tissue extension can be seen in one-half of cases. The extraskeletal variant can present as a well defined, lobulated soft tissue mass, with radiographic focal calcification. Grossly, skeletal MCS presents as a soft to firm, faintly lobulated mass with variable grossly obvious cartilage. Cortical expansion or bone destruction with invasion of adjacent soft tissues is frequent. Extraskeletal types can present as a multilobulated circumscribed pink to gray-white fleshy mass, with scattered foci of irregularly sized cartilage and bone. Small areas of necrosis and hemorrhage are possible. The microscopic hallmark of MCS is a combination of undifferentiated small round cells with foci of chondroid matrix. Matrix varies from large islands of well-differentiated cartilage having the appearance of low-grade chondrosarcoma to microscopic foci of barely perceptible chondroid matrix set in a sea of malignant cells as in our case. In some examples, the chondroid component predominates with only small, inconspicuous foci of malignant cells. Cells within the cartilage tend to have round to ovoid nuclei similar to those in the surrounding stromal cells with poorly-formed lacunae. Undifferentiated small cells have small, round to oval hyperchromatic nuclei with scant cytoplasm, and lack conspicuous pleomorphism or mitotic figures. Areas of frank spindling of cells can be found. Focally, cells are arranged around larger vascular spaces producing a hemangiopericytoma-like pattern. Calcification is sometimes seen in areas of well-differentiated cartilage. Electron microscopically, small cells have no distinctive features. A high nucleocyttoplasmic ratio and a smooth cell membrane is in close apposition with intercellular matrix. Nuclei have a smooth envelope and indistinct nucleoli. Paucicellular cytoplasm has few organelles, with scattered free ribosomes, swollen mitochondria, and minimal endoplasmic reticulum (ER). Cells in the well-differentiated cartilaginous areas have irregular to scalloped configuration with short cytoplasmic processes, large ovoid nuclei, abundant rough ER, well-developed Golgi, and variable amounts of glycogen. Staining is positive in small cells with CD99 (membranous), desmin (50%), EMA (30%), and a positive result with S-100 only in cartilaginous foci. Both
components are positive for vimentin, CD57, and may also stain for neuron-specific enolase (NSE). There is typically no reactivity for synaptophysin, muscle-specific actin, and pan-keratins (AE1/3, CAM5.2).

A master regulator of chondrogenesis, the transcription factor Sox 9, has been demonstrated to be helpful in the differentiation of small cell malignancies. In 22 cases of MCS positive nuclear staining in both the primitive mesenchymal and cartilaginous component occurred in all but one. This antibody was negative in all other types of malignant small round cell tumors. Most cytogenetic studies performed in MCS have demonstrated complex cytogenetic alterations.

MCS must be differentiated from other "malignant small cell tumors" of bone and soft tissue. Given the dimorphic nature of MCS, several diagnoses need to be considered especially in small samples when only 1 of the 2 components is represented. If chondroid foci are absent, the entire list of "malignant small round cell tumors" enters into the diagnosis. These include Ewing Sarcoma/PNET, rhabdomyosarcoma, poorly differentiated synovial sarcoma, small cell osteosarcoma, and malignant lymphoma. When both components are present, the cartilaginous foci are the differentiating feature. Cytoplasmic glycogen and CD99 positivity are shared by Ewing's sarcoma/PNET, synovial sarcoma, and MCS, and can make the differential diagnoses among these tumors challenging. Ewing sarcoma lacks spindle cells. FLI-1 immunostaining is a possible marker to help differentiate Ewing sarcoma/PNET from other small, round blue cell tumors, including MCS in the setting of small biopsies. FLI-1 is expressed in over 70% of Ewing sarcomas with a specificity of 90% and is negative in MCS.

Rhabdomyosarcoma (RMS) only rarely presents as a bone mass. It lacks foci of chondroid differentiation in both major histologic subtypes, embryonal and alveolar. Positive staining with myogenic markers including myogenin, muscle specific actin, and desmin are helpful. Sox 9 staining has been shown to distinguish MCS from RMS and Ewing's sarcoma.

Poorly differentiated synovial sarcoma (SS) is composed of small round cells rather than spindle cells, and may exhibit a hemangiopericytoma-like vascular pattern and have foci of metaplastic cartilage. Evidence of epithelial differentiation using antibodies against cytokeratin and EMA, and FISH test using the SSX1 probe help rule out MCS.

Small cell osteosarcoma is distinguished by the presence of lace-like osteoid. Although small cell osteosarcoma may have chondroid differentiation and a hemangiopericytomatous pattern, it is extremely unusual to see well-developed islands of cartilage. On the other hand, MCS may contain amorphous, sharply demarcated islands of collagen resembling osteoid, but lacks the delicate, lace-like appearance of osteoid in osteosarcomas. Clinico-radiologic correlation is mandatory for separating these 2 tumors if chondroid or osteoid foci are missing which can be problematic in small tissue specimens.

When both cartilage and malignant small cells are represented, dedifferentiated ChS must be considered. Histologic features such as the rather abrupt boundaries between the cartilaginous component and the high grade anaplastic component of dedifferentiated ChS contrast sharply with the gradual blending of the two components and the lack of pleomorphism in MCS. Dedifferentiated ChS most often occurs in the elderly and more often involves the appendicular skeleton.

Finally, metastatic small cell neuroendocrine carcinoma is ruled out by a thorough clinical history, by radiographic studies, and by positive keratin and neuroendocrine marker staining.

The long-term prognosis of MCS is poor with local recurrence and distant metastases. The latter may appear long after the initial diagnosis. Common metastatic sites include lungs, regional and distant lymph nodes, other bones and viscera. Histologic features do not predict prognosis. Surgical resection is the primary treatment of choice, but there is some evidence that radiation and combination chemotherapy may be efficacious. Five-year survival up to 54% has been reported with median survival of 37.9 months, varying from 6 months to 13.5 years (11).

REFERENCES


• Muller S, Soder S, Oliveira AM, et al. Type II collagen as specific marker for mesenchymal chondrosarcomas compared to other small cell sarcomas of the skeleton. Mod Pathol. 2005 Feb 25;


Clinical History: A 55 year old woman was admitted for fever and chills for 5 days. She had a history of chronic glomerulonephritis with ESRF and deceased donor renal transplant 4 years ago, stable coronary artery disease, tertiary hyperparathyroidism and lipodermatosclerosis. The clinical examination and routine laboratory investigations were unremarkable. Chest x-ray showed infiltrates in left lung, lower lobe and she was treated empirically with augmentin with good effect. During the stay the patient appeared restless and displayed right sided neglect. An MRI of the brain was done and this showed a 3.5 x 3.0 cm nodular lesion at the base of the left fronto-temporal lobe with significant perilesional edema, mid-line shift and early hydrocephalus. Blood tests were negative for CMV DNA, galactomannan, Cryptococcal Ag and Toxoplasma IgM. CT and ultrasound examination of the abdomen showed no mass lesions. She underwent left decompressive craniectomy and excision of the mass. The intraoperative findings were those of a lobulated, whitish, fleshy tumor with a dural base and the surrounding brain tissue was significantly edematous. The frozen section was reported as: “spindle cell lesion with no evidence of lymphoma or metastatic carcinoma” (clinical queries). Subsequent MRI of the whole spine showed no enhancing and/or mass lesions.

Gross Findings: Multiple pieces of firm, lobulated tissue measuring 2.7 x 2.6 x 2.0 cm. No haemorrhagic or necrotic areas were identified.

Microscopic findings: The somewhat cauterized tissue revealed a relatively well circumscribed, nodular, moderately cellular tumor composed of vague interlacing fascicles of spindle cells with mostly bland, blunt-ended nuclei and variably distinct eosinophilic cytoplasm. In some areas the tumor displayed a rather prominent edema. Relatively abundant, albeit patchy, lymphocytes and also plasma cells were present. In addition to the spindly lesional cells a component of similar, but smaller, “primitive”, discohesive cells were also present. The relative abundance of these cells was somewhat difficult to appreciate on the H&E sections and also to clearly distinguish from the intratumoral lymphocytes. Their abundance was more readily appreciated on sections from the immunohistochemical study; smooth muscle actin and h-caldesmon. Occasional lesional cells displayed mild nuclear atypia, but neither significant nuclear pleomorphism nor necrosis was present. Rare mitotic figures were seen. There was a well-developed vasculature predominantly composed of rather fine caliber blood vessels with occasional larger sized vessels. The lesional spindle cells blended in with the blood vessels, but only in a few areas was vague whorling seen.

Histochemistry: PAS, GMS and ZN were negative for fungi and acid fast bacilli. Alcian-blue stained sections showed no increased amount of acid mucosubstances.

Immunohistochemistry and special studies: The tumor cells were diffusely immunoreactive for h-caldesmon and smooth muscle actin. As mentioned above, these studies readily highlighted a significant presence of (positive), discohesive, “primitive, small, round” cells. Desmin, S100 protein, CD34, EMA and GFAP were all negative. The proliferative activity (Mib-1/Ki-67) was difficult to interpret due to the significant number of intratumoral lymphocytes, but there appeared to be expression of Ki-67 in some of the ovoid, lesional cell nuclei. EBV (EBER) in-situ hybridization was positive. Combined EBER-ISH and CD3/CD79a (respectively) IHC did not reveal any EBV-positive B- or T-cells.

Diagnosis: Epstein-Barr virus associated smooth muscle tumor

Comments: In 1970 and 1971, smooth muscle tumors associated with immunosuppression were reported [1, 2]. In the 1980s, there were steadily increasing numbers of patients with AIDS and transplant related immunosuppression and smooth muscle tumors, variably considered as leiomyomas or leiomyosarcomas. However, it was not until 1995 that the causative link between these tumors and Epstein-Barr virus was established [3, 4]. In addition, these tumors have been associated with autoimmune disease and common variable immunodeficiency syndrome [5, 6]. EBV-SMTs have been described in a wide variety of anatomical locations, including liver, spleen, gall bladder, tonsils, palate, nasopharynx, skin, pharynx, cribriform plate, orbita, larynx, mesentery, lung, iris, bone, skin, brain, meninges, spinal cord, common bile duct, myocardium, lymph nodes, adrenals, breast, pleura, urinary bladder,
stomach, duodenum, gallbladder, spleen, small bowel, pericardium and bronchi (endobronchial). EBV-SMTs may be well circumscribed associated with a fibrous pseudocapsule or may display poor circumscription with an infiltrative border and radiological evidence of destruction in the surrounding tissues [7]. The histological spectrum of EBV-SMT is wide and this is reflected in the literature where EBV-SMTs have been variably labeled as leiomyoma, leiomyosarcoma, benign and malignant variants of myopericytoma and smooth muscle tumors of uncertain malignant potential (STUMP). The unifying term EBV-SMT is preferable since this group of tumors have characteristic clinicopathological features that separate them from SMTs not associated with EBV (odd locations, frequent multi-centricity, association with immunosuppression and good prognosis as far as tumor related mortality is concerned. The latter is especially important in relation to bona-fide (somatic) leiomyosarcoma not associated with EBV which is a highly aggressive neoplasm that frequently kills the patient. Despite this and the lack of correlation between histopathological features of EBV-SMTs and prognosis, in a recent series of EBV-SMTs comprising 27 AIDS-related tumors [7], the authors insisted in separating the tumors into “leiomyomas”, “STUMP”, “leiomyosarcomas” and “benign and malignant variants of myopericytomas”. The effort in sub-classifying this group of tumors contrasts with the reported findings of a lack of correlation between histopathological features and prognosis and low mortality rate in this study (only 9% of the patients died from direct effects of the tumors). These facts have consistently been reported in the literature [8-10]. The classical description of these tumors include: (1) A relatively monomorphic population of spindle/myoid cells arranged in short, interlacing fascicles and (2) a primitive round cell population that may appear intermixed with (1) or as separate/discrete nodules. Reportedly, the latter component is present in approximately 50% of cases. A variably prominent vascular (arteriolar) component is frequently present. The vasculature may have a haemangiopericytomatus/myopericytomatosus appearance including staghorn-type vessels and myoid tumor cell-whorls blending imperceptively with the smooth muscle cells of the vessel walls. The cellularity is variable and both fibrosis and hyalinization may be present. In most cases, a variably intense infiltrate of lymphocytes (CD3+ T-cells) is present within the tumor. Mitotic activity may on occasion be brisk (with up to 23 mitotic figures/ 10 HPF reported) [7], but most commonly the mitotic activity does not exceed 3/10HPF [8]. This degree of mitotic activity associated with nuclear atypia is worrisome for a somatic leiomyosarcoma [11] and we have seen one laryngeal EBV-SMT that mimicked LMS on biopsy [12]. The impression of LMS was further strengthened by the absence of multi-focality which is frequently (>50%) seen in patients with EBV-SMTs. Moreover, the impression of LMS may be further strengthened by the fact that necrosis and myxoid change can be seen in EBV-SMTs [7, 8, 13]. On the other hand, we have also encountered a tumor at the other end of the histological spectrum of EBV-SMTs, a very bland cutaneous EBV-SMT which displayed perfectly well the histological features of an angioleiomyoma [14]. A similar case (although multi-centric) had been published earlier [15]. These cases begged the question whether cutaneous angioleiomyomas that are not associated with immunosuppression may in reality be EBV-SMTs. This turned out not to be the case [16].

The cell of origin for EBV-SMT remains unclear. However, investigators have noted that minute EBV-SMTs have a close relationship to the muscle cells of small caliber vessels [8]. In one study the authors noted dysplastic changes of the cells in vessels walls, thus raising the possibility that this may represent a precursor lesion [17]. On the other hand, the presence of EBV (EBER) positive (desmin negative) spindle cells within the vessel walls in the tumors, as noted in a relatively recent study [18], could well be attributed to invasion/replacement of the native smooth muscle cells of the vessel wall by tumor cells. The authors supported such a view by also identifying EBER-, desmin+, “residual” vascular smooth muscle cells.

Immunohistochemically, EBV-SMTs express smooth muscle actin, alpha-smooth muscle actin, h-caldesmon and muscle specific actin. Desmin is variably positive, but not uncommonly with a weak and focal staining. Negativity for desmin is most consistently seen in the small primitive round cell component [7]. Reportedly, S100 protein, CD34, c-kit, CD99, Factor VIII, Factor XIIIa, HMB-45, EMA, cytokeratins are all negative. The proliferative activity (Mib-1/Ki-67) shows great variability: 1-2% to 25%.

That EBV-SMTs are clonal proliferation has been firmly established in several studies [3, 4, 8]. Exploiting the fact that during EBV infection of a cell, the viral DNA circularizes and a random number of long terminal base-pair repeats (LTRs) at the 3’ end are lost, it has been shown that tumors at different sites most likely represent separate transformation events rather than metastasis [8, 19]. The molecular mechanisms linking EBV to tumorigenesis of smooth muscle cells are unclear.
EBV exists as two distinctive strains [20] which differ in geographic distribution and epidemiology. EBV type 1 is considered to have a greater transforming ability and is commonly associated with neoplasms in immunocompetent individuals with Hodgkin lymphoma and Burkitt lymphoma whereas type 2 is associated with immunodeficiency states and is consistently associated with post-transplant lymphoproliferative disorder (PTLPD). EBV-SMT has been associated with both EBV types [8, 21], although based on small numbers it appears that EBV type 2 is more commonly the culprit [8].

The main targets for EBV infection are B-lymphocytes via the cellular receptor CD21. Some investigators have identified CD21 in EBV-SMTs [3, 4, 19], but others have failed to do so [13, 22, 23]. Another possibility for EBV to get access to smooth muscle cells may be via fusion with EBV infected lymphocytes [24, 25]. Furthermore, based on the absence of CD21 in EBV-associated gastric carcinomas it has been suggested that there may exist other receptors for EBV than CD21 [26]. There is serological evidence that the EBV in EBV-SMTs may be of both donor or recipient origin [27, 28].

In addition to lytic replication in host cells (where viral particles are released), EBV may exist in a latency stage where a limited number of genes are switched on. This limited gene expression clusters into three combinations referred to as types 1-3. In type 1, only EBV early RNA (EBER) and EBV nuclear antigen (EBNA) 1 are expressed (seen in Burkitt lymphoma). In addition to the above, in type 2, the genes for latent membrane proteins (LMPs) 1, 2A and B are expressed (characteristically present in non-keratinizing nasopharyngeal carcinoma). In type 3, in addition, all other types of EBNAs; 2, 3A-C are expressed and this is the pattern associated with EBV associated LPD. EBNA 2 is a sine qua non for in vitro immortalization of B-lymphocytes. There are several reports that have identified EBNA 2 in EBV-SMT [3, 29-31]. It has thus been claimed that EBV-STMs exhibit the EBV type 3 latency pattern [32]. However, the data on LMP-1 and EBNA 2 is not consistent. The majority of EBV-SMTs appear immunonegative for LMP-1, but weak expression (IHC) has been detected in few cases and few RT-PCR-positive (IHC negative) cases are on record [8, 17, 33]. The number of viral particles varies with at least a factor of 100 (Deyrup). It is believed that EBV DNA is most commonly not incorporated in the host cell DNA of EBV-SMTs, but one case of hepatic EBV-SMT (in a 10 year boy with renal transplant) has been published where EBV-DNA was integrated within the ALK locus of the tumor cells [34].

From a differential diagnostic point of view a few entities need to be considered. The list of differential diagnoses is wide and varies of course with the site and morphology of the particular EBV-SMT, but some entities that need to be considered are bona fide leiomyomas/leiomyosarcomas (including the inflammatory variant), cellular Schwannoma and other nerve sheath tumors including MPNST, meningioma, inflammatory myofibroblastic tumor, infective (mycobacterial, cryptococcal) spindle cell pseudotumor, inflammatory pseudotumor-like, follicular dendritic cell tumor (which may show EBV positivity, mainly in hepatosplenic locations), myofibroma/myofibromatosis, myopericytoma, glomangiopericytoma, GIST, SFT-hemangiopericytoma and endometrial stromal sarcoma with myoid differentiation.

Based on the fact that a few cases with both EBV-SMT and EBV-associated lymphoproliferative disease (PTLPD) are on record [3, 35, 36], the rather brisk lymphoplasmacytic infiltrate seen in this case prompted us to rule out a superimposed EBV-associated lymphoproliferative disease by performing EBER-ISH combined with IHC for CD3 and CD79a, but we could not detect any EBV infected lymphoid cells.

Treatment for EBV-SMT continues to be a problem. There are no randomized or clinical controlled trials and most of the data on this topic is based on case reports and small series. Unlike conventional sarcomas, there appears to be no relation between classical histopathological features of malignancy (nuclear atypia, mitotic activity etc) and the prognosis of SMT [7-10] which appears more closely related to the site(s) of involvement and the immune status of the patients. Surgical resection, reduction of immunosuppressive therapy and antiviral treatment are all modalities that have been used either in isolation or in various combinations. Cytotoxic chemotherapy and radiotherapy appear to be ineffective [37, 38]. A few cases of AIDS associated EBV-SMT have shown stable disease and even regression with increased CD4 cell counts related to highly active antiretroviral therapy (HAART) [5, 38, 39]. Similarly, limited data in patients with PTLPD suggests that improving the immune status in these patients leads to improved survival [5]. Activation of the Akt/mTOR signal pathway has been shown to play an essential role in AIDS-related Kaposi sarcoma (KS) and sirolimus (an mTOR inhibitor) has been shown to block the progression of KS. Overactivation of the Akt/MTOR pathway has recently been detected in an EBV-SMT [38] and in one transplant patient, sirolimus-induced complete remission of a hepatic EBV-SMT [40] was observed.
One intriguing aspect of this case is that despite its relatively small size and non-invasive features, there was significant cerebral pathology (restlessness and neglect) and radiologically significant perilesional edema, midline shift and early hydrocephalus. As stated above, there was also significant edema within the tumor itself. Speculatively, this may perhaps be attributed to the rather prominent inflammatory cell component present within the neoplasm (where based on the literature the prominent B- and plasma cell component is distinctly unusual) and that this brisk inflammatory infiltrate may underpin a cytokine driven effect on the permeability of the vasculature, both in the tumor itself and the surrounding brain parenchyma, with ensuing prominent edema. There was no surrounding brain tissue submitted so we were not able to evaluate whether the inflammatory cell component as seen in the tumor was also present there.

PICTURES

MRI (T2-weighted image) revealed a well circumscribed 3.5 x 3.0 cm hypointense mass (arrow) in the left frontotemporal perisylvian region. There was extensive peritumoral edema in the left frontal and temporal lobes and the deep grey-white matter with effacement of sulci associated with a mild midline shift to the right.

The tumor was well circumscribed and had a nodular appearance.
The cellularity was moderate.

In some areas the tumor displayed a rather prominent edema.

The spindle cells were arranged in a vague fascicular pattern. No high-grade nuclear atypia or pleomorphism was present.

Some of the tumor cells were smaller, round and discohesive.
Case 27

EBV (EBER-ISH) was positive.

In several areas, a rather brisk, mononuclear, inflammatory cell content was present in many areas of the tumor. Plasma cells were easy to identify.

The spindly tumor cells were strongly positive for SMA.

In addition to expressing SMA, the small round "primitive", discohesive tumor cells were positive for h-caldesmon.

Abundant B-cells were focally present in the tumor (combined EBER-ISH; brown and CD79a IHC; red).

Combined EBER-ISH; brown and CD79a IHC; red showed that the B-cells did not harbor EBV.

Combined EBER-ISH; brown and CD3 IHC; red showed that also the T-cells did not harbor EBV.
REFERENCES


Case 28

Eduardo Zambrano, M.D., Medical College of Wisconsin, Milwaukee, WI, USA

The patient is a 36 year-old female patient presenting with a 6.5 cm soft tissue tumor of the left axilla, and a presumptive clinical diagnosis of liposarcoma. No other relevant past medical or family histories were obtained.

The patient underwent a marginal tumor resection, which yielded a 12.3 x 8.5 x 6.2 cm soft tissue specimen with overlying skin, containing a 6.5 x 4.8 x 4.5 cm well-circumscribed multilobulated light tan soft mass, which abutted a 3.5 x 0.3 cm portion of nerve, and extended to the deep and lateral margins. Histological sections revealed a well-circumscribed, partially encapsulated tumor with pushing borders, composed of aggregates and strands of small, cytologically bland spindle cells in a hyalinized stroma with prominent thick-walled vessels and focal myxoid change (see figure). A segment of nerve with degenerative changes was present adjacent to the neoplasm. Neither necrosis nor cytologically malignant cells were seen, and mitotic activity was minimal/absent. Immunohistochemical stains revealed that tumor cells were positive for vimentin, with focal weak EMA expression (see figures). In addition, focal staining was seen with bcl-2, CD34 (see figure) and CD56, while S100, MSA, SMMS-1, CD31, chromogranin, CD117, CD57 and CK AE1/AE3 were negative. Electron microscopy studies showed numerous slender processes with partial basal lamina, with some of the processes surrounding collagen bundles (see figures).

Diagnosis:
Extraneural soft tissue perineurioma (ESTP)

Discussion:
First described by Lazarus and Trombetta in 1978, perineurioma is an uncommon and underrecognized neoplasm defined as a peripheral nerve sheath tumor composed exclusively of neoplastic perineurial cells that demonstrate ultrastructural and immunohistochemical features similar to those of their normal cell counterpart. Normal perineurial cells constitute the perineurium, a protective barrier situated between the epineurium and endoneurium layers of the nerves that surround both myelinated and unmyelinated axon-Schwann cell complexes of peripheral nerve fascicles. The perineurium has direct continuity with the pia-arachnoid membrane of the central nervous system. In contrast to other peripheral nerve sheath tumors, perineuriomas have not been found to be associated to neurofibromatosis. They mainly affect adults, but some cases have been described in children.

Two main forms of perineurioma exist: intraneural and extraneural. Intraneural perineuriomas are restricted to peripheral nerve boundaries, while extraneural perineuriomas are found mainly in soft tissues and skin. Extraneural perineuriomas seem to be more common than intraneural perineuriomas, and although they usually have no connection to peripheral nerves, sometimes such an association may be apparent in small lesions. In some cases, extraneural perineuriomas and intraneural perineuriomas may contain residual entrapped Schwann cells, axons, and fibroblasts. On the basis of different clinical and pathologic characteristics, extraneural perineuriomas are further subclassified into soft tissue, sclerosing, and reticular (retiform) subtypes. Although historically the intraneural variety was interpreted as a reactive hypertrophic process, the presence of 22q deletions in both intraneural and soft tissue perineurioma supports a neoplastic origin for both types. Intraneural perineuriomas are characterized by localized, solitary expansion of peripheral nerves, due to involvement of one or more nerve fascicles. These tumors remain stable over time or progress very slowly. On gross examination, multinodularity secondary to firm, enlarged individual fascicles when exposed is the main finding. Histologically, it is characterized by a complex perineurial cell proliferation extending into the endoneurium and concentrically surrounding individual nerve fibers and endoneurial capillaries producing characteristic “pseudo-onion bulbs”, which are best appreciated on cross sections of nerve fascicles. Soft tissue perineurioma almost always lacks an associated nerve, is usually well circumscribed and may have a capsule. Slender cells with very delicate, overlapping elongated cellular processes, arranged in loose fascicles or whorls are the typical pattern. Atypical histologic features, such as pleomorphic cells and limited infiltration, do not seem to have prognostic significance. Abundant myxoid change, creating a microcystic or “reticular” pattern is present in a subset of cases (so-called reticular perineurioma). Sclerosing perineurioma is a distinctive variant most often seen in the hand of young men, and is characterized histologically by extensive collagen deposition and epithelioid cytomorphology.
Ancillary studies are required for the diagnosis of perineurioma. Among immunohistochemical markers, epithelial membrane antigen (EMA) is the most widely used and stains the majority of perineuriomas. Nevertheless, the use of EMA as a perineural marker presents some drawbacks since the cytoplasmic processes of perineurial cells are extremely thin and widely separated, and EMA reactivity may be difficult to demonstrate without using higher antisera concentrations or longer incubation times than routinely employed in the diagnosis of epithelial neoplasms; even when these precautions are taken, sometimes EMA positivity may be focal and weak. In fact, the literature contains examples of ultrastructurally well documented EMA-negative perineuriomas. Additional immunohistochemical markers of perineurioma include claudin 1, a marker of tight junctions, and GLUT1, a glucose transport protein involved in the formation of the blood–nerve barrier. In addition, staining for CD34 has been reported in up to 64% of tumors. Neither of these markers is entirely specific for perineural differentiation, and they are best used as part of a multi-antibody panel. Ultrastructural features include the presence of elongated, tapered nuclei with delicate chromatin; long thin cytoplasmic processes with pinocytotic vesicles; cell envelopment by basal lamina; and the presence of intercellular junctions, including tight junctions.

The differential diagnosis of soft tissue perineurioma depends primarily upon whether it is superficial or deep-seated and the characteristics of the tumor stroma. For tumors involving the dermis and superficial subcutis, the primary differential diagnosis is DFSP. Soft tissue perineuriomas frequently have a storiform architecture and high cellularity similar to DFSP. In addition, CD34, which is uniformly positive in DFSP, is often positive in soft tissue perineuriomas. However, soft tissue perineuriomas are usually well circumscribed and lack the diffuse infiltration of subcutaneous adipose tissue typified by DFSP. Immunostaining for EMA can separate the two entities. For subcutaneous and deep seated tumors, the differential diagnosis may include other benign nerve sheath tumors (which will typically show more diffuse S-100 protein positivity), solitary fibrous tumor (SFT), perineurial MPNST, low-grade fibromyxoid sarcoma (LGFM), and, for cases with prominent myxoid stroma, cellular myxoma and low grade myofibrosarcoma. Perhaps the closest histologic mimic of deep-seated soft tissue perineurioma is LGFM. Unlike perineurioma, LGFM shows prominent stromal collagen deposition and an “abrupt” transition into myxoid nodules, displaying a curvilinear vascular pattern. EMA expression may be present in up to 40% of LGFM, a potential pitfall. Demonstration of t(7;16) or the corresponding fusion gene is diagnostic of LGFM.

Conventional extraneural perineuriomas have thus far followed a benign clinical course, and surgical resection with margins free of neoplasm is typically curative, regardless of subtype. However, malignant perineurioma (also known as MPNST with perineural differentiation or perineural MPNST) has recently been recognized as a rare variant of MPNST (all cases were S100 protein negative and EMA positive and showed ultrastructural features of perineural differentiation). Malignant perineurioma is very rare, and its diagnosis may be difficult without confirmatory ultrastructural studies because EMA positivity is also seen in other high-grade spindle cell sarcomas (eg, epithelioid sarcoma and monophasic synovial sarcoma), as well as in spindle cell squamous cell carcinoma. Claudin-1 and GLUT-1 may be helpful in confirming this diagnosis. Hornick and Fletcher reported 14 perineuriomas with atypical features in their series, 10 of which had clinical follow-up ranging from 12 to 134 months. In this series, the low grade atypical features included scattered pleomorphic cells, abrupt transition from typical morphology to a markedly hypercellular area with cytologic atypia, and diffuse infiltration of skeletal muscle by tumor cells; of the 10 cases with such features, only 1 recurred locally, but no case metastasized. On the basis of their findings, Hornick and Fletcher suggested that perineuriomas with such features probably would be better called atypical perineuriomas instead of low-grade malignant perineuriomas. The term perineurioma of uncertain malignant potential has also been proposed for cases with atypical but not overtly malignant features.

REFERENCES


Case 29

Eduardo Zambrano, M.D., Medical College of Wisconsin, Milwaukee, WI, USA

The patient is a 19 year-old-woman status post extraction of second right inferior molar. Clinical history was significant for obesity and type 2 diabetes mellitus, and was otherwise unremarkable. One month following tooth extraction, the patient was referred to a medical center due to a slowly growing 1.5 cm mass occupying the right posterior quadrant of the oral cavity. The surface of the mass was of similar color to the surrounding mucosa and was associated with difficulty swallowing. Imaging studies revealed an expansile lesion occupying the right posterior body, angle and ramus of the mandible, with destruction of the medullary and cortical bone and extension to surrounding soft tissues. A right hemimandibulectomy was performed (Please see figures).

Histologically, the lesion was composed of cytologically-bland spindle cells with elongated nuclei containing 1-3 small, but frequently distinct, nucleoli. The cells were arranged in long intersecting fascicles within a variably collagenous to slightly edematous and myxoid stroma. Frequent compressed slit-like, thin-walled vessels were present throughout the lesion. The tumor was noted to erode through cortical bone and extend into surrounding soft tissues. Rare mitotic figures were identified, none of which appeared atypical. Lesional cells were strongly, diffusely positive for vimentin and showed focal moderate staining for smooth muscle actin and muscle specific actin. Desmin, S100 and CD34 were negative in lesional cells. The lesion was originally interpreted as a low-grade fibromyxoid sarcoma at an outside institution; however, FISH for FUS performed at our institution was negative, whereas immunohistochemical stain for β-catenin was strongly positive in a nuclear distribution.

Diagnosis:
Desmoplastic fibroma of the mandible

Discussion:
Desmoplastic fibroma (DF) is a rare, myofibroblastic tumor, comprising 0.06% of all tumors of bone and 0.3% of all benign osseous tumors. It was initially described by Cappell in 1935 in the fibula as an endosteal fibroma; however, Jaffe popularized the term “desmoplastic fibroma” a quarter of a century later (1958) for benign fibrous bone lesions involving the tibia, scapula and femur, which had histologic features similar to desmoid-type fibromatosis. The first report of gnathic involvement by DF is attributed to Griffith and Irby in 1965, and since then numerous similar cases have been described.

DF can occur at any age but is most frequently seen between 15 and 40 years, with no apparent gender predilection. Any bone may be involved, but the mandible is the most common site of involvement, whereas in extragnathic sites the metaphyseal region of the femur, tibia, humerus, or radius, as well as the pelvic bones, are well reported as other primary sites. In a review of 184 cases, DF most commonly involved the mandible (22%), followed by the femur (15%), pelvic bones (13%), radius (12%), and tibia (9%). Of DF involving gnathic bones, most appear to involve the mandible (84%) and the remaining the maxilla (16%). According to Freedman et al, 70% of desmoplastic fibromas of the mandible occur in the molar-ramus region, 21% in the premolar region, and only 9% anterior to the premolars.

The epidemiology and histology are identical to extraabdominal desmoid-type fibromatosis, and most investigators believe that DF represents the osseous counterpart of soft tissue fibromatosis, although definitive molecular confirmation is still lacking. Similar to desmoid-type fibromatosis, desmoplastic fibroma of bone is a non-metastasizing, locally aggressive tumor with high risk for local recurrence. Radiographically, the features of desmoplastic fibroma are nonspecific and nearly always demonstrate benign features with respect to the pattern of destruction, margins, and reactive bone formation; however, soft tissue extension can be present. Radiographic features include a unilocular or multilocular, well-demarcated or irregular radiolucency with variably expressed marginal sclerosis. Therefore, DF often mimics other common as well as unusual pathologies of the jaws including ameloblastoma, odontogenic myxoma, aneurysmal bone cyst, chondromyxoid fibroma, central hemangioma, low-grade central osteosarcoma, eosinophilic granuloma, fibrosarcoma, central ossifying fibroma, giant cell lesions, monostotic fibrous dysplasia, traumatic bone cysts and solitary bone cysts.

The lesions are composed of slender to slightly ovoid cells often containing multiple, yet small nucleoli, mostly arranged in long sweeping fascicles, and embedded
within an extensively collagenous stroma. Cellularity is variable; however, nuclear polymorphism and mitotic activity are rare to non-existent. Arguably, low-grade fibrosarcoma is the most challenging differential diagnosis; however, the presence of a fascicular growth pattern with so-called “herringbone” appearance and overlapping spindle cells, increased mitotic activity and pleomorphism, are characteristic features of fibrosarcoma and not DF. Another feature that favors a diagnosis of DF is the presence of indistinct cell borders with cytoplasm that merges with the supporting collagenous background. In certain circumstances, the distinction between the 2 conditions may not be possible and all cases must be followed up carefully.

Variable treatment modalities have been used for DF including surgery, radiation therapy, and chemotherapy with or without additional procedures. Radiation is seldom recommended since it has been shown to be only rarely successful and, because of its potentially mutagenic effect, may lead to post-radiation sarcoma. The recommended treatment includes surgery; however, the surgical approach to the lesion has been a source of controversy. While some surgeons prefer curettage, others prefer wide local excision or recommend resection with a wide margin. Iwai et al. reported that patients who were treated with resection or wide excision showed no recurrence, whereas the recurrence rate in those treated with simple excision or enucleation was 20-40%, as compared to 70% recurrence rate in those treated with curettage alone. Some authors have alluded to the fact that the high recurrence of DF is not only a result of inadequate surgical excision but also is a function of the innate biology. Kwon et al. reported that tumors with high cellularity have higher recurrences than those with lower cellularity. Given the recurrence rates of DF, the current accepted minimum follow-up period is at least 3 years.

REFERENCES:

Case 30

Thomas Mentzel, M.D., Dermatopathology Bodensee, Friedrichshafen, Germany

Clinical History: A 56-year-old male patient presented with an indurated infiltration on the right cheek.

Pathological Findings: Histological stainings reveal a dermal specimen with subcutaneous fat and an ill-defined, infiltrating neoplasm. The neoplasm is composed of enlarged, spindled tumour cells containing enlarged, plump spindled nuclei with irregular borders. In addition lymphoid cells with enlarged nuclei are seen. Immunohistochemical stainings show a homogenous expression of CD20 and CD79a by spindled tumour cells, whereas only scattered CD3 and CD2 positive T-cells as well as CD68 positive histiocytes are noted. In addition, most tumour cells show a nuclear expression of bcl-6 and a high proliferative activity is seen with Ki-67 immunohistochemical antibodies.

Diagnosis: Spindle cell cutaneous B-cell lymphoma

Comments: B-cell lymphomas may involve the skin as a primary cutaneous B-cell lymphoma (without evidence of extracutaneous spread for at least 6 months after presence of dermal lesions) or as part of a systemic disease. Primary cutaneous B-cell lymphomas fall into three main groups:
1) primary cutaneous marginal zone B-cell lymphoma
2) primary cutaneous follicle center cell lymphoma
3) primary cutaneous diffuse large B-cell lymphoma (PCDLBCL)

Cases of PCDLBCL are further divided in to lesions of the so-called “leg type” and “others” not otherwise specified (NOS). In regard to clinical behaviour, cases of PCDLBCL involving the lower extremities are characterized by a more aggressive behaviour in comparison to cases found in patients with localized neoplasms at other sites. Immunohistochemically, cases of PCDLBCL of the “leg-type” are characterized by an expression of MUM1 and bcl-2 independent of anatomic site. The presence of spindled cells has been reported in rare cases of cutaneous sclerosing B-cell lymphoma, however, these spindled cells represented a stromal reaction in most cases. The presence of a prominent, neoplastic spindle cell component in a B-cell lymphoma mimicking a mesenchymal neoplasm is very rare and has been first described in a small series of 5 cases in 2000. These high-grade neoplasms are composed of neoplastic, spindled B-lymphocytes that show a nuclear expression of bcl-6 and bcl-6 mutations as well whereas MUM1 is not expressed. These findings suggest that tumour cells of the spindle cell variant of diffuse large B-cell lymphoma are strongly related to germinal center cells or in other words, that these neoplasms show markers characteristic of a germinal center B-cell origin.

The differential diagnosis of cutaneous spindle cell B-cell lymphoma includes spindle cell malignant melanoma, spindle cell carcinoma, and spindle cell sarcomas of different lines of differentiation that can be easily excluded with the help of immunohistochemical markers. Tumour cells of rare histiocytic lymphoma are negative for B-cell markers but express so-called histiocytic antigens such as CD68. Follicular dendritic reticulum cell sarcoma is seen in lymph nodes and soft tissues and is composed of CD20+, CD21+, CD23+, CD35+ and neoplastic cells.

LITERATURE

Case 31

Jonathan I. Epstein, M.D., The Johns Hopkins University Hospital, Baltimore, MD, USA

Clinical History: A 44 year-old man with a history of seminoma 1 year earlier was noted to have an enlarged left lobe of the prostate on MRI. Serum PSA levels was between 2.5 and 3.0 ng/ml. After a diagnosis rendered on needle biopsy, a radical prostatectomy was performed.

Pathologic Description: Grossly, a 2.5 cm. mass was noted in the posterior/lateral region of the left lobe. Microscopically, the lesion was fairly well circumscribed composed of benign prostate glands, some which were cystically dilated. The intervening stroma varied from normocellular to hypercellular with many nuclei exhibiting atypia. Stromal nuclei were enlarged, pleomorphic, and hyperchromatic yet had a degenerative appearance with smudgy chromatin. Mitotic figures were rare. The lesion lacked stromal overgrowth and necrosis.

Diagnosis & Follow-up: Stromal Tumor of Uncertain Malignant Potential (STUMP).

An incidental small focus of organ-confined adenocarcinoma of the prostate, Gleason score 3+3=6 was also noted. Several years later the patient was without evidence of recurrence.

Discussion: Prostatic stromal tumors arising from the specialized prostatic stroma are rare and distinct tumors with diverse histological patterns. In the past, these tumors have been reported under a variety of terms including atypical stromal (smooth muscle) hyperplasia, phyllodes type of atypical stromal hyperplasia, phyllodes tumor, and cystic epithelial-stromal tumors. As the phyllodes “leaf-like” pattern is only seen in a subset of both benign and malignant stromal tumors, we prefer to designate stromal tumors of the prostate in more general descriptive terms as STUMPs and stromal sarcomas. To date, there have been three large studies on these lesions (1-3). STUMPs have been reported to occur between the ages of 27 and 83 years, with a median age of 58 years and a peak incidence in the 6th and 7th decades. Patients present most commonly with lower urinary tract obstruction, followed by an abnormal digital rectal examination, hematuria, hematospermia, rectal fullness, a palpable rectal mass or elevated serum PSA levels. On gross examination, STUMPs appear white-tan and may demonstrate a solid or solid-cystic pattern with smooth-walled cysts filled with bloody, mucinous or clear fluid. These tumors may involve either the transition zone or the peripheral zone and may range in size from microscopic lesions (which are typically incidentally found) to large, cystic lesions up to 15 cm in size.

Microscopically, four patterns of STUMP have been described and include: (1) hypercellular stroma with scattered atypical, but degenerative appearing cells admixed with benign prostate glands; (2) hypercellular stroma consisting of bland fusiform stromal cells admixed with benign glands; (3) leaf-like hypocellular fibrous stroma covered by benign appearing prostatic epithelium similar in morphology to a benign phyllodes tumor of the breast; and (4) myxoid stroma containing bland stromal cells and often lacking admixed glands. Cases can exhibit a mixture of the above patterns. All patterns of STUMP may have associated glandular proliferations including: glandular crowding; papillary infolding; cystically dilated glands, basal cell hyperplasia; urothelial and squamous metaplasia; cribriform hyperplasia; and adenosis. In some cases the epithelial proliferation may mask the diagnosis of STUMP. Approximately half of all reported cases of STUMP demonstrate the first pattern of hypercellular stroma containing atypical cells intermixed with, but not compressing, benign glands. The atypical stromal cells in these cases are pleomorphic and hyperchromatic, with a marked degenerative appearance. Mitotic figures are typically absent and atypical mitoses should not be seen. Although the admixed glands resemble normal benign prostatic glands, the glands within a STUMP may appear more crowded than acini in the surrounding uninvolved prostate. Cases of STUMP demonstrating hypercellular, elongated bland stromal cells with admixed glands may be occasionally misdiagnosed as a cellular stromal proliferation associated with BPH, although the extent of hypercellularity and often more eosinophilic nature of the cytoplasm is unique. The benign, phyllodes pattern of STUMP may also contain atypical, degenerative-appearing stromal cells and may be associated with a variety of benign epithelial proliferations, including basal cell hyperplasia, adenosis, and sclerosing adenosis. Finally, the myxoid pattern of STUMP may be confused with stromal nodules of BPH, although the myxoid pattern of STUMP consists of extensive sheets of myxoid stroma without the nodularity identified in
BPH. Occasionally the extensive myxoid stroma is admixed with benign prostate glands. Immunohistochemical stains do not necessarily aid in distinguishing STUMPs from other spindle cell lesions of the prostate. Most cases of STUMP are positive for CD34 and vimentin and variably positive for smooth muscle actin, and desmin. Due to the derivation of these tumors from the prostatic stroma, progesterone receptor is frequently present on immunostaining, although estrogen receptor is less commonly positive. C-kit and S-100 have been negative in all cases examined.

A subset of STUMPs has been associated with stromal sarcoma on concurrent biopsy material or has demonstrated stromal sarcoma on repeat biopsy, suggesting a malignant progression in at least some cases. There appears to be no correlation between the pattern of STUMP and association with stromal sarcoma. As most STUMPs are confined to the prostate and rarely progress to sarcoma, STUMPs are in general associated with a good prognosis.

In contrast to STUMPs, stromal sarcomas tend to affect a slightly younger population, with a reported age range of 25 to 86 years. Approximately half of all reported cases of stromal sarcoma occur before the age of 50 years. Stromal sarcomas may arise de novo or may exist in association with either a pre-existent or concurrent STUMP.

Gross examination of stromal sarcomas demonstrates predominantly tan-white, solid, fleshy lesions ranging in size from 2 to 18 cm. Occasionally, areas of edema, hemorrhage, or small cysts may be identified. Microscopically, stromal sarcomas demonstrate either a solid growth of neoplastic stromal cells, which may have storiform, epithelioid, fibrosarcomatous, or patternless patterns, or may infiltrate between benign prostatic glands. Less commonly stromal sarcomas may demonstrate leaf-like glands with underlying hypercellular stroma, which are also termed malignant phyllodes tumors. Stromal sarcomas have one or more of the following features within the spindle cell component: hypercellularity, cytological atypia, mitotic figures, and necrosis. Stromal sarcomas may additionally be subclassified into low and high grades with high grade tumors defined by moderate-marked pleomorphism and hypercellularity often with increased mitotic activity and occasional necrosis.

Immunohistochemical findings are similar to those of STUMPs, with positivity for CD34 and progesterone receptor. Stromal sarcomas can extend out of the pro-state and metastasize to distant sites, such as bone, lung, abdomen and retroperitoneum.

The variability in behavior of STUMPs and stromal sarcomas, and their occasional co-existence, lead to challenges in patient management. Although many STUMPs may behave in an indolent fashion, their unpredictability in a minority of cases and the lack of correlation between different histological patterns of STUMPs and sarcomatous dedifferentiation, warrant close follow-up and consideration of definitive resection in younger individuals. Factors to consider in deciding whether to proceed with definitive resection for STUMPs diagnosed on biopsy include patient age and treatment preference, presence and size of the lesion on rectal exam or imaging studies, and extent of the lesion on tissue sampling. Expectant management with close clinical follow-up could be considered in an older individual with a limited lesion on biopsy where there is no lesion identified on digital rectal exam or on imaging studies.

REFERENCES
Clinical History: A 66 year-old African American women presented with hematuria. Cystoscopy revealed mild mucosal irregularity but no mass. However, a CT scan of the bladder showed a markedly thickened bladder wall, suspicious for carcinoma. A small mucosal biopsy was performed which was diagnosed as “atypical glandular proliferation” with associated cautery artifact. The possibility of nephrogenic adenoma was raised but additional tissue was requested. A subsequent transurethral resection was diagnosed as carcinoma and a radical cystectomy was performed.

Pathologic Description: The cystectomy specimen revealed an ulcerated tumor at the trigone measuring 2cm. x 1.5cm. x 0.4 cm. In terms of the tumor’s architecture, it is composed of uniform small nests of urothelium that extensively invade the muscularis propria and extend through the muscle wall associated with a desmoplastic stromal response. Whereas most of the nests are solid, a minority demonstrate focal luminal differentiation. Cytologically, the nests vary from those that are relatively bland to others with more prominent cytological atypia including prominent nucleoli. Mitotic figures are infrequent. Metastatic carcinoma was present in one pelvic lymph node.

Diagnosis & Follow-up: Infiltrating urothelial carcinoma with nested features. The patient was without evidence of recurrent disease 7 years following surgery.

Discussion: The nested variant of urothelial carcinoma is a rarely encountered subtype of bladder carcinoma, with a prevalence of approximately 0.3% (1). According to one report, nested variant of urothelial carcinoma comprises less than one percent of invasive bladder carcinomas (2). In 1979, Stern observed a bladder lesion of closely packed epithelial nests closely resembling von Brunn nests. Although the nests appeared morphologically benign, the lesion recurred and may represent the first reported case of nested variant of urothelial carcinoma (3). Later, Talbert and Young described three bladder carcinomas with bland foci and features resembling von Brunn nests, nephrogenic adenoma, and inverted papilloma (4). In 1992, Murphy and Deana reported four cases of bladder carcinoma with nests of uniform cells that infiltrated the lamina propria. Each case showed aggressive or persistent disease, and the authors designated the entity “nested variant of transitional cell carcinoma” (5). More recently, studies have described additional cases of nested variant of urothelial carcinoma (6-11) as well as other examples of deceptively bland bladder carcinomas (12-14).

Nested variant of urothelial carcinoma is generally seen in older male patients who present with hematuria, although obstructive symptoms have been reported. To date, nested variant of urothelial carcinoma has been reported in only 4 women. At cystoscopy, nested variant of urothelial carcinoma has a widely variable appearance and has been described as a flat tumor, papillary tumor, a submucosal bump, indurated mucosa, or just slightly irregular or hemorrhagic mucosa. Reported tumor size has varied from 1-8 cm. While some early observations led to the conclusion that nested variant of urothelial carcinoma arises mostly at the trigone or ureteral orifices, additional reports have disputed this. We are aware of only two cases of nested variant of urothelial carcinoma in the ureter (5,7) although one other patient had apparent extension of a bladder nested variant of urothelial carcinoma into the ureter and kidney (1).

Histologically, nested variant of urothelial carcinoma is characterized by small, closely packed nests of epithelial cells infiltrating the lamina propria, at times anastomosing to form confluent nests. Accounts of cyst formation within the nests have been variable. Microcystic (7,1) and tubular (5,7) variants have been described, and large dilated cysts may be seen within tumor nests (2). Young has also reported a trabecular variant consisting of an irregular arrangement of anastomosing cords, as well as a variant with “spiked” nests, reminiscent of invasive squamous cell carcinoma (12). The nests may be surrounded by stroma that varies from dense and collagenous to loose and myxoid, or even edematous. A notable eosinophilic stromal infiltrate was observed in one study (12). The overlying urothelium may be normal in appearance. The diagnosis is most easily made by identifying muscle invasion. Nested variant of urothelial carcinoma has been reported in association with conventional urothelial carcinoma, adenocarcinoma, and squamous carcinoma (1). Cytologically, nested variant of urothelial carcinoma may show very uniform, bland cells with only focal moderate atypia. Some have observed significant pleomorphism, particularly within regions of muscle invasion. Nucleoli may be prominent and mitoses may be seen, but are usually not numerous. 

Case 32

Jonathan I. Epstein, M.D., The Johns Hopkins University Hospital, Baltimore, MD, USA
Lymphatic invasion may be seen, although some authors have found it to be uncommon.

Several groups have reported ancillary testing in nested variant of urothelial carcinoma, including special histochemical and immunohistochemical stains, polymerase chain reaction, and ploidy analysis. The tumor cells have been negative for prostate specific antigen (2,5-7), prostatic acid phosphatase (2,5,7), neuron specific enolase (6), chromogranin (6,9), S-100 protein (9), bcl-2 (10), EGF-R (10), desmin (9), vimentin (9), and Thrombomodulin (9). Staining with alcian blue and mucicarmine have generally been reported as negative (5,6). In some instances, amorphous debris within cystic spaces has stained for mucin, although no intracellular mucin vacuoles have been identified. In a recent abstract, Lin et al. presented a particular pattern of p21 and p27 expression in nested variant of urothelial carcinoma: p21 staining was preferentially present in the deepest tumor regions, while p27 was limited to the most superficial areas (10). Lin and coworkers also found 15-30% of nested variant of urothelial carcinoma cells to stain for MIB-1. Overexpression of p53 has been shown in conventional urothelial carcinomas and staining for p53 is more often positive in invasive bladder tumors (15-17). However, overexpression of p53 has not been detected by polymerase chain reaction or immunohistochemistry in nested variant of urothelial carcinoma (2,10). Flow cytometry on a small sample of cases showed nested variant of urothelial carcinoma to be diploid (2). In a study from our institution, immunohistochemical studies for MIB-1, p53, p27, and cytokeratin 20 showed some differences in staining but staining was highly variable and except for the occasional nested carcinoma with very high MIB-1 rates, our studies do not indicate that these tests will be routinely helpful in the differential diagnosis of florid proliferation of von Brunn nests and nested variant of urothelial carcinoma (11).

Despite its innocuous appearance, the clinical course of nested variant of urothelial carcinoma is generally aggressive. In a review of 24 cases, Drew et al. reported 55-60% of the tumors to show aggressive behavior, with mortality rates similar to high grade conventional urothelial carcinoma (7). The same study showed only 3/12 nested variant of urothelial carcinoma patients to be alive without disease at an average of 16 months follow-up. Few relatively indolent cases have been reported, including one patient who underwent radiation treatment and showed no recurrence at 72 months follow-up, one patient with apparently stable disease over a period of 8 years with nested variant of urothelial carcinoma in multiple consecutive biopsies, and one case in which the patient was treated only with TUR and BCG and has shown no recurrence over the ensuing 12 months (1,5,11).

Confusion between benign urothelial proliferations and nested variant of urothelial carcinoma has led to delay in diagnosis and subsequent treatment (4). If muscularis propria is available, these entities may be more easily distinguished, although it has been our experience that even when muscularis propria invasion is present pathologists are hesitant to diagnose nested variant of urothelial cancer due to its bland cytology. In the setting of repeated negative urine cytology and negative transurethral biopsies, some cases have required open biopsy to make the diagnosis.

In contrast to nested variant of urothelial carcinoma, examples of florid von Brunn nests in the bladder generally show larger nests with more regular shapes and regular spacing (11). Cystic formation is more pronounced in florid von Brunn nests, and involves a higher proportion of nest structures. Apical glandular differentiation and eosinophilic secretions are also more common. Atypia is absent, and the lesions have a flat non-infiltrative base. Cases of florid von Brunn nests in the ureter show small nests similar to nested variant of urothelial carcinoma. Distinguishing features include in florid von Brunn nests a flat non-infiltrative base, a lobular or linear array of the nests, and a lack of cytologic atypia. The diagnosis of nested variant of urothelial carcinoma in the ureter or renal pelvis should also be made with caution in the absence of muscularis propria invasion, given the rarity of this variant of carcinoma at these sites and the recognition that florid von Brunn nests mimicking cancer has a predilection for the upper urinary tract.

REFERENCES


---

**Table:** Morphology of florid proliferation of von Brunn nests compared to nested variant of urothelial carcinoma

<table>
<thead>
<tr>
<th>Architecture</th>
<th>Bladder Florid von Brunn Nests</th>
<th>Ureter Florid von Brunn Nests</th>
<th>Nested Variant of Urothelial Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nests</td>
<td>Larger, more uniform nests with even spacing in some cases</td>
<td>Small or mixed size crowded nests with linear or lobular arrangement</td>
<td>Small crowded nests with variable shape and spacing</td>
</tr>
<tr>
<td>Cysts</td>
<td>Large cysts, often involving 70–80% of nests</td>
<td>Small cysts rare, involve less than 10% of nests</td>
<td>Small cysts or clefts involving 20-30% of nests</td>
</tr>
<tr>
<td>Cytology</td>
<td></td>
<td></td>
<td>At least focal moderate atypia noted in most</td>
</tr>
<tr>
<td>Atypia</td>
<td>Significant atypia absent</td>
<td>Significant atypia absent</td>
<td>Dense and collagenous, less often edematous</td>
</tr>
<tr>
<td>Stroma</td>
<td>Edematous, some with delicate concentric layering</td>
<td>Variable, edematous stroma is unusual</td>
<td></td>
</tr>
<tr>
<td>Muscle invasion</td>
<td>Absent</td>
<td>Absent</td>
<td>Often present</td>
</tr>
</tbody>
</table>
Case 33

Volkan Adsay, M.D., Emory University School of Medicine, Atlanta, GA, USA

History: 44 year old male with a history of end-stage renal disease requiring dialysis was found to have “an enhancing Bosniak 4 left lower pole renal mass” while undergoing evaluation for transplant. Nephrectomy was performed. There were 2 close but separate tumors, 2.9 and 2.8 cm in size, respectively. The smaller one had a substantial cystic component. The slides submitted for your review is from this smaller tumor which was well circumscribed with a capsule.

Microscopic findings: The kidney showed signs of end-stage kidney disease with acquired cysts. The larger tumor (which is probably not available in your slides) had the characteristic morphologic features of a papillary renal cell carcinoma of what used to be called basophilic/type-1 variant. In addition to small papillary units lined by cells with round-to-ovoid nuclei and sparse cytoplasm (creating the distinctive basophilic appearance), there were also clusters of macrophages characteristic of this tumor type. In some foci, the papilla formation was more prominent and in these areas the cells acquired foamy/microvesicular cytoplasm, thus raising the differential of the so-called clear cell papillary renal cell carcinoma but did not fully qualify for that diagnosis. The tumor represented in your slides, however, displayed the characteristic morphologic features of “acquired cystic-disease related renal cell carcinoma” including circumscription, capsule formation, association with a cyst, oncocytoid cytology (without oncocytoma growth pattern), and presence of abundant oxalate crystals.

Diagnosis: Acquired cystic-disease related renal cell carcinoma in an end-stage renal disease patient. A separate papillary RCC is also present.

Discussion: Significant developments have taken place in our understanding and classification of renal neoplasia in the past decade. In fact, this appears to be a rapidly growing field with criteria being modified by the day. While morphology has taken the central action in this process, molecular and genetic studies have also played a major role.

End-stage renal disease (ESRD) is quite fascinating because it can give rise to a variety of kidney tumors, sometimes within the same kidney. While any RCC type can occur in ESRD, the acquired cystic disease-related RCC (ACD-RCC) type carcinoma is unique to this setting, almost never encountered in otherwise healthy kidneys. Additionally, almost half of the renal cancers seen in ESRD are of this type. In some studies, it was found that the duration of hemodialysis may be a factor in the type of RCC, and patients with more than 10 years of hemodialysis, ACD-RCC is much more common. In general, the RCCs arising in the background of ESRD, including ACD-RCC, appear to have more favorable clinical, pathologic and outcome features; although some authors claim this too may be dependent on the duration of hemodialysis. Some studies have demonstrated that ESRD kidneys acquire the chromosomal changes typical of papillary renal cell lesions (e.g., trisomies of 7 and 17) in the uninvolved parenchyma, which then serve as the base upon which a variety of RCCs develop.

Patients with ACD-RCC tend to be relatively young and predominately male. These patients often have multifocal and bilateral tumors. ACD-RCCs have many characteristic morphologic features. They tend to be relatively small (mean, 3cm) as seen in this case. They are also often fairly circumscribed, often with a capsule, with the exception of really small ones. Calcifications are common on the capsule, and hemorrhage and necrosis are also frequent. Additionally, two-thirds are cystic and give the impression of arising within a cyst.

Cytology of ACD-RCC is highly distinctive. They have abundant acidophilic granular cytoplasm and large, round-to-oval nuclei with a prominent nucleolus and nuclear contour irregularities. Overall morphology often has a degenerative appearance. Often there are tubular and tubuocystic arrangements of the cells, and the presence of intracellular and intercellular spaces impart a peculiar vacuolated (cribriform) arrangement to the tumor cell clusters. A very helpful clue is the presence (and often the abundance) of oxalate crystals which are seen in about 80% of cases. Other types of calcifications may also be seen in the tumor. Immunohistochemistry is not needed in the diagnosis since the morphology is so distinctive but, for the record, ACD-RCCs are typically positive strongly and diffusely for AMACR and usually negative for CK7.
REFERENCES


Case 34

Ivan Damjanov, M.D., University of Kansas, Kansas City, KS, USA

Tumor signed out and worked up by:
Dr. Rashna Madan, The University of Kansas School of Medicine, Kansas City, Kansas, USA

Clinical History: A 51-year-old woman was found to have a right renal mass measuring on CT approximately 7 cm in largest diameter. Following total nephrectomy, adrenalectomy and the removal of the tumor the patient recovered uneventfully. During the follow up period 3 month after nephrectomy she was found to have a liver mass, which was biopsied and found to have the same microscopic features as the renal tumor.

Pathological Findings: The tumor located in the mid-portion of the right kidney measured 7.9 x 3.2 x 5.0 cm. It was found to be poorly demarcated from the renal parenchyma and did not have a capsule. It was abutting on the hilar fat but did not invade the hilar vessels or the urether. On sectioning it appeared grayish tan, and showed areas of necrosis. Microscopically the tumor was predominantly composed of polygonal epithelioid cells, accounting for approximately 75% of the total tumor volume. Parts of the tumor were composed of fat cells admixed to thick walled arteries. Epithelioid cells had a well developed clear or finely granular eosinophilic cytoplasm. Tumor cell nuclei varied in size from small to large. Most often the nuclei were mostly large and vesicular with prominent nucleoli and irregularly clumped chromatin. Parts of the tumor were composed of larger cells with pleomorphic irregularly shaped nuclei, showing variable hyperchromasia. Some cells were multinucleated and some had abundant eosinophilic cytoplasm resembling ganglion cells. Mitotic counts were 3 per 10 high power fields. No atypical mitoses were seen. Areas of coagulative tumor necrosis were present. There was no lymphovascular invasion. The liver tumor was composed of epithelioid cells.

Immunohistochemical stains showed that the epithelioid cells were strongly positive for vimentin, MART-1/Melan A, CD 117 and negative for S-100 protein, epithelial membrane antigen, pancytokeratin and keratin CAM 5.2, AMACR (P504S),and epithelial membrane antigen. Smooth muscle cells and vessels were positive for smooth muscle cell actin and fat cells were positive for S-100 protein.

Diagnosis: Epithelioid angiomyolipoma with marked atypia

Comment: Renal angiomyolipomas are usually benign tumors composed of smooth muscle cells, fat cells and thick-walled blood vessels. Some of the smooth muscle may have epithelioid morphology, which in itself does not change the basic nosology of this tumor. Some tumors are composed predominantly or almost exclusively of epithelioid cells. Some of these epithelioid angiomyolipomas (EAML) show cytologic atypia and are thus classified as epithelioid angiomyolipomas with atypia (1). Recent studies of a large number of EAML with atypia, such as the study of Brimo et al (2), indicate that EAML can be divided into two clinical-pathological groups: EAML without atypia and EAML with atypia. The latter group comprises tumors with malignant potential evidenced by local recurrence of the tumor after surgery and distant metastases, and even death due to the spread of the tumor.

EAML are composed predominantly or exclusively of epithelioid cells which represent express one of the melanocytic markers such as MART-1 or HMB45, which are useful for diagnosis. Brimo et al (2) list four pathologic features predictive of malignancy of EAML: >70% of atypical epithelioid cells, > 2 mitotic figures per hpf, atypical mitotic figures, and necrosis. Presence of three of these features, as found in our case, predicts malignancy. In the differential diagnosis one must consider renal cell carcinoma, unclassified type; t (6;11) translocation-related renal cell carcinomas; epithelioid smooth muscle tumors; and adrenal carcinomas. Metastases to the kidneys of melanomas, epithelioid GIST or liver cell tumors deserve to be considered as well.

REFERENCES


Case 35

Jonathan I. Epstein, M.D. The Johns Hopkins University Hospital, Baltimore, MD, USA

Clinical History: A black male was born with unbalanced common atrioventricular canal with malposition of the great arteries which was surgically corrected with several operations over multiple years. The patient was subsequently diagnosed with sickle cell trait and asthma. At age 17 the complained of right flank pain, hematuria, and nausea and vomiting. A MRI demonstrated a 6.5 cm. x 5.6 cm. mass in the inferior pole of the right kidney. A radical nephrectomy was performed.

Pathologic Description: The tumor grossly extended through the capsule and into the perinephric fat. The tumor consists of infiltrating cribriform/reticular glands and a minor component of small nests and cords of cells. Tumor cells have an eosinophilic cytoplasm with marked nuclear pleomorphism with prominent nucleoli. Mitotic figures are common and rhabdoid appearing cells may be seen. There is an associated prominent desmoplastic stromal reaction and chronic inflammatory infiltrate. Within the tumor itself, there are numerous admixed neutrophils. The tumor infiltrates extensively into the surrounding kidney with prominent lymphovascular invasion seen. Focal necrosis is present. In areas, the red blood cells have a sickled morphology.

Diagnosis & Follow-up: Medullary carcinoma of the kidney.

Within 6 months of the surgery liver and lung masses were detected by CT scan and the patient underwent chemotherapy. The patient progressed with spread to skull, spine, multiple other bones, and brain. The patient died 1 year following nephrectomy with grossly metastatic disease in the brain, hilar, subcarinal, and paratracheal nodes. Microscopic foci of metastases were in the heart, lung, liver, spleen, esophagus, and bone marrow.

Discussion: Renal medullary carcinoma is a rare tumor arising from the terminal collecting ducts, typically affecting individuals with sickle cell hemoglobinopathies. (1-2) Where ethnicity has been reported the overwhelming majority of patients are African American, with a small number of Hispanic/Brazilian patients. Medullary carcinoma has only rarely (<10 cases) been reported in Caucasians. Virtually all patients have sickle cell trait/disease. The male to female ratio is 1.9:1. Patients present with either gross hematuria, flank, abdominal pain or symptoms associated with distant metastases.

The tumors are poorly circumscribed, often with hemorrhage and necrosis. The morphology seen in the current case is classic for this entity with reticular, microcystic, tubular, trabecular, solid, and adenoid-cystic formations. Suppurative necrosis resembling abscesses within tumor nests and stromal desmoplasia are typical, also seen in the current case. The major differential diagnosis is between collecting duct carcinoma and urothelial carcinoma. Gene expression profiling shows an expression most closely resembling urothelial carcinoma. (3) The most critical feature is differentiating between these entities is whether the tumor is affecting a patient with sickle cell hemoglobinopathies. A further differentiating feature is that urothelial carcinoma may contain pelvic mucosal urothelial carcinoma in situ or an exophytic papillary component. The prognosis is poor with frequent metastasis at presentation. Common metastatic sites are lymph nodes, lung, liver, and adrenal gland.

REFERENCES
Case 36

Ivan Damjanov, M.D., University of Kansas, Kansas City, KS, USA

**Clinical History:** An 80-year-old woman was found to have microscopic hematuria. Subsequent CT examination revealed a left renal mass measuring on CT examination 7 cm in the largest diameter. Following total nephrectomy, adrenalectomy and the removal of the tumor, the patient recovered. Two and half years after surgery the patient is healthy and has no signs of renal neoplasia.

**Pathological Findings:** The tumor located on the superior pole of the left kidney. It measured 7.0 x 6.0 x 6.0 cm. It was encapsulated and sharply demarcated from the kidney and the perinephric fat. On cross section it was uniformly tan yellow. No metastases were found in one hilar lymph node.

Microscopically the tumor was composed of low cuboidal cells forming elongated tubules, which were frequently serpentine or angulated. The tubules were mostly densely compacted with no distinct extracellular material. Focally direct transition of cuboidal into spindle cell stromal cells was noticed. In some areas the stroma appeared loose and contained amorphous acellular material which however did not stain with the alcian blue at pH 2.5 or Hale’s colloidal iron stain. Tubular cells appeared relatively bland, the nuclei were small and vesicular, with occasional nucleoli. There were no mitoses and no necrosis. Papillation of tubular cells without formation of fibrovascular papillae was seen focally and there were some groups of clear and oncocytic cuboidal cells.

Immunohistochemically the tumor cells reacted with antibodies to cytokeratin 7 (CK7), [alpha]-methylacyl-CoA racemase (AMACR), epithelial membrane antigen (EMA) and were negative for CD10. MIB-1 staining showed low proliferative activity in the range of 3-4%. FISH analysis disclosed no gains of chromosomes 7 and 17.

**Diagnosis:** Mucinous tubular and spindle cell carcinoma of the kidney.

**Comment:** Mucinous tubular and spindle cell carcinoma (MTSCC) of the kidney is a relatively rare low grade epithelial tumor of the kidney that usually has a good prognosis. Typical MTSCC are composed of cuboidal cells forming tubules, with areas of transition into spindle cell areas. Stroma usually contains alcian blue positive mucinous material, which is however not always present (1). We classified our case as MTSCC into this mucin poor category.

Immunohistochemical studies of MTSCC show reactivity with antibodies to CK7, AMACR, EMA and are usually not very useful for distinguishing MTSCC from other renal tumors, most notably type I and solid papillary renal cell carcinoma (2). Cytogenetic studies, which typically show a gain of chromosomes 7, 17 and Y in papillary carcinoma were initially thought to provide a clear distinction of papillary carcinomas and MTSCC, but the data of Brandal et al (3) indicate that the cytogenetic distinction is not as clear-cut as originally thought (3). The report of a metastasizing MTSCC shows that some tumors may be malignant even if they do not show sarcomatoid stroma (4). The histogenesis of MTSCC remains controversial, and the term loopoma (implying the origin from the loops of Henle), albeit catchy and simple, remains mostly part of the pathology jargon.

In view of the overlapping features between MTSCC and some papillary renal cell carcinomas, histopathology, immunohistochemistry and even FISH analysis, the diagnosis of MTSCC remains less than certain. To paraphrase a private remark of my Czech friend Dr Ondra Hes regarding the present case and MTSCC in general, the nephropathologists interested in MTSCC can be divided into “purists”, who have their strict diagnostic criteria for MTSCC, and second group comprising those who have been expanding the spectrum of MTSCC. We chose to label the present case as MTSCC even though it contained no interstitial mucin and focally contained clear cells and papillation, and thus joined the “non-purist group”. So far the tumor has not recurred and had a benign clinical course. However that does not exclude the possibility that our case is just a solid papillary carcinoma as reported by Argani et al (5). In this context it is worth mentioning that there are pat-
hologists who believe that MTSCC are just variants of papillary RCC with spindle cell features (6). As long as our urologist colleagues know that there is this controversy among the pathologists I think that we are on safe grounds. In my opinion, only time will show whether MTSCC is a bona fide tumor entity or just a variant of papillary carcinoma.

REFERENCES


Case 37

Franco Fedeli, M.D., Anatomia Patologica, Ospedale S. Andrea, La Spezia, Italy

Clinical History
In April 2009 a 23-year-old woman with a history of Familial Adenomatous Polyposis (FAP) was found to have a fixed mass in the rectum during a clinical examination for a pregnancy. Her mother and sister had an history of colo-rectal cancer. Subsequent diagnostic procedures included a colonoscopy with biopsy, chest and abdominal computed tomography (CT), lower abdomen magnetic resonance imaging (MRI), and rectal endoscopic ultrasonography. CT showed a large inhomogeneous mass with circumferential and transmural extension of the rectum. The mass had a caudo-cranial extension of 14 cm and was inseparable from the cervix and vaginal pouch. Enlarged lymph nodes (up to 2 cm) were identified in the pericolic fat tissue. In addition, pre-contrast CT scan showed a voluminous, apparently capsulated, solid mass with gross calcification in the left adrenal region. The imaging results were consistent with a metastasis from rectal cancer or a primary adrenal neoplasm. Clinical and radiological assessment plus rectal biopsy showing an infiltrating adenocarcinoma led to a diagnosis of stenotic locally advanced rectal adenocarcinoma with pulmonary, hepatic, adrenal, nodal and bone metastases. Because of the high risk of bowel obstruction and to define the origin of the adrenal gland lesion (which was suspected to be a primary adrenal neoplasm on imaging), a left iliac colostomy and a transabdominal laparoscopic adrenalectomy was performed. The patient started systemic chemotherapy for the metastatic rectal cancer. One year after she developed seizures and ataxia and the clinical condition worsened. CT and MRI of the brain revealed a solitary cerebellar metastasis of 2 cm. She underwent whole brain irradiation. One month after the patient died suddenly at home. Autopsy was not performed.

Macroscopic Findings
Gross pathological examination of the surgical specimen of the adrenal revealed a 14-cm lesion with an irregular grey surface and a central cavity containing mucinous material.

Microscopic findings
Histopathological examination showed the presence of a malignant tumor with 2 distinct components. The 20% of the specimen consisted of a metastatic rectal cancer with massive necrosis. The remaining tumor consisted of a pleomorphic proliferation of cells. The neoplastic cells were arranged in solid masses and in fascicular haphazard pattern with fibrosis and myxoid degeneration. Necrotic and hemorrhagic areas were conspicuous. The majority of the cells was polygonal and some were composed of spindle shaped elements with eosinophilic cytoplasm and frequently had a vacuolation of the cytoplasm. In some areas the neoplastic cells were surrounded by osteoid matrix. Nuclei were ovoid to round showing dense clumped chromatin and small eosinophilic nucleoli. Frequent mitotic figure were observed. In some areas giant cells with multiple irregular nuclei were also present. Several clumps of lymphocytes and plasma cells were also seen throughout the tumor. A fibrous capsule with areas of calcification surrounded the tumor and a residue of adrenal gland consisting of compressed medulla and cortex was observed in a section.

Special studies
Immunohistochemical stains showed strong nuclear positivity of the neoplastic cells of the metastatic rectal cancer for CDX-2. The cells of the other major component were diffuse positive for vimentin and in some areas focally positive for keratin, Cam 5.2 and MNF 116, Melan-A, Inhibin, calretinin, CD56, synaptophysin and S-100; the tumor cells were negative for CDX-2, EMA, Hepar-1, chromogranin, actin, desmin, caldesmon and neurofilaments.

Diagnosis
Sarcomatoid carcinoma of adrenal.

Comment
Adrenocortical carcinoma is a rare but highly aggressive malignancy with an estimated annual incidence of between 1.5 to 2 per million population. Women are more commonly affected. There is a bimodal age distribution with cases a peak occurring before age 5 years and a second in the fourth to fifth decades. The prognosis is poor with a significant proportion (21% to 39%) of patient having distant metastasis at the time of presentation and a 5 year overall survival ranges between 38% to 60%. Even after an apparently curative resection, the majority of patients develop early tumor recurrence or distant metastasis. Adrenal sarcomatoid carcinoma represents an extremely rare variant and a poorly dif-
differentiated form of adrenal carcinoma, with only nine detailed reported cases in the literature. The 9 patients ranged from ages 23 to 79 with a mean age of 52, which appears similar to conventional adrenocortical carcinoma and these tumors most often lacked any endocrine dysfunction. Sarcomatoid carcinoma is defined as a tumor that contains carcinomatous and pleomorphic elements with a sarcomatous component that has heterologous areas, such as malignant cartilage, bone, or skeletal muscle. In the case described was found only bone differentiation. The immunohistochemical profile of the reported cases of adrenal sarcomatoid carcinoma is almost consistent with the immunoreactivity described for adrenocortical neoplasms, namely, Melan-A, synaptophysin, calretinin. In this case there was a diffuse positivity for vimentin and focally for keratin. Positive immunoreactivity for S-100 has been reported only in an other case. A generous sampling (at least one section per centimeter of tumor diameter) is necessary to confirm the biphasic pattern and disclose a clear-cut carcinomatous component, allowing to prove the adrenal origin and to rule out other important differential diagnoses in this site such as retroperitoneal sarcoma, leiomyosarcoma, and poorly differentiated metastatic carcinoma. Sarcomatoid renal cell carcinoma or hepatocellular carcinoma with sarcomatoid dedifferentiation both may show morphologically similar appearance with clear and eosinophilic cytoplasm. However, positive staining of CD56, inhibin, Melan-A, synaptophysin, calretinin and negative EMA and Hepar-1 in adrenocortical sarcomatoid carcinoma may be of help in the differential diagnosis. Metastatic melanoma with heterologous elements might enter the differential diagnosis since this will also be positive for Melan-A but negative for calretinin, synaptophysin and inhibin. All cases presented with a dramatically aggressive behavior. Despite aggressive multi-modality therapy, they rapidly developed recurrences or metastases and died in 3 to 12 months (mean, 6 months). 12 cases of adrenocortical carcinoma have been reported in patients with FAP as an extracolonic manifestation. Collision tumors comprising adrenal gland carcinosarcoma and metastatic rectal cancer have been reported only in one case.

REFERENCES


CT image of the left adrenal region. A) Pre-contrast graphic scan shows gross and diffuse calcification of the lesion in the left adrenal region. The left adrenal gland is not recognizable. Dynamic imaging during contrast medium administration (B, arterial phase; C, equilibrium phase) shows that the lesion is hypervascular in the periphery with almost no enhancement in the central zone due to a colliquative necrotic component.

Surgical specimen
Case 38
Franco Fedeli, M.D., Anatomia Patologica, Ospedale S. Andrea, La Spezia, Italy

Clinical History
A 79 year-old-female presented with a left adrenal mass.

Macroscopic findings
There was a 11x9.5x6 cm tumor that weighed 450 g. Cut surface was brownish with diffuse necrotic appearance. The patient died 7 month after the surgical resection for disseminated disease.

Microscopic findings
The microscopic appearance was that of an invasive cellular proliferation obscuring the normal appearance of the adrenal cortex.
Extensive foci of necrosis and hemorrhage were observed. The tumor cells were arranged in solid sheets or nests and frequently lined vascular spaces. The morphology of the tumor cells lining the vascular spaces was epithelioid with round vesicular nuclei with prominent centrally placed eosinophilic nucleoli. The cytoplasm was eosinophilic. Mitotic activity and pleomorphism were readily found. The tumor cells showed rare intracytoplasmic lumina, often contained red blood cells. Inflammatory cells were present in the surrounding connective tissue.
Residual adrenal cortical tissue could be identified at the periphery of the neoplastic proliferation.

Immunohistochemical findings
The tumor cells were intensely positive for CD31, FVIII-Rag, CK Cam5.2, WT1, Vimentin. Cd34 and CK7 were focal and weak positive. Negative for CK 20, P63, 34βE12, S-100 protein, Chromogranin, Synaptophysin, Desmin, HMB–45 and D2-40 and FLI-1

Diagnosis
Epithelioid Angiosarcoma of the Adrenal Gland

Comments
Primary adrenal gland soft tissue sarcomas are rare. They include leiomyosarcoma, malignant peripheral nerve sheath tumor, synovial sarcoma and malignant vascular tumor. To the best of mine knowledge less than thirty-five cases of epithelioid angiosarcomas of the adrenal gland are described in the literature. Nine of these were described by Bruce Wenig in 1994. The disease generally affects more men than women (3:1) with a wide age range from 34 to 85 years, the predominantly patients in the sixties and seventies of their life.
The disease usually starts with pain and presence of abdominal mass, followed by significant weight loss, fever episodes and weakness.
Macroscopically the tumors varied from well-circumscribed to invasive retroperitoneal masses, solid to cystic, with dimensions from 5 to 16 centimeters at its greatest diameter.
A definite diagnosis is based on histomorphology and immunohistochemistry, with the most typical findings including tumor cells arranged in solid sheets or nests, vascular lakes with papillae protruding inside, cellular pleomorphism with increased mitotic activity, vesicular nuclei, prominent nucleoli, eosinophilic cytoplasm and intracytoplasmatic red cells.
Epithelioid variant of angiosarcoma occurs principally in the skin, thyroid and deep soft tissues. For unknowledge reasons all adrenal angiosarcomas share an epithelioid cell appearance.
Immunohistochemical studies play a major role in establishing the vascular nature of this tumor. The neoplastic cells were intensely positive for CD31, FVIII-Rag; Cd34 was focal and weak positive.
This case as well as the cases reported in Wenig’s papers was intensely positive for keratin. On the other hand the same immunoreactivity has not been observed in a study of eighteen cases in the skin as reported by Carlos Bacchi in 2010. The positive staining for CK was achieved with antibodies to low-molecular-weight CK (CAM 5.2) but not with antibodies to high-molecular-weight keratin (34βE12). Thus, the histology and the staining pattern of CK antibodies in epithelioid vascular tumors are similar to that of adenocarcinomas rather than squamous cell carcinomas.
Moreover the identification of epithelial markers, may confuse epithelioid angiosarcoma with adrenal cortical carcinoma.
The absence of S-100 protein and HMB–45 excludes metastatic malignant melanoma.
The etiology of the epithelioid angiosarcoma remains unknown. There are only four cases described in the literature where the malignancy could be linked with prolonged exposure to arsenic containing insecticides and presence of mesenteric fibromatosis. Not any other connection nor correlation with a family history of adrenal neoplasms (suggesting Multiple Endocrine Neoplasia Syndrome), a prior history of abdominal
radiotherapy or long-term androgenic anabolic steroid treatment could be found. Because of the limited experience with this disease, the best treatment of patients with epithelioid angiosarcoma of the adrenal gland is still controversial. A review of the literature revealed that 12 cases described underwent exclusively adrenalectomy. Four of these were alive and well after 1, 6, 11 and 13 years respectively; four patients died due to postoperative complications two with no evidence of disease and another four died with evidence of disease. In this case the patient died 7 month after the surgical resection for disseminated disease.

REFERENCES


Case 39
Michele Bisceglia, M.D.
Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy

Clinical History
A 26 year-old unmarried woman underwent splenectomy because of splenomegaly.

Pathological Findings
The spleen weighed >2400 gr and measured 28 x 22 x 18 cm. Its external surface was lobulated and covered by an intact purple ochre capsule. The cut surface showed a spongy appearance. Myriads of variably sized cysts, ranging in between a few mm to 4 cm (mostly within 1.0 cm in diameter) extensively replaced the splenic pulp. Histologically, the cystic spaces corresponded to thin-walled lymphatic cavities filled with eosinophilic proteinaceous fluid that were lined by bland endothelium. There was only a small residual amount of splenic pulp remaining in the intercavitary compartment. The endothelial lining was immunoreactive for CD34, CD31, FVIII-Rag, and D2-40/podoplanin.

Preliminary Diagnosis
Microcystic lymphangiomatosis of the spleen.

Clinical Antecedents
Upon review of the patient’s medical chart, we discovered that she had undergone excision of a 7 cm suprapubic subcutaneous lymphangioma and a 25 cm left abdominal wall hemangioma at the ages of 4 and 7 years, respectively. At the age of 16 she also underwent removal of a complex venous malformation involving the left femoral-iliac axis, during which surgical reconstruction angioplasty of the common ipsilateral femoral vein was also performed. Finally, at the age of 26 the patient was admitted for a voluminous angiomatous mass, 10 cm in size, involving the right labium majus of vulva, which was managed with repeated trials of sclerotherapy using injections of 95% alcohol directly into the venous lakes of the lesion. At physical examination two more subcutaneous masses were noticed in the medial region of the left thigh, 5 and 10 cm size, respectively, clinically interpreted as lymphangiomas, which were not biopsied. Notably and during the course of this hospitalization, left abdominal distension due to enormous splenomegaly was noticed, though causing only mild subjective discomfort to the patient.

Abdominal ultrasound showed a large, heterogeneous left flank mass with multiple hypoechoic foci, causing extrinsic compression of the left lobe of the liver and left kidney. Computed tomographic scan of the intrabdominal mass demonstrated innumerable low-attenuation cystic cavities that were nonenhancing after administration of intravenous contrast, except for 2 large pools, each enhancing during the early arterial and late venous phases, respectively. Angiomatosis of the spleen was suspected, but other aggressive lesions could not be excluded. Liver, pancreas and kidneys were normal. No retroperitoneal mass lesion was discerned, but the left psoas muscle was reduced in volume. At the time of splenectomy hematological examination revealed mild anemia (hemoglobin 11.1 g/dL), mild thrombocytopenia (105,000/mm3), and a normal white blood cell count. Other routine laboratory tests were within normal limits. The patient underwent surgery after receiving systemic medical antibacterial prophylaxis.

No other person in the patient’s pedigree had a history of cystic disease or vascular malformations.

Final Diagnosis
Splenic lymphangiomatosis associated with abdominopelvic and left lower limb venolymphatic malformations.

Follow-up
The postoperative course was uneventful and the patient was discharged 6 days later. To prevent overwhelming post-splenectomy infection (OPSI), vaccinations against pathogens, that normally require opsonization and phagocytosis by macrophages in the spleen, such as Streptococcus pneumoniae, Neisseria meningitidis, and Hemophilus influenzae, were recommended. Two and a half years after splenectomy the patient is doing well. She also received additional trials of sclerotherapy with significant reduction in volume of the vulval angioma.

Discussion
Benign lymphatic vessel proliferations may involve the spleen either as a discrete, solitary, usually multiculated cystic lesion (lymphangioma) of various sizes, as multicentric intraparenchymal lesions, or as a diffusely infiltrative form involving the entire organ, and replacing the splenic pulp (lymphangiomatosis) (Morgentsern). Three histological types of lymphangioma and lymphangiomatosis of the spleen have been recognized: capillary, cavernous and cystic.
Lymphangiomatosis of the spleen may involve only the spleen (isolated lymphangiomatosis) or be part of multisystemic involvement (generalized or systemic or disseminated or “diffuse” lymphangiomatosis) (Wadsworth, Morgenstern). Occasionally, splenic lymphangiomatosis has been seen also associated with Gorham’s disease (4 cases) and Klippel-Trenaunay-Weber syndrome (3 cases). Lymphangiomatosis of the spleen may occur both in children and adults.

In children it is often diagnosed as part of a multisystemic involvement, affecting viscera, more often lung, liver, pancreas, kidney, and intestine, and soft tissue (mainly neck, axilla, retroperitoneum, and mediastinum), and even bone (Yang, Faul), but may also occur without extra-splenic involvement (Wadsworth). In adults the isolated form of splenic lymphangiomatosis is more often encountered (Barrier, Pistoia, Rao, Solomou, Gomez, Tuttle), with around 15 such cases reported so far (personal review), although occasionally cases of the systemic form involving the spleen have also been diagnosed at this age (O’Sullivan). Involvement of accessory spleens has also been reported in 2 adult patients (Barrier, Qutub). The clinical symptoms are related to the splenic dimensions and include left upper quadrant pain and a sense of fullness with abdominal distension, but may also be asymptomatic (Solomou), as in our case. Complications can supervene, usually hypersplenism, consumptive coagulopathy, bleeding or rupture, and portal hypertension. Intrabdominal (portal or mesenteric) phlebothrombosis may also complicate lymphangiomatosis.

Lymphangioma and lymphangiomatosis in general are considered to be congenital malformations of the lymphatic vessels, due to a not yet elucidated dysfunction of the molecular mechanism governing lymphatic vascular development (Rockson LRB2011, Rockson-ANY-AS2010, Butler). Since lymphatic vessels arise as buds from the primitive cardinal veins and retain stable anatomical as well as functional interconnections with the central venous circulation after development is completed, it is not surprising to find lymphatic malformations associated with other complex vascular lesions, such as hemangiomias or arteriovenous fistulas (Rockson-ANY-AS2010). As a lymphoid organ, the spleen is in the path of these interconnections and as such may be a target of these developmental disturbances.

The lymphatic vessels, though of undoubted significance in clinical practice, perhaps because of their deceptively simple structure and non-vital functions, have attracted relatively little attention in the past and as a consequence of that the classification of lymphatic vessel disorders still remains imprecise (Rockson JACC2008, Rockson ANYAS2008). Our case cannot be classified as isolated splenic lymphangiomatosis because it was associated with other venolymphatic abnormalities, nor it can be considered generalized lymphangiomatosis, because it was restricted in its involvement to spleen and somatic soft tissue only. Limited forms of splenic lymphangiomatosis involving another single organ, mainly liver (Burgess, Schmid, McQuown), thymus (Santoro**), adrenal (Castellon), or the somatic soft tissues (Qutub) have been rarely reported. To the best of our knowledge, this case which apparently does not fit into any recognized hereditary or syndromic pattern (Rockson ANY-AS2008) is likely a singular example in the spectrum of lymphatic and venous vascular diseases, including diffuse lymphangiomatosis of spleen, multiple lymphangiomas of soft tissue of the left thigh and pubis, a complex vascular venous malformation affecting the left femoral-iliac axis, venous angioma of vulva, and finally a minor somatic asymmetry consisting of a left atrophic psoas muscle. Laterality may have clinical and anatomical significance in this case since all these lesions, except for the vulval angioma, were left sided: in fact spleen is the only lateralized organ in humans which embryologically develops on the left side and the left sided venous system, which is longer than the right, is more prone to vascular complications. There is only one other single case on record of left hemilateral hemangiomias involving the upper limb and chest wall in association with lymphangiomatosis of the spleen and this occurred in a patient diagnosed with Klippel-Trenaunay-Weber syndrome (Yamazaki*), which in turn is a non-hereditary pathologic condition not infrequently manifesting associated hemangiomias and lymphangiomias of various sites, mainly of soft tissue.

The preoperative diagnosis may be achieved by ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI) and angiography. By US, lymphangiomatosis appear as general hypoechoic masses with internal septations. CT scan demonstrates thin-walled low-attenuation masses with sharp margins. MRI shows cystic lesions that appear hypointense on T1-weighted images and hyperintense on T2-weighted images. Celiac angiography reveals multiple avascular defects in the parenchymal phase, exhibiting the so called Swiss-cheese appearance (Pistoia, Yamazaki*). The radiological differential diagnosis includes parasitic cysts, nonparasitic cysts, and other benign and malignant splenic vascular proliferations (Komatsuda, Abbott, Urrutia, Pistoia). Additionally, in certain clinical context metastatic disease has also been suspected (Qutub). The definitive diagnosis of lymphangiomatosis is estab-
lished histologically. The eye-catching eosinophilic proteinaceous fluid filling the ectatic spaces lined by flat endothelium are sufficiently characteristic. However, when the differential diagnosis with other types of cysts is uncertain, immunohistochemistry is helpful in assessing the correct diagnosis (Ramani). The main differential consideration for pathologists is represented by hemangiomas and hemangiomatosis, especially in those cases of lymphangioma(tosi)s with blood-tinged content due to intraluminal bleeding. In these occurrences, if it is not possible to morphologically distinguish hemangiomas from lymphangiomas, immunohistochemical stainings for specific lymphatic endothelium markers, such as D2-40/podoplanin, Prox-1, and LYVE-1 can be used to discriminate between these two types of vasomformative lesions, keeping in mind that D2-40/podoplanin can be negative in macrocystic lymphangioma(tosi)s.

Treatment of lymphangiomatosis depends on the extent of the disease. Isolated disease of the spleen with marked splenomegaly, especially in adults, is usually managed by splenectomy. Splenectomy is also indicated in cases of hypersplenism or consumption coagulopathy. Preoperative antibacterial prophylaxis and postoperative immunization is mandatory in these patients to prevent OPSI. Interferon alpha (Dupond) and radiation treatment have been applied when surgery is not feasible, and very recently sildenafil monotherapy has been used in a case (Swetman). In isolated lymphangiomatosis, the prognosis is generally favourable, while in multisystemic form it depends on the extent of involvement and impairment of other visceral organs, with lung involvement generally correlating with an unfavourable prognosis (Faul).

* Case of splenic lymphangiomatosis reported as lymphangioma.
** Case of splenic lymphangiomatosis reported as hemolymphangiomatosis.

REFERENCES


Case 40

David Ben-Dor, M.D., Barzilai Medical Center, Ashkelon, Israel

Clinical presentation: a 59 year old woman underwent resection of an enlarged cervical lymph node. No other clinical information was provided with the specimen.

Pathological description: the lymph node measured 4x2.5 cm and was composed of tan tissue. Histologically there is a diffuse proliferation of mostly small lymphocytes with interspersed large pleomorphic cells with features of Hodgkin- Reed-Sternberg cells (H-RS) of Hodgkin's disease. These latter indeed showed classical immunohistochemical positivity for CD30 and CD15. There is extensive CD20 positivity of the smaller cells. Focally there are scattered eosinophils and plasma cells In an attempt to integrate these findings my initial diagnosis was "classical lymphocyte rich Hodgkin's disease".

Further evaluation: upon receipt of the diagnosis the hematologists performed a bone marrow biopsy which showed numerous small lymphocytes that were CD20 positive. None of the Reed-Sternberg cells found in the lymph node were seen. This puzzled me- if the disease as diagnosed spread to the bone marrow could this involvement be represented by the small lymphoid cells only (representing the Hodgkin milieu) without the large H-RS cells? Since the entity originally diagnosed was somewhat unusual I decided to enlist the help of a foremost hematopathologist, Dr John Chan, Hong Kong, a member of our AMR group.

It was only when I discussed this development with the hematologists that they provided me with significant clinical information heretofore unavailable to me: the patient was diagnosed with rheumatoid arthritis 15 years previously and had been receiving methotrexate during that interval. In addition (as was later explained to me by her rheumatologist, whom I questioned in preparing this case for submission) for the past few years she was also treated with anti-tumor necrosis factor. The lymph node was discovered 6 months prior to the biopsy, at which point the pharmacological treatment was interrupted (despite that the node didn't regress). So besides the complexity of the histopathology itself, the issue of lymphoproliferative disease secondary to the underlying rheumatoid arthritis and/or its treatment presented itself.

Dr Chan confirmed the diagnosis of Hodgkin's disease, replicating the immunohistochemical findings as presented above. In addition he pointed out that amongst the smaller background lymphocytes there were larger immunoblast like cells with prominent nucleoli. In his hands the CD20 positivity was weak, and there was concurrent positivity with CD5 and CD23. Only a few cells were positive for Epstein-Barr virus (using EBER). Thus his diagnosis was well differentiated small lymphocytic cell lymphoma with superimposed Hodgkin's disease (as he put it). As the Hodgkin's cells were in the appropriate milieu of T cells and eosinophilic and plasma cell infiltrates were seen, this fit the criteria for full blown Hodgkin's disease as a distinct component and not just Reed Sternberg like cells appearing in the context of SLL (see below).

On imaging lymph nodes on both sides of the diaphragm were found, making this stage IIIB. It should be pointed out that no peripheral blood lymphocytosis was ever put in evidence at any point in time.

Following receipt of the final diagnosis treatment appropriate for Hodgkin's disease (ABVD) was given. The disease responded to treatment and has not recurred in the two years since diagnosis. The patient is now being treated with rituximab only for rheumatological and not hematological indications; methotrexate and anti – alpha- TNF were not resumed.

Discussion: this complex case needs to be discussed from the point of view of two aspects:

First, are the lymphoproliferative disorders diagnosed in this patient associated with the underlying conditions and medical treatments? Rheumatoid arthritis is a condition of immune dysregulation treated, as this patient was, by immunomodulatory agents. The WHO recognizes four categories of immuno-deficiency associated lymphoproliferative disorders: 1- primary immune disorders (such as Wiskott-Aldrich, ataxia telangiectasia, and others); 2- HIV; 3- post-transplant; and 4- other iatrogenic. Many (but not all) of these conditions are related to Epstein-Barr virus infection. In general the lymphomas that arise in these conditions are of both Hodgkin’s and non-Hodgkin’s type and are histologically identical to those that are seen in patients without a predisposing immune disorder, possibly with the exception of the polymorphic post-transplant lymphoproliferative tumors which seem to be unique to these conditions.

The fourth category of the WHO classification includes
Jonathan Said has studied the development of Hodgkin's disease in the setting of immune deficiency and points out that the issue of whether the immunomodulatory therapy itself further increases this risk is controversial, since these treatments can be considered to be double edged swords: on one hand, the immunosuppression they engender can potentiate tumor development, but on the other, they suppress the inflammation which may drive it. The fact that those patients whose disease is the most active are most likely to receive high doses of medication make it difficult to tease apart the contributions of these factors. The most common lymphomas to develop in this setting are diffuse large B cell lymphoma and Hodgkin disease. There appears not to be any increased susceptibility to develop well differentiated lymphoma in this setting. In some cases the disease can regress following the discontinuation of the medical therapy without the need for chemotherapy, especially where EBV is implicated, which may be seen in up to about 40% of rheumatoid arthritis patients taking methotrexate and/or other immunomodulator agents who develop lymphoma (and apparently uncommon in RA patients not on immunosuppressive treatment), which was not the situation regarding the patient presented here.

A different complexity manifested by this case is the simultaneous appearance of well-differentiated lymphocytic lymphoma and Hodgkin's disease in the same lymph node. This is discussed in the literature in the context of Richter syndrome, which is diagnosed when chronic lymphocytic leukemia/well differentiated small lymphocytic cell lymphoma becomes complicated by a supervening clinically aggressive lymphoma, classically diffuse large cell lymphoma in the great majority of occurrences (and described in the case published by Maurice Richter in 1926 as "reticulum cell sarcoma"). The fact that in this case both conditions were first diagnosed at the same time (and not the aggressive condition developing only after the underlying one became established) doesn't necessarily negate it being considered as Richter but the clinicians resisted this concept since this patient had more a favorable clinical course than that which would be expected in Richter syndrome. Also, the literature on Richter syndrome uses CLL/SLL interchangeably to describe the underlying condition but this begs the question as to whether illness limited to the lymph nodes as in this patient without ever having had documented leukemic manifestations would meet the definitional criteria for Richter syndrome. Since the initial description of this entity, cases were described in which Hodgkin's disease rather than large cell lymphoma constituted the Richter syndrome. According to Han et al (1971- cited by Brecher and Banks), 17 such cases were published until 1967. Additional cases were published in coming years. In this regard I would like to bring to your attention the article published in 1987 by Suster and Rywlin, of a case of Richter syndrome characterized by a component of large pleomorphic cells, some of which were thought to resemble Reed-Sternberg cells, but also showing phagocytic properties. Using the immunohistochemical markers available at the time, these cells stained positively for muramidase and alpha-1-antichymotrypsin, but also for Leu-M1 (now known as CD15). Staining for CD30 (or Ki-1) was not done. These cells were classified as histiocytes and despite their morphological resemblance to Reed-Sternberg cells the possibility of
Hodgkin’s disease though considered was ruled out because the background was not typical for that disease. However this was not the only occasion during that period in which the diagnosis of a histiocytic tumor was favored over that of Hodgkin’s disease in Richter syndrome; in their publication of a few years later describing 8 cases of the Hodgkin’s disease variant of Richter syndrome Brecher and Banks mention an earlier paper by Long and Aisenberg from 1975 which described two cases in which the same problem arose. These latter authors point out that “atypical neoplastic ‘histiocytes’ could be easily mistaken for variants of Reed-Sternberg cells”. Especially given the CD15 positivity already demonstrated, it would be interesting if the case of Suster and Rywlin were to be reconsidered using modern methodologies and criteria in which case it might indeed to turn out to be one of the earlier descriptions of the Hodgkin’s variant of Richter syndrome. In any case Drs. Suster and Rywlin were among the first to point out the possibility of a variant tumor condition arising in the context of Richter syndrome.

As cited by Tsimberidou et al (2006) in a clinical review, Hodgkin transformation of CLL/SLL can exist in two histological forms: in type I the H-RS cells are scattered in a background of CLL cells, while in type II they are found in the “typical polymorphous inflammatory background separate from the CLL cells”. Type I was considered to constitute a “histologic progression of the underlying CLL cells” while type II may represent the coexistence of two separate diseases. Various pathological descriptions of Hodgkin’s variant of Richter syndrome likewise emphasize the milieu in which the Reed-Sternberg cells appear. Unlike cases described in previous publications, such as that of Brecher and Banks, in which histologically typical Hodgkin’s disease appeared in a separate lymph node which didn’t show the presence of SLL, Momose et al described 13 cases in which typical Reed Sternberg cells were surrounded by the small lymphocytes of SLL without the milieu characteristic of Hodgkin’s disease; in 7 cases the Reed-Sternberg cells stained with both CD30 and CD15, one was positive for CD15 only, while 5 were CD20 positive and CD15 negative (some of the latter were also CD30 positive). EBV was found in the Reed-Sternberg cells. Three patients subsequently developed Hodgkin’s disease elsewhere, all of them belonging to the former group. These authors broach the possibility of Hodgkin’s disease being the result of a transformation of B lymphocytes initiated by infection with Epstein-Barr virus.

John Chan along with others (Tsang et al) published a case of CLL in which the lymph nodes showed large cells resembling Reed Sternberg cells which were positive for LCA, B lineage markers, and CD30, but negative for CD15, surrounded by the small lymphoid cells of the underlying condition. These R-S like cells were positive for EBV LMP-1. This was not considered to be evidence of Hodgkin’s disease. Analyzing previously published cases, they delineated three groups of cases in which a connection between CLL and Hodgkin’s can be raised: group A - appearance of typical Hodgkin’s disease (morphologically and immunohistochemically correct R-S cells in the right milieu) together with CLL; group B - morphologically and immunohistochemically correct Reed-Sternberg cells surrounded by the small lymphocytes of CLL without the milieu appropriate for Hodgkin’s disease, and group C- cells with the typical histological features of RS cells but with the immunohistochemical features of activated B cells (CD20+ CD30+ CD15-) and not of true R-S cells. Group B and C were not considered to represent authentic Hodgkin’s transformation of CLL but it was hypothesized that they compose a spectrum which shows Hodgkin’s disease developing in stages starting with group C, where cells with the morphologic features of R-S cells but not the immunohistochemical characteristics first appear; passing through group B in which these cells acquire the immunohistochemical properties of R-S cells, and ending in group A, when all the features of Hodgkin’s disease appear with recruitment of the appropriate milieu. Similarly Shin et al describe cells morphologically characteristic of R-S cells but with the immunohistochemical features of activated B cells in other low grade B cell lymphomas besides CLL/SLL.

In more recent papers the relationship between the Hodgkin’s cells and the background CLL/SLL was studied using molecular techniques applied to the resected lymph nodes. In one such study published by Ohno et al, the Reed-Sternberg cells in two cases were found to be clonally related to the SLL; in both cases the Reed Sternberg cells were CD30+ and CD15+: in one case the R-S cells were surrounded by SLL cells, while in the second they were seen on the polymorphous inflammatory background characteristic of HD. In another study by de Leval et al, the two were not clonally related (in this paper both cases showed areas of classical HD and SLL simultaneously though not necessarily mixed). The R-S cells in this study were LCA-, CD30+, but CD15-; the diagnosis of Hodgkin’s was supported also by the histological findings deemed to be characteristic of that disease. In both these studies microdissected R-S cells were studied with PCR amplification of IgH-CDRIII. A third paper (Kanzler et al) studied 5 gene rearrangements using PCR in 3 cases of CLL which contained
H-RS cells interspersed amongst the small neoplastic lymphocytes without the typical Hodgkin's background. In two cases the H-RS cells were CD15+/CD30+ and in one CD30+/CD15-. In one case the SLL and the H-RS cells were clonally related; in two cases they were not, and it was postulated that the inciting event for proliferation of the latter was EBV infection.

One particular situation in which Hodgkin's transformation of CLL can occur is when the latter is treated with fludarabine. One such patient was seen personally in my department and previously published (Nemets et al) and similar cases were published by others (Fong et al).

REFERENCES

Case 41

Carlos Bacchi, M.D., Botucatu, Brazil

Clinical History:
This is a 21 year-old male with a 3.5 x 3.0 x 2.4 cm nodular lesion of the left kidney. A left nephrectomy was performed.

Pathological findings
The tumor was well demarcated from the renal parenchyma and was formed by sheets of oval to polygonal cells traversed by a prominent, arborizing vascular network. The blood vessels were abundant with thin walls. The tumor cells varied in size, and show clear cytoplasm that sometimes contained delineated fine vacuoles. The tumor cell nuclei showed moderate variation in size, and some were enlarged, pleomorphic, or even bizarre. Mitotic figures were very rare.

Immunohistochemistry Studies:
The tumor (polygonal) cells were diffusely positive for alpha-inhibin, vimentin and S-100 protein with no expression of cytokeratin, gp100, CD31, CD34, chromogranin A and synaptophysin.

Diagnosis: Renal hemangioblastoma mimicking renal cell carcinoma

Comment: This is the description of one case of sporadic extraneural primary hemangioblastoma of the kidney. The final diagnosis is based on the presence of typical morphology and immunophenotype (cytokeratin-, S100+ and alpha-inhibin+). Hemangioblastoma can be easily underrecognized tumor of the kidney, because it mimics several tumor types morphologically and it is usually not considered in the differential diagnosis. A correct diagnosis is important because hemangioblastoma is benign even if there are highly atypical tumor cells, and the patient has to be evaluated for possible von Hippel-Lindau disease. Due to the prominent vasculature and some large neoplastic cells with atypical nuclei, renal hemangioblastoma can be mistaken by renal cell carcinoma and epithelioid angiomylipoma, adrenal cortical carcinoma, and paraganglioma (pheochromocytoma). Immunohistochemically, renal cell carcinoma is positive for cytokeratin (most commonly low-molecular weight), although some cases can be negative for cytokeratin. In addition, in contrast to hemangioblastoma, renal cell carcinoma is usually negative for alpha-inhibin and S-100. Renal hemangioblastoma usually reveals striking morphologic similarities with angiomyolipoma. The tumor cells of epithelioid angiomylipoma often shows homogeneous or somewhat reticulated cytoplasm, sometimes with granular basophilic material, instead of lipid containing vacuolated cytoplasm. Fat cells and thick walled blood vessels with spindly cells related to the wall, if present, provide further support to the diagnosis. By immunohistochemistry angiomylipoma is usually gp100+, melan-A+, and alpha-inhibin-. Another differential diagnosis that should be considered in this case is adrenal cortical carcinoma as this tumor may directly invade or metastasize to the kidney. The tumor cells commonly show lipid cytoplasmic vacuoles, similar to those observed in the hemangioblastoma. On the other hand, cellular atypia and mitotic activity are obvious, and infiltrative growth and vascular invasion are often identifiable. Although adrenal cortical carcinoma is positive for alpha-inhibin, it is also positive for “adrenocortical” markers such as melan-A and calretinin. Paraganglioma/pheochromocytoma often shows a definite nested pattern in at least some foci, and the tumor cells have a granular quality without cytoplasmic vacuoles. In contrast to hemangioblastoma, it is negative for alpha-inhibin, and positive for synaptophysin and chromogranin. Another unique finding of paraganglioma/pheochromocytoma is the presence of S100+ sustentacular cells surrounding the nests of tumor cells. Although renal hemangioblastoma mimics various malignant neoplasms, it can be recognized or suspected on morphologic grounds. According to the description by John Chan (see reference #1) the clues to the diagnosis are: circumscribed borders, paucity of mitotic figures despite prominence of atypical cells, fine vacuoles in some tumor cells indicating presence of intracytoplasmic lipids, and rich capillary network with focal pericytomatos pattern. The diagnosis can be readily confirmed by immunohistochemistry. In this particular case, the patient had no history of von Hippel-Lindau disease.

REFERENCES
2. Fanburg-Smith JC, Gyure KA, Michal M, et al. Retroperitoneal peripheral hemangioblastoma: a case


Case 42

Carlos Bacchi, M.D., Botucatu, Brazil

Clinical History:
This is a 34-year-old male with nodular lesions in cervical, popliteal and abdominal regions. One remarkable finding was the presence of a huge lymphadenopathy (>15 cm) in right the supraclavicular region.

Pathological findings
The histological sections revealed a lymph node almost entirely replaced by highly malignant epithelioid cells with somewhat nodular growth pattern. The cells demonstrated cohesiveness and showed monomorphic appearance with very large immunoblastic-like cytology, i.e., round nuclei and large single central nucleoli. The cytoplasm was basophilic and sometimes a paranuclear hof was seen suggestive of plasmablastic differentiation. Binucleate cells resembling Reed-Sternberg cells were also present. Mitotic figures were numerous.

Immunohistochemistry Studies:
The tumor cells were strongly positive for ALK (cytoplasmic pattern only), CD4 and CD138 with monoclonal expression of kappa light chain immunoglobulin. The following markers were negative: CD45, cytokeratins, S-100 protein, P63 protein, EBV-LMP1, CD30, lambda light chain immunoglobulin, g-100 and melan A.

Diagnosis: Right cervical lymph node: ALK-positive large B cell lymphoma.

Comment: ALK-positive large B-cell lymphoma is a neoplasm of ALK-positive monomorphic large immunoblastic-like B cells, sometimes, like in this case plasmablastic differentiation. Synonymous: large B-cell lymphoma expression the ALK kinase and lacking t(2;5) translocation; ALK-positive plasmablastic B-cell lymphoma. Georges Delson described this special type of B-cell lymphoma in 1997. It is very rare (<1% of diffuse large B-cell lymphoma). It seems to occur more often in male adults and spans all age groups (9-70 years). The tumor mainly involves lymph nodes but may present as a mediastinal or abdominal mass. Involvement of extranodal sites has been reported. Most patients like the cases presented here present with advanced disease (stage III/IV). In this type of lymphoma, the tumor cells have an immunoblastic or plasmablastic appearance, and sinusoidal infiltration is common. Like in this case, they can appear deceptively cohesive and thus may be misinterpreted as carcinoma cells. The frequency of expression of the various immunophenotypic markers is as follows: CD45, 70%; CD20, 3%; CD79, 16%; EMA, 100%; CD30, 6% (weak and focal); kappa or lambda light chain, 90%; CD138, 100%; CD4, 64% and CD57, 40%. By definition, this lymphoma expresses ALK, with staining frequently confined to the cytoplasm, usually in granular pattern. One important piece of information about immunohistochemistry is the expression of cytokeratin (and EMA) that can be expressed in some cases increasing the potential misinterpretation of this type of lymphoma as carcinoma. Upregulation of the ALK gene is mainly due to the presence of t(2;17) (p23;q23), which leads to fusion of the CLTC (clathrin) gene with the ALK gene. Rare cases with t(2;5)(p23;35) (NPM-ALK) translocation and nuclear and cytoplasmic expression have also been reported. ALK-positive large B-cell lymphoma should be distinguished from ALK+ anaplastic large cell lymphoma (of T/null phenotype), plasmablastic lymphoma, and diffuse large B-cell lymphoma with a sinusoidal pattern. The overall survival of high stage III/IV patients was reported to be 11 months. As these tumors are mostly CD20-negative and thus insensitive to rituximab.

REFERENCES


Case 43

Michele Bisceglia, M.D.
Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy

Clinical History
A 47-year-old woman with normal renal function and intractable arterial hypertension (160/110 mm Hg) was investigated by abdominal arteriography, which demonstrated: a small left kidney with tubular stenosis of the corresponding renal artery and an aneurysm proximal to it; beaded fibromuscular dysplasia (FMD) of the right renal artery; and multiple aneurysms of the splenic artery. Aortic arch angiography also revealed fibromuscular dysplasia of both carotid arteries. As the kidney was small and appeared to be non-functioning based on a negative scintigraphic examination and due to the presence of the proximal aneurysm of the renal artery, left nephrectomy was performed in 2006, instead of transluminal renal angioplasty or reconstructive vessel surgery.

Gross Pathological Findings
A small, slightly scarred and firm 52 g (expected 115-155 g), 6 x 4 x 3 cm (expected 11 x 5 x 2.5-3.0 cm) left kidney was fed by a narrow renal artery entering the hilum which showed increased peripelvic fat. After a short course beyond the ligated end (proximal aneurysm not included), a thick walled, renal artery was seen which divided into 8 vessels (usually 4-5 branches) outside the kidney. The arterial diameter measured 2-3 mm. Five tributaries joined to form the renal vein. On the cut surface of the kidney, the cortical arches were 4-6 mm thick and well demarcated. Seven pyramids, some with accentuation of the usual striations, were discerned in the medulla. No architectural parenchymal distortion was noticeable. The pelvis and ureter were small, but commensurate with the size of the kidney.

Histological Findings
The salient, but mostly uncomplicated, microscopic findings were in the renal medulla. Tortuous, cylindrically dilated collecting ducts converged in the papillae. The collecting ducts which converged in the papillae were remarkable for being cylindrically dilated and tortuous. By polarizing microscopy, scattered deposits of calcium complex debris were seen in the lumens of the corrugated ducts and incrusted in the interstitium, engulfed by giant cells. The low columnar collecting duct epithelial lining contained coarsely granular PAS positive pigment in the apical half. There was patchy chronic calyceal and interstitial inflammation associated with mild tubulointerstitial sclerosis. Other than a rare cystically distended Bowman’s space and focal prominence of the juxtglomerular apparatuses, the cortex was unremarkable. The renal artery, the basis for the clinical manifestations, exhibited narrowing of the lumen, thickening and disordered arrangement of the fibromuscular tunica media, and slight prominence of the adventitial elastic tissue. The collecting ducts which converged in the papillae were remarkable for being cylindrically dilated and tortuous. By polarizing microscopy, scattered deposits of calcium complex debris were seen in the lumens of the corrugated ducts and incrusted in the interstitium, engulfed by giant cells.

Diagnosis
Medullary sponge kidney – early stage - associated with multivessel fibromuscular arterial dysplasia.

Follow-up
The patient, about 6 years following nephrectomy, is normotensive (130/70-80 mm Hg), taking beta-adrenergic blocker (atenolol [tenormin] 50 mg/daily) and ACE-inhibitor (altace [ramipril] 2.5 mg/daily) drugs.

Discussion
Cysts in the renal medulla may be seen in various cystic renal conditions affecting children and adults (1). The designation medullary sponge kidney (MSK) is restricted to a congenital disorder characterized by dilatation of the precalyceal collecting ducts of Bellini associated with several functional tubular anomalies (e.g. defective urinary acidification, in form of incomplete distal tubular acidosis, hypocitraturia, hypercalciuria, hyperoxaluria, hyperuricosuria, hypermagnesiuria, and defective urinary concentration) (2). Common synonyms referring to MSK are: Cacchi-Ricci or Lenarduzzi-Cacchi-Ricci disease, papillary duct ectasia, and cystic disease of renal pyramids (3). MSK typically affects all papillae in both kidneys, but may be unilateral or segmental, involving one or more renal papillae. The incidence is between 1 case per 5,000 and 10,000 in the general population. Dilatation of the collecting ducts is present at birth, but the usual clinical manifestations of hematuria, urinary tract infection, and nephrocalcinosis and nephrolithiasis (calcium oxalate, apatite or struvite) are delayed and emerge over a wide age range. Most cases of MSK are sporadic, while a few are inherited in an
autosomal dominant pattern. Generally, MSK becomes symptomatic in adulthood, but pediatric cases are increasingly being recognized (4). Important associations of MSK include overgrowth syndromes such as Beckwith-Wiedemann syndrome and hemihypertrophy (4). Other reported associations are Ehlers-Danlos syndrome, autosomal dominant polycystic kidney disease, Caroli syndrome, hepatic fibrosis, Marfan syndrome, anodontia, growth failure, renal arterial fibromuscular dysplasia (prevalence 10%), congenital small kidney, congenital pyloric stenosis, hyperparathyroidism, multiple endocrine neoplasia type 2A, and Young's (immotile cilia) syndrome (2, 4). Four patients with MSK were found in a large kindred of northern European and Scandinavian ancestry with familial ureteral abnormalities syndrome (5).

The pathogenesis of MSK and the involved genes have not been well elucidated yet, but the RET and GDNF genes seem to be involved and it has been hypothesized that the medullary pyramid cysts result from disruption of the interdependence of the ureteral bud and metanephric blastema due to faulty signaling between the RET tyrosine kinase receptor (located at the tips of the dichotomic outgrowths from the ureteral bud which are of mesonephric Wolffian duct origin) and the glial-cell-line derived neurotrophic factor (GDNF) from the metanephric blastema which is of mesodermal origin, thus explaining the alterations both in the collecting duct and the nephron, which form an anatomical continuum of different embryological origins (2,3,4,6,7,8). Resulting impaired urinary acidification, hypocitraturia, hyperoxaluria, hyperuricosuria, and hypercalciuria, and urinary stasis in the papillary duct ectasias, all are well known risk factors for nephrocalcinosis and stone formation and contribute to precipitation of calcium in the collecting medullary tubules (9,10).

The external examination of the kidney in most cases of MSK is unremarkable, a few are modestly enlarged, still others are shrunken and scarred due to chronic pyelonephritis. Characteristically, the cut surface reveals ectatic ducts and small cysts, sometimes containing calculi, and or dark brown or translucent mucus-like material, confined to the medulla, mostly towards the papillae. The histologic hallmark is the presence of ectatic collecting ducts extending to the draining pores in the papillae and calyces, with or without associated medullary interstitial inflammation and/or fibrosis. Generally, the cortex is unremarkable. The diagnosis is almost always established radiographically. Until recently intravenous pyelography has been the mainstay of diagnosis, revealing radial linear striations in the papillae (“paintbrush” appearance) or documenting an accumulation of contrast media in the ectatic collecting ducts (“bouquets of flowers”). Computed tomographic urography is currently considered to be the most accurate modality for identifying MSK (11). The abdominal plain film may reveal nephrocalcinosis/nephrolithiasis. Conventional computed tomography is less sensitive, but may disclose papillary calcifications and can help to detect other renal abnormalities, such as associated cysts, renal abscess, and papillary necrosis. Ultrasound may reveal hyperechoic medulla, due to calcification. In early cases, the papillae of MSK without calcification may appear bright on ultrasound. A grading scheme based on intravenous urography, correlating with severity of disease, has been recently proposed (12).

Among the phenotypic mimics of MSK is familial juvenile nephronophthisis (NPHP1), caused by a mutation in the nephrocystin gene, located in chromosome 2q13, due to faulty mediator of focal adhesion signaling. This condition follows a progressive clinical course due to symmetrical tubulo/glomerular damage with cysts forming at the corticomedullary interface (1). Potentially confused with MSK are also medullary cystic kidney disease type 1 (MCKD1), an autosomal dominant tubulo-interstitial nephropathy that causes renal salt wasting, and end-stage renal failure in the 4th to 7th decade of life, localized to chromosome 1q21, and medullary cystic kidney disease type 2 (MCKD2), an autosomal dominant tubulointerstitial nephropathy with renal salt wasting, hyperuricemia, gout, and end-stage renal failure in the 5th decade of life, resulting from a mutation in the gene encoding uromodulin in chromosome 16p12.3 (1).

MSK is per se asymptomatic, as was this patient. Nephrocalcinosis and nephrolithiasis are common complications of MSK. Treatment is directed at reducing the effects of defective urinary acidification by restoring urinary citrate excretion and reducing calcium excretion: in this sense therapy with potassium citrate, allopurinol, and thiazide diuretics has been proved to be effective (13,14).

However, this case of MSK was associated with FMD of the corresponding renal artery, an association which - as previously mentioned - has already been recorded (2,4) and was the cause of her arterial hypertension. FMD is one of the most common causes of curable arterial hypertension and accounts for 1-2% of all cases of hypertension and for <10% of cases of renovascular hypertension (15). FMD tends to affect young to middle aged white women, and may involve almost any single artery as well as multiple arterial beds (15,16). Often, bilateral renal, splanchic, extremity, and asymptomatic cerebrovascular involvement is found during angio-
graphic investigation (associated FMD of both carotid arteries was found in our case). While the distinctly layered components of the vascular wall form the basis for classifying FMD into intimal (rare), medial (~ 85%), and adventitial (uncommon) types, combined involvement of more than one tunica is not unusual (15,16,17). An autosomal dominant pattern of inheritance has been proposed for renal FMD (18). Poststenotic aneurysms are common (16), although in our case the aneurysm of the left renal artery was proximal. The presence of multiple aneurysms should raise the possibility of Ehlers-Danlos syndrome type IV (15), which in our case (found with left renal artery and splenic artery aneurysms ) however was clinically excluded.

Our case of renovascular hypertension due to FMD of the left renal artery in association with an ipsilateral small kidney treated with nephrectomy is reminiscent of the first similar case (renal artery FMD with corresponding small kidney in a child) reported by Leadbetter and Burkland in 1938 on the reversal of severe hypertension after nephrectomy (19), that established nephrectomy as an acceptable treatment modality of hypertension four years after the association between renovascular disease and hypertension was proven in the experimental canine model by Goldblatt and collaborators (20).

Percutaneous transluminal angioplasty is the current treatment of choice for FMD, which in our case in its particular context was not considered as appropriate. Auto-renal transplant with ex-vivo vascular reconstruction has also been used in complexly branching cases.

*This case was the subject of a separate publication (21).

REFERENCES

Renal Artery Trichrome

Renal Artery - Elastic

Gross kidney

Kidney low power
Case 44

Manuel Sobrinho-Simões, M.D., PhD Hospital de São João, Oporto, Portugal

Clinical history
33-year old female with a cervical nodule adjacent to the right carotid artery.

Macroscopic description
The surgical specimen was almost totally occupied by a well circumscribed nodule weighting 3g and measuring 2.2x1.6x2.0cm. The cut surface was tan-brown.

Histologic description and immunohistochemistry
The tumour is limited by a fairly well defined capsule and displays a mixture of alveolar and trabecular architecture. In some areas, the alveolar pattern clearly dominates assuming the so-called “zellballen” (cell nests) appearance. The neoplastic cells are round to polyhedric with a central nucleus and relatively abundant pink cytoplasm. There is some nuclear pleomorphism. Mitoses were extremely rare and there were no foci of necrosis. Taking together the clinical and imagiological data with the morphological aspects of the tumour, we think there is no other diagnostic alternative than Paraganglioma of the carotid body. Despite this, and for the sake of completeness, we have confirmed the diagnosis demonstrating the absence of immunoreactivity for cytokeratins and positivity for chromogranin A. The presence of sustentacular cells can also be highlighted by S100 immunoreactivity but this finding has no differential diagnostic relevance (And does not also help for predicting the malignant potential). The same holds true regarding the ki67 index and that is why we do not perform routinely any proliferative marker in cases like the present one.

Diagnosis
Paraganglioma of the carotid body (Familial form with SDHD mutation – see below).

Comments
We have selected this pretty classical and easily diagnosable paraganglioma to address three issues: a) differential diagnosis of cervical paraganglioma whenever occurring as an intrathyroidal tumour; b) diagnosis of malignancy; and c) diagnosis of familial cases.

Intrathyroidal paragangliomas are rare but one has to consider such a diagnosis in thyroid tumours displaying the cytoarchitectural characteristics of the present case, after having ruled out medullary thyroid carcinoma (TTF1 and calcitonin positive), follicular adenoma with a trabecular growth pattern, including the hyalinizing trabecular tumour (TTF1 and thyroglobulin positive) and metastasis from neuroendocrine carcinoma originated in the lung or elsewhere (3). Another diagnostic problem one may encounter is the extremely rare “calcitonin-free primary neuroendocrine carcinoma of the thyroid”. At variance with paraganglioma all the aforementioned tumours are cytokeratin positive. The diagnosis of malignancy can only be made when there is metastasis to sites where paraganglial tissue is not normally found. In other words, besides the demonstration of metastatic deposits, there are no absolute histological or immunohistochemical criteria, nor any “magical” algorithm, for consistently predicting malignant potential in parasympathetic paragangliomas (3,7). The situation is unfortunately similar regarding pheochromocytomas and extraadrenal sympathetic paragangliomas despite the numerous prognostic studies on record (3,7,9).

The last point concerns the sporadic or familial nature of the tumour. In the present case, there was not any familial history of paraganglioma or “related” tumours, and the classical criteria pointing to a hereditary condition (early age of onset and bilaterality) (5,7,8,9) were not present in this unilateral tumour diagnosed in a 33-year-old patient. The available evidence shows that excluding syndromatic forms, it is not possible to use clinical data to predict in most cases of cervical paraganglioma whether the tumour is sporadic or not (5,9). It was shown that up to 30% of sporadic-looking cervical paragangliomas are familial (5,7), mainly as a consequence of germline mutations of succinate dehydrogenase (SDH) genes that act in this setting as tumour-suppressor genes (1,2,9). Taking this into consideration we, like many other groups, systematically search for such mutations in every cervical paraganglioma.

The simplest way to screen for mutations of SDHA, SDHAF2, SDHB, SDHC and SDHD genes is to perform the immunohistochemical detection of SDHA and SDHB. Since SDHA and SDHAF2 mutations are very rare (2,4,9), strong immunoreactivity for SDHA serves usually as a sort of positive control. Whenever present, the immunoreactivity for SDHA, like for any other SDH gene, is very strong due to the abundance of mitochondria in the cytoplasm of paraganglioma cells (6). If there is immunoreactivity for SDHA and no (or very weak) immunoreactivity for SDHB, mutations in SDHB...
or SDHD should be searched for. The immunohistochemical results obtained in the rare cases with mutation of SDHC are not as clear as those obtained in tumours with SDHB or SDHD mutations.

In the present case there was strong immunoreactivity for SDHA and negativity for SDHB. The molecular study disclosed a germline frameshift mutation in SDHD, demonstrating the hereditary nature of the tumour. This finding does not alter the clinico-pathological evaluation of the case but has genetic counseling importance.

REFERENCES


Ovarian mass found in a 68 year old patient.

**Diagnosis:** mixed high grade ovarian carcinoma with different patterns including undifferentiated, microcystic and serous carcinoma.

The purpose of discussing this case is the problem that we are facing today with the terminology in high grade ovarian carcinomas. Some pathologists are proposing to call all these cases high grade serous carcinoma based on two facts, one is that they are frequently associated with high grade serous carcinoma and the other is that they are all positive for p53. I believe that undifferentiated, microcystic and transitional cell carcinomas are different from papillary serous carcinoma. We all agree that they have a different histological appearance and we are uncertain why they have these different histologic appearance. It seems obvious that different morphologic changes have to be due to different genes or different gene expressions. Grouping all these types of tumors together we will never find out why they are different and if there is any difference in their clinical behavior or their response to the treatment from anyone from these different types.

I agree that TCC, undifferentiated, and microcystic carcinomas are usually associated with serous carcinoma; however, the following are some reasons why we should keep these 3 types separate from serous carcinoma:

1. They have different microscopic features, and we do not know why they are different.
2. Some cases are pure, without areas of serous carcinoma.
3. Patients with TCC respond better to chemotherapy than patients with pure serous carcinoma.
4. Undifferentiated carcinoma. – The main issue with this tumor is that it is recognized in different organs, for example, in the endometrium. How are you going to teach a resident that an undifferentiated carcinoma if the ovary is different from an undifferentiated carcinoma in every other organ and that it should be diagnosed as serous carcinoma.
5. Microcystic carcinoma – During a USCAP meeting, I submitted the case of a metastatic microcystic carcinoma in the peritoneum at the Surgical Pathology evening conference. Everyone on the panel called it a metastatic carcinoma with signet-ring cells, most probably from the GI tract. Grouping these cases with serous carcinoma will not improve the diagnostic abilities of surgical pathologists.
6. The different components of a high grade ovarian carcinoma always need to be specified because often only one is present in a metastasis. Pathologists receiving a metastasis showing undifferentiated carcinoma and a report of previous serous carcinoma cannot be certain about the relationship between the two tumors.

I believe these are some reasons to keep these cases separate from those of serous carcinoma, but the main reason is that we do not know why they are different, and, by grouping them with serous carcinoma, we will never know. I propose listing TCC, undifferentiated, and microcystic under other types or under mixed carcinomas, frequently associated with serous carcinomas.

There are some studies that did not confirm our findings of a very response to the chemotherapy regarding transitional cell carcinoma; however, those studies have a very high proportion of transitional cell carcinomas and obviously there is a problem with the selection of the cases.

**REFERENCES**

Case 46

Elvio G. Silva, M.D., MD  Anderson Cancer Center, Houston, TX, USA

Hysterectomy specimen: A 62 year-old patient with an endometrial biopsy diagnosed as adenocarcinoma Grade I.

Diagnosis: deeply invasive minimal deviation adenocarcinoma of the endometrium with abundant MELF.

We have started a multi-institutional study to find predictors of lymph node metastasis and extrauterine disease in low grade endometrial carcinoma. We included 9 different institutions and we evaluated the patient’s age, tumor size, myometrial invasion, FIGO grade, percentage of solid component, percentage of papillary component, presence of MELF (microcystic elongated and fragmented glands), single cell invasion, lymphovascular invasion, involvement of the lower uterine segment and of the cervix. The traditional variables associated with lymph node metastasis for extrauterine disease are the size of the tumor, the depth of invasion and lymphovascular invasion. We have found that one of the most important predictors of lymph node metastasis is the presence of MELF. If we add MELF with single cell invasion it is possible to determine what cases are going to have lymph node metastasis. We have started this study because it is almost impossible for a well formed gland, without fragmentation, to involve lymphovascular spaces. The glands need to be fragmented and single cells needs to invade the stroma in order to get within the lymphatic vessels. We believe that this feature is more important that the depth of invasion because in some cases with only superficial invasion there were several lymphovascular spaces containing tumor in the lumen and the tumor that superficially infiltrated the myometrium has several areas of fragmented glands. We are currently reviewing more cases in this multi-institutional study, and we have now 100 cases with positive lymph nodes and 200 cases with negative lymph nodes to compare. There have been some previous studies evaluating MELF in low grade endometrial tumors; however, since previous studies have very few cases with lymph node metastasis it was difficult to compare MELF with all the current factors which are known to be associated with lymph node metastasis. The presence of MELF in the myometrium is usually easily seen however, there are cases where it is difficult to identify areas of MELF. One of the main problems is that MELF could be a type of invasion very focal in the myometrium, sometimes present in only one or two of ten sections from the myometrium. A few clues to identify areas of MELF is to obtain deeper sections when foci of mixoid, inflammatory, or desmoplastic areas are seen in the myometrium. The elongation of the cells in the invasive component could be of a magnitude that it is difficult to appreciate the cytoplasm of the cells. In these cases, a keratin stain will clearly show the residual, barely seen cytoplasm. Most cases of MELF are associated with lymphovascular invasion. MELF is not seen in high grade endometrial carcinomas or non endometrioid tumors.

REFERENCES


Case 47

Michele Bisceglia, M.D.
Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy

Clinical History
A 33 year-old female was referred to our hospital in April 2007 after she detected an abdominal wall mass on self examination while taking a shower. The patient was the mother of two children, at the time 9 and 3 years of age. Her past medical history was remarkable for having undergone three laparoscopic uterine leiomyomectomies at other institutions six, three, and one year earlier. She took oral contraceptives (estrogen and progestin) from October 2005 to October 2006 and then received transdermal hormonal patch therapy or injections of medroxy-progesterone acetate up to the time of admission for polycystic ovarian syndrome. Ultrasonography and CT scan with and without contrast demonstrated 4 retroperitoneal and intra-abdominal nodular masses measuring between 1 cm and 7 cm. Laparoscopic intervention was scheduled and seven separate subserosal nodules, between 1 cm and 10 cm in size, were resected and submitted to our anatomic pathology division for examination with the suspected diagnosis of metastatic leiomyosarcoma versus metastatic (extra-gastrointestinal) GIST.

Pathological Findings
Grossly, the subserosal nodules were well-circumscribed, discrete, firm, solid, white-grey-tan, and exhibited a fasciculated pattern on cut surface. No necrosis, myxoid, microcystic changes, or hemorrhages were seen. Histologically, these masses were made up of bundles of uniform spindle cells without cytological atypia, necrosis, or atypical mitoses, and had an extremely low mitotic activity. In places some small blood vessels, located in the submesothelial connective tissue adjacent to the excised tumor nodules, showed early leiomyomatous changes in the media.

Immunohistochemistry
Smooth muscle differentiation was determined by positivity for muscle specific actin and alpha-SMA as well as for calponin and H-caldesmon. CD34, CD117, EMA, and S-100 protein all were negative. Strong and diffuse immunopositivity for progesterone receptors (> 80%) as well as focal expression of estrogen receptors (30%) were documented.

Review of the previous pathological specimens
Upon review of the histological sections from the uterine tumors previously removed elsewhere (two different hospitals), we concurred with the original diagnoses of conventional uterine leiomyomas.

Diagnosis
The diagnosis of leiomyomatosis peritonealis disseminata was rendered as opposed to other possible pathogenetic interpretations (see differential diagnosis below). This diagnosis was based on the following data: i. clinical history (i.e. patient's age, hormonal therapy, association with previous excision of uterine leiomyomas); ii. gross and microscopical features suggesting benignity; iii. the finding of early leiomyomatous changes in some vessel walls, as stated above, anticipating the formation of new smooth muscle nodules and attesting to the autochthonous origin of all the nodules from the subcelomic pelvic mesenchyme.

Follow-up
The postoperative course was uneventful, and the patient was discharged with the recommendation to discontinue hormonal treatment. No adjuvant therapy was suggested. The patient has been well and free of disease during the four years following the diagnosis.

Discussion
Leiomyomatosis peritonealis disseminata (LPD) is a rare, hormonally dependent condition affecting females. Synonyms: Disseminate peritoneal leiomyomatosis, diffuse abdominal leiomyomatosis, diffuse peritoneal leiomyomatosis; and – currently abandoned term - disseminated fibrosing deciduosis. LPD was first reported by Wilson and Peale in 1952 and then recognized as a distinct entity by Taubert and collaborators in 1965. So far less than 140 cases have been reported (1,15). Characteristically, it presents with peritoneal nodules in the lower abdomen and pelvis (21,23). Tumor nodules range in quantity from a few to more commonly innumerable, and, though usually small (tumorlets) they can vary in size from a few to even several cm, as in our case. Clinically and radiologically LPD mimics widespread peritoneal metastatic malignancies (peritoneal carcinomatosis, metastatic leiomyosarcoma, metastasis from various other sarcomas, including gastrointestinal stromal tumor).
LPD predominantly occurs in women during the later reproductive years and early perimenopause. During childbearing years LPD is seen more commonly in association either with pregnancy or with oral contraceptive drug use (1,15,20,21). In two cases it has also been reported in association with functioning endocrine ovarian tumors, including the above mentioned first case of Wilson and Peale. In a few cases LPD may occur in women outside of pregnancy, as in our case, and with no association with birth control pills or any other hormonal influence. Few postmenopausal cases are also on record (3,9,13,14,17,6,18,19). Young women in the third decade can be affected, but this is a rare occurrence. Malformations relating to a special type of caudal regression syndrome (Curarino syndrome) were seen in a relatively young patient of 27 years and diverse developmental defects have been observed in a unique female fetus with LPD. LPD occurred also in 2 patients with a previous history of breast cancer who were taking tamoxifen, in both cases coexisting with ovarian Brenner tumor. Occasionally LPD has been diagnosed in adult males, with 3 sporadic cases (8,24,25) so far on record and 3 more in a unique familial cluster (8).

In general, LPD is very often associated with leiomyomas of the uterus, as in our case, and is usually asymptomatic; occasionally it is found at the time of a cesarian section or unexpectedly discovered during abdominal surgery for other reasons. However, abdomino-pelvic pain or palpable masses, dysmenorrhea, menorrhagia, and intestinal obstruction may be the presenting symptoms of this disease. The clinical history in LPD patients may include laparoscopic excision of uterine leiomyomas with morcellation (1,12,22), as in our case. Histologically LPD typically shows classic morphological, immunohistochemical and ultrastructural features consistent with complete or partial smooth muscle differentiation (4,21), in the absence of significant cytological atypia. The mitotic index is usually extremely low (< 1-3 M:10HPF). In a single case LPD exhibited sex cord-like pattern (11). Either estrogen or progesterone receptors or both are uniformly or focally expressed in LPD nodules from premenopausal women. In postmenopausal LPD tumor nodules progesterone receptors are also expressed (4) and luteinizing hormone receptors have also been documented in a case (6), all findings supporting hormonal influence even after menopause. In around 10% of cases LPD is associated with endometriosis: endometriosis can be found distinctly from LPD nodules in different parts of the abdominal peritoneum and other pelvic organs (i.e. ovaries) or can be found even within the same myomatous tumor nodules (adenomyosis type). A case of LPD with endometriosis and another case with adipocytic differentiation have also been documented. Intravenous LPD growth/extension was noticed in one case and a concomitant distinct intravenous leiomyomatosis in another. Notably early development of a leiomyoma in a vessel wall has been recorded too (7), this finding closely recalling the leiomyomatous changes we observed in our case in the walls of some subperitoneal vessels adjacent to frankly developed LPD nodules. LPD is considered to be a proliferative or metaplastic process derived from the subcelomic pluripotential mesenchyme which is part of the hormonally-sensitive secondary mullerian system, with estrogen and progesterone supposedly playing a major etiologic role, a concept which was substantiated by experimental studies in guinea pigs treated with injections of various doses of estradiol acetate. However, the sequential presentation of LPD metachronous to the uterine leiomyomas, which is known to occur, gives support to the interpretation that in some susceptible patients LPD may be secondary to dissemination and implantation of fragments of uterine leiomyomas when morcellated during laparoscopic removal (1,12,22), an occurrence also noticed in other secondary forms of (multiple) peritoneal leiomyomata (12: refs therein). Molecular and cytogenetic analyses have documented that LPD exhibits clonality, consistent either with a metastatic unicentric neoplasm or a clonal multicentric lesion (16). Associated chromosomal aberrations similar to those seen in leiomyomas have also been demonstrated (16). As mentioned, clustering of LPD has been observed in a unique family, where six members (3 males) were diagnosed as definitely affected by LPD and 3 additional members as suspected (8).

Multimodality imaging (US, CT, and MRI) findings all are non-specific, and thus both primary and secondary peritoneal tumors enter the differential diagnosis versus LPD, which in an appropriate context should be included by radiologists among the possibilities, keeping in mind that not all disseminated intraabdominal lesions are malignant (5,10). The diagnosis of this pathologic entity is based on histological assessment only, thus intraoperative biopsy and histological analysis is crucial. The differential diagnosis includes other conditions derived from uterine leiomyomas (i.e., intravenous leiomyomatosis, parasitic leiomyomas, pelvic leiomyomas originating in the same secondary mullerian system, metastasizing benign leiomyoma), conventional leiomyosarcomas of intra-abdominal soft tissue, and metastatic GIST or extragastrointestinal GIST. LPD generally behaves as a benign disease. It is noteworthy that of the 10 cases of sarcomatous transformation mentioned above, the
majority occurred in patients who either did not have uterine leiomyomas or were not exposed to exogenous or increased endogenous estrogens or progestins (2). The standard therapy is medical. LPD is a benign disease, and the tumorous nodules often spontaneously regress following delivery or after discontinuation of the hormonal treatment (20,21). Surgical exploration is indicated for diagnostic purposes, for the removal of voluminous masses, as was the case with our patient, or for treatment of supervening intestinal complications or other associated tumors. Whenever possible surgery should be conservative, and surgical extirpation of all nodules is not warranted. Several cases, especially in the past decades, have been erroneously treated aggressively with radical surgery, and other cases were repeatedly (up to 6 times) operated on for “recurrences”, when the causative factors were not eliminated. Recurrence has been reported even after radical surgery. Discontinuation of exogenous hormonal treatment is necessary. Antagonists of GnRH and aromatase inhibitors are indicated. Bilateral oophorectomy is an alternative choice to eliminate endogenous hormonal stimulation in case of failure of the other procedures. Chemotherapy is used only in cases with malignant transformation. Finally, fertility in LPD patients is a controversial issue. Though pregnancy is discouraged in these patients because hormonal stimulation risks provoking LPD progression or “recurrence”, this advice should be individually tailored. In some cases in which maternity is strongly desired pregnancy should be closely monitored and assisted reproductive technology pregnancy can also be considered, but this is still being debated.

REFERENCES


Case 48

Ira Bleiweiss, M.D., The Mount Sinai Medical Center, New York, N.Y., USA

Brief clinical history: A 73 year old woman presented with a 7x8 cm mass in the right breast with skin ulceration.

Short summary of case: A 73 year old woman presented to another institution with a palpable mass in the right breast, upper outer quadrant with overlying skin ulceration and axillary adenopathy. Core biopsy was performed and the breast lesion was diagnosed as invasive well differentiated duct carcinoma. The patient underwent a 6 month course of neoadjuvant chemotherapy with little clinical response in the breast or axilla. She breast or axilla. After she refused mastectomy, a right quadrantectomy and axillary dissection was performed (intraoperatively there were multiple enlarged lymph nodes up to level III). The slides are from the quadrantectomy specimen which contained a very well circumscribed 7x6x5 cm tumor with solid tan and cystic hemorrhagic (see gross photographs). Microscopically it is made up of a proliferation of two types of cells in a glandular pattern: an inner layer of epithelial cells and an outer layer of enlarged myoepithelial cells with clear cytoplasm. In some areas the myoepithelial cells predominate, growing in sheets and showing moderate nuclear atypia, occasional mitoses, and focal infiltration of surrounding breast. Many areas of the tumor are associated with intraductal papilloma and collagenous spherolysis. Immunohistochemical stains for cytokeratins and myoepithelial markers demonstrated the two cell types. Both components were negative for estrogen receptor, progesterone receptor, and Her-2-neu.

Diagnosis: Malignant adenomyoepithelioma, with the myoepithelial component being malignant.

Comment: A number of points are noteworthy. First, while the lesion measures 7 cm, clearly the invasive tumor was not this large. Second, the core biopsy diagnosis was not really correct and demonstrates the importance of radiologic/pathologic correlation in breast core biopsy interpretation. In other words, invasive well differentiated duct carcinoma should not be diagnosed in the face of a well circumscribed tumor. Knowledge that a core derives from such a mass should cause the pathologist to rethink the initial diagnosis. We reviewed the core biopsy from the other institution, and it looked identical to the excised lesion. The patient probably derived no benefit from neoadjuvant chemotherapy. The skin was not infiltrated by tumor, and the ulceration was probably secondary to pressure effects. All six lymph nodes removed were enlarged, reactive, and negative for tumor.

SELECTED REFERENCES

Case 49

Ira Bleiweiss, M.D., The Mount Sinai Medical Center, New York, N.Y., USA

Brief clinical history: A 43 year old woman presented with a 1.2 cm left breast mass.

Short summary of case: A 43 year old woman presented to another institution dimpling of the left breast but no underlying palpable mass. Mammography and sonography demonstrated a partial ovoid and lobulated, partially spiculated solid mass measuring 1.2 cm. Core biopsy was diagnosed as invasive moderately differentiated duct carcinoma. Sonography of the axilla demonstrated two abnormal lymph nodes, core biopsies of which showed metastatic carcinoma partially replacing one and involving extranodal adipose tissue. The patient opted for bilateral mastectomy with the left breast revealing a 2.3 cm invasive tumor with one additional axillary node focally positive. The tumor was positive for estrogen and progesterone receptors and negative for Her-2-neu.

The slides from the mastectomy show an invasive micropapillary and mucinous carcinoma, poorly differentiated by standard grading criteria, with focal lymphatic invasion.

Diagnosis: Infiltrating micropapillary and mucinous carcinoma

Comment: In my experience, invasive micropapillary carcinoma of the breast is still an under-diagnosed tumor, since it is under-recognized in community practice. It is not unusual to find it combined with mucinous carcinoma, and, in such cases, it may show combined radiologic features as well (partially ovoid, partially speculated). The micropapillary component’s most diagnostic feature is the presence of nests of tumor surrounded by retraction spaces. Lymphatic invasion is quite common, and in fact these tumors have been termed “lymphotropic” because of their very high rate of axillary metastasis even when small. They are frequently positive for hormone receptors and more often positive for Her-2-neu (about 60%) than ordinary invasive duct carcinomas. Although they will always be moderately or poorly differentiated, standard grading does not appear to matter, since the pattern predominates in terms of predicting lymph node metastasis. While they frequently present with higher stage (positive nodes despite small invasive tumor size), prognosis seems to be the same as ordinary breast carcinoma, stage for stage. A diagnosis of pure mucinous carcinoma should be reserved for a uniformly well circumscribed tumor whose cells have uniformly low grade nuclei.

SELECTED REFERENCES

Case 50

David Ben-Dor, M.D., Barzilai Medical Center, Ashkelon, Israel

Clinical history: a 30 year old woman underwent surgery for removal of a breast mass which was clinically considered benign. The mass was originally discovered 1 yr previously, and imaging showed a well defined lesion which gave measurements of 30 and 33 mm. A biopsy attempt yielded a few breast acini and stromal cells; tumor was not diagnosed on the basis of that material.

Gross pathology: two fragments described as “breast tissue” were submitted, the larger measuring 6x2.7x1.5 cm and the smaller 2.8x1.7x1.5 cm. Apparently a defined mass was not identified.

Histology: microscopic examination shows a hypercellular atypical stromal proliferation with areas of adipose differentiation. The fat tissue shows variability in the size of the fat cells with hyperchromatic nuclei, and lipoblasts were identified. Amidst this stroma there are distorted spaces lined by hyperplastic epithelial cells into which tongues of stroma protrude. Included in the lesion also are breast lobules which are of regular appearance with the exception of their being infiltrated by pleomorphic stromal cells, some multinucleated. In places the acini appear to be numerous resembling a tubular adenoma. In any case all these epithelial structures are benign. Where seen the lesion appears to be well circumscribed with regard to the extra-lesional breast tissue but in places approached the inked specimen surface.

Diagnosis: malignant phyllodes tumor with liposarcomatous differentiation.

Discussion: Biphasic tumors are characterized by a proliferation of stroma and epithelium. The most common type is the benign fibroadenoma, with which all pathologists, including neophytes, are familiar. In this lesion both elements can be said to proliferate in a proportional fashion, though the quality of the proliferation can vary among tumors, with some examples, notably juvenile fibroadenoma, showing a greater degree of stromal cellularity than the usual adult variant. Phyllodes tumors are characterized by a more exuberant stromal proliferation than is seen in fibroadenoma. Macroscopically these are usually in the vicinity of 4-6 cm and appear as often well circumscribed nodules which can show clefts or papillary processes. On histology these tumors are typified by a greater degree of cellularity than usual fibroadenomas (though the boundary between a cellular or juvenile fibroadenoma and a low grade phyllodes tumor isn’t always unambiguous or clear cut). Along with the stromal proliferation itself another hallmark of this tumor is the presence of cleft like or dilated epithelial spaces in which the lining epithelium is pushed into the lumen by the stroma, producing the classical “leaf-like” structures. In this case the presence of the latter define the lesion as liposarcoma arising in a phyllodes tumor rather than just liposarcoma. In fact when considering the possibility of a breast sarcoma the pathologist is advised to perform a diligent search for evidence of an epithelial component inherent to the lesion, which may be focal, in which case the tumor would be a malignant phyllodes tumor. The stromal hypercellularity of phyllodes tumors can be present to variable extents in different portions of the lesion and is often accentuated surrounding the epithelium. The epithelium can be hyperplastic and the stroma can show various types of metaplastic differentiation (adipose as in this case, bone, cartilage, muscle) which can be either benign or malignant. According to the recent WHO blue book (2003) phyllodes tumors can be stratified into benign→borderline→malignant types based on evaluation of the following parameters: stromal hypercellularity (on a scale of modest (benign)→marked (malignant)), cellular pleomorphism (little → marked), mitoses (few if any→numerous (more than 10%), margins (well circumscribed→invasive), stromal pattern (uniform→marked stromal
overgrowth (as defined by a low power field- 4x10 magnification- showing only stroma to the exclusion of epithelium), heterologous differentiation (rare → uncommon). Using this methodology 60% of phyllodes tumors are benign, 20% borderline, and 20% malignant. Another approach is espoused in the new AFIP fascicle: using two categories of low grade (replacing benign), and high grade or malignant tumors. Low grade tumors which have a potential for local recurrence but are unlikely to metastasize are defined as having a pushing margin, low to moderate (1+- 2+) atypia, and fewer than 3 m.f./10 h.p.f.

The high grade tumors which have a potential for distant metastasis will have invasive or pushing margins, moderate to severe (2+- 3+) atypia, 3 or more m.f./10 h.p.f., and sarcomatous overgrowth (defined as was stromal overgrowth – see above).

It is pointed out that there are no absolute criteria which can accurately predict the behavior of any specific tumor, and statistical analysis of tumor behavior in relationship to pathological parameters varies among studies performed. It is accepted by most authors that one aspect that correlates with recurrence is the adequacy of excision. A general overall estimate of recurrence frequency is about 30%, which can vary with grade. Figures of 15-25% are cited for metastatic frequency. An overall survival rate of 90% is cited, reduced in high grade cases. Lymph node metastases are rare. In order to ensure adequate resection margins it would be helpful to the extent possible to have an accurate preoperative diagnosis of phyllodes tumor. That this is not always possible is attested to by a false negative needle biopsy rate of 25-30%. This is understandable due to the heterogeneity of the histological structure of phyllodes tumors. Several studies have been performed in order to elucidate which histological factors would be most reliable in differentiating phyllodes tumors from fibroadenomas. In one such recent study (Lee et al), the following factors are suggested as being most helpful: stromal cellularity increased in at least 50% of the tissue; stromal overgrowth (here defined as 10x10 magnification); the presence of tissue fragments composed of stroma with epithelium at one or both ends; and adipose tissue within the lesion.

Endothelin 1 is a factor which is released by epithelial cells and acts on receptors found in stromal tissues. It is increased in various malignancies including breast tumors and acts by inducing mitoses and promotes angiogenesis by induction of vascular endothelial growth factor. The activity of this factor in phyllodes tumors was studied by Esposito et al, who found it to be present to a greater degree in the epithelial component of tumors that were graded as benign in comparison with borderline or malignant ones. However diffuse cytoplasmic positivity was found in stromal cells of the latter which may be interpreted as up-regulation of the receptors. This might signify the acquisition by the stroma of the ability to proliferate autonomously. In a similar vein Tan et al noted that histological epithelial hyperplasia was inversely correlated with tumor grade. To the contrary Tse et al showed that the expression of this factor was positively correlated with grade in both the epithelial and stromal components. For these authors this finding demonstrates the role of the epithelium in promoting stromal growth in these tumors.

**Note:** this case was originally published - Uriev et al: Malignant phyllodes tumor with heterologous liposarcomatous differentiation and tubular adenoma like epithelial component. Int. J. Med. Sci. 3: 130–134, 2006.

**REFERENCES**

- Lee A.H.S. et al, Histological features useful in the distinction of phyllodes tumour and fibroadenoma on needle core biopsy of the breast. Histopathology 51: 336–344

Case 51

Carlos Bacchi, M.D., Botucatu, Brazil

Clinical History: This is a 47-year-old woman with ill-defined painless masses and nodules in both breasts. Patient underwent core biopsies and lumpectomies with diagnoses of MALT lymphoma, lobulitis and pseudotumor of the breast. A bilateral adenectomy with skin and nipple sparing was performed. Mammography was not helpful due to a very dense breast parenchyma.

Pathological findings
The histological sections of both breasts revealed similar findings, which was basically characterized by the presence of dense mass-forming lymphoplasmacytic infiltrate accompanied by prominent stromal sclerosis and loss of breast lobules. The lymphoid infiltrate was comprised of small lymphocytes with many plasma cells, forming diffuse sheets of nodular aggregates with interspersed reactive lymphoid follicles with germinal centers. Stromal sclerosis was conspicuous. One finding that was remarkable in this case was the presence of multiple foci of phlebitis sometimes with obstruction of the lumen.

Immunohistochemistry Studies:
Mixed population of non-neoplastic B and T cells with no light chain restriction formed the lymphoid infiltrate. BCL2 was negative in the germinal center cells. There were about 130 IgG4+ plasma cells per HPF with 81% ration IgG/IgG4.

Diagnosis: Right and left breasts: bilateral IgG4-related sclerosing mastitis.

Comment:
This case represents an example of IgG4-related sclerosing mastitis with bilateral presentation. Morphologically, IgG4-related sclerosing mastitis is characterized by feature dense lymphoplasmacytic infiltrates with lymphoid follicle formation, extensive sclerosis, and atrophy of mammary lobules. Phlebitis is occasionally found. On immunostaining, large numbers of IgG4+ plasma cells are present. In previous small biopsies of this patient, the diagnosis of low-grade B-cell lymphomas was considered. In the histological sections of the removed breasts we were unable to find any definitive findings of lymphoma including the presence of lymphoepithelial lesions. In the breast, IgG4-related sclerosing was described by Cheuk et al (reference #1) who proposed the term IgG4-related sclerosing mastitis. According to these authors, the reasons that this lesion of the breast belongs to the syndrome of IgG4-related sclerosing disease are the following findings that were described in these author's series of 4 cases: (1) identical morphologic features to other organs involved by IgG4-related sclerosing disease, even with occasional occurrence of phlebitis; (2) large numbers of IgG4+ plasma cells and increased proportion of IgG4+/IgG+ cells; (3) elevated serum IgG4 in 1 tested patient, and elevated serum Ig in another; (4) frequent presence of circulating autoantibodies, and (5) diffuse lymphadenopathy (with histologic features of IgG4-related) and eyelid swelling in 1 patient each, which are also well-known sites of involvement by IgG4-related sclerosing disease. Besides lymphoma, the others entities that are in the differential diagnosis are: lymphocytic or diabetic mastopathy (here fibrosis predominates over the lymphoplasmacytic infiltrate), idiopathic granulomatous mastitis (it features lobulocentric granulomas), plasma cell mastitis (usually characterized by dilated ducts, inspissated secretions and foamy histiocytes besides the plasma cells) and lupus mastitis (usually inflammation of the skin with extension to the breast).

IgG4-related sclerosing mastitis represents another member of the family of IgG4-related sclerosing diseases with usually good outcome when treated with corticosteroid. A subgroup of the patients has localized disease but other show systemic involvement. The patient described here has no systemic disease and she is doing well after surgery.

REFERENCES


Fig. 1 Left breast

Fig. 2 Right breast
Case 52

Janez Lamovec, M.D., The Institute of Oncology, Ljubljana, Slovenia

**History:** A 38-year-old woman presented with a tumor in the upper outer quadrant of the left breast of a few months duration. Carcinoma was diagnosed by FNAB. The quadrantectomy with a biopsy of three sentinel lymph nodes was performed.

**Pathologic findings:** In the excised quadrant a 3 x 2 cm well circumscribed tumor of pale gray-brown color and firm consistency was found. Excision margins were free of tumor. Histologically, the larger parts of the tumor are composed of solid masses and nests of dense small round or more irregular glandular structures with generally moderate, focally more abundant stroma; the latter appears focally myxoid. The glandular nests merge with solid masses of tumor cells in which the glandular outlines are lost. Comedo type necrosis is seen in one or two cell nests. In some foci, the glands are not so dense and are somewhat reminiscent of microglandular adenosis (MGA) or atypical MGA (AMGA). In rare foci, tumor cells form ducts and/or cribriform structures. Single cell pattern of growth is also present focally; some cells have signet-ring cell appearance. Tumor is microscopically less circumscribed as judged grossly; neoplastic tissue infiltrates surrounding adipose tissue or form islands dissociated from the dominant tumor mass. Glands are mostly solid with barely discernable lumina, their cells as well as cells in solid areas have no clear boundaries. They show moderate amount of amphotophilic or eosinophilic cytoplasm that is in many foci vacuolated; glands with clear cells are also seen. Focally, the cyttoplasm of occasional glands and duct structures possess small to large deeply eosinophilic granules/globules, similar to those in intestinal Paneth cells. Larger globules are also seen in some duct lumina, in places such globules form confluent intraluminal masses. Nuclei of neoplastic cells are irregular, roundish or oval, many with thick nuclear membrane and prominent nucleoli. Mitoses, also atypical, are numerous (up to 20 mitoses/high power field). In some areas, many apoptotic bodies are present. PAS staining demonstrates many small positive granules in the cytoplasm that disappears following diastase treatment, while large granules and globules remain intensively stained. Alcian blue staining shows accumulation of acidic mucin in some lumina of ducts and also in relatively numerous individual cells of more solid nests; the latter are signet-ring cell type. Matrix around such foci is also imbibed with mucin. Small glands composing the bulk of the tumor show no mucin substances in their cytoplasm.

Immunohistochemically, tumor cells were strongly and diffusely positive for S-100 protein, lysozyme, E-cadherin and CK-7, CK8 and CK18; most cell were also positive for alpha-1-chymotrypsin and EMA; tumor cells were mitochondrion-rich. The cells were negative for CK-5, CK14, CK20, GCDFP-15, CD68, lactalbumin, chromogranin and synaptophysin and also for salivary type amylase. The reaction for smooth muscle actin and p63 failed to reveal any myoepithelial cell investment around glands and collagen IV staining did not demonstrate basal membrane material encircling them except around a few dissociated glands. Tumor was also triple negative. In one of the three sentinel lymph nodes isolated tumor cells were found. Ultrastructurally, in some cells electron-dense secretory granules were seen that were consistent with zymogen type granules.

**Diagnosis:** Infiltrating carcinoma with acinic cell carcinoma-like features and mucocellular component

**Follow up:** The patient was postoperatively treated with chemotherapy and locally irradiated. She shows no evidence of disease three and a half years after surgery.

**Discussion:** Acinic cell carcinoma (ACC) is a rare variant of infiltrating breast carcinoma histologically characterized by small acinic cell-type neoplastic glands often merging with solid or microcystic areas. The cells composing the glands or solid areas are quite large with relatively abundant eosinophilic, granular or clear cytoplasm. Some other patterns of growth such as single cell invasion similar to infiltrating lobular carcinoma may also be present as a minor component. In several foci, Paneth cell-like eosinophilic cytoplasmic granules or globules are seen in some glands. Characteristic immunohistochemical features include positive cytoplasmic reaction for salivary type amylase, alpha-1-chymotrypsin, lysozyme, S-100 protein and EMA. GCDFP-15 may be focally positive, estrogen and progesterone receptors are negative. Histologic and immunohistochemical features of the tumor are in many ways similar to those in acinic cell carcinoma of salivary glands (1, 2).
Since only a few cases of ACC were reported, the significance of acinic cell differentiation in the breast carcinoma is not clear, particularly in regard to prognosis. ACC may metastasize to axillary lymph nodes; a single report of distant metastasis 8 years after breast surgery is also on record (3).

Our case shows many features of ACC with two important differences: tumor cell were repeatedly amylase negative and in several foci alcian blue positive mucin secretion, mainly in dissociated signet-ring type cells was present. All bona fide reported cases of ACC showed positive reaction for amylase and no mucinous component was mentioned as a component of this particular type of tumor.

The similarity of AMGA and carcinoma arising in MGA (MGACA) with ACC may be in some cases quite striking and the relationship of the two conditions was suggested (4, 5). It was even suspected that some reported cases of ACC represented variants of carcinoma arising in MGA (6). It logically follows, that MGA, AMGA and carcinoma arising in MGA (MGACA) are the main differential diagnostic options in ACC. EMA negative staining as demonstrated in MGA and its positivity in ACC is not so helpful in differentiation of the latter lesion from AMGA and MGACA since the latter two may be EMA positive.

Paneth type cells described in ACC of the breast also do not appear to be as characteristic feature of this type of cancer as thought. They were observed in areas of typical ductal carcinoma and also in benign breast epithelium and they probably represent a nonspecific morphologic feature in the breast (7).

Except for the main differential diagnostic possibilities mentioned above, some other type of carcinoma may also be considered such as apocrine carcinoma, oncocytoma and neuroendocrine carcinoma. The majority of these lesions are relatively easily differentiated from ACC even on H&E, in less clear cases immunohistochemical reactions may be helpful.

Our case is in most features consistent with the diagnosis of ACC; although because of already mentioned characteristics it is not quite typical. In any case, it further expands the morphological spectrum of breast carcinomas of salivary type.

REFERENCES

A 44-year-old patient with a diagnosis by PAP and biopsy of the endocervical adenocarcinoma.

**Diagnosis:** endocervical adenocarcinoma with pattern A of invasion.

During a multi-institutional study we have developed a new method of evaluating the pattern of growth of endocervical adenocarcinoma. The treatment of endocervical adenocarcinoma (EAC) is largely based on tumor depth of invasion (DOI); however, this crucial prognostic parameter is pathologically difficult to measure accurately or consistently. Greater than 95% of lymph nodes (LN) resected in EAC are negative, yet such aggressive LN dissections cause significant morbidity without obvious clinical benefit to patients, many of whom are at a young age. Therefore, we investigated other pathologic parameters that may better identify patients at risk of developing LN metastases.

Cases diagnosed and treated as EAC from 12 institutions were reviewed. Clinical information and pathologic features were assessed, including: DOI, tumor size, LVI and pattern of tumor invasion using a newly devised system, defined as follows:
- Pattern A = well-demarcated glands, regardless of DOI
- Pattern B = early stromal invasion arising from well-demarcated glands
- Pattern C = diffuse, destructive invasion

360 cases were identified (stage IA1 to IVB). Ages ranged from 20 to 83 years (mean 44.9) and DOI ranged from 0.5 to >40mm (mean 7.7mm). LVI was present in 145 cases.

Table I shows outcome data comparing the standard method of tumor evaluation (DOI) vs. the newly proposed pattern-based method:

The conclusions of our studies are:
1. Classifying EAC by histologic pattern would identify 22% of patients who do not need lymph node resection (pattern A, all stage I disease).
2. Patients with pattern B rarely have lymph node metastases and 98% have stage I disease.
3. Aggressive treatment should be offered to patients with pattern C since 24% of these patients have lymph node metastases and all patients with high stage disease have pattern C tumors.
4. This pattern-based classification of adenocarcinoma is simple, reproducible and clinically significant.

**REFERENCES**

Case 54

Masaharu Fukunaga, M.D.
Jikei University School of Medicine, The Daisan Hospital, Komae, Japan

Case: a 37-year-old female (gravida 2, para 2) with a right ovarian tumor

Clinical history: the patient presented with lower abdominal pain. Physical examination, CT and EMR indicated a right ovarian tumor. Abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and pelvic lymph node dissection were performed. Serum calcium levels were within normal range. The patient died of the spread disease 4 months after surgery.

Macroscopic findings: The right ovary revealed a 15x9x8cm, yellowish white, soft solid tumor with prominent hemorrhage and necrosis. The left ovary showed 1cm solid tumor on the surface and there were numerous white nodules in the omentum.

Immunostaining: Some tumor cells arranged in follicles or nests showed CAM5.2, CK7 and EMA immunostaining. The tumor was uniformly negative for inhibin-alpha, calretinin, CD99, and LCA.

Pathologic diagnosis: small cell carcinoma of the ovary, hypercalcemic type.

Discussion: The tumor was composed of a proliferation of small to medium-sized round cell in a solid sheet or follicular arrangement. Follicles contained PAS-positive proteinaceous material. The tumor cells had hyperchromatic round or oval nuclei and moderate amount of cytoplasm. Atypia was moderate. The stroma was fibrous but inconspicuous. Tumor necrosis and hemor-rhage was prominent. The mitotic activity was 20/10 HPF. The small nodules in the left ovary and omentum revealed the same histology of the right ovarian tumor.

The immunohistochemical studies confirmed an epithelial nature. Electron microscopical examination failed to reveal specific features to identify the cell type of the tumor. The tumor cells had desmosomes, moderate amounts of mitochondria and dilated rough endoplasmic reticulum. No neurosecretory granules were identified.

The patients with small cell carcinoma, hypercalcemic tumor have ranged from 14 months to 43 years of age (1-6). Most patients present with signs and symptoms related to an abdominal or pelvic mass, but rarely the clinical presentation is related to the hypercalcemia. Approximately 66% of patients presented with hypercalcemia (2). Some studies have documented serologically the presence of parathyroid hormone-related protein (PTHrp). This type of ovarian carcinoma has a dismal prognosis. About 5% of the tumors have spread beyond the ovary at the time of laparotomy. The overall survival rate is approximately 16%.

The tumors are almost always unilateral, usually large, solid, soft and white. An important feature that is seen in about 80% of the tumors is follicles that vary from small to large. There is a variant of “large cell type” in which large cells have eccentric nuclei and dense globular cytoplasm (5,6).

This tumor is often confused with a granulosa cell tumor, adult type and the juvenile type (7, 8). Adult granulosa cell tumor is rare in the young. Small cell carcinoma has spread beyond the ovary at presentation, which would be unusual for either variant of granulosa cell tumor. In granulosa cell tumors, tumors are usually positive for inhibin-alpha and calretinin, but negative for EMA. These profiles are opposed to those of small cell carcinoma.

REFERENCES


Case 55

Masaharu Fukunaga, M.D.
Jikei University School of Medicine, The Daisan Hospital, Komae, Japan

**History:** A 36-year-old, gravida 1, para 1, female presented with abdominal discomfort. CT, MRI and physical examination revealed a mass with calcification in the pelvic cavity. At laparotomy, a mass was found in the right broad ligament. The uterus and bilateral ovaries and tubes showed no abnormality. She underwent excision of the broad ligament mass and right salpingo-oophorectomy. The patient is alive with no evidence of disease at 4 months after surgery.

**Macroscopic features:** A yellowish, white solid mass measuring 6.5x6.0x5.0cm. No hemorrhage or necrosis was seen.

**Immunohistochemical studies:** CAM5.2, vimentin, calretinin, CD10: (++). EMA, CEA, ER, PGR, D2-40, indhibin -alpha: (-).

**Diagnosis:** Wolffian tumor of the broad ligament (female adnexal tumor of probable Wolffian origin)

**Comments:** The present case shows clinically and histologically typical features of Wolffian tumor of the broad ligament. The tumors are unilateral and usually found in the leaves of the broad ligament, occasionally in the fallopian tube or ovary. Histologically, it is a solid tumor with scattered cysts or dilated glands. The solid areas consist of sheets of cells or hollow tubules. No atypia or necrosis is observed. Coffee bean-like nuclear grooves are observed. The stoma is fibrous with hyalinization and small calcifications. The differential diagnoses include sex-cord stromal tumor and adenocarcinoma. The behavior of the tumor is unpredictable, with a potential to develop delayed local recurrence or distant metastasis after many years. All tumors should be considered to have a malignant potential and the follow-up should be prolonged.

**REFERENCES**

Case 56

Ira Bleiweiss, M.D., The Mount Sinai Medical Center, New York, N.Y., USA

**Brief clinical history:** A 42 year old woman presented with a palpable 1.7 cm right breast carcinoma with radiographically suspicious axillary nodes. PET/CT scan revealed ascites and peritoneal carcinomatosis. The slides are from omental biopsies

**Short summary of case:**
A 42 year old woman presented with a palpable right breast mass which was radiographically solid and irregular, without associated calcifications, and measuring 1.7 cm. A 2.8 cm lymph node had suspicious radiologic features. Core biopsy of the breast mass showed infiltrating poorly differentiated duct carcinoma with tumor giant cells and chronic inflammatory infiltrate. The tumor was negative for estrogen receptor, progesterone receptor, and Her-2-neu proteins. Of note the patient had a sister and aunt with perimenopausal breast carcinoma, and testing for BRCA mutations eventually was positive for a BRCA1 mutation. A few days after the breast cancer diagnosis, a PET/CT scan revealed ascites and peritoneal carcinomatosis with thickened omentum, bilateral ovarian, masses, and metastasis in a left external iliac lymph node. Exploratory laparoscopy yielded omental biopsies. The slides of the omentum show an anaplastic carcinoma without papillary or glandular structures or psamomma bodies. The histology was similar to that of the breast; however, immunohistochemically both were distinct. The omental tumor was positive for WT-1 and, oddly, positive for estrogen receptor and progesterone receptor and negative for breast antigen (GCDFP-15) and mammaglobin. The breast cancer was restained and was negative for WT-1 and focally positive for ER and PR. Thus, two separate primaries were diagnosed with extensive peritoneal carcinomatosis and five positive lymph nodes in the inguinal and external iliac regions. The patient received chemotherapy with a regimen intended to treat both the breast and ovarian carcinoma. Approximately 4 months later, a bilateral mastectomy was performed. Only focal residual intraductal carcinoma was found in the right breast. One out of twenty-two axillary lymph nodes showed a 6mm metastasis amidst a larger area of fibrosis. Both the intraductal carcinoma and the metastatic carcinoma exhibited chemotherapy-induced cytologic change with mitoses evident in the metastasis.

**Diagnosis:** Synchronous primary breast and bilateral ovarian carcinoma in a patient with BRCA-1 mutation.

**Comment:** This case demonstrates the value of immunohistochemical panels performed in parallel on two separate lesions which are histologically similar. While ER/PR staining typically correlates with nuclear grade (negative with more pleomorphism) it was surprising to see positivity in the most anaplastic of the two tumors (the ovarian) whereas the breast carcinoma was negative as expected. The breast and gynecologic markers stained as they should have, so I guess these tumors "read the book", at least partially.

**REFERENCES**

Case 57

Masaharu Fukunaga, M.D.
Jikei University School of Medicine, The Daisan Hospital, Komae, Japan

History: A 33-year-old, gravida 1, para 1, pregnant (at eight gestational weeks) female presented with abdominal vaginal bleeding. Echogram and physical examination indicated spontaneous abortion. Dilatation and curettage was performed. Her serum HCG levels were elevated (>100,000 mIU/ml). Echogram did not show vesicular changes (snow storm pattern).

Macroscopic features: Villi and decidua tissue without vesicles. No fetal parts were observed.

Immunohistochemical studies: Cytotrophoblasts and villous stromal cells failed to express p57.

Diagnosis: Early complete hydatidiform mole

Comments: With the increased use of ultrasound hydatidiform mole (HM) is being diagnosed at increasingly early stages of gestation. As villous edema is not fully developed, we cannot make a diagnosis of HM by macroscopic observation. Furthermore, microscopically the classic features of complete mole (CM) may be lacking and CM can be easily misdiagnosed as partial mole (PM) or hydropic abortion (HA). Since the risk of persistent disease is 10 to 15% in CMs and 1 to 2% in PMs, and no serious consequences are observed in the majority of patients with PM, practically, a correct diagnosis of early CM is most important. This case looks PM or HA, However, you can see mild trophoblastic hyperplasia, capillary proliferations, stromal cell hyperplasia and karyorrhexis. These histologic findings are very characteristic to early CM. Following are histologic features of early CM; diffuse or focal hydropic change of villi, bulbous or polypoid villi, focal or circumference trophoblastic hyperplasia, cellular villous stroma, network of capillaries, karyorrhexis in villous stroma, prominent placental site intermediate trophoblasts, and absence of embryo. Criteria of PM are; two populations of villi, normal sized villi and edematous villi, irregular villous outlines, focal mild syncytiotrophoblastic hyperplasia, central cistern, trophoblastic inclusion, the presence of an embryo or fetus (1). p57 immunostaining is useful for differential diagnosis between CM and PM (2). Villous cytotrophoblasts and stromal cells are negative for p57 in CM.

REFERENCES
Case 58

Ivan Damjanov, M.D., University of Kansas, Kansas City, KS, USA

Clinical History: A 64-year-old woman presented with a right breast mass which was initially thought to be related to an insect bite. A follow-up including ultrasound examination revealed enlargement of the mass and also enlargement of the right axillary lymph nodes. The initial core needle biopsy revealed infiltrates of lymphoid cells and the lesion was initially thought to be a lymphoma. An excisional biopsy followed which enabled us to make the final diagnosis. The lesion recurred six months later and was reexcised. Six months later a mass was noticed in the other breast. Upon excision it proved to have the same morphology as the first lesion in the right breast. Eleven months after the initial presentation she developed a flank mass which was resected; it had had the same morphology.

Pathological Findings: The breast tissue was infiltrated with lymphocytes and macrophages. CD20+ B lymphocytes predominated but there were also scattered CD3+ T lymphocytes. Macrophages were positive for S-100 protein and negative foc CD1a. Many macrophages showed prominent emperipolesis. Flow cytometry of the lesion disclosed no monoclonality or other evidence of B cell lymphoma. The axillary lymph nodes and the lesion from the other breast and the flank showed the same morphology.

Diagnosis: Rosai-Dorfman disease of the breast

Comment: Rosai-Dorfman disease (RDD) was originally described in 1969 as sinus histiocytosis with massive lymphadenopathy (1). As its name indicates, most often it affects the lymph nodes, but it also may involve other organs, including the breast. The present case has already been published as an example of Rosai-Dorfman disease with bilateral breast involvement (2).

In our review of the literature we found 27 published cases of RDD of the breast. Of these reported cases, 25 were women and 2 were men. One died of disseminated RDD, two had local recurrence, and the remaining patients were free of recurrence and showed no evidence of disease in other sites.

The diagnosis of RDD of breast in core needle biopsy may be difficult, but it is important to think of that possibility when-ever the breast tissue is infiltrated with lymphocytes and macrophages. The differential diagnosis includes diabetic (lymphocytic) mastopathy, and lymphoma. The removal of the breast mass is curative in most instances, but the disease may by occasionally bilateral (as in the present case); it may recur; or it may end in systemic dissemination and death. The outcome of the disease cannot be predicted from the microscopic features of the breast lesion.

REFERENCES


Case 59

Giovanni Falconieri, M.D., "S. Maria della Misericordia" General Hospital, Udine, Italy

Case History
A 50 year-old lady was admitted to the Hospital for a palpable nodule of the right breast. A fine needle aspiration cytology revealed “malignant” cells. The patient underwent radical mastectomy plus sentinel lymph node biopsy.

Gross and microscopic features.
The specimen was centered by a fleshy, fairly delimited 2.5 cm mass. The remainder of the specimen was unremarkable. The sentinel lymph node was sliced in halves and submitted in toto.

Microscopic examination of tumor HE stained sections revealed a cellular lesion made up of large polygonal elements often featuring eosinophilic cytoplasm. Several tumor cells were arranged in rudimentary gland formations suggesting poorly differentiated carcinoma. A routine prognostic/predictive panel was ordered including ER, PR and Her2. In addition, an extended battery of antibodies was ordered including cytokeratins, EMA, S100 protein, Melan A, HMB45, desmin, actins, CD31, CD34. Tumor cells were positive for S100 protein, HMB45, Melan A, and negative for all the remainders of antibodies. The microscopic features were deemed consistent with melanoma. Clinicopathologic correlations were recommended. Further patient inquiry and review of medical records disclosed that the patient had been treated for cutaneous melanoma 7 years before.

Comment
Metastatic tumors to the breast are rare with an incidence of 0.5–2% of all breast malignancies, however melanoma is one of the the most common solid tumor metastasizing to the breast. Young women seem to be more often affected, perhaps because of a physiological increased vascularization of mammary tissue. Recognition of metastatic melanoma (MM) is generally promoted by several microscopic clues such as epithelioid or spindle cell morphology; cell discohesion; eosinophilic cytoplasm; and vesicular nuclei with inclusion-like nucleoli. Tumor cells with melanin were an obvious clue to the diagnosis of MM; however, this particular feature was seen in two cases only. Although poorly differentiated carcinoma was the main pathological condition a remarkable phenotypically tumor diversity substantially expanded the spectrum of differential diagnosis in a sizable minority of cases as to include medullary carcinoma, high-grade malignant lymphoma, atypical lipomatous tumor/liposarcoma, leiomyosarcoma or peripheral nerve sheath tumor. Immunohistochemical stains in these tumors showed positivity for S-100 protein and, in most of the cases, for HMB-45 and Melan-A, whereas antibodies against other antigens such as cytokeratins, CD45, and desmin were nonreactive. Furthermore, ER and PR were negative. Negative result for cytokeratins should, therefore, raise the index of suspicion for MM. It is important to be mindful, however, that cytokeratin reactivity has been seen occasionally in melanoma and for patients, resulting from an ensuing incongruous treatment, not to mention serious medicolegal implications for pathologists. The matter seems further compounded in cases of MM presenting as isolated tumors of the mammary gland when the medical history is noncontributory or when the patient neglects to convey promptly a history of melanoma as the case at issue. It is important also to be mindful that melanoma can metastasize many years after a primary lesion has been removed. Adding to the diagnostic complexity is the paucity of reported studies.

In a series of MM to the breast recently evaluated by Bacchi et al (submitted for publication; Abstract #762, 2012 UsCap Meeting, Vancouver, Canada) detailing 20 cases, the age range of patients was relatively broad, with a slight preponderance of premenopausal patients (9/17) and an overall median age of 47.5 years. Three patients were men. The majority of the cases had been submitted for a second diagnostic opinion, for the assessment of ER and PR, or for “unusual” high-grade breast cancer. Most of the cases were characterized by proliferating epithelioid or mixed epithelioid and spindle cell tumors. These changes appear basically comparable to published observations of MM to the breast suggesting by morphologic appearance of a poorly differentiated, high-grade metaplastic carcinoma. Microscopic features seen in this group, which could retrospectively suggest melanoma, were cell discohesiveness, eosinophilic cytoplasm, and inclusion-like nucleoli. Tumor cells with melanin were an obvious clue to the diagnosis of MM; however, this particular feature was seen in two cases only. Although poorly differentiated carcinoma was the main pathological condition a remarkable phenotypically tumor diversity substantially expanded the spectrum of differential diagnosis in a sizable minority of cases as to include medullary carcinoma, high-grade malignant lymphoma, atypical lipomatous tumor/liposarcoma, leiomyosarcoma or peripheral nerve sheath tumor. Immunohistochemical stains in these tumors showed positivity for S-100 protein and, in most of the cases, for HMB-45 and Melan-A, whereas antibodies against other antigens such as cytokeratins, CD45, and desmin were nonreactive. Furthermore, ER and PR were negative. Negative result for cytokeratins should, therefore, raise the index of suspicion for MM. It is important to be mindful, however, that cytokeratin reactivity has been seen occasionally in melanoma and
that the antibodies included in the melanoma immuno-histochemical pattern may have a variable sensitivity, including S-100 protein, which may be negative in late metastatic diseases. On the other hand, in addition to MM, several pigmented lesions have been described in the breast, including ductal carcinoma showing aberrant melanocytic differentiation (also labeled as "melanotic carcinoma"; pigmented mammary Paget's disease, blue nevi of the mammary gland proper 6, and merely breast carcinoma that has phagocytized melanin from the adjacent skin 14. In essence, the use of all these markers should be taken in account along with the clinical and morphological findings in order to diagnose MM.

Based on these observations, the differential diagnosis of MM to the breast appears more complex than might have been previously thought. In addition to poorly differentiated carcinoma, MM can simulate other malignant tumors, including medullary carcinoma, lymphoma, leiomyosarcoma, and liposarcoma. Medullary carcinoma may be considered by virtue of the syncytial growth pattern of tumor cells and the lymphoplasmacellular infiltrate within the background. In two cases the tumor growth simulated malignant lymphoma both architecturally and cytologically, being composed of diffuse sheets of widely infiltrating cell cords. Noteworthy, primary lymphoma is rare but not exceptional in the breast, with a broad spectrum of clinical and microscopic presentation 3, 7, including anaplastic large-cell lymphoma, a well-known mimic of epithelioid tumors such as carcinoma and melanoma. 10 Primary leiomyosarcoma in the breast has been rarely, but not exceptionally, reported 5, 11. Immunostaining for muscle markers proves useful in these cases, but it should be relied on judiciously because desmin may be only focally positive in leiomyosarcoma of the breast and muscle actin antibodies have a low specificity, as muscle actin can be positive in myofibroblastic lesions. In addition, an erratic positivity for S-100 protein has also been seen in cases of primary leiomyosarcoma of the breast 1, 12.

Application of immunohistochemistry is a critical diagnostic step. In fact, tumor cell immunoreactivity for S-100 protein, Melan-A, and HMB-45 along with no expression of cytokeratin proved useful in differentiating MM from other malignant tumors, including breast carcinoma, lymphoma, and leiomyosarcoma. However, certain positive results, especially for S-100 protein, should be interpreted with caution and always in the proper clinicopathological context. A thorough clinical history remains the best approach to avoid misdiagnosis, which may result in inappropriate patient treatment.

REFERENCES

**Case 60**

Franco Fedeli, M.D., Anatomia Patologica, Ospedale S. Andrea, La Spezia, Italy

**Clinical History**
A 21-year-old woman with abdominal swelling was found to have a left adnexal mass and underwent a left salpingo-oophorectomy.

**Macroscopic findings**
The ovarian tumour measured 14 cm and was solid and cystic. Ultrasound showed an unremarkable pancreas. The patient has been followed for 21 months and is free of disease.

**Microscopic findings**
Histologically, the neoplastic cells were arranged in a pseudopapillary pattern, focally interrupted by cysts, some of which were filled with colloid-like material. The pseudopapillae were composed of central fibrovascular cores, and covered by tumor cells whose nuclei were oriented away from the vessels. A moderate amount of cytoplasm was present and varied from pale to brightly eosinophilic. At the periphery of the tumor were nests of neoplastic cells with abundant pale foamy cytoplasm surrounded by fibrous septa. These foci merged with conventional areas of tumor. Innumerable extracellular PAS-positive diastase resistant eosinophilic globules were identified. The nuclei were round to oval with many having longitudinal nuclear grooves. Nuclear atypia was lacking and mitoses were virtually absent. Compressed but otherwise unremarkable ovarian tissue was present at the periphery of the tumor.

**Special Studies**
The neoplastic cells including those with foamy cytoplasm showed intense nuclear positivity for β-catenin and complete loss of E-cadherin staining. A CD117 stain showed focal membranous reactivity. Immunostains for inhibin, calretinin, pancytokeratin, Hep-1, α-fetoprotein, PLAP, CDX2, progesterone, and thyroglobulin and chromogranin were negative.

**Diagnosis**
Pancreatic Type solid/papillary tumor of ovary.

**Comments**
A solid/papillary tumor of the pancreas, first reported by Frantz in 1959, is an uncommon but distinct pancreatic neoplasm with low malignancy, accounting for 1–2% of all pancreatic tumors. A solid/papillary tumor is a rare neoplasm that typically occurs in young women 35 years of age. Solid/papillary tumor are most commonly found in the body or tail of the pancreas and may contain both solid and cystic components and occasional calcifications. Extrapancreatic solid/papillary tumors are quite rare worldwide. There are only twelve previous reports of extrapancreatic solid/papillary tumors, seven of which were solid/papillary tumors arising in the mesenterium, peritoneum, liver and adrenal gland.

A review of 553 cases of solid pseudopapillary neoplasm in the Chinese literature also cites 9 extrapancreatic cases, but details are not available other than the sites of involvement (retroperitoneum, mesentery, and adrenal gland).

The morphologic and immunohistochemical features of the ovarian tumor described in this case are compatible with those of solid pseudopapillary neoplasm of the pancreas. Given the negative findings in the pancreas on imaging studies and lack of subsequent evidence of tumor elsewhere, this neoplasm is of primary ovarian origin. This case is one of the 3 cases recently reported by Deshpande et al. Recently other two cases was described, one of this had a clinically aggressive behaviour. Among the 5 cases with known information, a mean age of 26.4 years (range: 17–57 year), who presented with large tumors (mean size, 13.3 cm). Grossly, it can vary from entirely cystic with a small mural nodule to solid but usually is solid and cystic, like the neoplasm we described in the ovary. Histologically, this tumor closely resembled its pancreatic counterparts, showing solid and pseudopapillary patterns. The nuclear features including oval nuclei, variable longitudinal nuclear grooves, and fine chromatin are identical to those seen in the pancreatic counterpart. This case showed cells with brightly eosinophilic cytoplasm, a finding which has also been occasionally noted in solid/papillary tumor of the pancreas. In concordance with findings in the pancreas, the ovarian tumors described herein showed strong and diffuse nuclear reactivity for β-catenin and loss of membranous E-cadherin staining. Ovarian neoplasms that display a solid and pseudopapillary or a real papillary growth pattern should be included in the differential diagnosis. Probably the most realistic consideration is within the category of sex-cord...
stromal tumors of the ovary, including granulosa cell tumor and to a somewhat lesser extent, the oxyphilic variant of Sertoli cell tumor.

A pseudopapillary pattern has occasionally been observed in both Sertoli cell tumors and granulosa cell tumors.

Moreover the adult form of granulosa cell tumor shows grooved nuclei, a feature occasionally seen in pancreatic type solid/papillary tumor of ovary. In addition, they are positive for calretinin and inhibin.

Neuroendocrine tumors of the ovary like carcinoids frequently show insular and trabecular patterns, and thus are unlikely to be in the differential diagnosis of a pancreatic type solid/papillary tumor of ovary. Carcinoid tumors of the ovary are almost uniformly positive for chromogranin whereas this tumor is negative.

The presence of a band of neoplastic cells with abundant pale to lightly eosinophilic cytoplasm bordering the more conventional morphology was a morphologic feature of this case. This is most likely to cause confusion with the lipid-rich form of steroid cell tumor, steroid cell tumors are characteristically positive for inhibin and calretinin.

If the histogenesis of solid/papillary tumor of the pancreas is enigmatic, it is even more so for the ovarian examples. An obvious reflection is a potential origin in pancreatic tissue within an ovarian dermoid cyst. However, pancreatic tissue is rare in mature cystic teratomas, being documented in only 1% of cases.

In the 5 cases described in literature in the ovary only one exhibits features suggestive for an aggressive behavior, including cytologic atypia, high mitotic rate, elevated Ki-67, necrosis, vascular invasion, invasion of the ovarian capsule and involvement of the omentum and adjacent organs, and liver metastasis. In the other cases follow-up information is limited or not available.

REFERENCES


**Case 61**

Volkam Adsay, M.D. Emory University School of Medicine, Atlanta, GA, USA

**History**: 63 year old male with history of colonic polyps presented to the emergency room with severe upper GI symptoms and 10-pound weight loss over two months (reported intentional). MRI and CT revealed a 2-cm liver mass as well as a pancreatic tumor, however, these were undetected on PET analysis. Resection of the pancreas was performed and is shown in your slides.

**Microscopic findings**: The tumor is composed of a fairly cellular neoplasm with nested growth pattern. The monotony of the cells is evident even in low power examination. The cells have fair amount of cytoplasm and the nuclei show a distinctive salt-and-pepper chromatin pattern, characteristic of a neuroendocrine tumor, and in particular, one that is of mid-gut origin. The cytoplasmic amphophilia is also characteristic for a WDNET (carcinoid) of mid-gut origin. Immunohistochemical stains were also supportive of a “carcinoid” by showing diffuse strong labeling with CDX2 while Isl-1 was negative.

**Diagnosis**: METASTATIC WELL-DIFFERENTIATED NEUROENDOCRINE TUMOR OF “MID-GUT” ORIGIN (CLASSICAL CARCINOID OF SMALL INTESTINE) METASTATIC TO THE PANCREAS. GRADE 1 OF 3 IN THE WHO-2010/ENETS CLASSIFICATION

**Discussion**: Morphologic considerations

The morphologic features of well-differentiated neuroendocrine tumors (WD-NET; classical carcinoids of GI tract, and ordinary pancreatic neuroendocrine tumors – PanNETs) are well recognized and their diagnosis is relatively easy in most cases. These include nested growth pattern of monotonous cells with round uniform nuclei, salt-pepper chromatin, and fair amount of cytoplasm. Trabecular, acinar or rosette-like growth patterns can also be seen. Those of “mid-gut” origin often have a distinctive morphology in which the nesting pattern and monotony are ever more striking. In these mid-gut NETs, there are other features that allow their recognition even at metastatic sites including overt NE pattern of the chromatin that is strikingly salt-pepper type, cytoplasmic granularity evident that imparts the cells a characteristic amphophilia/basophilia, and the condensation of the granules at the periphery of the nests prominent in some cases. WDNETs are relatively easy to diagnose. There are, however, few situations that lead to diagnostic problems. Because the growth is often predominantly submucosal, a mucosal biopsy may disclose only very limited amount of the tumor. With crush artifact, these cells can mimic lymphocytes or crushed glandular cells. Some of the morphologic variations that commonly lead to diagnostic problems include tubular pattern and intraluminal mucin formation. In particular, ampullary glandular psammomatous carcinoids (ampullary somatostatinoma) often have tubule formation and intraluminal mucin. However, intracytoplasmic mucin is almost non-existent. These can also express CEA and CA19-9, further exacerbating the diagnostic challenge.

More problematic are the rare morphologic variants of the pancreatic ones (PanNETs) that are under-recognized. Although most PanNETs show diffuse, stroma-poor, sheet-like growth pattern, some show abundant stromal sclerosis and may exhibit tubule formation, mimicking invasive ductal adenocarcinoma. The pleomorphic variant is also often mistaken as a high-grade adenocarcinoma, although it is prognostically no different from a regular PanNET. Clear cell or lipid-rich variants are often misdiagnosed as carcinomas from adrenal, liver or kidney. Oncocytic variants do occur, therefore it is important to recognize these variations in the theme. It should also be kept in mind that about 5% of PanNETs present as a cystic mass.

**Classification and prognostic considerations**

In general, GAP-NETs should be regarded as low-grade indolent malignant neoplasia. It is also clear that very small and incidental examples, especially in certain clinical settings, may represent precursors, or evolving malignancies, i.e., GI/pancreatic counterparts of pulmonary tumorlets. In fact, some authors do regard such lesions conceptually as dysplastic or “Tis” type lesions. In particular, the incidental lesions detected in patients with MEN (in the pancreas) or autoimmune gastritis (in the stomach; enterochromaffin-like cell lesions) are good examples of the “precursor” (Tis) NET phenomenon.

The primary location of the tumor seems to be an important determinant of the outcome as well. This should
not be surprising since adenocarcinoma of colon is very different than adenocarcinoma of stomach, and there is no reason why NETs of these two sites should be expected to be similar. Most appendiceal classical carcinoids are asymptomatic (detected in %2 of the autopsies) and similarly, most rectal carcinoids are also non-metastatic.

However, part of the more “benign behavior” of NETs of some regions such as appendix and rectum may also be related to the stage at which these tumors are detected. Most of these are detected incidentally and are typically small (< 0.5 cm) at the time of diagnosis. The fact that both appendix and rectum are narrow zones of the GI tract and thus lead to symptoms and early detection of the lesions may be a factor. In support of this impression, rectal and appendiceal carcinoids with the size of >2cm have a much higher metastatic risk. In contrast, ileal (mid-gut) “carcinoids” are often detected when they are metastatic, presumably because the primary tumors do not manifest until they metastasize and lead to carcinoid syndrome or other symptoms.

For PanNETs, hormonal activity is known to have some correlation with biologic behavior. One of the reasons for recognizing the syndromic nature of PanNETs is that a specific prognosis has been ascribed to each different variety. For example, clinically functioning insulinomas pursue an indolent clinical course in 90% of cases and have often been regarded as benign. In contrast, most other syndromic PanNETs result in recurrence or metastases in 50-70% of cases. It is possible that the favorable outcome of patients with insulinomas is due, at least in part, to the relatively small size at which these tumors are typically detected relative to other syndromic PENs (most insulinomas are < 2 cm at the time of diagnosis). However, duodenal gastrinomas often result in metastases even when the primary measures less than 1 cm.

While there are different approaches to terminology and classification of NETs, between NANETs, ENETS, AJCC/UICC and others, it is now widely agreed upon that NETs ought to be graded and staged separately. According to the WHO-2010:

1. The entire spectrum of tumors with neuroendocrine pattern is called NET, and graded as NET 1, NET 2, and NET 3 based on either mitotic activity (per 10 HPF) or Ki-67 index (percent of cells): NET-1 as < 2, NET-2 as 2-20, and NET-3 as >20. This is applied regardless of the location.
2. Staging parameters are separated out from the diagnostic terminology (unlike in the WHO-2004) and are reported separately. ENETs stage and TNM/ AJCC staging, however, have substantial differences, and therefore, it will be important to clarify in pathology reports which staging system is being employed.

For PanNETs, there was also a separate classification proposed by Hochwald and Klimstra which categorizes PanNETs as low grade (no necrosis and mitosis< 2/50 HPF) versus an intermediate grade (necrosis and/or mitosis >2/50 HPF). For this reason, we also typically include necrosis in the comment section of our report, along with vascular and perineural invasion and extension to neighboring sites. Additionally, there is strong evidence from multiple studies that CK19 may have some predictive value; for this reason we included this stain to the panel, although this is not a requirement, unlike Ki67.

Ki67 is now a requirement for complete diagnosis of NETs, including metastatic ones. However, there are issues about the methodology of counting Ki67. One thing for sure is that the “eye-balling” approach is highly unreliable and should be avoided. The method we prefer is to capture an image of the “hot-spot,” take a print of this image, and count manually on this printout, then calculate the percentage of staining cells accordingly.

It is important to recognize that lymphocytes and other non-tumoral elements often lead to over-counting of the Ki67. This pitfall becomes even more pronounced with automated (computer-facilitated) counting.

Carcinoid versus PanNET
The distinction of a NET arising in the GI tract versus the pancreas may be of some importance. On occasion, it may be helpful to gear the clinicians in the right direction to search for the correct primary, when these tumors are encountered in metastatic sites such as liver. On the other hand, we do not believe the pathologists need to feel cornered to make a specific diagnosis as to the origin, since this is not always possible, and the morphologic criteria discussed above not always reliable to make such distinctions. Further, with the current powerful radiologic methods such as PET and octreotide scan, it has become much easier to localize the primary tumor by imaging studies. If needed, some immunohistochemical stains may be of some help. Isl-1 and PdX-1 is significantly more common in PanNETs, while CDX2 is often more commonly positive in GI-NETs. However, there are overlaps, and these stains should not be regarded as the definitive answer.
REFERENCES


Case 62

Volkan Adsay, M.D., Emory University School of Medicine, Atlanta, GA, USA

**History:** 47 year old female patient presented with abdominal pain, nausea, and back pain. CT scan revealed an 8-cm tumor involving the distal pancreas and extending to the left kidney.

**Microscopic findings:** Diffuse sheets and nests of tumor cells with no significant intervening stroma is seen. The tumor cells are relatively monotonous but show high grade cytology with high nucleocytoplasmic ratio. Chromatin is finely clumped, with focal salt-and-pepper pattern. The overall appearance is highly suggestive of a neuroendocrine neoplasm of high-grade. Nucleoli are not prominent. The cytoplasm is basophilic; cytoplasmic borders are indistinct. Immunohistochemically, synaptophysin is positive and chromogranin is focal, but trypsin also shows fairly diffuse and strong labeling.

**Diagnosis:** Acinar cell carcinoma with prominent neuroendocrine differentiation

**Discussion:** Acinar cell carcinomas (ACCs) of the pancreas are uncommon, accounting for no more than 1% of pancreatic carcinomas. Most patients are adults in the 7th decade, and there is a male predominance. Pediatric cases have also been described, but are very rare. The presenting symptoms are generally non-specific. Elevated serum AFP levels are noted in some patients and a minority of patients present with a lipase hypersecretion syndrome characterized by subcutaneous fat necrosis, polyarthralgia, and occasionally eosinophilia. Most cases have liver metastases early in the course of the disease.

Macroscopically, acinar cell carcinomas tend to be large (mean size, 10 cm) by the time they are diagnosed. The tumors are generally highly cellular, lacking the desmoplastic fibrous stroma of ductal adenocarcinomas. The cellular population is monotonous and arranged in solid sheets and nests, often, but not always, punctuated by acinar and small glandular spaces. Occasional trabecular patterns may also occur. Some cases have more solid growth pattern without any obvious acinar formations. The cells exhibit evidence of polarization, even in solid areas, with the nuclei in cells adjacent to the stroma having a basal location. The cytoplasm is moderate to focally abundant and shows eosinophilic granularity in the apical regions, reflecting aggregates of zymogen granules. The nuclei are usually only moderately atypical, although occasional anaplasia may be encountered. These cytologic characteristics are very helpful in small biopsies and cytologic smears. The combination of prominent single nucleoli, chromophilia of the cytoplasm, lack of gland formation, presence of syncitial and trabecular patterns are helpful clues to the diagnosis. As in acinic cell carcinomas of salivary glands, some examples of ACC show a distinct basophilia.

Documentation of enzyme production is necessary for the diagnosis. Acidophilic granules on H&E are rarely present and PAS/d-PAS positivity is helpful (mucin should be excluded). Most useful is the immunohistochemical stains for specific enzymes: trypsin, lipase and chymotrypsin, of which trypsin is the most useful. Electron microscopy can be diagnostic for experts that can recognize zymogenic granules and distinguish them from neurosecretory granules, mucigen granules and others. Molecular alterations characteristic of ductal neoplasia, such as mutation in k-ras gene (seen in >95% of ductal carcinomas), and loss of DPC4 (present in about 50% of the cases) is absent in ACCs but B-catenin is expressed.

Rarely, ACCs may show intraductal growth or papillary/papillocystic patterns and mimic intraductal neoplasia. Some studies suggest a more indolent behavior for these variants. Rare ACCs presenting as cystic lesions are also recorded.

Neuroendocrine cells are commonly present in ACCs in variable distribution ranging from scattered cells to patchy areas to large zones of the tumor. If there is a distinct neuroendocrine component that constitutes >25% of the tumor, the neoplasm is designated as “mixed acinar-neuroendocrine carcinoma.” Limited experience in the literature indicates that these behave more like acinar than neuroendocrine carcinomas. More intriguing and difficult, however, is how to classify the ACCs that have prominent neuroendocrine differentiation; not as a separate, distinct component, but throughout the tumor as seen in this case. We have seen cases in which virtually all the neoplastic cells had dual acinar and NE features, not only immunohistochemically but also ultrastructurally, by showing trypsin and chromogranin immunoexpression in the same cells as...
well as co-presence of neuroendocrine and zymogenic granules. Technically, these cases are regarded as mixed acinar-neuroendocrine carcinomas but we often classify these as acinar cell carcinomas with prominent neuroendocrine differentiation.

It is important to note here that a significant proportion of the cases originally classified as high-grade NET of the pancreas (Grade 3 of WHO-2010) prove to be acinar cell carcinomas (with or without NE differentiation) after careful examination.

ACCs are fairly aggressive neoplasms but recent studies show that their overall survival is significantly better than that of pancreatic ductal adenocarcinomas; 5-yr survival of ACC is reported to be about 30%, and in some studies as high as 45%. About 50% of the cases have metastases to liver, often at the time of diagnosis. On the other hand, some patients with large and highly invasive tumors may have unusually protracted clinical course, especially if they have a significant intraductal component.

REFERENCES


Case 63

David Ben-Dor, M.D., Barzilai Medical Center, Ashkelon, Israel

Clinical summary: A 73 year old man without any remarkable previous clinical history was investigated for weight loss and fever. Physical examination was negative for peripheral lymphadenopathy or splenomegaly; however, on CT a mass in the spleen was discovered. Otherwise there was no specific radiological evidence of lymphadenopathy or for pancreatic tumor. Splenectomy was performed, during the course of which a mass was palpated in the pancreatic tail which was also resected.

Pathological examination: The spleen measured 18x8 cm and weighed 673 gram. The parenchyma was extensively replaced by neoplastic tissue with areas of necrosis. The pancreatic specimen measured 5x3 and contained a grayish nodule measuring 3 cm in diameter. In addition a group of matted nodules measuring 5 cm in the aggregate, with individual nodules measuring up to 1 cm each, was found adjacent to the pancreas.

Histological examination: The splenic tumor was composed of large pleomorphic cells which were positive for LCA and B cell markers (CD20 and CD79); 40% of the cells were CD30 positive. The pancreatic nodule was composed of nests of large cells with eosinophilic granular cytoplasm and whose nuclei showed varying degrees of pleomorphism, such as can be seen in endocrine tumors. There were scattered mitoses (maximum 2-3 m.f. per 50 hpf.) The tumor cells were positive for cytokeratin and synaptophysin. Studies with immunohistochemical markers for specific hormonal substances were negative. The peripancreatic nodules consisted of lymph nodes which were involved jointly by the splenic and pancreatic tumors (please see attached images).

Note: The material was reviewed at the time by Dr John Chan who also kindly performed part of the immunohistochemical studies referred to above, and by Dr Allen Gown, who kindly performed the hormonal studies.

Diagnosis:
Spleen: pleomorphic large B cell lymphoma
Pancreas: oncocytic pancreatic neuroendocrine carcinoma (synaptophysin positive, trypsin and chromogranin negative)
Peripancreatic lymph nodes: involved by metastatic carcinoma and splenic lymphoma

Postscript: The patient was referred to the hematology clinic and was treated with CHOP chemotherapy for the lymphoma. A new nodule was reported in the pancreatic remnant about 2 months after diagnosis and apparently not investigated. The patient went abroad about 6 months after diagnosis and had not been heard from since.

Discussion:
Since my colleague and friend Dr Volkan Adsay, who is an internationally recognized expert on pancreatic diseases and was instrumental in the conception of the new diagnostic schemas, has already laid out the theoretical infrastructure for diagnosing these tumors, I will go into this issue in a summary fashion.

The diagnoses listed above were made in 2003 and are quoted from the original diagnostic reports. The pancreatic neuroendocrine tumor was an incidental finding discovered during surgery (it had no clinical manifestations and was not picked up by imaging) and the diagnosis of neuroendocrine carcinoma was based on the lymph node involvement diagnosed on microscopical examination.

In the interval since then the diagnostic criteria for neuroendocrine tumors in general and for pancreatic neuroendocrine tumors in particular have changed not only once but actually twice. At about the same time that this diagnosis was made a new diagnostic framework for pancreatic neuroendocrine tumors was being prepared and subsequently published by the WHO in 2004 in the endocrine tumor blue book. According to that schema these tumors were divided into three categories, replacing the time honored designation of "carcinoid tumors" with: "well differentiated endocrine tumor" grossly confined to the pancreas- some of which were anticipated to show benign behavior based on size and proliferation criteria (<2cm size, <2 mitoses per 10 hpf, Ki-67<2%); while tumors of larger size, with higher proliferation/mitotic rates, or showing angioinvasion or perineural invasion were considered to be of "uncertain behavior". Well differentiated tumors with gross local invasion and/or metastases were grouped in a second category of "well differentiated carcinomas (low grade malignant)", and a third category of "poorly differentiated carcinomas" consisted of those rare tumors with obvious high grade malignant features, necrosis, and high mitotic rates (>10/10 hpf). Thus this tumor with demonstrable
lymph node metastases would easily fit into the second group. The majority of pancreatic neuroendocrine tumors are well differentiated and non-functional; most non-functioning tumors (as this was based on clinical and pathological findings) are well-differentiated carcinomas (AFIP).

Though this attempt at standardization and rationalization of the diagnostic schema for neuroendocrine tumors of the pancreas in particular and the gastrointestinal tract in general was considered an advance over what had been used previously, it was felt that it was not fully adequate in conveying sufficient information to the clinician regarding prognosis and therapy. Thus in 2006 Rindi et al proposed using a TMN system based on the guidelines of the European Neuroendocrine Society (ENETS), the T score reflecting whether the tumor was confined or not to the pancreas and the size. This case could be T2 based on size (2-4 cm.) but the final stage is IIb regardless of T status based on the presence of lymph node metastasis (N1) in the absence of distant metastasis. The tumors would in addition be graded according to mitotic rate/10 hpf (< 2, 2-20, and >20) and/or proliferation rate measured by Ki-67 (≤2%, 3-20%, and >20%), corresponding to G1, G2, and G3, respectively. G3 would roughly overlap with the high grade tumors. Subsequently in 2010 Scarpa et al suggested further modifications regarding the criteria for T3 and T4, and also proposed a Ki-67 positivity of 5% as the cutoff for G2 (instead of 3%). In their system this tumor would be stage III again by virtue of the presence of lymph node metastases. In this way data for size, infiltration, and metastasis would be independent of the formal WHO differentiation categories. The AJCC/UICC system uses different criteria for T scores and staging, which could be a source for confusion.

Most recently, the above WHO formulation was supplanted by a new one published in the most recent revision of the WHO gastrointestinal tumor blue book (2010), allowing only two categories – pancreatic neuroendocrine tumors and pancreatic neuroendocrine carcinomas, the former subsuming well differentiated neuroendocrine tumors and well differentiated carcinomas, and the latter reserved for high grade malignancies. In the new classification, pancreatic neuroendocrine tumors are subdivided by proliferative activity (determined by mitotic counting and/or Ki-67 proliferation rate) into G1 and G2. The implication is that pancreatic NET- G1 and G2 of the new classification are homologous respectively to well differentiated neuroendocrine tumor and well differentiated neuroendocrine carcinoma of the old classification. However I don’t think that these concepts are necessarily equivalent in that tumors such as this which were classified as carcinoma under the previous schema would be obligated to be G2 in the new one. Though it is intuitively tempting to draw this parallel this may not necessarily be the case. This case could be considered G1 on the basis of mitotic count alone (this could change after Ki-67 staining which is pending at the time of writing) despite the fact that it has already metastasized. However the Ki-67 proliferation index does place this tumor in the G2 category. This new classification reflects the currently accepted understanding that pancreatic neuroendocrine tumors are malignant (or at least are until proven otherwise). The pancreatic tumor group would be further stratified by TMN status which, together with tumor grade (G score), would be informative regarding the tumor’s malignant potential or already malignant behavior. By this framework this tumor would be formally labeled as a pancreatic neuroendocrine tumor and not a “carcinoma” and its already malignant behavior would be expressed only by the N1 score and the derivative stage.

Asides from the complexities presented by typing and staging, this tumor also shows the peculiarity of being composed of oncocyes. These are large epithelial cells with abundant brightly staining eosinophilic cytoplasm. This staining property is generally known as oxyphilia, which can be seen in a variety of circumstances. True oncocytosis change refers to a specific subset of cells characterized by cytoplasmic accumulation of mitochondria; otherwise oxyphilia may also result from an accumulation of lysozymes (as in granular cell tumors) or different types of cytoplasmic filaments. Oncocytic change is well known in solid visceral organs such as the thyroid, salivary glands, and kidney, where there are specific neoplasms named oncocytomas after the defining cytological feature (in the thyroid these are known as Hurthle cell tumors), and the parathyroid. Oncocytic change in of itself is not predictive for malignancy. In the pancreas, oncocytic change can be seen as a metaplastic phenomenon in otherwise unremarkable pancreatic parenchyma (AFIP Pg 18), and constitutes a specific entity first observed and published by Dr Adsay, the intraductal oncocytic papillary neoplasm. Otherwise it can be seen as a component or variant of serous tumors (AFIP Pg 38), and neuroendocrine tumors. A few cases of oncocytic ductal carcinoma are on record (Papotti et al). With regards to acinic cell carcinoma, while pronounced cytoplasmic eosinophilia when seen usually results from accumulated zymogen granules, oncocytic change resulting from a high content of mitochondria is rare but can be seen (AFIP, pg 199). Pancreatoblastomas can have large eosinophilic cells which are not true oncocyes (Papotti et al).
Specifically regarding oncocytic neuroendocrine tumors: an abstract presented to the 2005 USCAP meeting by Hussain et al consisted of 16 cases out of a total of 242 neuroendocrine tumors (or 7%) labeled as oncocytic by virtue of at least 25% of the tumor cells showing that feature. The proliferation fraction of these tumors was less than 5%. Lymph node metastases were found in 8 of the evaluable cases, and 5 of the surveyed patients died from the disease. Similarly, Volante et al describe 11 oncocytic tumors out of a total of 227 neuroendocrine tumors (4.85%). The tumors were relatively large (mean diameter- 8 cm.) and a high proportion (8/11) were metastatic at the time of diagnosis, but most (9/11) of the patients were alive when the article was written. Average Ki-67 proliferation rate was 4.2%.

To complete the discussion, some pancreatic neuroendocrine tumors can show rhabdoid morphology resulting from whorled intracytoplasmic filaments (AFIP, p. 265) which needs to be differentiated from true oncocytic changes.

REFERENCES

Peri-pancreatic node (low power)

Rim of peripancreatic lymph node shows positivity for synaptophysin

High power shows proliferation of large pleomorphic lymphoid cells in inner portion of node

Inner portion of lymph node positive for CD20

Peri-pancreatic node  outer portion of node replaced by oncocytic carcinoma metastatic from pancreas
Case 64

Kumarasen Cooper, M.D., The Vermont University Medical Center, Burlington, VT, USA

Clinical History
A 27-year-old male with a twelve-year history of a primary gastric GIST with previous liver and lung metastases presented with a well-circumscribed dural-based mass.

Radiologic Imaging
Computed Tomography (CT) scan of the brain showed a right-sided 3.5 x 4.5 cm heterogeneous parietal hemorrhage with 5 mm of midline shift and extension of the hemorrhage into the subarachnoid and subdural spaces. Magnetic resonance imaging (MRI) of the brain showed a 2.1 x 3.4 cm contrast-enhancing mass surrounded by hemorrhage and vasogenic edema with broad dural attachment and expansion into the inner table of the skull.

Gross Specimen
The mass was well circumscribed tan-gray, slightly lobulated, and focally hemorrhagic. The mass abutted the dura but did not extend through it. The cut surface was composed of tan-red slightly firm predominately solid tissue with one small cystic area. A portion of bone with erosion on the concave surface was also received.

Microscopic Examination
The mass is composed of whorled nests of cells with intervening fibrovascular bands of varying thickness. The cells are spindled to epitheliod with eosinophillic cytoplasm. They have increased nuclear to cytoplasmic ratios, and variable mitotic rates with the highest of 7 per 10 high power fields. There are scattered foci of necrosis. Tumor invades the lymphovascular spaces and meninges.

The whorled morphology, gross appearance, and radiographic findings were suggestive of an atypical meningioma. However, given the clinical history of metastatic GIST, immunohistochemistry was performed to further characterize the tumor. Immunohistochemical stains were negative for epithelial membrane antigen. C-KIT and DOG-1 immunostains were positive, consistent with metastatic GIST. These findings correlate with the patient’s history of prior metastatic GIST.

Diagnosis
Metastatic Gastrointestinal Stromal Tumor (GIST)

Follow up
Following the craniotomy, the patient was treated with Nilotinib. Nine months later, he developed enlarging lesions on CT and was switched to Imatinib. He developed a superior mesenteric vein thrombus and began low dose anticoagulation. Liver function declined. The patient died one year following the resection of the brain mass.

Discussion
We present a rare case of intracranial metastatic GIST, confirmed with immunohistochemical staining. The diagnosis of a primary GIST at 16 years old and subsequent multiple liver and lung metastasis exemplifies this uniquely aggressive tumor. While intestinal GISTs metastasize 40% to 50% of the time, gastric GISTs, as seen in the present case, metastasize in only 20% to 25% of cases [1]. The most common metastatic sites include liver (15.9%) and peritoneum (14%). Rarely, lung and bone (2%) metastases may occur as well [1]. There are only five reported cases of suspected intracranial GIST metastases, only three of which have been confirmed with tissue diagnoses [2-6]. There is only one other report of dura associated GIST metastases.

Reports of suspected intracranial GIST metastases:
- Hughes et al. described a 47 year-old man with a jejunal GIST that metastasized to the liver and eye and was eventually found to have intracranial parasagittal metastases [2].
- Kaku et al. described a 68 year-old woman who initially presented with a perisacral GIST, likely metastatic, that was surgically removed. The patient later was found to have a parietal lobe metastasis [3].
- Puri et al. described a 42 year-old man who initially presented with a parietal lobe tumor initially thought to be a sarcoma. Six months later, the patient was found to have a large mesenteric mass that was consistent with a GIST [4].
- Akiyama et al. described a 60 year-old man with a history of metastatic GIST who presented with a cavernous sinus tumor compressing the optic nerve. The mass was not biopsied and, therefore, not confirmed to be a GIST metastasis [5].
- Brooks et al. described a 75 year-old man with a mesenteric GIST who developed a meningeal tumor infiltrating bilateral cerebral hemispheres. However, a tissue diagnosis was not obtained [6].
This is a case of a uniquely aggressive metastatic GIST in a young man with a gastric primary diagnosed as an adolescent. We conclude that intracranial metastases should be considered in any patient with a history of GIST presenting with a new brain mass, whether dural or parenchymal. Additionally, there may be sites, such as the CNS, where Imatinib does not achieve adequate concentrations.

REFERENCES


**Case 65**

Markku Miettinen, M.D., National Institutes of Health, Bethesda, USA

**History:** 49 year-old woman. A gastric antral mass of 3.5 x 2.5 x 2.5 cm was removed via wedge resection.

**Diagnosis:** plexiform fibromyxoma

Histologically, there is a multinodular fibromyxoid proliferation involving gastric muscularis propria. This is highly vascular with a prominent capillary pattern. Between the vessels there are bland spindled cells with oval nuclei and indistinct cytoplasm (highlighted by vimentin immunostain). There is no detectable mitotic activity. Immunohistochemically the tumor cells are positive for vimentin and SMA and variably for CD10. They are negative for KIT and retain SDHB-expression.

**Discussion:**

Plexiform fibromyxoma is a rare benign gastric tumor. It has also been reported under name "plexiform angiomyxoid (myofibroblastic) tumor of the stomach". Earliest report of this entity from 1959 named it as "gastric fibromyxoma. The tumor occurs at various ages, even in children with apparent predilection to young middle age. The tumor is almost invariably located in the prepyloric region and it may also involve the external aspect of duodenum. Tumor size varies from a 2-10 cm gastric mass. Currently experience does not show a connection with familial myxomas associated with Carney complex. Histologically typical if a plexiform, multinodular involvement of gastric muscularis propria, but outside of this in the extragastric extension there is a diffuse pattern. The tumor has a variably prominent myxoid to myxocollagenous matrix. Bland spindled cells with uniform oval nuclei are dispersed between prominent capillaries. Vascular involvement is possible, with intravascular tumor plugs. This does not have any adverse significance according to the present information, and the tumor is benign.

Immunohistochemically typical is positivity for vimentin and SMA and variably positivity for CD10. The tumor cells are negative for KIT and DOG1/Ano-1, CD34, and desmin and are positive for SDHB, which helps to separate it from various forms of GIST. The tumor does not KIT or PDGFRA mutations. Both the distinct histology and immunohistochemical findings help to separate this entity from GIST.

**REFERENCES**

Case 66

Markku Miettinen, M.D., National Institutes of Health, Bethesda, USA

**History:** 26 year old woman with a 6.1 x 4.8 x 3.8 cm gastric antral mass and a separate 2 cm antral submucosal mass.

**Diagnosis:** Gastrointestinal stromal tumor, succinate dehydrogenase deficient.

**Description:** The tumor shows a multinodular gastric wall involvement. It is composed of spindled to epithelioid cells with a mitotic rate of 13/50 HPFs. The tumor was immunohistochemically positive for KIT and CD34 and negative for SDHB. A large wedge resection type of partial gastrectomy and a separate tumor excision was performed.

**Discussion**
Most gastrointestinal stromal tumors (GISTs) are known to have gain-of-function KIT or PDGFRA mutations. However, there is a subgroup of tumors with no such mutations, referred to KIT/PDGFRA wild type GISTs. Similar to other GISTs, these tumors usually express KIT. The most significant and pathogenetically interesting group among KIT/PDGFRA wild type GISTs are the succinate dehydrogenase (SDH) deficient GISTs. These tumors do not have functional mitochondrial succinate dehydrogenase complex, and therefore essentially run on glycolytic metabolism. Immunohistochemical loss of succinate dehydrogenase subunit B is a practical marker for this group of GISTs. Loss of SDHB inevitably leads to inactivation of the SDH-complex and loss of capacity to oxidative phosphorylation. Similar losses of SDH complex were previously known in paragangliomas and in a very small subgroup of renal cell carcinomas.

The molecular mechanisms leading to inactivation of SDHB-complex are not well understood. However, some patients have been found to have germline mutations in SDHA and less frequently in other SDH subunits: SDHB, SDHC, and SDHD. Many of these patients also have paragangliomas, and this combination: Germline SDH mutation with GIST and paraganglioma is known as Carney-Stratakis syndrome inheritable in an autosomal dominant manner. It is not known with certainty why SDH-deficiency links with tumorigenesis. However, its loss activates HIF1 alpha and result in activation of certain oncogenic pathways. Also, Insulin-like growth factor 1-receptor (IGF1R) signaling is activated in these tumors. This signaling is rarely activated in other GISTs, although is common in various carcinomas and sarcomas.

Clinicopathologically SDH-deficient GISTs are a very distinctive group. These tumors occur only in stomach. They have a predilection to young age and comprise the vast majority of GISTs in children and young adults. However, they may occur in older adults, although with a low frequency. Among children, there is a marked female predominance so that nearly all patients below age 16 years are female. Some patients also have pulmonary chondroma or parangangioma, without SDH-germline mutations, and this is known as Carney Triad (GIST + parangangioma, pulmonary chondroma, or both).

Similar to other GISTs, SDH-deficient GISTs often present with gastrointestinal hemorrhage due to tumor ulceration. They typically occur in the gastric antrum and are frequently multifocal. Tumor size varies, but median size in our series of 66 cases was 5 cm. Histologically SDH-deficient GISTs are distinctive. They are multinodular with “plexiform” pattern of involvement and often show distinctly epithelioid cytology. Mitotic rate varies widely but is often low. Peculiar features include lymphovascular invasion (up to half of cases) and occurrence of lymph node metastases and peritoneal micrometastases in a minority of patients.

Clinicopathologically, these tumors are characteristic in their tendency to gastric recurrences necessitating multiple operations and ultimately leading to total gastrectomy for some patients. Lymph node and peritoneal metastases tend to be indolent but notable in a portion of patients. Liver metastases develop in 15-20% of patients. Remarkably, many patients survive long time even with liver metastases, which is not the case with KIT mutant GIST prior to imatinib mesylate based modern therapy. Long-term mortality is around 15% in our experience. These patients die of complications of liver metastases. Prognostication is less clear than for KIT mutant GISTs. Some patients with tumors with low mitotic rates develop metastases, whereas others with high mitotic rates do not show tumor progression. Interval between primary tumor and recurrence or metastasis can be long.
The longest interval in our experience is 42 years between primary tumor and liver metastasis and 45 years between primary tumor and gastric recurrence (vs. new tumor).

Generally, the patients do not respond to KIT/PDGFRα inhibitor imatinib mesylate. However, some responses have been obtained after multi-kinase inhibitors, sunitinib, nilotinib and vandetanib therapy.

REFERENCES


**Clinical History:** This specimen was from a 51 year old man with a history of Crohn’s disease diagnosed in 1991. The patient lived in Richmond, Virginia. He had had erythema nodosum in 1997 and a history of ileal strictures (1997). The patient developed steroid-induced diabetes when treatment with steroids was used. He subsequently failed therapy with Cipro, Flagyl, Imuran, and 6-Mercaptopurine. In 12/01, he began methotrexate 25 mg IM qwk and Remicade (infliximab, anti-tumor necrosis factor-α) 5mg/kg (12/01). Remicade was increased to 10mg/kg q16 wks (6/02), to 10mg/kg q8 wks (8/04), and to 10mg/kg q6 wks (2/05). The patient developed progressive low-grade fevers, chills, anorexia, and dry cough (5/05) and was admitted to The Johns Hopkins Hospital (JHH) Gastroenterology service with jejunocolitis. An abdominal abdominal CT showed marked bowel thickening and focal narrowing consistent with Crohn’s disease with a possible fistula (5/05). The patient was discharged to home (06/05). Remicade was effective for symptomatic control for 4 wks when the patient developed abdominal pain and cramps. Despite increasing Remicade, the patient was readmitted to the JHH for continued fevers and chills. Despite aggressive treatment and bowel rest with total parenteral nutrition, he underwent an emergency resection of a segment of jejunum containing a fistula.

**Diagnosis:** Histoplasmosis Complicating Treatment with Anti-tumor Necrosis Factor-α

The sections of small bowel show mucosa with active chronic enteritis with pyloric metaplasia. There is transmural inflammation and many granulomas are seen. At first glance this looks like classic Crohn’s disease but the process differs by having granulomas that are “too good to be true” for Crohn’s disease and indeed that is the case. The granulomas display necrosis. On careful examination, organisms in keeping with histoplasmosis are apparent in macrophages in the granulomas on routine staining, an impression confirmed by additional staining with Gomori methenamine silver.

The patient probably had underlying Crohn’s disease. Treatment with Remicade provided relief for a time, but the ensuing immunosuppression resulted in an unusual but well-described complication of this opportunistic infection(1, 2). Unfortunately the patient died with widely disseminated histoplasmosis.

Histoplasmosis is the most prevalent endemic infection in the US and a common opportunistic infection (3). Immunosuppressed individuals are at high risk for severe infection. Murine models have shown that cell-mediated immunity, including that mediated by tumor necrosis factor-α, is critical for host defense against *Histoplasma capsulatum*(4).

Remicade is a monoclonal (IgG) antibody targeting soluble and cellular tumor necrosis factor-α. It has been used to treat a host of inflammatory disorders including psoriasis, rheumatoid arthritis, and Crohn’s disease. Since it results in immune modulation, reported associated opportunistic infections have included aspergillosis, tuberculosis, and histoplasmosis (1, 2, 5, 6). The latter is a dimorphic fungus endemic to the Central and Eastern United States, where it is found in bat and bird droppings. Histoplasmosis encompasses a wide spectrum of presentations, ranging from indolent pulmonary infections to fatal disseminated cases. Disseminated cases may present, like this one, with fever, malaise, and cough with dyspnea.

In a large Mayo Clinic study of 500 patients treated with Remicade, 8.2% (48 patients) had associated infections. Twenty patients had life-threatening infections, including one with histoplasmosis (7). Other authors have reported about a dozen cases. In general, these patients had severe infections, were undergoing simultaneous treatment with other immune modulators in addition to Remicade, and lived in endemic areas.

Gastrointestinal histoplasmosis is not exclusively a disease of the immunodeficient but can also mimic Crohn’s disease in immunocompetent individuals, a phenomenon to which Lamps et al called attention (8). They evaluated 56 specimens from 52 patients with H&E and silver stains. The presentation was with gastrointestinal rather than pulmonary disease in 43% of their patients. Gross gastrointestinal features included ulcers (49% of patients), nodules (21%), hemorrhage (13%), obstructive masses (6%) and normal mucosa (23%). Microscopic gastrointestinal findings included diffuse lymphohistiocytic infiltration (83%), ulceration (45%), lymphohistiocytic nodules (25%), or minimal inflammatory reaction (15%) but only rare well-formed granulomas (8.5%). The most common hepatic finding was portal lymphohistiocytic inflammation; discrete hepatic granulomas were seen in less than 20% of involved livers. In their series about half of patients were im-
munocompetent, underscoring the need to consider this possibility before making a new diagnosis of Crohn’s disease.

The differential diagnosis of granulomatous enterocolitis includes enterocolitis from the range of processes that result in granuloma formation elsewhere in the body but some infections are relatively specific to the GI tract. These processes include primarily yersiniosis (either with Y. enterocolitica or pseudotuberculosis) and some examples of salmonellosis. The granulomatous process in yersiniosis is centered around Peyer’s patches and there may be histologic features of chronicity in specimens, although features of acute self-limiting enterocolitis may similarly accompany yersiniosis(9, 10). Yersinia genetic material has been detected from specimens from patients with Crohn’s disease where it may better reflect an accomplice than a perpetrator(10). Of course tuberculosis also sometimes affects the GI tract. Malakoplakia is also a possibility.

Several forms of immunodeficiency disease can also result in granulomatous enterocolitis. Chronic granulomatous disease is an inherited disorder manifesting as immune deficiency caused by mutations in any of the genes which encode the various subunits of the superoxide-generating phagocyte NADPH oxidase system responsible for the respiratory burst involved in organism killing. This disease affects around 1 in 250,000 children and is associated with significant morbidity and mortality, with the predicted life expectancy reduced to around 25–30 years of age, with recurrent severe bacterial and fungal infections with granuloma formation. Treatment usually involves the use of prophylactic and therapeutic antibiotics, and newer therapies have been developed such as interferon (IFN)-γ, bone marrow transplantation and gene therapy. Chronic granulomatous disease can affect the colon in about a third of patients (11, 12), and displays prominent macrophages and eosinophils. Granulomas, if present, are poorly-formed. Macrophages are often pigmented (13). Occasional cases of common variable immunodeficiency also show granuloma formation (14, 15) but of course the hallmark is the absence of lamina propria plasma cells and apoptosis.

Once the remainder of other granulomatous lesions are considered and excluded, sarcoidosis can rarely be diagnosed in the lower GI tract.

REFERENCES

13. Levine S, Smith VV, Malone M, Sebire NJ. Histopathological features of chronic granulomatous

Case 68
Elizabeth Montgomery, M.D., The Johns Hopkins University Hospital, Baltimore, MD, USA

Case History
This patient had a history of familial adenomatous polyposis and underwent a colectomy in adolescence. At age 46, the patient had small bowel obstruction and was diagnosed with a small intestinal adenocarcinoma believed to be a second primary. This sample was from the surrounding "normal small bowel".

Diagnosis
Familial adenomatous polyposis involving the small bowel. This patient has a separate small intestinal adenocarcinoma.

Small Bowel Adenomas
Small intestinal adenomas are usually found in the duodenum, and like their colon counterparts, have three major histologic types: Tubular, tubulovillous, and villous. Though rare and not fully reported in the literature as of this writing, traditional serrated adenoma of the duodenum is also rarely encountered. In patients with familial adenomatous polyposis (FAP), endocrine cells are often a prominent component. Though classically described in the stomach, pyloric gland adenomas can also be encountered in the duodenum (1-2). Most adenomas occur singly; the presence of multiple adenomas in the small intestine is unusual in the absence of FAP. In FAP patients, after colectomy, the main cause of death is upper GI tract malignancy (3). The majority of FAP patients also develop upper GI polyps; those in the gastric antrum and duodenum are usually neoplastic. One study documented the occurrence of ileal pouch adenomas in 22.8% (8/35) of FAP patients who underwent proctocolectomies. Eight of those patients also had jejunal and ileal adenomas diagnosed by capsule endoscopy (4). Therefore, surveillance of FAP patients with upper endoscopy and/or wireless capsule endoscopy with biopsies is recommended (3, 5). Because of their potential to undergo malignant transformation, adenomas should be removed via endoscopic polypectomy for pedunculated tumors and endoscopic mucosal resection, or surgical resection, for large sessile lesions. Many surgical colleagues manage high grade dysplasia in these lesions with radical surgery so the pathologist should have a high threshold for diagnosing high grade dysplasia in these lesions. Probably the biggest pitfall in interpreting adenomas in the small bowel is the proclivity of reparative lesions to mimic them. When peptic duodenitis has a nodular configuration, together with marked reactive epithelial changes on microscopic exam, it is easily confused with an adenoma. One clue to recognizing peptic duodenitis is that it often has surface gastric mucin cell metaplasia in the atypical focus. Also, adenomas have their initiation point just beneath the surface epithelium (6), whereas reparative lesions that occur with peptic duodenitis have theirs at the base of the mucosa. Additionally, the surface cells of duodenal adenomas tend to have lipid accumulation in the neoplastic enterocytes. Presumably, since they are neoplastic, these cells can absorb lipid but then are unable to package it for further digestion such that there is often prominent "lipid hang-up" in the surface of duodenal adenomas. This is nicely highlighted on PAS/AB stains since fat does not take up the PAS stain.

Unfortunately, there are occasional cases in which it is impossible to distinguish adenomas from reparative processes and we designate them as "indefinite for dysplasia" and request additional samples. This distinction is not trivial in the small intestine, particularly in the area of the ampulla. There is a precedent for treating large ampullary adenomas with pancreatoduodenectomy, based on their high likelihood of harboring an occult invasive carcinoma (7). More recently, however, endoscopic papillectomy has been increasingly advocated with some success as an alternative to surgery (8).

Primary Small Bowel Adenocarcinoma
Adenocarcinomas are the most common malignancies of the small intestine (30% to 50% of small bowel malignancies). However, primary adenocarcinomas are still rare lesions, accounting for 2% of GI tract tumors and 1% of GI tract cancer deaths (9). They present in older adults (median age, 67 years), have a male predominance, and are more common in African-Americans than Caucasians. The vast majority is sporadic and, like sporadic colorectal adenocarcinomas, shares both clinical risk factors and development from adenomatous polyps. The remaining minority of cases arise in the background of certain predisposing conditions, including several of the polyposis syndromes (primarily FAP, MUTYH polyposis, hereditary nonpolyposis colon carcinoma syndrome [HNPCC], PJ syndrome, juvenile polyposis syndrome); Crohn disease; gluten-sensitive enteropathy (GSE) (10);
ileostomy; and ileal conduits, among others. Inflammatory bowel disease-associated neoplasia in the small bowel is included in colitis-associated neoplasia in Chapter 4. The greatest risk of small intestinal adenocarcinomas is seen with FAP. In these patients, the relative risk of duodenal adenocarcinoma is striking (relative risk, 330.82) as is that for ampullary adenocarcinoma (relative risk, 123.72) (5). As an aside, there seems to be no significant increased risk for gastric or nondonduodenal small intestinal cancer in FAP patients. The risk of small intestinal cancer in Crohn disease and celiac disease are each about 50- to 100-fold. Both sporadic lesions and predisposing condition-associated lesions are most common in the duodenum, where 65% are periampullary, and their prevalence decreases progressively through the rest of the small intestine. An important exception to the proximal location occurs in patients with Crohn disease, in which 70% of adenocarcinomas are ileal, corresponding to the primary site of the inflammatory process in this disease. Small bowel adenocarcinomas are similar histologically to colorectal adenocarcinomas. Most adenocarcinomas are moderately differentiated, and one third is poorly differentiated. Degree of differentiation and special histologic subsets (mucinous, adenosquamous, sarcomatoid, etc.) have little bearing on prognosis and so we mention them only as comments when reporting such cases. The majority of small bowel adenocarcinomas have invaded through the bowel wall by the time of diagnosis.

Residual adenomatous epithelium is found with the majority of resected proximal tumors (those likely to be biopsied prior to resection), but often cannot be demonstrated with large distal small intestinal adenocarcinomas, presumably due to tumor overgrowth. Adenomatous epithelium is readily mimicked by tumors metastatic to the GI mucosa and thus the pathologist should be leery of reporting an in situ component, consistently suggesting correlation with appropriate imaging and other studies (11). To this end, immunohistochemistry is used primarily to exclude metastatic disease, specifically metastatic adenocarcinomas (e.g., colon, breast, lung) or spread from pancreas cancer or other mimickers of poorly differentiated carcinoma (e.g., melanoma and lymphoma). Coordinate labeling for cytokeratins 7 and 20 (CK7 or CK20) might be helpful in distinguishing small bowel adenocarcinomas from metastatic colon adenocarcinomas. However, such labeling would not distinguish adenocarcinomas from other adjacent sites (such as pancreaticobiliary, stomach, lung, ovarian and endometrial tumors), which may share the same CK7 or CK20 pattern as seen in small bowel adenocarcinomas. Immunohistochemistry should be tailored to differential diagnostic considerations and can frequently help in cases of poorly differentiated malignancies. We have found the use of DPC4 (smad4) antibodies helpful in identifying some cases of pancreatic carcinomas because about 60% of pancreatic carcinomas show loss of this marker in their nuclei (12), a relatively uncommon occurrence in colorectal and small intestinal adenocarcinomas. Based on SEER data, the overall survival for patients with small bowel adenocarcinoma is about 30% (13).

REFERENCES


Case 69

Paul E Wakely, Jr., M.D., The Ohio State University, Columbus, OH, USA

**History:** A 53-year-old HIV-positive man presented for evaluation of pain and swelling of his posterior hard palate and maxilla. He had no relevant medical history. A 5-6 cm ulcerated irregular mass involving the hard palate and buccal mucosa was biopsied.

**History:** A 53-year-old HIV-positive man presented for evaluation of pain and swelling of his posterior hard palate and maxilla. A 5-6 cm ulcerated irregular mass involving the hard palate and buccal mucosa was biopsied.

**Pathology:** A solid proliferation of monomorphic large cells with immunoblastic morphology focally penetrated the overlying mucosa. Large vesicular nuclei displayed one or more distinct nucleoli or very coarse chromatin. A modest amount of eosinophilic cytoplasm was present, but a perinuclear area of clearing (hof) was not seen. Individual cell necrosis was common, but a “starry-sky” pattern was absent. Cells labeled with CD138, CD38, and vimentin, and in-situ hybridization for EBER was strongly and diffusely positive. Staining with negative with CD3, CD20, CD56, HHV-8, cytokeratin AE1/3, CD10, bl-1, bcl-2, CD5, actin, desmin, and CD30.

**Diagnosis:** Plasmablastic lymphoma of oral cavity (PLOC)

**Comment:** Plasmablastic lymphoma of the oral cavity PLOC is one of the known AIDS-associated non-Hodgkin lymphomas. Others include: a) diffuse large B-cell lymphoma (DLBL), b.) Burkitt Lymphoma, c.) Primary Effusion Lymphoma, and d.) Plasmablastic Lymphoma Associated with Multicentric Castleman’s disease. In the most recent WHO classification, plasmablastic lymphoma (PL) is considered a variant of DLBL. It may also occur in other settings of immunosuppression such as autoimmune disease, and immunosuppression induced as a consequence of solid organ transplant as well as in immunocompetent individuals.

The initial report of PL and its association with HIV was recognized by Delecluse et al. when they presented 16 patients with a lymphoma of the oral cavity. Only 2 of these 16 had bone marrow involvement, and unlike multiple myeloma none had a serum monoclonal protein. Though it has a predilection for the oral cavity, PL has been described in multiple other sites including the nasal cavity, GI tract, bone, skin, and lung. There is a definite male predominance of almost 5:1 with a mean age of 40-50 years.

Cells of PL have immunoblastic morphology with coarse chromatin, a distinct nucleolus, and a plasma cell immunophenotype. Some examples show multinucleation and binucleation. Mature plasma cells are often inconspicuous if present. Immunohistology shows positive staining with CD138, CD38, and MUM-1 and usually positive for EBER. PL lacks CD45 and B-cell markers CD20, PAX-5, and CD79a, as well as CD3, HHV-8; most cases show light chain restriction. Unlike plasma cell myeloma PLOC is rapidly growing with a high mitotic index with some authors reporting a “starry sky” pattern. The Ki-67 index is typically > 90% nuclear staining.

The principal differential diagnosis is an anaplastic plasmacytoma. The clinical context of immunosuppression, oral cavity involvement, absence of a serum monoclonal protein, negative bone marrow, and absence of multiple myeloma help distinguish the two. Also, the high proliferation index and EBER positivity separate PL from anaplastic plasmacytoma. Burkitt lymphoma is differentiated from PL by its small cell size, and positive staining with CD20, CD45, and bcl-6 while having no evidence of plasmacytic differentiation.

PL is a very aggressive lymphoma with > 70% of patients dying at a median interval of less than one year.

**REFERENCES**


Case 70

Janez Lamovec, M.D., The Institute of Oncology, Ljubljana, Slovenia

**History:** A 53-year-old woman presented with a nodule of the thyroid gland of 10 months duration. FNAB was performed and a diagnosis of oncocytic variant of papillary carcinoma was suggested. Tumor was clinically staged as T2N0M0. A near total thyreoidectomy was performed.

**Pathologic findings:** The resected gland weighed 18.5 grams. Both lobes were vaguely nodular or lobular on cut surface, white-gray in color. The isthmus was completely occupied by a solitary relatively well delineated white-gray firm nodule that measured 2.4 cm in its larger dimension. Microscopically, the tissue of both thyroid lobes showed features of Hashimoto thyroiditis. The tumor in the isthmus is relatively well circumscribed and focally infiltrative, accompanied by a sclerotic stroma, mostly centrally, and dense chronic inflammatory cell infiltration. Neoplastic cells form irregular islands that are either solid or fenestrated by multiple irregular or oval spaces empty or filled with faintly basophilic mucin-like substance. At the periphery of cell nests empty retraction vacuoles or spaces are seen. Some islands feature squamous cells with vague intercellular bridges but no keratinization, other cells are squamoid. Nuclei are clear and vesicular but show no characteristic features of papillary carcinoma nuclei. Occasional intracytoplasmic vacuoles contain intracytoplasmic mucin that is alcian blue and mucicarmin positive; the latter is also present in some cystic spaces inside cell nests. In some slides, a rare psammoma bodies are seen. Mitoses are exceptional. Inflammatory infiltrate in the stroma is composed of lymphocytes and plasma cells, eosinophils are very rare. Russel bodies are scattered among plasma cells. Immunohistochemically, tumor cell were positive for high and low molecular weight keratins (CK5, CK14, CK8, CK19), for p63, for TTF-1, unevenly for E-cadherin, and focally (mucocytes) for CEA. Thyroglobulin, calcitonin, chromogranin A and synaptophysin were negative.

In a close vicinity of the tumor nodule, a small microscopic, 2.5 mm focus of conventional papillary carcinoma was found.

**Diagnosis:** Mucoepidermoid carcinoma (?sclerosing) of thyroid.

**Follow-up:** Two years following surgery, the patient shows no evidence of disease.

**Discussion:** Mucoepidermoid carcinoma (MEC) of the thyroid is a rare type of thyroid carcinoma accounting for less than 0.5% of thyroid malignancies (1). Two types of this particular tumor are recognized: MEC and sclerosing mucoepidermoid tumor with eosinophilia (SMECE). Although there is still some controversy in regard to histogenesis of both tumors the prevailing view is that both variants arise from metaplastic squamous follicular cell nests (2). Histologically, MEC are usually well circumscribed but non-encapsulated while SMECE are usually ill defined; both tumors microscopically infiltrate surrounding thyroid parenchyma and may even spread into adjacent extrathyroid tissue. In MEC, most of the neoplastic cells are represented by squamoid or squamous cells that may show intercellular bridges or even individual cell keratinization and rarely horny pearl formations. Mucocytes may differ in number, from rare to numerous and cystic spaces are also present; they are usually filled with mucin. In some cases, mucocytes are only identified using mucin stains. In other cases, glandular lumina and cysts may be numerous. Nuclei resembling those of conventional papillary carcinoma may be present. Mitotic figures are rare. Stroma is often sclerotic, infiltrated by lymphocytes and plasma cells. Surrounding tissue shows different degree of lymphocytic thyroiditis; oncocytic metaplasia of follicular epithelium should be rarely seen (3,4). In SMECE, the surrounding tissue typically shows features of Hashimoto thyroiditis, often those of fibrous variant of the disease. The thyroid follicles are usually small, lined by oxyphilic epithelium. The tumor is infiltrative and merges with the surrounding tissue. Its stroma is sclerohyaline and moderately to heavily infiltrated by eosinophils admixed with lymphocytes and plasma cells. The neoplastic cells form narrow cords or small nests of epidermoid cells with intercellular bridges and sometimes with keratin pearls. In some epidermoid islands mucin filled spaces are seen; cells with intracytoplasmic mucin droplets are rare. Mitoses are rare. Perineural infiltration may be seen. At the periphery, tumor nests could merge imperceptibly with metaplastic squamous epithelium of the surrounding tissue. Immunohistochemically, in SMECE tumor cells show no thyroglobulin reactivity while this may be focally

**Immunohistochemically, in SMECE tumor cells show no thyroglobulin reactivity while this may be focally...**
present in MEC, TTF-1 positivity is much more commonly and widely expressed in SMECE than in MEC (5, 6).

In both tumors, in the adjacent tissue, even in the close vicinity to the tumor, foci or areas of conventional papillary carcinoma may be found.

Prognostically, both tumors follow an indolent course, with a good long-term prognosis although lymph node and distant metastases are possible (7, 8).

In differential diagnosis, several other tumors should be considered; sclerosing and solid variants of conventional papillary carcinoma, anaplastic carcinoma with squamous foci, extremely rare squamous cell carcinoma of thyroid, intrathyroid thymic carcinoma and metastatic carcinomas or carcinomas arising in adjacent tissues (larynx, trachea, etc) and spreading into thyroid. Clinical evaluation and careful study of morphology are usually enough to recognize the differences between those entities and MEC/SMECE.

Our case is not quite typical for neither of the two variants of the tumor. It is relatively well delineated though infiltrative, stromal fibrosclerotic changes are predominant in the central areas of tumor, tumor nests and islands are relatively prominent, an occasional psammoma body is also seen. These features would well fit with the diagnosis of MEC. However, mucinous component is less obvious, no real duct or cyst formations lined by goblet cell are evident and in addition, surrounding tissue shows features of Hashimoto thyroiditis with oxyphilic transformation of follicular epithelium. On the other hand, the relatively meager mucinous component and inflammation of the surrounding tissue with oncocytic epithelium would be more in line with SMECE. However, non-diffuse type of fibrohyaline stromal changes, lympho-plasmacytic infiltrate almost devoid of eosinophils, and good circumscription of the tumor are against this variant. It appears that more similarities than differences exist between the two variant, and a gray zone between the two should be acknowledged.

LITERATURE


Case 71

Manuel Sobrinho-Simões, M.D., PhD Hospital de São, João, Oporto, Portugal

Clinical history
66-year-old woman with a large “cold” nodule in the right lobe of the thyroid submitted to total thyroidectomy.

Macroscopic description
The right lobe of the surgical specimen (30g) was almost totally occupied by a well circumscribed, apparently encapsulated brownish nodule measuring 4.7x3.2x3.2cm. Histologic description and immunohistochemistry
The tumour has a capsule and is composed by Hürthle (oncocytic) cells with fairly typical nuclei of oncocytic follicular cells (large and regular nuclei with prominent nucleoli). In some areas, the nuclei are slightly more irregular and clearer than common oncocytic-cell nuclei without reaching the threshold of papillary carcinoma nuclei. The tumor has pushing borders and there are no signs of extension beyond the capsule. At least in two spots there were unequivocal signs of invasion of capsular veins. In our institution we do not use immunohistochemistry to detect vascular invasion (Whenever in doubt we ask for deeper sections and for additional samples of the tumour capsule). We do not also perform, routinely, any immunohistochemical markers of cell proliferation (ki67, MIB1, PCNA).

Diagnosis
Hürthle cell (oncocytic) variant of follicular carcinoma

Comments
Almost all histological types of benign and malignant epithelial thyroid tumours have a Hürthle cell counterpart (9). In other words, there are Hürthle cell variants of follicular adenoma (FTA), papillary carcinoma (PTC), follicular carcinoma (FTC), medullary carcinoma (MTC) and poorly differentiated carcinoma (PDTC) (6). Undifferentiated (anaplastic) carcinomas represent the only exception to the aforementioned rule – there is no Hürthle cell counterpart of undifferentiated carcinoma – probably because the neoplastic cells divide too often to allow the accumulation of mitochondria. The criteria used in the diagnosis of the Hürthle cell variants of PTC, FTC and PDTC are those used in the diagnosis of their non-Hürthle cell counterparts: nuclear characteristics of the PTC-type, signs of capsular and/or vascular invasion, and the morphologic features of the so-called Turin algorithm, respectively (5,8,9,14).

In all these instances, the Hürthle cell appearance is thought to represent a phenotype that is superimposed on the genotypic and conventional histopathologic features of the tumours (11). This assumption is confirmed by the similar prevalence of RET/PTC rearrangement and BRAF V600E mutation in Hürthle and non-Hürthle cell variants of PTC (1,13). The existence of a Hürthle cell variant of RET mutated MTC supports the assumption that the Hürthle cell appearance represents a phenotype that can occur in very different genotypic settings (3). In the present case, since there were not PTC-nuclei in the neoplastic cells, the challenge is to separate FTA from FTC and composed but Hürthle cells, i.e., like in cases without Hürthle cells, the search for signs of invasion is crucial to achieve the differential diagnosis between Hürthle cell FTA and Hürthle cell FTC (9,10). Capsular and, more importantly, vascular invasion is also crucial in any encapsulated follicular patterned thyroid tumour in which the diagnosis of PTC is suspected. This holds particularly true in Hürthle cell tumours because the typical features of PTC-nuclei are more difficult to evaluate in Hürthle cells than in normal-looking cells. Immunohistochemistry and molecular genetics are useless in concrete, difficult cases; in these cases, searching intensively for unequivocal signs of invasion remains the best (and only) way to achieve a firm diagnosis (9,10,12).

The existence of unequivocal signs of invasion in venous vessels of the capsule in a tumour without signs of extracapsular parenchymatous extension led in the present case to the final diagnosis of Hürthle cell (oncocytic) variant of follicular carcinoma, minimally invasive and angioinvasive.

The disclosure of vascular invasion leads, in our Institute, to total thyroidectomy and radiiodine therapy. The prognosis of patients with Hürthle cell variants of FTC and PTC is similar to that of patients with the respective conventional, non-Hürthle cell carcinomas, provided the completeness of the surgery, the age of the patients and the staging of the tumours are comparable (4,5,8,10). From a clinical standpoint, the (very) negative aspect of Hürthle cell FTC and Hürthle cell PTC is their lesser ability to trap iodine, thus rendering them much less responsive to radioactive iodine (2,5, 8,10).

A last point to refer that despite the “old” idea that Hürthle cell FTCs tended to carry a guarded prognosis, there is consistent evidence showing that encapsulated,
non-angio-invasive Hürthle cell FTC and Hürthle cell PTC carry, like their non- Hürthle cell counterparts, an excellent prognosis even after being treated conservatively, regardless of nuclear pleomorphism, mitotic index and ki67 value (7,10,15,16).

REFERENCES


Case 72

Janez Lamovec, M.D., The Institute of Oncology, Ljubljana, Slovenia

**History:** A 17-year old girl was admitted because of a solitary thyroid nodule. Ten years earlier, when she was 7-year old she was operated and irradiated for medulloblastoma of cerebellum. A total thyroidectomy was performed.

**Pathologic findings:** The resected gland weighed 9.3 grams. In the lower pole of left lobe, a solitary nodule measuring 17 x 15 mm in two dimensions was found. It was brownish-gray, well circumscribed, with suggested lobulation. The rest of the gland was red-brown in color, with some vague nodularity. Microscopically, the tumor nodule is encircled by irregularly thick band of hyalinized fibrous tissue forming irregular pseudocapsule. Tumor tissue is partly solid, partly follicular with empty lumina and focally cystic with numerous papillae. The latter are of different forms: broad with edematous stalks, some alike to pseudopapillae in nodular goiter, some of moderate size and with fibrosed and hyalinized core. Solid areas exhibit trabeculae and nests of cells separated by delicate vascular stroma. In some foci, small empty cribriform spaces are present inside solid tumor tissue. The cells of the papillae and follicular foci are generally cuboid to columnar, focally stratified with relatively abundant eosinophilic cytoplasm and oval, focally irregular slightly hyperchromatic nuclei with small nucleoli. Rare nuclei are clear, some of ground glass appearance, some with intranuclear inclusions and other with grooves. Mitoses are extremely rare. No colloid is seen neither in follicular nor in cribriform lumina. The cells in the solid areas are mostly spindle shaped, with lighter and oval to spindle nuclei and slightly eosinophilic, moderately to quite abundant cytoplasm. Several nuclei show grooves, typical ground glass nuclei or nuclear inclusions in these areas are very rare. Different patterns of growth intricately merge with each other. The surrounding thyroid tissue is compressed, in fibrous pseudocapsule around the tumor there are some suspicious foci for lymphatic invasion. Resection margins were free of tumor. In the tissue of the right lobe there were several colloid macrofollicular and some microfollicular nodules, some with regressive changes. Immunohistochemically, tumor cells showed weak and very focal positivity for thyroglobulin but strong and diffuse reaction for cytokeratins, including cytokeratin 19, vimentin, bcl-2, CD117, beta catenin (nuclear and cytoplasmic), TTF1, estrogen and progesterone receptors (nuclear reactions) and mitochondrial antigen; several other reactions were negative, including those for HBME-1, S-100 protein, Melan-A, calcitonin, chromogranin A, synaptophysin and CEA. Cyclin D1 and p53 were positive in up to 40 % of cells in solid foci. Proliferation marker MIB-1 decorated around 1% of tumor nuclei. No APC gene mutation was demonstrated by PCR.

**Diagnosis:** Cribriform-morular variant of papillary carcinoma of thyroid.

**Follow-up:** Two and a half year after surgery, there is no evidence of disease.

**Discussion:** The cribriform-morular variant of papillary carcinoma of the thyroid (CMPC), the name coined by Cameselle – Teijeiro and Chan (1) was first reported as a special type of thyroid carcinoma of follicular epithelial derivation by Harrach et al in 1994 (2). The latter authors observed that this type of thyroid cancer is associated with familial adenomatous polyposis (FAP), while the 4 reported cases by former authors occurred sporadically, without such an association. The group from Mayo Clinic reported on 12 cases of thyroid tumors associated with FAP, in 11 of them morphologic appearance was of unusual type such as described by Harach et al (3).

The histologic appearance of CMPC is rather distinctive: tumors may be uni- or multinodular, encapsulated, and microscopically show a mixture of cribriform, papillary, follicular, trabecular and solid growth and often with squamous cell-like nests without keratinization, called morules. Cribriform spaces and follicles are characteristically empty, the former lined by flattened or cuboid epithelium, the latter by tall cells with abundant eosinophilic cytoplasm; similar epithelium covers papillary structures. In solid areas, the cells are plumper or spindly – such areas somewhat resemble the appearance of hyalinizing trabecular adenoma. Nuclei of tumor cells are generally more hyperchromatic, focally with grooves, pallor, and pseudoinclusions; morules were found in one third of the cases of Mayo Clinic series.

Clinical and histological characteristic of CMPC may be summarized as follows: 1. tumor occurs in young...
women as a single or multiple thyroid nodule, 2. it is encapsulated or circumscribed, 3. shows a distinct cribriform pattern of growth with little or no stroma, 4. exhibits follicles devoid of colloid, 5. papillary structures are always present and covered by tall, sometimes stratified epithelium with abundant oxyphilic cytoplasm, 6. shows solid areas with trabecular arrangement of spindle cells resembling hyalinizing trabecular tumor, 7. nuclei are usually hyperchromatic but pale, grooved nuclei with pseudoinclusions are at least focally always present, 8. morular metaplasia is another feature of CMPC with biotin rich nuclei when avidin or streptavidin biotin binding is used as a detection system, 9. immunohistochemical evidence of thyroglobulin positivity is at least focally present (1). Although conventional PTC shares many of the mentioned characteristics, the totality of them are quite typical for this particular variant.

In differential diagnosis, some other subtypes of thyroid tumors should be considered, particularly tall cell and columnar cell variants of PTC, poorly differentiated (insular) carcinoma, and hyalinizing trabecular tumor. Tall cell variant of PTC lacks cribriform, morular and solid spindle cell structures and shows more pronounced papillary structures, columnar cell variant of PTC occurs in older patients, mostly men, shows remarkable cellular pseudostatification, cytoplasm of tumor cells is less abundant and nuclei show no typical PTC nuclei. Poorly differentiated thyroid carcinoma may show microfollicles and prominent solid areas but cells have little cytoplasm and mitotically active nuclei, and areas of necrosis are seen. Hyalinizing trabecular tumor resembles solid trabecular areas in CMPC but lacks other architectural features.

Cytogenetically, CMPC in contrast to conventional PTC, exhibit no BRAF gene mutation that is one of the characteristic findings in the latter tumor (4, 5). It appears that many of the cases of CMPC are associated with FAP, and some are sporadic (1-3). In addition, FAP cases with associated CMPC may also develop other tumors such as medulloblastoma, hepatoblastoma and desmoids tumors. The former may predate diagnosis of FAP for many years or may even be first followed by CMPC and than at later age FAP is diagnosed (6-7). In our case, the patient developed CMPC 10 years after the treatment of medulloblastoma; currently she shows no evidence of FAP but she reported to have had one maternal uncle with colon cancer. However, PCR didn’t show mutation of APC gene in her case.

In regard to treatment of CMPC, a total thyroidectomy is recommended, particularly in FAP associated cases, but extensive lymph node dissection is not recommended. The behavior of the tumor is indolent and prognosis is excellent (8). The most important implication of the diagnosis of this variant of PTC is to alert clinicians of its possible association with FAP and consequently to undertake appropriate diagnostic procedures.

REFERENCES
Case 73

Manuel Sobrinho-Simões, M.D., PhD, Hospital de São João, Oporto, Portugal

Clinical history
24-year-old male with a 5cm nodule in the left lobe of the thyroid. The patient was euthyroid and was submitted to left lobectomy. A couple of months later, following a diagnosis of “poorly differentiated thyroid carcinoma”, the patient was submitted to right lobectomy plus isthmectomy and left cervical lymphadenectomy, followed by radioactive iodine treatment. The case was sent to us for consultation after this second surgery. The patient is alive and well 12 years after the first surgery.

Macroscopic description
whitish nodule measuring 5.3cm in its largest dimension. The isthmus and the right lobe (2nd surgery) were apparently normal. The same holds true – no signs of neoplastic disease, i.e., no metastases – in the left cervical lymph nodes.

Histologic description and immunohistochemistry
The tumour has pushing borders and a lobectomy periphery except in some foci displaying an infiltrative growth pattern. The whole tumour is composed by fairly regular nests of neoplastic cells that occasionally present entrapped follicular structures. The neoplastic cells are monotonous, have an epithelioid phenotype, high nucleo-cytoplasmic ratio and large, uniform nuclei exhibiting prominent nucleoli. The mitotic index is very high and comedo-type necrosis were observed in several neoplastic cell nests.

The neoplastic cells diffusely expressed AE1/AE3, CAM 5.2, CK19, p63, p53 and CD99. There was focal expression of 34βE12, CEA and bcl2. The neoplastic cells did not express PAS, thyroglobulin, calcitonin, TTF-1, CK5, CK7, CK20, chromogranin, synaptophysin, S100 protein, desmin, CD5, CD56, WT1 and c-KIT. The Ki67/ Mib1 labeling index was about 50%.

Molecular study
The cytogenetic study using fluorescent in situ hybridization disclosed the presence of a structural rearrangement of the EWSR1 gene.

Diagnosis
Primary small cell carcinoma of the thyroid with peripheral neuroectodermal tumour (PNET) features.

Comments
The diagnosis of poorly differentiated thyroid carcinoma (PDTC) made when the tumour was first seen was not confirmed by the negativity for TTF1 and thyroglobulin in the neoplastic cells (Immunoreactivity for such markers was indeed restricted to entrapped “normal” follicular cells) (6,11).

After having ruled out the possibility of PDTC we were left with the diagnosis of small cell malignant tumour, primary or metastatic (7,10). The histologic appearance was compatible with the second hypothesis, i.e., it might be an intrathyroidal metastasis from a clinically occult small cell (neuroendocrine?) carcinoma (Primary in the lung? Other site?). The age of the patient (24y) and the absence of any neuroendocrine immunohistochemical marker did not support, however, such possibility. Total body computed tomography and magnetic resonance imaging excluded the existence of any other primary tumour, contributing to rule definitively out the possibility of a metastatic carcinoma. (The benign course of the disease we are now aware of settles any doubt one might have had about its metastatic nature). Most authors question the existence of bona fide primary small cell neuroendocrine carcinomas of the thyroid, whereas others think they may exist, constituting a sort of almost undifferentiated counterpart of medullary carcinoma (2,6,7,10). The unequivocal absence in the case herein described of any immunohistochemical marker of neuroendocrine differentiation (Chromogranin, synaptophysin and CD56 negativity) turned the aforementioned discussion useless in spite of its academic interest. Furthermore, the immunoreactivity for AE1/AE3, CAM5.2, CK19 and 34βE12, showed the carcinomatous (non-neuroendocrine) nature of this primary small cell tumour of the thyroid.

While progressing in the characterization of the neoplastic cells regarding their cytokeratin profile we decided, taking into consideration the young age of the patient and the diffuse CD99 immunoreactivity (and despite the absence of PAS positivity in the neoplastic cells and of any rosette-like pattern in the tumour), to search for the EWSR1 gene translocation. A structural rearrangement of the EWSR1 gene was detected throughout the tumour and the diagnosis of primary peripheral neuroectodermal tumour (PNET) of the thyroid was advanced.
There are at least three cases of PNET/Extraosseous Ewing sarcoma (EWS) of the thyroid on record (1,4,9) that resemble the case here reported except regarding the prominence of epithelial differentiation. Cruz et al (5) reported recently a primary small cell tumour with basaloid features in the thyroid that also shares similar morphological and immunohistochemical features with the present case (e.g. diffuse positivity for cytokeratins and p63 and negativity of neuroendocrine markers). The expression of cytokeratins has been variably reported in PNET/EWS and thought to be related with different EWS variants (8). Taking all this into consideration we propose to classify our case as “Primary small cell carcinoma of the thyroid with PNET features”. The study of a much larger number of cases is necessary to clarify the histogenesis of this (these?) type(s) of thyroid tumours (3,5,9), and to have an idea on its (their?) natural history, namely whether the benign course of the present case, despite its highly malignant histological and immunohistochemical features, is an exception or not.

REFERENCES


Jöns Jacob Berzelius, one of the most prominent natural scientists of the 19th century, was born in 1779 in Väversunda, in the county of Östergötland in southern Sweden, a region with rich cultural traditions. Orphaned at an early age, he went to several foster-homes and received his schooling in nearby Linköping. After graduating in medicine at the University of Uppsala, he moved to Stockholm, where he became assistant master without pay at the so-called »Surgical School«, and earned his keep by working as a doctor for poor people. At the age of 28 he became professor of medicine and pharmacy.

In 1808 Berzelius was one of the seven men who founded The Swedish Society of Medicine »For the perfection of science through mutual mediation of knowledge and collective experience, for the promotion of friendly confidence between doctors«.

Berzelius have enriched our knowledge of nature of life phenomena, established the atomic weights of most of the known elements, presented his electrochemical theory for the understanding of the nature of chemical compounds and laid the foundation for the sciences of the chemistry of rock types. He also found that elements combine with each other according to fixed numerical relationships. In addition to this, in his striving for order and method, with his talent for simplicity and clarity in expression, he created the chemical symbolic language in 1813, which since that time has been an essential instrument of chemistry.

With time he became a practised lecturer but preferred to express himself in writing and this he did superbly. Impressive are the great scientific works where he also demonstrated his interest and ability to spread knowledge about the latest advances of natural sciences.

Berzelius delight in research and debate was united with a great humility before the great scientific questions. Both his attitude and artistry of formulation is illustrated by the following passage in his Manual of Chemistry (vol 3, 1818):

»All our theory is but a means of consistently conceptualizing the inward processes of phenomena, and it is presumable and adequate when all scientifically known facts can be deduced from it. This mode of conceptualization can equally well be false and, unfortunately, presumable is so frequently. Even though, at a certain period in the development of science, it may match the purpose just as well as a true theory. Experience is augmented, facts appear which do not agree with it, and one is forced to go in search of a new mode of conceptualization within which these facts can also be accommodated; and in this manner, no doubt, modes of conceptualization will be altered from age to age, as experience is broadened, and the complete truth may perhaps never be attained. But even if the goal can never be reached, let us never abandon our endeavor to get closer to it.«

Parts of this text is found in
»Berzelius – Creator of the chemical language«
by Carl Gustaf Bernhard,
The Royal Swedish Academy of Sciences
BRIEF HISTORY
OF THE SWEDISH SOCIETY OF MEDICINE

Further education impossible
At the beginning of the 19th century, there were slightly more than 200 physicians in Sweden. Concerned that the radicalism of the French Revolution would spread to Sweden, King Gustav IV Adolf issued extremely strict regulations regarding the importation of books and publications. As a result, opportunities for people to keep up with scientific developments in Europe were virtually non-existent. The only publication that could be imported was a French fashion magazine read by the queen.

Growing membership
The number of physicians in Sweden and membership in the Swedish Society of Medicine has increased over time. In 1809, the Society’s membership was 50, a majority of Stockholm’s physicians. One hundred years later, the Society’s membership was 1 039. In 2008, the Society has about 18 000 members, the majority of which live outside of Stockholm.

Reading society necessary
Many people were dissatisfied with these restrictions. In 1802, a medical lecturer named Jacob Berzelius and an instructor for the Surgical Educational Board named Eric Gadelius sought the king’s permission to form a physicians’ reading society. This request was justified on the grounds that foreign medical literature would result in “the promotion of true information of universal benefit to the state among virtuous and industrious citizens”. The request was denied on the grounds that “two young and already proficient physicians could be diverted from a profession that for the enlargement of their knowledge and experience requires their full attention”. The decision was made by the court chancellor Baron Christoffer Bogislaus Zibet.

Decided by fistula?
Berzelius and Gadelius, however, did not despair, and by 1807, seven physicians from Stockholm were advocating for the creation of a reading society. That same year Baron Zibet suffered an acute and very painful fistula of the urinary tract for which he was treated by Carl Fredrik von Schulzenheim, a senior surgeon at Seraphim Hospital, Zibet’s personal physician, and one of the seven reading society advocates. This may have contributed to Zibet’s decision on 31 December 1807 to approve another request for a reading society. On 25 October 1808, the Society held its first Tuesday Meeting.
**THE SWEDISH SOCIETY OF MEDICINE (SSM)**

- is the scientific organisation of the Swedish medical profession. Its aim is to promote research, education and development in the healthcare sector,
- was founded in 1808 and is one of Europe’s oldest medical organisations
- is responsible, with the support of its 66 sections for the advanced training of Swedish physicians
- promotes research and education in order to improve the quality and the development in the health care sector,
- contributes more than SEK 20 million to medical research every year,
- holds an Annual General Meeting for Physicians – Medicinska Riksstämman

**MEMBERSHIP**

SSM members
- can apply for grants from SSM research funds
- can attend SSM scientific programmes, Tuesday Meetings, symposias and courses
- can use SSM premises and library
- receive a discount on the participants fee on Berzelius symposia, Physician Days in Örebro and at the Annual General Meeting for Physicians – Medicinska Riksstämman
In 1879, the Swedish Society of Medicine moved from what was then the home of Karolinska Institute at Norr Mälarstrand to its own premises in Jakobsgatan in Stockholm. It soon outgrew this location and a search for new premises was resumed. On Walpurgis night in 1889, six men were inside the Katarina lift at Slussen in Stockholm.

A fault developed in the machinery, causing the lift cage to fall. One of the passengers, Carl Westman, was injured, but a fellow passenger, Johan Rissler, a surgeon and member of the building committee of the Society of Medicine, immediately assisted him.

In 1904, the Society announced an architectural competition for a building on a site it had purchased in Klara Östra Kyrkogata. The winner was Carl Westman, and the building was finished two years later.

The Society’s building which dates from 1906, was a breakthrough for the architect Carl Westman and the national romantic style architecture he favoured.

The building itself is work of art – from its facade of handmade brick and Christian Eriksson’s granite reliefs in the entrance to its mosaic floors, carved balustrades, chandeliers, and ventilation grilles – all Westman signatures. The building today is a Swedish, turn of the century architectural treasure.