Surveys and Anatomic Pathology Education Programs

Performance Improvement Program in Surgical Pathology

PIP-D 2023

Case Critiques and Educational Questions

Review the slides and indicate the case diagnosis on the result form before reading this.
In this design, the Clinical Summaries and Master List of Diagnoses are printed on the result form. The Case Critiques and Educational Questions are included in the shipment for the use of each pathologist enrolled in the program.

Claiming CME/CE
Claim credit immediately after submitting results online:
1. Please refer to the kit instructions for information on claiming CME/CE Credit.

Learning Objectives:
1. Recognize clinical and pathologic characteristics that facilitate accurate diagnosis of surgical pathology specimens, distinguishing them from mimics.
2. Discuss important and relevant information (clinical and imaging findings, epidemiology, pathogenesis, prognosis, etc.) pertaining to pathological diagnosis.
3. Identify ancillary tests, including but not limited to special and immunohistochemical stains, genetic and molecular tests, that may help confirm diagnosis, determine prognosis or predict therapeutic response for pathological diagnosis.
4. Use the program as a benchmark for diagnostic performance and as a source of information for quality improvement

The Participant Summary Report (PSR) will be provided online only, three months after the ship date. To find the PSR, log onto cap.org

- Click on the Member Resources section
- Click on Councils and Committees
- Select Surgical Pathology Committee
- Click on Surgical Pathology Topic Center
- Under Surgical Pathology Resources, select PIP Participant Summary Reports (PSR)

To view the current online Pathology Case Challenge, log onto cap.org

- Click on the Member Resources section
- Click on Councils and Committees
- Select Surgical Pathology Committee
- Click on Surgical Pathology Topic Center
- Under Surgical Pathology Resources, select Online Case of the Month
Or go to:
- https://www.cap.org/member-resources/pathology-case-challenge
## TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>PIP 2023-31</th>
<th>Classic follicular lymphoma</th>
<th>.................................................................</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIP 2023-32</td>
<td>Mixed epithelial and stromal tumor</td>
<td>.................................................................</td>
<td>5</td>
</tr>
<tr>
<td>PIP 2023-33</td>
<td>CMV placentitis</td>
<td>.................................................................</td>
<td>9</td>
</tr>
<tr>
<td>PIP 2023-34</td>
<td>Mesenchymal hamartoma</td>
<td>.................................................................</td>
<td>13</td>
</tr>
<tr>
<td>PIP 2023-35</td>
<td>Diffuse thyroid hyperplasia (Graves disease)</td>
<td>.................................................................</td>
<td>16</td>
</tr>
<tr>
<td>PIP 2023-36</td>
<td>Fibroma</td>
<td>..................................................................</td>
<td>20</td>
</tr>
<tr>
<td>PIP 2023-37</td>
<td>Chordoid glioma</td>
<td>..................................................................</td>
<td>24</td>
</tr>
<tr>
<td>PIP 2023-38</td>
<td>Renal cell carcinoma, not otherwise specified (NOS) with sarcomatoid features</td>
<td>.................................................................</td>
<td>28</td>
</tr>
<tr>
<td>PIP 2023-39</td>
<td>Schwannoma</td>
<td>..................................................................</td>
<td>33</td>
</tr>
<tr>
<td>PIP 2023-40</td>
<td>Autoimmune pancreatitis, type 2</td>
<td>..................................................................</td>
<td>37</td>
</tr>
</tbody>
</table>

---

**SURGICAL PATHOLOGY COMMITTEE**

Raul Gonzalez, MD, FCAP, Chair  
Vinita Parkash, MBBS, MPH, FCAP, Vice Chair

Aaron Auerbach, MD, MPH, FCAP, Advisor  
Nadine S. Aguilera MD, FCAP  
Phyu P. Aung, MD, FCAP  
John M. Carney MD, FCAP  
Bonnie Choy, MD, FCAP  
Miriam Conces, MD, FCAP  
Kossivi Dantey, MD, FCAP  
Patrick Henn MD, BS, FCAP  
Juan C. Hernandez-Prera, MD, FCAP  
Mojgan Hosseini, MD, FCAP  
Taylor McAneney Jenkins, MD, FCAP

Xiaoyin Jiang, MD, FCAP  
Mitra Mehrad, MD, FCAP  
Ekene Okoye MD, FCAP  
Anwar Sultana Sabiha Raza, MD FCAP  
Nicole D. Riddle, MD, FCAP  
Lauren Schwartz MD, FCAP  
Robert Alan Schwartz, MD, FCAP  
Steven S. Shen, MD, PhD, FCAP  
Sabrina C. Sopha, MD, FCAP  
Sara E. Wobker MD, MPH, FCAP  
Maximillian Weigelt, MD, (Jr. Member)
## Diagnosis
Classic follicular lymphoma

## Site
Bilateral ovaries

## Clinical Summary
A 62-year-old woman presents with pelvic pain. A CT scan shows bilateral ovarian masses, which are resected and show an extensive lymphoid infiltrate amidst sclerosis and scattered atypical lymphoid follicles. The lymphoid proliferation consists of small, cleaved cells with admixed large, non-cleaved cells with multiple eccentric nucleoli (>15 per high-power field). Flow cytometry reveals a monotypic B-cell population with expression of CD10. Immunohistochemistry shows that the atypical germinal centers are positive for CD20, CD10, BCL6, HGAL, and BCL2; they are negative for CD5. IgG4 is not increased. Fluorescence in situ hybridization (FISH) studies show a t(14;18) (IGH::BCL2) translocation.

For the most representative view, see the online, whole slide image, as all morphological features may not be apparent on all physical glass slides.

## Master List
- Castleman disease
- Classic follicular lymphoma
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Florid lymphoid hyperplasia (Follicular hyperplasia)
- IgG4-related disease
- Mantle cell lymphoma

## Criteria for Diagnosis and Comments
The sections show ovarian tissue involved by a diffuse infiltrate of small irregular lymphocytes (centrocytes) with frequent large, non-cleaved lymphocytes with multiple eccentric nucleoli (centroblasts) (>15 per high-power field [HPF]). Scattered atypical follicles are present at the periphery of the tissue. The follicles lack polarization and tingible-body macrophages. The lymphocytes inside and outside the follicles show the following immunophenotypic profile of the follicles: positive for CD20, BCL6, CD10, HGAL, LMO2, and BCL2. Staining for CD23 and CD21 reveals an intact follicular dendritic network within the follicles, but not in the diffuse areas. FISH studies reveal a t(14;18) (IGH::BCL2) translocation, which is the most common genetic finding in this classical follicular lymphoma (FL).

FL is a B-cell neoplasm composed of neoplastic germinal center cells. The 5th edition World Health Organization (WHO) Classification of Haematolymphoid Tumours has made significant changes to the diagnosis of low-grade FL: grading is now optional, and FL grades 1, 2, and 3A are now grouped together as “classic FL” and considered low-grade. There are a number of reasons for this change, namely: patients with FL grade 1, 2, or 3A are treated with similar regimens; the enumeration of centroblasts is not consistently reproducible; and the outcomes are similar with modern treatment regimens.

In the present case, the architecture is partially diffuse. The cells in the diffuse areas, similar to the nodular areas, show small cleaved centrocytes and large centroblasts (> 15 per HPF). The 5th edition WHO Classification of Haematolymphoid Tumours does not make recommendations for classification of such diffuse areas with greater than 15 centroblasts per HPF and no sheets of large cells. The previous classification of this entity according to the revised 4th edition WHO Classification of
**Criteria for Diagnosis and Comments**

*Haematolymphoid Tumours* FL, grade 3A and diffuse large B-cell lymphoma. The International Consensus Classification (ICC) diagnosis remains the same as the revised 4th edition WHO *Classification of Haematolymphoid Tumours*.

**Castleman disease** is a clinicopathologic diagnosis which can manifest in nodal or extranodal sites characterized by distinctive changes in the follicles, however ovarian involvement is extremely rare. The follicles show a spectrum of follicular hyperplasia progressing to small sclerotic follicles with penetrating vessels. Mantle zones are expanded and frequently merge, leading to the appearance of multiple germinal centers within one follicle (“twinning”). Interfollicular or hilar plasma cells (in lymph nodes) may be increased, but kappa and lambda are polytypic. Genetic findings include alterations in PI3K/AKT/mTOR, MAPK, and JAK-STAT pathways and interleukin signaling abnormalities. Genetic changes characteristic of B-cell lymphoma such as *IGH* rearrangement should be absent.

**Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)** is an indolent lymphoma that can have nodular architecture similar to this case. There may be reactive follicles, and the follicles may be infiltrated (colonized) by neoplastic lymphocytes. The neoplastic cells are small and mature and can show plasmacytoid, monocytoi, or lymphoid appearances. The follicular dendritic networks will appear expanded and fragmented by staining for CD21 or CD23. The neoplastic cells are positive for CD20, and negative for CD5 (most cases) and CD10, distinguishing MALT lymphoma from follicular lymphoma. Kappa /lambda in demonstrates light chain restriction. The most common genetic abnormalities include t(11;18) (*BIRC3::MALT1*), t(1;14) (*IGH::BCL10*), t(14;18)(*IGH::MALT1*), and t(3;14)(*IGH::FOXP1*), which are frequently seen in the thyroid, ocular adnexa, orbit, and skin.

**Florid lymphoid hyperplasia (follicular hyperplasia)** is the most common benign process seen in lymph nodes but can also occur in extranodal sites. Variably sized reactive lymphoid follicles with mantle zones and polarized germinal centers are present. Tingible-body macrophages are often prominent within the follicles. Immunohistochemical stains show the follicles are positive for CD20. Germinal centers are positive for CD10 and BCL6 but negative for BCL2. There are no genetic abnormalities.

**IgG4-related disease** (IgG4-RD) can manifest as lymphoid proliferations in lymph nodes and extranodal sites. Follicular hyperplasia with a dense plasmacytic infiltrate and sclerosis is one of the common patterns in IgG4-RD in the ovary. Rare ovarian cases have been reported as bilateral. Immunohistochemistry shows benign follicles that are CD20 positive and BCL2 negative. Increased IgG4-positive plasma cells are present (> 40% IgG4/IgG or 10 to 200 per HPF depending on site). Immunohistochemistry for kappa and lambda reveals polytypic plasma cells. The lack of IgG4 staining militates against this diagnosis in the present case. Genetic studies are negative for IGH rearrangement or any specific mutations.

**Mantle cell lymphoma** is a non-Hodgkin lymphoma composed of mature mantle zone B cells, which show a mantle zone, nodular, or diffuse pattern architecturally. The lymphocytes characteristically are small and cleaved without significant numbers of large, transformed cells or proliferation centers. Immunohistochemical studies show the neoplastic cells are positive for CD20, CD5, CD19, cyclin D1 and SOX11; they are negative for CD10 and CD23. Kappa / lambda ISH demonstrates light chain restriction. FISH studies show t(11:14) (*CCND1::IGH*) in most cases. The neoplastic lymphocytes in this case are CD5 negative.
1. What is the most common characteristic genetic finding in follicular lymphoma (FL)?
   a) Alterations in JAK-STAT pathway
   b) t(11;14) (CCND1::IGH)
   c) t(11;18) (BIRC3::MALT1)
   d) t(14;18) (IGH::BCL2)
   e) t(14;18) (IGH::MALT1)

Answer: D, a) Feedback: The correct answer is D, t(14;18) (IGH::BCL2). The most common genetic finding in follicular lymphoma is t(14;18) (IGH::BCL2), which is usually demonstrated by fluorescence in situ hybridization.

Objective: 3

2. What is the characteristic immunophenotype of follicular lymphoma?
   a) CD20+, CD10+ CD5+, BCL2+
   b) CD20+, CD10+, BCL6+, BCL2+
   c) CD20+ CD10-, CD5-, BCL2+
   d) CD20-, CD5+, BCL6-, BCL2+
   e) CD20-, CD5+, BCL6-, BCL2-

Answer: B, Feedback: The correct answer is B, the most characteristic immunophenotype of follicular lymphoma is CD20+, CD10+, BCL6+, BCL2+.

Objective: 3

3. Which of the following best describes the morphology of follicular lymphoma?
   a) Centrocytes and centroblasts
   b) Plasmacytic cells, monocytoid cells or small lymphocytes
   c) Polarized germinal centers
   d) Small, cleaved mantle cell-like lymphocytes
   e) Tingible-body macrophages

Answer: A, Feedback: The correct answer is A, follicular lymphomas are comprised of centrocytes and centroblasts.

Objective: 1
References


© 2023 College of American Pathologists
Performance Improvement Program Critique
Case # 2023-32

Diagnosis
Mixed epithelial and stromal tumor

Site
Kidney

Clinical Summary
A 55-year-old woman presents with abdominal pain. CT shows a complex cystic mass involving the left kidney; the right kidney is unremarkable. A nephrectomy is performed and reveals a 12 cm mass composed of multiloculated cysts and small stromal nodules. The stroma is positive for estrogen receptor (ER) and progesterone receptor (PR).

For the most representative view, see the online, whole slide image, as all morphological features may not be apparent on all physical glass slides.

Master List
- Angiomyolipoma with epithelial cysts
- Autosomal-dominant polycystic kidney disease
- Mixed epithelial and stromal tumor
- Multilocular cystic renal neoplasm of low malignant potential
- Tubulocystic renal cell carcinoma

Criteria for Diagnosis and Comments
Histologic sections show a neoplasm composed of variably sized cysts and regions of cellular and fibrous stroma. The cysts are lined by flat, low cuboidal to focally hobnail epithelial cells with predominantly eosinophilic cytoplasm. The nuclei are uniform and without significant cytologic atypia. The bland spindle cell stroma is variably cellular, with areas resembling ovarian stroma. In combination with the immunophenotype (ER and PR positive), the histologic features support a diagnosis of mixed epithelial and stromal tumor (MEST).

MEST and adult cystic nephroma (CN) represent a morphologic spectrum of biphasic cystic renal tumors and are both classified as mixed epithelial stromal tumor of the kidney in the 2022 World Health Organization (WHO) Classification of Urinary and Male Genital Tumours. MEST and CN are distinguished from each other by the presence of a variable solid component in MEST, while cystic nephroma is entirely cystic. These tumors occur most frequently in perimenopausal women and show an association with long-term hormone treatment. Symptoms may include hematuria and abdominal pain, but most tumors are identified incidentally. Tumors are unilateral and typically located centrally within the kidney. MEST are benign neoplasms, but rare cases of malignant transformation have been reported and usually appear as a sarcoma arising from the stroma.

Grossly, MEST is well-circumscribed and unencapsulated, and frequently involves the renal pelvis. Cut surfaces are cystic with a variable solid component, although some tumors may be entirely solid. Microscopically, cysts are variable in size. Smaller cysts are clustered or scattered within the stroma and may contain eosinophilic material. Cysts are typically lined by a flat, cuboidal, or hobnail epithelium, but urothelial, ciliated, and mucinous epithelium have been described. The cytoplasm is typically eosinophilic but may have a clear cell appearance. Solid components consist of variably cellular spindle cells resembling ovarian stroma and may be hyalinized or edematous. Smooth muscle and fat may be seen. Mitoses are rare, and cytologic atypia and necrosis are generally absent. By immunohistochemistry, the stromal component is typically positive for smooth muscle actin (SMA), desmin, CD10, ER, and PR. The epithelial lining is positive for CK7 and PAX8.
Pediatric cystic nephroma (PCN) is a distinct pathologic entity from adult CN. PCN typically presents as an abdominal mass in a young child (less than 24 months of age). These tumors are well-circumscribed, often have a fibrous pseudocapsule, and are composed entirely of variably sized cysts divided by thin septa. There are no expansile solid nodules. Cysts are lined by a simple epithelium similar to that seen in MEST/CN. The fibrous septa are generally hypocellular but may show focal cellular condensations that stain positive for ER. The septa may contain well-differentiated tubules, but no blastemal elements are present. *DICER1* mutations are identified in more than 90% of PCN, and up to two-thirds of these are associated with a germline mutation. *DICER1* mutations are not present in MEST or adult cystic nephroma.

**Angiomyolipoma with epithelial cysts (AMLEC)** is a distinct histologic variant of angiomyolipoma characterized by a mixed solid and cystic appearance similar to MEST. The epithelial cysts are lined by cuboidal to hobnail epithelium, and the stroma typically shows a compact subepithelial cambium layer. Prominent perivascular epithelioid cells "spinning off" from abnormal, thick-walled blood vessels is a classic feature that may be seen in angiomyolipoma and variants thereof. Similar to MEST, the stroma of AMLEC is positive for SMA and ER/PR. However, coexpression of melanocytic markers (HMB45 and MelanA) and cathepsin K in AMLEC is helpful in distinguishing these tumors.

**Autosomal-dominant polycystic kidney disease** is a cystic renal disease associated with mutations in *PKD1* and *PKD2*. Patients typically present in adulthood with bilateral markedly enlarged kidneys replaced by innumerable cysts. The cysts range in size from a few millimeters to centimeters, contain hemorrhagic or clear yellow fluid, and are lined by a single layer of flat to cuboidal epithelial cells. Unlike the fibrous stroma in MEST, kidney parenchyma is present between cysts and shows interstitial fibrosis, tubular atrophy, chronic inflammation, and glomerulosclerosis.

**Multilocular cystic renal neoplasm of low malignant potential** is an indolent, entirely cystic, multiloculated renal neoplasm with thin septations and no solid or expansile nodules. The cysts are lined by simple or focally stratified epithelial cells with clear cytoplasm and small, uniform nuclei. The septa often contain clusters or nests of tumor cells with abundant clear cytoplasm, but solid or expansile nodules are not present. Unlike MEST, ovarian-type stroma is not present. Further, these tumors tend to show alterations in the von Hippel–Lindau (*VHL*) gene, which are absent in MEST.

**Tubulocystic renal cell carcinoma** is a rare renal carcinoma with a strong male predominance. Tumors are well-circumscribed, usually involve the cortex, and have a "sponge-like" cut surface. Microscopically, there are closely packed small to medium-sized tubules and larger cysts lined by a simple flat, cuboidal, or hobnail epithelium. Unlike MEST, nuclei are large and irregular and contain a prominent nucleolus. The cysts are separated by thin fibrous septa. Ovarian-type stroma is absent.
Educational Questions

1. Which of the following is most characteristic of mixed epithelial and stromal tumor (MEST)?
   a) Abundant necrosis
   b) Frequent mitoses
   c) Large, irregular nuclei with prominent nucleoli
   d) Nests of clear cells within fibrous septa
   e) Ovarian-type stroma

   Answer: E,
   Feedback: The correct answer is E, ovarian stroma. Ovarian-type stroma is a defining feature in mixed epithelial and stromal tumor. Rare mitotic figures may be present, but necrosis and significant cytologic atypia are absent.

   Objective: 1

2. Which of the following is true of MEST?
   a) Patients often present with hematuria and hypertension.
   b) There is a strong male predominance.
   c) These tumors carry a high risk of malignant transformation.
   d) Tumors are poorly circumscribed and infiltrative.
   e) Tumors are unilateral and often involve the renal pelvis.

   Answer: E,
   Feedback: The correct answer is E, e) Tumors are unilateral and often involve the renal pelvis. Mixed epithelial and stromal tumor has a strong female predominance, and patients are most often asymptomatic. Tumors are well-circumscribed, are unilateral, and often involve the pelvis. Most are benign, although rare cases of malignant transformation have been reported.

   Objective: 2

3. Which of the following can be used to distinguish angiomyolipoma with epithelial cysts (AMLEC) from mixed epithelial and stromal tumor?
   a) Expression of ER and PR
   b) Expression of HMB45 and MelanA
   c) Point mutation in PKD1
   d) Presence of smooth muscle within the stroma
   e) Solid and cystic cut surface

   Answer: B,
   Feedback: The correct answer is B, expression of HMB45 and MelanA. Both AMLEC and mixed epithelial and stromal tumor (MEST) have a solid and cystic cut surface and show expression of ER and PR within the stroma. Smooth muscle is common in AMLEC and may be present in MEST. Unlike MEST, AMLEC shows expression of melanocytic markers HMB45 and MelanA.

   Objective: 3
References


Miriam R. Conces, MD, FCAP
Surgical Pathology Committee
Nationwide Children’s Hospital
Columbus, OH
**Diagnosis**  
CMV placentitis

**Site**  
Placenta

**Clinical Summary**  
A 23-year-old G1P0110 at 17 weeks gestation presents with decreased fetal movement. Her past medical history is notable only for obesity, and her prenatal care has been routine to date. Bedside ultrasound demonstrates absent fetal heart tones, consistent with intrauterine fetal demise (IUFD). She delivers a nonviable male fetus and placenta. Gross examination of the placenta reveals it is appropriate weight for gestational age, with scattered calcifications.

_For the most representative view, see the online, whole slide image, as all morphological features may not be apparent on all physical glass slides._

**Master List**
- Acute villitis associated with Listeria infection
- Chronic villitis of unknown etiology (CVUE)
- CMV placentitis
- Fetal vascular malperfusion
- Syphilitic placentitis

**Criteria for Diagnosis and Comments**
Sections of the placenta show immature chorionic villi with extensive, diffuse villous involvement by a lymphoplasmacytic infiltrate with areas of necrosis and calcifications. Villous stromal-vascular karyorrhexis (VSVK) is noted in some villi, although the majority of the villi involved by the infiltrate are avascular. Numerous large cells with “owl’s eye” intranuclear inclusions with surrounding halos and eosinophilic cytoplasmic inclusions are seen within the villi. In some foci, the inflammatory infiltrate spills out into the intervillous space, although the majority is confined to the villi. Immunohistochemical staining for cytomegalovirus (CMV) is positive within the large cells with intranuclear and cytoplasmic inclusions. The combined clinical, morphologic, and immunophenotypic findings are consistent with the diagnosis of **CMV placentitis**.

CMV is the most common congenital viral infection, occurring in approximately 1% of all pregnancies. CMV can be transmitted in three main ways: 1) vertical transmission in utero through hematogenous spread through the placenta, 2) intrapartum transmission through cervical secretions, and 3) postpartum transmission through breast milk. The risk of vertical transmission is highest in primary infections (approximately 30% to 50%); however, transmission can occur with CMV reactivation. The earlier the infection occurs in the gestation, the more devastating the symptoms and outcomes. Presentation includes infant sensorineural hearing loss (of which CMV is the most common cause), hepatosplenomegaly, jaundice, thrombocytopenia, fetal growth restriction (FGR), and IUFD in severe cases. Detection of maternal serum CMV IgM antibodies suggests recent primary infection or reactivation. The presence of CMV IgG antibodies does not indicate when infection occurred, but comparison to prior serum CMV IgG tests may provide evidence for recent primary infection particularly if the first sample was IgG negative. It is important not to miss CMV infection in the placenta, as CMV may not be diagnosed in the mother and the neonate is at high risk for sensorineural hearing loss and should have close clinical follow-up.
Criteria for Diagnosis and Comments

Grossly, placentas with CMV infection can be large and edematous or small and fibrotic. Histologic findings within the placenta differ depending on the gestational age. In the first trimester, necrotizing villitis with viral inclusions is seen. In the second trimester, a chronic lymphoplasmacytic villitis with viral inclusions is seen. In third trimester placentas, a milder chronic villitis is seen with increased villous calcifications and hemosiderin deposition. Whenever extensive intravillous calcifications are seen, it is prudent to perform CMV immunohistochemistry or PCR.

Acute villitis associated with *Listeria* infection is a significant cause of late second and early third trimester fetal demise. *Listeria monocytogenes* is hematogenously spread through maternal infection from ingestion of contaminated food such as unpasteurized cheese, deli meats, or unwashed produce. Amniotic fluid in cases of *L. monocytogenes* is frequently meconium stained. Histologic findings in the placenta include an acute villitis with abscess formation. A lymphoplasmacytic infiltrate is not seen. Immunohistochemistry for *Listeria* organisms is diagnostic, as other infectious organisms such as *Streptococcus* and *Yersinia* can yield similar histologic findings.

Chronic villitis of unknown etiology (CVUE) is a chronic villitis comprised of a lymphohistiocytic infiltrate that is most common in the third trimester and affects 3% to 5% of term pregnancies. Unlike viral etiologies, plasma cells are usually rare within the villi, although they can be seen in the decidua (chronic deciduitis with plasma cells). Although the etiology is unknown, CVUE is theorized to represent an alloimmune maternal response to fetal cells in the villi versus an unrecognized infection. CVUE is graded as low grade or high grade depending on the number of villi involved. If more than 10 contiguous villi and multiple foci across multiple sections are involved, this meets criteria for high grade. If more than one focus is seen but less than 10 contiguous villi, this is low grade. Vascular damage, including stem vessel obliteration and avascular villi, is often seen in high-grade CVUE. High-grade CVUE is important to identify, as it is more likely to recur in subsequent pregnancies and can result in neurodevelopmental problems and FGR. Of note, chronic histiocytic intervillositis (a similar entity with a high recurrence rate) shows only intervillous involvement by histiocytic inflammation, whereas in CVUE the villi are involved with occasional spill of inflammation into the intervillous space.

Fetal vascular malperfusion (FVM) occurs due to obstruction of fetal blood flow from the placenta to the fetus, resulting in poor fetal oxygenation. FVM is seen in a variety of conditions, including umbilical cord compromise such as intermittent cord compression, tight nuchal/body cords, true knots, or thrombi; chorionic plate or stem villous thrombi; hypercoagulability; and fetal cardiac dysfunction. Histologic findings in FVM include VSVK, avascular villi, stem vessel obliteration, and fibrin deposition within fetal chorionic vessel walls. In the setting of fetal demise, it can be challenging to distinguish true FVM from IUFD changes. Histologic IUFD changes are similar with VSVK, avascular villi, and stem vessel obliteration; however, the changes should be diffuse throughout the placenta. In contrast, FVM can be segmental or global, depending on the location of the upstream obstruction. While VSVK, avascular villi, and stem vessel obliteration can be seen in CMV placentitis and other forms of chronic villitis, an inflammatory infiltrate is not seen in FVM.

Syphilitic placentitis, or congenital *Treponema pallidum* infection, results from vertical transmission of *T. pallidum* from mother to fetus and often results in IUFD. The characteristic finding is a villous proliferative vasculitis with endovascular proliferation, luminal narrowing, and perivascular fibroblastic proliferation. Other findings may include villous edema, focal acute villitis, and a chronic lymphohistiocytic villitis. Severe necrotizing funisitis is present in approximately 50% of cases, which is not usually seen in CMV placentitis. Spirochetes should be present.
Criteria for Diagnosis and Comments
in cases where antibiotics have not been given and can be identified via immunohistochemistry for *T. pallidum* antibodies or by a Warthin–Starry stain, although the latter can be difficult to interpret. Correlation with serum RPR or VDRL studies can be helpful.

Educational Questions

1. A G2P1 mother presents to her obstetrician at 35 weeks gestation and is found to have an intrauterine fetal demise. Placental histologic examination reveals foci of enlarged villi filled with lymphocytes and histiocytes. Viral inclusions and plasma cells are not seen. What is the most likely diagnosis?

   a) Acute villitis with Yersinia infection  
   b) Chronic histiocytic intervillositis  
   c) Chronic villitis of unknown etiology (CVUE)  
   d) CMV placentitis  
   e) Fetal vascular malperfusion

   **Answer: C,**
   **Feedback:** The correct answer is C, chronic villitis of unknown etiology (CVUE). In CVUE, a chronic lymphohistiocytic infiltrate is seen predominantly within the villi, although it can spill out into the intervillous space. In contrast, chronic histiocytic intervillositis is present only within the intervillous space, without villous involvement. An infectious etiology is not identified.

   **Objective:** 1

2. Which of the following findings is most characteristic of CMV placentitis?

   a) Acute villitis with abscess formation  
   b) Extensive lymphoplasmacytic infiltrate  
   c) Intervillous histiocytic infiltrate  
   d) Severe necrotizing funisitis  
   e) Villous proliferative vasculitis

   **Answer: B,**
   **Feedback:** The correct answer is B, extensive lymphoplasmacytic infiltrate. CMV infection should always be considered when numerous intravillous plasma cells are identified.

   **Objective:** 1

3. A G1P0 mother delivers a viable male infant at 36 weeks gestation. Clinically, the infant is noted to have hepatosplenomegaly, jaundice, thrombocytopenia, and hearing loss. Which of the following findings was most likely seen on placental examination?

   a) Acute villitis with abscess formation  
   b) Fetal chorionic vessel fibrin deposition  
   c) “Owl’s eye” intranuclear inclusions  
   d) Severe necrotizing funisitis  
   e) Villous proliferative vasculitis

   **Answer: C,**
   **Feedback:** The correct answer is C, “owl’s eye” intranuclear inclusions. These viral inclusions are characteristic of CMV, and CMV infection in utero often results in infant hepatosplenomegaly, jaundice, thrombocytopenia, and hearing loss.

   **Objective:** 2
References


Brett R. Kurpiel, MD
Pathology Resident, PGY-3
University of Virginia
Charlottesville, VA 22908

Taylor M. Jenkins, MD, FCAP
CAP Surgical Pathology Committee
Virginia Commonwealth University Health System
Richmond, VA 23219
Diagnosis  Mesenchymal hamartoma

Site  Liver

Clinical Summary  An 8-month-old boy with no significant past medical history presents with 3 months of gradually increasing abdominal distention. Serum AFP is mildly elevated. Imaging reveals a 12 cm mass in the right lobe of the liver, which is resected. Gross examination shows a well-circumscribed myxoid lesion containing fluid-filled cysts.

For the most representative view, see the online, whole slide image, as all morphological features may not be apparent on all physical glass slides.

Master List
- Bile duct adenoma
- Bile duct hamartoma
- Cholangiocarcinoma
- Hepatoblastoma
- Mesenchymal hamartoma

Criteria for Diagnosis and Comments
Sections demonstrate an intrahepatic mass consisting of scattered, variably sized nodules. The nodules are composed of spindled cells with a loose fibromyxoid background and scattered inflammation. The nodules contain both epithelial components (angulated, branched bile ducts) and mesenchymal components (dilated arteries and veins). There is no necrosis, and mitotic activity is minimal. Benign hepatocellular parenchyma is seen between the nodules. The findings support a diagnosis of mesenchymal hamartoma (MH) of the liver.

MH is the third most common intrahepatic mass in children, after hepatoblastoma and infantile hemangioma, and represents approximately 6% of pediatric liver tumors. It usually occurs during the first year of life, with a slight male predilection. MH manifests as a large (up to 25 cm), well-circumscribed, solitary lesion with multiple fluid-filled cysts that may be pedunculated. Approximately 75% arise in the right lobe of the liver. Cases often cause abdominal distention but may be asymptomatic; rare patients may experience cardiopulmonary complications due to abdominal distention or rapid lesional growth. Surgery is curative for this benign lesion, but large tumors may require liver transplantation.

The aforementioned gross and histologic features are typical of MH. Extramedullary hematopoiesis is frequently observed. Cases in very young patients may show small or no cysts, and rare examples presenting in adulthood appear fibrotic rather than myxoid. MH appears to result from a developmental abnormality involving mesenchymal-epithelial transition, and some cases are associated with placental mesenchymal dysplasia. Malignant transformation has rarely been described, though some patients may also develop undifferentiated embryonal sarcoma (UES) of the liver. Accordingly, both MH and UES often demonstrate 19q13 alterations causing activation of the chromosome 19q microRNA cluster. Rare cases of MH may lack this alteration and instead arise in other settings, such as in DICER1 syndrome.
**Criteria for Diagnosis and Comments**

**Bile duct adenoma (BDA)** is an uncommon biliary proliferation usually seen in adults. It consists of a well-circumscribed focus of small, tightly arranged biliary structures without bile. Mucin is frequently seen, and peripheral inflammation is common. BDA are usually encountered incidentally and rarely measure more than 1 cm in size.

**Bile duct hamartoma (BDH)** is a common microscopic finding in the liver that likely represents a localized ductal plate malformation. Also known as von Meyenburg complex, BDH consists of a sub-centimeter arrangement of bland, angulated, dilated biliary structures in a fibrotic bed. Insipssated bile is commonly seen. In children, multiple BDH can be seen in fibrocystic liver diseases such as autosomal dominant polycystic liver disease.

**Cholangiocarcinoma** is a malignant proliferation of bile ducts. It is extremely rare in children. Histology is variable but generally demonstrates a proliferation of malignant bile ducts, which may be small and tightly packed or larger, haphazard, and dilated. Very well-differentiated examples may be challenging to characterize as malignant based on nuclear features and even architecture. Cholangiocarcinomas are infiltrative and should not contain prominent admixed blood vessels or entrapped regions of background hepatocytes.

**Hepatoblastoma**, though rare, is the most common liver tumor in children. This malignant entity usually occurs in the first two years of life and causes abdominal distention alongside nonspecific symptoms. Serum AFP is markedly elevated in the majority of patients. There are several histologic subtypes of hepatoblastoma. Epithelial forms include fetal, embryonal, macrotrabecular, small-cell undifferentiated, and cholangioblastic, while mixed epithelial-mesenchymal forms include teratoid and hepatoblastoma with stromal derivatives. Of these, the two most likely to potentially mimic MH are cholangioblastic (due to a proliferation of bile duct-like structures) and those with stromal derivatives (due to a spindled component). However, evidence of malignancy (such as nuclear atypia) would support a diagnosis of hepatoblastoma. Additionally, MH (and the other listed diagnoses) almost never causes marked elevate on of serum AFP.
1. Which of the following is true about mesenchymal hamartoma of the liver?
   a) Chemoradiotherapy is the mainstay of treatment.
   b) It usually occurs in teenagers.
   c) It is the most common hepatic neoplasm of childhood.
   d) Nuclear atypia is often encountered.
   e) They are grossly large and cystic.

   **Answer: E**
   **Feedback:** The correct answer is E, they are grossly large and cystic. MH have a classic gross appearance, namely a large, myxoid, well-circumscribed mass containing fluid-filled cysts.

**Objective # 1**

2. Mesenchymal hamartoma of the liver shares molecular alterations with what other hepatic neoplasm?
   a) Cholangiocarcinoma
   b) Hepatoblastoma
   c) Hepatocellular carcinoma
   d) Infantile hemangioma
   e) Undifferentiated embryonal sarcoma

   **Answer: E**
   **Feedback:** The correct answer is E, undifferentiated embryonal sarcoma (UES). Both MH of the liver and UES often demonstrate 19q13 abnormalities. The two lesions can rarely occur in the same patient.

**Objective # 3**

3. Which of the following liver tumors is most likely to cause marked elevation of serum AFP?
   a) Bile duct adenoma
   b) Bile duct hamartoma
   c) Cholangiocarcinoma
   d) Hepatoblastoma
   e) Mesenchymal hamartoma

   **Answer: D**
   **Feedback:** The correct answer is D, hepatoblastoma. The majority of hepatoblastomas cause striking serum AFP elevation, which is helpful in establishing the diagnosis. This finding is rarely seen in the other listed tumors.

**Objective # 2**
References


Raul S. Gonzalez, MD, FCAP
Surgical Pathology Committee
Emory University Hospital
Atlanta, GA
Diagnosis | Diffuse thyroid hyperplasia (Graves disease)
---|---
Site | Thyroid
Clinical Summary | A 45-year-old woman with a history of autoimmune disease presents with muscle weakness, irritability, weight loss, tachycardia, and tremor. On physical exam, she is found to have lid retraction, exophthalmos, pretibial myxedema, and a diffusely enlarged thyroid. Thyroidectomy is performed.

For the most representative view, see the online, whole slide image, as all morphological features may not be apparent on all physical glass slides.

Master List
- Chronic lymphocytic thyroiditis (Hashimoto disease)
- Diffuse thyroid hyperplasia (Graves disease)
- Follicular adenoma with papillary architecture
- Follicular nodular disease
- Papillary thyroid carcinoma

Criteria for Diagnosis and Comments
The slide shows diffusely hyperplastic thyroid tissue composed predominantly of irregularly shaped follicles containing scalloped and depleted colloid, lined by cuboidal or columnar hyperplastic papillary epithelium, containing scalloped and depleted colloid. Follicular epithelial cells are cuboidal or columnar in shape with increased cytoplasm and basally located, mildly enlarged nuclei. There is a paucity of inflammatory cells. These morphologic findings are most consistent with diffuse thyroid hyperplasia (Graves disease).

Graves disease (GD) is an autoimmune disorder wherein thyrotropin receptor antibodies (TRAb) bind and activate the thyrotropin receptor, inducing both hypertrophy and hyperplasia of the thyroid follicles. This proliferation results in a diffusely hyperplastic thyroid gland. Binding of the autoantibody to the thyrotropin receptor prompts an increase in thyroid hormone production, giving rise to the clinical hyperthyroidism seen in GD. Thyrotropin receptor is also expressed in retro-orbital and dermal fibroblasts, where autoantibody binding induces proliferation via the accumulation of glycosaminoglycans and results in the findings of exophthalmos and pre-tibial dermopathy seen in some cases.

GD has an incidence of approximately 30 to 200 cases per 100,000 persons in Western countries, with a female:male ratio of approximately 4-8:1. The risk of developing GD is increased for those with siblings who are affected by the disease and further increases with the number of affected siblings. GD often manifests in concert with other autoimmune disorders. Diagnosis is confirmed with detection of TRAb in the context of elevated serum free or bound thyroxine (T4) and/or elevated triiodothyronine (T3). Thyroid-stimulating hormone (TSH) should be suppressed. Treatment involves the administration of beta-adrenergic blocking agents for symptomatic relief, thionamide drugs, and radioactive iodine ablation. Surgical resection of the thyroid may be used for those patients in whom there are contraindications to radioactive iodine (RAI) ablation therapy or refractory disease.
Upon gross examination, the gland will appear red and have diffuse symmetric enlargement and prominent surface vascularity. Sectioning will expose a shiny, uniformly gray or red parenchyma, depending on the vascularity of the specimen. Histologically, the architecture of a thyroid gland affected by GD will most commonly exhibit marked follicular hyperplasia and papillary infolding. Colloid will be pale throughout the gland and will be vacuolated predominantly along the epithelial lining of the follicles. This peri-epithelial vacuolization gives rise to the colloid’s characteristically scalloped appearance. The background may show lymphoid aggregates and associated germinal centers. Cytologically, thyroid follicular epithelial cells affected by GD will be columnar, oncocytic, or cuboidal with basally oriented, normo- or hyperchromatic, round or ovoid nuclei. The cytoplasm may be basophilic or amphophilic and may also be vacuolated in some cases. In longstanding cases, the thyroid may exhibit mild fibrosis. In untreated cases, the gland may have a highly cellular appearance with minimal colloid. In treated cases, these classic histologic findings of GD may be minimal to absent. Foci of bizarre endocrine-type atypia can be seen in patients who have been treated with methimazole or RAI.

Immunohistochemical analysis plays a limited role in the diagnostic workup of GD.

**Chronic lymphocytic thyroiditis (CLT)** is an autoimmune disorder with a nonspecific etiology. Early in the disease process, affected patients may experience a transient period of clinical hyperthyroidism much like that seen in patients with GD. However, as CLT progresses and as the thyroid follicular cells are destroyed, patients will enter a chronic state of hypothyroidism requiring substitution therapy. Morphologically, these glands will show abundant lymphocytic infiltrate with lymphoid follicle formation, oncocytic change of the follicular epithelium, and fibrosis. Papillary hyperplasia and scalloped colloid are typically absent in CLT.

**A follicular adenoma with papillary architecture** is an encapsulated, hormonally active nodule of thyroid follicular epithelium (“hot nodule”). Like in patients with GD, the clinical picture will be one of hyperthyroidism. However, the papillary proliferations are confined to the nodule, unlike the diffuse glandular enlargement seen in GD.

**Follicular nodular disease** is a common proliferative disorder of the thyroid gland brought on by either an iodine deficiency or several other environmental or genetic factors. The term follicular nodular disease is recommended by the WHO rather than the variety of terms that have historically been used to describe this entity (for example, “colloid nodules,” “adenomatoid nodules,” “hyperplastic”). Clinically, the gland can enlarge to the point of generating compressive symptoms. Most patients remain euthyroid. Histologically, the gland shows multiple follicular nodules, which may be hyperplastic or neoplastic. Papillary hyperplasia and scalloped colloid may be focally present but should not be diffusely present, as in GD.

**Papillary thyroid carcinoma (PTC),** like GD, is also characterized by papillary growth. Unlike GD, however, PTC is a mass-forming lesion that exhibits optical nuclear clearing, nuclear grooves, and nuclear pseudoinclusions. These features are generally not prominent in the thyroid follicular epithelium affected by GD, though the endocrine atypia seen in GD can raise concern. Generally, these foci of endocrine atypia show bizarre cytology rather than typical PTC nuclear features. Unlike GD, PTC often harbor a **BRAF** V600E mutation. A panel of galectin3, HBME1, and CK19 may also be helpful to distinguish PTC from morphologic mimics.
1. Which of the following entities characteristically shows hyperplasia and scalloping of thyroid colloid throughout the gland?
   a) Chronic lymphocytic thyroiditis (Hashimoto disease)
   b) Diffuse thyroid hyperplasia (Graves disease)
   c) Papillary thyroid carcinoma
   d) Thyroid follicular adenoma with papillary architecture
   e) Thyroid follicular nodular disease
   **Answer:** B
   **Feedback:** The correct response is B, diffuse thyroid hyperplasia (Graves disease). While other entities may also exhibit papillary growth of the thyroid follicular epithelium, scalloping of the colloid seen throughout the gland is most characteristic of Graves disease (GD).

2. Which of the following is true of diffuse thyroid hyperplasia (Graves disease)?
   a) It is commonly associated with exophthalmos.
   b) It is often associated with a history of iodine deficiency.
   c) It is seen more commonly in men than in women.
   d) Patients will often initially present with symptoms of clinical hypothyroidism.
   e) The thyroid gland of an affected patient will likely exhibit asymmetrical hypertrophy.
   **Answer:** A
   **Feedback:** The correct response is A, it is commonly associated with exophthalmos. As the thyrotropin receptor is expressed both in the thyroid gland and elsewhere in the body, thyrotropin receptor antibodies (TRAb)-induced hypertrophy also commonly occurs in several locations outside the thyroid gland (eg, in retro-orbital and pretibial tissues).

3. Which architectural feature is characteristically shared by both GD and papillary thyroid carcinoma?
   a) Cystic change
   b) Lymphoid follicles
   c) Microfollicular proliferation
   d) Papillary architecture
   e) Thyroid parenchymal atrophy
   **Answer:** D
   **Feedback:** The correct response is D, papillary architecture. Papillary architecture is not limited to thyroid tissue affected by GD. It is important to consider other features like cytologic atypia, colloid scalloping, and the patient’s clinical presentation when making a diagnosis of GD.

**Objective:** 1.
References


Ian Taylor-Cho, BA
Medical Student
Duke University School of Medicine
Duke University Medical Center
Durham, NC

Xiaoyin “Sara” Jiang, MD, FCAP
Surgical Pathology Committee
Duke University Medical Center
Durham, NC
Performance Improvement Program Critique
case # 2023-36

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Fibroma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>Ovary</td>
</tr>
</tbody>
</table>

Clinical Summary
A 57-year-old woman presents with pelvic pain and is found to have torsion of a 12 cm ovarian mass, which is excised. Sectioning of the mass reveals a homogenous pink cut surface with focal hemorrhage.

For the most representative view, see the online, whole slide image, as all morphological features may not be apparent on all physical glass slides.

Criteria for Diagnosis and Comments
Histologic examination reveals a diffuse proliferation of uniform spindled cells. The spindled cells are bland, with “wavy” nuclei and ill-defined cell borders, and devoid of significant atypia or mitotic activity. There is focal prominent intercellular edema with interspersed fibrillary collagen bands. In some sections, perivascular hyalinization is present. These histologic features are diagnostic of ovarian fibroma.

Fibromas are the most common stromal tumor of the ovary and typically present in women in the 4th or 5th decades. They are benign but may recur, occasionally after a long interval, especially if adherent or ruptured at surgery. In approximately 2% of cases, fibromas are associated with ascites and right-sided pleural effusion (Meigs syndrome), which disappear after tumor resection. Fibromas associated with Meigs syndrome often show prominent edema and may have cystic degeneration. Ovarian fibromas arising in young patients, bilaterally, with extensive calcifications, or in multiples raise concern for basal cell-nevus syndrome (Gorlin syndrome), which is associated with a germline mutational inactivation of either SUFU or PTCH1.

Typical fibromas are composed of spindled cells without cytologic atypia and variable amounts of collagen. Focal hemorrhage and necrosis may be present. Due to a continuum in histology between fibromas and thecomas, many pathologists combine these under a single label of “fibrothecoma.” However, experts recommend the use of stringent criteria for the diagnosis of thecomas, which show a syncytial growth of rounded cells with pale “gray” cytoplasm. They often show keloid-type scarring, calcification, or sclerosis. Using stringent criteria, thecomas are rare neoplasms. Uncommon features in fibroma include minor sex-cord elements, eosinophilic hyaline globules, and melanin pigment. Fibromas with minor sex-cord elements have less than 10% sex-cord elements, typically of the granulosa cell type. They are benign.

Some fibromas may be densely cellular with intersecting fascicles and storiform growth (cellular fibromas). Increased mitotic activity, often in a “hotspot” type distribution and surrounding areas of sharply demarcated “infarct-type” necrosis may also be present. Early studies suggested that cellular fibromas with a mitotic activity of 4 or more mitoses per 10 high-power had malignant potential and recommended labeling these tumors as fibrosarcoma. However, contemporary data do not bear this out. High mitotic activity in an otherwise typical or cellular fibroma does not portend a poor prognosis. Tumors with increased cellularity and high mitotic activity (>4 per 10
HPF, without cytologic atypia, are designated as mitotically active cellular fibromas. These are benign. Fibrosarcomas of the ovary are extremely rare tumors. These demonstrate increased mitotic activity in a background of diffuse moderate to severe atypia. Coagulative necrosis is often present.

Fibromas have a nonspecific immunohistochemical profile and may be immunoreactive for inhibin and calretinin, although typically in a focal or weak pattern. WT1, CD56, SF1, and hormone receptors may also be positive.

**Adult granulosa cell tumor (AGCT), diffuse or spindle cell pattern** is perhaps the most difficult and consequential differential diagnosis, as it is a low-grade malignancy with the potential for recurrence that requires follow-up. AGCT shows significant morphologic overlap with cellular fibroma and is composed of sheets of rounded spindled cells. Careful search combined with a high level of suspicion will often reveal subtle areas with insular, trabecular, or cored growth composed of epithelioid cells with nuclear grooves. Reticulin stains are useful in separating AGCT from fibroma. AGCT shows reticulin investing groups of tumor cells, unlike fibroma where reticulin invests single cells. Strong, diffuse calretinin and inhibin staining also supports the diagnosis of AGCT. However, none of these criteria is absolute. The detection of the somatic missense point mutation c.402C>G (C134W) of the FOXL2 gene is considered diagnostic for adult granulosa cell tumors.

A particularly challenging situation arises when one has true mixed tumors, the so-called granulosa-theca cell tumors, which show a 10% to 40% granulosa cell tumor component in a fibrothecomatous background. Two relatively small contemporary series suggest that these tumors behave in a benign fashion. Tumors with large nests of granulosa cells more frequently harbored a FOXL2 mutation, which was concordant between the granulosa cell and ‘fibrothecomatous’ component. Of note, tumors with <30% granulosa cell tumor component did not demonstrate a mutation.

A practical approach to this conundrum has been to recommend mutation testing for challenging, cellular spindled “fibrothecomatous” tumors that either have a subtle epithelioid look or show a significant nested component of granulosa cells.

**Leiomyoma** of the ovary is rare and is characterized by a proliferation of uniform spindled cells with cigar-shaped nuclei arranged in intersecting parallel fascicles. The tumor cells are positive for desmin. Smooth muscle actin positivity is not discriminatory, as some fibromas may show positivity. Ovarian leiomyomas are benign.

**Massive ovarian edema** is a rare, benign tumor-like condition arising in young women in their second or third decades, where edematous fluid accumulates in the ovarian stroma secondary to partial intermittent torsion of the ovarian pedicle. It may be associated with stromal fibrosis (fibromatosis). The normal ovarian architecture is maintained with a rim of preserved cortex and intervening ovarian follicles. Clusters of lutein cells may be present.

**Sclerosing stromal tumors** are rare unilateral ovarian neoplasms most common in young women in their third decade. The tumors show characteristic alternating cellular and edematous hypocellular areas, imparting a pseudolobular appearance. A prominent staghorn vascular pattern is invariably present. The cellular areas are composed of spindled and round to oval, eosinophilic to vacuolated “luteinized” cells. The tumor cells are generally positive for calretinin and inhibin. TFE3 and Melan-A positivity is reported in a small number of cases. Recurrent FHL2::GLI2 gene fusion is reported in ~65% of cases, and other GLI2 rearrangements in an additional 15%. To date, only one tumor with recurrence has been reported.
Educational Questions

1. A cellular fibromatous tumor of the ovary without cytologic atypia has a mitotic activity of 6 per 10 high-power fields. It is negative for desmin. What is the diagnosis for this tumor?
   a) Cellular fibroma
   b) Fibroma
   c) Fibrosarcoma
   d) Leiomyoma
   e) Mitotically active cellular fibroma

Answer: E.
Feedback: The correct answer is E, this would be diagnosed as a mitotically active cellular fibroma. Although some original papers suggested that increased mitotic activity (4 or more mitoses per 10 HPF) was concerning for a diagnosis of fibrosarcoma, contemporary data show that increased mitotic activity, absent cellular atypia, does not portend a negative prognosis. A fibrosarcoma would show moderate to marked cytologic atypia, increased mitotic activity and often coagulative necrosis. A leiomyoma should stain positively for desmin. A specific cut-off based only in mitotic activity, is not set for the diagnosis of fibrosarcoma.

Objective: 1

2. A 6 cm ovarian mass in a 20-year-old woman shows marked edema and a bland spindle-cell proliferation. There is a preserved cortical rim of ovarian stroma, and entrapped follicles are identified. What is the most likely diagnosis?
   a) Cellular fibroma
   b) Fibroma with minor sex cord elements
   c) Granulosa-theca cell tumor
   d) Massive ovarian edema
   e) Sclerosing stromal tumor

Answer: D.
Feedback: The correct answer is D, massive ovarian edema. A preserved cortical rim and entrapped follicles is only seen in massive ovarian edema, a condition secondary to intermittent torsion of the ovarian pedicle. Fibroma with sex cord elements and granulosa-theca cell tumor would show defined, if subtle, sex cord elements admixed with a fibrothecomatous stroma. The former would show less than 10% sex-cord elements, while the latter would have 10% to 40% of the tumor composed of granulosa cell elements. Sclerosing stromal tumor shows alternating edematous and compact areas. The cells in the compact area are "luteinized" with eosinophilic to vacuolated cytoplasm.

Objective: 1

3. What gene is altered in sclerosing stromal tumor?
   a) FOXL2
   b) GLI2
   c) PTCH1
   d) SUFU
   e) TP53

Answer: B.
Feedback: The correct answer is B, GLI2. Sclerosing stromal tumors show recurrent FHL2::GLI2 fusions in approximately 65% of cases, and other GLI2 rearrangements in an additional 15%. Germline mutational inactivation of either the SUFU or PTCH1 gene is seen in Gorlin syndrome, and patients often have bilateral calcified fibromas presenting at a young age. FOXL2 mutation is characteristic of adult granulosa cell tumor. TP53 mutations are seen in many high-grade tumors, including high-grade serous ovarian carcinoma.

Objective: 3
References


Veronica Brooks
Undergraduate Student
Yale College
New Haven, CT

Vinita Parkash MBBS, MPH, FCAP
Surgical Pathology Committee
Yale University School of Medicine
New Haven, CT
Diagnosis: Chordoid glioma

Site: Brain

Clinical Summary: An autopsy is performed on a 46-year-old woman following a motor vehicle accident. Medical records indicate that the decedent had been experiencing headaches with associated nausea and vomiting. Serial sectioning of the cerebral hemispheres reveals a well-circumscribed, tan-brown, solid 5.4 cm mass obliterating the third ventricle and displacing adjacent midline structures. Immunohistochemical staining demonstrates that the tumor cells are positive for GFAP and patchy TTF1.

For the most representative view, see the online, whole slide image, as all morphological features may not be apparent on all physical glass slides.

Master List:
- Chordoid glioma
- Conventional chordoma
- Diffuse midline glioma, H3 K27-altered
- Meningioma, chordoid variant
- Metastatic chondrosarcoma

Criteria for Diagnosis and Comments:
Microscopic sections of the brain mass at autopsy demonstrate epithelioid tumor cells arranged predominantly in cords separated by a basophilic or amphophilic mucinous matrix. Other areas of the tumor are arranged in solid sheets and clusters. The tumor cells have abundant eosinophilic cytoplasm with round to oval nuclei and vesicular chromatin. No significant mitotic activity is noted, though focal necrosis is present. Rare intranuclear pseudoinclusions are identified. There is an intratumoral lymphoplasmacytic infiltrate, and the surrounding brain tissue shows reactive gliosis with occasional Rosenthal fibers and chronic inflammation. These findings are characteristic of a chordoid glioma.

Chordoid gliomas are rare, accounting for fewer than 0.1% of all primary brain tumors. They are well-circumscribed, solid glial neoplasms that occur in or around the third ventricle. They are thought to arise from tanycytic ependymal cells in that region. They most frequently occur in adults with a median age of 45 years and bear a slight female predominance. On T1-weighted MRI, they are isointense to background brain and show avid homogenous contrast enhancement.

Patients most often present with symptoms of obstructive hydrocephalus such as headache, nausea, vomiting, and/or ataxia. Chordoid gliomas have also been associated with psychiatric symptoms, memory disruption, and personality changes. Given their proximity to the optic chiasm, visual field defects may occur. Moreover, the tumor can cause endocrine dysfunction such as amenorrhea, diabetes insipidus, and hypothyroidism from compression of the hypothalamus.

Histopathologically, chordoid gliomas are commonly composed of clusters and cords of epithelioid cells with a variably mucinous stroma. Less common histological variants include a solid pattern with sheets of polygonal epithelioid cells with no significant mucinous stroma, a fusiform pattern with groups of spindle-shaped cells scattered among a loose collagenous stroma, and a fibrosing pattern with abundant collagenization, the latter of which is most common in older patients. Mitoses are usually rare or absent, and classically there is a stromal lymphoplasmacytic infiltrate, often with numerous Russell bodies. The surrounding non-neoplastic tissue often has reactive astrocytes, Rosenthal fibers, and chronic inflammation.
**Criteria for Diagnosis and Comments**

Chordoid gliomas have a unique immunophenotypic profile. Similar to other gliomas, they demonstrate strong and diffuse expression of GFAP. Consistent TTF1 expression, albeit in varying degree and intensity, can assist in differentiating chordoid gliomas from other tumors with chordoid morphology. Chordoid gliomas may also show immunoreactivity for cytokeratins and should not be mistaken for metastatic carcinoma. Immunohistochemistry for CD34 is strongly positive, while EMA and S100 can be variable. Neuronal and neuroendocrine markers are negative.

Chordoid gliomas have a hallmark p.D463H missense mutation in the \textit{PRKCA} gene, which can be used as an ancillary diagnostic tool. While other central nervous system (CNS) tumors may demonstrate \textit{PRKCA} gene alterations (e.g. fusions in papillary glioneuronal tumor), the aforementioned mutation is specific to chordoid glioma. Chordoid gliomas also have a distinct DNA methylation profile and in rare diagnostically challenging cases, this modality can be used as another diagnostic tool. Chordoid gliomas lack other mutations associated with infiltrating gliomas, involving genes such as \textit{IDH1/2}, \textit{ATRX}, and \textit{TP53}.

Chordoid gliomas are assigned CNS WHO grade 2 because they are well-circumscribed; however, given their typical location, gross total resection in the third ventricle is often not possible without significant endocrine or personality-related sequelae. For this reason, maximal safe resection is the goal, with potential recurrence possible. The role of adjuvant radiation has not been established.

**Conventional chordomas** are tumors of notochordal derivation that largely arise within bones of the axial skeleton, commonly within the clivus or sacrum. They are composed of large epithelioid cells with clear to eosinophilic bubbly cytoplasm (physaliphorous cells) often separated into cords, nests, and nodules by a fibrous to chondromyxoid stroma. They are traditionally immunoreactive to keratins, EMA, and S100, though all can be focal or negative, especially after treatment. Brachyury is uniformly positive, and this immunostain can be ordered in cases where more traditional markers are not supportive. Unlike chordoid glioma, GFAP and TTF1 are negative. There are poorly differentiated and dedifferentiated chordomas; the former is associated with \textit{SMARCB1} mutation and loss of INI1, and the latter may have focal keratin expression but is negative for brachyury and can only be confirmed by a previous or adjacent conventional chordoma.

**Diffuse midline gliomas (DMG), H3 K27-altered**, as their name implies, are diffuse (infiltrative) and usually midline with a diagnostic molecular alteration, loss of H3 p.K28me3 (K27me3), and fall into several subtypes: diffuse midline glioma H3.3 K27–mutant, diffuse midline glioma H3.1 or H3.2 K27–mutant, diffuse midline glioma H3-wildtype with EZHIP overexpression, and diffuse midline glioma EGFR-mutant. This tumor is listed as a pediatric subtype within the WHO but occurs in any age group and should be ruled out in any midline tumor. Histologically, DMG commonly consist of small, monomorphic cells, but similar to other gliomas, they can have more astrocytic, piloid, oligodendrogial, giant cell, undifferentiated, or epithelioid cytomorphology. Mitotic figures, necrosis, and microvascular proliferation are often present but are not needed for the diagnosis, as DMG are considered CNS WHO grade 4 regardless. Most DMG express OLIG2, except in the \textit{EGFR}-mutant subtype, where OLIG2 is often negative. The combination of positive nuclear staining for HK27M along with a loss of H3K27me3 immunostaining is confirmatory. Of note, tumors associated with H3 K27I mutation or EZHIP overexpression will not express HK27M but will have loss of H3K27me3 and should be diagnosed by further molecular analysis.
**Criteria for Diagnosis and Comments**

**Meningioma, chordoid subtype** consists of cords and small nests of epithelioid cells, often with vacuolated cytoplasm, embedded in a myxoid/mucoid stromal matrix. While meningiomas can occur intraventricularly, they more frequently arise on the cerebral convexity. Although they usually lack the features associated with higher-grade meningiomas, the chordoid subtypes have a rate of recurrence similar to atypical meningiomas and therefore are automatically considered CNS WHO grade 2. They are immunoreactive for SSTR2A, variably positive for EMA and PR, and negative for GFAP and TTF1.

**Metastatic chondrosarcoma** is extremely rare but could be in the histologic differential for chordoid glioma, especially on small biopsies of grade 2-3 chondrosarcomas with prominent myxoid stroma. However, they can be differentiated from chordoid glioma by their negativity for GFAP and TTF1.

**Educational Questions**

1. Alteration of which gene is most frequently identified in chordoid gliomas?
   a) \(BRAF\)
   b) \(IDH1\)
   c) \(PDGFR\)
   d) \(PRKCA\)
   e) \(PTEN\)
   **Answer:** D
   **Feedback:** The correct answer is D, \(PRKCA\). Chordoid gliomas have a hallmark missense mutation on \(PRKCA\), specifically a p.D463H mutation.
   **Objective:** 3

2. Which of the following immunohistochemical stains **best** differentiates a chordoid glioma from its mimics?
   a) Brachyury
   b) Chromogranin
   c) IDH1
   d) Progesterone receptor
   e) TTF1
   **Answer:** E
   **Feedback:** The correct answer is E, TTF1. This immunostain is positive in chordoid gliomas and posterior pituitary tumors, as is expected given the TTF1-positivity in non-neoplastic diencephalic brain tissues including hypothalamus and third ventricle.
   **Objective:** 1

3. Which of the following is **true** regarding treatment of chordoid gliomas?
   a) Complete surgical resection is optimal but may result in neurologic deficits.
   b) Given their well-circumscribed nature, observation is acceptable.
   c) Similar to infiltrating gliomas, chemoradiation therapy is standard of care.
   d) Targeted therapy for PRKCA mutation is available.
   e) The PRKCA mutation portends short overall survival regardless of treatment modality.
   **Answer:** A
   **Feedback:** The correct answer is A, complete surgical resection is optimal but may result in neurologic deficits. Chordoid gliomas, like other focal or well-circumscribed gliomas, are treated by complete surgical resection. Unfortunately, given the location, complete resection in this region may lead to endocrine dysfunction such as diabetes insipidus or other neurologic deficits.
   **Objective:** 2
References


Eduardo Medina Parrilla, MD, FCAP
Neuropathology Fellow
University of Florida
Gainesville, FL

Jesse Lee Kresak, MD, FCAP
Neuropathologist
University of Florida
Gainesville, FL

Nicole Riddle, MD, FCAP
Surgical Pathology Committee
Tampa General Hospital
Ruffolo, Hooper, and Associates / USF Health
Tampa, FL
### Diagnosis
Renal cell carcinoma, not otherwise specified (NOS) with sarcomatoid features

### Site
Kidney

### Clinical Summary
A 61-year-old woman presents with hematuria, right flank pain, and weight loss. Imaging reveals an 11 cm mass in the upper portion of the right kidney. Radical nephrectomy is performed and reveals a large, heterogenous renal mass with hemorrhage and necrosis, extending into the perirenal fat. The tumor cells are positive for AE1/AE3, focally positive for PAX8, and negative for GATA3, p63, and TLE1 by immunohistochemistry.

*For the most representative view, see the online, whole slide image, as all morphological features may not be apparent on all physical glass slides.*

### Master List
- Angiomyolipoma
- Dedifferentiated liposarcoma
- Renal cell carcinoma, NOS with sarcomatoid features
- Sarcomatoid urothelial carcinoma
- Solitary fibrous tumor
- Synovial sarcoma

### Criteria for Diagnosis and Comments
Sections show a high-grade tumor composed of spindled-to-epithelioid cells with significant atypia and frequent mitoses, scattered giant cells, and focal necrosis. There is no recognizable histologic subtype of renal cell carcinoma (RCC) component. This combination of morphology and immunophenotype (positive for AE1/AE3 and PAX8, and negative for GATA3) supports the diagnosis of renal cell carcinoma, NOS with sarcomatoid features (sRCC).

sRCC is not considered a specific subtype of renal cell carcinoma (RCC) but rather a pattern of dedifferentiation in which the tumor loses epithelial morphology and gains high-grade spindle cell morphology, ranging from fibrosarcomatous-like to undifferentiated and pleomorphic. Heterologous differentiation into chondrosarcoma, osteosarcoma, or rhabdomyosarcoma is rarely reported. To make this diagnosis, extensive sampling is required to identify the primary RCC subtype. Any amount of sarcomatoid features is enough to diagnose a tumor as having sarcomatoid differentiation, which qualifies for WHO/ISUP nucleolar grade 4. Most patients with sRCC are symptomatic and present with locally advanced or metastatic disease. In general, sRCC has a poor prognosis with a median survival of 6-13 months; greater proportions of sarcomatoid differentiation within the tumor are directly correlated with worse outcomes. It is recognized that many specific RCC types can develop sarcomatoid differentiation. Most sRCC are associated with clear cell RCC, probably because it is the most common type of RCC. However, it has been reported that chromophobe RCC has a higher rate of sarcomatoid differentiation than other common types of RCC.
In cases where no visible RCC subtype component can be identified despite extensive sampling, immunohistochemistry can aid in the diagnosis of sRCC. Positive immunoreactivity with pan-cytokeratin, low molecular weight cytokeratin, and EMA would favor a sarcomatoid carcinoma over sarcoma. Expression of PAX8 and PAX2 support the diagnosis of RCC. Recently, next generation sequencing has been used to investigate the different genomic alterations in sRCC. The most commonly mutated gene in the sarcomatoid component of sRCC is TP53, while the most commonly shared single nucleotide variants between the epithelial and sarcomatoid components are VHL, BPRMI, PTEN, and SETD2.

Angiomyolipoma (AML) is the most common mesenchymal neoplasm of the kidney. It has a triphasic proliferation composed of adipose tissue, smooth muscle cells, and irregularly thick-walled (dysmorphic) vessels. The tumor is usually well-circumscribed and unencapsulated. In its typical triphasic morphology, AML is a straightforward diagnosis. However, when AML is composed of predominantly smooth muscle cells (fat-poor variant), or displays epithelioid morphology, it is a mimicker of sarcomatoid RCC, leiomyosarcoma, or dedifferentiated liposarcoma. Approximately 80% of AML are sporadic, are more frequent in women, and tend to be unilateral. In contrast, AML associated with tuberous sclerosis syndrome tend to be bilateral and have no sex predilection. While typical AML is considered benign, rarely AML can be aggressive with vascular invasion or lymph node involvement. Rare distant metastases have been reported for epithelioid angiomyolipoma. The diagnosis can be confirmed by immunoreactivity with smooth muscle markers (smooth muscle actin, calponin), Cathepsin K, and melanocytic markers (HMB45, Melan-A).

Dedifferentiated liposarcoma is a rare malignant soft tissue sarcoma most commonly located in the retroperitoneum. Kidney involvement by dedifferentiated liposarcoma is frequently reported. Morphologically, most are high-grade non-adipocytic sarcomas forming a cellular proliferation of spindle cells with significant pleomorphism resembling that of undifferentiated pleomorphic sarcoma. They rarely contain heterologous elements such as neural differentiation, leiomyosarcoma, osteosarcoma, chondrosarcoma, or rhabdomyosarcoma. Less commonly seen is the so-called low-grade dedifferentiated liposarcoma, similar to fibromatosis or well-differentiated fibrosarcoma. A diagnosis of dedifferentiated liposarcoma can be made by identification of typical well-differentiated liposarcomatous areas by adequate sampling of grossly adipocytic areas, immunohistochemical stains with MDM2 and CDK4, or fluorescence in situ hybridization for MDM2 amplification.

Sarcomatoid urothelial carcinoma is a subtype of urothelial carcinoma, which occurs in all urinary tract including kidney. Approximately 5% to 10% of all urothelial carcinomas are arising from the upper urinary tract. Patients usually present with urinary symptoms including hematuria and dysuria, with upper urinary tract tumors also having obstructive symptoms. Sarcomatoid urothelial carcinoma is characterized by a high-grade spindle cell component that can be histologically indistinguishable from high grade sarcoma. The tumor tends to express urothelial markers including GATA3, p63, and high molecular weight cytokeratin, which may be focal. It is important to know that renal urothelial carcinoma can be positive for PAX8. Appropriate sampling and identification of conventional invasive urothelial carcinoma or urothelial carcinoma in situ and/or noninvasive high-grade urothelial carcinoma are particularly helpful in making the correct diagnosis.
Critera for Diagnosis and Comments

**Solitary fibrous tumor** (SFT) is a fibroblastic/myofibroblastic neoplasm that was first described in the pleura but has since been found in many anatomic sites, including the kidney. It is typically a slow-growing mass in middle-aged patients with a slight male predominance. SFTs are usually well-circumscribed and sometimes encapsulated with a homogenous cut surface. Histologically, it is composed of bland ovoid or spindled cells arranged in a “patternless” distribution with the presence of collagen bundles. SFTs are usually negative for EMA and positive for CD34, BCL2, CD99, and STAT6, which is the most sensitive and specific marker. The vast majority of SFTs harbor a NAB2::STAT6 fusion, which accounts for the STAT6 positivity by immunohistochemistry.

**Synovial sarcoma** (SS) is a sarcoma with partial epithelial differentiation. While SS is usually seen in the deep soft tissue, it has been described in multiple anatomic sites including the kidney. It is defined by the presence of a t(X;18) (p11.2;q11.2) translocation involving the SS18 gene and one of several SSX genes. It is most commonly seen in young adults aged 15 to 40 years, but it can occur in early childhood to late adulthood. Usually, they present as multinodular masses with a cut surface ranging from solid and firm to smooth and glistening. Two major histologic subtypes exist: monophasic spindle type, which is composed entirely of spindle cells, and biphasic subtype, which has a mixture of fibroblast-like spindle cells and epithelial cells that usually form gland-like structures. The tumor is usually positive for cytokeratins, EMA, and TLE1.
1. Which of the following features would **best** support a diagnosis of a malignant sarcomatoid neoplasm in kidney as renal cell carcinoma (RCC) with sarcomatoid features (sRCC)?
   a) Advanced stage at presentation
   b) Cells positive for low weight cytokeratin
   c) Cells positive for PAX8
   d) Component of a recognizable histologic subtype of RCC
   e) Multiple mitotic figures
   
   **Answer: D,**
   
   **Feedback:** The correct answer is D, component of a recognizable histologic subtype of RCC. While all the other options are often found in a case of sRCC, a recognizable type of RCC component would be the best evidence of sarcomatoid dedifferentiation. All the other answer choices can also be seen in other types of tumor.

2. What is the **most** commonly mutated gene in the sarcomatoid component of sRCC?
   a) KIT
   b) PTEN
   c) TP53
   d) TSC1
   e) VHL
   
   **Answer: C,**
   
   **Feedback:** The correct answer is C, TP53. TP53 is the most commonly mutated gene in the sarcomatoid component of sRCC. VHL and PTEN mutations are frequently shared between the epithelial and sarcomatoid components but are not the most common mutation in the sarcomatoid component. TSC1 and KIT mutations are not frequent in sRCC. **Objective: 3**

3. Which immunohistochemical profile would be **most** supportive of a diagnosis of sRCC?
   a) AE1/AE3 (+), PAX8 (+), GATA3 (-)
   b) AE1/AE3 (+), PAX8 (-), GATA3 (+)
   c) AE1/AE3 (+), PAX8 (-), TLE1 (+)
   d) AE1/AE3 (-), HMB45 (+), SMA (+)
   e) AE1/AE3 (-), PAX8 (-), STAT6 (+)
   
   **Answer: A,**
   
   **Feedback:** The correct answer is A, AE1/AE3 (+), PAX8 (+), GATA3 (-). Positive staining for AE1/AE3 and PAX8, with negative staining for GATA3, would be most supportive of sRCC. Option B would be most consistent with sarcomatoid urothelial carcinoma, option C would be most consistent with a synovial sarcoma, option D would be most consistent with an angiomyolipoma, and option E would be most consistent with a solitary fibrous tumor.

**Objective: 3**
References


Fernando Zazueta Leon-Quintero, MD
Anatomic Pathology Resident (PGY-4)
Department of Pathology and Genomic Medicine
Houston Methodist Hospital
Houston, Texas

Steven Shen, MD, PhD, FCAP
Surgical Pathology Committee
Houston Methodist Hospital
Houston, Texas
**Performance Improvement Program Critique**  
**Case # 2023-39**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Schwannoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>Right paraspinal thoracic tumor</td>
</tr>
</tbody>
</table>

**Clinical Summary**  
A 47-year-old man presents with increasingly intense intermittent back pain. Imaging demonstrates a thoracic paraspinal soft tissue mass. Gross examination of the resected specimen shows a circumscribed 7 cm mass that upon sectioning exhibits a tan to yellow cut surface without necrosis. Immunohistochemistry demonstrates strong and diffuse S100 and SOX10.

*To view this case, see the online, whole slide image.*

**Master List**
- Leiomyosarcoma
- Malignant peripheral nerve sheath tumor
- Neurofibroma
- Schwannoma
- Spindle cell melanoma

**Criteria for Diagnosis and Comments**
Sections show a well-circumscribed tumor surrounded by a fibrous capsule, displaying two distinct morphologies. There are more cellular areas (Antoni A) composed of spindle cells with eosinophilic cytoplasm, indistinct cytoplasmic borders, and wavy nuclei with tapered ends arranged in compact fascicles. Scattered Verocay bodies are seen, which are nuclei aligned into rows (like a picket fence) separated by eosinophilic fibrillary processes. The hypocellular Antoni B areas contain haphazardly arranged spindle cells set in a loose myxoid stroma with delicate collagen fibers, microcystic changes, and scattered inflammatory cells. Numerous ectatic vessels with irregular lumens and hyalinized walls are noted especially in the Antoni B areas. These features support a diagnosis of **schwannoma**.

Schwannoma is a benign, slowly growing, painless peripheral nerve sheath tumor that occurs in all ages (more common in adults), equally affects both sexes, and typically forms in association with a peripheral nerve. Malignant transformation can occur but is exceptionally rare. Schwannomas occur usually as solitary and sporadic tumors. In 3% of cases, they occur in association with neurofibromatosis type 2 and in 2% with schwannomatosis; in these settings, they may be multiple. Inactivating mutations involving the *NF2* gene are seen in schwannomas associated with neurofibromatosis type 2 but have also been described in about 2/3 of sporadic schwannomas.

On gross examination, schwannomas are typically surrounded by a true capsule composed of epineurium, and the cut surface is white to yellow and may show cystic degeneration. Histologic examination shows the classic alternation of a cellular component (Antoni A) and a loose myxoid hypocellular component (Antoni B). Schwannomas may contain glands and benign epithelial structures. Large schwannomas of longstanding duration may display degenerative changes in the form of cyst formation, calcification, hemorrhage, and hyalinization. Notably, these tumors, referred to as ‘ancient’ schwannomas, demonstrate marked cytologic atypia in the form of scattered large pleomorphic nuclei with hyperchromasia and...
multilobation; however, they lack mitotic activity. The cellular variant of schwannoma contains exclusively Antoni A areas and lacks Verocay bodies. The cells are arranged in short fascicles and whorls but also in long herringbone fascicles reminiscent of the pattern seen in malignant peripheral nerve sheath tumor (MPNST), fibrosarcoma, or leiomyosarcoma. In addition, mitotic figures up to around 5/10 high-power fields (HPF) may be seen. In these cases, the immunoprofile (including H3K27me3 and p16, discussed below) becomes of utmost importance. A plexiform pattern may be seen in about 5% of schwannomas. In contrast to plexiform neurofibroma, which is considered pathognomonic for neurofibromatosis type 1, plexiform schwannoma is only weakly associated with neurofibromatosis type 1 or type 2.

All schwannomas strongly and diffusely express S100 and SOX10, which serve as useful diagnostic markers, particularly versus neurofibroma (‘loose’ diffuse staining) and MPNST (variable to negative staining). Positivity for glial fibrillary acidic protein (GFAP) and keratin may be seen in schwannomas, especially retroperitoneal ones. In addition, they demonstrate retained H3K27me3, which can be useful when MPNST or melanoma are in the differential.

Leiomyosarcoma are malignant tumors with smooth muscle differentiation. As such, they are composed of tightly packed fascicles of spindle cells with elongated cigar-shaped nuclei and eosinophilic cytoplasm that may resemble schwannoma, particularly the cellular variant and cases with ‘ancient change’. In contrast to schwannoma, leiomyosarcoma is not encapsulated, lacks Verocay bodies, and is negative or only focally positive for S100. Smooth muscle markers (eg. SMA, SMM) will also be positive, though it is important to note that high-grade leiomyosarcomas may not express desmin. And skeletal muscle markers (Myo-D1 and myogenin) are negative.

Malignant peripheral nerve sheath tumor is a malignant mesenchymal tumor with differentiation towards various elements of the nerve sheath. They may be confused with schwannoma, especially the cellular variant. In contrast to cellular schwannoma, MPNST often demonstrates areas of geographic necrosis, greater nuclear atypia, and increased mitotic activity (more than 4/10 HPF – note the overlap with cellular schwannoma). In addition, high-grade MPNST often lacks the diffuse expression of S100 and SOX10 and demonstrates a loss of H3K27me3 and p16 a majority of the time. It should be noted that MPNST with diffuse S100/SOX10 staining do occur, particularly when they arise from a schwannoma or neurofibroma. Loss of S100 staining, along with p16 and H3K27me3, in the more cellular areas is a good diagnostic feature to support malignant progression.

Neurofibroma is also a benign peripheral nerve sheath tumor that arises from nerve and may demonstrate a centrally located entering and exiting nerve. There are three main variants: localized, plexiform, and diffuse. They may be circumscribed but are usually not encapsulated. Classic histology includes a myxoid matrix containing cells with wavy nuclei, wire-like strands of collagen, and increased numbers of mast cells. In contrast to schwannoma, neurofibroma lacks Antoni A and B areas and does not mark strongly with S100 (‘looser’ / more space between the staining cells portends a lighter stain overall). There is also typically staining of CD34 (intraneural CD34-positive fibroblasts) and neurofilament protein in residual neurites. GFAP is more often negative in tumor cells than in schwannoma. EMA stains the periphery of neurofibroma when it is still intraneural. In contrast to plexiform schwannoma, plexiform neurofibromas are essentially pathognomonic for neurofibromatosis.
Spindle cell melanoma enters the differential diagnosis due to spindle cell morphology and strong expression of S100 and SOX10. In contrast to schwannomas, they demonstrate greater nuclear atypia, increased mitotic activity, and an infiltrative growth pattern, as well as melanin pigment and/or PRAME positivity in a subset of cases. Other melanoma markers, including HMB45, Melan-A, and tyrosinase are often negative in spindle cell melanoma. It is also important to note that approximately 30% of melanomas will demonstrate loss of H3K27me3 staining.

Educational Questions

1. Which of the following tumors has ‘loose’ wispy positive staining for S100, rather than diffuse and strong S100 staining, helping to differentiate it from schwannoma?
   a) Leiomyoma
   b) Leiomyosarcoma
   c) Malignant peripheral nerve sheath tumor
   d) Neurofibroma
   e) Spindle cell melanoma

   Answer: D

   Feedback: The correct answer is D, neurofibroma. Schwannoma and spindle cell melanoma both typically show strong and diffuse staining for S100. Neurofibroma will have a paler, loose, though still diffuse staining pattern. Malignant peripheral nerve sheath tumor (MPNST) can be variable in its S100 staining but is often negative or only focal. Leiomyoma and leiomyosarcoma are negative for S100.

   Objective: 2

2. Which of the following markers best differentiates between cellular schwannoma and MPNST?
   a) EMA
   b) GFAP
   c) H3K27me3
   d) S100
   e) Tyrosinase

   Answer: C

   Feedback: The correct answer is C, H3K27me3. H3K27me3 is a newer marker that is lost in a majority of MPNST but is retained in schwannoma. S100 is often negative in MPNST, but strong and diffuse staining does not rule it out. EMA, GFAP, and tyrosinase are noncontributory in this differential.

   Objective: 3

3. Which of the following statements is correct regarding schwannoma?
   a) A majority demonstrate inactivating mutations of NF2.
   b) Malignant transformation is common.
   c) Plexiform schwannoma is pathognomonic for neurofibromatosis type 1.
   d) Plexiform schwannoma is pathognomonic for neurofibromatosis type 2.
   e) They are benign lesions but are often poorly circumscribed.

   Answer: A

   Feedback: The correct answer is A, a majority demonstrate inactivating mutations of NF2. Schwannoma is associated with NF2, and 2/3 of sporadic lesions demonstrate inactivating NF2 mutations. They rarely undergo malignant transformation. Plexiform variants are not indicative of NF1 or NF2. Schwannoma are usually well circumscribed and often encapsulated.

   Objective: 1
References


Nicole D. Riddle, MD, FCAP
Surgical Pathology Committee
Tampa General Hospital
Ruffolo, Hooper, and Associates / USF Health
Tampa, FL
Diagnosis: Autoimmune pancreatitis, type 2

Site: Pancreas

Clinical Summary: A 45-year-old woman presents with a 2-year history of vague abdominal pain, recent 10-pound weight loss, and jaundice. A computed tomography scan of the abdomen reveals an ill-defined pancreatic body mass measuring 6 cm. The main pancreatic duct is narrowed. Serology for IgG4 is negative. Fine needle aspiration of the mass is inconclusive and is followed by surgical resection of the mass.

To view this case, see the online, whole slide image.

Master List
- Autoimmune pancreatitis, type 1
- Autoimmune pancreatitis, type 2
- Chronic pancreatitis, NOS
- Infection-related pancreatitis
- Pancreatic ductal adenocarcinoma

Criteria for Diagnosis and Comments: Histologic sections demonstrate a duct-centric fibroinflammatory process with dense periductal cuffing by lymphocytes and plasma cells. The epithelium of the small and medium-sized ducts are infiltrated by neutrophils with occasional intraluminal abscess formation. This pattern of injury is called “granulocytic epithelial lesions.” Focal ductal epithelial erosion and ulceration are present. Granulocytic acinar lesions (neutrophilic inflammation within the acini) may or may not be present, and are observed in this case. The pancreatic stroma is fibrotic. IgG4 immunostain demonstrates very rare IgG4-positive plasma cells. These findings are consistent with a diagnosis of autoimmune pancreatitis, type 2.

Autoimmune pancreatitis (AIP) is a mass-forming inflammatory lesion of the pancreas that may mimic pancreatic adenocarcinoma. AIP is divided into two distinct subtypes: lymphoplasmacytic sclerosing type or type 1, and idiopathic duct-centric type or type 2. See the table for distinguishing features.

Idiopathic duct-centric autoimmune pancreatitis is a very rare inflammatory disease of the pancreas and is not an IgG4-related disease. No biomarkers or serologic tests are available. Fifteen percent of type 2 AIP patients have concurrent inflammatory bowel disease. The most common clinical presentation is abdominal pain and acute pancreatitis with a pancreatic head mass on imaging. Serum IgG4 levels may be normal. Histologically, AIP type 2 shows duct-centric dense inflammation comprised of lymphocytes, plasma cells, and neutrophils. Lobular and ductal neutrophilic micro-abscesses with ductal epithelial damage, the so-called granulocytic epithelial lesions, are characteristic of this entity. Veins are rarely involved, and therefore phlebitis is uncommon. Fibrosis is not a prominent feature. IgG4 immunostaining shows rare positive plasma cells.
Cri
teria for
Diagnosis and
Comments

AIP (both types combined) accounts for 5% of all patients with chronic pancreatitis. The incidence is approximately 1.4 per 100,000 people. Abnormal pancreatic exocrine function tests (80% of patients) and diabetes mellitus (70%) are common. The potential etiologies include genetic predilection, infection, and autoimmunity. Initially the pancreas is enlarged, but eventually it becomes fibrotic and shrinks. Distinct mass-like lesions may be present, associated with a narrowed pancreatic duct. Imaging findings can closely mimic pancreatic adenocarcinoma. Radiologically, the two types of AIP are indistinguishable. Both are treated with high-dose corticosteroids with gradual taper.

Autoimmune pancreatitis, type 1 (lymphoplasmacytic sclerosing type) is generally considered to be the pancreatic manifestation of IgG4-related sclerosing systemic disease. The most common clinical presentation is obstructive jaundice in older men. Elevated serum IgG4 (typically two-fold elevation or >280 mg/dL) is the most useful biomarker for this entity and is seen in 80% of patients but can also be elevated in normal individuals and up to 10% of patients with pancreatic ductal adenocarcinoma. Nearly half of patients have established autoimmune conditions such as mediastinal lymphadenopathy, primary sclerosing cholangitis, thyroiditis, or Sjögren disease. Patients may also present with synchronous or metachronous fibroinflammatory lesions in other organs such as the liver and biliary tract. Diagnostic criteria according to the International Consensus Diagnostic Criteria (2011) are dense duct-centric lymphoplasmacytic inflammation, periductal and interlobular storiform fibrosis, periphelebitis, and obliterator venulitis. Granulocytic epithelial lesions exclude a diagnosis of AIP Type 1. While not an absolute diagnostic criterion, numerous IgG4-positive plasma cells are seen on IHC (on average 20-50/high-power field (HPF), a variable number depending if the specimen is a biopsy or resection). Disease relapse is more frequent in type 1 than in type 2.

Chronic pancreatitis, NOS is a progressive fibroinflammatory disorder in which the pancreatic acini are replaced by fibrosis. The most common causes of chronic pancreatitis in developed countries are alcohol and smoking. The characteristic features of chronic pancreatitis, NOS are diffuse fibrosis of the pancreatic parenchyma and acinar atrophy. The degree of parenchymal inflammation is usually less than what is seen in autoimmune pancreatitis. In later stages, the islets of Langerhans are very prominent (so-called "pseudohypertrophy" of the endocrine cells).

Infection-related pancreatitis is extremely rare in immunocompetent patients. Tuberculous pancreatitis can manifest as a pancreatic mass and jaundice. Intrapancreatic abscesses and necrotizing granulomas are common. Correlation with PCR and culture study is helpful. Other infectious etiologies in the pancreas include Ascaris lumbricoides, CMV, and Strongyloides stercoralis. Prominent eosinophilic infiltrate is usually a clue to the diagnosis of parasitic infections.

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive, mass-forming malignancy that can mimic AIP, both histologically and radiologically. The classic clinical presentation is an elderly patient with painless jaundice and high CA19-9. Radiologically, significant dilation of the duct with abrupt cutoff is common. Microscopically, the tumor shows an infiltrative growth pattern with incomplete and irregular glands embedded within desmoplastic stroma. Background benign pancreatic parenchyma often shows chronic pancreatitis with fibrosis. Perineural and vascular invasion are diagnostic of malignancy. Rare cases of PDAC can show a prominent intratumoral and peritumoral lymphoplasmacytic infiltrate, which may also be rich in IgG4-positive plasma cells and can be a diagnostic pitfall. PDAC commonly harbor activating mutations in the KRAS oncogene. Inactivating mutations in tumor suppressor genes such as CDKN2A/p16, TP53, and SMAD4 cooperate with KRAS mutations and lead to aggressive clinical behavior.
Criteria for Diagnosis and Comments

### Table 1: Features of autoimmune pancreatitis type 1 and 2

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lymphoplasmacytic Sclerosing Pancreatitis/ Autoimmune Pancreatitis Type 1</th>
<th>Idiopathic Duct Centric Pancreatitis/ Autoimmune pancreatitis Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual age at presentation</td>
<td>Seventh decade of life</td>
<td>Fifth decade of life</td>
</tr>
<tr>
<td>Serum IgG4 levels</td>
<td>Usually elevated (about 80% of cases)</td>
<td>Rarely elevated</td>
</tr>
<tr>
<td>IgG4 plasma cells</td>
<td>Typically &gt; 20-50/HPF</td>
<td>Infrequent (&lt;10/HPF)</td>
</tr>
<tr>
<td>Appearance</td>
<td>Dense “duct-centric” lymphoplasmacytic infiltration</td>
<td>Ductal and lobular neutrophilic microabscesses /granulocytic epithelial lesions in addition to dense “duct-centric” lymphoplasmacytic infiltration</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>Prominent storiform fibrosis</td>
<td>Mild fibrosis</td>
</tr>
<tr>
<td>Obliterative venulitis</td>
<td>Common</td>
<td>Not present</td>
</tr>
<tr>
<td>Inflammatory association</td>
<td>Frequently with extrapancreatic inflammatory disorders</td>
<td>Typically with inflammatory bowel disease</td>
</tr>
<tr>
<td>Steroid response</td>
<td>Responds but frequently relapses</td>
<td>Responds and rarely relapses</td>
</tr>
</tbody>
</table>

### Educational Questions

1. Which one of the following is a characteristic morphologic feature of autoimmune pancreatitis, type 2?
   - a) Dense lymphoplasmacytic infiltrate
   - b) Granulocytic epithelial lesions
   - c) Numerous IgG4-positive plasma cells
   - d) Obliterative phlebitis
   - e) Storiform-type fibrosis

   **Answer:** B.
   **Feedback:** The correct answer is B. Granulocytic epithelial lesions are a typical feature of AIP, type 2, along with duct-centric dense inflammation.
   **Objective:** 1

2. Which one of the following is typically seen in autoimmune pancreatitis, type 1?
   - a) Diffuse pattern of injury
   - b) Granulocytic epithelial lesions
   - c) Low IgG4 levels by serology
   - d) Obliterative venulitis
   - e) Rare IgG4-positive plasma cells

   **Answer:** D.
   **Feedback:** The correct answer is D, Obliterative venulitis is a typical feature of AIP, type 1.
   **Objective:** 1

3. Which is the most common genetic alteration in pancreatic ductal adenocarcinoma (PDAC)?
   - a) BRCA1 mutation
   - b) KRAS mutation
   - c) Microsatellite instability
   - d) NRAS mutation
   - e) PTEN mutation

   **Answer:** B.
   **Feedback:** The correct answer is B, KRAS mutation. PDAC commonly harbors activating mutations in the KRAS oncogene.
   **Objective:** 3
References


---

**JingJing Hu, MD, PhD**
Assistant Professor
University of California San Diego
La Jolla, CA

**Mojgan Hosseini, MD, FCAP**
Surgical Pathology Committee
Associate Professor
University of California San Diego
La Jolla, CA
This concludes the report.