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Performance Improvement Program in Surgical Pathology
PIP-B 2022

Case Critiques and Educational Questions

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PIP-B 2022
Performance Improvement Program Critique
Case # 2022-11

Diagnosis

Central chondrosarcoma, grade 2

Site

Pelvis

Clinical Summary

A 62-year-old man presents with right hip pain for 6 months that has been increasing gradually over time and is aggravated with activity. On physical examination, there is a palpable mass over the groin. Imaging reveals an 8 cm lesion that arises from the right ischium with soft tissue extension and patchy calcifications but no malignant ossification. Histology demonstrates a cartilaginous neoplasm with prominent myxoid change, patchy increased cellularity, variable nuclear pleomorphism, and scattered mitotic figures.

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

Master List

- Central atypical cartilaginous tumor
- Central chondrosarcoma, grade 2
- Chondroblastic osteosarcoma
- Chondromyxoid fibroma
- Periosteal chondrosarcoma

Criteria for Diagnosis and Comments

Histologic sections demonstrate variable-sized nodules with loose intervening fibrous stroma. The matrix of the tumor comprises pale, hyaline cartilage with prominent myxoid change. The cartilage is variably cellular with chondrocytes displaying cytologic atypia including increased cell size, increased nucleus-to-cytoplasm ratio, focal nuclear spindling, binucleation, irregular nuclear contours, and mitotic activity. These histologic features are consistent with a **central chondrosarcoma, grade 2** (intermediate grade).

Chondrosarcomas are cartilage-forming tumors usually characterized by rather slow, indolent growth. They arise as primary tumors from normal bone or occasionally as secondary tumors originating from benign pre-existing cartilaginous lesions, such as enchondroma and osteochondroma. Individuals with Ollier disease (multiple enchondromas) and Maffucci syndrome (enchondromas and hemangiomas) are at an increased risk of developing chondrosarcomas. Likewise, patients with multiple osteochondromas also have an increased risk for development of chondrosarcomas. Chondrosarcomas occur most commonly in the fifth to seventh decade of life and the most frequent presentation is slowly increasing pain, with or without a palpable mass. Chondrosarcomas may arise in almost any location, but the axial skeleton (ribs, spine, and pelvic girdle), as well as proximal femur and humerus, tend to be the most common sites. These tumors frequently go undetected for many years, often leading to large, ultimately palpable masses by the time the patient finally seeks medical attention. Radiologic imaging most often demonstrates a very large and permeative lesion centered in the medullary cavity with cortical disruption or destruction, and extension into adjacent soft tissues. Smaller lesions will often show endosteal scalloping of the cortex. Chondrosarcomas are frequently partially calcified, often with a “popcorn-like” pattern on imaging.

Criteria for Diagnosis and Comments

Histologically, chondrosarcomas consist of lobules of pale hyaline cartilage with varying amounts of myxoid change and cytologic atypia depending on the overall grade (increases with increasing grade). An infiltrative border with trapped islands of native bone (permeative growth pattern) with cortical destruction is considered the single best diagnostic criterion to support a diagnosis of chondrosarcoma. Without these features, central atypical cartilaginous tumor / chondrosarcoma grade 1 can be very difficult to distinguish from enchondroma. Features such as necrosis, hemorrhage, and cyst formation are indicative of a higher-grade lesion. As with any area of dystrophic calcification, bone formation may be seen. However, it would not be the lacey osteoid laid down by malignant osteocytes as seen in osteosarcoma. Dedifferentiation may occur and histologically demonstrates an abrupt transition from a cartilaginous tumor to a high-grade mesenchymal tumor resembling undifferentiated pleomorphic sarcoma.

The classification of chondrosarcomas has been recently updated in the World Health Organization Soft Tissue and Bone Pathology 5th edition and include central atypical cartilaginous tumor / chondrosarcoma grade 1, secondary peripheral atypical cartilaginous tumor / chondrosarcoma grade 1, central chondrosarcoma grades 2 and 3, secondary peripheral chondrosarcoma grades 2 and 3, periosteal chondrosarcoma, clear cell chondrosarcoma, and dedifferentiated chondrosarcoma. The grade is based on overall cellularity and cytologic atypia of the lesion. Low-grade (grade 1) chondrosarcomas are the least cellular and exhibit minimal cytologic atypia with an appearance very similar to benign cartilage / enchondromas, with the notable exceptions of having bone permeation (entrapped native trabeculae), cortical breakage, and variable amounts of myxoid change. Grade 3 chondrosarcomas are hypercellular with marked cytologic atypia, including marked nuclear pleomorphism, binucleation, and prominent nucleoli. In addition, high-grade lesions can also show cellular spindling, increased mitotic activity, necrosis, and prominent cystic myxoid change. Grading of these lesions is important because it correlates with prognosis. Patients with low-grade lesions (grade 1) have very high 5-year survival rates (approaching 90%), whereas patients with intermediate and high-grade lesions (grade 2 to 3) have much lower 5-year survival rates (approximately 40%).

Central atypical cartilaginous tumor / chondrosarcoma grade 1 (ACT/CS1) is a locally aggressive cartilaginous neoplasm arising in the medulla of bone. Primary lesions arise without an associated benign precursor lesion, whereas secondary lesions arise in association with a pre-existing enchondroma. The diagnostic criteria for chondrosarcoma grade 1 have not changed (infiltrative border with trapped islands of native bone [permeative growth pattern] with cortical destruction and myxoid matrix changes), but this terminology is now reserved for cases arising in the axial skeleton. For reasons similar to the classification of well-differentiated liposarcoma as atypical lipomatous tumors in the extremities, chondrosarcomas arising in the appendicular skeleton are now classified as atypical cartilaginous tumors. This is to signify the relative ease of treatment versus tumors in the axial skeleton (surgical resection is the mainstay) and the better prognosis associated therewith. Similar to enchondromas, approximately 50% of primary central and upwards of 80% of secondary central ACT/CS1 harbor mutations in *IDH1* or *IDH2.* When the lesion arises from a pre-existing osteochondroma, it is termed secondary peripheral ACT/CS1, again based on whether it is in the appendicular or axial skeleton. Of note, using the 2 cm cutoff for cartilaginous cap thickness (measured perpendicular to the bone/cartilage interface) has a sensitivity of 100% and a specificity of 98% for malignancy. While osteochondromas have been shown to have inactivation of *EXT*, chondrosarcomas arising within them are associated with a mix of *EXT*-mutated and *EXT*-wildtype alleles.

Criteria for Diagnosis and Comments

Central chondrosarcoma, grade 2-3 is the new terminology for intermediate and high-grade cartilaginous lesions in both the appendicular and axial skeleton. They often (~50%) demonstrate mutations in *IDH1/2*, suggesting possible progression from enchondroma and/or ACT/CS1. In addition, alterations in the RB1 pathway are seen in 86% of cases, including loss of p16 and amplification of *CDK4*, as well as *TP53* mutations, likely leading to progression to a higher histologic grade. Secondary peripheral chondrosarcoma, grade 2-3 refers to a high-grade chondrosarcoma that arises from a pre-existing osteochondroma. Unlike in secondary peripheral ACT/CS1, *EXT*-wildtype cells predominate.

Chondroblastic osteosarcomas are high-grade osteosarcomas that have an abundance of chondrosarcoma-like matrix. Chondroblastic osteosarcoma is an aggressive neoplasm and is best treated with a combination of surgery and chemotherapy or radiation therapy. These lesions are often difficult to separate from true chondrosarcomas, particularly on small biopsy specimens if malignant osteoid is not sampled. The distinction between these two histologically similar tumors is critical, as treatment and prognosis vary greatly (chondrosarcomas typically do not respond well to chemotherapy or radiation). Chondroblastic osteosarcoma is more likely to occur in younger individuals, and chondrosarcoma tends to occur in middle age to older adults. Nevertheless, there is some age overlap and as such, patient age is not a reliable discriminator. Likewise, tumor location and radiographic appearance are often similar. Detection of *MDM2* mutations would be indicative of osteosarcoma (or the rare osteosarcomatous dedifferentiated liposarcoma). In addition, the presence of *IDH1/2* mutation is helpful if present, but not all chondrosarcomas have this mutation. The best way to discriminate between these two entities is by histology; chondroblastic osteosarcoma will contain areas of malignant osteoid matrix, whereas chondrosarcomas lack this feature.

Chondromyxoid fibroma demonstrates a lobulated architecture with a hypocellular center and a stellate hypercellular periphery, separated by mononuclear spindle cells and admixed multinucleated giant cells. The stroma is variably myxoid to chondromyxoid, and the cells have variable pink cytoplasm, bipolar to multipolar cytoplasmic extensions, and oval to spindled nuclei. Marked nuclear pleomorphism with nucleoli may rarely be seen, but there are few if any mitotic figures, and necrosis and cystic degeneration are rare. Few cases will have aneurysmal bone cyst-like changes. Chondromyxoid fibroma, which is most commonly seen in the distal femur or proximal tibia of younger adults, is driven by a recombination of the glutamate receptor gene *GRM1*, leading to upregulated expression in approximately 90% of cases. *GRM1* expression is very low to absent in other cartilaginous tumors, making it highly specific for chondromyxoid fibroma and possibly useful in diagnosis.

Periosteal chondrosarcoma is a malignant cartilaginous lesion that occurs on the surface of bone with invasion of the underlying cortex and typically is greater than 5 cm. They can arise from a pre-existing periosteal chondroma or *de novo*. A subset has been shown to harbor the same *IDH1/2* mutations as enchondroma and central chondrosarcoma.

Educational Questions

1. Which of the following is the single **best** diagnostic criterion for chondrosarcoma?
   a) Cytologic atypia and chondrocyte binucleation
   b) Hypercellularity
   c) IDH1/2 mutation status
   d) Infiltrative borders with permeative growth pattern
   e) Large confluent nodules of cartilage

2. Which of the following is the **best** way to separate chondrosarcoma from chondroblastic osteosarcoma?
   a) Absence of malignant osteoid matrix
   b) Cellularity and cytologic atypia
   c) Imaging showing irregular calcifications within the tumor
   d) Patient age and location of tumor
   e) Tumor size

3. Which of the following lesions has the **best** prognosis?
   a) Chondroblastic osteosarcoma
   b) Central chondrosarcoma, grade 2-3
   c) Enchondroma (solitary)
   d) Enchondroma in the setting of Maffucci syndrome
   e) Enchondroma in the setting of Ollier Disease

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Nicole D. Riddle, MD, FCAP
Surgical Pathology Committee
Ruffolo, Hooper, & Associates / USF Health
Tampa, FL Surgical Pathology Committee

PIP-B 2022
Performance Improvement Program Critique
Case # 2022-12

Diagnosis

IgG4-related thyroiditis

Site

Thyroid

Clinical Summary

A 45-year-old man presents with progressive painless neck swelling. Laboratory tests reveal elevated levels of serum IgG4. Ultrasound imaging of the thyroid shows diffuse low echogenicity. Fine needle aspiration is nondiagnostic due to low cellularity. On gross exam, the thyroid is diffusely enlarged with a firm cut surface. On immunohistochemical staining, the lymphocytes are a mix of CD20- and CD3-positive cells, and the plasma cells demonstrate kappa and lambda staining without restriction. Immunoglobulin G4 (IgG4) staining highlights foci of 50 positive plasma cells per high-power field (HPF) and an IgG4:IgG ratio of 50%.

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

Master List

- Classic Hodgkin lymphoma, nodular sclerosis subtype
- Graves disease
- IgG4-related thyroiditis
- Papillary thyroid carcinoma, diffuse sclerosing variant

Criteria for Diagnosis and Comments

Microscopically, there is extensive fibrosis, marked lymphoplasmacytic inflammation, and lobules of atrophic thyroid follicles with focal oncocytic metaplasia. The fibrosis is keloid-like, with irregular broad bands coursing through residual thyroid parenchyma. Cytologic atypia, including nuclear features of papillary thyroid carcinoma, are absent. These morphologic features in addition to the increased number of IgG4-positive plasma cells by immunohistochemistry, elevated ratio of IgG4 to IgG-secreting plasma cells, and clinical evidence of elevated serum IgG4 support the diagnosis of **IgG4-related thyroiditis**.

IgG4-related thyroiditis is a recently recognized subtype of thyroiditis. It is an evolving classification that is believed to encompass a spectrum of disease varying from early IgG4-related Hashimoto thyroiditis (HT) pattern to late fibrosing HT or Riedel thyroiditis patterns. IgG4-related HT usually affects a younger age group compared to classic HT, with a lower female:male ratio. The disease has a more rapid course, and patients often present with a large goiter, subclinical hypothyroidism, diffuse low echogenicity on ultrasound, and very high titers of antithyroid peroxidase (TPO) antibodies. Fine-needle aspiration is often low yield because of marked fibrosis.

Macroscopically, in IgG4-related HT, the thyroid is markedly enlarged without a dominant mass, and the cut surface is tan-yellow and firm, with a non-adherent and easily separated capsule. Histologically, thick collagen bands often with dense storiform-type fibrosis separate lobules of atrophic thyroid follicles. Other changes seen in the classic type of HT, including follicular atrophy, oncocytic metaplasia, and marked lymphoplasmacytic infiltration, are present. Squamous metaplasia may also be seen. Unlike IgG4-related disease in other organs, obliterative phlebitis or intense eosinophilia are not common features. Diagnostic criteria for IgG4-related disease

Criteria for Diagnosis and Comments

and an IgG4 cut-off value in the thyroid have not yet been established, but increased numbers of IgG4-positive plasma cells by immunohistochemistry and an IgG4:IgG-secreting plasma cell ratio of more than 40% have been suggested by some experts as features of the IgG4-related HT, although lower ratios have also been proposed.

Riedel thyroiditis (RT) is also part of the IgG4-related disease spectrum and is associated with systemic fibrosclerosing diseases such as retroperitoneal fibrosis and sclerosing mediastinitis. It mainly occurs in women aged 30 to 60 years. Patients present with painless goiter, which progresses to produce symptoms of pressure and compression of surrounding structures. Histologically, there is dense, sclerotic, keloid-like fibrous tissue extending to the adjacent extrathyroidal soft tissue and parathyroid glands and a marked inflammatory infiltrate. Distinction between the IgG4-related HT and RT can be difficult. RT shows more prominent obliteration of follicles, and unlike HT, the fibrosis extends to adjacent structures, such as skeletal muscle and adipose tissue. In addition, the presence of oncocytic cells suggests HT, but these cells are typically absent in RT. Also, Riedel patients do not have high serum antibody titers.

About 10% of HT cases fall into the category of the fibrous (sometimes called sclerosing) variant, which was first described in 1974 and is characterized by fibrous replacement of more than one-third of the thyroid parenchyma but with preservation of lobulated architecture and changes typical of HT in the remaining tissue. As compared to the classic HT, the fibrous variant is more common in men than in women, and unlike IgG4-related HT, it mostly occurs in older patients. There is some controversy over whether some of these cases are part of the spectrum of IgG4-related disease. Immunostaining for IgG and IgG4 and correlation with clinicopathologic and laboratory findings may allow for determining whether any given case might be classified as IgG4-related thyroiditis.

Primary thyroid **classic Hodgkin lymphoma, nodular sclerosis subtype** is rare and has a female predominance. Patients often present with a rapidly enlarging, firm thyroid mass causing compression or infiltration of the surrounding neck organs. A subset of patients have a prior history of HT. Imaging studies reveal a diffusely enlarged thyroid, mimicking thyroiditis. Histologically, there is prominent fibrosis admixed with cellular areas that contain a mixed population of lymphocytes, histiocytes, plasma cells, eosinophils, and large atypical mononuclear and multinucleated cells, consistent with Reed–Sternberg (RS) cells and variants. By immunohistochemistry, the RS cells are CD30- positive, confirming the diagnosis of classic Hodgkin lymphoma.

Graves disease is an autoimmune process characterized by hyperthyroidism due to circulating autoantibodies against the TSH receptor. Grossly, the gland is diffusely enlarged with a beefy-red cut surface. Histologically, the follicles are hyperplastic with papillary infoldings and scant colloid. These features may not be seen in medically treated patients. There is also a variable patchy lymphoid infiltrate in the stroma. However, unlike IgG4-related thyroiditis, there is minimal fibrosis. A small subset of patients with Graves disease are found to have elevated serum IgG4 levels and elevated ratios of IgG4:IgG; but the histologic changes in this subset are not fully defined.

Papillary thyroid carcinoma (PTC), diffuse sclerosing variant mostly occurs in younger patients, accounting for approximately 30% of PTC in those under 20. It is often associated with lymphocytic or autoimmune thyroiditis, and antimitochondrial and antithyroid antibodies may be present. Radiologically, a “snowstorm appearance” is common due to excessive calcifications within the tumor. The thyroid undergoes rapid and diffuse enlargement of one or both lobes, showing prominent

Criteria for Diagnosis and Comments

stromal fibrosis, dense lymphoplasmacytic infiltrates, numerous psammoma bodies, and squamous metaplasia. The neoplastic cells, which are not a feature of IgG4-related HT, are arranged in solid, papillary, or follicular patterns and have characteristic papillary carcinoma cytomorphologic features, including enlarged cells with irregular contours and nuclear clearing, membrane irregularity, grooves, and pseudoinclusions. This variant is more aggressive than classical PTC and is commonly associated with local recurrence and lymph node and distant metastasis, mainly to lungs. *RET/PTCH1* gene rearrangements are seen in 30% of cases.

Educational Questions

1. Which of the following is **true** regarding IgG4-related Hashimoto thyroiditis?
   a) Fibrosis often extends beyond the thyroid capsule and into the surrounding structures.
   b) Foci of oncocytic metaplasia are commonly found.
   c) Obliterative phlebitis is commonly observed.
   d) Patients present with a slow-growing mass in one lobe.
   e) Thyroid follicles show papillary infoldings with frequent nuclear pseudoinclusions.

2. Which of the following is **correct** regarding papillary thyroid carcinoma, diffuse sclerosing variant?
   a) Indolent behavior
   b) Lack of psammoma bodies
   c) Mostly in older patients
   d) Prominent lymphoplasmacytic infiltrate
   e) Rare lymph node metastasis

3. Which of the following is a feature of IgG4-related Hashimoto thyroiditis?
   a) Beefy-red cut surface on gross examination
   b) Cellular fine needle aspirate
   c) Circulating antibody against TSH receptor
   d) Enlarged thyroid gland
   e) Large atypical mononuclear and multinucleated CD30 positive cells

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Mitra Mehrad, MD, FCAP
Surgical Pathology Committee
Vanderbilt University Medical Center
Nashville, TN

PIP-B 2022
Performance Improvement Program Critique
Case # 2022-13

Diagnosis

Sertoli–Leydig cell tumor (moderately to poorly differentiated)

Site

Ovary

Clinical Summary

A 25-year-old woman presents with hirsutism and mild abdominal pain for 6 months. Imaging reveals a unilateral solid 8 cm ovarian mass. On resection, the cut surfaces are lobulated and yellow-brown with focal hemorrhage. The tumor cells stain positive for inhibin and are negative for CK7. A molecular test for *DICER1* is positive and *FOXL2* c.402C>G is negative.

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

Master List

- Adult granulosa cell tumor
- Carcinoid tumor
- Endometrioid carcinoma with sex cord-like features
- Fibrosarcoma
- Sertoli–Leydig cell tumor (moderately to poorly differentiated)

Criteria for Diagnosis and Comments

Microscopic sections reveal two distinct tumor components. The hypercellular areas consist of sheets of Sertoli cells with plump oval to spindle-shaped cells with minimal cytoplasm and small hyperchromatic round nuclei. The second Leydig cell component is composed of eosinophilic spindled cells with ample cytoplasm with round to oval nuclei and prominent nucleoli. Tubules and cords of basophilic cells with round nuclei with intermixed eosinophilic cells with ample cytoplasm and round to oval nuclei can be found. In combination with the immunophenotype, these features are diagnostic of a **moderately to poorly differentiated Sertoli–Leydig cell tumor** (SLCT).

SLCT are rare tumors that occur most often in young women (<30 years of age). Symptomatology is nonspecific but may include abdominal fullness and pain. Up to half of patients may have signs of virilization due to androgen secretion, and rarely signs and symptoms associated with estrogen secretion are present. The tumors often present as a unilateral ovarian mass with yellow to tan cut surfaces; poorly differentiated tumors may have necrosis and hemorrhage. There are four histologic subtypes, including well-differentiated, moderately differentiated, poorly differentiated, and retiform. Moderately differentiated SCLT are the most common. Well-differentiated tumors are composed of sertoliform tubules admixed with solid nests or fascicles of Sertoli cells. The Leydig cell component is arranged in nests or cords in well- to moderately differentiated SLCT or sheets and fascicles in poorly differentiated tumors. Moderately and poorly differentiated subtypes may also have heterologous elements. Retiform architecture is more common in younger patients and shows more slit-like or retiform tubules composed of Sertoli cells. Heterologous elements are more often associated with intermediate to poorly differentiated SLCT and may consist of intestinal, hepatoid, carcinoid, or granulosa cell components. By immunophenotype, SLCT are usually positive for inhibin, calretinin, and WT1 and negative for CK7.

Criteria for Diagnosis and Comments

Mutations in *DICER1* have been identified in 62% to 80% of cases and can be associated with DICER1 syndrome. These mutations are nearly always found in moderately to poorly differentiated SLCT. The other components of DICER1 syndrome include pleuropulmonary blastoma, cervical embryonal rhabdomyosarcoma, cystic nephroma, and multinodular goiter, among others. Patients with one or more of these tumors have a high likelihood of having a germline *DICER1* mutation, but the penetrance of *DICER1* mutations is low and carriers may be unaffected by these tumors. *FOXL2* mutations have been found in approximately 8% of SLCT.

Adult granulosa cell tumor (AGCT) can demonstrate many different architectural patterns but most often has a diffuse or trabecular growth pattern. It can be associated with macro and microfollicles (so-called Call–Exner bodies), but these classic features are not required for a diagnosis. Tumor cells have scant eosinophilic cytoplasm and ovoid nuclei with fine chromatin and nuclear grooves. A fibrothecomatous background or stroma may be present. Staining with reticulin will demonstrate reticulin fibers wrapping around clusters or nests of cells as opposed to reticulin fibers surrounding single cells, as seen in a fibroma. By immunohistochemical staining, AGCT is positive for inhibin and calretinin. It has a characteristic *FOXL2* c.402C>G mutation in most cases.

Primary ovarian **carcinoid tumors** can be subdivided by architecture and cytology into insular, trabecular, strumal, mucinous, and mixed types. The insular subtype, a midgut derivative, is the most common and demonstrates uniform groupings of nests with small acini and lumina. The insular and mucinous types of carcinoid tumor can stain positively for CDX2 by immunohistochemistry, which can be a pitfall if considering a gastrointestinal tract metastasis to the ovary. Generally, primary ovarian carcinoid tumors harbor a similar appearance to carcinoid tumors elsewhere in the body. The most common mixed subtype contains both insular and trabecular patterns. All five subtypes often include features unique to neuroendocrine tumors, such as salt-and-pepper chromatin. Ovarian carcinoid tumors will stain positively for keratin and neuroendocrine markers like synaptophysin and chromogranin and are negative for inhibin and hormonal markers. They also lack mutations in *FOXL2*.

Endometrioid carcinoma with sex cord-like features (ECSCLF) of the ovary may occur with background endometriosis and demonstrates a variety or spectrum of morphologic patterns. It is a morphologic pattern of endometrioid carcinoma that may be confused with sex cord stromal tumors. In particular, the tubular pattern can mimic sex cord-stromal tumors including Sertoli cell tumors and granulosa cell tumors. ECSCLF are typically positive for pankeratin, ER, PR, and PAX8, and negative for inhibin. The most common mutations in sporadic endometrioid carcinomas of the ovary involve the Wnt/beta-catenin pathway (*CTNNB1*), PI3K pathway (*PIK3CA* and *PTEN*), MAPK pathway (*KRAS*), and SWI/SNF complex (*AIRID1A*). Around 10% to15% of ovarian endometrioid carcinomas will also have mutations in mismatch repair proteins, and a subset are associated with Lynch syndrome.

Ovarian **fibrosarcoma** (FS) demonstrates a “herringbone” or fascicular growth pattern at low power and is composed of spindled cells with moderate to marked cytologic atypia. The tumor cells have scant eosinophilic cytoplasm and ovoid nuclei with pointed ends. Atypical mitoses may also be found. On gross examination, the tumors are typically large (on average 17 cm) and unilateral. Their cut surface can be fleshy, with associated hemorrhage and necrosis. Thorough examination of these tumors should not reveal the presence of areas distinguishable as Sertoli or Leydig cells. By immunohistochemistry, FS may show focal staining for inhibin or calretinin and may be positive for ER/PR. FS has been associated with trisomy 8.

Educational Questions

1. A mutation in what gene is most commonly encountered in adult granulosa cell tumor?
   a) CTNNB1
   b) FOXL2
   c) KRAS
   d) MLH1
   e) *TP53*

2. Which of the following ovarian tumors is associated with DICER1 tumor predisposition syndrome?
   a) Adult granulosa cell tumor
   b) Sertoli–Leydig cell tumor
   c) Endometroid carcinoma
   d) Fibrosarcoma
   e) Strumal carcinoid tumor

3. Which immunophenotype is most consistent with a Sertoli–Leydig cell tumor?
   a) Calretinin+/CK7+/Inhibin+/WT1+
   b) Calretinin+/CK7-/Inhibin+/WT1+
   c) Calretinin+/CK7-/Inhibin-/WT1+
   d) Calretinin-/CK7+/Inhibin-/WT1-
   e) Calretinin-/CK7-/Inhibin-/WT1-

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Sarah Thornton
Medical Student
University of Wisconsin School of Medicine and Public Health
Madison, WI

Megan Fitzpatrick, MD
Assistant Professor
University of Wisconsin Hospitals and Clinics
Madison, WI

Byron Barksdale Jr., MD
Surgical Pathology Committee-Jr Member
Pathology Resident
University of Wisconsin Hospitals and Clinics
Madison, WI

PIP-B 2022
Performance Improvement Program Critique
Case # 2022-14

Diagnosis

Acinic cell carcinoma

Site

Parotid gland

Clinical Summary

A 62-year-old woman presents with a 1-year history of an enlarging painless mass of the left parotid gland, which was excised. On gross examination, the parotid shows an ill-defined, variegated 4.2 cm nodular mass with fibrosis, cystic change, and focal hemorrhage.

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

Master List

- Acinic cell carcinoma
- Adenoid cystic carcinoma
- Carcinoma ex pleomorphic adenoma
- Mucoepidermoid carcinoma
- Secretory carcinoma

Criteria for Diagnosis and Comments

At low power, the slide shows a lobulated, basophilic neoplasm with solid, cystic, and focally microcystic architecture. The lobules are separated by fibrous septa. At higher power, the neoplastic cells range from plump, polygonal cells with abundant basophilic cytoplasmic granules and eccentric nuclei with minimal pleomorphism, to areas with more amphophilic cytoplasm and central, vesicular nuclei with higher nucleus-to-cytoplasm ratios and mild pleomorphism. Perineural invasion is also present in some sections. These findings are consistent with **acinic cell carcinoma** (AciCC).

AciCC is a salivary malignancy comprising tumor cells with acinar features. It represents about 6% of salivary tumors and affects the parotid in approximately 90% of cases. It accounts for approximately 15% of malignant parotid neoplasms. There is a slight female predominance, and it affects individuals of nearly all ages, with a median age of 52 years. Risk factors are not yet well established.

Imaging, if performed, reveals benign-appearing features, including circumscription and cystic change. Fine needle aspiration and needle core biopsies are often the initial modalities for sampling. Macroscopically, the lesions are well circumscribed, rubbery, gray-white masses that are variably encapsulated and/or cystic. Tumors are most commonly 1 to 4 cm; however, lesions upwards of 13 cm have been reported. Necrosis is not uncommon.

Microscopically, AciCC demonstrates a solid or cystic lobulated growth of variably basophilic to eosinophilic cells separated by fibrous septa. Microcystic, follicular, and papillary architectural patterns also occur, and while often one pattern predominates, varying patterns within the same tumor are common. Tumors may be composed of varying cell types, including serous acinar (most common), intercalated duct-type, and nonspecific glandular cells. Due to the varied appearance, thorough sampling is paramount to identify the defining acinar cells, as well as look for areas of high-grade

Criteria for Diagnosis and Comments

transformation (see below). Serous acinar cells are polygonal cells with prominent cell borders, eccentric nuclei, and basophilic cytoplasmic zymogen granules with minimal to mild atypia. Intercalated duct-type cells are smaller, eosinophilic cells with central nuclei and indistinct cell borders. Intracytoplasmic vacuoles are characteristic, and psammoma bodies are sometimes seen. A prominent tumor-associated lymphoid proliferation (TALP) is often seen, which can lead to a misdiagnosis of lymph node metastasis and subsequent upstaging of the tumor.High-grade transformation (HGT) may be seen in approximately 15% of cases and is defined as an abrupt transformation of a conventional “well-differentiated” carcinoma into a high-grade morphology that lacks the original distinct histologic and immunohistochemical features. This could be poorly differentiated adenocarcinoma, a carcinoma not otherwise specified, a small cell carcinoma, or an undifferentiated carcinoma. Although no WHO grading system exists, it is imperative to identify HGT, as these cases have a significantly worse prognosis.Other histologic features associated with a poorer prognosis are atypical mitoses, Ki67 index >5%, necrosis, perineural invasion, and nuclear pleomorphism. These cases have higher rates of recurrence and may benefit from radiotherapy.

Ancillary studies for AciCC are not generally required for the diagnosis; however, they may be helpful in small samples or tumors that do not show classic morphologic features. A periodic acid–Schiff stain with diastase may be used to highlight the zymogen granules of serous acinar cells. Immunohistochemical analysis demonstrates reactivity with DOG1 and SOX10. Tumor cells are negative for mammaglobin, S100 (may be positive in a subset of tumors), and p63, which can be helpful to exclude secretory carcinoma and mucoepidermoid carcinoma. AciCC harbors recurrent t(4;9)(q13;q31) chromosomal rearrangement at high frequency. This rearrangement results in upregulation of *NR4A3* via enhancer hijacking. Immunohistochemistry for NR4A3 is a highly sensitive and specific marker for AciCC.

AciCC is generally regarded as an indolent process with a favorable prognosis; however, recurrence occurs in up to 44% of cases. Nodal metastases are uncommon. The treatment of choice for AciCC is surgical excision with possible lymph node dissection, especially in cases with high-grade features. Radiotherapy may be utilized for recurrent or advanced disease. Reported survival rates vary, and a recent population-based study showed survival rates at 5, 10, and 20 years to be 97%, 94%, and 90%, respectively.

Adenoid cystic carcinoma is a neoplasm composed of ductal epithelial and myoepithelial cells. A cribriform pattern with “punched out” areas of basement membrane material is classically associated with this tumor, but various other patterns including solid and tubular are seen as well. Perineural invasion is a hallmark of this tumor. Acinar-type cells are not typical. Immunohistochemically, the epithelial cells are positive for low molecular weight keratins and CD117, while the myoepithelial cells are positive for p63, SMA, and calponin. Molecular studies have demonstrated activation of *MYB* via t(6;9) *MYB-NFIB* translocation in a variable number of cases (40% to 80%).

Carcinoma ex pleomorphic adenoma is a malignant tumor arising in a pleomorphic adenoma (PA). Histologic evidence of pre-existing PA is required for the diagnosis and is present in variable proportions. The carcinoma component may be any salivary malignancy or an adenocarcinoma, NOS. Immunohistochemistry will be dependent on the type of carcinoma present. Overexpression of p53 and HER2 have been reported.

Criteria for Diagnosis and Comments

Mucoepidermoid carcinoma (MEC) is the most common malignant salivary gland tumor. Unlike AciCC, it is composed of 3 cell types: mucinous, intermediate (basaloid), and squamoid cells, which form solid and/or cystic patterns. Prominent mucinous lakes may be present. Low-grade lesions have a predominant mucinous component with cystic architecture, whereas high-grade lesions tend to be more solid and infiltrative. Immunohistochemistry shows p63 and p40 reactivity in intermediate and squamoid/epidermoid cells, but other myoepithelial markers are negative. MEC is characterized by t(11;19) *CRTC1-MAML2*.

Secretory carcinoma (SC) is a low-grade tumor composed of intercalated duct-like cells and may closely resemble acinic cell carcinoma; prior to the description of SC, some were diagnosed as "zymogen-poor AciCC." SC lacks the defining cytoplasmic zymogen granules of AciCC. Growth patterns include microcystic, tubular, and solid, which may overlap with the morphology of AciCC. SC usually shows diffuse and strong concomitant reactivity for S100 and mammoglobin, unlike AciCC. Also, SC most commonly harbors a characteristic *ETV6-NTRK3* fusion, which is not seen in AciCC.

Educational Questions

1. Which of the following is **true** regarding acinic cell carcinoma?
   a) Characteristically has mucinous, intermediate, and squamoid cells
   b) Characterized by the presence of cells with basophilic granules
   c) Clinically aggressive tumor with poor prognosis
   d) The treatment of choice is chemotherapy.
   e) There is no correlation between high-grade transformation and survival.

2. Which of the following molecular alterations is characteristic of acinic cell carcinoma?
   a) *ETV6-NTRK3* fusion
   b) HER2 overexpression
   c) t(6;9) *MYB-NFIB*
   d) t(11;19) *CRTC1-MAML2*
   e) Upregulation of *NR4A3*

3. Which of the following is **true** regarding acinic cell carcinoma?
   a) High-grade transformation (HGT) is seen in approximately half of cases.
   b) Immunohistochemistry for mammaglobin is diffusely positive.
   c) Intracytoplasmic vacuoles are rarely seen.
   d) Patients commonly present with metastatic disease.
   e) Tumor-associated lymphoid proliferation might mimic lymph node metastasis.

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David McKenzie, MD
Surgical Pathology Resident
Duke University Health System
Durham, NC

Xiaoyin "Sara" Jiang, MD, FCAP
Surgical Pathology Committee
Duke University Health System
Durham, NC

PIP-B 2022
Performance Improvement Program Critique
Case # 2022-15

Diagnosis

Serous cystadenoma

Site

Pancreas

Clinical Summary

A 62-year-old woman involved in a motor vehicle accident is found to have a 4.3 cm well-circumscribed, lobular, cystic mass in the tail of the pancreas on CT, with no lesions elsewhere. Multiple attempts at biopsy of the mass are unsuccessful, and a distal pancreatectomy is performed. Gross examination reveals a circumscribed multilocular mass that contains straw-colored cyst fluid and has a central scar.

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

Master List

- Metastatic clear cell renal cell carcinoma
- Pancreatic ductal adenocarcinoma
- Serous cystadenocarcinoma
- Serous cystadenoma
- Well-differentiated neuroendocrine tumor, clear cell variant

Criteria for Diagnosis and Comments

Sections show a lobulated tumor composed of innumerable microcysts of variable size with intervening fibrous stroma. The microcysts are lined by a monolayer of bland, cuboidal, or flattened epithelial cells. Scattered micropapillae and epithelial tufting can be focally seen. Tumor cells have well-defined borders with optically clear cytoplasm and a small round to ovoid nucleus. The chromatin appears homogeneous with an inconspicuous nucleolus in some cells. Nuclear atypia is minimal, and mitoses are scant. Dilated or congested capillaries are often identified adjacent to the tumor epithelium. The overall gross and microscopic features lead to the diagnosis of **serous cystadenoma** (SC).

SC is uncommon, accounting for 1% to 2% of pancreatic neoplasms. It most commonly arises in the body or tail of the pancreas, with a female predilection (3:1). Diagnosis is most frequently made in the late 5th or early 6th decades, but a range of 18 to 91 years has been reported. Historically, SC typically presented with symptoms of abdominal pain, weight loss, palpable mass, or jaundice. In more recent years, smaller asymptomatic masses are often detected; this has been partly attributed to improved imaging modalities. Imaging shows a well-defined, lobulated, cystic mass. A characteristic stellate scar is present in approximately 30% of cases and may include calcifications. This translates to the classic gross appearance of a well-defined cystic mass that is often described as sponge-like or honeycomb in appearance. A centrally located fibrotic stellate scar is noted in up to 30% of cases. Cyst fluid is described as yellow/straw-colored. A PAS stain highlights abundant intracytoplasmic glycogen that is sensitive to diastase. On immunohistochemistry, the tumor cells show positivity for EMA, pan-cytokeratin, CK7, α-inhibin, GLUT1, CAIX, calponin, and MUC6; many cases are also positive for CD56 and synaptophysin. They are negative for CK20 and chromogranin A.

Criteria for Diagnosis and Comments

The WHO Classification of Tumours: Digestive System Tumours, 5th Ed. recognizes five histologic subtypes of serous neoplasms of the pancreas: microcystic serous cystadenoma, macrocystic (oligocystic) serous cystadenoma, solid serous adenoma, VHL-associated serous cystic neoplasm, and mixed serous-neuroendocrine neoplasm. Macrocystic (oligocystic) subtypes are poorly circumscribed and may be unilocular or multilocular, having fewer than 10 cysts, each ranging from 1 to 3 cm in diameter. Additionally, the macrocystic type usually lacks a central scar; however, the cyst lining is identical to that of the microcystic subtype. Solid serous adenomas grossly appear as solid, well-circumscribed masses. Architecturally, tumor cells form crowded acini with no cyst spaces.

Patients with von Hippel–Lindau (VHL) can develop multiple microcystic and/or multicystic serous cystic neoplasms, which may partially or entirely involve the gland. In the setting of VHL, patients are also prone to develop the mixed serous-neuroendocrine subtype, which can provide a clue to suspect VHL if not previously known. Importantly, prognosis of these mixed tumors reflects that of the neuroendocrine component.

The pathogenesis of SC is not well known, but loss of heterozygosity and somatic mutations in the *VHL* tumor suppressor gene are found in all familial and most sporadic cases. Preoperative cyst fluid analysis may be used for diagnostic purposes, with identification of mutant *VHL* and absence of *KRAS, GNAS, CDKN2A*, and *SMAD4* mutations, which are instead found in pancreatic ductal adenocarcinoma and its precursors (e.g., pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasm).

SC is considered a benign neoplasm with an excellent prognosis. They are typically indolent, with a median annual growth rate of 0.4-0.6 cm. Rare tumors can be locally aggressive, which warrants post-op follow-up. In asymptomatic patients with typical cyst fluid and radiology features, SC may be managed conservatively. Resection, if necessary, is curative.

Pancreatic ductal adenocarcinoma (PDAC) is the most common pancreatic malignancy and has a wide range of histologic variability. Pertinent to this case, it may show clear to foamy cytoplasm, as well as cystic degeneration. The majority of PDAC demonstrate marked nuclear pleomorphism, in contrast to the bland, monotonous cytology seen in SC. While aggressive-appearing features such as perineural and vascular invasion may occur in SC, they are far more common in PDAC. Immunohistochemistry is positive for mesothelin, CEA, and S100P, and negative for α-inhibin and calponin. PAS staining is negative in PDAC.

Metastatic clear cell renal cell carcinoma (CCRCC) may closely resemble SC in both cystic architecture, clear cytoplasm, and low-grade nuclei. The presence of increased hemorrhage and necrosis can be a helpful distinguishing characteristic by morphology. VHL, EMA, and α-inhibin immunohistochemistry may be positive in both renal cell carcinoma and SC. Additionally, CCRCC is typically positive for PAX2, PAX8, and vimentin, while SC is negative for these.

Serous cystadenocarcinoma (SCA) is an exceptionally rare diagnosis and must demonstrate unequivocal distant extra-pancreatic metastasis. Direct spread to adjacent tissues or features such as vascular or perineural invasion are insufficient for the diagnosis of SCA. Histologically, SCA shows benign-appearing features indistinguishable from SC.

Criteria for Diagnosis and Comments

Well-differentiated neuroendocrine tumor (WD-NET) is the second most common pancreatic malignancy. The **clear cell variant** or lipid-rich variant is uncommon but can resemble SC due to the relatively uniform, round nuclei and absence of prominent nucleoli. Additionally, pancreatic WD-NETs may undergo cystic change. Unlike SC, WD-NET should be strongly positive for both synaptophysin and chromogranin. They should be negative for CK7, CAIX, α-inhibin, and calponin.

Educational Questions

1. Which of the following is **true** about serous cystadenoma (SC) of the pancreas?
   a) It is always symptomatic.
   b) It is most common in older male patients.
   c) It often has a central scar.
   d) It often metastasizes.
   e) Prominent nucleoli are a classic feature.

2. Which of the following genes is often mutated in SC of the pancreas?
   a) CDK2NA
   b) GNAS
   c) KRAS
   d) SMAD4
   e) *VHL*

3. Which immunohistochemical stain is usually positive in both pancreatic SC and pancreatic well-differentiated neuroendocrine tumor?
   a) α-inhibin
   b) CAIX
   c) Calponin
   d) Chromogranin A
   e) Synaptophysin

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Adam L. Booth, MD
Northwestern Memorial Hospital
Chicago, IL

Raul S. Gonzalez, MD, FCAP
Surgical Pathology Committee
Beth Israel Deaconess Medical Center
Boston, MA

PIP-B 2022
Performance Improvement Program Critique
Case # 2022-16

Diagnosis

Adult cystic nephroma

Site

Kidney

Clinical Summary

A 51-year-old woman with no relevant familial or personal history presents to the Emergency Department with abdominal pain. CT shows an incidental 6 cm anterior mid- to upper pole complex cystic renal lesion (Bosniak III). A robotic partial nephrectomy is performed. Gross examination reveals a multiloculated tumor with smooth cysts and clear, thin fluid. No solid areas are identified.

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

Master List

- Adult cystic nephroma
- Autosomal dominant polycystic kidney disease
- Clear cell renal cell carcinoma
- Multilocular cystic neoplasm of low malignant potential
- Tubulocystic renal cell carcinoma

Criteria for Diagnosis and Comments

Histologic sections show variably sized cysts separated by cellular spindled ovarian-like stroma. The cysts are lined by a single layer of flat, cuboidal, or hobnail cells with eosinophilic to amphophilic cytoplasm that contain uniform nuclei without cytologic atypia. The stroma is moderately cellular throughout and marks with estrogen receptor and inhibin. There is no invasive component and no solid component. The morphologic features and immunophenotype support a diagnosis of **adult cystic nephroma** (CN).

Adult cystic nephroma was previously classified along with pediatric cystic nephroma. However, based on demographics, immunohistochemistry, and the unique *DICER1* mutation found only in pediatric cystic nephromas, adult cystic nephromas are now classified in the mixed epithelial and stromal tumor (MEST) family, with cystic nephromas representing the more cystic end of the spectrum. Most are benign, but rare local recurrences and malignant transformation have been reported. Tumors within the MEST/CN family typically occur in perimenopausal women with a mean age of 52 years, often with a history of hormone therapy. Usual presenting features are abdominal pain and hematuria. The female-to-male ratio is 7:1.

Grossly, tumors are solitary, unencapsulated, and unilateral, involving the renal medulla or cortex. The mean size is 9 cm. Solid and cystic areas are present in variable proportions. Microscopically, the cysts are lined by flattened cuboidal, hobnail, or columnar cells with eosinophilic, amphophilic, or vacuolated cytoplasm. The epithelium is positive for CK7 and PAX8 and negative for CAIX and may show focal endometrioid, tubal, intestinal, or urothelial features. The spindled, ovarian-like stroma is variably cellular and may show luteinization or smooth muscle metaplasia. The stromal component is typically positive for estrogen and progesterone receptors and may express inhibin or calretinin if luteinized.

Criteria for Diagnosis and Comments

Autosomal dominant polycystic kidney disease is the most common type of renal cystic disease and fourth most common cause of renal failure, accounting for 5% to 10% of patients with end-stage renal disease on hemodialysis. The disease is caused by alterations in *PKD1* and *PKD2*, located at 16p13.3 and 4q21, respectively. Renal survival is 20 years longer with *PKD2* as compared with *PKD1* mutations. Unlike adult CN, cysts are innumerable and distributed evenly in the renal cortex and medulla, with significant size variation. There is a putative association with renal cell carcinoma. The reported precursor lesion is termed intracystic papillary tuft-like proliferation.

Clear cell renal cell carcinoma (CCRCC) is a morphologically heterogeneous tumor accounting for nearly 70% of all renal carcinomas. Risk factors for CCRCC include smoking, hypertension, polycystic kidney disease, obesity, and exposure to trichloroethylene (metal degreaser). It is also a component of von Hippel–Lindau (VHL) syndrome, hereditary leiomyomatosis, and renal cell carcinoma syndrome, Cowden syndrome, succinate dehydrogenase-deficient RCC, and other lesser-known familial syndromes. Tumor cells are arranged in nests with a delicate meshwork of vessels. Extensive hemorrhage, necrosis, and/or cystic degeneration can be present. Common variants include microcystic and macrocystic patterns, especially in the context of VHL syndrome. These tumors do not show ovarian stroma or mark with estrogen receptor, progesterone receptor, inhibin, or calretinin. CCRCC express PAX8, CAIX, and CAM5.2 but unlike adult CN, are negative for CK7. Alterations in the *VHL* tumor suppressor gene at chromosome 3p25-26 are found in the majority of sporadic and syndromic CCRCC.

Multilocular cystic neoplasm of low malignant potential (formerly multilocular cystic renal cell carcinoma) is a rare, indolent tumor occurring in middle-aged adults. Tumors are composed of cysts lined by clear epithelial cells of low nuclear grade. More than 90% of the lesion is cystic, and there are no mass-forming areas of tumor cells. The cysts also lack associated ovarian-type stroma. With strict criteria, there are only rare reports of recurrences or metastases. Tumors express PAX8 and CAIX and show loss of chromosome 3p in more than 80%. Solid or grossly visible tumor nodules exclude multiloculated cystic renal neoplasm of low malignant potential from the differential diagnosis.

Tubulocystic RCC was first recognized as a new entity in the 2016 4th edition of the World Health Organization Classification of Tumours of the Urinary System and Male Genital Organs, representing 1% of all renal carcinomas found in adults. Tubulocystic RCC shows a predilection for males and for the left kidney (70% of cases). Grossly, tumors are solitary, well-circumscribed, and multicystic, with a spongy or “bubble wrap”-like cut surface. Histology shows small to intermediate-sized tubules and cysts, with occasional large cysts. Papillary structures may be present. Cells are cuboidal to hobnail, are enlarged, and show ISUP grade 3 nucleoli. The cytoplasm can be abundant and eosinophilic. The stroma is minimal and fibrotic. Tumor cells express CK7 and AMACR and demonstrate gains of chromosomes 7 and 17. This tumor is CAIX negative. Tubulocystic RCC is largely an indolent tumor, with only rare reports of metastasis.

Educational Questions

1. Which of the following is **true** regarding adult cystic nephroma?
   a) It is more common in males.
   b) It is associated with *DICER1* mutations.
   c) It is genetically related to pediatric cystic nephroma.
   d) It typically occurs in perimenopausal females.
   e) Malignant transformation has not been reported.

2. Which of the following histologic features is **most** supportive of a diagnosis of adult cystic nephroma?
   a) Innumerable, evenly distributed cysts in the renal cortex and medulla
   b) ISUP grade 3 nucleoli
   c) Multicystic mass with expansile nodules of tumor cells with clear cytoplasm
   d) Numerous cysts lined by epithelial cells with abundant clear cytoplasm and no spindled stroma
   e) Ovarian-like stroma positive for estrogen and progesterone receptors.

3. Which of the following immunohistochemical and/or molecular profiles is **most** consistent with the mixed epithelial stromal tumor of the kidney/adult cystic nephroma family of renal cell tumors?
   a) CAIX- epithelium, gain of chromosome 17
   b) CAIX+ epithelium with ER+ stroma
   c) PAX8+/CK7+ epithelium, chromosome 3p abnormality
   d) PAX8+/CK7+ epithelium, *DICER1* mutation
   e) PAX8+/CK7+ epithelium, inhibin+ stroma

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Lola Hoover, MD
Associate Pathologist
University of Maryland Baltimore Washington Medical Center
Glen Burnie, MD

Sabrina C. Sopha, MD, FCAP
Surgical Pathology Committee
University of Maryland Baltimore Washington Medical Center
Glen Burnie, MD

PIP-B 2022
Performance Improvement Program Critique
Case # 2022-17

Diagnosis

Nonseminomatous mixed germ cell tumor

Site

Scrotum

Clinical Summary

A 30-year-old man status post chemotherapy and left orchiectomy for a testicular tumor presents with a left scrotal mass, which is resected. Serum alpha-fetoprotein, hCG, and LDH levels are elevated. On resection, the 10 x 8 x 6 cm nodular mass has a variegated appearance with hemorrhage and necrosis. A subset of cells are CD30 and OCT3/4 positive and another subset stains with alpha fetoprotein (AFP) and glypican 3 (GPC3).

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

Master List

- Choriocarcinoma
- Nonseminomatous mixed germ cell tumor
- Seminoma
- Sex cord–stromal tumor, mixed
- Teratoma, post-pubertal type

Criteria for Diagnosis and Comments

The sections show a mixed neoplasm with focal necrosis. Scattered papillary structures are seen lined by columnar to cuboidal tumor cells with a high N:C ratio and scant clear to eosinophilic cytoplasm. Separate areas show sheets of primitive-appearing cells with higher nuclear atypia and prominent nucleoli; these areas are. No seminomatous component is identified. These features are consistent with a diagnosis of a recurrent **nonseminomatous mixed germ cell tumor** (MGCT), with a combination of yolk sac tumor (YST), described first above, and embryonal carcinoma (EC), described second above, components.

Testicular neoplasms are divided into primary germ cell tumors (GCT), which account for 95% of cases of testicular cancer, and non-GCT, which account for fewer than 5% of cases. Testicular GCT typically occurs in males aged 15 to 40. In Western industrialized nations, its incidence has approximately doubled over the last 4 decades. Risk factors include cryptorchidism, affected siblings, subfertility, testicular microlithiasis, testicular dysgenesis, Li– Fraumenisyndrome, and prior testicular GCT. Testicular GCT (TGCT) are divided into two major groups, based on whether they are derived from precursor germ cell neoplasia in situ (GCNIS) or not. Non-GCNIS-derived TGCTs are mainly pre-pubertal, and GCNIS-derived TGCTs are mainly post-pubertal. Non-GCNIS-derived TGCTs show diploidy or aneuploidy with gain of chromosomes 1q, 12, and 20q, and loss of chromosomes 1p, 4, and 6p. GCNIS-related TGCTs are associated with aneuploidy or triploidy; chromosome 12p amplification (often isochromosome 12p); gain of chromosomes X, 7, 8, 21; and loss of chromosomes Y, 1p, 11, 13, and 18. In contrast with other non-GCNIS-derived TGCTs, genetic features of spermatocytic tumor include gain of chromosome 9. Molecular testing with i(12p) analysis is helpful to confirm TGCT origin in metastatic tumors, particularly those with somatic-type differentiation, and to differentiate between pre-pubertal- and post-pubertal-type teratomas (TE).

Criteria for Diagnosis and Comments

MGCT of the testis contains two or more GCT types. This is the second most common GCT in adults, following pure seminoma (SE). It comprises 30% to 50% of cases, with an average age at diagnosis of 30 years. Presenting symptoms may include testicular pain, testicular enlargement, or metastasis. Serum AFP and hCG may be elevated, depending on the presence of YST elements and syncytiotrophoblastic cells**,** respectively**.** MGCT has a variegated appearance on cut surface, reflecting the various tissue components, with accompanying necrosis and hemorrhage. The common subtypes in a MGCT in order of frequency are EC and TE; EC and SE; EC, YST and TE; and EC, TE, and choriocarcinoma (CC). The components are present in variable proportions throughout the tumor. All components and their approximate percentages should be reported. The proportion of the EC component has important prognostic value in predicting metastatic disease in patients with clinical stage 1 disease. Other adverse prognostic indicators in germ cell tumors include a mediastinal primary, AFP $\geq$10,000 ng/ml, hCG $\geq$ 50,000 mIU/ml, lactate dehydrogenase (LDH) $\geq$ 10 x upper limit of normal, and non-pulmonary metastases.

Embryonal carcinoma (EC) is a malignant GCT composed of primitive epithelial tumor cells recapitulating early stages of embryonic development. It is a common component of MGCT (40%). Most patients present in their 20s to 30s with a testicular mass. AFP, hCG, and LDH levels may be elevated. There is frequent hemorrhage and tumor necrosis. The classic architectural patterns are solid, glandular, and papillary. The cytological features include cells with large overlapping vesicular nuclei, prominent nucleoli, amphophilic cytoplasm, and indistinct cell borders. Mitoses are numerous. In a MGCT, EC may be admixed with a YST, as in this case. CD30 is a highly sensitive and specific marker for EC. Other positive stains are OCT3/4 (also positive in seminoma and GCNIS), SALL4, PLAP, SOX2, keratin AE1/AE3, and focally AFP. ECs are negative for CD117, EMA, CEA, vimentin, and hCG.

Yolk sac tumor (YST) is a malignant GCT and occurs in two age peaks. Pre-pubertal YST is the most common GCT in the pediatric population (mean age is 16 to 18 months) occurring in a pure form, is not associated with GCNIS, and is associated with a better prognosis. Post-pubertal YST occurs mainly in adults (25 to 35 years), is associated with GCNIS, and is usually admixed with other GCTs. Serum AFP is elevated in more than 95% of patients. Histologically, numerous architectural patterns are seen in varying proportions: Microcystic is the most common, while less common patterns include solid, myxomatous, papillary, glandular, macrocystic, alveolar, sarcomatoid, polyvesicular vitelline, hepatoid, parietal, and mixed. Intra- and extracellular PAS-positive hyaline globules may be seen. Tumor cells are epithelioid with clear or vacuolated pale eosinophilic cytoplasm, cuboidal, columnar, or frankly spindled. Around 50% of YSTs contain Schiller–Duval bodies (papillary structures within cystic spaces, lined by cuboidal/columnar cells with a distinct central vessel). YSTs are positive for AFP (more specific and less sensitive), glypican 3 (more sensitive and less specific), SALL4, pancytokeratin, and villin. YSTs are negative for OCT3/4, CD30, CD117, and PLAP.

Pure seminoma (SE) is the most common testicular GCT, comprising up to 40% of GCT, and presents in young adult men (average age of diagnosis of 33 years) with painless testicular enlargement. Serum LDH, hCG, and PLAP may be elevated, while AFP is not increased. Cytogenetics include i(12p) and *KIT* mutations. Grossly, SE has a light tan, lobulated homogenous appearance, with no necrosis or hemorrhage. Tumor cells have a solid or nested growth pattern separated by thin fibrous septa rich in lymphocytes. Individual tumor cells are large, uniform, and round to polygonal with distinct cell membranes and lightly eosinophilic to clear cytoplasm due to the presence of glycogen, demonstrable by a periodic acid-Schiff (PAS) stain. The nuclei contain one or more prominent nucleoli. Syncytiotrophoblasts and granulomatous

inflammation can occur. Mitoses are readily identifiable. SE cells are positive for OCT3/4, CD117, SOX17, and D2-40. CD30 stain is negative. Treatment consists of orchiectomy and radiotherapy. Prognosis is excellent, with greater than 95% cure rates.

Choriocarcinoma (CC) are seen in approximately 8% of MGCT; pure CC is rare. CC occurs in young men in the second and third decades of life, mostly presenting with metastatic symptoms due to hematogenous spread rather than a testicular mass. CC has a worse prognosis than other types of GCT due to its predilection for rapid hematogenous dissemination and a high incidence of brain metastasis. HCG levels are markedly increased (more than 100,000 mIU/mL). CC is nodular and hemorrhagic on gross examination. It is composed of varying amounts of syncytiotrophoblasts (large multinucleated cells with eosinophilic cytoplasm), cytotrophoblasts (polygonal cells with single nuclei and prominent nucleoli), intermediate trophoblasts (cells larger than cytotrophoblasts, with clear cytoplasm, and single nuclei), and adjacent testicular parenchyma with GCNIS. Immunohistochemically, CC are positive for hCG, PLAP, HPL, GATA3, EMA, cytokeratin 7, SALL4, and glypican 3, and negative for CD30, OCT3/4, inhibin, and SF1. CC is also associated with isochromosome 12p.

Teratoma (TE) originates from germ cells with tissue derived from more than one embryonic germ layer (endoderm, ectoderm, mesoderm). Pre-pubertal-type TE is the second most common GCT in children and occurs in a pure form. Post-pubertal-type TE usually occurs as a component of MGCT, with a median age of presentation of 25 to 35 years and is associated with GCNIS and chromosome 12p amplification. Serum markers are usually normal. TE have a heterogeneous gross appearance; histologically, they show varying tissue types such as squamous epithelium, glandular tissue, cartilage, or neuropil. Rarely, malignancies can arise within the tissue types, referred to as TE with somatic-type malignancy. TEs are negative for PLAP, OCT3/4, and CD30. Unlike all other GCT, TE is negative for SALL4.

Sex cord–stromal tumors (SCSTs) are uncommon, averaging 2% to 5% of adult testicular tumors and 25% of testicular tumors in infants and children. SCSTs are classified into Leydig cell tumors, Sertoli cell tumors, granulosa cell tumors, tumors of fibroma-thecoma group, mixed SCSTs, and unclassified SCSTs. Leydig cell tumors are the most common pure SCSTs. On gross examination, SCSTs present with a yellow to white lobulated cut surface. Histology varies among the tumor types. There is absence of GCNIS. SCSTs are positive for SF1, α-inhibin, and calretinin and are negative for SALL4, OCT3/4, and glypican 3.

Educational Questions

1. Which of the following is **true** regarding nonseminomatous germ cell tumors?
   a) Localized mixed germ cell tumors have an excellent prognosis.
   b) OCT3/4 can be used to differentiate seminoma from embryonal carcinoma.
   c) Prepubertal type teratomas are associated with germ cell neoplasia in situ.
   d) Serum tumor markers are usually elevated in testicular teratomas.
   e) Yolk sac tumors generally occur as part of a mixed germ cell tumor in children.

2. Which of the following chromosomal abnormalities is **most** frequently seen in germ cell neoplasia in situ-associated post-pubertal germ cell tumors of the testis?
   a) del(12p)
   b) i(9p)
   c) i(12p)
   d) inv(9)
   e) t(11;18)

3. A testicular tumor in a 25-year-old shows diffuse positivity for SALL4, with focal areas positive for CD117 and negative for CD30, and separate areas focally positive for CD30 and negative for CD117. What is the **most** likely diagnosis of this tumor?
   a) Mixed germ cell tumor, with seminoma and choriocarcinoma
   b) Mixed germ cell tumor, with seminoma and embryonal carcinoma
   c) Pure yolk sac tumor
   d) Seminoma
   e) Sertoli–Leydig cell tumor

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Shehla Aman, MD, MPH
PGY-1, Anatomic/Clinical Pathology
Loma Linda University Health
Loma Linda, CA

Rob Propst, DO
PGY-3, Anatomic/Clinical Pathology
Loma Linda University Health
Loma Linda, CA

Anwar Sultana Raza, MD, FCAP
Surgical Pathology Committee
Loma Linda University Health
Loma Linda, CA

PIP-B 2022
Performance Improvement Program Critique
Case # 2022-18

Diagnosis

Leiomyoma

Site

Uterus

Clinical Summary

A 39-year-old G1P1001 woman presents with pelvic pain and is found to have an enlarged, distorted uterus by bimanual examination. Imaging shows multiple myometrial and subserosal lesions. The patient undergoes a supracervical hysterectomy and salpingo-oophorectomy. Gross examination of the uterus reveals an overall weight of 2410 grams, with multiple lesions measuring up to 15 cm. The myometrial lesions all show firm, white, whorled, bulging cut surfaces.

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

Master List

- Fumarate hydratase-deficient leiomyoma
- Leiomyoma
- Leiomyosarcoma
- Low-grade endometrial stromal sarcoma
- Smooth muscle tumor of uncertain malignant potential

Criteria for Diagnosis and Comments

Sections of the masses show cellular spindle-cell lesions arranged in fascicles that are well demarcated from the surrounding myometrium. No tumor necrosis, atypia, or increased mitotic activity is seen. This appearance, along with the gross presentation, is diagnostic of a **uterine leiomyoma**.

Leiomyomas are benign mesenchymal tumors arising from smooth muscle and represent the most common tumor of the female reproductive organs. Up to 70% of hysterectomy specimens will have at least one leiomyoma, and these are typically considered an incidental finding. Leiomyomas can be intramural, submucosal, or subserosal; subserosal lesions may appear pedunculated. They are well-circumscribed and non-encapsulated. Leiomyomas can become hemorrhagic and necrotic or undergo degenerative changes, including calcification, cystic change, and hyaline degeneration. Leiomyomas are also variable in size and can become quite large. There are some racial variations in presentation and frequency of leiomyomas, with increased prevalence and earlier presentation in African American women and lower prevalence in Asian women, likely relating to epigenetic factors.

Patients are usually asymptomatic, though patients with bulky or numerous leiomyomas may experience feelings of fullness or infertility and pregnancy loss. A leiomyoma may also cause increased or abnormal uterine bleeding, especially when submucosal in location. Some patients may experience pain if lesions infarct or become hemorrhagic, or if there is torsion of a pedunculated leiomyoma. Rarely, benign leiomyomas may exhibit intravenous growth and cause thromboembolism or vascular insufficiency. Resection of leiomyomas through morcellation, myomectomy, or hysterectomy are used as definitive therapy, though more conservative treatment with gonadotropin-releasing hormone agonists and uterine artery embolization are also used to treat large or symptomatic lesions. Incomplete resection often leads to local recurrence. Morcellation can cause tumor spill and peritoneal growth.

Criteria for Diagnosis and Comments

Histopathologic examination of a leiomyoma reveals intersecting fascicles of spindle cells with eosinophilic, fibrillary cytoplasm, elongated "cigar-shaped" nuclei, and indistinct cell borders. Nucleoli are often visible but small. Palisading of cells may be seen. Acellular areas due to hemorrhage, ischemia, hyaline change, or calcification are common. Some subtypes, listed below, may display larger atypical cells, increased mitotic activity, increased cellularity, or other changes that in most other lesions would denote aggressive or malignant activity. Some rare subtypes even metastasize and show vascular invasion; benign metastasizing leiomyomas and intravenous leiomyomatosis may present primarily or with recurrence in extrauterine sites such as lung, bone, or lymph nodes. Benign leiomyoma variants should only display one concerning feature, not several in concert, and remain rather well-circumscribed.

Numerous subtypes of leiomyomas have been described, which together account for approximately 10% of cases. Among these are cellular leiomyoma, leiomyoma with bizarre nuclei, mitotically active leiomyoma, hydropic leiomyoma, apoplectic leiomyoma, lipoleiomyoma, epithelioid leiomyoma, myxoid leiomyoma, and dissecting leiomyoma. These subtypes are named descriptively for grossly or histologically apparent features that differentiate them from a typical leiomyoma. All are still considered benign lesions but may exist as a component of a systemic process or as part of a syndromic constellation of findings.

Immunohistochemical stains are not usually necessary for diagnosis, but conventional leiomyomas will display smooth muscle markers (desmin, caldesmon, SMA, MSA, calponin, SMMHC) as well as ER, PR, and nuclear WT1. Conventional leiomyomas rarely overexpress p16 or p53.

The most frequent molecular alterations in uterine leiomyomas are *MED12* mutations (approximately 70%), followed by *HMGA2* and *HMGA1* rearrangements (25% to 29%). *COL4A5* and *COL4A6* deletions can be seen in about 4% of cases and are associated with Alport syndrome with diffuse leiomyomatosis.

Fumarate hydratase-deficient leiomyoma is a type of leiomyoma seen often in younger patients (typically 20 to 30 years of age). These patients tend to present with multiple symptomatic leiomyomas. Genetic studies can show a range of somatic or germline fumarate hydratase (*FH)* mutations. Those with germline *FH* mutations are at a higher risk of renal cell carcinoma (hereditary leiomyomatosis and renal cell carcinoma syndrome). This type of leiomyoma represents approximately 1% of all leiomyoma cases. Histologic features suggestive of this type of leiomyoma include staghorn vasculature, eosinophilic nucleoli, perinuclear halos, and eosinophilic cytoplasmic inclusions. Diagnosis can be confirmed with immunohistochemistry showing loss of expression for fumarate hydratase and tumor testing for mutations in the *FH* gene.

Leiomyosarcoma typically presents as a single lesion with a soft, bulging, fleshy cut surface, often with areas of hemorrhage and necrosis. Many are quite large at diagnosis, but up to 25% may be less than 5 cm in diameter at diagnosis. The most common subtype is composed of spindle cells in long fascicles that appear disorganized in relation to each other. The cells can be relatively uniform, but pleomorphism is usually apparent and often includes multinucleated cells. Mitotic figures are frequently seen, with apparent atypical mitoses. Tumor cell necrosis, or single cell necrosis, is an important diagnostic feature and essentially rules out leiomyoma. Essential diagnostic criteria defined by the WHO are marked cytologic atypia, tumor cell necrosis, and 4 or more mitoses per square millimeter; a conventional uterine leiomyosarcoma meets at least 2 of these criteria. Epithelioid and myxoid subtypes are defined, with different diagnostic criteria. A leiomyoma can

Criteria for Diagnosis and Comments

rarely progress to a leiomyosarcoma (described in <3% of cases). Prognosis is poor, even when the mass is confined to the uterus and completely resected, perhaps due to poor response to chemotherapy.

Low-grade endometrial stromal sarcomas (LGESS) are typically symptomatic tumors of the uterine corpus, presenting with abnormal uterine bleeding or pelvic pain; some cases present with lymph node or lung metastasis. They appear yellow-tan and are ill-defined, with an infiltrative growth pattern. They show a predilection for vascular invasion, which may be grossly apparent. LGESS typically resemble proliferative-phase endometrial stroma, with a dense population of oval to fusiform nuclei and scant cytoplasm; however, variants can show smooth muscle differentiation. These tumors tend to be diffusely positive for CD10 and harbor gene fusions commonly involving *JAZF1*.

Smooth muscle tumor of uncertain malignant potential (STUMP) is typically a diagnosis of exclusion. The tumor shows a gross appearance similar to that of a leiomyoma, but a subset may have more irregular or ill-defined borders. Histologically, the lesion may appear similar to that of a leiomyoma or a leiomyoma variant but will exhibit one of the diagnostic criteria for a leiomyosarcoma (cytologic atypia, tumor cell necrosis, or high mitotic count). Tumors must be generously sampled to fully rule out leiomyosarcoma. STUMP often recur, with variants diagnosed based upon high mitotic count least likely to recur and those diagnosed based on tumor cell necrosis most likely to recur.

Educational Questions

1. Which of the following is **true** regarding the clinical presentation of uterine leiomyomas?
   a) Every woman with a leiomyoma will experience fertility issues.
   b) Leiomyomas are rare and only present in a small percentage of women.
   c) Many leiomyomas will be asymptomatic or will have nonspecific symptoms.
   d) The tumor is aggressive and causes rapidly progressive weight loss and fatigue.
   e) Uterine bleeding is the only expected symptom of a leiomyoma presenting at any age.

2. Multiple uterine leiomyomas can be a feature in which of the following syndromes?
   a) Congenital adrenal hyperplasia
   b) Hereditary Leiomyomatosis and Renal Cell Cancer Syndrome
   c) Mayer-Rokitansky-Kuster Hauser Syndrome
   d) Turner syndrome
   e) Von Hippel-Lindau Disease

3. Which single feature is incompatible with the diagnosis of typical or variant leiomyoma?
   a) Any mitotic activity
   b) Calcifications
   c) Hemorrhage
   d) Myxoid matrix
   e) Tumor cell necrosis

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Emily Kay Hutson, MD
Pathology Resident
Hospital of the University of Pennsylvania
Philadelphia, PA

Lauren E. Schwartz, MD, FCAP
Surgical Pathology Committee
Assistant Professor of Clinical Pathology and Laboratory Medicine
University of Pennsylvania Perelman School of Medicine
Philadelphia, PA

PIP-B 2022
Performance Improvement Program Critique
Case # 2022-19

Diagnosis Smoking-related interstitial fibrosis

Site Lung

Clinical Summary A 56-year-old man, active 20 pack-year smoker, presents with new onset of dyspnea on exertion. A computerized tomography (CT) scan shows upper lobe-predominant reticulations with ground-glass opacities. The patient undergoes a wedge biopsy of the right upper lobe.

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

Master List

- Fibrotic nonspecific interstitial pneumonia
- Pulmonary Langerhans cell histiocytosis
- Respiratory bronchiolitis interstitial lung disease
- Smoking-related interstitial fibrosis
- Usual interstitial pneumonia

Criteria for Diagnosis and Comments The lung sections show uniform eosinophilic fibrosis of the alveolar septa. The fibrosis is acellular, has a distinctive dense, hyalinized appearance, and follows a subpleural and peribronchiolar distribution. Reactive type 2 pneumocytes are noted lining the alveolar septa. Mild airspace enlargement is noted associated with the fibrosis; however, significant underlying architectural distortion or remodeling is absent. The bronchioles and airspaces contain intraluminal lightly pigmented macrophages, consistent with respiratory (smoker's) bronchiolitis. Granulomas, diffuse inflammatory infiltrate, and fibroblastic foci are absent. Foci of hypertrophic smooth muscle bundles are present. The histologic features are diagnostic of **smoking-related interstitial fibrosis (SRIF)**.

As indicated by the name, initially coined by Katzenstein and colleagues, smoking-related interstitial fibrosis (SRIF is a smoking-related process). It is usually an incidental finding in lung wedge biopsies removed for cancer or other radiologic abnormalities in either active or former smokers. Most patients are asymptomatic, although occasional patients may have mild shortness of breath or a cough. Other names for SRIF draw upon the defining histologic features, such as Yousem's "respiratory bronchiolitis-associated interstitial lung disease with fibrosis" or "airspace enlargement with fibrosis." The histology is defined by a few main features: a marked thickening of the alveolar septal walls by an acellular eosinophilic collagenized or hyalinized fibrosis (so called "ropey" collagen) with associated mild airspace enlargement (emphysema), preserved underlying lung architecture, a subpleural or peribronchiolar distribution of the fibrosis, and varying degrees of hypertrophic smooth muscle bundles. Respiratory bronchiolitis (RB), aka "smoker's bronchiolitis," an almost uniform finding in active smokers, is another characteristic feature of SRIF. RB is defined as a localized accumulation of macrophages within the lumen of respiratory bronchioles and extending into adjacent alveolar ducts and alveoli.

SRIF is only one of many disorders of the lung of which fibrosis is an integral component. Some of these are also manifestations of smoking, such as emphysema and Langerhans cell histiocytosis, but others occur in nonsmokers. Features of the fibrosis in SRIF that are important in distinguishing it from other entities are the ropey collagen identifiable on low power (in emphysema, septal fibrosis, if present, is subtle and wispy in appearance and is seen on high power, not low power), the zonation of the fibrosis (subpleural and peribronchiolar as opposed to diffusely involving the lung), and lastly the minimal to absent inflammation. Important features that are absent in SRIF, which are

Criteria for Diagnosis and Comments

also helpful in excluding possible mimics, include the lack of underlying architectural distortion or remodeling, absent to rare fibroblast foci, and absence of Langerhans cells. It is important to also note that while emphysema is usually a component of SRIF, in rare cases it can be absent.

Recognition of SRIF is important, as in most cases SRIF is benign and does not progress. Therefore, it is important to separate it from other entities, some of which are more aggressive.

Nonspecific interstitial pneumonia (NSIP) can arise in the setting of a collagen vascular disorder, infection, drug reaction, or transplantation, or it can be idiopathic. It has been separated into cellular and fibrotic morphologic patterns. Both forms are characterized by a diffuse uniform expansion of the alveolar septa without significant architectural distortion. Type 2 pneumocyte hyperplasia is usually present along the alveolar septa. NSIP is a temporally uniform process. In the cellular form the expansion is due to infiltration of the alveolar septa by a chronic inflammatory infiltrate. In the fibrotic form, the cellular infiltrate is replaced by collagen deposition, although scattered inflammatory cells often are still present. Fibroblast foci are typically absent, but occasionally one or two may be found. If an underlying cause or association is known, then it is referred to as a F-NSIP pattern. If it is idiopathic, then it is diagnosed as F-NSIP. The pulmonary architecture is preserved in NSIP, and honeycomb change (HC) is not a feature. Hyperplasia of type 2 pneumocytes is often present. The diffuse nature of the fibrosis, the presence of respiratory bronchiolitis, and the interstitial inflammatory component separate F-NSIP from SRIF.

Honeycomb change is a form of end-stage, irreversible pulmonary scarring resulting in remodeling of the lung parenchyma and architectural distortion. Histologically, it is composed of remodeled dilated airspaces partially lined by respiratory-type epithelium often with intraluminal inspissated mucin and inflammatory cells. The surrounding stroma is fibrotic and contains reactive hyperplastic smooth muscle bundles and thick-walled vessels. Residual bronchioles can also be present. Honeycomb change is not a component of SRIF and differs from it in the destruction of the underlying lung parenchyma.

Pulmonary Langerhans cell histiocytosis (PLCH) is a clonal proliferation of myeloid cells with a Langerhans cell phenotype, ie, expression of CD1a and langerin/CD207. Solitary PLCH is primarily a disease of young adults in their third to fourth decade and is considered a smoking-related interstitial lung disease. The cellular phase of PLCH consists of bronchiolocentric lesions with a mixed inflammatory infiltrate and Langerhans cells. In late stage of the disease, these lesions can become fibrotic and form stellate scars that are visible on low power and can be confused with other interstitial lung diseases, including SRIF. This can be problematic, as SRIF and PLCH can coexist in the same patient. A clue to the diagnosis of PLCH is finding the presence of rare residual clusters of Langerhans cells. *BRAF* V600E mutations are identified in 38 to 57% of cases, and this alteration can be identified by immunohistochemistry.

Respiratory bronchiolitis interstitial lung disease (RB-ILD) is another smoking-induced disorder. Unlike the other disorders, it is a clinicopathologic entity. The histology is that of respiratory bronchiolitis, ie, lightly pigmented macrophages within bronchioles and peribronchiolar airspaces. The addition of clinical symptoms, such as dyspnea and abnormal pulmonary function tests showing impaired diffusing capacity, define it as RB-ILD. Mild bronchiolar wall fibrosis may be present, but alveolar septal wall fibrosis as seen in SRIF is not a feature of RB or RB-ILD.

Usual interstitial pneumonia (UIP) is the most common interstitial lung disease. In contrast to NSIP, which is a diffuse uniform process, on low power the lung parenchyma in UIP shows marked variation with areas of honeycomb change and remodeled lung adjacent to areas of relatively normal lung parenchyma (spatial heterogeneity). There is also temporal heterogeneity characterized by the presence of fibroblast foci, which indicate active, ongoing lung injury juxtaposed to areas of old fibrosis. Therefore, UIP shows areas of fibrosis without active injury alternating with areas of new or ongoing injury (fibroblast foci). If the patient is a smoker, areas of RB can be seen. UIP tends to involve the lower lobes, as opposed to SRIF, which is more common in the upper lobes. The important morphologic features separating UIP and SRIF are the presence in UIP of foci of HC,

Criteria for Diagnosis and Comments

architectural distortion and patchwork fibrosis, the absence of the dense uniform interstitial fibrosis of SRIF, and the presence of fibroblast foci. Unlike SRIF, UIP is a chronic progressive lung disease that may need anti-fibrogenic medications to prevent progression of the disease as well as a bridge to lung transplantation.

The following table helps summarize some of the important features separating SRIF, UIP, and NSIP.

Table 1. Pathologic features useful in distinguishing SRIF, UIP, and NSIP

Feature	SRIF	UIP	NSIP
Distribution of fibrosis	Subpleural	Subpleural and paraseptal	Diffuse in F-NSIP
Location	Upper lobe	Lower lobe	Lower lobe predominant
Pattern	Uniform	Heterogeneous	Uniform
Collagen	Ropey, hyalinized densely eosinophilic acellular collagen	Light-staining collagen with mild inflammation	Light-staining collagen with variable inflammation
Honeycomb change	Absent	Present	Absent
Respiratory bronchiolitis	Present	May be present	May be present
Emphysema	Present	Not a feature	Not a feature
Fibroblast foci	Absent/rare	Present	Absent/rare

Educational Questions

1. Which of the following features is **most** characteristic of smoking-related interstitial fibrosis (SRIF)?
   a) Diffuse interstitial chronic inflammation
   b) Honeycomb change
   c) Lower lobe predominance
   d) Numerous fibroblast foci
   e) Subpleural hyalinized alveolar septa

2. Peribronchiolar stellate fibrotic scars are associated with which of the following disorders?
   a) Fibrotic-nonspecific interstitial pneumonia
   b) Honeycomb change
   c) Langerhans cell histiocytosis
   d) Smoking-related interstitial fibrosis.
   e) Usual interstitial pneumonia

3. Which of the following statements regarding SRIF is **true?**
   a) It is a chronic progressive disorder.
   b) The most common clinical presentation is dyspnea.
   c) It is usually an incidental finding on lung sampling.
   d) The lower lobe is the most commonly affected lobe.
   e) Temporal heterogeneity is a characteristic finding..

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Deborah Belchis, MD, FCAP
Surgical Pathology Committee
Adjunct Assistant Professor of Pathology
Johns Hopkins University School of Medicine
Baltimore, MD

PIP-B 2022
Performance Improvement Program Critique
Case # 2022-20

Diagnosis

Intramuscular myxoma

Site

Thigh

Clinical Summary

A 43-year-old woman presents with a swelling of the mid aspect of the left thigh. A magnetic resonance imaging (MRI) study shows a well-circumscribed, deeply seated mass within skeletal muscle. The tumor shows hyperintense signaling on T2 and is hypointense to muscle on T1-weighted images. The patient undergoes surgical resection of the mass. Immunohistochemical staining reveals that the tumor cells are positive for CD34, while negative for MUC4, SMA, desmin, and S100. *DDIT3* gene break-apart fluorescence in-situ hybridization is negative.

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

Master List

- Deep (aggressive) angiomyxoma
- Intramuscular myxoma
- Low-grade fibromyxoid sarcoma
- Myxofibrosarcoma
- Myxoid liposarcoma

Criteria for Diagnosis and Comments

Histological sections show a demarcated tumor; however, entrapment of skeletal muscle bundles is observed at the periphery. The lesion is hypocellular and composed of spindle and stellate-shaped cells embedded in an abundant myxoid stroma. A few inconspicuous vessels are present, while nuclear atypia, mitoses, and necrosis are absent. The overall features are those of an **intramuscular myxoma.**

Intramuscular myxomas are benign mesenchymal neoplasms that most commonly occur in middle-aged females and present as a slow-growing and painless mass. They often affect the extremities, preferentially the quadriceps muscle. The tumors have characteristic MRI findings (high signal intensity on T2 and low signal intensity on T1) that assist in their preoperative recognition. Surgical resection is the treatment of choice, and recurrences are rare if completely excised. Malignant transformation has not been described.

On gross examination, the tumors show a gelatinous and lobulated cut surface, and cystic changes can be appreciated. Most intramuscular myxomas shows the aforementioned histological features, and their Immunohistochemical (IHC) profile is characterized by variable CD34 positivity, rare SMA reactivity, and negativity for MUC4, desmin, and S100. A subset of tumors referred to as cellular myxomas can show hypercellular areas and have increased vascularity; these still show bland cytomorphology and behave in a benign fashion.

Most (> 90%) intramuscular myxomas, including cellular variants, harbor activating point mutations in exon 8 or 9 of *GNAS*. Assessing the *GNAS* mutation status of a myxoid tumor in small biopsies or diagnostically challenging cases is a useful tool that separates intramuscular myxoma from its mimickers. *GNAS* mutations are also

Criteria for Diagnosis and Comments

involved in the pathogenesis of fibrous dysplasia, and the association of intramuscular myxomas and fibrous dysplasia is known as Mazabraud syndrome. Patients with this syndrome tend to have multiple intramuscular myxomas and the polyostotic form of fibrous dysplasia. The onset of bone lesions precedes the appearance of the intramuscular myxomas, which usually present in the 5th or 6th decade.

Deep (aggressive) angiomyxoma occurs in the deep soft tissues of the pelvis and perineal region, including the vulvovaginal area in women and the inguinoscrotal soft tissue in men. The tumor cells show spindled morphology and are embedded in a myxoid stroma characterized by a prominent vascular component composed of medium-sized to large vessels. Desmin is typically positive in the spindle cells. *HMGA2* gene rearrangements are present in a significant percentage of tumors; however, HMGA2 IHC is not a specific marker despite good sensitivity (90% sensitivity and 80% specific).

Low-grade fibromyxoid sarcoma shows alternating fibrous and myxoid areas and exhibits bland spindle cells arranged in whorls or short fascicles. One-third of cases contain hyalinized collagen nodules surrounded by a cuff of epithelioid tumor cells, so-called collagen rosettes. MUC4 is a highly sensitive and specific IHC marker for this tumor, and it harbors either *FUS-CREB3L2* or *FUS-CREB3L1* gene fusions.

Myxofibrosarcoma shows a multinodular infiltrative growth, incomplete fibrous septa, variable pleomorphism, and variable myxoid stroma containing a network of elongated curvilinear blood vessels. Low-grade myxofibrosarcoma is relatively hypocellular due to prominent areas of myxoid matrix and contains hyperchromatic and pleomorphic tumor cells. In contrast, high-grade myxofibrosarcoma is more cellular and shows sheets and fascicles composed of spindle and pleomorphic tumor cells with marked atypia. Myxofibrosarcoma does not have a specific IHC profile, and no definable/recurrent molecular events have been described.

Myxoid liposarcoma is composed of bland round to ovoid cells embedded in a myxoid stroma characterized by branching capillary vasculature. Variable numbers of small lipoblasts are identified. The tumor harbors *FUS-DDIT3* or *EWSR1-DDIT3* fusion genes, and the identification of *DDIT3* gene rearrangement by fluorescence in-situ hybridization is diagnostic.

Educational Questions

1. Which molecular event is **commonly** present in intramuscular myxomas?
   a) *DDIT3* gene rearrangement
   b) *FUS-CREB3L1* gene fusion
   c) *FUS-CREB3L2* gene fusion
   d) *GNAS* mutation
   e) *HMGA2* gene rearrangement

2. Which myxoid mesenchymal neoplasm is **most** likely to be positive for MUC4?
   a) Deep (aggressive) angiomyxoma
   b) Intramuscular myxoma
   c) Low-grade fibromyxoid sarcoma
   d) Myxofibrosarcoma
   e) Myxoid liposarcom*a*

3. The association of intramuscular myxomas and fibrous dysplasia is known as:
   a) Carney syndrome
   b) Li–Fraumeni syndrome
   c) Mazabraud syndrome
   d) McCune–Albright syndrome
   e) Rothmund–Thomson syndrome

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Juan C. Hernandez-Prera, MD, FCAP
Surgical Pathology Committee
Moffitt Cancer Center
Tampa, FL

Educational Questions Answer Key

View these answers after the critiques have been read and the questions have been answered.

2022-11
1. Infiltrative borders with permeative growth pattern (d)
2. Absence of malignant osteoid matrix. (a)
3. Enchondroma (solitary) (c)

2022-12
1. Foci of oncocytic metaplasia are commonly found. (b)
2. Prominent lymphoplasmacytic infiltrate (d)
3. Enlarged thyroid gland (d)

2022-13
1. *FOXL2* (b)
2. Sertoli–Leydig cell tumor (b)
3. Calretinin+/CK7-/Inhibin+/WT1+ (b)

2022-14
1. Characterized by the presence of cells with basophilic granules (b)
2. Upregulation of *NR4A3* (e)
3. Tumor-associated lymphoid proliferation might mimic lymph node metastasis. (e)

2022-15
1. It often has a central scar. (c)
2. *VHL* (e)
3. Synaptophysin (e)

2022-16
1. It typically occurs in perimenopausal females. (d)
2. Ovarian-like stroma positive for estrogen and progesterone receptors. (e)
3. PAX8+/CK7+ epithelium, inhibin+ stroma (e)

2022-17
1. Localized mixed germ cell tumors have an excellent prognosis. (a)
2. i(12p (c)
3. Mixed germ cell tumor, with seminoma and embryonal carcinoma (b)

2022-18
1. Many leiomyomas will be asymptomatic or will have nonspecific symptoms. (c)
2. Hereditary Leiomyomatosis and Renal Cell Cancer Syndrome (b)
3. Tumor cell necrosis (e)

2022-19
1. Subpleural hyalinized alveolar septa (e)
2. Langerhans cell histiocytosis (c)
3. It is usually an incidental finding on lung sampling. (c)

2022-20
1. *GNAS* mutation (d)
2. Low-grade fibromyxoid sarcoma (c)
3. Mazabraud syndrome (c)

NOTES

NOTES

This concludes the report.

COLLEGE of AMERICAN PATHOLOGISTS
Laboratory Quality Solutions

325 Waukegan Road
Northfield, IL 60093-2750
800-323-4040
847-832-7000 (Country code: 001)