Illinois Registry of Anatomic Pathology
10/26/2020
University of Wisconsin – Madison

Case #1
Presenter: Dr. Natalie Taylor
Attending: Dr. Erin Brooks

Clinical History: The patient is a 51-year-old male who presented with one week of left upper quadrant pain, weakness, vomiting, and diarrhea. There was severe splenomegaly and diffuse jaundice on physical exam. His initial labs revealed leukocytosis, anemia, and thrombocytopenia; as well as elevated liver function tests. His clinical status quickly deteriorated with a dramatic increase in liver function tests, and he died with the following clinical diagnoses: fulminant liver failure, disseminated intravascular coagulation, and acute kidney failure. An autopsy was performed.

Final Diagnosis: EBV-associated aggressive natural killer cell leukemia

Differential diagnosis:
- Kikuchi Disease
- Infectious Etiology
- Lymphoproliferative Disorder

Ancillary studies:
- Epstein-Barr Virus (EBV; *human gammaherpesvirus 4*) DNA copies at >1,000,000 IU/mL.
- **IHC:** The atypical lymphocytes on hepatosplenic histologic sections were positive for EBER and CD56, consistent with EBV-infected natural killer (NK) cells. Circulating EBV-infected NK cells were also seen in sections of vessels.

Occupational Safety and Health Administration (OSHA) Investigation: The state OSHA was subsequently contacted due to a third parties' concern that this represented a workplace-acquired viral infection and death. While there is a *Bovine gammaherpesvirus 4* (BHV-4) linked to respiratory and reproductive clinical manifestations in dairy cattle, it is not known to commonly infect and/or cause disease in humans. Due to presumed genetic similarity between the human (EBV) and bovine (BHV-4) herpesviruses, there was concern that the polymerase chain reaction (PCR) primer used for the antemortem EBV test could have amplified BHV-4, and thus been erroneously reported as an EBV DNA PCR copy number. To address this concern, real-time PCR (rtPCR) was repeated on a patient blood sample obtained at the time of autopsy and the amplicon generated from rtPCR was Sanger sequenced. Sequence comparison of the amplification product to various nucleotide sequence databases using Basic Local Alignment Search Tool confirmed the viral infection to be EBV (human origin) rather than BHV-4 (bovine origin).

Discussion: EBV is one of the most common human viruses in the world. Antibodies to EBV have been demonstrated in all population groups with a worldwide distribution; approximately 90-95% of adults are EBV-seropositive. EBV infection has been associated with the development of an array of hematologic malignancies, including NK cell leukemia. Aggressive NK cell leukemia is a rare hematologic malignancy that is most commonly seen in Asia, Central America and South America. The disease has a highly aggressive course with a median survival of <2 months. High levels of circulating plasma EBV at the time of diagnosis (as were found in the current case) have been suggested to portend a worse prognosis. Hepatosplenomegaly and acute hepatic failure have been reported in conjunction with aggressive NK cell leukemia. In conclusion, the cause of death in this case was fulminant acute hepatic failure due to EBV-associated aggressive NK cell leukemia. This case serves to illustrate the utility of molecular diagnostic testing in distinguishing human vs. bovine viral origin in cases in which there is concern for occupational exposure to the infectious agent.

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Case #2
Presenter: Lixia Bai MD, PhD
Attending: Rashmi Agni MD

Clinical History: The patient is a 43-year-old man who presented with a complex hepatic cyst incidentally found on a CT chest for right upper back pain and cough. A subsequent MRI showed an 8.2 cm multiloculated lesion, centered within the caudate lobe and extending into hepatic segments 8 and 4A with diffuse intra and extrahepatic biliary duct dilation. Bile duct biopsy revealed benign biliary epithelium and underlying fibrotic stroma with active chronic inflammation. An exploratory laparotomy and en bloc left hepatectomy with caudate resection was performed.

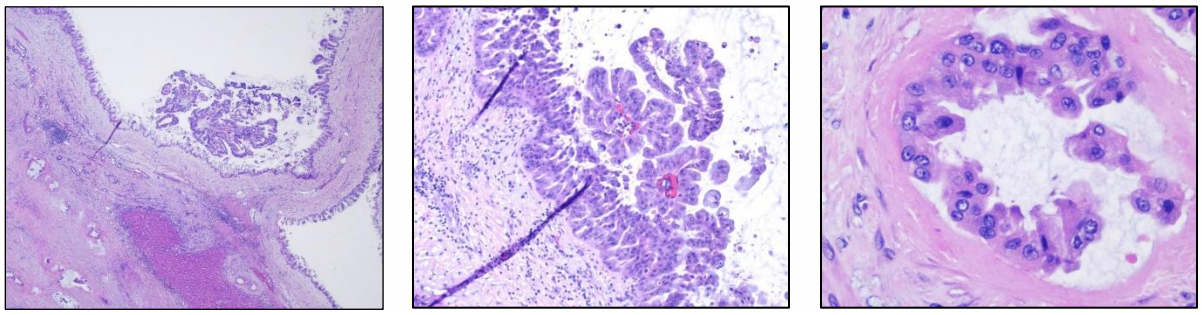
Fingal Diagnosis: Intraductal papillary neoplasm of the bile duct (IPNB), oncocytic variant, with high grade dysplasia, and with associated invasive adenocarcinoma, high grade

Differential Diagnoses

- Mucinous cystic neoplasm (MCN)
- Intraductal papillary neoplasm of the bile duct (IPNB)
- Cholangiocarcinoma with areas of cystic degeneration
- Hepatocellular carcinoma (HCC) with bile duct invasion
- Intraductal metastasis of colorectal cancer

Key Features

- Multiloculated hepatic cyst lined by papillae
- With biliary duct dilation
- Oncocytic type epithelium
- Cytologic transition from low-grade to high-grade, to invasive carcinoma
- Lymphovascular invasion present
- Lacks ovarian type stroma
- Molecular finding: DNAJB1-PRKACA gene fusion



Discussion: Intraductal papillary neoplasms of the bile duct (IPNB) are the biliary tract counterparts of the intraductal papillary mucinous neoplasms of the pancreas (IPMNs). The

epithelium may demonstrate pancreatobiliary, gastric, intestinal, or oncocytic phenotypes. Cytologic dysplasia can range from low-grade to high-grade with associated invasive carcinoma.

DNAJB1-PRKACA fusion occurs due to a 400kb deletion on the short arm of chromosome 19 and leads to upregulation of protein kinase activity, which plays a significant role in tumorigenesis of fibrolamellar HCC. DNAJB1-PRKACA fusion had been considered specific and diagnostic for fibrolamellar HCC. However, recent studies demonstrated that DNAJB1-PRKACA fusion also occurs in intraductal oncocytic papillary neoplasms (IOPNs) of pancreas and bile duct. DNAJB1-PRKACA, ATP1B1-PRKACA, ATP1B1-PRKACB gene fusions have been identified in pancreatic and biliary IOPNs, as well as in associated invasive carcinomas and pancreatic cyst fluid and biliary duct cells (brushings) from the same patients. This is clinically significant. Identifying gene fusions in pancreatic cyst fluid and biliary duct cells (brushings) by FISH will improve the diagnosis of IOPNs. Protein kinase inhibitors or modality inhibiting protein kinase pathway may provide potential therapy for IOPNs.

Learning Points

- MCN has ovarian type stroma
- IPNB lacks ovarian type stroma
- Extensive sampling of IPNB surgical specimen is required to search for invasive carcinoma
- Lifelong surveillance is required
- DNAJB1-PRKACA gene fusion is not specific or diagnostic for fibrolamellar HCC; it also occurs in intraductal oncocytic papillary neoplasms (IOPNs) of pancreas and bile duct
- DNAJB1-PRKACA, ATP1B1-PRKACA, ATP1B1-PRKACB gene fusions in IOPNs can be identified by FISH in pancreatic cyst fluid and biliary duct brushing cells

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Case #3
Presenter: Joe Krenzer, DO
Attending: Rong Hu, MD, PhD

Clinical History: The patient is a 74-year-old previously healthy woman who developed bronchogenic mucoepidermoid carcinoma. During the management of her pulmonary cancer, she was found to have an incidental 5.3 cm left renal mass discovered on imaging. There were no reported symptoms related to her renal mass, which was confined to the kidney. A biopsy of the renal mass as well as the subsequent partial nephrectomy was performed at an outside institution and referred to the University of Wisconsin Pathology department for consultation.

Final Diagnosis: Eosinophilic, solid, and cystic renal cell carcinoma (5.1 cm), confined to the kidney

Differential Diagnosis

- Oncocytoma/Chromophobe RCC,
- Hybrid oncocytic/chromophobe renal tumors
- Papillary RCC, oncocytic
- Clear cell (conventional) RCC, eosinophilic
- Hereditary Leiomyomatosis- associated RCC
- MiTF Translocation carcinomas
- SDH deficient RCC
- Eosinophilic solid and cystic RCC

Key Features

- Solid and cystic growth
- Round to oval nuclei, and prominent nucleoli
- Voluminous, eosinophilic cytoplasm
- Granular cytoplasmic stippling
- Hobnail arrangement of cells lining septa
- Diffuse or tightly compact acinar or nested growth in solid foci
- Scattered foamy histiocytes, lymphocytes, and multinucleated cells
- Capsule typically absent

Discussion: Eosinophilic, solid, and cystic renal cell carcinoma is a recently described, distinct renal neoplasm. It is a rare entity, with few cases series reported in the literature thus far. It has a striking female predominance and typically follows an indolent clinical course, with only a very small number of metastatic cases reported. Histologically, this tumor is identical to the eosinophilic-microcytic type renal cell carcinoma in Tuberous Sclerosis (TSC) patients and patients are frequently found to harbor TSC I/II mutations with activation of the mTOR signaling complex. However, these tumors appear to occur in the sporadic setting with patients not exhibiting other phenotypic manifestations of TSC. Histologically, these neoplasms exhibit prominent solid and cystic growth with nuclei that are typically round to oval and display

prominent nucleoli. The cytoplasm is quite voluminous and eosinophilic with conspicuous granular cytoplasmic stippling. In the cystic component, there is a hobnail arrangement of cells lining the septa. The solid component may demonstrate a diffuse, tightly compact acinar or nested growth pattern. Scattered foamy histiocytes, lymphocytes, and multinucleated cells may be present, and a capsule is typically absent. Immunohistochemically, this neoplasm is distinguished by CK20 positivity that can be diffuse or focally cytoplasmic. This finding has been found to have relatively good specificity in the reported literature and even when patchy, it is typically present throughout the entire tumor. The additional immunohistochemical profile typically demonstrates negativity for CK7, CD117, CAIX, and HMB45, and positivity for PAX8 and Pancytokeratin. AMACR and CD10 can be positive or negative.

Learning Points: The differential diagnosis for eosinophilic renal cell neoplasms is expansive. The distinct morphologic features of eosinophilic, solid, and cystic renal cell carcinoma help to significantly narrow this differential and when combined with the appropriate immunohistochemical work-up, allow the diagnosis to be obtained in a reliable manner. So far, this neoplasm has demonstrated indolent behavior and occurs in the sporadic setting even though patients are frequently found to have TSC mutations. These frequently CK20-positive/CK7-negative neoplasms have been observed to have a marked female predominance and although not currently in the WHO, it may possibly be included in future revisions.

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Case #4
Presenter: Oyewale Shiyanbola, MBBS, PhD
Attending: Paul Weisman, MD

Clinical History: The patient is an 84-year-old male with a past medical history significant for multiple basal and squamous cell carcinomas of the face and upper extremities. He presented to the clinic with a slowly growing skin lesion on the nasal dorsum. A shave biopsy showed "poorly-differentiated basaloid carcinoma." The patient received radiation therapy. Nine months later, he presented with a locoregional recurrence. Clinical examination revealed a pink-violaceous dermal plaque with a small pink papule at the distal aspect of the lesion. An initial shave biopsy was performed, and he subsequently had a wide local excision with left selective neck dissection.

Final Diagnosis: Mixed neuroendocrine carcinoma/squamous cell carcinoma

Differential Diagnosis

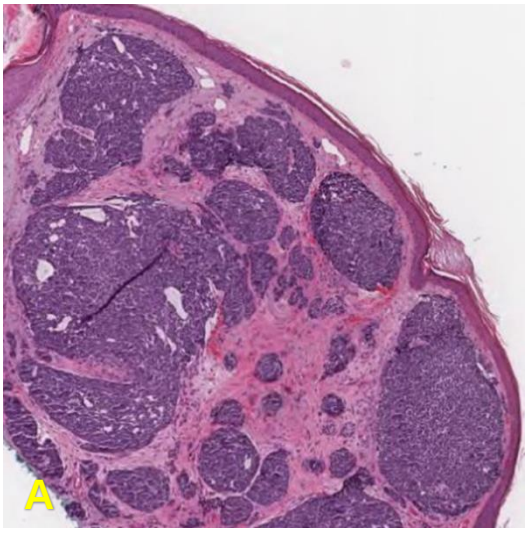
- Merkel cell carcinoma
- Metastatic small cell carcinoma
- Basal cell carcinoma
- Small cell variant of melanoma

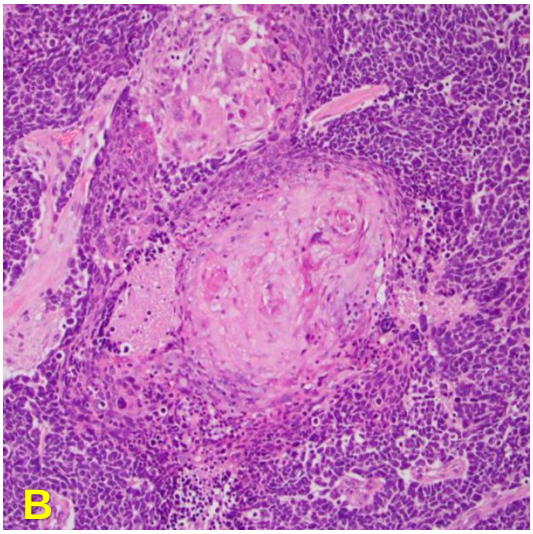
Key Features

- Sun-damaged skin with nests and trabeculae of basaloid cells with nuclear molding, numerous mitotic figures and apoptotic bodies, infiltrating the dermis
- Scattered pleomorphic squamoid cells indicating squamous differentiation

Immunohistochemistry

- Positive: Synaptophysin, chromogranin, INSM1, p63, focal CAM5.2
- Negative: CK20, Merkel cell Polyomavirus, TTF-1, S100





Figures.

A. High-grade neuroendocrine carcinoma. B. Areas of squamous differentiation

Discussion Mixed tumors with components of both conventional carcinoma and high-grade neuroendocrine carcinoma have been described in various organ systems such as the skin, gastrointestinal tract, lung, gynecological tract and the lower anogenital squamous tract, among others. The high-grade neuroendocrine carcinomatous component in such cases shows the expected morphologic and immunophenotypic features of either small cell neuroendocrine carcinoma or large cell neuroendocrine carcinoma. In this case, the features were more in keeping with small cell neuroendocrine carcinoma (i.e. nuclear molding, even chromatin, a high mitotic index with numerous apoptotic bodies). Either type of high-grade neuroendocrine carcinoma should show expression of neuroendocrine markers, such as synaptophysin, chromogranin and INSM1.

The conventional carcinomatous component, on the other hand, is often a useful clue to the etiology and site of origin. For instance, in combined neuroendocrine carcinoma/cutaneous carcinomas, the conventional carcinomatous component is frequently squamous cell carcinoma and focal squamous differentiation is a useful clue. Conversely, in organs in which microsatellite instability (MSI)/mismatch repair protein deficiency (MMR-D) is common, such as the gastrointestinal and gynecologic tracts, the high-grade neuroendocrine carcinomatous component often shows the same pattern of mismatch repair protein loss as the original conventional carcinoma helping to establish the site of origin, even at metastatic sites. In HPV-related tumors, such as those arising in the oropharynx or the uterine cervix, the high-grade neuroendocrine carcinomatous component frequently remains transcriptionally active, which may be demonstrated by RNA in situ hybridization for high-risk HPV subtypes. Targeted therapies applied to conventional adenocarcinomas can also drive differentiation to high-grade neuroendocrine carcinoma. Key examples include conventional prostate adenocarcinoma treated with androgen-deprivation therapy and *EGFR*-mutated lung adenocarcinomas treated with

tyrosine kinase inhibitors. Accordingly, knowledge of a patient's prior malignancies and associated treatments can also be very useful in establishing the site of origin of a high-grade neuroendocrine carcinoma.

Mixed high-grade neuroendocrine carcinoma/conventional carcinoma of the skin is rare and it is important to rule out a Merkel cell carcinoma or metastasis from small cell carcinoma of pulmonary or visceral origin. Merkel cell carcinoma may be excluded by demonstrating the lack of a dot-like expression pattern for CK20 and negative Merkel cell Polyomavirus immunohistochemistry. As noted above, the presence of a minor squamous component is also an important clue. Metastatic small cell carcinoma is more difficult to exclude and, as outlined above, requires careful correlation with patients' history and imaging findings as well as the judicious use of ancillary testing.

Generally, mixed neuroendocrine carcinoma/conventional carcinoma of the skin tends to have a poorer prognosis than conventional cutaneous carcinomas and this is evident in our patient's case. Despite wide local excision and lymph node dissection, the tumor progressed to involve nearly half of his face within only a few months.

Learning points

- Mixed neuroendocrine carcinoma/conventional carcinoma of the skin is rare.
- More common considerations such as Merkel cell carcinoma or metastatic small cell carcinoma should be ruled by clinical and imaging correlation and, where applicable, ancillary testing.
- Focal squamous differentiation, the absence of dot-like staining for CK20 and negative Merkel cell Polyomavirus IHC are all helpful in establishing the diagnosis.

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Case #5
Presenter: Jessica Gulliver, MD
Attending: Jin Xu, MD

Clinical History: The patient is a 63-year-old woman who presented with post-menopausal bleeding, characterized by daily bleeding with intermittent heavy clots, abdominal cramping, and lower back ache. The patient did not report any other symptoms or significant past medical history. A 3.8 cm endometrial mass was identified in the uterine fundus. The patient underwent a total vaginal hysterectomy.

Final Diagnosis: Endometrioid adenocarcinoma with divergent primitive neuroectodermal differentiation (central type)

Differential Diagnosis

- Endometrioid adenocarcinoma, FIGO grade 3
- High grade neuroendocrine carcinoma
- Undifferentiated carcinoma
- Primitive neuroectodermal tumor (PNET)
- High grade endometrial stromal sarcoma (*YWHAE-NUTM2* fusion)
- Metastatic neoplasm (Melanoma or Lymphoma)

Key Features

- Morphology
    - Sheets of poorly differentiated small round blue cells
    - Features of CNS neuroectodermal tumors:
        - Rosettes
        - Fibrillary background
        - Serpentine necrosis with pseudopalisading
    - Usually associated with another neoplasm
- Immunophenotype
    - Prominent neuroendocrine marker expression
- Ancillary Studies
    - Lacks *EWSR1* rearrangement

Discussion: Within the gynecologic tract, primitive neuroectodermal tumors (PNETs) are rare and may occur in adolescents or older individuals. PNETs can be categorized into peripheral/Ewing sarcoma type and central type. Peripheral/Ewing sarcoma PNETs are more common in patients of reproductive age. Common sites include the cervix, vagina, and vulva. Histologically, they usually present in a pure form and are composed of primitive small round blue cells with diffuse strong complete membranous CD99 staining and nuclear expression of Fli-1. They are characterized by *EWSR1* rearrangements which can be detected by FISH and/or RT-PCR. In contrast, central type PNETs occur in the ovary in women of reproductive age and in the uterus in women who are post-menopausal typically. Uterine central type PNETs in post-menopausal patients commonly present with abnormal vaginal bleeding similarly to

endometrioid adenocarcinoma and unfortunately, are often at advanced stage at the time of diagnosis. Central type PNET is often associated with another type of neoplasm. In the ovary, they may be associated with teratoma. Within the uterus, they may be associated with neoplasms such as uterine carcinoma, carcinosarcoma, or sarcoma. Histologically, they are also composed of primitive small round blue cells but features resembling CNS neuroectodermal tumors such as rosettes, a fibrillary background, and serpentine necrotic foci with pseudopalisading are characteristic. Central type PNETs do not harbor an *EWSR1* rearrangement.

Learning Points

- Primary Primitive Neuroectodermal Tumor (PNET) of the uterus is rare, but necessitates early diagnosis and treatment due to the aggressive behavior of the tumor.
- Morphologic features resembling CNS neuroectodermal tumors in combination with prominent neuroendocrine marker expression are helpful diagnostic clues.
- Identification of a secondary neoplastic component by thorough sampling is essential.
- Loss of MMR distinguishes central type PNET from peripheral type PNET.

References:

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Case #6
Presenter: Kelly Olson, MD
Attending: Darya Buehler, MD

Clinical History: A 30-year-old man with no significant medical history presented with a slow-growing, left calf mass over the course of 4 months. He recalled no inciting injury, and it started to cause pain and numbness with weight bearing. On examination, there was tenderness to palpation over the area, with full range of motion. A DVT was initially suspected, but ultrasound did not support that. An MRI demonstrated a 15 cm, solid and cystic mass in the deep soft tissue, involving the neurovascular bundle. An open biopsy was obtained.

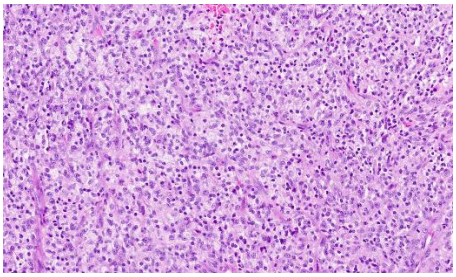
Final Diagnosis: Inflammatory leiomyosarcoma

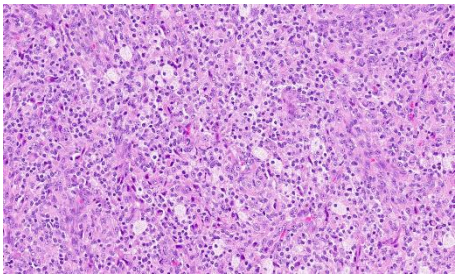
Differential Diagnosis

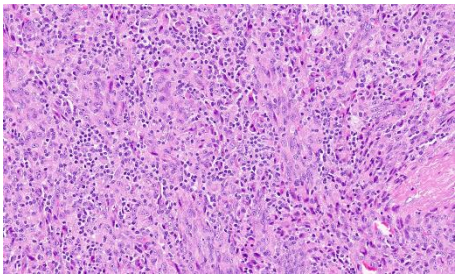
- Inflammatory myofibroblastic tumor
- Histiocytic/dendritic cell tumors
- Pleomorphic sarcoma rich in inflammatory cells (formerly IMFH)
- Myxoinflammatory fibroblastic sarcoma
- Tumors with rhabdoid features
- Obscure entities

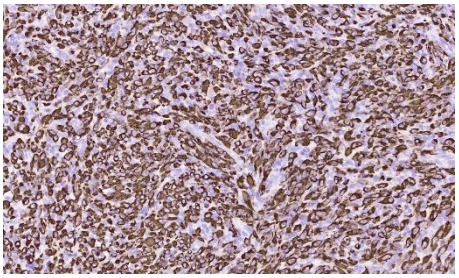
Key Features

- Spindle cells
- Intrinsic inflammatory component
- Epithelioid to rhabdoid cells
- Fascicular to haphazard pattern
- Variable nuclear pleomorphism
- Foamy histiocytes
- Low-to-intermediate grade sarcoma
- Psammomatous calcifications possible









Immunophenotype

- Desmin+
- SMA+ (focal and weak)
- MYOD1+
- Myogenin+

Additional testing

- Karyotype – haploid/hyperhaploid

Discussion: Inflammatory LMS is a very rare, distinct entity, first described in 1995 by Merchant and Fletcher, but newly added to the WHO classification. There is near equal incidence between men and women. The mean age is 36 years, with an age range from 25-54 years. There is a predilection for intramuscular sites of the lower limbs and back. The clinical course tends to be indolent with low metastatic rate.

The molecular nature of this tumor is unique. No fusion transcripts have been detected. Rare cases showed mutations in NF1. ILMS has a unique karyotype, with the most prominent feature being haploidization of the genome, with or without doubling. Often times there is retained disomy of chromosomes 5, 18, 20, 21, and 22. They typically express desmin and smooth muscle markers. It also shows a variety of transcription factors, including, most importantly, skeletal muscle transcription factors, like MYOD1, myogenin, PAX-7. This translates immunophenotypically more into a skeletal muscle phenotype, or myogenic differentiation.

While added into the WHO classification as inflammatory leiomyosarcoma, this is probably a misnomer. Inflammatory LMS likely consists of primitive myogenic cells, or the haploidization of a precursor cell, has allowed for dual expression of smooth and striated muscle genes. Therefore, based on the most recent literature, the proposal is to revise this into a low-grade tumor with myogenic differentiation. The diagnostic challenge in these cases will be with other tumors with smooth or skeletal muscle differentiation and prominent inflammatory cells.

Learning Points

- Inflammatory LMS is a rare entity recently added to the WHO classification with distinct karyotype demonstrating a haploid population.
- The diagnostic challenge is with other tumors with smooth and skeletal muscle differentiation and inflammatory cells.
- With smooth and skeletal muscle differentiation, proposal is to revise this classification into a low-grade tumor with myogenic differentiation.

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