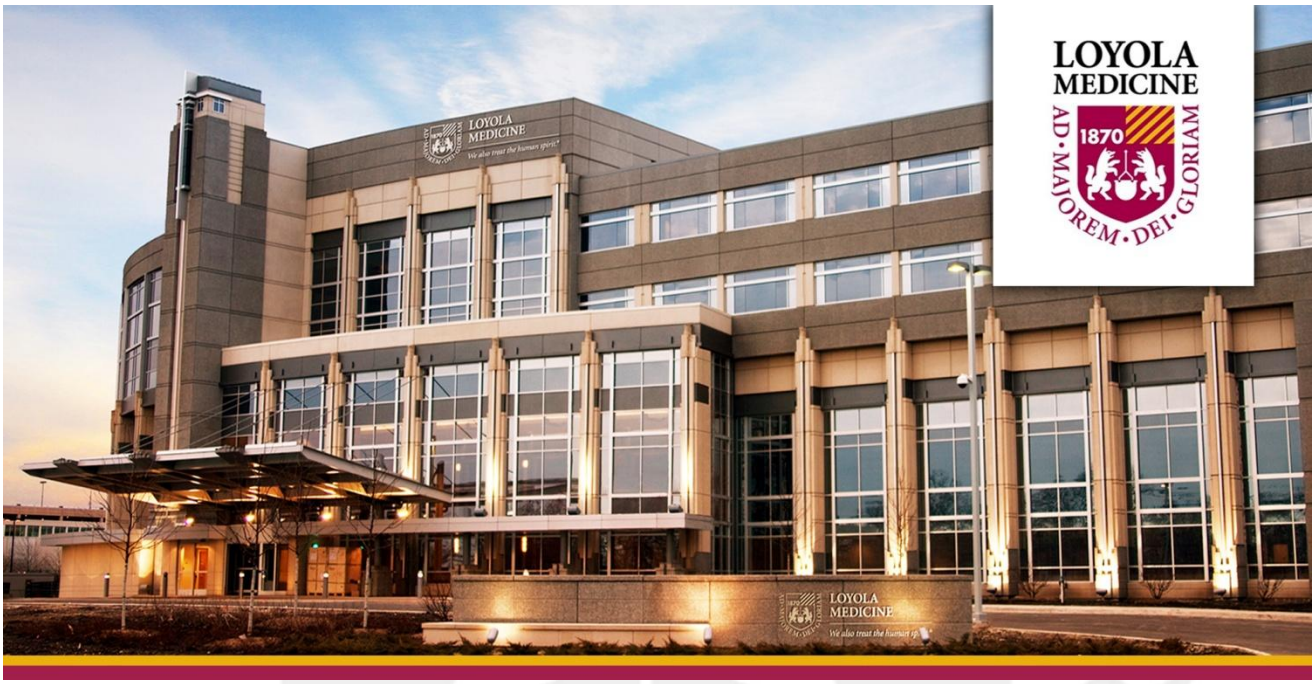


Illinois Registry of Anatomic Pathologists (IRAP)

Chicago Pathology Society - Case Presentations

Loyola University Medical Center

November 19, 2018

Case 1

Presenter: Alessa Aragao, MD (PGY-II)
Attending(s): Dariusz Borys, MD

Clinical History: A 51-year-old woman presents with intermittent chest pain. Her past medical history is significant for a diagnosis of left-sided breast cancer diagnosed in 2009 and right-sided breast cancer diagnosed in 2013, treated with bilateral mastectomy and chemoradiation.

Imaging studies reveal multiple small nodules in the lung and a 2.9 cm nodule in her right upper extremity. An excisional biopsy of the right upper extremity lesion is performed; a section of which was submitted for your review.

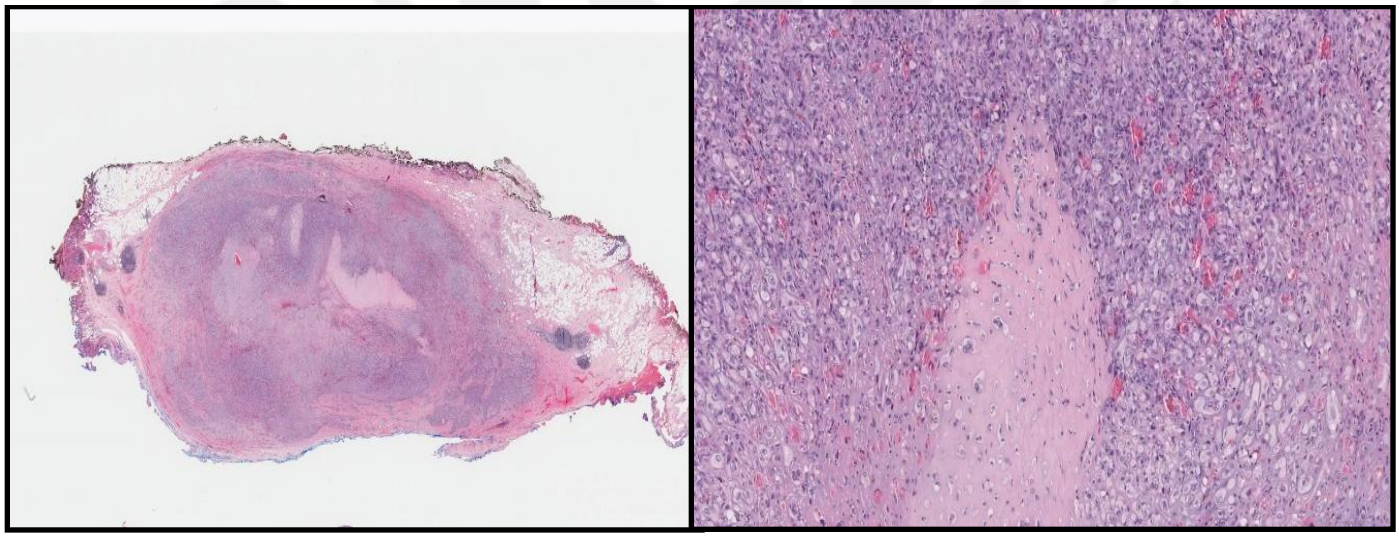
Final Diagnosis: Epithelioid Hemangioendothelioma

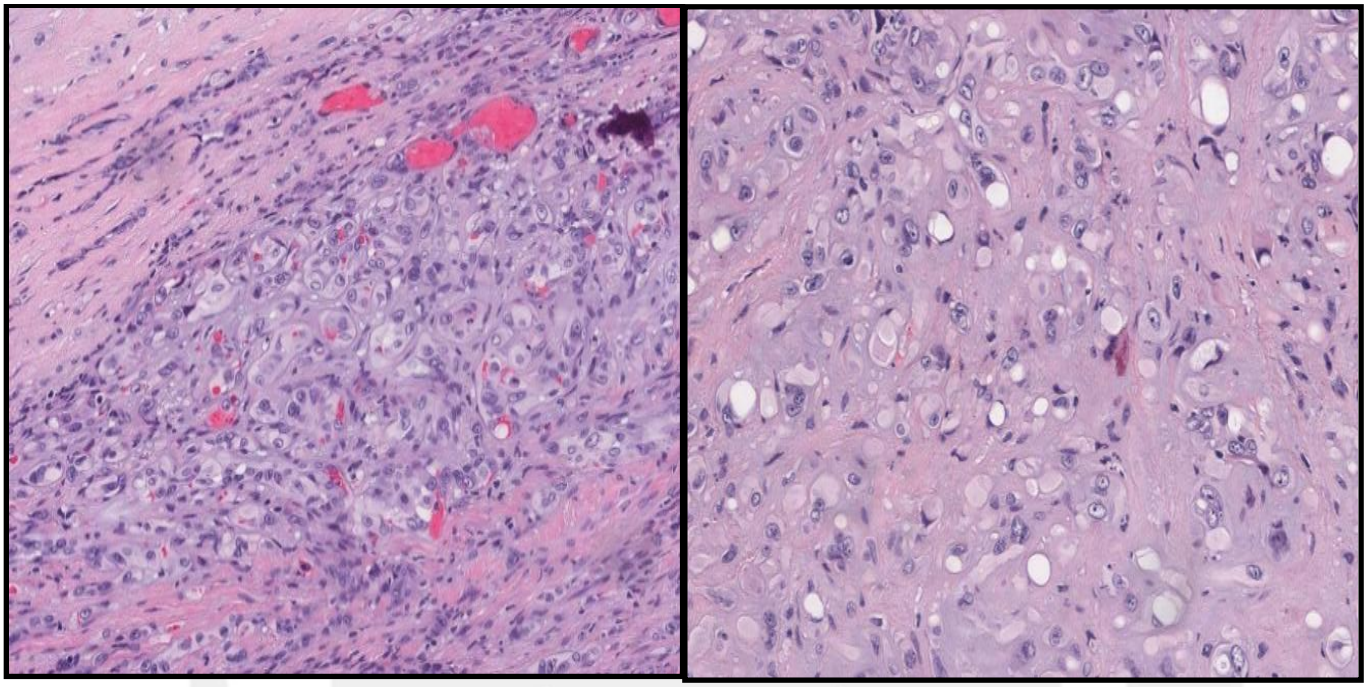
Differential Diagnosis:

- Metastatic ductal carcinoma
- Melanoma
- Epithelioid angiosarcoma
- Epithelioid sarcoma
- Epithelioid hemangioendothelioma

Key Features:

Histology: The lesion is well-circumscribed and demonstrates both hyper- and hypocellular areas. Higher magnification demonstrates cords and nests of epithelial cells with intracytoplasmic vacuoles ("blister cells") and slightly eosinophilic cytoplasm embedded in myxo-hyaline stroma with prominent vascularity. No atypical mitoses, prominent pleomorphism or areas of necrosis were noted. The Ki-67 proliferation index is 1-2%. Results of immunophenotyping study by IHC are given in the table below.





Positive IHC	Negative IHC
CD34	AE1/AE3
CD31	CK7
D2-40	CK20
CAMTA-1	ER
	DESMIN
	S100

Discussion:

Epithelioid hemangioendothelioma (EHE) is a rare, malignant tumor of endothelial origin with metastatic potential. It can be found anywhere in the body with the most common sites being liver, lung and bone (1). The majority of EHEs (90%) are characterized by translocation involving chromosomal regions 1p36.3 and 3q25 leading to WWTR1-CAMTA1 fusion gene. A subset of the cases will have YAP1-TFE3 fusion gene (4).

Histology may show cords, strands or nests of epithelioid endothelial cells with eosinophilic to glassy cytoplasm embedded in a myxohyaline background. The cells contain intracytoplasmic vacuoles that deform the cytoplasm known as “blister cells” (10). Necrosis, high mitotic activity and amphophilic cytoplasm commonly seen in angiosarcoma are usually not appreciated in this entity (3).

EHEs express vascular markers including CD31, CD34, ERG and FLI1 and in 25-40% of cases may also express keratins (CK7, CK8, CK18 and EMA) (10). Nuclear expression of CAMTA1 (calmodulin-binding transcription activator 1) is a useful marker to distinguish EHE from other histologic mimics, including epithelioid angiosarcoma and to confirm the diagnosis with high sensitivity and specificity (2). A subset of cases (10%) will be positive for TFE3 and will present with distinct morphologic features including well-formed vessels and voluminous eosinophilic cytoplasm (3).

The clinical course of EHE is unpredictable, ranging from indolent tumors to highly aggressive disease with considerable morbidity and mortality (4). Although no reliable prognostic features are known, tumors with >3cm in diameter and >3 mitoses per 50 HPF have been used to stratify tumors into low and high-risk group as tumors with these features showed a 5-year disease specific survival of 59% compared to 100% compared to those that lacked these features (10).

Take home points:

- EHE is a rare vascular tumor which mimics other epithelioid tumors
- CAMTA1 is good marker to distinguish EHE from other epithelioid tumors and will be positive in 90% of the cases
- A subset of EHE will be TFE3 positive and can present with distinct morphologic features

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Case 2

Presenter: Recep Nigdelioglu, MD (PGYII)
Attending(s): Xianzhong Ding, MD, PhD

Clinical History: A 29-year-old man is referred from an outside hospital for workup of persistent mild elevation of transaminases for the past three years. His past medical history is pertinent for hypercholesterolemia.

Laboratory studies reveal his AST is in the range of 30-40 (N: 1 5-45IU/L) and his ALT in the 50s (N:10-40 IU/L). Autoantibody tests for ANA (1:160) and ASMA (1:80) are both positive.

He is a social drinker and doesn't have a family history of liver disease. He has no relevant past surgical history, and his physical examination was unremarkable.

Ultrasound examination demonstrates a normal-sized liver with normal parenchymal echogenicity and scattered calcifications. Due to his persistent elevated transaminase levels and positive autoimmune markers, a percutaneous liver biopsy is performed. A representative section was submitted for your review.

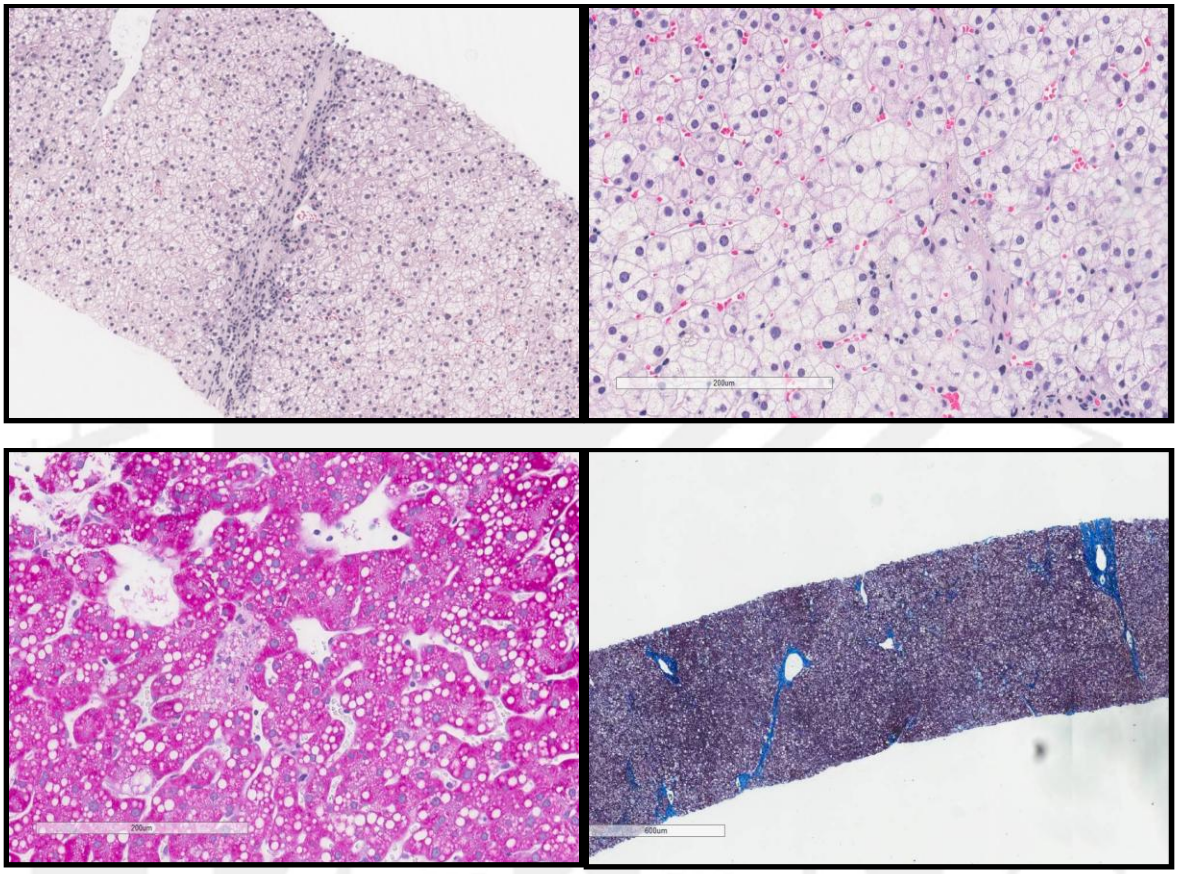
Final Diagnosis: Lysosomal Acid Lipase Deficiency (LAL-D)

Differential Diagnosis:

- Nonalcoholic fatty liver disease
- Alcoholic fatty liver disease
- Drug induced liver injury
- Metabolic Diseases
- Disorders of mitochondria
- Lysosomal disorders
- Lipid transport disorders
- Glycogenic hepatopathy

Key Features:

Histology: Liver biopsy shows diffuse enlarged hepatocytes with intracytoplasmic vacuoles, mostly consistent with microvesicular and medium droplet steatosis. There are no significant large droplet fat vacuoles that would suggest macrovesicular steatosis. Clusters of pigmented and foamy Kupffer cells are present in the lobules. Focal thin bridging fibrosis with stage 2-3 fibrosis is identified. There is no hepatocyte ballooning and Mallory-Denk body formation. Lobular inflammation is inconspicuous. Portal inflammation is minimal with a few small mature lymphocytes and ceroid macrophages. No significant interface activity or plasma cell infiltrate is identified. Bile ducts are unremarkable. Overall the histological findings are consistent with diffuse microvesicular steatosis without any large fat droplet accumulation.



Discussion:

Lysosomal Acid Lipase Deficiency (LAL-D) is a rare genetic lipid storage disorder caused by mutations in the (LAL)-encoding gene (*LIPA)* gene. Metaanalysis studies showed that LAL-D disease is most common in white people of European origin, followed by those of North American and Latin American origin. Disease prevalence is unknown but is estimated to be from 1:40,000 to 1:300,000 depending on the population studied. More than 100 *LIPA* gene mutations have been identified so far, the most common of which is E8SJM. Individuals with homozygous E8SJM mutation account for more than half of all patients with LAL-D.

Mutations in *LIPA* gene cause two diseases in humans that differ in severity; Wolman Disease and Cholesterol Ester Storage Disease (CESD). Wolman disease is characterized by a failure to thrive, progressive hepatosplenomegaly, adrenal calcification and death within the first year after birth. CESD has a similar phenotype but a later onset and a much slower progression. Both conditions are caused by reduced LAL activity, giving rise to excessive cholesteryl ester and triacylglycerol accumulation in lysosomes. Individuals with Wolman disease invariably lack the enzyme, individuals with CESD frequently exhibit some remnant enzyme activity. The spectrum of disease manifestation and progression in CESD ranges from severe liver disease and liver failure in children to no apparent clinical features until adulthood. The outcome is often independent of the magnitude of remnant LAL activity.

Grossly, the liver appears bright yellow–orange in color, and histological analysis shows varying degrees of portal and perilobular fibrosis and intense microvesicular steatosis due to accumulation of cholesteryl esters and triglycerides in the lysosomes of hepatocyte. A characteristic feature is the presence of markedly hypertrophic Kupffer cells and portal macrophages, with a foamy, tan-coloured cytoplasm that stains strongly with periodic acid–Schiff (PAS). The

membranes of such vacuoles are well stained by PAS diastase. In unfixed biopsy samples, the presence of birefringent-stored liquid crystals of cholesteryl esters is an additional diagnostic clue in LAL-D. Immunohistochemical detection of luminal cathepsin D and lysosomal markers (lysosomal-associated membrane protein [LAMP1, LAMP2] and lysosomal integral membrane protein 2) around the lipid droplets is experimentally shown useful. A diagnosis of LAL-D can be obtained by demonstration of deficient LAL activity or mutations in the *LIPA* gene.

Enzyme replacement therapy (sebelipase) was recently approved for the treatment of individuals with LAL-D. Sebelipase treatment was beneficial for many patients with LAL-D. It improved liver function, normalized plasma transaminase activities and decreased hepatic triglyceride content.

Take home points:

- Lysosomal acid lipase (LAL) deficiency is characterized by lack or deficient lysosomal acid lipase enzyme activity
- LAL-D may go unrecognized
- New replacement enzyme therapy for LAL-D is promising

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Case 3

Presenter: Schuharazad Abro, MD (PGYII)
Attending(s): Swati Mehrotra MD and Vijayalakshmi Ananthanarayanan MD

Clinical History: A 66-year-old woman presents with dysphagia, change in voice, and an oral lesion. Her past medical history is significant for a diagnosis of acute myeloid leukemia (AML), treated with stem cell transplantation. Therapy was complicated by graft versus host disease.

Physical examination showed a 3.0 cm exophytic mass in her left oropharynx. An excisional biopsy is performed. A representative slide of that mass was submitted for your review.

Final Diagnosis: Spindle cell Rhabdomyosarcoma (RMS)

Differential Diagnosis:

- Spindle squamous cell carcinoma
- Pyogenic granuloma
- Kaposi sarcoma
- Malignant nerve sheath tumor
- Schwannoma
- Spindle cell melanoma
- EBV associated smooth muscle tumor
- Leiomyosarcoma
- Rhabdomyosarcoma
- Inflammatory myofibroblastic tumor
- Myoepithelial carcinoma
- Solitary fibrous tumor

Key Features:

Histology: Excisional biopsy of the mass was composed of polypoidal tissue fragments (Fig 1) showed submucosal monomorphic spindle cells arranged in fascicles with acute inflammatory cells and mononuclear cells (Fig 2). At higher power the spindle cells appear monotonous with centrally located elongated nuclei and small prominent nucleoli. There were focal areas of loose myxoid stroma and necrosis with inconspicuous mitotic activity. The immunohistochemistry is detailed in Table 1.

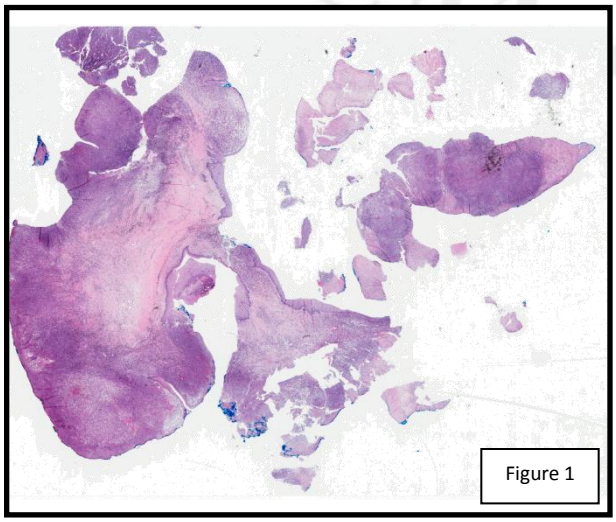


Figure 1

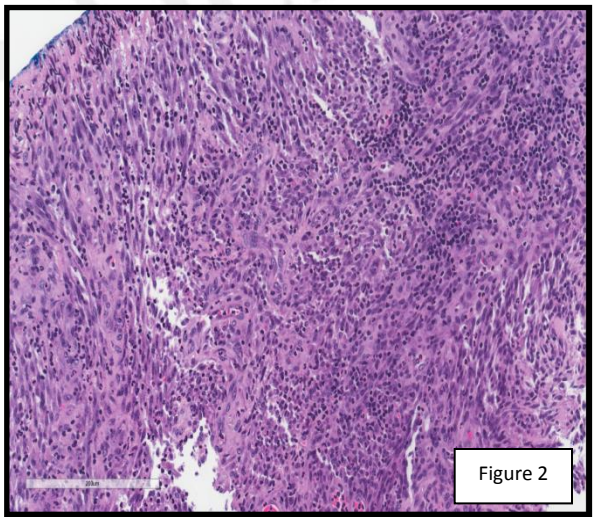
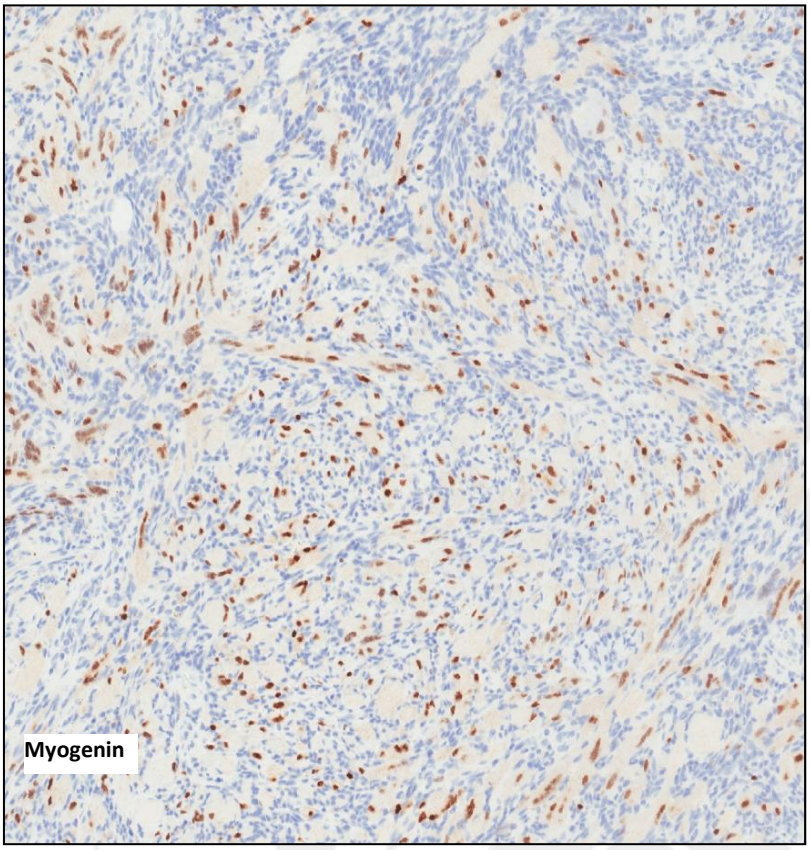
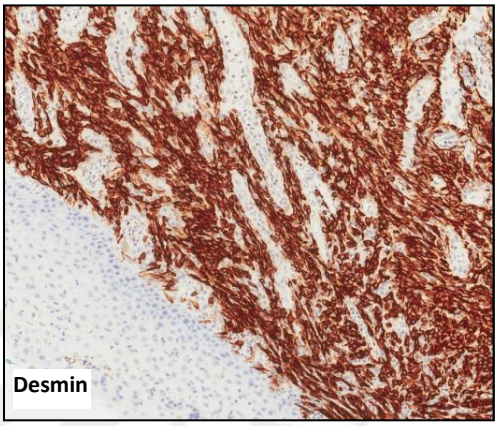
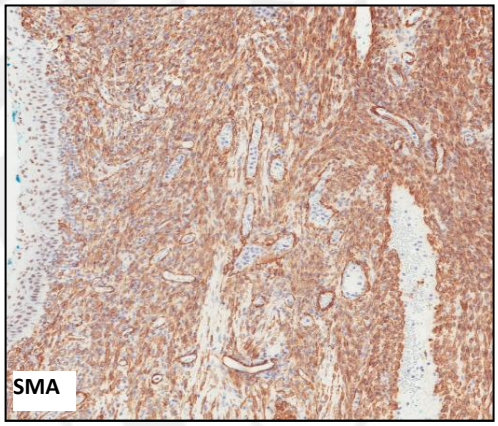


Figure 2







Positive IHC	Negative IHC
SMA	Keratin AE1/AE3, Keratin 34BE12, Keratin 8/18
Desmin	P63
Myogenin	EMA
	CD31, CD34
	S-100
	ALK
	EBER-ISH
	EBV-LMP
	CD21, CD117
	Her2neu

Discussion:

Spindle cell RMS is a rare variant of RMS. The mean age is 29 years with a predilection for males, involving paratesticular and intra-abdominal regions. They are rarely seen in adults and commonly involve extremities and head and neck region.

Initially the spindle cell and sclerosing RMS were considered as a part of the embryonal variant. In 2013, WHO combined spindle cell and sclerosing variants together to form a single new entity. The etiology is unclear but most of the cases are sporadic. MYOD1 (L122R) genetic alteration is commonly seen in these tumors and is associated with poor outcome.

Microscopically, the tumor is composed of relatively monotonous spindle cell proliferation with scant eosinophilic cytoplasm and centrally located, pale, vesicular, elongated nuclei. Usually there is necrosis and dense inflammation in the background.

Spindle cell RMS is positive for muscle differentiation markers like SMA and Desmin. Nuclear expression of Myogenin and MyoD are specific immunohistochemical stains for skeletal muscle differentiation and are helpful to differentiate it from tumors with smooth muscle differentiation.

Take home points:

- Spindle cell/sclerosing RMS are grouped together and as a single new entity
- In adults, head and neck region is most common site; pediatric population has a predilection for paratesticular and intra abdominal regions
- Differential diagnoses include a variety of spindle cell tumors
- Locally aggressive tumors, hence correct diagnosis is crucial
- Tumors with molecular alterations are associated with poor prognosis
- Molecular studies (MYOD1 and PIK3CA) should be considered in patients with first time diagnosis for risk stratification

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Case 4

Presenter: A. Irem Kilic, MD (PGYII)
Attending: Stefan Pambuccian, MD

Clinical History: A 70-year-old man presents to the ER with fatigue, poor appetite and abdominal pain. His past medical history is significant for cirrhosis, portal hypertension and coagulopathy.

Imaging studies show multiple liver lesions, an 8 mm solitary lesion in the lower lobe of the right lung, and irregular thickening of the walls of the esophagus and stomach. Transabdominal CT-guided fine needle aspiration and needle core biopsy of the liver is performed.

Flow cytometry of the aspirate and initial immunohistochemical stains for cytokeratin (AE1/AE3 and 8/18), S100, CD3, CD20 and CD45 are negative. Representative images of the liver aspirate and core biopsy were submitted for your review.

Final Diagnosis: SMARCA4-Deficient undifferentiated malignant neoplasm

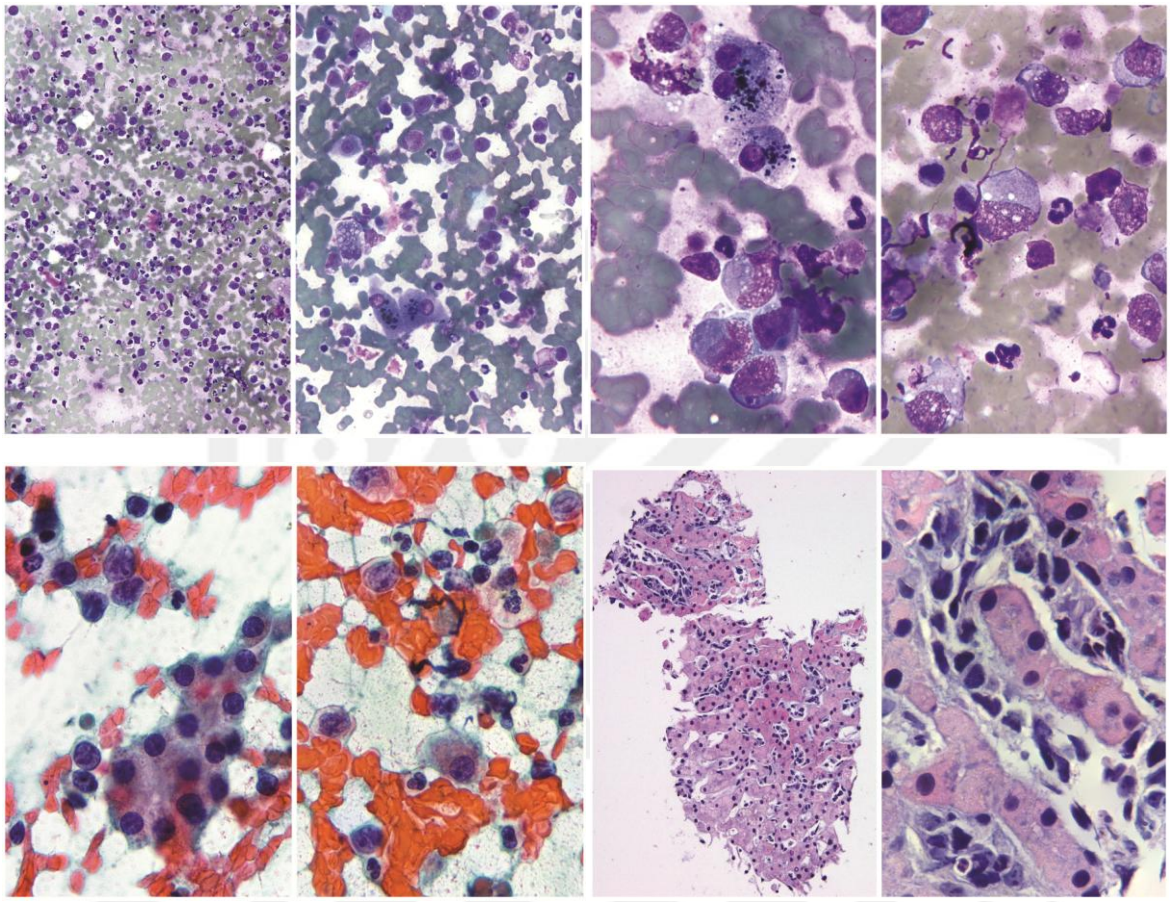
Differential Diagnosis:

- Primary carcinoma
- Hepatocellular carcinoma
- Cholangiocarcinoma
- Metastatic carcinoma
- Poorly differentiated gastric adenocarcinoma
- Poorly differentiated adenocarcinoma of lung
- Large cell neuroendocrine carcinoma
- Hematolymphoid malignancies
- Diffuse large B-cell lymphoma
- Anaplastic large cell lymphoma
- Plasmablastic lymphoma/myeloma and myeloid sarcoma
- Sarcoma
- Rhabdomyosarcoma
- Ewing and Ewing-like sarcoma
- Melanoma

Key Features:

Cytology: An FNA of the liver lesion was performed and showed a cellular smears composed of a rather uniform population of discohesive cells, with very rare loosely cohesive groups of 2-6 cells showing nuclear molding. Interspersed between these monotonous tumor cells, there were clusters and sheets of large polygonal hepatocytes with coarse bile pigment in their cytoplasm. Although the tumor cells were smaller than the hepatocytes, their nuclei were slightly larger than the hepatocyte nuclei, had less condensed and coarse chromatin, irregular contours and visible to prominent nucleoli. Although some cells had very high N/C ratios, showing only minimal amounts of cytoplasm surrounding the large rounded nucleus, most nuclei were eccentrically located frequently bean-shaped, showing cytoplasmic indentations. The cytoplasm was finely granular and showed 1-5 small vacuoles (microvesicles).

Focally, there was nuclear streaking and crush artifact of the malignant cells as well as clusters of necrotic cells and necrotic debris in the background. The background also contained numerous red blood cells, occasional neutrophils and lymphocytes as well as lymphoglandular bodies. Rhabdoid-like cytoplasmic inclusions were seen in some cells and globular structures of similar size and staining characteristics were also seen in the background.



Histology: A liver core biopsy was performed and showed an infiltration of undifferentiated cells within the sinusoids. On higher magnification the tumor is characterized undifferentiated cells with high N/C ratio and prominent nucleoli. Focally there were intracytoplasmic microvesicles and rhabdoid-like features. More than 3 mitosis/HPF were noted. Ki-67 showed a very high proliferation index.

Positive IHC	Negative IHC
CD138	CKAE1/AE3, CK8/18, CK OSCAR, EMA
PAX5 (weakly)	CD3, CD20, CD30, CD43, CD45, OCT2
Ki67 proliferation index (very high)	CD79A, MUM1, ALK, LYSOZYME, MPO
INI1 (RETAINED)	KAPPA, LAMBDA, EBER ISH, HHV8
	SYNAPTOPHYSIN, CHROMOGRANIN, CD56
	CD34, CD117, CD99
	S100, SOX10
	BRG1 (LOSS)

Discussion:

The switch/sucrose-nonfermenting (SWI/SNF) chromatin-remodeling complex, also referred to as *BAF* (*BRG1/BRM* associated factor) complex contains two important catalytic proteins (BRG1 and BRM) encoded by *SMARCA4* and SMARCA2 respectively. *SMARCA4* and *SMARCA2* genes are located on chromosome 19p (3, 8, 22).

The SWI/SNF complex acts on multiple pathways involved in carcinogenesis, such as the cell cycle regulation pathway, WNT/beta-catenin pathway, sonic-hedgehog-GLI pathway and polycomb pathway (through its action on EZH2). The latter is important because it gives the opportunity for potential targeted therapy. Targeted EZH2 inhibitors have been shown to stop tumor proliferation by inactivating the polypcomb pathway in the preclinical trial of SMARCA4-deficient small cell carcinoma of the ovary, hypercalcemic type (SCCOHT). Abnormalities involving different subunits of SWI/SNF complex can lead to different cancer types. These subunits usually act as tumor suppressors, i.e. the loss or dysfunction of both alleles is required for carcinogenesis. Germline abnormalities of the genes encoding for members of this complex have been described and lead to familial cancer syndromes (2, 3, 6, 10, 16, 17, 18, 19, 21, 22).

Rhabdoid tumors, associated with SMARCB1 loss, are the best known of these tumors. SMARCB1 (INI1) was the first subunit of the SWI/SNF complex to be determined to be associated with cancer. The loss of SMARCB1 (INI1) was first discovered in rhabdoid tumors, but later also in epithelioid sarcoma and SMARCB1-deficient sarcomas, and in benign neoplasms such as schwannomas seen in schwannomatosis and in meningiomas. Loss of ARID1A expression is associated with colorectal cancer that is not induced by typical colon cancer mutations such as APC, KRAS and p53. Loss of SMARCA4 is associated with lung cancer and small cell carcinoma of ovary, hypercalcemic type.

The tumorigenic effects of abnormalities in the members of the SWI/SNF chromatin-remodeling complex are usually caused by loss of one or more of the members of the complex. Interestingly, synovial sarcoma is characterized by gains of function of SS18, which is also a member of the SWI/SNF chromatin-remodeling complex (7, 11, 14, 16, 20).

SMARCA4 deficient tumors described to date are mostly thoracic tumors, predominantly seen in males, with a median age of 59 years. Mostly diagnosed at a stage with metastases, they have aggressive behavior and very poor prognosis with median survival of only 2-years. Tumor showing the co-deficiency of BRG1 and BRM proteins has an even worse prognosis (2, 3, 4, 15). The most common metastases are to lymph nodes, adrenal, pericardium, lung, bone, and brain. The cytologic features of these tumors are consistent with high grade histomorphologic characteristics and are similar to those of INI1 (SMARCB1)-deficient tumors (renal and extrarenal rhabdoid tumor, atypical rhabdoid/teratoid tumor, and SMARCB1 (INI-1)-deficient Sinonasal Carcinoma). They have vesicular chromatin with prominent macro nucleoli and rhabdoid morphology, including discohesive tumor cells with abundant eosinophilic cytoplasm, eccentric nuclei, and intracytoplasmic inclusions with sheet-like growth pattern. Mitotic activity and necrosis are seen (2, 3, 5, 9). SMARCB1-deficient sinonasal tumors and malignant rhabdoid tumors in childhood show sheet-like growth pattern of atypical undifferentiated epithelioid cells with eosinophilic intracytoplasmic inclusions and vesicular nuclei with prominent nucleoli with rhabdoid morphology and occasional necrosis (1, 9, 10, 11). The cytologic features of SMARCA4-deficient thoracic sarcoma have only been rarely described and include atypical cells as single discohesive cells. Some cells have intracytoplasmic microvesicles with large atypical nucleus with vesicular chromatin and prominent nucleoli. Some cells show rhabdoid morphology with intracytoplasmic inclusions (12, 13). The SMARCA4-deficient tumors show loss expression of BRG1 protein and retained INI1 protein. BRG1 and INI1 immunoexpression are helpful to confirm the diagnosis. Pancytokeratin, CD34 show variable staining pattern in rare SMARCA4-deficient tumors; S100 and desmin immunostaining is negative in

BRG1-deficient tumors (2, 3). In addition to IHC for BRG1 and INI1, molecular studies for SMARCA4 and SMARB1 are also helpful to diagnose SMARCA4-deficient neoplasms (9).

Take home points:

- SMARCA4-deficient malignancies are recently described tumors that show morphologic similarities to the better known previously reported tumors with abnormalities in other genes of the BAF (SWI/SNF) complex, especially INI1 (SMARCB1)-deficient tumors (renal and extrarenal rhabdoid tumor, atypical rhabdoid/teratoid tumor, and SMARCB1 (INI-1)-deficient sinonasal carcinoma).
- When faced with an aspirate with dispersed undifferentiated cells and all more common possibilities are excluded (lymphohematopoietic malignancies, melanoma, undifferentiated carcinoma, EWS and other small blue cell tumors) think about staining for INI1 and BRG1
- Prognosis is currently very poor, but some targeted therapies show some promise.

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Case 5

Presenter: Daniel E. Dresser, MD (PGY III)
Attending: Ewa Borys, MD

Clinical History: A 31-year-old female presented with six months of headaches, night sweats and diplopia. Her past medical history included asthma and a TSH-secreting pituitary adenoma which was treated with partial resection and radiation therapy.

Brain MRI performed at the current presentation demonstrated a 2.8 cm lobulated mass within the right aspect of the sella turcica. Transsphenoidal partial resection of this lesion was preformed and the lesional tissue was submitted for your review.

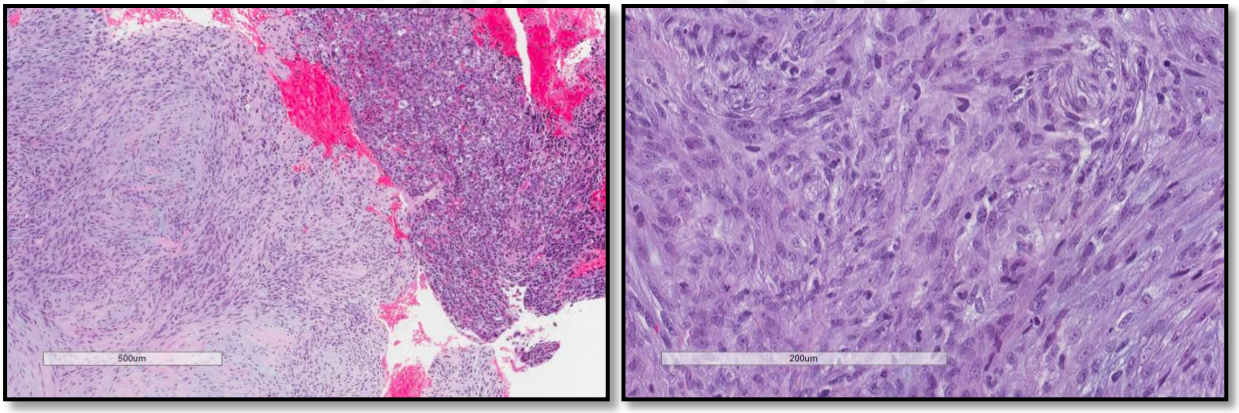
Final Diagnosis: High grade sarcoma, not otherwise specified

Differential Diagnosis

- Cellular schwannoma
- Fibroblastic meningioma
- Pituicytoma
- Solitary Fibrous Tumor
- High grade sarcoma/ undifferentiated sarcoma
- Malignant peripheral nerve sheath tumor
- High Grade glioma/ Gliosarcoma

Key Features:

*Cytology/Histology: H*ematoxylin and Eosin stains of the sellar mass revealed a mixture of patterns, comprised mostly of highly atypical spindled cells growing in fascicles, along with more epithelioid tumor cells focally, the latter surrounded by thin rims of unremarkable non-neoplastic pituitary gland. The region containing enlarged, epithelioid cells with prominent nucleoli is suggestive of pituitary adenoma, whereas the spindled component has markedly pleomorphic nuclei, poorly-defined cell borders, and variably eosinophilic to pale cytoplasm suggestive of sarcoma. The latter also features foci of necrosis and an increased mitotic index, reaching up to 4 mitoses per 10 high-powered fields.



Immunohistochemistry:

Positive IHC:

S100 (Focal)
SMA (Focal)
Bcl-2 (Focal)
CD56 (Focal)

Negative IHC:

GFAP
HMB-45
EMA
CD34
Progesterone receptor
Synaptophysin
Cytokeratin
CAM 5.2
Calponin
Caldesmon
Chromogranin
TTF-1
Desmin
STAT6
SOX10

Discussion:

Radiation-induced sarcomas (RIS) are a rare and delayed complication of radiation therapy. These tumors have been described in the sellar region after standard-dose radiation management of pituitary adenomas, however, they can occur at any site. The original diagnostic criteria for RIS were initially proposed by Cahan *et al.* in 1948 [1] for osteosarcomas and have since been revised many times with ongoing controversy and a lack of consensus for definitive criteria[5][6]. Although the exact mechanism for the development of RIS has yet to be elucidated, there are some described risk factors associated with these tumors such as radiation exposure during childhood, high-dose radiation, concomitant use of alkylating chemotherapy agents and genetic familial conditions (Werner syndrome, Li-Fraumeni syndrome, neurofibromatosis type I, retinoblastoma, familial gastrointestinal stromal tumors (GIST), Costello syndrome, and Nijmegen breakage syndrome)[2][3].

Due to the embryonic mesenchymal cell origin of these lesions, histologic and immunohistochemical staining patterns vary, however, the most commonly reported histologic types of RIS are fibrosarcoma, sarcoma not otherwise specified and undifferentiated sarcoma [4]. Histologically, high-grade sarcomas are typically highly cellular lesions composed of spindle cells arranged in a fascicular, storiform or herringbone patterns. Cytologic features such as nuclear hyperchromasia, pleomorphism, indistinct cell borders and increased mitotic figures are observed. These lesions show no reproducible immunohistochemical staining patterns, however, these lesions may show focal staining for actin, desmin, SMA, EMA, keratin, vimentin or CD34. It is important for the pathologist to form a clear list of differentials to rule out histologically similar tumors based on the immunophenotypic profiles.

Take Home Messages:

- Radiation therapy is a common modality utilized in the management of various neoplastic processes
- RIS are a rare but recognized long-term complication associated with high-dose radiation therapy
- Criteria for differentiating RIS from sporadic sarcomas remain controversial
- These lesions typically follow an aggressive clinical course with limited treatment options

References:

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Case 6

Presenter: Shahad Abdulameer MD (PGY III)
Attendings: Darius Borys, MD

Clinical History: A 24-year-old woman at 16 weeks 4 days gestation presented with fatigue, lower back and left leg pain. Imaging showed an ill-defined radiolucent lesion in the left femoral greater trochanter.

Surgical resection was undertaken during her second trimester of pregnancy. A section of the excision specimen is provided for your review.

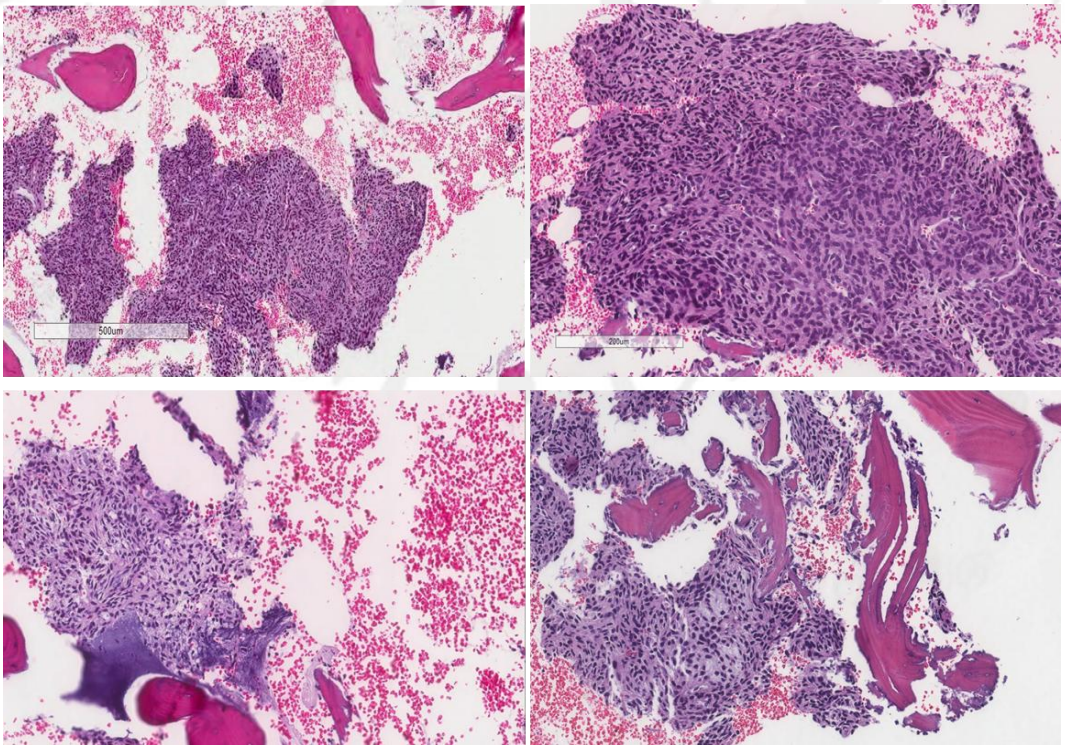
Final Diagnosis: Phosphaturic Mesenchymal Tumor (PMT)

Differential Diagnosis:

- Solitary Fibrous Tumor
- Giant Cell Reparative Granuloma
- Brown Tumor
- Non ossifying fibroma
- Giant Cell Tumor of Bone
- Phosphaturic Mesenchymal Tumor
- Mesenchymal Chondrosarcoma

Key Features:

Histology: H&E stained sections demonstrated an infiltrative growth pattern with encasement of preexisting trabecular bone. Findings were of a cellular mesenchymal neoplasm with stellate to spindle-shaped cells, focal cartilaginous type myxoid matrix, hemangiopericytoma like pattern involving the bone marrow spaces with so-called purple "grungy calcifications".



Positive Stains	Negative Stains
Vimentin	CD34
CD56	CD68
Low Ki-67	

Discussion:

PMT is a distinctive mesenchymal tumor associated with oncogenic osteomalacia due to phosphate wasting (paraneoplastic phenomenon). It was first reported by McCance et al. in 1947 as a tumor inducing osteomalacia, and was first identified by Prader et al. in 1959.

Clinically, patients present with bone pain often for many years and fractures. Laboratory tests will show hypophosphatemia; hyperphosphaturia, and decreased 1,25-dihydroxyvitamin D3 levels. Most intraosseous PMTs are benign; and oncogenic osteomalacia is reversible after removal of the tumor.

Phosphaturic mesenchymal tumor usually occurs in middle age adults. More common in females. Most common presentation sites are the femur and the sacrum, but they also can present in phalanx, metacarpal, iliac crest, cervical vertebra, mandible, and tibia.

Fibroblast growth factor 23 (FGF23) is located on chromosome 12 and is composed of three exons. Mutations in FGF23 render the protein resistant to proteolytic cleavage, and lead to increased activity of FGF23.

The best-established receptor of FGF23 is FGFR1, which on ligand binding and activation conducts its signaling pathways to regulate cell proliferation, survival, migration, and differentiation. There is a central role of FGFR1 signaling in the pathogenesis of phosphaturic mesenchymal tumors.

Fibronectin 1 (FN1), a protein-coding gene on chromosome 2. Altered fibronectin expression has been associated with a number of disorders. Both fibronectin and FGF1 are secretory proteins, when secreted at high levels, could presumably function like normal FGF1 in excess and acts as a potent mitogen of fibroblasts. The FGFs secreted by the tumor cells could bind the ligand-binding domains of the FGFR1 part to facilitate the dimerization and activation of the fusion protein, which would likely dimerize and bind the membranous FGFR1 in a 2:2 ternary fashion. This will converge in the activation of FGFR1 signaling, which upregulates the expression of FGF23.

Though phosphaturic mesenchymal tumors are benign entity, more concerning features should be always looked for and consider, including pleomorphism, increase N/C ratio, and mitotic rate > 5 /10HPF.

The definite diagnosis is often delayed to due multiple factors include the failure to correlate the nonspecific symptoms of fatigue, bone pain, and hypophosphatemia with the presence of a tumor; and to be treated for hypophosphatemia without further workup. Difficulty in tumor localization is the next obstacle to prompt treatment. In addition to the histologic recognition of the entity.

Take Home Messages:

- Phosphaturic mesenchymal tumor (PMT) is an exceptionally rare disease, it is crucial not to miss.
- Should be consider with vague clinical presentation of fatigue, bone pain, hypophosphatemia, and decreased 1,25-dihydroxyvitamin D3 levels.

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Questions

1. Which of the following is <u>not</u> characteristic of epithelioid hemangioendothelioma?

a) Low mitotic activity
b) Intracytoplasmic vacuoles ("blister cells")
c) Myxohyaline stroma
d) Necrosis

2. What is the most common gene fusion seen in epithelioid hemangioendothelioma?

a) YAP-TFE3
b) TAZ-TFE3
c) WWTR1-CAMTA1
d) ASPSCR1-TFE3

3. Regarding TFE3 positive epithelioid hemangioendothelioma mark the correct option.

a) They are characterized by poorly formed vessels
b) The cytoplasm of the cells is more eosinophilic
c) Represents 90% of the cases of epithelioid hemangioendothelioma
d) Are associated with TAZ-TFE3 fusion gene

4. Which of the following dyslipidemia is more characteristic for Lysosomal Acid Lipase Deficiency (LAL-D)?

a) Type I
b) Type IIa
c) Type III
d) Type IV

5. What is the most common *LIPA* gene mutation causing Lysosomal Acid Lipase Deficiency (LAL-D)?

a) PTEN
b) MT-ND1
c) E8SJM
d) MT-TS1

6. Regarding Lysosomal Acid Lipase Deficiency (LAL-D) mark the incorrect option

a) Mutations in LIPA gene causes two diseases that differ in severity
b) Histology shows diffuse microvesicular steatosis with foamy portal macrophages and Kupffer cells
c) Lysosomal acid lipase deficiency result in downregulation of de novo cholesterol biosynthesis
d) Grossly, the liver from patients with LAL-D is bright yellow-orange

7 Choose the correct statement regarding epidemiology of spindle cell RMS:

a) Common in adult population
b) Head and neck is most commonly effected in pediatric population
c) Spindle/sclerosing RMS is not a variant of embryonal RMS
d) Females are commonly affected

8. Which stain would be helpful to differentiate spindle cell rhabdomyosarcoma from leiomyosarcoma?

a) Desmin
b) SMA
c) Myogenin
d) S-100

9. Which mutation in spindle cell/sclerosing rhabdomyosarcoma is associated with poor outcomes?

a) *NCOA2* or *VGLL2* mutation
b) *MYOD1* genomic alteration
c) *PAX3-FOXO1* fusion
d) *PAX7-FOXO1* fusion

10. All of the following cytologic features are characteristically associated with SMARCA4-Deficient neoplasms?

a) Discohesive cells
b) Prominent nucleoli
c) Squamous differentiation
d) Cytoplasmic microvesicles
e) Rhabdoid inclusions

11.Which of the following immunostains is most useful to confirm the diagnosis of SMARCA4-Deficient neoplasms?

a) Pancytokeratin
b) S100
c) INI1
d) BRG1
e) CD34

12. Regarding neoplasms resulting from abnormalities in genes encoding proteins of the SWI/SNF-complex, which of the following is not true?

a) The loss of SMARCA4/BRG1 is found in most cases of small cell carcinoma of the ovary-hypercalcemic type (SCCOHT)
b) Synovial sarcoma is the only tumor characterized by a gain of function of a member of the BAF (SWI/SNF) complex
c) SMARCB1 loss characterizes renal, CNS and sinonasal tumors with rhabdoid or small blue cell morphology.
d) ARID1A gene mutations can result in colorectal cancer even in the absence of APC, KRAS and p53 mutations.
e) All tumors caused by a loss of function of members of the BAF (SWI/SNF) complex are highly malignant and have very poor prognosis.

13. Which of the following options would favor high-grade sarcoma over gliosarcoma?

a) A biphasic reticulin staining pattern
b) The presence of PTEN mutation
c) Absence of GFAP staining
d) Almost exclusively occurring in older adults

14) Which of the following is the most commonly encountered histologic subtype of radiation-induced sarcoma

a) MPNST
b) Synovial sarcoma
c) Leiomyosarcoma
d) Fibrosarcoma

15. Which of the following is not a part of Cahan's criteria for diagnosing RIS?

a) History of high-dose radiation therapy
b) Tumor location in a previously radiated area
c) Asymptomatic latency period of several years (time frame controversial)
d) Pathologically-proven difference between the new tumor and the primary lesion
e) No other predisposing conditions to tumor development

16. What is responsible for the paraneoplastic phenomenon in phosphaturic mesenchymal tumors?

a) Parathyroid hormones
b) Fibroblast growth factor 23
c) Calcitonin
d) Aldosterone hormone
e) 1,25- dihydroxyvitamin D3

17 What is not considered a histological feature of phosphaturic mesenchymal tumor?

a) Necrosis
b) "Grungy" like calcification
c) Vessels arranged in pericytoma like pattern
d) Composed of spindle to stellate bland cells
e) Myxo-cartilaginous matrix may be present

18 Which immunohistochemistry stain may be useful in diagnosis of phosphaturic mesenchymal tumor?

f) P63
g) CD56
h) Cytokeratin (CK8/18)
i) CD34
j) SOX-9

Answer key:

1. D
2. C
3. B
4. B
5. C
6. C
7. C
8. C
9. B
10. C
11. D
12. E
13. C
14. D
15. A
16. B
17. A
18. B