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Department of Pathology and Laboratory Medicine
Loyola University Health System
2160 S. First Ave., Maywood, IL 60153

IRAP Case Summaries

Case #1

Presenter: Nolan Donahue, DO
Attending: Phillip McMullen, MD PhD

Clinical history

A 30-year-old female with a history of hypothyroidism on levothyroxine and an intentional 50-lb weight loss over the last year. The patient noticed non-specific back and hip pain in 4 months prior to presentation, with significant worsening three weeks prior to presentation. She was initially seen at an outside hospital for fevers, body aches, diffuse musculoskeletal pain, intermittent headaches, dizziness, nausea. Laboratory evaluation uncovered an acute kidney injury and cytopenias. A malignant process involving the lungs, liver, left acetabulum, and left pelvic sidewall was identified by imaging. An H&E slide from the bone marrow core is provided for review. (Scanned slide only).

Final diagnosis: Alveolar Soft Part Sarcoma

Differential diagnosis:

- **Carcinoma**
  - Fibrolamellar hepatocellular carcinoma
  - Choriocarcinoma
  - Poorly differentiated carcinoma, NOS
- **Hematolymphoid**
  - Histiocytic sarcoma
  - Mast cell sarcoma
  - Anaplastic large cell lymphoma
- **Clear cell neoplasms**
  - PEComa
  - Clear cell sarcoma
- **Other**
  - Melanoma
  - Mesothelioma

Key features:

Histopathology: H&E-stained sections of the bone marrow core show total effacement of the marrow by a high-grade neoplasm (A). The neoplasm features large anaplastic cells with moderate to abundant, weakly eosinophilic cytoplasm, variably chromatic nuclei with prominent nucleoli, and occasional syncytial forms (B).

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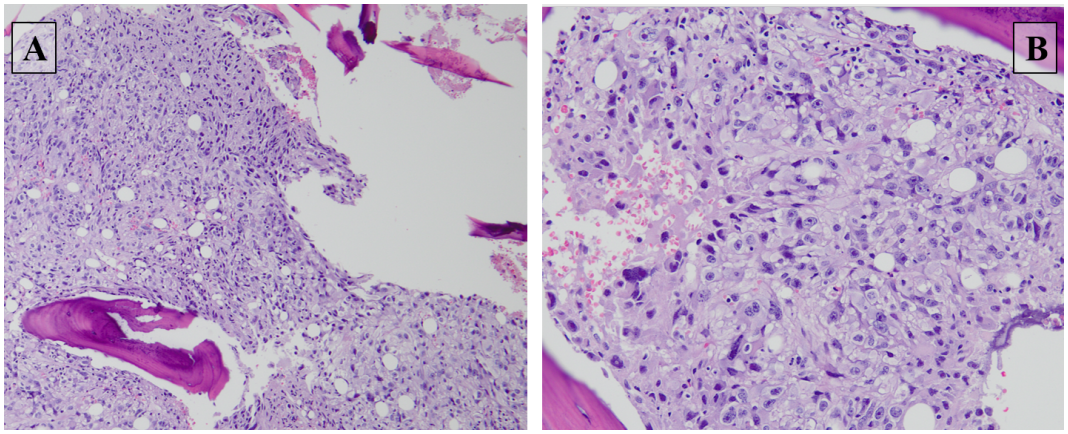
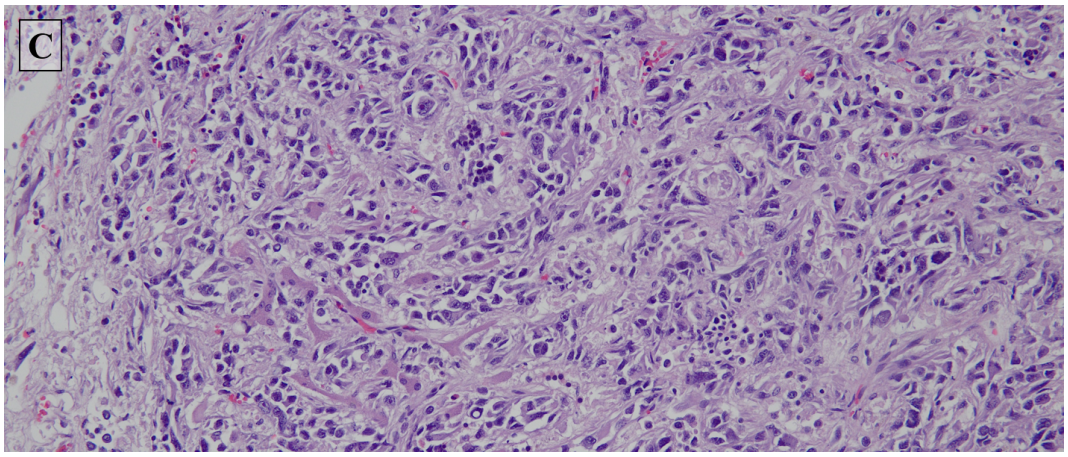
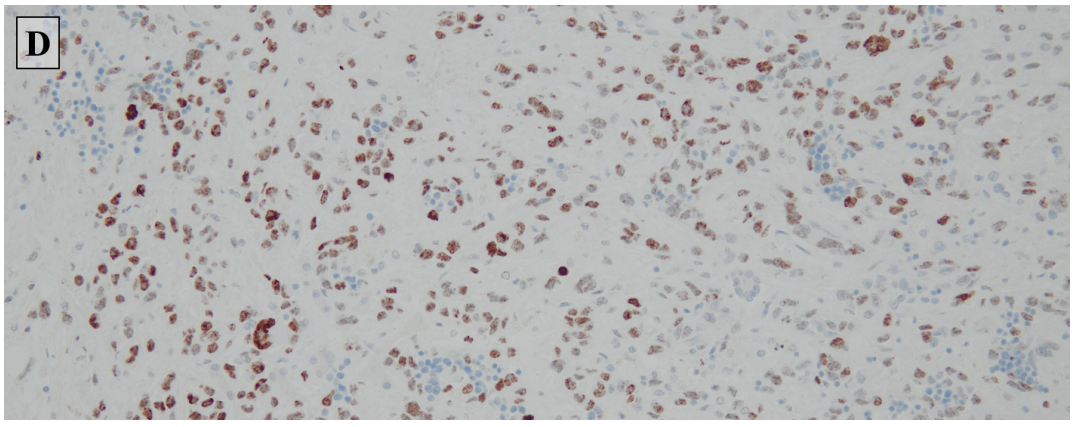


Post-mortem sections from the liver showed a vaguely organoid–or nested–appearance to the tumor, with discohesion of the cells within the center of the nests (C).



An extensive immunohistochemical panel was performed on the tumor, which is listed below. Due to the organoid appearance of the tumor, IHC for TFE3 was ordered, and showed moderate-to-strong nuclear staining of the tumor cells (D).



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Immunohistochemical Stains					
Epithelial		**Hepatocellular**		**Hematolymphoid**	
Keratin AE1/AE3	Negative	HepPar1	Negative	CD20	Negative
CK8/18	Negative	Arginase-1	Negative	CD3	Negative
EMA	Negative			CD34	Negative
Neuroendocrine		**Mesenchymal**		CD21	Negative
Synaptophysin	Negative	Vimentin	***Positive***	CD23	Negative
Chromogranin	Negative	SMA	***Patchy***	ALK-1	Negative
Neural Crest/Melanocytic		Desmin	Negative	CD117	Negative
S100	Negative	Myogenin	Negative	CD68	Negative
HMB-45	Negative	CD31	Negative	Tryptase	Negative

Discussion:

Alveolar soft part sarcoma (ASPS) is a rare soft tissue tumor of unknown origin which makes up less than 1% of all soft tissue sarcomas. The median age at diagnosis is 25 years, with a slightly higher frequency among females. Clinically, this lesion often presents as a slow-growing, painless mass, and mass effect may involve surrounding anatomic structures. It is not uncommon for the tumor to be widely metastatic at diagnosis due to its insidious clinical behavior. Histologically, ASPS consists of large, polygonal cells with eosinophilic cytoplasm and variably prominent nucleoli.[1] The cells may show variable amounts of intracytoplasmic crystals and granules which are PAS positive and diastase resistant.[2] The tumor is often negative for the vast majority of epithelial and mesenchymal markers, positive for cathepsin K, and rarely positive for vimentin, smooth muscle actin, and calretinin.[3,4] Immunohistochemical evidence of TFE3 nuclear expression is essential per the WHO, and TFE3 rearrangement or presence of the ASPSCR1-TFE3 fusion by molecular techniques is considered desirable and nonessential.[1]

The ASPSCR1-TFE3 fusion protein is the product of a translocation of ASPSCR1 on chromosome 17 with TFE3 on the X chromosome.[5] This protein translocates to the nucleus where it is associated with acetylated histones, and upregulates a number of cellular survival and proliferation pathways.[1,6,7]

Overall, the prognosis of ASPS is fair to poor, with tumor size, presence of metastasis at diagnosis, and truncal primary site being negative prognostic factors.[1,8] Crizotinib is under investigation as a possible therapy for ASPS, but current trial data is dismal regarding its effectiveness.[9]

Take home points:

Alveolar soft part sarcoma is a rare soft tissue tumor with no definitive cell of origin, which often presents as a slow-growing painless mass. Widely metastatic disease at

diagnosis is a frequent occurrence. The tumor is broadly negative for most immunohistochemical stains, and this entity must be considered when a pan-negative tumor with organoid morphology is seen. Nuclear positivity of TFE3 and the presence of PAS-D positive cytoplasmic crystals can aid the diagnosis, especially when the specimen is sub-optimal for FISH studies, as in decalcified or autolyzed.

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Case #2
Presenter: Chris Bell, DO
Attending: Dr. Alessa Aragao

Clinical History: Clinical History: A 30-year-old male presenting with difficulty defecating and blood in his stool. Colonoscopy showed a rectal cancer that is biopsied and then treated with neoadjuvant chemoradiation therapy for 5 months. The patient underwent subsequent abdominal perineal resection. An H&E slide of the rectal mass biopsy is provided for review. (Scanned slide only).

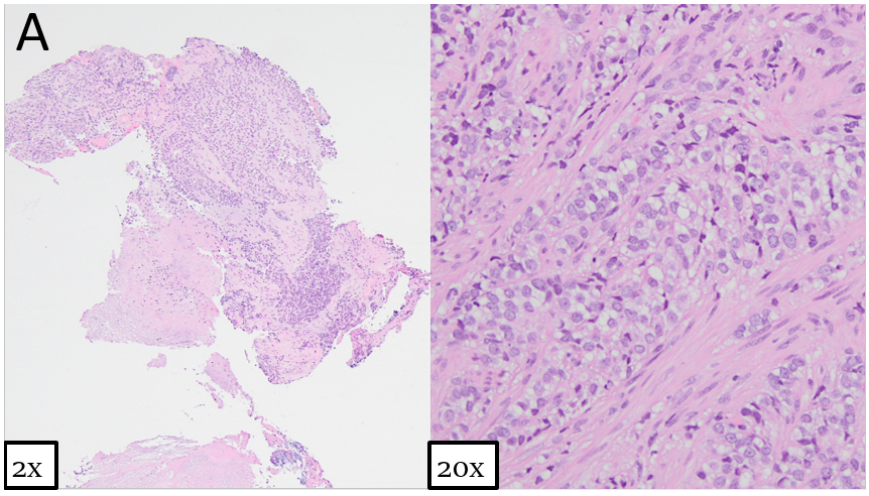
Final diagnosis: EWSR1-CREM Gene Rearrangement Tumor
Differential diagnosis 1:

- High-grade colorectal adenocarcinoma including medullary carcinoma of the colon
- Neuroendocrine tumor
- Epithelioid gastrointestinal stromal tumor
- Sclerosing epithelioid fibrosarcoma
- Gastrointestinal neuroectodermal tumor
- Gastrointestinal clear cell sarcoma
- Melanoma

Differential diagnosis 2 (post-molecular studies):

- Angiomatoid fibrous histiocytoma
- Clear cell sarcoma
- Gastrointestinal neuroectodermal tumor
- Primary pulmonary myxoid sarcoma

Key features:
Histopathology: Histological examination of the biopsy (A) and resection (B) shows an infiltrative nested tumor with monotonous cells, eosinophilic to clear cytoplasm, and surrounding necrosis and inflammation.



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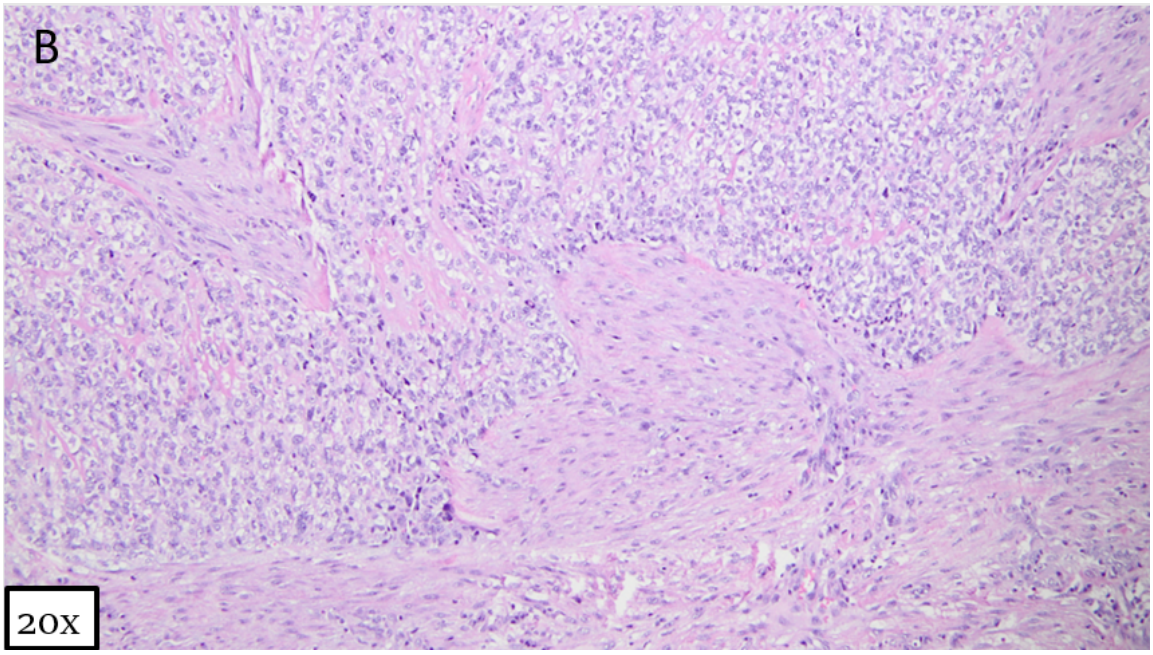
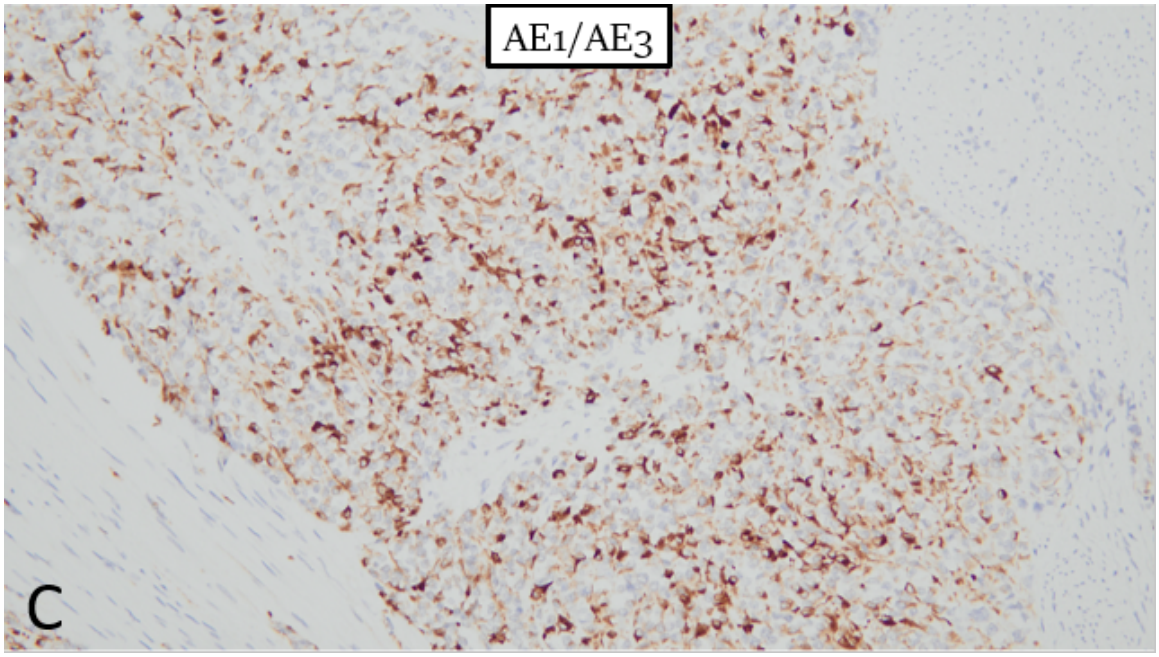


A large panel of immunohistochemistry stains were performed with tumor cells positive for AE1/AE3 (C), focal positive for Synaptophysin (D), EMA, CD56, CD99, BER-EP4, Vimentin, FLI1, ERG focal weak, non-specific chromogranin, and P16 weak positive. Negative stains for CDX-2, CK7, CK20, CD117, HMB45, Mart1, SOX10, S100, NKX2.2, WT1, Desmin, P63, P40, GFAP, and Villin. NGS testing showed an EWSR1: CREM chromosomal rearrangement.



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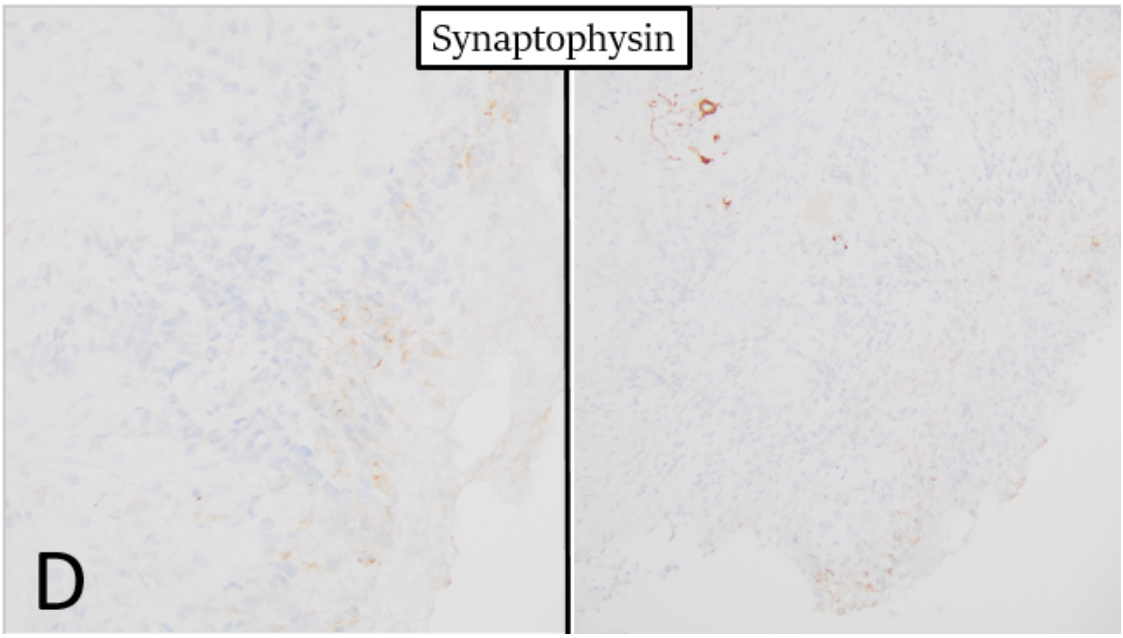

Discussion:

EWSR1 and CREM genes are well studied and important genes for cell function and proliferation. The fusion of these genes from molecular studies has been shown to characterize specific tumors like gastrointestinal neuroectodermal tumor (GNET) and angiomatoid fibrous histiocytoma (AFH). Recent studies have shown there is a newly unrecognized tumor that shares the EWSR1: CREM rearrangement.

It is important to note that this new tumor is not currently categorized, however; literature review shows this tumor is more prevalent than first thought with up to 50% of past AFH cases categorized for this new entity. Key features for this entity are keratin positivity, focal synaptophysin positivity, negative melanocytic markers, and an infiltrative/nested/epithelioid morphology. With a monotonous tumor appearing in a young patient, you must consider a translocation tumor. As pathologists, we must impress upon our clinical colleagues the worse prognosis of these tumors in comparison to AFH. There is no specific therapy other than resection currently available as seen by the minimal treatment response with our case. We must match the morphology of our tumors with the full picture of IHC and molecular studies.

Take Home Points:

- When encountering a known molecular translocation always revisit the morphological features taking in consideration emerging entities
- Think of translocation tumors in young patients with monotonous tumors
- EWSR1: CREM translocation tumors with a nonspecific immunophenotype do not always make it an angiomatoid fibrous histiocytoma
- High grade tumors of the gastrointestinal tract with non-specific staining and keratin positivity are not always high-grade adenocarcinoma or medullary carcinoma

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Case #3
Presenter: Rachel Lichtenberg
Attendings: Dr. Pooley, Dr. Hunter, Dr. McMullen

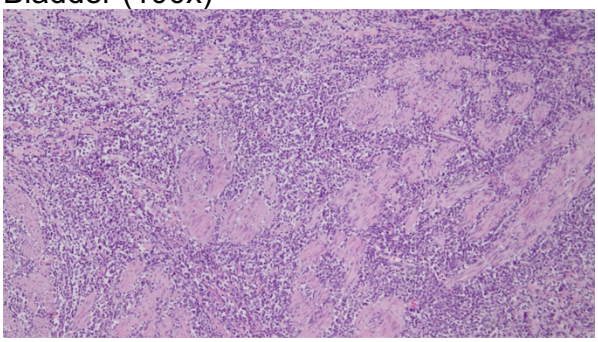
Clinical history: An 81-year-old female presented for evaluation of severe dysphagia. Her past medical history is significant for lymphoplasmacytic lymphoma, breast carcinoma, diabetes and hypertension. On admission she had shortness of breath, tachycardia, and lower extremity edema. Imaging showed enlarged mediastinal and hilar lymph nodes and bilateral interstitial pulmonary edema, worse compared to prior imaging. She developed atrial fibrillation with rapid ventricular rate and increasing shortness of breath, declined acutely and passed away two days into her admission. Autopsy showed widespread malignancy extensively involving the bladder, pelvic serosa, gynecologic tract, peritoneum, GI mesentery, lungs, heart, and paraspinal tissue, with positive lymph nodes above and below the diaphragm. A representative H&E slide from the autopsy (paraspinal nodules) is provided for review.

Final Diagnosis: B cell lymphoma with high proliferative rate. (High grade transformation of lymphoplasmacytic lymphoma).
Differential diagnosis:

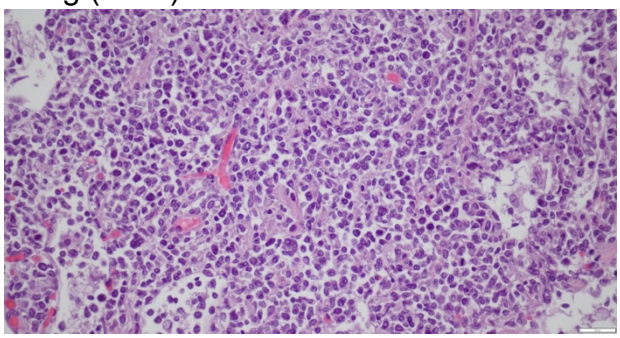
- Metastatic carcinoma (gynecologic, urothelial, breast)
- LPL with extranodal presentation
- High grade transformation to DLBCL or other large cell lymphoma
- Neuroendocrine carcinoma
- Other small round blue cell tumor

Key features:

Bladder (100x)



Lung (400x)



Histopathology:
Histologically, the malignant cells were small to intermediate with round to irregular nuclear contours, vesicular to dark chromatin, some with pale cytoplasm, admixed with scattered larger cells. Rare atypical mitoses were present. In bilateral lungs, malignant cells diffusely infiltrated interstitial, perivascular, peribronchiolar, and alveolar spaces. The bladder showed mucosal involvement and tumor cells dissecting through smooth muscle and into the perivesical adipose tissue. There was also dense involvement of

the uterine myometrium, serosa, parametrial tissue and fallopian tubes. In the esophagus, malignant cells infiltrated through the serosa and the muscular wall. Multiple lymph nodes were effaced by these small cells. Bone marrow and the pancreas were also focally involved.

A panel of immunohistochemical stains were performed and confirmed hematologic origin. PAX-8 staining was favored to reflect cross-reactivity with PAX-5 protein. *

Positive IHC	Negative IHC
CD20 (strong +)	Keratin AE1/AE3
CD5 (strong +)	GATA3
CD45	Synaptophysin
BCL2	Chromogranin
PAX-8 *	TTF-1
Ki-67 (> 80%)	CD3 (background T cells)
	CD10
	CD15
	CD23
	CD30
	BCL-6
	Cyclin-D1
	CD138 (plasma cells absent)

Molecular: MYD88 L265P mutation was detected with variant allele frequency of 75% in the bladder sample from autopsy, suggesting that the current B-cell lymphoma arose from the patient's prior LPL with the same MYD88 L265P mutation.

Conclusion: In the context of rapid clinical progression, shared mutation confirmed transformation of the previous indolent LPL to the morphologically aggressive lymphoma.

Discussion:

Lymphoplasmacytic lymphoma (LPL) is a neoplasm of mature small B cells, plasma cells, and plasmacytoid lymphocytes, with a typically indolent clinical course. Waldenstrom macroglobulinemia is a combination of LPL in the bone marrow and IgM monoclonal protein in the blood [1]. Clinical symptoms include cytopenias, lymphadenopathy, and complications of IgM paraproteinemia.

LPL is diagnosed by a combination of morphology, IHC, and molecular studies: bone marrow infiltration by small B lymphocytes with plasmacytoid or plasma cell differentiation, positive for CD20, PAX-5, and CD138, with light chain restriction (usually IgM). CD10 and CD5 are typically negative, but variable expression is reported. MYD88 p.L265P mutations are present in up to 97% of cases.

LPL is typically localized to the bone marrow and less frequently involves the lymph nodes and spleen. It is rarely documented at extra-nodal sites. A review of the existing literature revealed rare case reports of LPL and WM presenting with infiltration of lung, stomach, bowel, and liver [2-5]. However, in each of these cases, at most two extramedullary organs were involved, and there were no reports of dissemination to the extent noted here.

Transformations to diffuse large B cell lymphoma (DLBCL) occur rarely [6-14], with 1% cumulative incidence at 5 years [1]. In this case, a transformation was confirmed by identifying the emergence of an aggressive lymphoma in the setting of a previously known indolent lymphoma, with proof of clonal identity via molecular testing. These findings correlated with the clinical context of rapid progression. This case was unique in that this aggressive lymphoma did not morphologically resemble DLBCL, with overall small size cells. “B cell lymphoma with high proliferative rate,” the final diagnosis, is not an entity specifically listed in the current WHO or ICC. [1, 15]

This case highlights that high grade transformations have a range of morphologies which are not completely classified. In the context of rapid clinical progression, transformation should be on the differential diagnosis even when the morphology does not show large cells. Besides large cells, histologic changes that may indicate transformation include an aggressive sub-population overtaking a previously mixed population; here, CD5+, CD138- small B cells replaced the previously mixed population with plasmacytoid differentiation (CD138+, CD5-).

In cases of DLBCL, CD5 expression has been associated with progression, with more aggressive clinical features, and with inferior survival curve [16-18]. In one study, CD5+ DLBCL when compared with CD5- DLBCL was identified as a marker of poor prognosis, associated with elderly onset, female predominance, and involvement of extranodal sites [17]. Though this case was not DLBCL, the gain of CD5 expression is of note.

Take Home Points:

- Indolent lymphomas including LPL have potential to transform to high-grade lymphomas
- High grade transformations have variable histology and are still incompletely classified
- In context of rapid clinical progression, consider re-biopsy to look for changes besides large cells / DLBCL
- Regardless of morphologic appearance, establishing a case as de-novo versus transformation is critical to prognosis.
- Cross-reactions should be kept in mind when working up difficult cases of unknown origin (e.g. PAX-8 and PAX-5).

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Case #4
Presenter: Hunter Koster, MD
Attending: Dr. Phillip McMullen, MD, PhD

Clinical History**:** A 42-year-old male was undergoing clinical work up for his hypertension and was incidentally found to have a mediastinal mass. The patient was asymptomatic without any reported weight loss, shortness of breath, difficulty swallowing, or chest pain. CT chest with IV contrast showed a large well demarcated heterogeneous mediastinal mass measuring 9.5 cm x 5.8 cm partially encircling the aortic arch and
extending from the right atrium up to the subclavian vessels. The mass showed several cystic components with the largest measuring 4.0 x 3.4 x 2.0 cm. The mass appears to be hypodense surrounded by a wall with no definite calcification or septations within this mass. The mass was surgically resected, and an H&E slide from the specimen is provided for review. (Scanned slide only).

Final Diagnosis: Multiloculated Thymic Cyst
Differential Diagnosis:

- Benign cysts (duplication cyst, bronchogenic cyst, etc.)
- Cystic teratoma/ other cystic germ cell tumors
- Cystic thymoma
- Squamous Cell Carcinoma/ Thymic carcinoma

Key Features:
Histopathology: The specimen weighed 78.2 g and measured 9.7 x 9.5 x 2.6 cm and was a yellow-tan lobulated fragment of fibrofatty soft tissue. Serial sectioning of the specimen revealed a 6.8 x 6.3 x 2.7 cm tan-yellow, focally hemorrhagic, solid mass with multiloculated cysts. The cysts were smooth walled, ranging from 0.2-3.6 cm, and were filled with yellow grumous to mucinous material. The mass did abut the inked outer surface. The remaining uninvolved cut surfaces were yellow-tan and lobulated. Histological exam of the mass demonstrated multiple epithelial lined cysts with adjacent islands of thymic tissue, scattered fibrosis, and granulation tissue. The cysts containing cholesterol clefts and aggregates of lymphoid tissue (A). The cysts exhibited varying architecture complexity with foci of giant cell reaction, areas where the lining was more squamoid filling the lumen, and, in contrast, where the lining had metaplastic changes with respiratory epithelium with a hobnail appearance (B). The nuclear morphology began to have an increased N:C ratio with focal jagged to bizarre nuclei.

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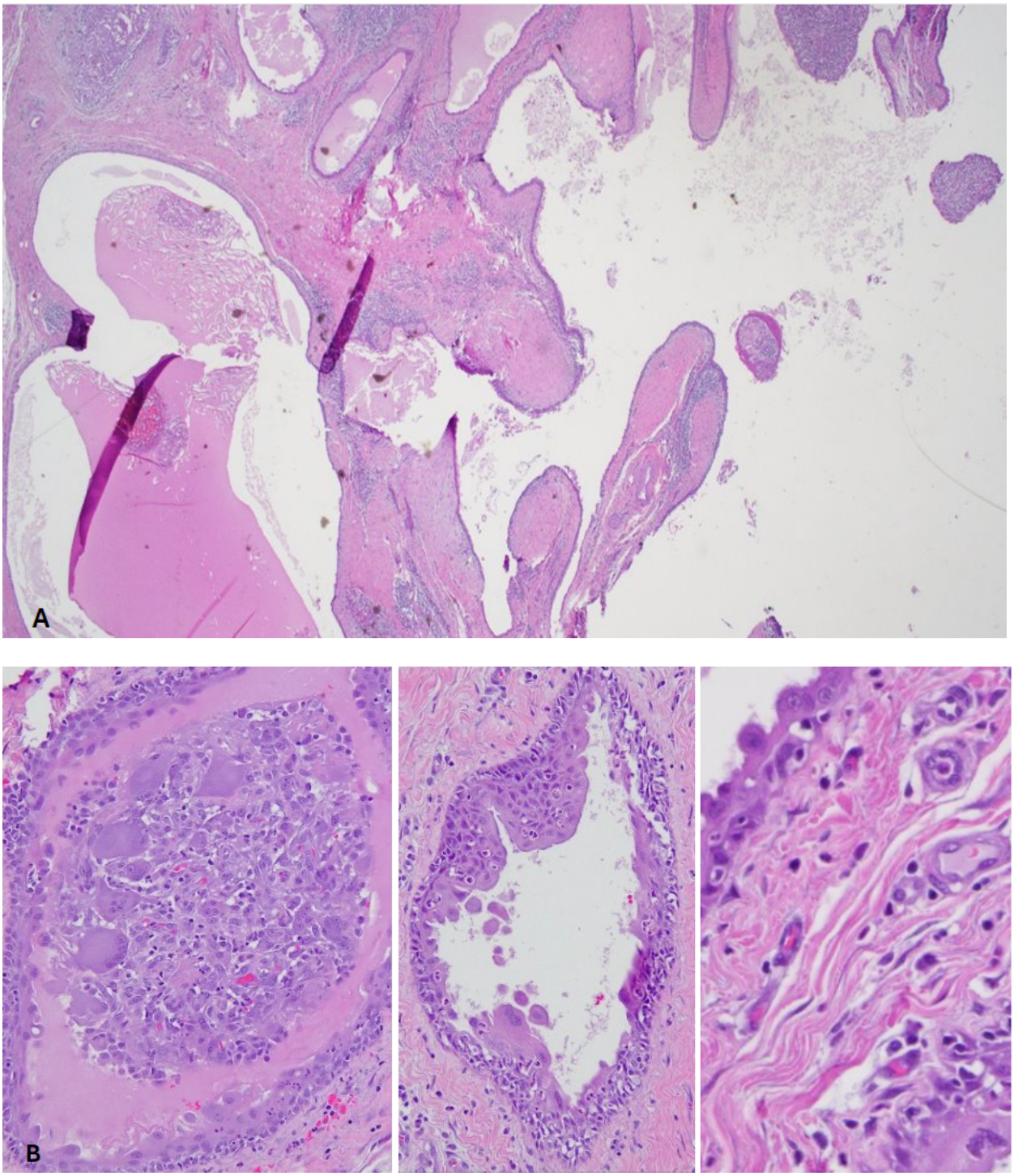

A large panel of immunohistochemistry stains were performed which were negative outside of internal controls: Glypican 3, CD117, TDT, Keratin (AE1/AE3), P40, and CD5. CD117 highlighted background mast cells and myeloid stem cells. TDT was positive only in the walls of the cysts and island of T-cells. AE1/AE3 highlighted the cyst lining

with P40 only staining the basal layer of the cysts. Then CD5 highlighted islands of normal T-cells.

Discussion:

Multiloculated thymic cyst (MTC) is an entity that is relatively rare in the literature, but it has been postulated that it is sparsely documented because of its benign diagnosis. It has been reported that thymic cysts represent only 1-5% of all mediastinal masses and only 5% of anterior mediastinal masses. On average, they are commonly diagnosed in those who are around the age of 45 years old. Diagnostic imaging plays an important role in the evaluation of MTC's to assess its size, shape, characteristics, involvement of surrounding structures, and sometimes even the discovery of them since many patients are commonly asymptomatic. When patients are symptomatic, they can range from have a vast array of nonspecific symptoms consisting of dyspnea, cough, recurrent infections, chest tightness, superior vena cava syndrome, and Horner syndrome. The symptomology is largely dependent on the size of the mass and where it is located, impinging on surrounding structures.

The etiology of MTC's is still not fully understood; however, it has been agreed that it stems from inflammatory reaction of the thymic parenchyma. The primary hypothesis at this time by Suster and Rosai is that they arise from the induction of cystic dilatation of medullary duct epithelium-derived structures by acquired inflammatory processes. MTC's have been correlated with underlying conditions/associations such as underlying infections, HIV, lymphomas, and autoimmune conditions such as rheumatoid arthritis, myasthenia gravis, and Sjogren's has been reported.

Grossly, these lesions can range widely in size where some have been reported greater than 15cm. The majority of the lesions are well-circumscribed and are described as easy to resect; however, there have been instances where the lesion is adherent to the pleura or pericardium making them more difficult to resect. This finding can raise the clinical suspicion for neoplastic entities. The cut surface of MTC's shows multiloculated cavities that are filled with turbid to hemorrhagic fluid. Sectioning of the specimen should be alert of areas of thickened cystic walls or excrescences protruding into the cyst lumen raising concern for an underlying neoplasm with cystic features versus this benign entity.

Histologically the lesions feature cysts lining that can contain many epithelial morphologies: squamous, columnar (including ciliated), or cuboidal. It is common to see areas of hemorrhage, necrosis, and inflammatory reactions, but one can also find cholesterol cleft granulomas, thymic tissue islands, germinal centers, calcifications, and areas of hyalinization. One feature that has been noted is atypical squamous pseudoepitheliomatous hyperplasia that can mimic a squamous cell carcinoma.

Of note, after the lesion is fully resected, it has been reported that most patients don't experience recurrent disease. If the patient has multiple comorbidities and is unable to undergo surgery, cases have been reported where ethanol injections are given into the

lesion to induce sclerosis of the mass. There has been cases where radiation and chemotherapy was administered, but it is believed that it could have been a result of the lack of experience with this entity and the development of a standardized surgical approach. With its association with other mediastinal diseases and neoplasms that can express cystic appearances is another perspective that could raise a challenging treatment option for the clinical team if they don't feel comfortable solely with an excision given the limited evidence beyond expert opinion.

Take Home Points:

- Multiloculated thymic cysts are a benign entity that has a low chance of recurrence with complete surgical resection
- When grossing this specimen, it is important to make sure to sample it well taking note to any thickened cyst walls or solid excrescences protruding into the cyst lumen
- This entity is most often sporadic but has been associated with underlying diseases such as HIV, lymphoma, and autoimmune diseases
- Presenting symptoms can range from asymptomatic to superior vena cava syndrome depending on the size and location of the mass

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