IRAP – January 27th, 2025

Presented by

All cases are available virtually:

https://uchicago.pathpresenter.com/public/presentation/display?token=57861fe6

Case 1: Drs. Stephany Ngombu and Peter Pytel

Diagnosis: Anaplastic sarcoma of the kidney

Clinical history: The patient is a 9-year-old female who originally presented in September 2016 (17 months old) with complaints of rash, fevers, and anemia for several weeks. A head CT performed was negative for a neurological etiology. However, CT of chest, abdomen and pelvis was significant for an enlarged liver and "homogenous parenchyma with multiple lucent defects" concerning for metastatic disease.

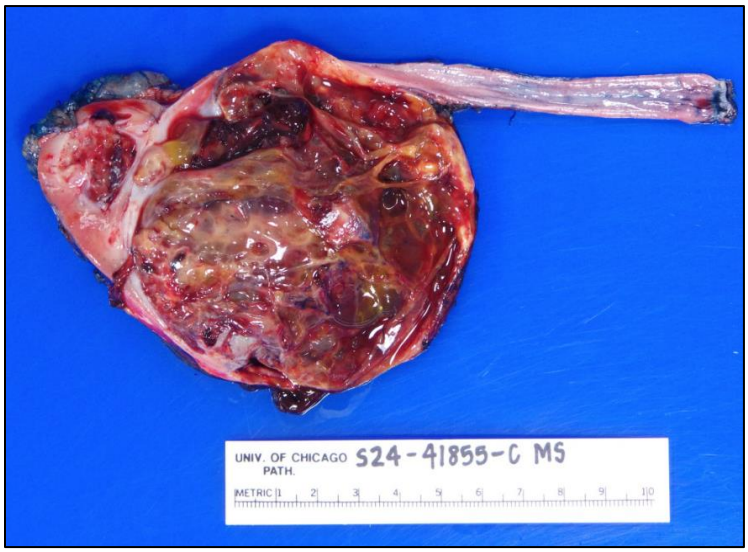
Further workup showed right adrenal gland mass found to be neuroblastoma with N-MYC gain on adrenalectomy. Patient underwent autologous hematopoietic stem cell transplant, radiation, and chemotherapy for high-risk adrenal neuroblastoma and successfully completed chemoradiation therapy. She is disease free since 2017.

During a follow-up appointment in October 2024, patient had new complaints of recurrent urinary tract infections and dark urine despite multiple rounds of antibiotics. Further evaluation is significant for new a 7 cm solid and cystic mass of the right kidney on CT abdomen. A percutaneous right kidney core biopsy is performed and submitted.

The patient underwent two rounds of chemotherapy followed by a radical right nephrectomy. A 9.9 cm mass with 50% viable tumor was described. The tumor extended into the renal vein, inferior vena cava, and renal pelvis however regional lymph node metastasis was not present.

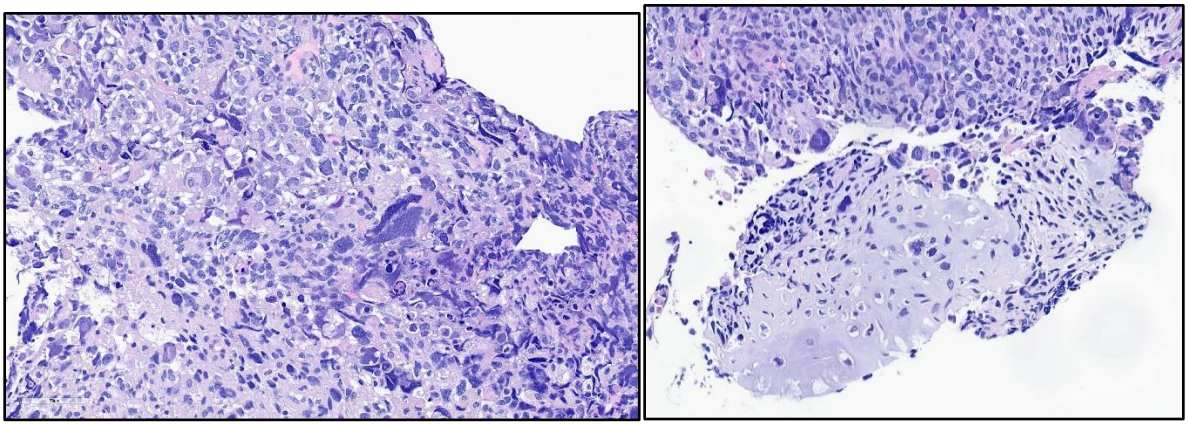
Gross Findings (on resection specimen):

A solid and cystic tumor with necrosis and hemorrhage.



Microscopic findings (on core biopsy): Cellular tumor with marked pleomorphism, nuclear atypia, frequent multipolar mitoses, and necrosis. The cells are primitive without a definitive growth pattern.

Rhabdoid and chondroid differentiation is appreciated. The kidney biopsy is compared to the patient's prior neuroblastoma and is distinctly different.



Differential Diagnosis:

- Neuroblastoma
- Wilms tumor
- Primary renal cell carcinoma with sarcomatoid differentiation
- Clear cell sarcoma of the kidney
- Malignant rhabdoid tumor of the kidney
- Anaplastic sarcoma of the kidney

Ancillary Studies:

The tumor was positive within the malignant cells for the following immunohistochemical studies: patchy SOX9, focal desmin, few cells staining with cyclin D1, focal CD34, p53 wild-type, minimal PGP9.5, and SALL4. In this context, the significance of PGP9.5 and p53 was uncertain. The important positive markers are SOX9 and desmin which highlighted cartilaginous and rhabdomyoblastic differentiation. The tumor was negative for the following immunohistochemical studies: myogenin, SMA, keratin AE1/AE3, PAX8, CD45, WT1, synaptophysin, PHOX2B, Oct3/4, and CD30. BRG-1 and INI-1 were retained and BCOR was negative.

Molecular Testing:

A DNA based NGS panel was performed with the following pathogenic findings: DICER1 (c.5439G>C, p.E1813D (NM_030621.4), TP53 loss equivocal (c.916C>T, p.R306 (NM_000546.6) and B2M loss (on chromosome 15q21.1). The DICER1 variant is the most significant finding. 1,005 genes are captured as part of the in-house DNA OncoPlus test. Additionally, an RNA-based fusion panel performed was negative. Germline testing was also negative.

Discussion:

We are presented with an undifferentiated, high-grade spindle cell sarcoma that is positive for desmin and negative for myogenin. Our favored diagnosed is anaplastic sarcoma of the kidney which is a rare entity in the literature that most commonly manifests in patients <15 years of age. It has an overall survival rate of 75%. Clinically it can present as a large renal mass with or without hematuria and flank pain. It is a predominantly solid tumor with cystic components and undifferentiated spindle cells that has anaplastic features. Rhabdoid and chondroid differentiation is known to occur.

A single case report (PMID 32568472) describes a similar scenario of a young male patient with neuroblastoma who later developed anaplastic sarcoma of the kidney. The link between these two entities is not well understood. Germline or de novo mutations in DICER-1 gene is part of a spectrum of "DICER-1 mutated sarcomas which can arise in many anatomical locations including the ovary, thyroid, lung and kidney. Germline testing was negative in our patient.

This case illustrates the importance of thorough immunohistochemical stains to help rule out other entities with anaplasia and cytomorphologic overlap. Molecular testing is required to find rare molecular variants associated with somatic or germline alterations. This case is also an example of two, independent primary tumors arising in the same patient without a known syndrome.

References:

1. WHO Blue Book Online2. Expertpath

3. College of American Pathologists Cancer Protocols

4. Chen, Chien-Chin, and Kai-Sheng Liao. "Anaplastic sarcoma of the kidney: Case report and literature review." *Tzu chi medical journal* vol. 31,2 (2019): 129-132. doi:10.4103/tcmj.tcmj_194_18

5. Kao, Jsun-Liang et al. "Rare anaplastic sarcoma of the kidney: A case report." *World journal of clinical cases* vol. 8,8 (2020): 1495-1501. doi:10.12998/wjcc.v8.i8.1495

6. Alaghehbandan, Reza et al. "What's new in the WHO 2022 classification of kidney tumours?." *Pathologica* vol. 115,1 (2022): 8-22. doi:10.32074/1591-951X-818

7. Pichler, Renate et al. "Renal Cell Carcinoma with Sarcomatoid Features: Finally New Therapeutic Hope?" *Cancers* vol. 11,3 422. 25 Mar. 2019, doi:10.3390/cancers11030422

8. Apellaniz-Ruiz, Maria et al. "A child with neuroblastoma and metachronous anaplastic sarcoma of the kidney: Underlying DICER1 syndrome?." *Pediatric blood & cancer* vol. 67,12 (2020): e28488. doi:10.1002/pbc.28488

9. Wu, Mona Kay et al. "Evolution of Renal Cysts to Anaplastic Sarcoma of Kidney in a Child With DICER1 Syndrome." *Pediatric blood & cancer* vol. 63,7 (2016): 1272-5. doi:10.1002/pbc.25959

10. Wu, Mona K et al. "Anaplastic sarcomas of the kidney are characterized by DICER1 mutations." *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc* vol. 31,1 (2018): 169-178. doi:10.1038/modpathol.2017.100

11. McCluggage, W Glenn, and William D Foulkes. "DICER1-associated sarcomas at different sites exhibit morphological overlap arguing for a unified nomenclature." *Virchows Archiv : an international journal of pathology* vol. 479,2 (2021): 431-433. doi:10.1007/s00428-021-03087-5

12. McCluggage, W Glenn, and William D Foulkes. “DICER1-associated sarcomas: towards a unified nomenclature.” *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc* vol. 34,6 (2021): 1226-1228. doi:10.1038/s41379-020-0602-4

Case 2: Drs. Victoria Duran Paredes and Peter Pytel

Diagnosis: Hansen's Disease (Leprosy)

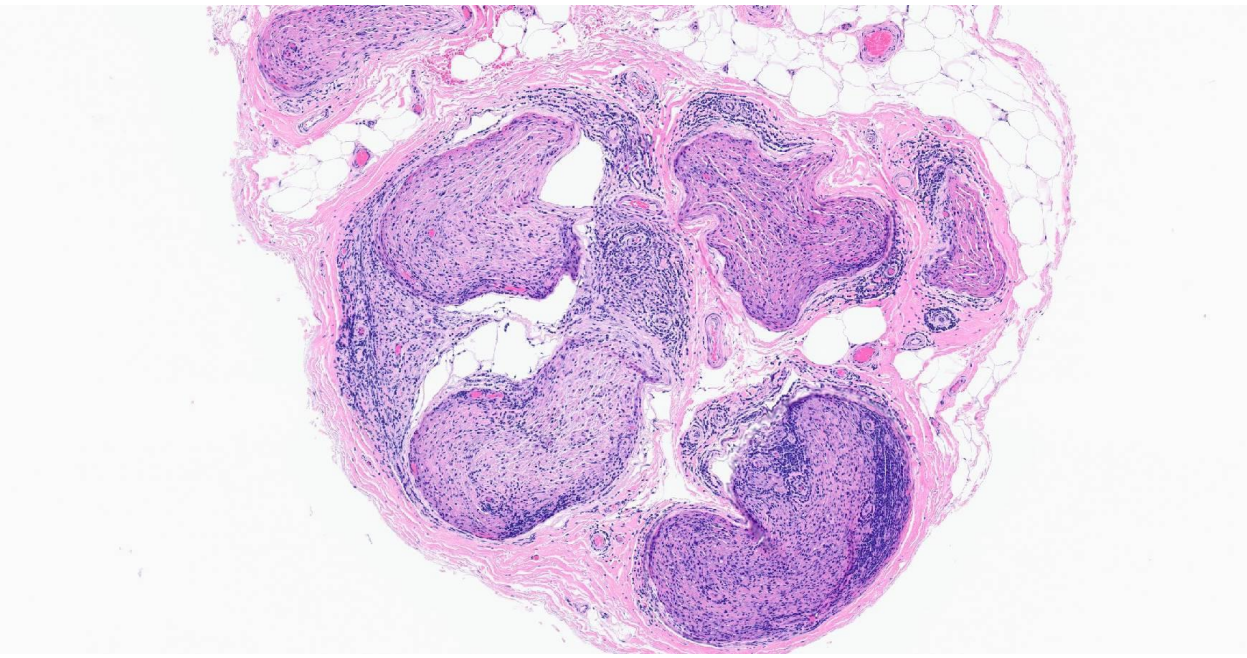
Clinical History: The patient is a 41-year-old otherwise healthy man who presented with a progressive multifocal neuropathy. The symptoms began as tingling in the right foot, gradually progressing to the left foot, and subsequently developing numbness in the right thumb, 4th, and 5th digits over a period of 6-8 months. These right-hand digits were also noted to be dry and cold compared to the others.

Electromyography and nerve conduction studies (EMG/NCS) revealed a multifocal sensory predominance with axonal polyneuropathy.

Patient’s symptoms initially improved with oral steroid treatment but recurred after discontinuation of therapy.

Pertinent Investigations: Extensive investigations were negative for common causes of neuropathy, including diabetes, vitamin deficiencies, vasculitis, collagen vascular diseases, HIV, paraneoplastic syndromes, and genetic neuropathies. Serum protein immunoelectrophoresis and immunofixation demonstrated polyclonal hypergammaglobulinemia, without evidence of a monoclonal spike. A left sural nerve biopsy was performed for further evaluation.

Microscopic Findings: Hematoxylin and eosin (H&E) stained sections from the sural nerve biopsy showed dense lymphoplasmacytic infiltrates in the endoneurial and epineurial connective tissues. These infiltrates included CD3-positive T cells, along with dense clusters of CD20-positive B lymphocytes. The B cells did not co-express CD5, CD10, LEF, or cyclin D1, which led to an initial interpretation suggesting the possibility of a low-grade B-cell lymphoma. Due to the small tissue sample, there was not enough tissue for clonality assessment. Imaging, and bone marrow biopsy were recommended in a note.



Further work-up: Peripheral blood smear revealed mild leukocytosis with no circulating abnormal lymphocytes. Positron emission tomography (PET) imaging was unremarkable, and bone marrow biopsy showed no morphological or immunophenotypic evidence of lymphoma. DNA Oncoplus on nerve biopsy did not reveal pathogenic findings.

The patient came to the office to discuss these new results and mentioned that he traveled to India 16 years prior to the onset of symptoms. He was also born there and moved to the U.S. when he was 5 years old.

Re-evaluation of the microscopy: The biopsy slides were re-evaluated. Further stains for acid-fast bacilli (AFB) and Fite stain were positive for small rod-shaped acid-fast organisms. Molecular sequencing confirmed the presence of *Mycobacterium leprae*.

Discussion: This case represents a rare form of leprosy with nerve involvement in the absence of skin lesions, also known as pure neuritic leprosy (PNL) or primary neural leprosy. PNL was first described in 1903 by Albert Neisser and remains a challenging clinical diagnosis. This form of leprosy is characterized by exclusive peripheral neuropathy without dermatological involvement and a negative slit-skin smear bacilloscopy.

Currently, the gold standard for diagnosis in PNL is the histopathological examination of a peripheral nerve biopsy. However, detection of Mycobacterium leprae in tissue can be difficult, and histological findings may be non-specific. In our case, the nerve biopsy findings initially suggested a B-cell lymphoma.

Leprosy-associated inflammation is typically T-cell rich; however, B-cell and/or plasma cell-rich inflammation can occur in certain scenarios, particularly in lepromatous leprosy (LL). This form of leprosy is characterized by a diffuse inflammatory infiltrate, often including increased B-cells and plasma cells, reflecting a humoral immune response rather than the robust T-cell-mediated response observed in tuberculoid leprosy (TL). Additionally, LL lacks the well-formed granulomas seen in TL, which can further complicate the diagnosis. Another possible explanation for the B-cell and plasma cell

predominance is persistent nerve damage in leprosy, which may lead to chronic inflammation and secondary B-cell activation.

The present case highlights the importance of considering a history of travel to endemic areas, even if the travel occurred many years prior to the onset of symptoms. This is particularly relevant given the slow progression of leprosy and the long incubation period of the disease. An accurate and early diagnosis of leprosy is crucial not only for appropriate treatment but also to prevent disability and interrupt the transmission chain.

References:

Scollard, David M., Richard W. Truman, and Gigi J. Ebenezer. "Mechanisms of nerve injury in leprosy." Clinics in dermatology 33.1 (2015): 46-54.

Bilbao JM, Schmidt RE. Biopsy diagnosis of peripheral neuropathy, second edition. Springer International Publishing, 2015

Chkheidze, Rati, and Peter Pytel. "What every neuropathologist needs to know: Peripheral nerve biopsy." Journal of Neuropathology & Experimental Neurology 79.4 (2020): 355-364.

Brandner, Sebastian. "The pathological diagnosis of nerve biopsies: a practical approach." Diagnostic Histopathology 22.9 (2016): 333-344.

National Hansen's Disease (Leprosy) Program www.hrsa.gov/hansens-disease

Cojocaru, Inimioara Mihaela, et al. "Peripheral nervous system manifestations in systemic autoimmune diseases." Mædica 9.3 (2014): 289.

Tomaselli, Pedro J., et al. "Primary neural leprosy: clinical, neurophysiological and pathological presentation and progression." Brain 145.4 (2022): 1499-1506.

Shetty, Vanaja P., Kinjal D. Rambhia, and Uday S. Khopkar. "Descriptive pathology of nerves in leprosy." International Textbook of Leprosy (2017): 8-13.

Case 3: Drs. Matthew Kleinjan and Jennifer Bennett

Diagnosis: *POLE*-mutated endometrial carcinoma (spindled variant)

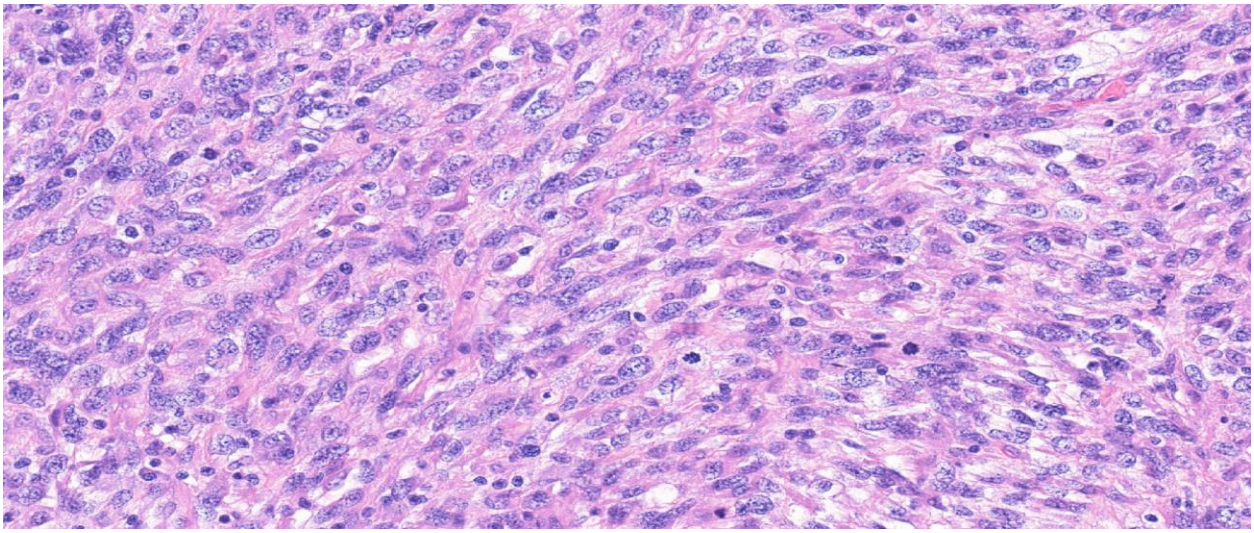
Clinical History:

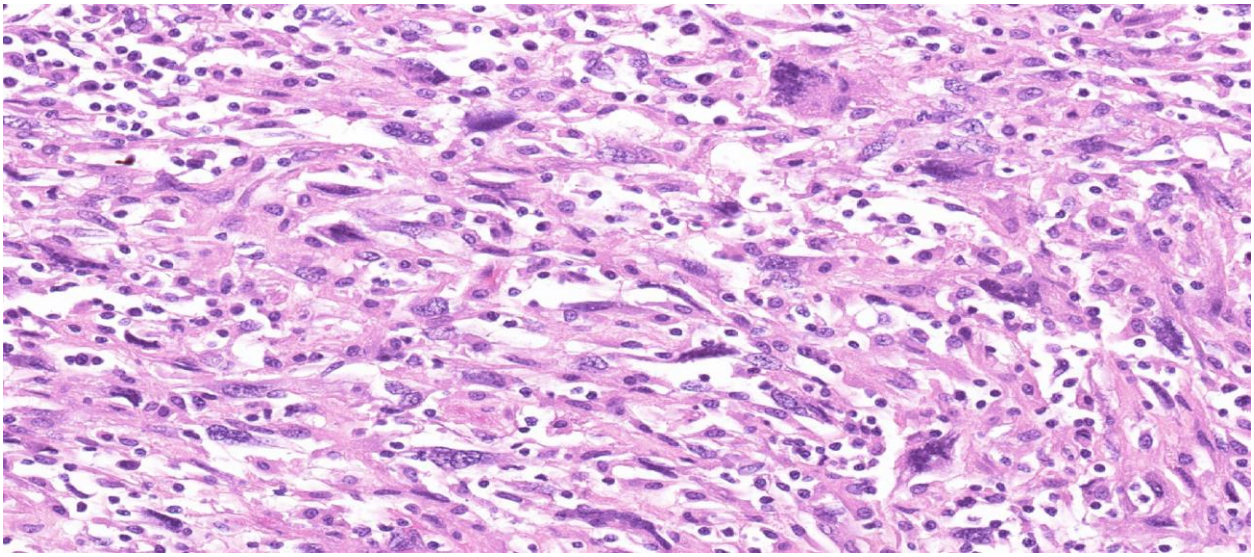
The patient is a 71-year-old female with no significant past medical history who presented with lower abdominal pain. Imaging studies revealed an enlarged uterus with focal wall thickening. Endometrial curettage at an outside hospital showed a high-grade, spindle-cell neoplasm. A total abdominal hysterectomy, bilateral salpingo-oophorectomy, and lymph node dissection were performed.

Gross and microscopic findings:

Sectioning of the uterus revealed a 9 cm white-tan, friable, polypoid mass involving the entire endometrium and focally extending into the myometrium. Hemorrhage and necrosis were present. Microscopically, the tumor was composed of spindle cells with ovoid nuclei, vesicular chromatin, and pale eosinophilic cytoplasm. The majority of the tumor demonstrated mild to moderate cytologic atypia; however, there was scattered foci with markedly atypical, “bizarre-type” degenerative nuclei. Mitoses

were brisk (up to 25/10 HPFs). Also noted were conspicuous tumor infiltrating lymphocytes and scattered stromal hyalinization. The tumor superficially invaded the myometrium, but lymphovascular invasion was not identified, and the cervix, adnexa, and lymph nodes were negative.





Differential diagnosis:

- Leiomyosarcoma
- Inflammatory myofibroblastic tumor
- NTRK-rearranged uterine sarcoma
- Low-grade endometrial stromal neoplasm
- Endometrial Carcinosarcoma
- Endometrial endometrioid carcinoma

Ancillary Studies

Immunohistochemistry

CD10:	Positive
PAX8:	Positive
AE1/AE3:	Positive
ER/PR:	Rare cells
EMA:	Rare cells
Desmin:	Negative
Caldesmon:	Negative
S100:	Negative
ALK:	Negative
CD34:	Negative
MMR:	Proficient
p53:	Negative (“null pattern”)

Molecular

***POLE* c.857C>G p.Pro286Arg**

PTEN c.19G>T p.Glu7*

PTEN c.895G>T p.Glu299*

TP53 c.637C>T p.Arg213*

EP300 c.5485C>T p.Arg1829Cys

FBXW7 c.1972C>T p.Arg658*

ATM c.748C>T p.Arg250*

ATM c.8249T>G p.Leu2750*

KMT2A c.9898G>T p.Glu3300*

FAT3 c.3106G>T p.Glu1036*

FAT3 c.8024C>A p.Ser2675*

MRE11 c.1378G>T p.Glu460*

RB1 c.409G>T p.Glu137*

MLH3 c.1756G>T p.Glu586*

TERT c.-124C>T p.?

FGFR1 c.1636A>G p.Asn546Asp

TMB=78 mutations/megabase

Microsatellite-stable

No fusions (1004 gene panel, which included *ALK, NTRK1-3, JAZF1, PHF1, EPC1, BCOR, BCORL1, YWHAE, ROS, RET)*

Discussion:

The Cancer Genome Atlas (TCGA) landmark study on endometrial carcinomas established four, prognostically significant molecular subgroups (*POLE*-ultramutated, microsatellite unstable, copy number low, and copy number high. Endometrial carcinomas harboring mutations in the DNA polymerase epsilon (*POLE*) gene have the best prognosis and account for 5-10% of tumors. *POLE* encodes the catalytic subunit of DNA polymerase epsilon which serves an essential role in DNA replication and repair. Mutations in the exonuclease domain impairs proofreading function, causing increased replication errors, resulting in an extremely high tumor mutational burden. This ultramutational environment is thought to generate an increased neoantigen load, making these tumors more likely to elicit an antitumor immune response.

POLE-mutated endometrial carcinomas often are of endometrioid histotype, but frequently demonstrate intratumoral heterogeneity, with "serous-like" nuclei. Prominent peritumoral and tumor infiltrating lymphocytes are typical, likely due to the high neoantigen load stimulating an increased antitumor immune response. Other features than can be observed include metaplastic changes (oxyphilic, clear cell, etc.) and giant cells/bizarre nuclei. In this unique POLE-mutated endometrial carcinoma, the tumor is entirely composed of sheets of low-grade spindled cells focally admixed with giant cells/bizarre nuclei. Despite the extensive spindled morphology, marked atypia (characteristic of the sarcomatous component of carcinosarcoma) is absent, consistent with a high-grade endometrioid carcinoma with spindle cells.

Identifying *POLE* mutations in endometrial carcinoma has prognostic and therapeutic significance. Despite the high mutational burden and frequent high-grade features, POLE-mutated endometrial carcinomas have favorable outcomes, with a five-year survival of 98- 100%. There is increasing evidence to suggest that these outcomes are independent of adjuvant therapy and that additional therapy beyond surgical resection may be unnecessary. In addition, the strong antitumor immune response and upregulation of PD-1/PD-L1 suggests that immune checkpoint inhibitors may be a good treatment option in patients with advanced stage disease or recurrence.

Recent studies have also provided evidence that *POLE* mutations can rarely occur in other endometrial carcinoma histotypes including carcinosarcoma. Carcinosarcoma is a high-grade biphasic neoplasm with malignant epithelial and mesenchymal components, often associated with a poor prognosis. However, in the small number of reported POLE-mutated carcinosarcomas, most patients have a favorable outcome, but follow-up overall is limited. Molecular testing is highly advantageous in endometrial carcinomas to guide prognostication and therapy.

References:

1. Cancer Genome Atlas Research Network; Kandoth C, Schultz N, et al. Integrated genomic characterization of endometrial carcinoma. *Nature*. 2013; 497: 67-73.
2. Henninger EE, Pursell ZF. DNA polymerase ε and its roles in genome stability. *IUBMB Life*. 2014; 66: 339-51.
3. Howitt BE, Shukla SA, Sholl LM, et al. Association of Polymerase e-Mutated and Microsatellite-Instable Endometrial Cancers With Neoantigen Load, Number of Tumor-Infiltrating Lymphocytes, and Expression of PD-1 and PD-L1. *JAMA Oncol*. 2015; 1: 1319-23.
4. Hussein YR, Weigelt B, Levine DA, et al. Clinicopathological analysis of endometrial carcinomas harboring somatic POLE exonuclease domain mutations. *Mod Pathol*. 2015; 28: 505-14.
5. Rayner E, van Gool IC, Palles C, et al. A panoply of errors: polymerase proofreading domain mutations in cancer. *Nat Rev Cancer*. 2016; 16: 71-81.
6. McAlpine JN, Chiu DS, Nout RA, et al. Evaluation of treatment effects in patients with endometrial cancer and POLE mutations: An individual patient data meta-analysis. *Cancer*. 2021; 127: 2409-2422.
7. Hammer PM, Momeni-Boroujeni A, Kolin DL, et al. POLE-Mutated Uterine Carcinosarcomas: A Clinicopathologic and Molecular Study of 11 Cases. *Mod Pathol.* Epub ahead of print.

Case 4: Drs. Sarah Mae Lammert, Tatjana Antic, and Aliya Husain

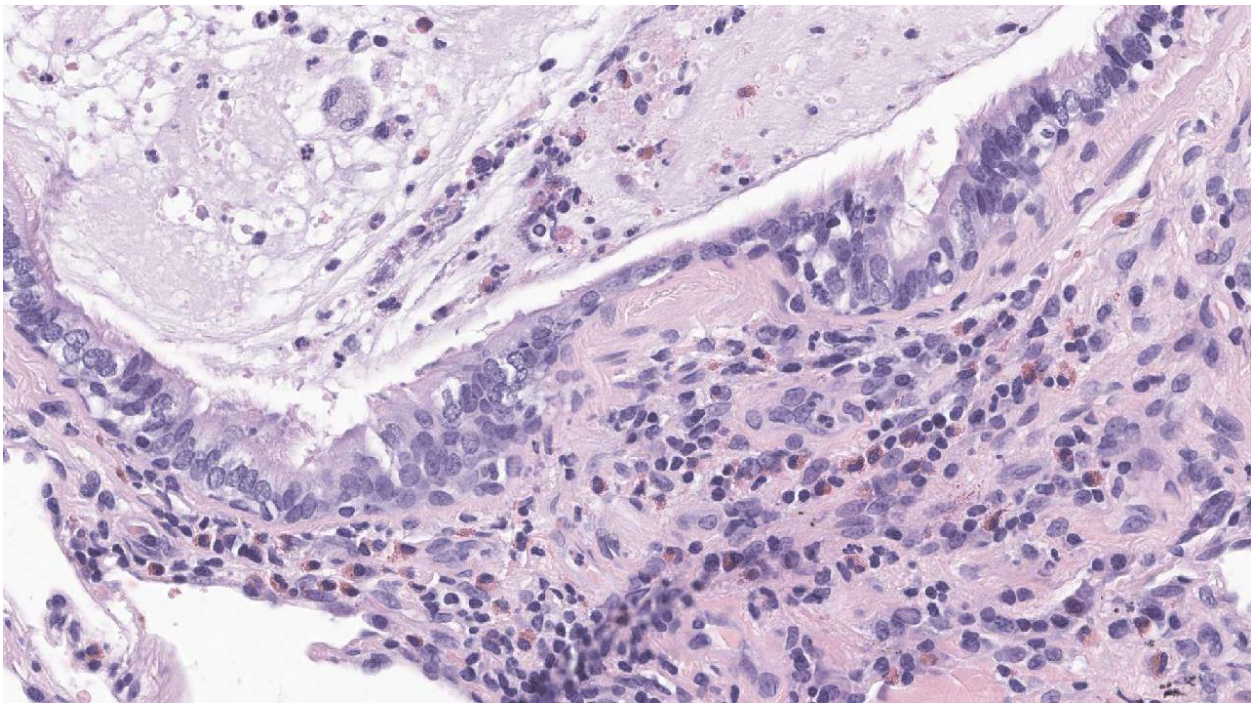
Diagnosis: Eosinophilic asthma; Allergic Bronchopulmonary Aspergillosis

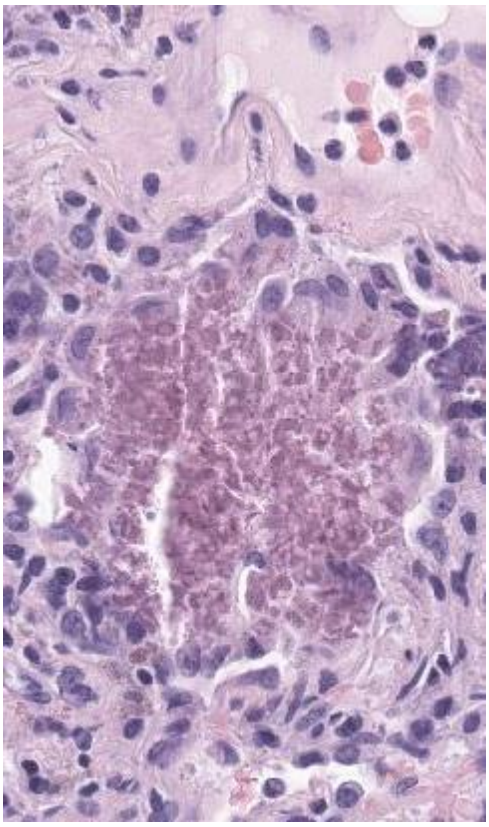
Clinical history: The patient is a 69-year-old female with a history of mild seasonal asthma and eosinophilic esophagitis who presented to the emergency department (ED) with a chief complaint of dysphagia. She eventually had a CT-scan of her chest which was only remarkable for multiple bilateral pulmonary nodules ranging in size from approximately 0.5 – 1.0 cm in greatest dimension. Her symptoms improved and she was discharged from the ED with outpatient pulmonology follow-up.

During outpatient follow-up, no infectious symptoms or worsening respiratory function were described. The patient had normal pulmonary function tests and basic lab work was only notable for very slightly elevated eosinophils on CBC. Repeat chest CT showed no change in the pulmonary nodules. She then underwent a PET scan which showed partial PET-avidity in the right-sided lung nodules. Due to this, she was scheduled for a bronchoscopy with endobronchial ultrasound-guided biopsies of the PET-avid right lung nodules.

Cytopathology: Major findings included abundant bronchial cells and mucin, pulmonary macrophages, inflammatory debris, and clusters of atypical mucinous cells concerning for a well-differentiated mucinous adenocarcinoma.

Surgical Pathology: The patient proceeded to right lung wedge resections. Major findings on initial H&E sections included: eosinophilic and lymphocytic inflammation, basement membrane fibrosis, mucus plugging of airways, airway dilation with accumulation of cell debris, interstitial debris clusters, and no evidence of malignancy.





Additional Studies & Findings: The wedge resection specimens were entirely submitted, and no neoplasm was seen. GMS stain was performed and was negative for microorganisms. Von Kossa stain showed that the patchy interstitial debris and debris within airways was not calcified.

Differential Diagnosis: The majority of our findings are asthma-defining, specifically the airway inflammation, basement membrane fibrosis, mucous plugging, and airway dilation. However, these findings may co-exist and overlap with other reactive processes, maybe a historical infection where micro-organisms had not currently colonized the airways or possibly an underlying autoimmune or immunodeficiency process had contributed to our findings as well, which require clinical correlation.

Final Diagnosis: Eosinophilic asthma with areas reminiscent of Splendore-Hoeppli phenomenon suggestive of Allergic Bronchopulmonary Aspergillosis or another hypersensitivity reaction.

Patient Follow-up: After our diagnosis, the patient followed up with infectious disease and pulmonology, who ran further tests. The patient was found to have elevated total IgE and IgE to *Aspergillus fumigatus*. Fungal cultures were negative, but it was clarified that the patient was an avid gardener, lived on several acres of forested land, and her spouse had a history of blastomycosis and possibly (per patient report) had been treated for a respiratory *Aspergillus* infection in the past. Follow-up chest CT showed expected surgical site changes, no difference in the non-PET avid nodules, and airway dilation with mucus plugging. The patient was prescribed an albuterol inhaler and a daily Dulera inhaler (mometasone/formoterol). Ultimately, her clinical picture was described as consistent with Allergic Bronchopulmonary Aspergillosis (ABPA).

Discussion:

Eosinophilic asthma is a specific subtype of asthma that is usually clinically defined by varying degrees of sputum and peripheral blood eosinophilia. Histologically, asthmatic pulmonary changes with increased eosinophilic inflammation are seen. Specifying this subtype or suspicion for this subtype may impact treatment, as eosinophilic asthma has been shown to exhibit increased severity of symptoms but also to respond well to corticosteroids and Th2 cell-targeted (i.e., IL-5 inhibition) therapy.

Splendore-Hoeppli Phenomenon refers to the presence of often starkly eosinophilic, stellate debris associated with granulomatous processes, most commonly seen in pulmonary fungal infections or with certain bacterial infections such as with *Actinomyces spp*. It has also been described with parasitic infections and in reactions to synthetic material. Comparing similar histological features in relevant clinical contexts may heighten your suspicion for one these specific hypersensitivity processes.

Allergic Bronchopulmonary Aspergillosis (ABPA) is an immunologic pulmonary disorder caused by *A. fumigatus* which is one of the most common airborne fungi. It easily affects the lungs because its small size enables it to reach pulmonary alveoli when inhaled. ABPA usually affects those with underlying lung disorders, such as cystic fibrosis or uncontrolled bronchial asthma. The excess mucous secretion and plugging in these disorders makes it challenging to clear spores. Its general pathophysiology in immunocompromised and some atopic individuals involves IgE and IgG production against inhaled spores and an overactive Th2 cell response. Airways may then become colonized which stimulates a chronic allergic inflammatory response and can result in tissue injury. Clinically, ABPA manifests with asthmatic symptoms including wheezing and imaging showing bilateral pulmonary infiltrates and bronchiectasis as well as peripheral blood eosinophilia. While usually a clinical diagnosis, identification of ABPA's characteristic histological findings can lead the clinical team toward the correct work-up and management.

Pulmonary mucinous adenocarcinoma (PMA) is a rare subtype of non-small cell lung carcinoma that is characteristically seen in female non-smokers. CT imaging can often mimic pneumonia and in cytopathology specimens, it may mimic mucinous metaplasia. Additionally, PMA usually lacks TTF-1 expression and more frequently carries *KRAS* mutations. It has an intermediate-to-poor prognosis and has a propensity for recurrence due to air-space spread.

References:

1. Agarwal R. Allergic Bronchopulmonary Aspergillosis. Chest. 2009;135(3):805-826. doi:10.1378/chest.08-2586
2. Agarwal R, Sehgal IS, Dhooria S, et al. Allergic bronchopulmonary aspergillosis. Indian J Med Res. 2020;151(6):529-549. doi:10.4103/ijmr.IJMR_1187_19
3. Camacho C, Velazquez V, Vicente M, Sierra C, Zayas P. Association between Eosinophilic Esophagitis and Asthma. Journal of Allergy and Clinical Immunology. 2017;139(2):AB52. doi:10.1016/j.jaci.2016.12.122
4. Doherty T, Walford H. Diagnosis and management of eosinophilic asthma: a US perspective. JAA. Published online April 2014:53. doi:10.2147/JAA.S39119
5. Ecimovic L, Tvedten H, Lindström L, Trägårdh C, Hillström A. Cytological description of splendore-hoeppli phenomenon in an actinomycetes mycetoma in the skin of a guinea pig. Comp Clin Pathol. 2024;33(6):877-883. doi:10.1007/s00580-024-03608-z
6. Ge L, Wang L, Pei D. Pulmonary mucinous adenocarcinoma: An overview of pathophysiology and advancements in treatment. Heliyon. 2024;10(9):e28881. doi:10.1016/j.heliyon.2024.e28881
7. Gupta N, Razik A, Soneja M. Staring at the stars: a case of gastrointestinal basidiobolomycosis from the Indian subcontinent. BMJ Case Reports. Published online September 5, 2018:bcr-2018-226693. doi:10.1136/bcr-2018-226693
8. Liu Y, Zhang HL, Mei JZ, et al. Primary mucinous adenocarcinoma of the lung: A case report and review of the literature. Oncology Letters. 2017;14(3):3701-3704. doi:10.3892/ol.2017.6615
9. Moon SW, Choi SY, Moon MH. Effect of invasive mucinous adenocarcinoma on lung cancer-specific survival after surgical resection: a population-based study. J Thorac Dis. 2018;10(6):3595-3608. doi:10.21037/jtd.2018.06.09
10. Paulk A, Tavora F, Burke A. Pulmonary mucinous adenocarcinomas: a clinicopathologic series with emphasis on the prognostic significance of spread through alveolar spaces, and presence of solid growth component. Surg Exp Pathol. 2018;1(1):3. doi:10.1186/s42047-018-0013-8
11. Sisodia J, Bajaj T. Allergic Bronchopulmonary Aspergillosis. In: StatPearls. StatPearls Publishing; 2025. Accessed January 28, 2025. http://www.ncbi.nlm.nih.gov/books/NBK542329/

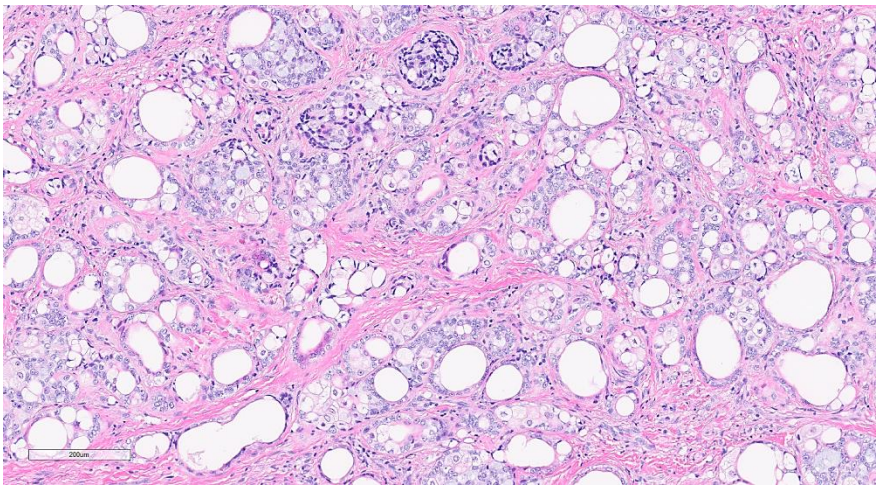
Case 5: Drs. Anisha Jacob, Nicole Cipriani

Diagnosis: Adenoid cystic carcinoma with sebaceous differentiation involving the external auditory canal.

Clinical History: The patient is a 53-year-old male with a history of chronic otitis media and associated ear pressure issues during air travel. Approximately one year ago, ENT identified a lesion in the right external auditory canal at the bony-cartilaginous junction. The lesion was initially presumed to be a cystic mass. The patient subsequently developed recurrent middle ear effusions with intermittent right-

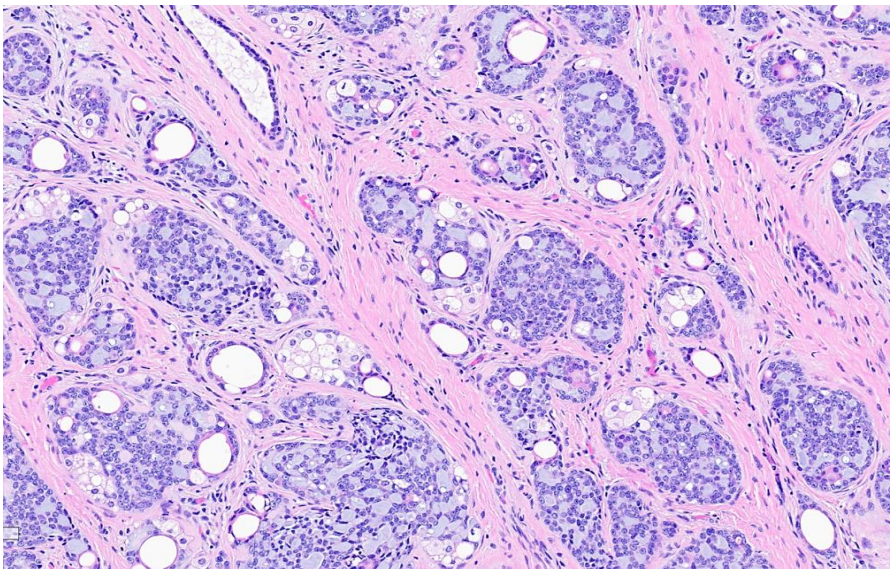
sided otalgia, and tube placement was performed. During this procedure, the lesion was biopsied for further evaluation.

Morphology and IHC of biopsy: Biopsy showed a dermal lesion with nests of tumoral cells with some areas showing cribriform pattern and tubular structures, mostly comprised of vacuolated cells reminiscent of sebocytes. P63 was positive. CK7 and CK5/6 was positive in a subset of cells. EMA showed strong positivity in the vacuolated cells. CEA showed focal internal luminal laminar pattern. CK20 and CD117 was negative.



Differential diagnosis: Sebaceous carcinoma, adenoid basal cell carcinoma with sebaceous differentiation, adenoid cystic carcinoma, adnexal adenocarcinoma, cribriform tumor, polymorphous sweat gland carcinoma, microcystic adnexal adenocarcinoma.

Morphology and IHC of resection: The carcinoma demonstrates cribriform and tubular growth with bluish myxoid matrix material within the cribriform spaces with admixed sebaceous cells. Tumor cells were diffusely positive for Sox10. The abluminal cells are positive for p40 and luminal cells were positive for CD117. The sebaceous cells showed nuclear positivity for Androgen Receptor.



Molecular: Next-generation sequencing of tumoral RNA revealed a *MYB::NFIB* fusion.

Discussion: EAC tumors are rare and only 20% have glandular origins. Most are squamous cell carcinomas. Adenoid cystic carcinomas (AdCC) are the most prevalent glandular tumor. They have the same characteristics as small salivary gland AdCC: silent growth, local recurrence, perineural invasion, and late metastasis. Adenoid cystic carcinoma is an invasive carcinoma composed of epithelial and myoepithelial neoplastic cells arranged in tubular, cribriform, and solid pattern, often associated with MYB, MYBL1, or NFIB rearrangement. Sebaceous differentiation in AdCC has been reported in other sites such as the mammary gland, parotid gland, sinonasal tract and vulvar region. Sebaceous differentiation has also been reported in other salivary gland tumors including pleomorphic adenoma and epithelial-myoepithelial carcinoma (EMCa). This case serves as an important reminder to keep in mind the possibility of aberrant differentiation in tumors (heterologous epithelial differentiation) and tumor heterogeneity with sampling variability. Also interesting to note was the immunophenotypic difference that occured in the biopsy and resection (CD 117 negative in biopsy and CD 117 positive in resection).

References:

1. Mahjabin F, Ordulu Z, Martinez-Duarte E*, et al* Sebaceous differentiation can occur in vulvar adenoid cystic carcinoma *International Journal of Gynecologic Cancer* Published Online First: 07 July 2023. doi: 10.1136/ijgc-2023-004323

2. Ooms KDW, Chiosea S, Lamarre E, Shah AA. Sebaceous Differentiation as Another Feature of Metatypical Adenoid Cystic Carcinoma: A Case Report and Letter to the Editor. Am J Surg Pathol. 2023 Jan 1;47(1):145-146. doi: 10.1097/PAS.0000000000001993. Epub 2022 Nov 1. PMID: 36525543.

3. Assiri SA, Altwairqi RG, Alotaibi R, Ibrahim M. External auditory canal sebaceous carcinoma. BMJ Case Rep. 2023 Sep 29;16(9):e255038. doi: 10.1136/bcr-2023-255038. PMID: 37775279; PMCID: PMC10546117.

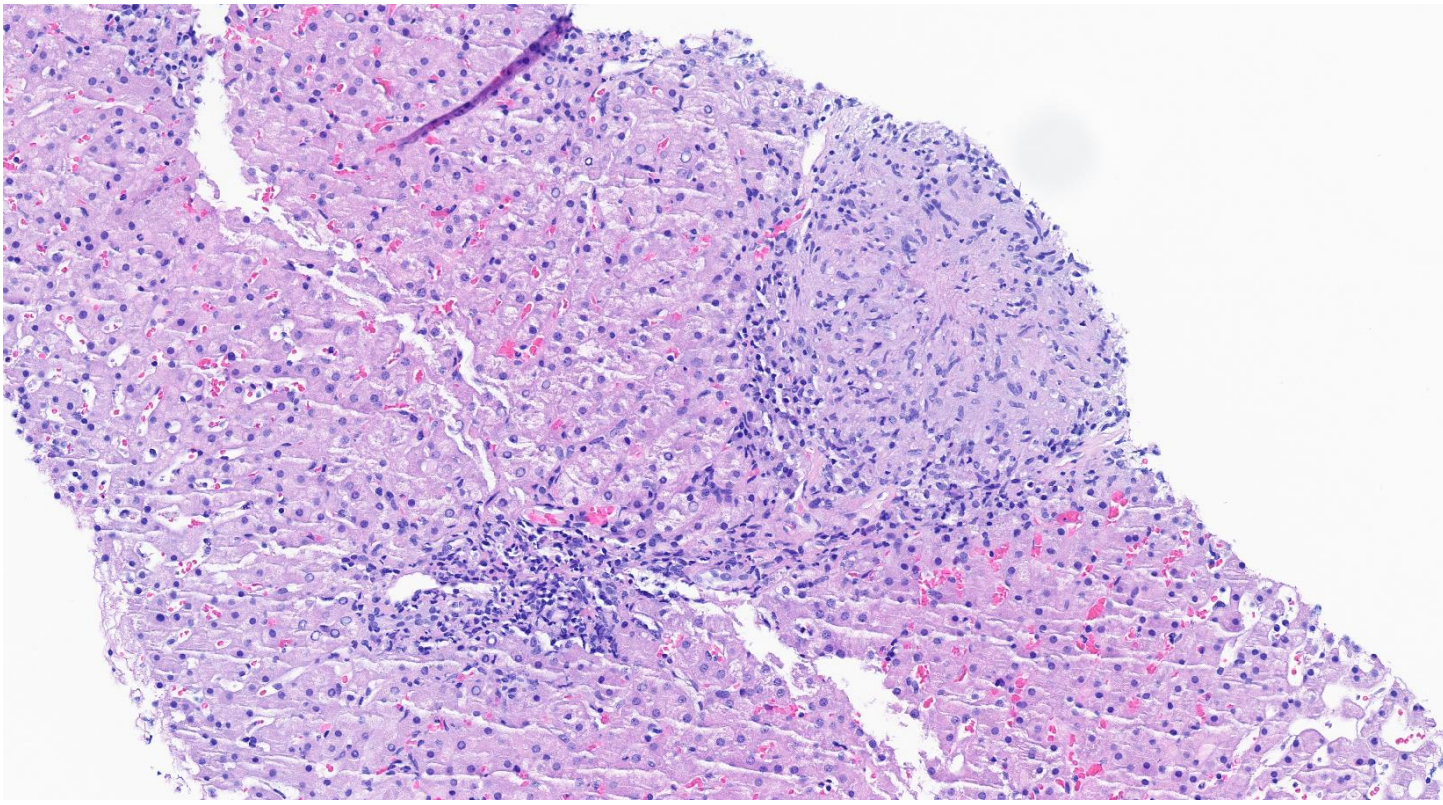
4. WHO Classification of Tumors online

Case 6: Leah Osnis and John Hart

Diagnosis: Unexpected hepatitis in a pediatric patient

Clinical History: The patient is a 6-year-old with no significant past medical history who presented with a fever of three weeks duration. Other symptoms included severe back pain with refusal to stand, abdominal pain, mild cough, and nausea. Two weeks prior to presentation, the patient was diagnosed with strep throat at an outside institution and treated with amoxicillin, although the fever persisted after completing antibiotics. There are no known sick contacts. CT demonstrated hepatosplenomegaly with numerous small lesions in the liver and spleen as well as lymphadenopathy predominantly in the mediastinum, porta hepatis and mildly in the axillary lymph nodes. MRI demonstrated multiple thoracic spinal enhancing lesions. Blood cultures were negative. The patient underwent liver biopsy for further evaluation.

Microscopic Findings: Targeted core biopsies demonstrated preservation of normal liver architecture. There is no evidence of fibrosis or cirrhosis. The biopsy demonstrates patchy lobular and portal inflammatory infiltrate with a focal non-necrotizing granuloma.



Differential Diagnosis	
Infectious	**Non-infectious**
Mycobacterial: Tuberculosis, Leprosy	Sarcoidosis
Bacterial: Brucellosis, Q fever, Bartonellosis	Primary biliary cholangitis
Fungal: Histoplasmosis, Blastomycosis	Drug-induced liver injury
Viral: EBV, CMV	BCG therapy
Parasitic: Schistosomiasis, Entamoeba histolytica	Foreign body

Ancillary Studies:

AFB: negative for mycobacterial organisms

GMS: negative for fungal organisms
Warthin-Starry stain: highlights scattered organisms that are consistent with *Bartonella henselae*

Discussion: The differential for hepatic granulomas is incredibly vast and often no specific etiology is identified. If the granulomas are well-formed, that is suggestive of sarcoidosis. In contrast granulomas in PBC tend to appear vague and poorly formed, adjacent to an injured bile duct, and occur in a female aged 40-60 years old. Drug induced liver injury should be suspected when a patient is immunocompetent with no infectious symptoms. If in an immunocompetent patient there is a single granuloma with no inflammation and no infectious symptoms, then it is recommended to polarize and look for a foreign body. An infectious etiology is likely when there are necrotizing granulomas, or the patient is immunocompromised or has systemic infectious symptoms. A negative GMS or AFB stain in this scenario does not exclude infectious etiology. This was highlighted in our patient who had systemic infectious symptoms. In our case of disseminated *Bartonella* infection, liver lesions in immunocompetent patients are more likely to reveal granulomas compared to immunocompromised patients where the non-specific finding of peliosis hepatis can occur.

References:

1. Crocetti D, Palmieri A, Pedullà G, Pasta V, D'Orazi V, Grazi GL. Peliosis hepatis: Personal experience and literature review. World J Gastroenterol. 2015 Dec 14;21(46):13188-94. doi: 10.3748/wjg.v21.i46.13188. PMID: 26675327; PMCID: PMC4674738.
2. Dehio C. Recent progress in understanding Bartonella-induced vascular proliferation. Curr Opin Microbiol. 2003 Feb;6(1):61-5. doi: 10.1016/s1369-5274(03)00006-7. PMID: 12615221.
3. Doppalapudi H, Markus JT, Parekh U. Granulomatous Hepatitis. [Updated 2024 Sep 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK564315/
4. Lamps LW, Scott MA. Cat-scratch disease: historic, clinical, and pathologic perspectives. Am J Clin Pathol. 2004 Jun;121 Suppl:S71-80. doi: 10.1309/JC8YM53L4E0L6PT5. PMID: 15298152.
5. Narayan, K.G., Sinha, D.K., Singh, D.K. (2024). Bartonellosis. In: Handbook of Management of Zoonoses. Springer, Singapore. https://doi.org/10.1007/978-981-99-9885-2_38
6. Mironova M, Gopalakrishna H, Rodriguez Franco G, Holland SM, Koh C, Kleiner DE, Heller T. Granulomatous liver diseases. Hepatol Commun. 2024 Mar 18;8(4):e0392. doi: 10.1097/HC9.0000000000000392. PMID: 38497932; PMCID: PMC10948139.
7. Pizzuti M, Bailey P, Derrick C, Albrecht B, Carr AL, Covington EW, Deri CR, Green SB, Hayes J, Hobbs ALV, Hornback KM, Keil E, Lukas JG, Seddon M, Taylor AD, Torrisi J, Bookstaver PB. Epidemiology and treatment of invasive Bartonella spp. infections in the United States. Infection. 2024 Aug;52(4):1307-1314. doi: 10.1007/s15010-024-02177-1. Epub 2024 Feb 1. PMID: 38300353.
8. Shah N, Mitra A. Gastrointestinal and Hepatic Sarcoidosis: A Review Article. Clin Liver Dis (Hoboken). 2021 May 1;17(4):301-307. doi: 10.1002/cld.1055. PMID: 33968393; PMCID: PMC8087901.