LOYOLA MEDICINE

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

IRAP Case Summaries (2023)

Case #1

Presenter: Yuanzhe Zhu, MBCHB
Attending: Dr. Ewa Borys, MD

Clinical history

A 19-year-old man who initially presented 3 years ago with a past medical history of focal epileptic seizures controlled on Oxcarbazepine presents for a breakthrough seizure. A head CT scan showed a calcified lesion in the left frontal lobe. On MRI, the lesion demonstrates T1 hypointensity and measures 12mm x 7 mm in the transverse plane. A craniotomy was performed to evacuate the lesion, and a representative section of this specimen was submitted for review. (Scanned slide only).

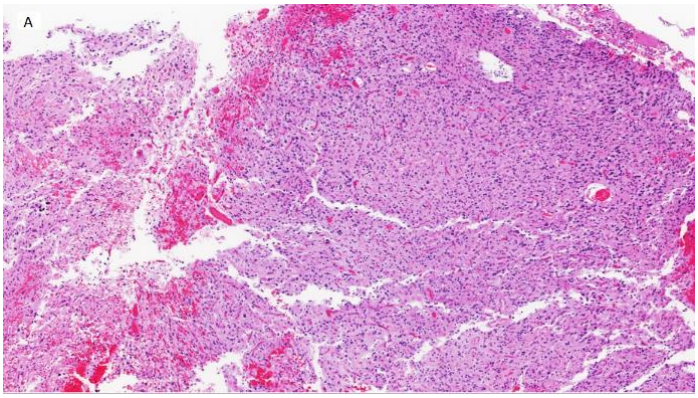
Final diagnosis: Polymorphous Low-grade Neuroepithelial tumor of the Young

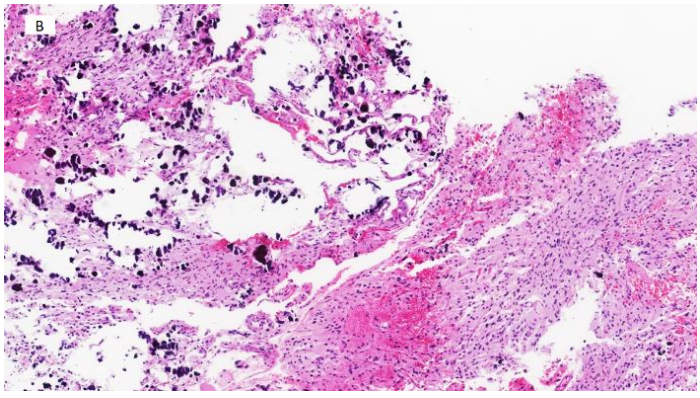
Differential diagnosis:

- Oligodendroglioma
- Diffuse Astrocytoma (IDH-mutated and pediatric type)
- Pediatric type diffuse low-grade gliomas (*MYB/MYBL1, MAPK* pathway altered)
- Pediatric type diffuse low-grade glioma (PLNTY)
- Ganglioglioma

Key features:

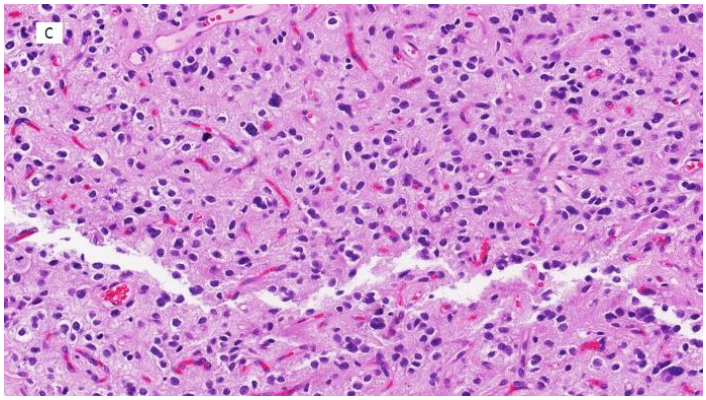
Histopathology: H&E stained sections from the frontal lobe evacuation shows a moderately cellular, infiltrative neoplasm with areas of coarse calcifications (A and B). Higher powers reveal areas of tumor cells with uniform rounded nuclei, small nucleoli, and perinuclear vacuoles (C). Other areas show tumor cells with more pronounced nuclear pleomorphism, occasional intranuclear pseudo-inclusions, and scattered eosinophilic granular bodies. Significantly there are no areas of mitotic activity, microvascular proliferation, or necrosis.





LOYOLA MEDICINE

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



Results of the immunophenotyping study by IHC and pathogenic findings by molecular testing are shown in the table below.

Positive IHC	Negative IHC
CD34	IDH (wildtype)
GFAP	
Additional stains	
Ki-67: <2%	
p53: weak staining in <10% of cells	
Pathogenic findings by Molecular testing	
BRAF c.1799 T>A, p.V600E	

Discussion: Polymorphous Low-grade Neuroepithelial Tumor of the Young (PLNTY) is a pediatric type diffuse low-grade glioma that was first published in 2017 (1). The median age of diagnosis is 16 without sex predilection (2). Clinically this lesion often presents with progressively worsening epilepsy. The diagnosis is made on histology and molecular testing. Histologic features include infiltrative and compact growth patterns with an oligodendroglioma-like component. This lesion is low-grade and should lack high-grade features such as mitotic figures, microvascular proliferation, or necrosis should be seen. This tumor is diffusely CD34 positive on immunohistochemistry (1) and should demonstrate IDH-wildtype status and no 1p/19q codeletion (2). Molecular diagnostic evidence of *BRAF p V600E* or another *MAPK* pathway-driving genetic is essential for diagnosis (3).
This tumor is amenable to excision without reoccurrence of the lesion and reduced/relief from seizures (1).

Take home points:
PLNTY is a pediatric-type diffuse low-grade glioma associated with epileptic seizures. Radiologically, these lesions appear as calcified masses on CT, hypo- to -iso intense lesions on T1 MRI, and can be mistaken for benign entities such as cavernous hemangiomas. This lesion

demonstrates prominent oligodendroglioma-like components on histology and is strongly positive for CD34 on immunohistochemistry. In addition, it must demonstrate a *MAPK* pathway abnormality for diagnosis. These lesions are important to differentiate from similar ones as they are treatable by excision alone.

References:

1. Huse JT, Snuderl M, Jones DT, Brathwaite CD, Altman N, Lavi E, Saffery R, Sexton-Oates A, Blumcke I, Capper D, Karajannis MA, Benayed R, Chavez L, Thomas C, Serrano J, Borsu L, Ladanyi M, Rosenblum MK. Polymorphous low-grade neuroepithelial tumor of the young (PLNTY): an epileptogenic neoplasm with oligodendroglioma-like components, aberrant CD34 expression, and genetic alterations involving the MAP kinase pathway. Acta Neuropathol. 2017 Mar;133(3):417-429.
2. Johnson DR, Giannini C, Jenkins RB, Kim DK, Kaufmann TJ. Plenty of calcification: imaging characterization of polymorphous low-grade neuroepithelial tumor of the young. Neuroradiology. 2019 Nov;61(11):1327-1332. doi: 10.1007/s00234-019-02269-y.
3. Rosenblum MK, Ellison DW et al. Polymorphous low-grade neuroepithelial tumour of the young. In: WHO Classification of Tumours Editorial Board. Central nervous system tumours [Internet]. Lyon (France): International Agency for Research on Cancer; 2021. (WHO classification of tumours series, 5th ed.; vol. 6). Available from: https://tumourclassification.iarc.who.int/chapters/45.

Case #2
Presenter: Yazan Alhalaseh, MD
Attending: Jodi J. Speiser, MD

Clinical History:
A 39-year-old African American male presents with anal pain and a diffuse rash of two weeks duration. Initially, he noted cutaneous lesions in the genital region that later spread to his trunk, face, and extremities. His past medical history is significant for poorly controlled HIV, sickle cell trait, and remote history of syphilis infection. His social history includes IV drug abuse and multiple sexual partners. Physical examination is remarkable for umbilicated, tan-colored cutaneous lesions on the face and trunk and indurated macerated plaques on his genital and perianal region. A biopsy from perianal lesions was taken and provided below for review. (Scanned slide only). Based on the clinical findings and histologic features, a monkeypox (Mpox) PCR test was sent, which returned positive.

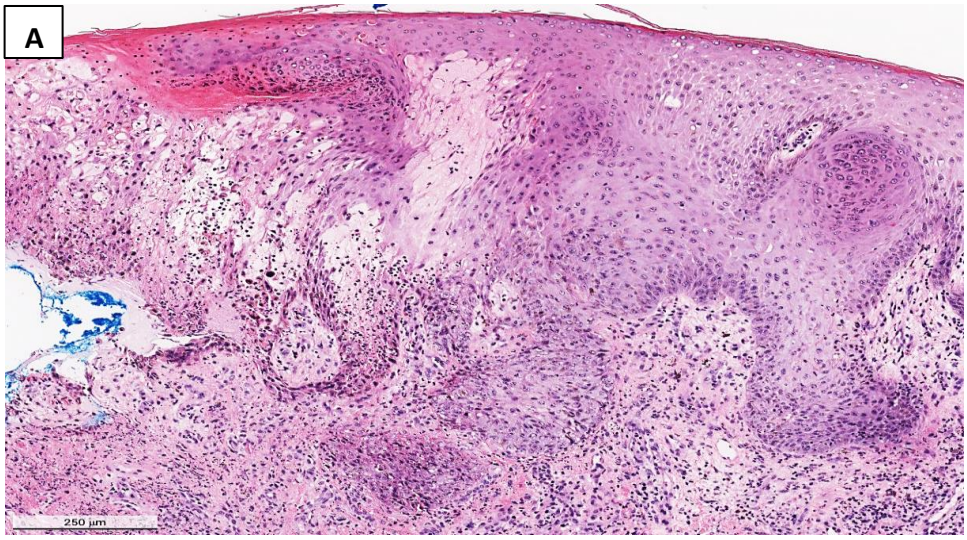
Final Diagnosis: Monkeypox (Mpox)

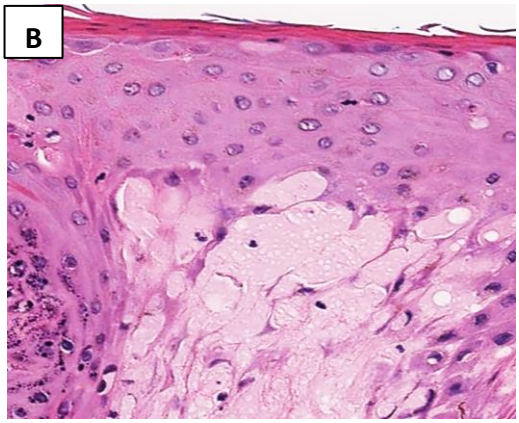
Differential Diagnosis:

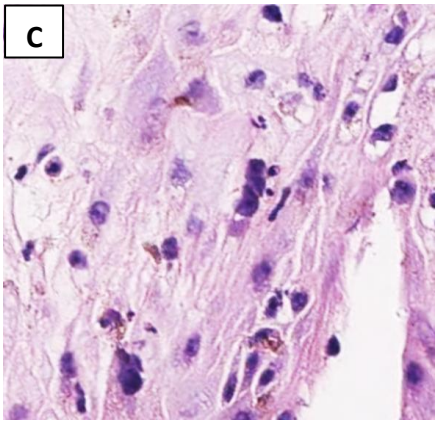
- Herpes Virus Infections (Herpes Simplex, Herpes Varicella/Zoster)
- Measles
- Secondary Syphilis
- Ecthyma Contagiosum (Orf)
- Monkeypox (Mpox)
- Vesicular Eruption of COVID-19

Key Features:

Histopathology: Perianal punch biopsy showed acanthotic epidermis with psoriasiform hyperplasia, and intraepidermal edema (spongiosis). The superficial dermis has lichenoid inflammatory infiltrate. High power examination revealed areas of keratinocytes ballooning (A), and epidermal reticular degeneration (B). In other areas, syncytial multinuclear keratinocytes (C), and keratinocytes with eosinophilic intracytoplasmic inclusions (D) are identified. Examination of the deep dermis showed peri-eccrine lymphohistiocytic infiltrate (E).

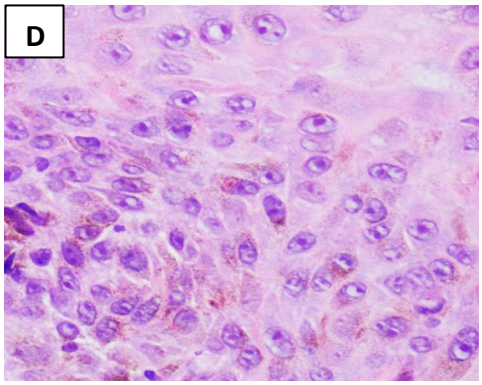


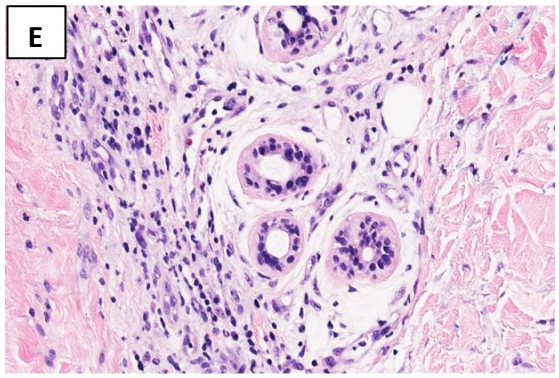




LOYOLA MEDICINE

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





Case discussion:

Monkeypox (Mpox) is an enveloped double-stranded DNA virus that belongs to the orthopoxvirus genus of the poxviridae family[1]. It is endemic in central and west Africa, and the primary host of this disease are rodents and non-human primates[2]. Traditionally, Mpox cases present with a 2-day prodrome before the onset of the rash, demonstrated by fever, malaise, and severe lymphadenopathy[2]. The rash initially manifests as maculopapular lesions 2–5mm in diameter. It spreads in a centrifugal fashion to become generalized in most cases[3]. The typical skin lesion progresses through a papular, vesicular, pustular, and crust stage over a 14- to 21-day period before sloughing the crust, leaving a depigmented scar[1].

On May 2022, there was an increase in Mpox cases, and the U.S. Department of Health and Human Services declared Mpox a public health emergency on August 2022. Moreover, the CDC gathered data from US cases reveals that most cases lack prodromal symptoms, and 94% had sexual or close intimate contact (especially in men who had sex with men)[4]. The observation highlights the change of viral transmission towards a sexual route. Proposed theories suggest that the virus may have made its way into highly interconnected sexual networks within the MSM community, where it can spread in ways that it cannot in the general population. Other contributing factors include cessation of smallpox vaccination and viral evolution[5].

Key histologic findings include a variable degree of acanthosis and psoriasiform hyperplasia with intraepidermal edema (spongiosis). Additionally, there are keratinocytes ballooning, epidermal reticular degeneration, syncytial multinuclear keratinocytes, as well as eosinophilic intracytoplasmic inclusions identified. The deep dermis showed peri-eccrine lymphohistiocytic infiltrate.

Mpox should be suspected in patients with prodromal symptoms, rash, and epidemiologic risk factors for infection. A diagnosis can be achieved through demonstration of orthopoxviral DNA (eg, by polymerase chain reaction (PCR) or next-generation sequencing of a clinical specimen) or through isolation of monkeypox virus in culture from a specimen. In challenging cases where epidemiologic risk is not well established, serologic studies can help rule out other differential diagnoses; however, false negative results may be encountered in immunocompromised

individuals. Performing cutaneous biopsy and histologic examination in these patients can be valuable in the diagnostic process.

Take home points:

- Viral exanthems have unique clinical and histopathologic features
- Serologic studies and molecular tests play a major role in the diagnosis
- Immunocompromised individuals can have a false negative serologic profile
- Histologic evaluation of cutaneous rash can be a very useful confirmation tool

References

1. Bayer-Garner IB. Monkeypox virus: histologic, immunohistochemical and electron-microscopic findings. J Cutan Pathol. 2005 Jan;32(1):28-34. doi: 10.1111/j.0303-6987.2005.00254.x. PMID: 15660652.
2. Di Giulio DB, Eckburg PB. Human monkeypox: an emerging zoonosis. Lancet Infect Dis. 2004 Jan;4(1):15-25. doi: 10.1016/s1473-3099(03)00856-9. Erratum in: Lancet Infect Dis. 2004 Apr;4(4):251. PMID: 14720564; PMCID: PMC9628772.
3. Jezek Z, Szczeniowski M, Paluku KM, Mutombo M. Human monkeypox: clinical features of 282 patients. J Infect Dis. 1987 Aug;156(2):293-8. doi: 10.1093/infdis/156.2.293. PMID: 3036967.
4. Philpott D, Hughes CM, Alroy KA, et al. Epidemiologic and Clinical Characteristics of Monkeypox Cases — United States, May 17–July 22, 2022. MMWR Morb Mortal Wkly Rep 2022;71:1018-1022. DOI: http://dx.doi.org/10.15585/mmwr.mm7132e3.
5. Endo, A., Murayama, H., Abbott, S., Ratnayake, R., Pearson, C.A., Edmunds, W.J., Fearon, E. and Funk, S., 2022. Heavy-tailed sexual contact networks and monkeypox epidemiology in the global outbreak, 2022. Science, 378(6615), pp.90-94.

Case #3

Presenter: Andreas Kontosis, MD
Attending: Vijayalakshmi Ananthanarayanan, MBBS MD

Clinical History:

A 71-year-old man with a past medical history of hypertension, diabetes mellitus type 2, and chronic sinusitis presented with a painless, firm right palatal mass (2 months duration). An MRI of the head demonstrated a 3.0 cm bilobed, solid, soft tissue mass located along the posteroinferior wall of the right maxillary sinus with extension into the ipsilateral nasopharynx and soft palate. The patient underwent a right palatectomy with a horizontal maxillectomy. An H&E slide from the resection specimen is provided for review. (Scanned slide only)

Final Diagnosis: Microsecretory adenocarcinoma with high-grade transformation

LOYOLA MEDICINE

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

Differential Diagnosis

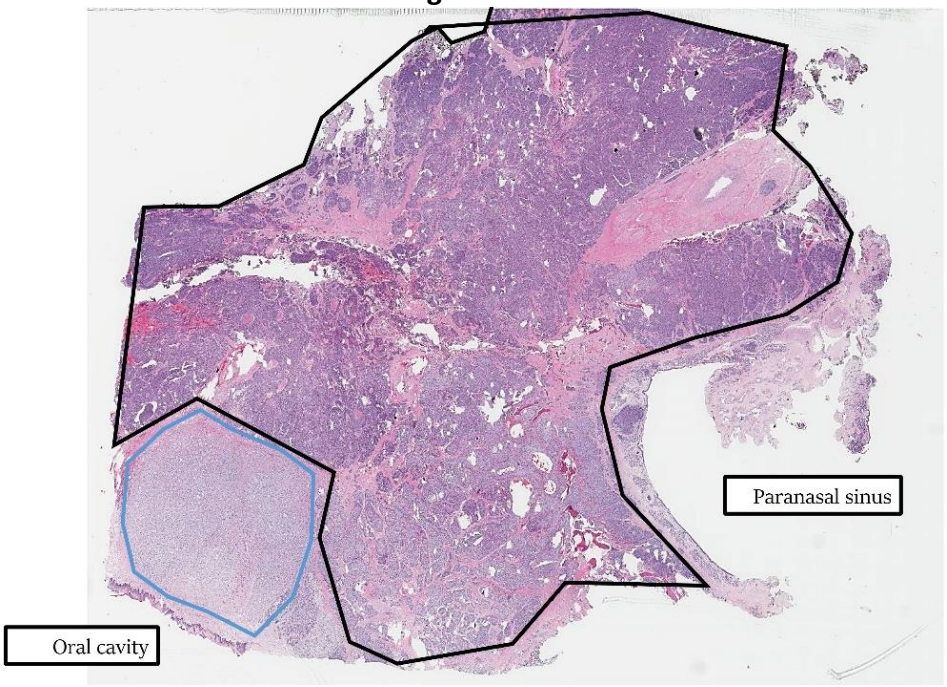
The differential diagnosis includes salivary gland carcinomas with high-grade transformation:

- Secretory Carcinoma
- Adenoid Cystic Carcinoma
- Sclerosing microcystic Adenocarcinoma
- Mucoepidermoid carcinoma
- Polymorphus adenocarcinoma
- Microsecretory adenocarcinoma

Key Features

Histopathology: Our tumor consisted of two components (Figure A): The largest component (delineated by the **black line**) showed mainly solid nests with frequent areas of central necrosis, as well as lymphovascular and bone invasion. On higher power, marked nuclear pleomorphism with vesicular chromatin and a markedly increased number of mitotic figures, including atypical ones, were identified. Thus, this part of the tumor showed high-grade features (Figures B-C). The smallest component (delineated by the **blue** line) appeared roughly nodular and circumscribed. It consisted of cords, cysts, and microcysts in a fibrous and fibromyxoid stroma. Bluish basophilic material was recognized in the cystic spaces. The cells had minimal eosinophilic cytoplasm on a higher power, with bland nuclei. No necrosis or increased mitotic figures were identified in this area. Based on these features, this part of the tumor was recognized as the "low-grade" component (Figures D-E).

Figure A



LOYOLA MEDICINE

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

Figure B

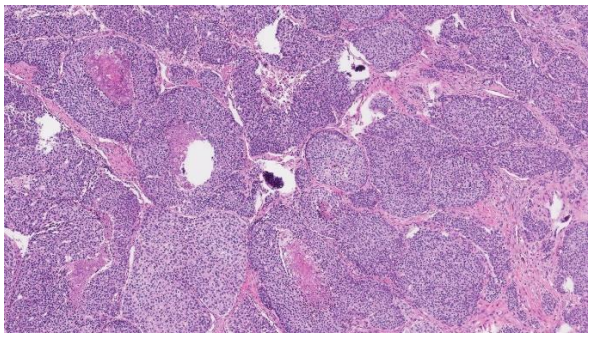


Figure C

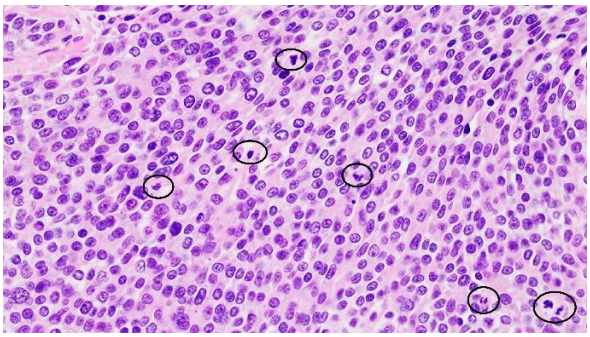


Figure D

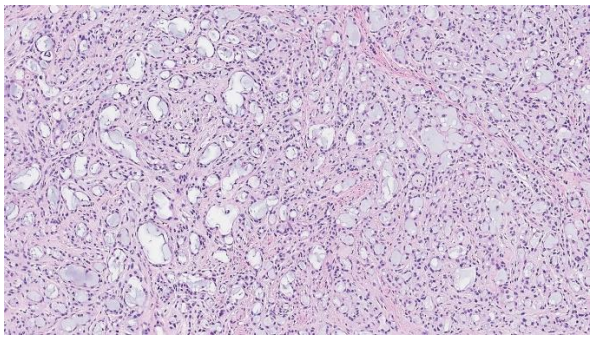
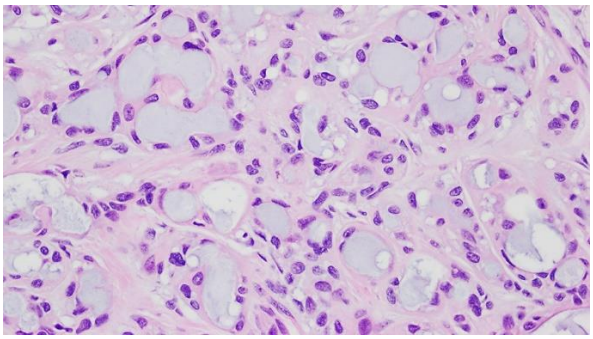


Figure E



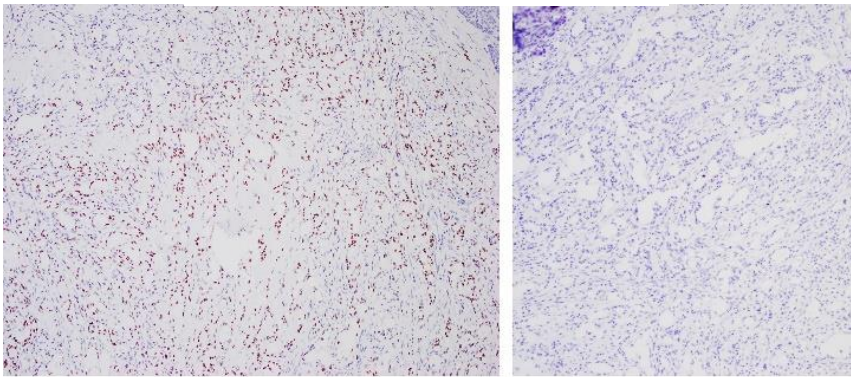
Work-up

Results of the histochemical and immunohistochemical studies (IHC) are shown in the table and figure below.

Next-Generation Sequencing (NGS) and RNA-transcriptome analysis were performed and revealed the presence of a *MEF2C::SS18* gene fusion.

	+	-
Low-grade component	SOX10 S100 p63	p40 mammaglobin GCDFP-15
Secretions	Mucicarmine	PAS-diastase
High-grade component	AE1/AE3 CK7 SOX10	CK 5/6 p40 p63 calponin SMA S100 GATA-3 mammaglobin GCDFP-15

Figure F



LOYOLA MEDICINE

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

Microsecretory adenocarcinoma was officially recognized as a distinct entity in the 5th edition of the WHO Classification and it is defined as a low-grade malignancy that shows intercalated-duct-like phenotype and characteristic *MEF2C::SS18* gene fusion [1]. The first cases were described by Dr. Bishop and his team in 2019 [2] and since then 33 cases have been described in the English literature [2,3,4,5]. In almost all the published cases the tumor arose in the oral cavity; the palate was the most common location followed by the buccal mucosa. Only one case has been described in the parotid gland so far [3].

Microsecretory adenocarcinoma has remarkably consistent and distinctive morphologic features, which are the following (1):

a. Microcystic-predominant growth pattern
b. Uniform intercalated duct-like cells with attenuated eosinophilic to clear cytoplasm
c. Monotonous oval hyperchromatic nuclei with indistinct nucleoli
d. Abundant basophilic luminal secretions
e. Variably cellular fibromyxoid stroma
f. Rounded borders with subtle infiltrative growth

The immunophenotype of the tumor is also markedly consistent. Tumor cells are always positive for S100, SOX10, and p63, and occasionally they can be positive for SMA. At the same time, they are negative for p40, calponin, and mammaglobin [1].
The *MEF2C::SS18* rearrangement can be detected by RNA sequencing, by PCR, or by FISH [1].
SS18 Break-Apart FISH, which is used as an adjunct for diagnosing synovial sarcoma, shows excellent sensitivity and can be used for the diagnosis of the *MEF2C::SS18* translocation [6].
MEF2C, the product of gene *MEF2C* (5q14.3), a is a transcription factor that has been involved in the development of cardiac and skeletal muscle, as well as B and T lymphocytes. 4 isoforms of the gene, have been discovered, named *MEF2A-MEF2D*. Interestingly, a *MEF2D::SS18* translocation has been found in cases of B-progenitor Acute Lymphoblastic Leukemia[7].
On the other side, SS18, together with other proteins, including SMARCA4 and SMARCB1, are components of the SWI/SNF chromatin remodeling complex, which fosters a state of open chromatin and promotes active transcription [9]. Lastly, *SS18* gene (18q11.2) participates in the *SS18::SSX1/2/4* translocation of synovial sarcoma.

The list of differential diagnoses for microsecretory adenocarcinoma is broad and includes the following diagnoses [1, 2]:

Entity	Secretory Carcinoma	Adenoid Cystic Carcinoma	Sclerosing Microcystic Carcinoma	Mucoepidermoid Carcinoma	Polymorphus Adenocarcinoma	Microsecretory Adenocarcinoma
Cell types	Ductal	Ductal and myoepithelial	Ductal and myoepithelial	Mucous, intermediate, squamoid	Ductal	Ductal
Cytologic Features	Abundant eosinophilic cytoplasm, monotonous oval nuclei	Minimal eosinophilic to clear cytoplasm, hyperchromatic nuclei	Minimal eosinophilic with round to oval nuclei	Low, intermediate and high-grade	Moderate eosinophilic to clear cytoplasm, monotonous oval nuclei, sometimes with clearing	Attenuated eosinophilic to clear cytoplasm, monotonous nuclei
Growth pattern	Variably, including cystic, microcystic and solid	Tubular, solid or cribriform (pseudocysts), perineural invasion common	Microcystic, strands/cords, nests, perineural invasion common	Cystic and solid areas	Variable including cord-like, tubular, cribriform, "targetoid" perineural invasion	Predominantly microcystic , cords, cribriform
Secretions	Extensive, basophilic or eosinophilic	Common, basophilic	Extensive, eosinophilic	Mucin	Uncommon	Extensive basophilic
Stroma	Typically minimal, occasionally sclerotic	Typically hyalinized	Extensive, fibrous/sclerotic	Extracellular mucin, fibrous	Often myxoid	Fibromyxoid, variably cellular
IHC	CK7, Mammaglobin, S100, SOX10 p63, p40, DOG-1	**Duct**: CK7, CD117 **Myoep**: p40/63, calponin, SMA	**Duct**: CK7, pancytokeratin **Myoep**: p40/63, calponin, SMA	p63, p40 SOX10, S100	CK7, S100 p63, CD117 (60%) Mammaglobin (variable) p40	SOX10, S100, p63 p40, mammaglobin calponin
Molecular findings	***ETV6***-rearrangements (***ETV6::NTRK3*** most common)	***MYB*** or ***MYBL1*** rearrangements	Putative loss of ***CDK11B***	***CRTC1::MAML2*** rearrangement	***PRKD1,2*** *or* ***3*** rearrangements or mutations	***MEF2C::SS18***

(Table legend: Green color: positive, Red color: negative)

Our case of microsecretory carcinoma showed high-grade transformation. High-grade transformation has been described in a variety of salivary gland tumors and is associated with a more aggressive clinical course and poorer prognosis, irrespective of the histologic type of the original tumor [8].
Only one case of microsecretory carcinoma of the salivary glands with high-grade transformation has been published in literature [4].

Take home points!

- Microsecretory adenocarcinoma is a novel salivary gland tumor with a characteristic histologic and immunophenotypic profile and recurrent *MEF2C::SS18* fusions
- Cases of microsecretory adenocarcinoma of the salivary gland with high-grade transformation are extremely rare.
- High-grade transformation can occur in any subtype of salivary gland carcinoma, including microsecretory adenocarcinoma. In excisional specimens that demonstrate a high grade/non-classifiable morphology or immunophenotype, thorough sampling of the lesion is required to unearth a low-grade component or a pre-existing pleomorphic adenoma (i.e., carcinoma ex PA).

References:

1. Skalova A, Thompson LDR, Bishop JA, et al. Salivary Gland Tumors. In: WHO Classification of Tumours Editorial Board. Head and neck tumours [Internet; beta

version ahead of print]. Lyon (France): International Agency for Research on Cancer; 2022 [cited 2023 01 15]. (WHO classification of tumours series, 5th ed.; vol. 9). Available from: https://tumourclassification.iarc.who.int/chapters/52

2. Bishop JA, Weinreb I, Swanson D, et al. Microsecretory Adenocarcinoma: A Novel Salivary Gland Tumor Characterized by a Recurrent MEF2C-SS18 Fusion. Am J Surg Pathol. 2019 Aug;43(8):1023-1032. doi: 10.1097/PAS.0000000000001273. PMID: 31094920.
3. Bishop JA, Sajed DP, Weinreb I, et al. Microsecretory Adenocarcinoma of Salivary Glands: An Expanded Series of 24 Cases. Head Neck Pathol. 2021 Dec;15(4):1192-1201. doi: 10.1007/s12105-021-01331-7. Epub 2021 May 12. PMID: 33982215; PMCID: PMC8633253.
4. Gui H, Shanti R, Wei S, et al. Transformed microsecretory adenocarcinoma demonstrates high-grade morphology and aggressive biological behaviour. Histopathology. 2022 Nov;81(5):685-688. doi: 10.1111/his.14777. Epub 2022 Aug 31. PMID: 36043435.
5. Jurmeister P, Haas C, Eisterer W, et al. New entity of microsecretory adenocarcinoma of salivary glands: first case with recurrence and metastases - proof of malignancy. Virchows Arch. 2022 Dec;481(6):963-965. doi: 10.1007/s00428-022-03374-9. Epub 2022 Jul 2. PMID: 35780228; PMCID: PMC9734237.
6. Bishop JA, Koduru P, Veremis BM, et al. SS18 Break-Apart Fluorescence In Situ Hybridization is a Practical and Effective Method for Diagnosing Microsecretory Adenocarcinoma of Salivary Glands. Head Neck Pathol. 2021 Sep;15(3):723-726. doi: 10.1007/s12105-020-01280-7. Epub 2021 Jan 4. PMID: 33394377; PMCID: PMC8385014.
7. Madugula K, Mulherkar R, Khan ZK, et al. MEF-2 isoforms' (A-D) roles in development and tumorigenesis. Oncotarget. 2019 Apr 12;10(28):2755-2787. doi: 10.18632/oncotarget.26763. PMID: 31105874; PMCID: PMC6505634.
8. Skalova A, Leivo I, Hellquist H, et al. High-grade Transformation/Dedifferentiation in Salivary Gland Carcinomas: Occurrence Across Subtypes and Clinical Significance. Adv Anat Pathol. 2021 May 1;28(3):107-118. doi: 10.1097/PAP.0000000000000298. PMID: 33825717.
9. Schaefer IM, Hornick JL. SWI/SNF complex-deficient soft tissue neoplasms: An update. Semin Diagn Pathol. 2021 May;38(3):222-231. doi: 10.1053/j.semdp.2020.05.005. Epub 2020 Jun 5. PMID: 32646614; PMCID: PMC7993547.

Case #4

Presenter: Thanchanok (Friend) Chaiprasit, MD
Attending: Dr. Xianzhong Ding, MD, Ph.D.

Clinical History:

LOYOLA MEDICINE

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

A 66-year-old male presented with fatigue, decreased appetite, and unintentional weight loss for the past 6 months. His past medical history is significant for granulomatous lung disease. CT chest and abdomen imaging revealed a large 10.2 x 8.6 x 8.0 cm hypoattenuating encapsulated mass within the right hepatic lobe. The rest of the liver parenchyma was otherwise unremarkable and demonstrates no gross stigmata of cirrhosis. Partial hepatectomy was performed. An H&E slide from the partial hepatectomy specimen is provided for review. (Scanned slide only).

Final Diagnosis: BAP1 deficient hepatic carcinoma

Differential Diagnosis:

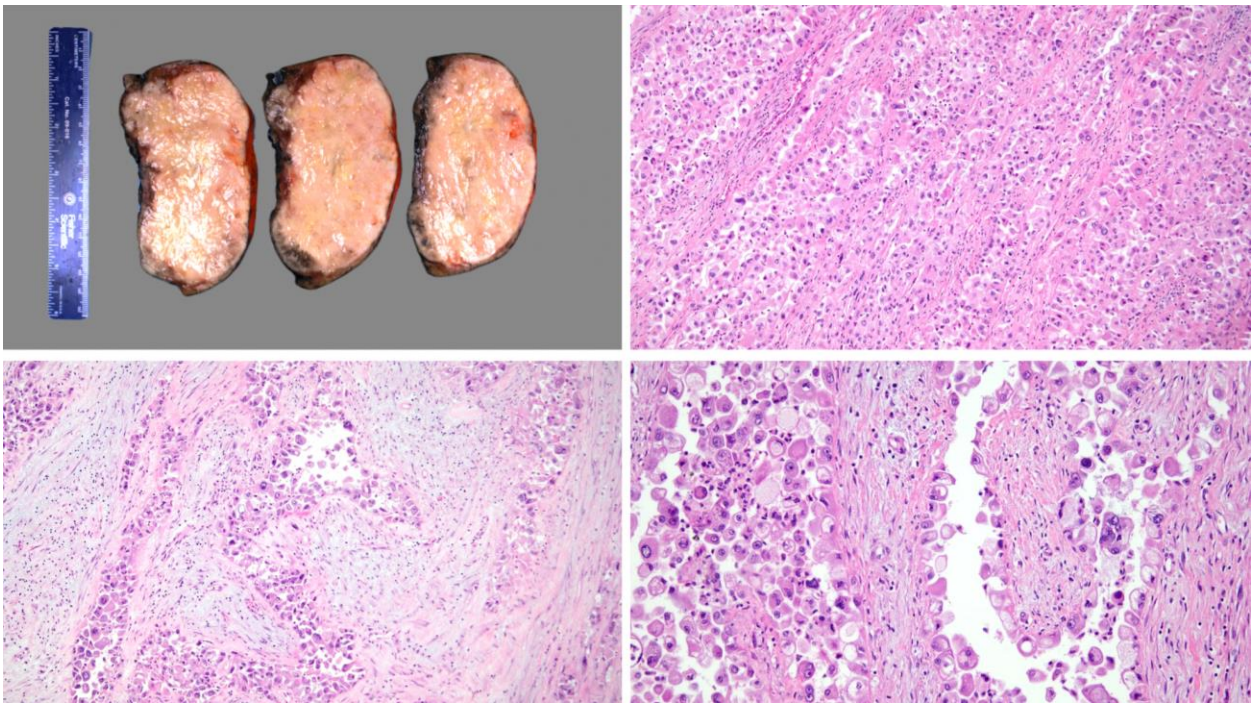
- Scirrhous hepatocellular carcinoma (S-HCC)
- Fibrolamellar hepatocellular carcinoma (FL-HCC)
- Intrahepatic cholangiocarcinoma (iCCA)
- Combined hepatocellular carcinoma-cholangiocarcinoma (cHCC-CCA)
- SMARCA4-deficient carcinoma
- SMARCB1-deficient carcinoma
- Carcinoma with other specific gene mutations
- Sarcoma with epithelioid morphologies (ASPS, rhabdomyosarcomas, and rhabdoid tumors)
- Metastatic carcinoma

Key features:

Histopathology: Serial sectioning of the right lobe revealed a single 13 x 12.4 x 7.2 cm well-circumscribed, homogenous, white-tan solid mass that abuts the hepatic capsule. Histological examination of the mass demonstrated polygonal to rhabdoid cells arranged in a poorly formed nest, tubular, and pseudo-alveolar patterns intersected by fibrotic bands of the desmoplastic stroma. The tumor cells are markedly pleomorphic and have abundant eosinophilic cytoplasm with fine vacuoles and prominent nucleoli. The background liver is non-cirrhotic as supported by trichrome and reticulin stains.

LOYOLA MEDICINE

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



Positive IHC	Negative IHC
CK7	ARG1
CK19	GPC3
BRG1 (retained)	HepPar1
INI1 (retained)	AFP
	BerEP4
	CA9-19
	CD68
	Polyclonal CEA
	GATA3

Discussion:

BRCA-1 Associated Protein (*BAP1*) is a deubiquitylase that is found both in the nucleus and the cytoplasm. The protein exerts its tumor suppressor effect through its role in transcription factor regulation, chromatin modification, double-strand DNA break repair, apoptosis, and ferroptosis. The *BAP1* gene is altered in a variety of tumors and is most commonly associated with malignant mesothelioma, uveal melanoma, cutaneous melanoma, and renal cell carcinoma. Recent publications have also shown *BAP1* gene mutations in a subset of hepatocellular carcinomas (HCCs), cholangiocarcinomas, and meningiomas. However, the literature on these BAP1 mutated hepatic malignant tumors is sparse due to their rarity.

It appears that the *BAP1*-associated cholangiocarcinomas present with similar morphology and immunophenotype to that of a classic cholangiocarcinoma. The literature on *BAP1*-associated HCC, to our best knowledge, is limited to one study by Hirsch and colleagues[5]. They described *BAP1* deficient HCCs to have an unusual clinical and morphologic presentation. These tumors mimic the rare fibrolamellar variant of hepatocellular carcinoma (FL-HCC) architecturally with desmoplastic stroma arranged in a lamellar pattern. Similar to FL-HCC, patients with BAP1 deficient tumors often have no known underlying etiologies of HCC and their background liver is typically non-fibrotic. Cytologically, *BAP1* deficient hepatic tumors have large, polygonal cells with abundant amphophilic or eosinophilic cytoplasm as described in other BAP1 mutated carcinomas. The immunoprofile of *BAP1* deficient HCC however is not discussed.

Our tumor exhibits similar clinical and morphologic features to the *BAP1* deficient HCCs described by Hirsch and colleagues, yet all of the HCC immunohistochemistry markers are negative in our case. The tumor stained diffusely positive for CK7 and CK19 but is completely negative for other cholangiocarcinoma markers including BerEP4, CEA, and CA19-9. Therefore, it is difficult to classify this tumor as HCC or cholangiocarcinoma based on current publications. The final diagnosis of a *BAP1* deficient hepatic carcinoma is rendered after careful correlation and consideration.

We believe that the *BAP1* gene mutation is the primary driver of our tumor based on the tumor's monotonous morphology, limited genetic abnormalities on next-generation sequencing, and unremarkable non-neoplastic background liver. Unlike other confirmed *BAP1*-associated tumors, there are currently no established treatment guidelines for *BAP1*-deficient hepatic carcinoma. These tumors are aggressive and associated with a poor prognosis.

Our patient does not have any other *BAP1*-associated tumors, making the presence of a germline mutation of BAP1 unlikely. Individuals with two or more *BAP1*-associated tumors may have *BAP1* Tumor Predisposition Syndrome *(BAP1*-TPDS*)*, which is established by the presence of heterozygous germline mutation of *BAP1* via molecular testing. The penetrance of *BAP1-TPDS* appears to be high and vigilant surveillance is recommended starting at a young age in affected patients since these tumors present earlier than in the general population. There are several ongoing trials for individuals with somatic *BAP1* pathogenic variants in progress, including *PARP* inhibitor therapies as single or combination therapies.

Take Home Points:

- Consider *BAP1* deficient tumor in a hepatic primary tumor with eosinophilic polygonal cells arranged in fibrolamellar hepatocellular carcinoma-like arrangement
- *BAP1* deficient hepatic carcinoma can possibly be a less common manifestation of the *BAP1* Tumor Predisposition Syndrome (*BAP1*-TPDS)
- These tumors are aggressive and are associated with poor prognosis
- Although there is no current *BAP1* targeted therapy, there are several ongoing trials for individuals with somatic *BAP1* mutation

References:

1. Carbone M, Harbour JW, Brugarolas J, Bononi A, Pagano I, Dey A, Krausz T, Pass HI, Yang H, Gaudino G. Biological Mechanisms and Clinical Significance of *BAP1* Mutations in Human Cancer. Cancer Discov. 2020 Aug;10(8):1103-1120. doi: 10.1158/2159-8290.CD-19-1220. Epub 2020 Jul 20. PMID: 32690542; PMCID: PMC8006752.
2. Gallan AJ, Parilla M, Segal J, Ritterhouse L, Antic T. BAP1-Mutated Clear Cell Renal Cell Carcinoma. Am J Clin Pathol. 2021 Apr 26;155(5):718-728. doi: 10.1093/ajcp/aqaa176. PMID: 33210135.
3. Louie BH, Kurzrock R. BAP1: Not just a BRCA1-associated protein. Cancer Treat Rev. 2020 Nov;90:102091. doi: 10.1016/j.ctrv.2020.102091. Epub 2020 Aug 20. PMID: 32877777; PMCID: PMC7655689.
4. Pilarski R, Carlo MI, Cebulla C, et al. BAP1 Tumor Predisposition Syndrome. 2016 Oct 13 [Updated 2022 Mar 24]. In:Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022.
5. Theo Hirsch, Ana Negulescu, Barkha Gupta, Stefano Caruso, Bénédicte Noblet, et al.. BAP1 mutations define a specific subgroup of hepatocellular carcinoma with fibrolamellar features and PKA activation Short title: BAP1 HCC have FLC features and activate PKA. Journal of Hepatology, 2019.
6. Zhang AJ, Rush PS, Tsao H, Duncan LM. BRCA1-associated protein (BAP1)-inactivated melanocytic tumors. J Cutan Pathol. 2019 Dec;46(12):965-972. doi: 10.1111/cup.13530. Epub 2019 Jul 11. PMID: 31233225.

Case #5

Presenter: Elnaz Panah
Attending: Xiuzhen Duan, MD, Ph.D.; Xianzhong Ding, MD, Ph.D.

Case history: A 69-year-old woman presented to the LUMC clinic with postmenopausal bleeding. An MRI of the pelvis demonstrated a polypoid lesion at the endometrial fundus.

Endometrial and endocervical biopsies were performed. An H&E slide from the endometrial biopsy is provided for review. (Scanned slide only).

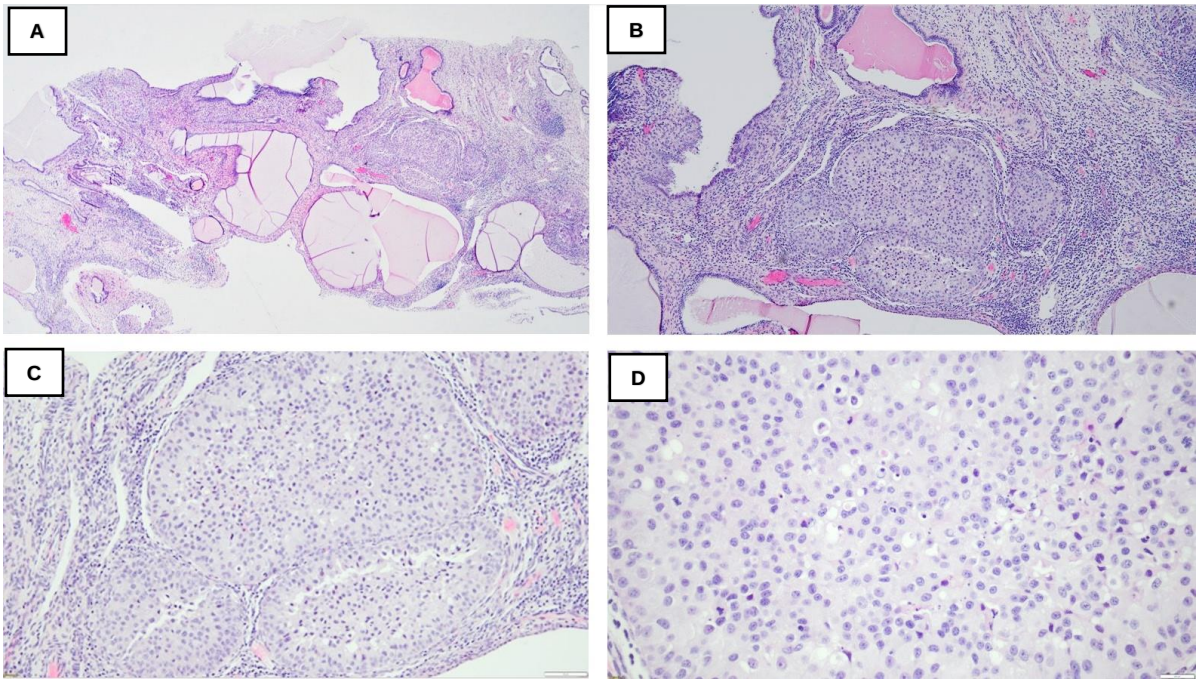
Final Diagnosis: Extramammary Paget disease metastatic to endometrium

Differential Diagnosis:

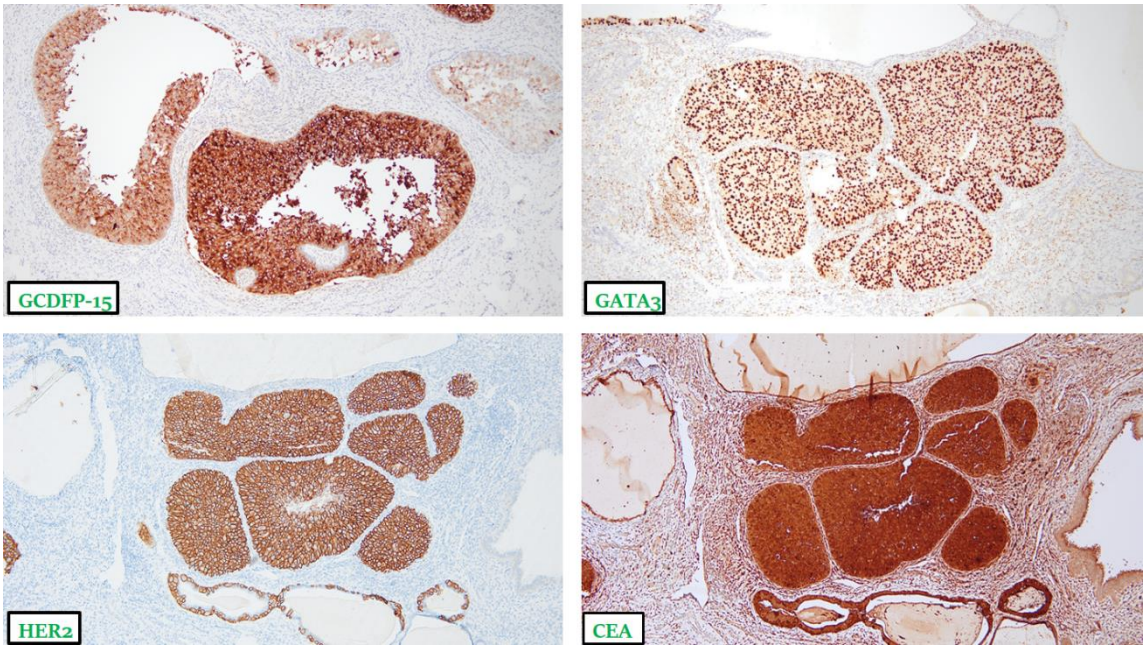
- Endometrium Cancer
  - Endometrioid adenocarcinoma
  - Clear cell carcinoma
- Cervical cancer:
  - Squamous cell carcinoma
  - Stratified Mucin-producing Intraepithelial Lesion (SMILE)
  - HPV dependent endocervical adenocarcinoma
  - HPV independent endocervical adenocarcinoma
- Metastatic Malignancy:
  - Breast, GI, Melanoma, others

Key Features:

Histopathology: Endometrial and endocervical biopsies revealed malignant cells in small solid nests and single cells infiltrating within the endometrial and endocervical stroma, associated with ulceration and hemorrhage. Tumor cells demonstrate an enlarged nucleus, prominent nucleoli, and occasional intracytoplasmic mucin. (Figure A-D, H&E). Results of the immunohistochemistry are listed in the table and figures below.



Positive IHC	Negative IHC
CK7	PAX8
Mucicarmine	ER
	PR
	p16
	P53 (wild)
	P63
	SOX10



Discussion:

Extramammary Paget disease (EMPD) was described as an intraepithelial adenocarcinoma by Radcliffe Crocker in 1889 (1). It is an uncommon disease involving anogenital areas such as the vulva, anus, scrotum, and penis, and less common in the face, axilla, buttock, and thigh (2). Most cases are seen in postmenopausal Caucasian women and Asian men around age 65 (1, 2). Metastasis of extramammary Paget disease is not common, which is associated with a higher grade of the disease with a poor prognosis (4). The most common sites of metastasis are lymph nodes, visceral organs, and the brain (5). Early diagnosis and treatment can be helpful to prevent metastasis (3).

Our patient presented at LUMC with an endometrial lesion and we later knew that she was diagnosed of extramammary Paget disease in the vulva 14 years ago at an outside institution. The histopathologic and immunohistochemistry features of her endometrial tumor were

originally considered metastatic breast cancer and the diagnosis of extramammary Paget disease was established after breast cancer was excluded by a clinical and radiologic workup.

Metastatic extramammary Paget disease to the endometrium is rare. To the best of our knowledge, only two cases of endocervical metastasis of extramammary Paget disease have been previously reported; one with concurrent invasive vulvar adenocarcinoma and the second case with multiple vulvar excisions with positive surgical margins; none showed invasive adenocarcinoma and the endometrium involvement reported as contamination of the endocervix (6).

The current case report demonstrates a rare clinical and pathologic presentation of extramammary Paget disease with endometrial and endocervical metastasis and shows the importance of clinical history in the correct diagnosis and treatment plan.

Our case is unique because on review of clinical history, the original diagnosis of Paget disease in this patient was confined to the epidermis without any invasion but later it was found to have metastasis to the endometrium. It is controversial that if primary extramammary Paget disease without invasion can be metastasis and further investigation is needed.

Take Home Points:

- If immunohistochemistry stains of a tumor point to metastatic breast cancer, and there is no breast history, think about extramammary Paget disease
- Primary extramammary Paget disease of the vulva, metastasis to the endocervix and endometrium are extremely rare
- Primary extramammary Paget disease of the vulva without invasion can be metastatic

References:

1. Simonds RM, Segal RJ, Sharma A. Extramammary Paget's disease: a review of the literature. Int J Dermatol. 2019;58(8):871 9.
2. 2. Ito T, Kaku-Ito Y, Furue M. The diagnosis and management of extramammary Paget's disease. Expert Rev Anticancer Ther .2018; 18(6):543 53.
3. KosmidisCS, SevvaC, RouliaP, Koulouris C, VarsamisN, KoimtzisG, et al. Extramammary Paget's Disease of the Vulva: Report of Two Cases. Medicina(Kaunas). 2021;57(10).
4. 4. Fernandes L, GracaJ, de Matos LV, Sampaio R, BaleirasMM, Ferreira F, et al. Metastatic extramammary pagetdisease, a remarkable clinical case and a brief review of a rare disease. Dermatol Reports. 2020;12(2):8841.
5. AselM, LeBoeufNR. Extramammary Paget's Disease. HematolOncol Clin North Am. 2019;33(1):73-85.
6. Clayton EF, Rubin SC, Dumoff KL. Paget Cells in Endometrial and Endocervical Curettings in a Patient With Recurrent Vulvar Paget's Disease. Int J Surg Pathol. 2014 Jun;22(4):374-7. doi: 10.1177/1066896913498819. Epub 2013 Aug 5. PMID: 23918905.

LOYOLA MEDICINE

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

Case #6
Presenter: Constantine E. Kanakis, MD MSc
Attendings: Kamran Mirza, MD Ph.D.

Clinical History: A 31-year-old male with a past medical history of congenital hydrocephaly and longstanding history of an indwelling ventriculoperitoneal shunt placed over twenty years prior who is status-post numerous revisions beginning shortly after shunt placement. Additionally, he had a notable, prominent bilateral subdural hemorrhage and hematoma status-post evacuation over fifteen years prior to a presentation that demonstrated chronicity and calcification on imagining. He had numerous neurological complications including tongue numbness and chronic baseline hyponatremia. The patient presented to an outside hospital with worsening headache, vomiting, and ataxia. A new, distinct cerebellar mass was noted on imaging. A subsequent neuropathology frozen section was performed. (Digitally scanned slides provided)

Final Diagnosis:
CD20-negative Diffuse Large B-Cell Lymphoma associated with chronic inflammation (CI-DLBCL)

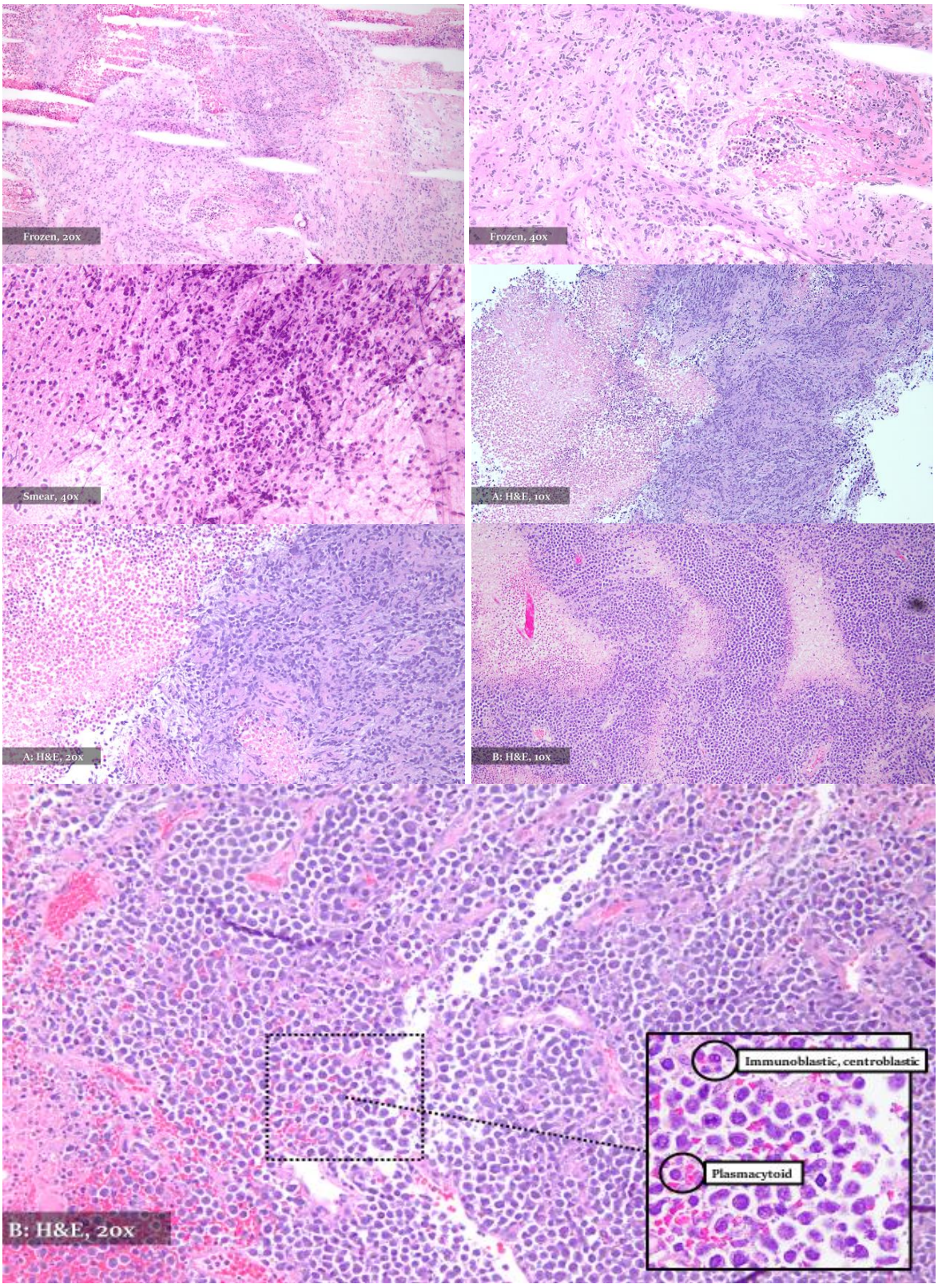
Differential Diagnosis:

● Peripheral T-cell lymphoma	PTCL, NOS
● ALK-negative Anaplastic Large Cell Lymphoma	ALK-, ALCL
● Primary Effusion Lymphoma	PEL
● Plasma cell neoplasm (and extramedullary plasmacytoma)	PCN (including EMP)
● Plasmablastic lymphoma	PBL
● Lymphomatoid granulomatosis	LG
● Diffuse, Large B-cell lymphoma	DLBCL, and other subtypes

Key Features:
Histology: Histologic examination of the biopsied cerebellar tissue showed large areas of necrosis with large, atypical cells with hyperchromatic nuclei. The background neuropil was somewhat cellular, but otherwise unremarkable. The infiltrative tumor cells ranged from small to large with somewhat bizarre, atypical nuclear features. Some cells had distinct borders while others did not; there were large areas of admixed necroinflammatory debris. The frozen smear slide demonstrated infiltrative cells with large nuclei in a background of lymphocytic crushed artifacts. Scant neuronal tissue was present. On higher power, the infiltrative tumor cell population appeared to have features focally reminiscent of plasmacytoid, immunoblastic/centroblasts, and anaplastic morphology.

LOYOLA MEDICINE

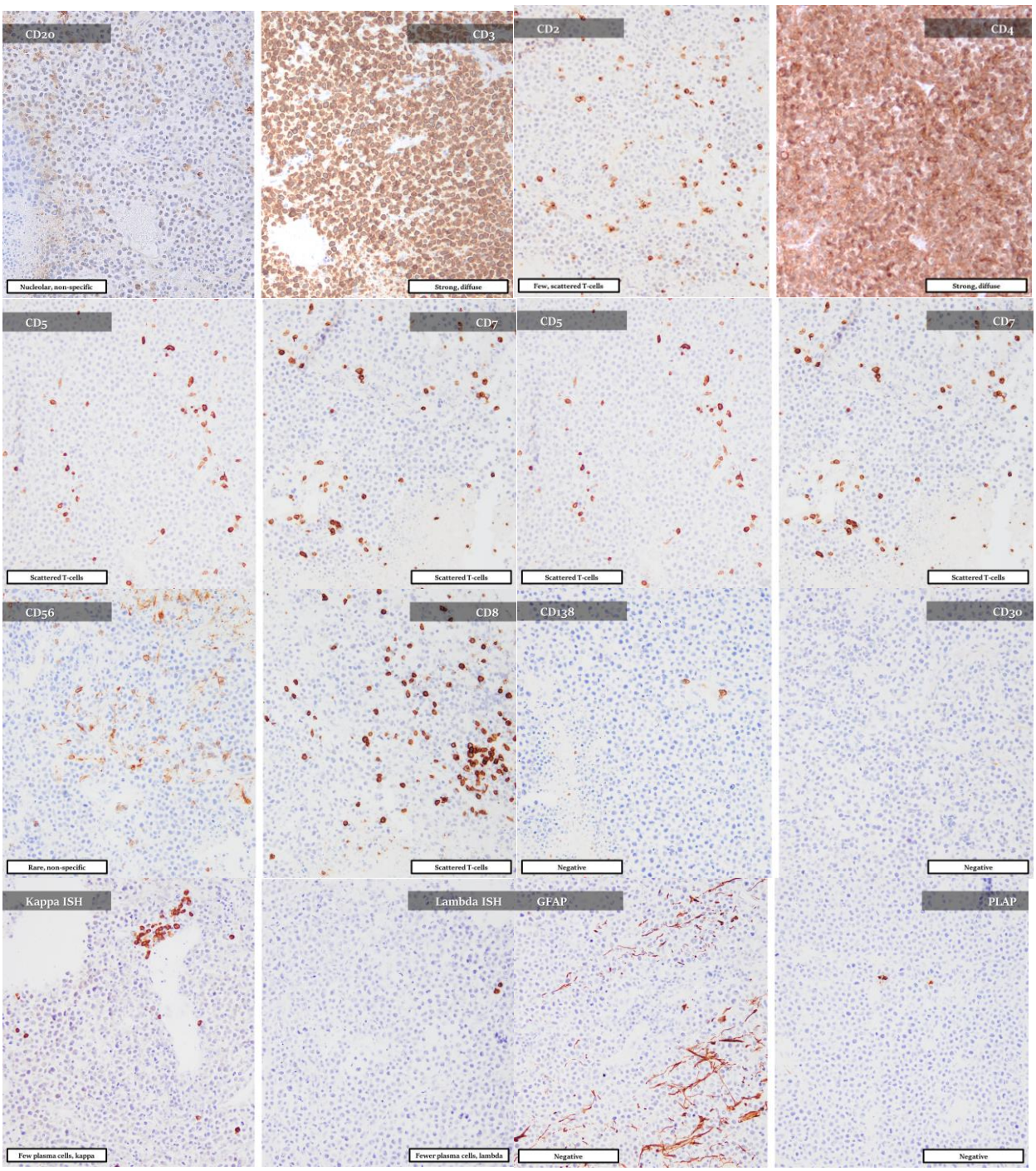
Department of Pathology and Laboratory Medicine
Loyola University Health System
2160 S. First Ave., Maywood, IL 60153



LOYOLA MEDICINE

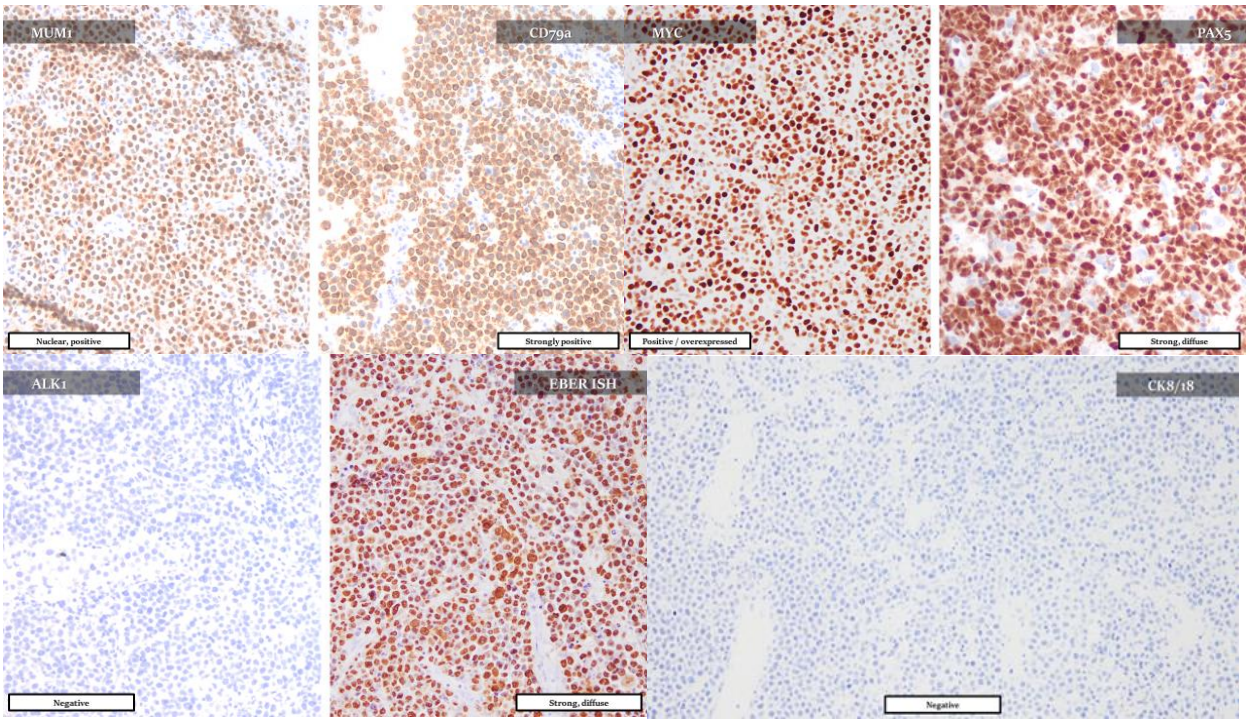
Department of Pathology and Laboratory Medicine
Loyola University Health System
2160 S. First Ave., Maywood, IL 60153

Immunohistochemical staining patterns of the tumor cells revealed nonspecific, nucleolar CD20 (considered negative), strong positivity CD3 and CD4, and negativity for CD138, CD2, CD5, CD7, CD8, CD56, CD34, ALK1, CD30, HHV8 (by previous records), PLAP, GFAP, Cytokeratin 8/18. Additional studies showed positivity for PAX5, CD79a, MUM1, EBER-ISH, scant, focal kappa and lambda ISH, as well as cMyc.



LOYOLA MEDICINE

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

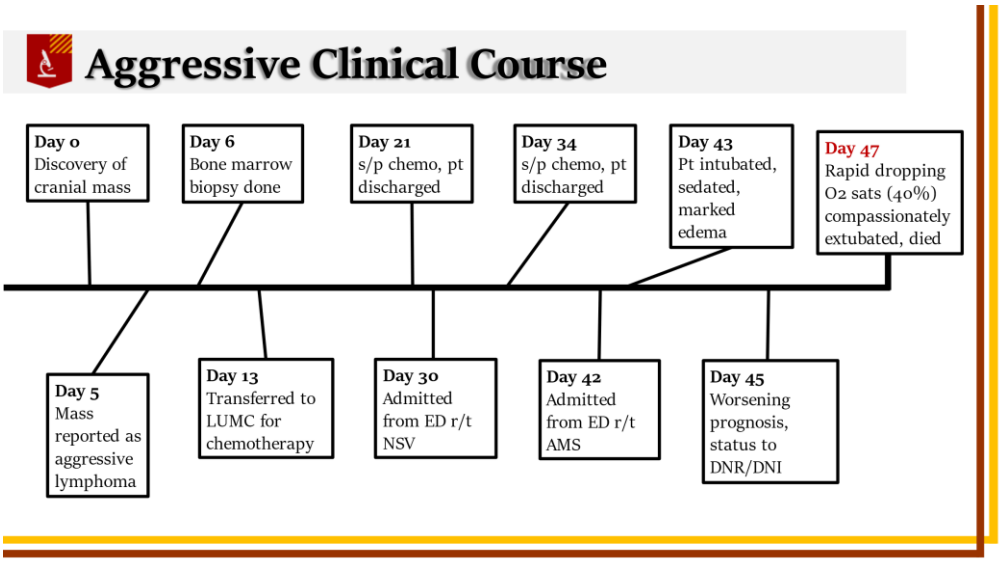


Discussion:

In the eventual final differential diagnosis of large B-cell lymphomas with plasmacytic morphology, especially those which match numerous phenotypic characteristics as seen in our case, a short list includes extramedullary plasmacytoma, plasmablastic lymphoma, primary effusion lymphoma, and fibrin-associated or diffuse large B-cell lymphoma associated with chronic inflammation. Extramedullary plasmacytoma did not match this patient's clinical history and presentation, and commonly associated findings were absent (i.e. clonal plasma cells, CRAB signs/symptoms). Plasmablastic lymphoma was also considered, however lacking similar clinical features along with PAX5 negativity, this was ruled out. Primary effusion lymphoma lacked the lymphomatous serous effusions commonly seen in this entity, and HHV8 positivity made this less likely. Distinguishing between fibrin-associated and chronic inflammation-associated DLBCLs is both clinically apparent in aggressiveness and course along with *MYC* expression. DLBCL associated with chronic inflammation (DLBCL-CI) met all the criteria to match our patient and this was the final diagnosis. Our case featured large, atypical lymphocytes with plasmacytoid morphology in areas of necrosis throughout the biopsy tissue. With the exception of CD20 most B cell lineage markers were strongly expressed along with EBV positivity. The loss of CD20 can be seen with plasmacytic differentiation in CD3 can be aberrantly expressed in this entity. Follow-up testing for B cell clonality came back showing positive rearrangements in the immunoglobulin Kappa and heavy chain showing definitive proof of B cell lineage. All of these features along with the aggressive clinical course seen below support the above diagnosis.

LOYOLA MEDICINE

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



In the traditional diagnostic algorithm for EBV-positive CD20 negative lymphomas, the algorithm tends towards the diagnosis of plasmablastic lymphoma or EBV-positive plasmacytoma—these were ruled out because of PAX5 and *MYC* expression. CI-DLBCL is a distinct entity in the WHL 5th edition. It is an EV-driven large B cell lymphoma occurring in the context of chronic inflammation happening in potential spaces whether acquired or congenital it was previously associated with pyothorax-related large B cell lymphoma but exists now as a separate diagnosis. Recent case reports show an association with chronic or indwelling implants and it is staged as traditional lymphomas are according to the Lugano staging criteria. Both The Who and the international consensus conference establish that for the diagnosis to be made these large B cell lymphomas must occur within the context of chronic inflammation and have B cell lineage lymphocytes which are the malignant cells. EBV positivity should be there however other EBV-positive lymphomas must be ruled out. Numerous cases in the literature report this entity arising in long-standing or slow-growing lesional areas associated with chronic inflammation and EB and have been reported in false cysts, hydroceles, myxomas, and metallic implant or other foreign devices.

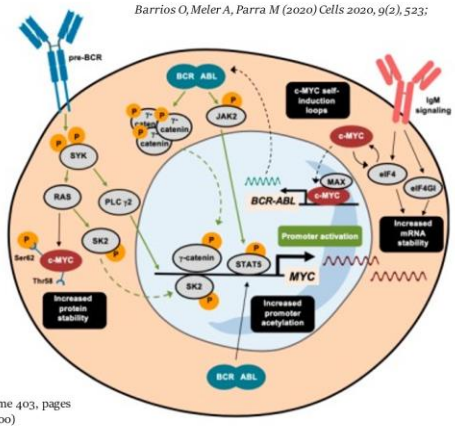
MYC and B-cell Lymphomagenesis

- Immune privileged areas, (i.e., less cytotoxic T-cells)
- EBV+ latent B-cells proliferate into a clonal population
    1. Overexpressed *MYC*
    2. Increased IL6, IL10
    3. Expression of BLC2

Farrell PJ (2019). "Epstein–Barr Virus and Cancer". Annual Review of Pathology. 14: 29-53.

- EBV driven changes to clonal lymphocytes produces a DLBCL with "activated B-cells" → aggressive *Nature* volume 403, pages 503–511 (2000)

Barrios O, Meler A, Parra M (2020) Cells 2020, 9(2), 523;



The combination of the immune privileged areas where this lymphoma arises and the EBV positivity translate to a lymphoma genesis mediated by infected B cell overgrowth. These EBV-positive B cells overexpress *MYC* have increased interleukins (i.e. IL6 and IL10), an overexpressed BCL2 gene—which are all pro-proliferative and anti-apoptotic leading to an aggressive activated B cell lymphoma.

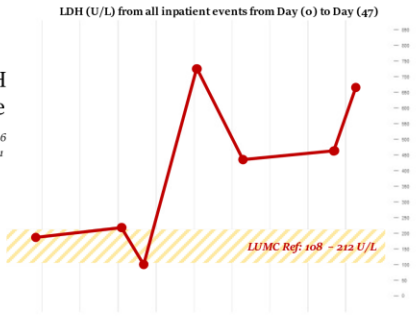
CI-DLBCL Prognostics

- 5 year overall survival (OS) in CI-DLBCL related to PAL is 20-35%
- Poor performance status, uptrending LDH levels, and clinical staging are unfavorable

Ann Oncol. 2007 Jan;18(1):122-128. doi: 10.1093/annonc/mdl349. Oct 16
J Clin Oncol. 2002 Oct 15;20(20):4255-60. doi: 10.1200/JCO.2002.09.021

Our patient's prognostic data:

LDH:	**189 to 669 U/L**
Lugano:	**IV, brain**
Zubroad:	**4, total disability**
Tumor cells:	**Activated B-cells**



While most prognostic data is related to pyothorax-associated lymphomas certain aspects of clinical and laboratory-derived data are of prognostic value in the clinical staging of CI-DLBCL.

Take-home Points:

- CD20- B-cell lymphoma is difficult to classify due to the loss of CD20

- **Proof of B-cell lineage, hx of chronic inflammation is critical**
- Loss of CD20 occurs with plasmacytoid differentiation
- Aberrant CD3 expression has been reported
- Malignant cell of origin: activated B-cell, aggressive prognostically
- Previously provisional (2010), then part of PAL, then expanded/provisional (2017), and now discreet entity by both WHO Heme 5 and ICC 2022
- PBL vs DLBCL, NOS vs FA-DLBCL/DLBCL-CI receive similar treatment regimens
-

References:

1. Histopathology. 2015 Aug;67(2):225-34.
2. WHO Classification of Tumours Editorial Board. Haematolymphoid tumours. Lyon (France): International Agency for Research on Cancer; 2022 . (WHO classification of tumours series, 5th ed.; vol. 11)
3. International Consensus Classification Blood 2022;140:1229
4. Barrios O, Meler A, Parra M (2020) Cells 2020, 9(2), 523;
5. Farrell PJ (2019). "Epstein–Barr Virus and Cancer". Annual Review of Pathology. 14: 29–53.
6. Nature volume 403, pages503–511 (2000)
7. Ha A, Choi Y, Kim SJ, et al (2011) The Korean Journal of Pathology; 45: 417-422
8. Loong F, Chan A, Ho B, et al (2010) Mod Pathol. Apr;23(4):493-501.
9. Mescum L, Camus V, Schiano JM, et al (2020) Blood. 135 (22): 2004–2009.
10. Ann Oncol. 2007 Jan;18(1):122-128. doi: 10.1093/annonc/mdl349. Oct 16
11. J Clin Oncol. 2002 Oct 15;20(20):4255-60. doi: 10.1200/JCO.2002.09.021
12. ClinicalTrials.gov

@loyolapathology | @CEKanakisMD | @ElnazPanah | @Thanchanok_Chai | @AKontosisMD | @AlhalasehY |
| @jason_y_zhu | @vijuananthan | @KMirza | @ewa_borys | @JJSpeiserMD |