DEC 2021 DIAGNOSIS LIST

21-1201: VEXAS syndrome (bone marrow; hematopathology)
21-1202: perineurioma (soft tissue; soft tissue path)
21-1203: Bruner gland hamartoma (small bowel; GI path)
21-1204: angiomatous fibrous histiocytoma (soft tissue; soft tissue path)
21-1205: malignant giant cell tumor (bone; soft tissue path)
21-1206: EWSR1-TFCP2 rearranged sarcoma of bone, c/w sclerosing intraosseous epithelioid rhabdomyosarcoma (bone; soft tissue path)
21-1207: malignant poorly differentiated neoplasm, favor osteosarcoma (spinal cord; soft tissue path)

Disclosures
December 6, 2021

Dr. Brent Tan has disclosed a prior (now ended) financial relationship (consultant) with Blueprint Pharmaceuticals. Dr. Bonnie Balzer has disclosed financial relationships (related to testing and research) with Castle Biosciences, PathologyWatch and Core Diagnostics. South Bay Pathology Society has determined that these relationships are not relevant to the clinical cases being presented; additionally, those portions of the presentation have been reviewed and determined to be free of bias. None of the other planners and faculty listed below for this educational activity have relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Presenters/Faculty:

Phoebe Hammer, MD
Dita Gratzinger, MD, PhD
Andrew Bandy, MD
Diane Libert, MD
Amanda Borgen MD
Yue Peng, MD
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Activity Planners/Moderator:

Kristin Jensen, MD
Megan Troxell, MD, PhD
Ankur Sangoi, MD
David Bingham, MD

21-1201

Phoebe Hammer/Dita Gratzinger/Brent Tan; Stanford

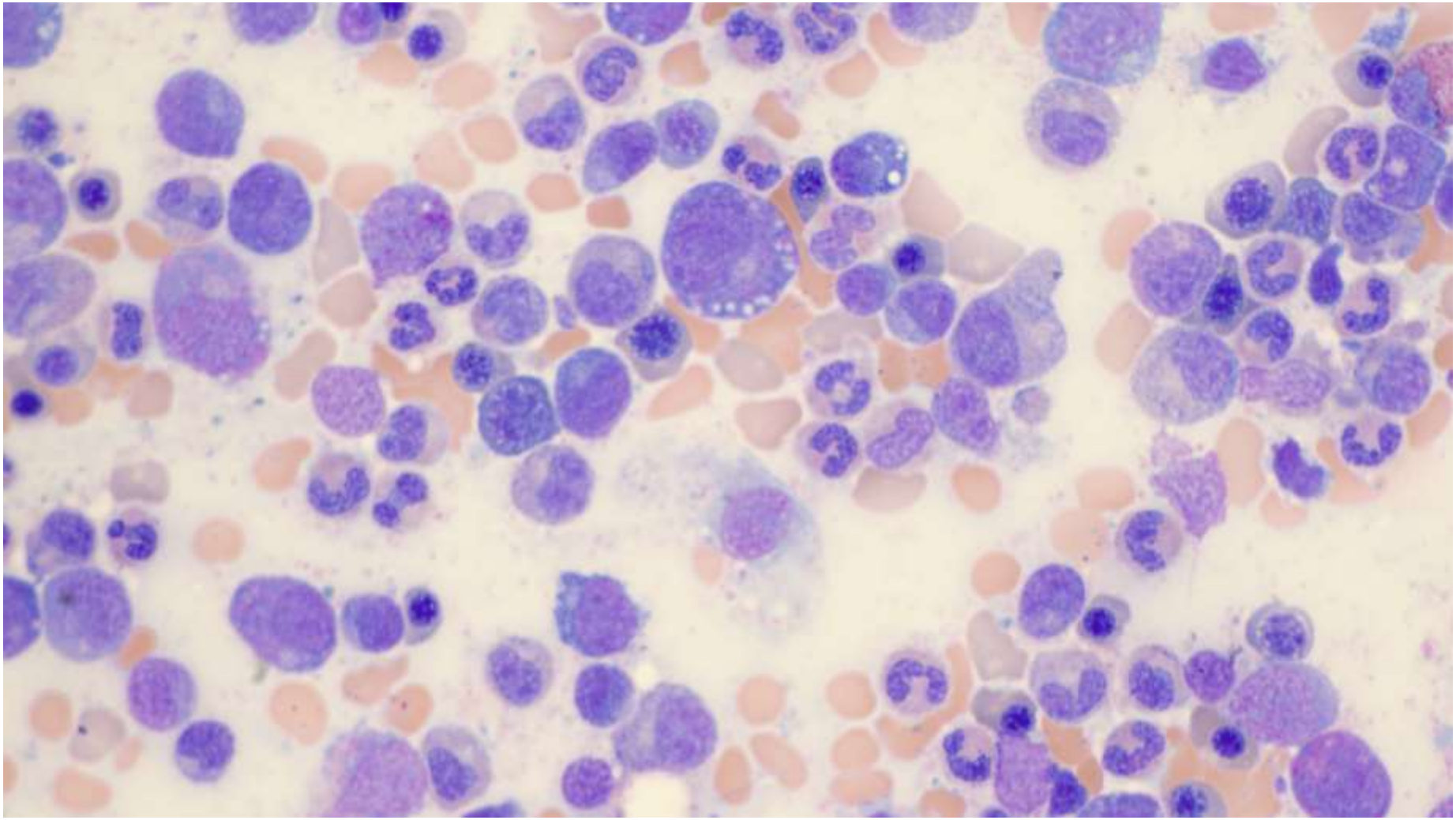
69-year-old M presenting with a 10-year history of worsening episodic fevers, night sweats, extreme fatigue, joint pain, pulmonary nodules, and painful skin rash. Biopsy of rash showed neutrophilic dermatosis, favor Sweet Syndrome. Symptoms improve with high-dose prednisone but return after taper of steroids.

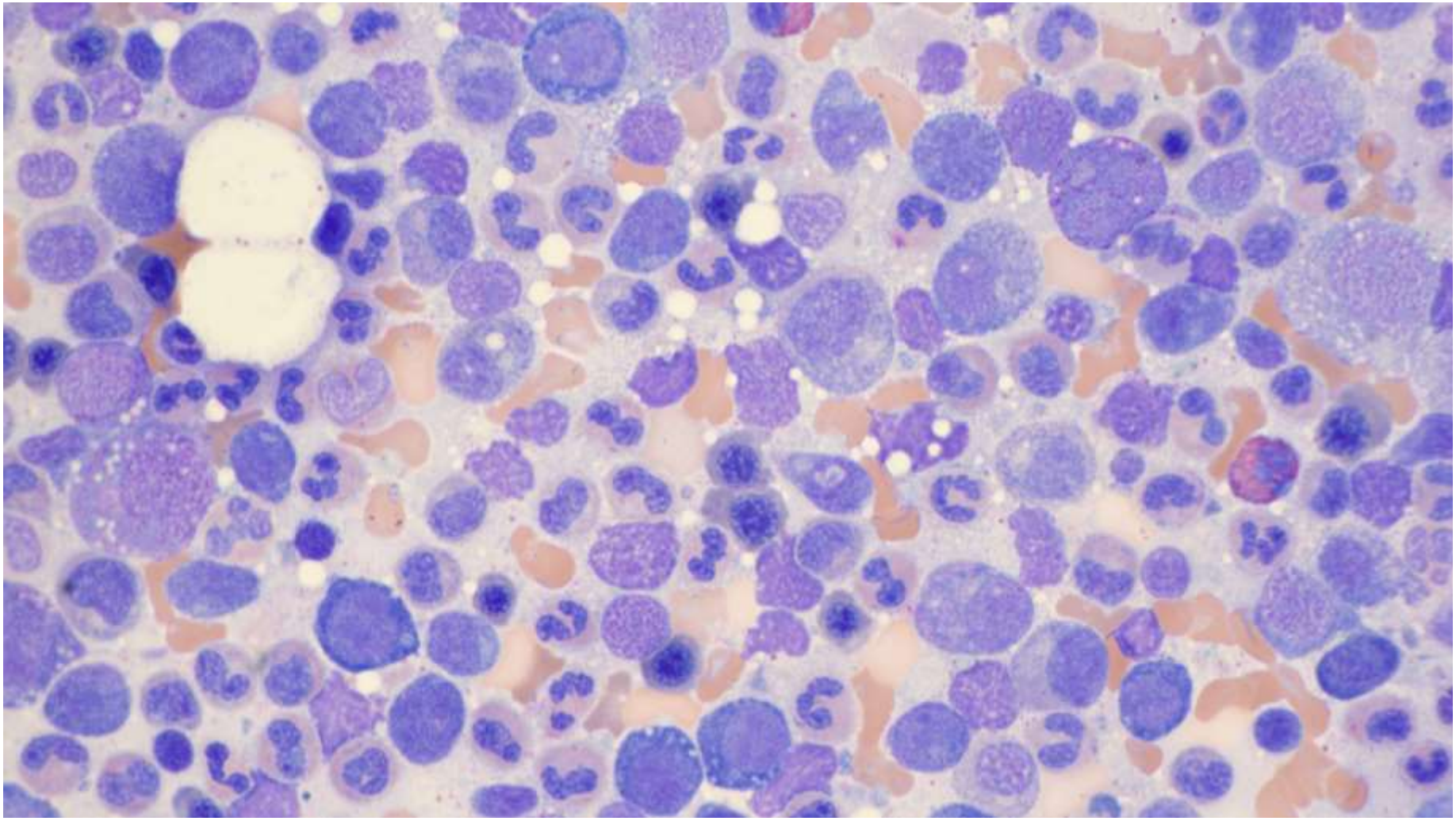
Labs

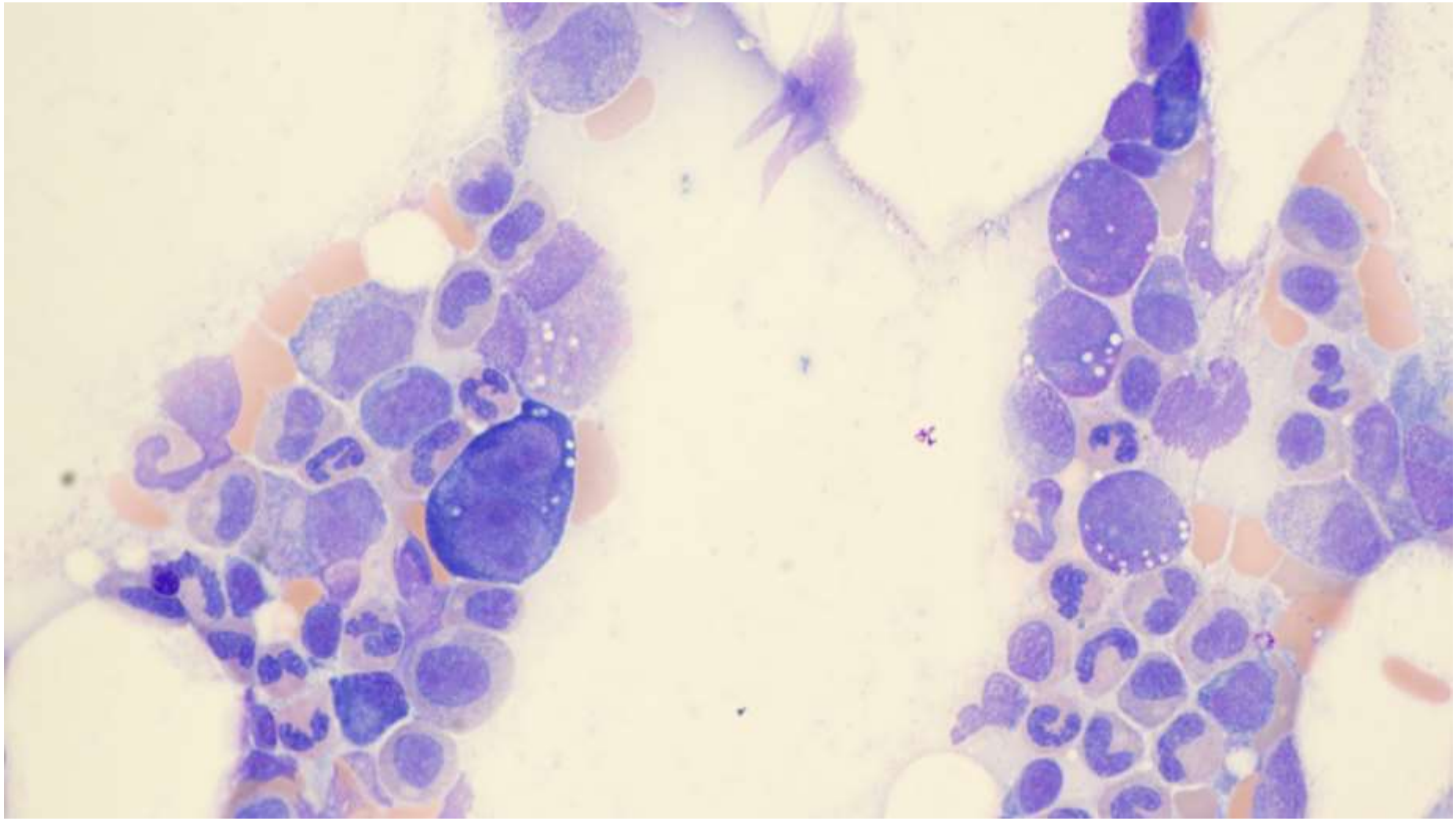
WBC	3.3 (L)
Hemoglobin	13.3 (L)
Hematocrit	40.0
Platelet count	128 (L)
MCV	114.3 (H)
RDW	13.4
RBC	3.5 (L)
MCH	38.0 (H)
MCHC	33.3
Lymphocytes, ABS	0.58 (L)
Monocytes, ABS	0.0 (L)

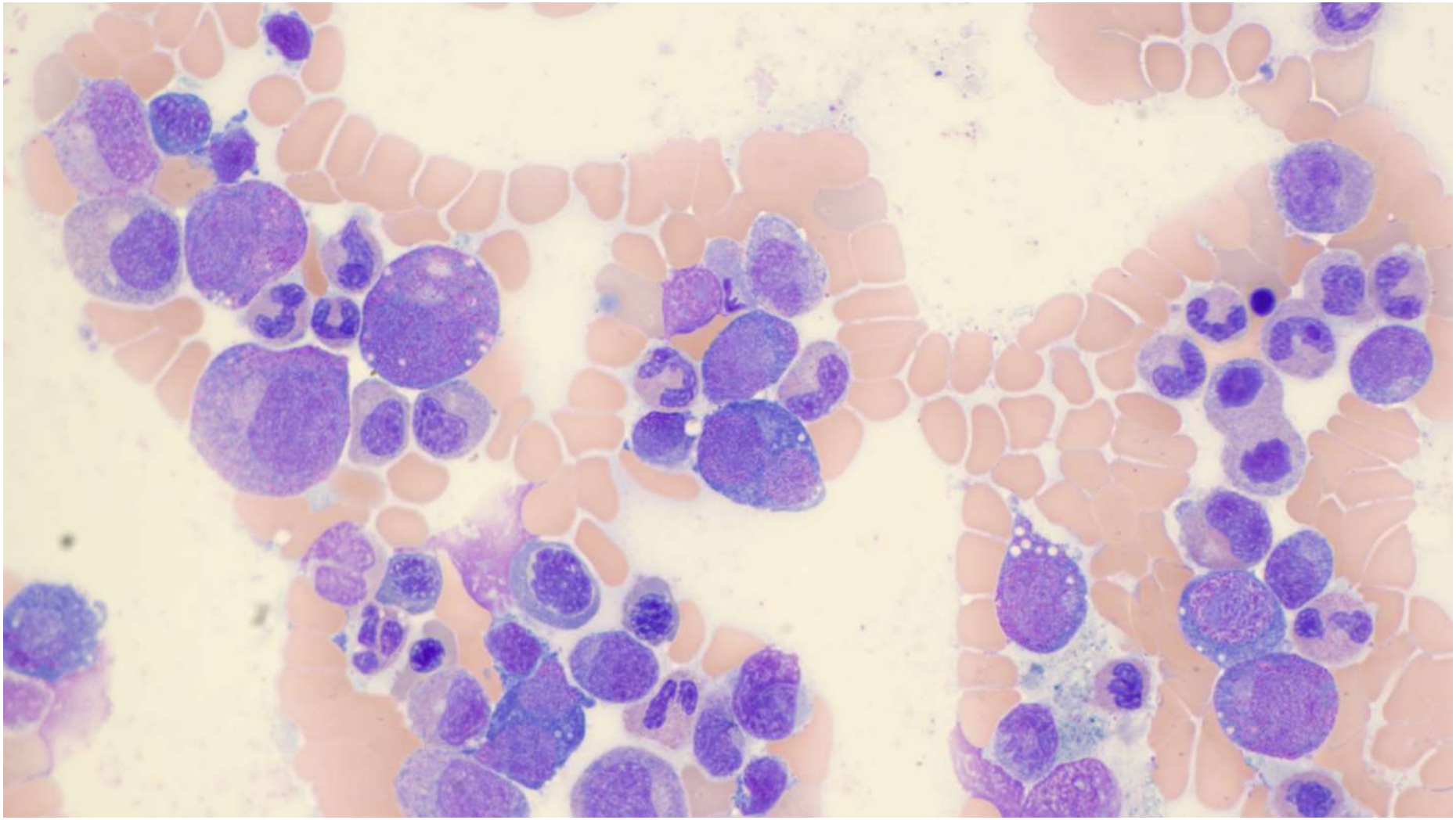
Normochromic macrocytic anemia
Mild thrombocytopenia
Lymphopenia
Monocytopenia

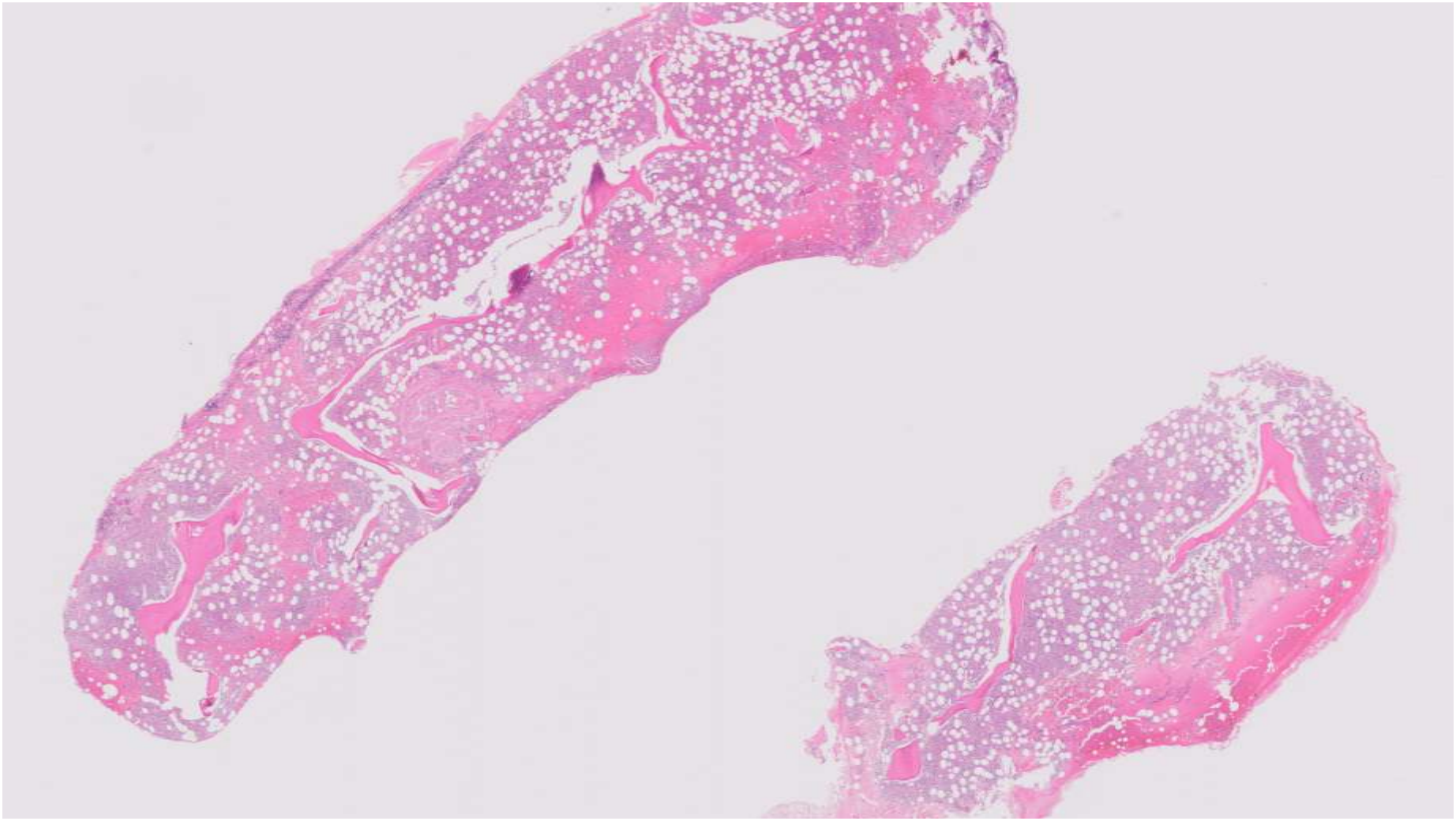
Bone marrow biopsy performed

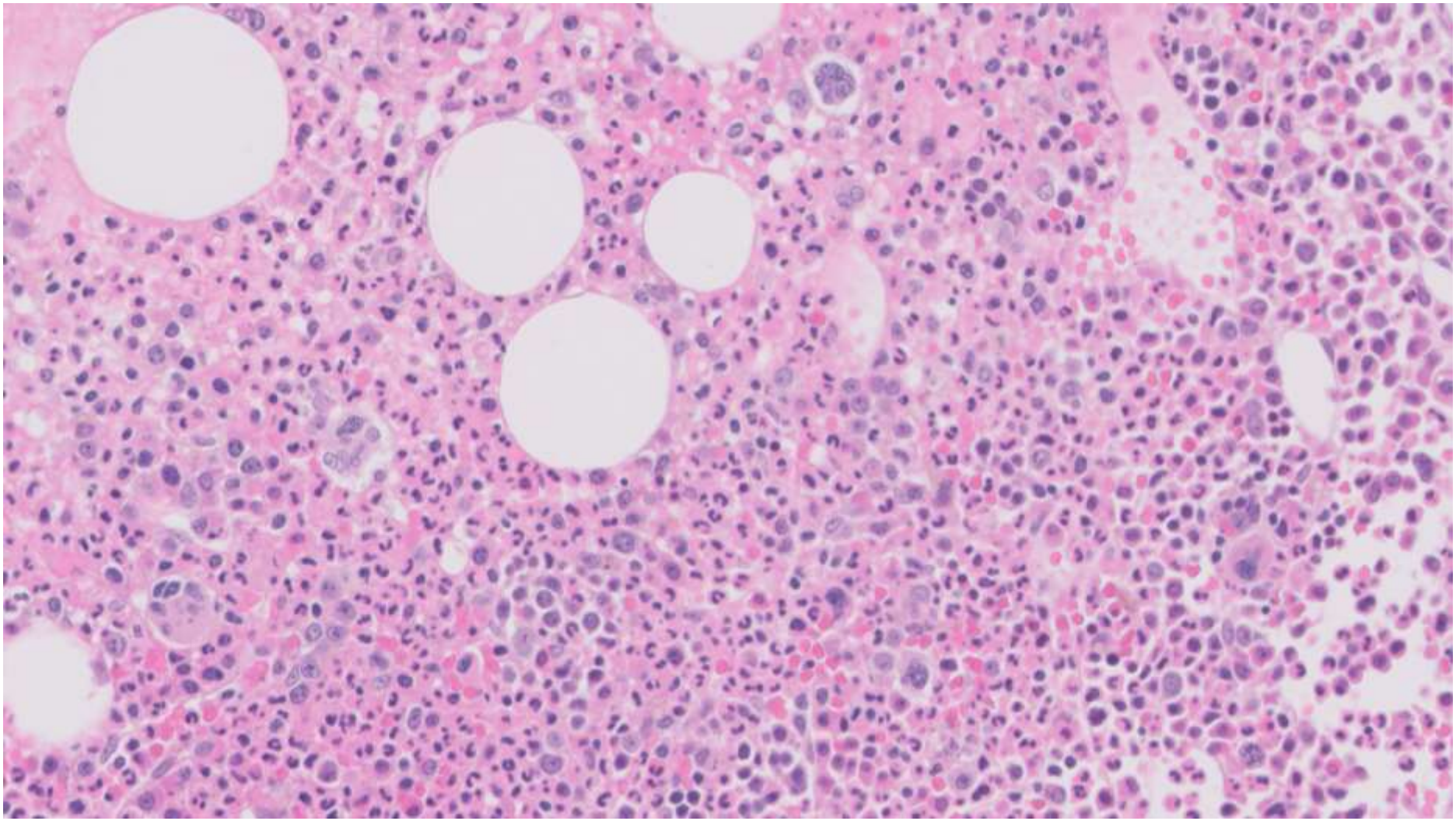












DDX

Vacuoles in bone marrow myeloid / erythroid precursors:

- Myelodysplastic syndrome
- Acute leukemias
- Alcohol use disorder
- Copper deficiency
- Zinc toxicity
- Heavy metal toxicity
- VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome

Answer:
VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Somatic Mutations in *UBA1* and Severe Adult-Onset Autoinflammatory Disease

D.B. Beck, M.A. Ferrada, K.A. Sikora, A.K. Ombrello, J.C. Collins, W. Pei, N. Balanda, D.L. Ross, D. Ospina Cardona, Z. Wu, B. Patel, K. Manthiram, E.M. Groarke, F. Gutierrez-Rodrigues, P. Hoffmann, S. Rosenzweig, S. Nakabo, L.W. Dillon, C.S. Hourigan, W.L. Tsai, S. Gupta, C. Carmona-Rivera, A.J. Asmar, L. Xu, H. Oda, W. Goodspeed, K.S. Barron, M. Nehrebecky, A. Jones, R.S. Laird, N. Deuitch, D. Rowczenio, E. Rominger, K.V. Wells, C.-C.R. Lee, W. Wang, M. Trick, J. Mullikin, G. Wigerblad, S. Brooks, S. Dell'Orso, Z. Deng, J.J. Chae, A. Dulau-Florea, M.C.V. Malicdan, D. Novacic, R.A. Colbert, M.J. Kaplan, M. Gadina, S. Savic, H.J. Lachmann, M. Abu-Asab, B.D. Solomon, K. Retterer, W.A. Gahl, S.M. Burgess, I. Aksentijevich, N.S. Young, K.R. Calvo, A. Werner, D.L. Kastner, and P.C. Grayson

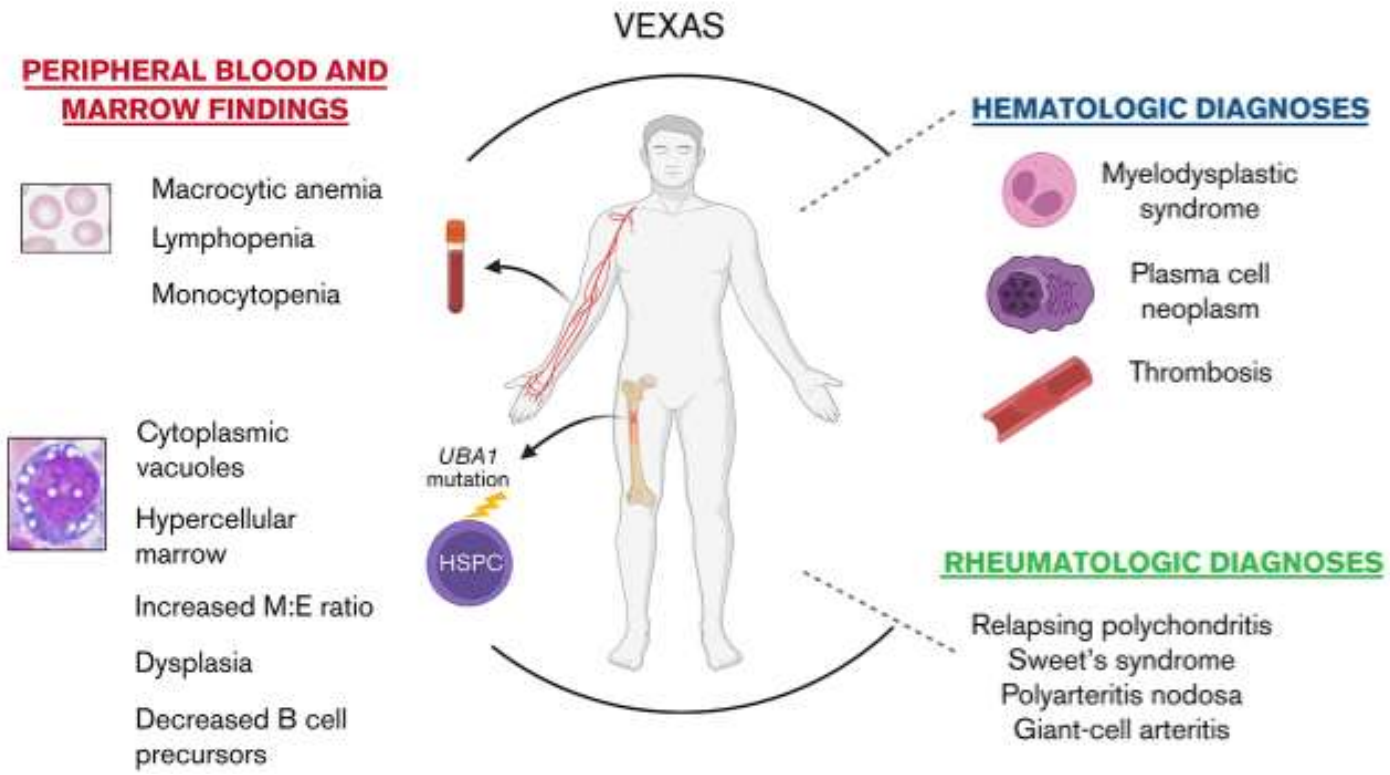
CONCLUSIONS

Using a genotype-driven approach, we identified a disorder that connects seemingly unrelated adult-onset inflammatory syndromes. We named this disorder the VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome. (Funded by the NIH Intramural Research Programs and the EU Horizon 2020 Research and Innovation Program.)

VEXAS syndrome

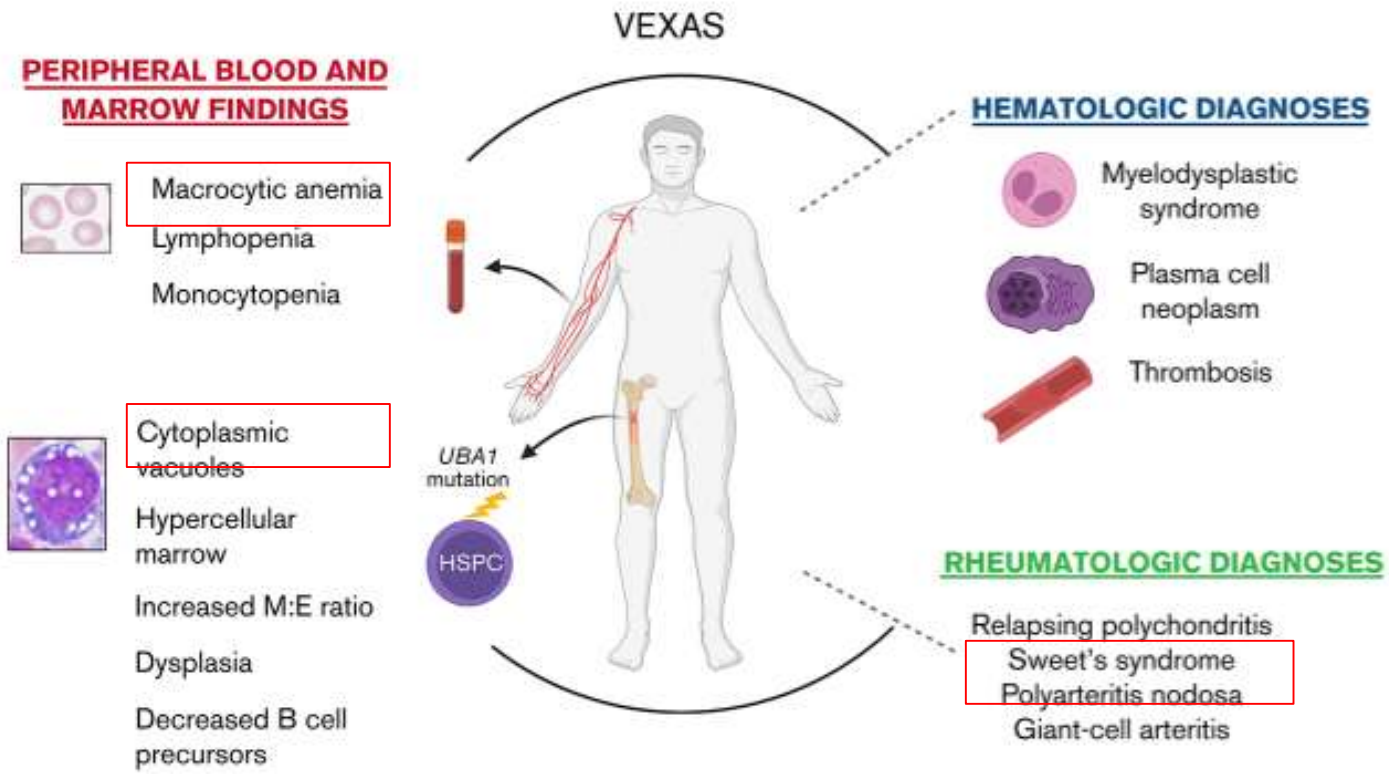
- Severe, progressive systemic inflammatory condition with hematologic, rheumatologic, and dermatologic manifestations
- Largely treatment refractory except for high dose steroids, often fatal
- Affects men in fifth decade or later
- Caused by a somatic missense mutation in ***UBA1*** (p.Met41) on the **X chromosome**
  - The major ubiquitin-initiating enzyme (E1)
  - Regulates the innate immune response

Clinical Features



(Obiorah et al., 2021)

Clinical Features: Our Patient



(Obiorah et al., 2021)

Take home points

- Diagnosis to know, especially on hemepath and dermpath services
- Vacuolization of myeloid and erythroid cells = Hallmark feature
- If diagnosis is established, rule out underlying MDS or plasma cell neoplasm
- Clinical history is paramount:
  - Consider the diagnosis in **male patients** who present with severe/treatment-resistant inflammatory disorders and hematologic abnormalities
  - Consider the diagnosis in patients with MDS who present with an inflammatory or autoimmune syndrome
- Recommend genetic testing for *UBA1* mutation at p.Met41

References

- Beck DB, Ferrada MA, Sikora KA, Ombrello AK, Collins JC, Pei W, Balanda N, Ross DL, Ospina Cardona D, Wu Z, Patel B, Manthiram K, Groarke EM, Gutierrez-Rodrigues F, Hoffmann P, Rosenzweig S, Nakabo S, Dillon LW, Hourigan CS, Tsai WL, Gupta S, Carmona-Rivera C, Asmar AJ, Xu L, Oda H, Goodspeed W, Barron KS, Nehrebecky M, Jones A, Laird RS, Deuitch N, Rowczenio D, Rominger E, Wells KV, Lee CR, Wang W, Trick M, Mullikin J, Wigerblad G, Brooks S, Dell'Orso S, Deng Z, Chae JJ, Dulau-Florea A, Malicdan MCV, Novacic D, Colbert RA, Kaplan MJ, Gadina M, Savic S, Lachmann HJ, Abu-Asab M, Solomon BD, Retterer K, Gahl WA, Burgess SM, Aksentijevich I, Young NS, Calvo KR, Werner A, Kastner DL, Grayson PC. Somatic Mutations in UBA1 and Severe Adult-Onset Autoinflammatory Disease. N Engl J Med. 2020 Dec 31;383(27):2628-2638. doi: 10.1056/NEJMoa2026834. Epub 2020 Oct 27. PMID: 33108101; PMCID: PMC7847551.

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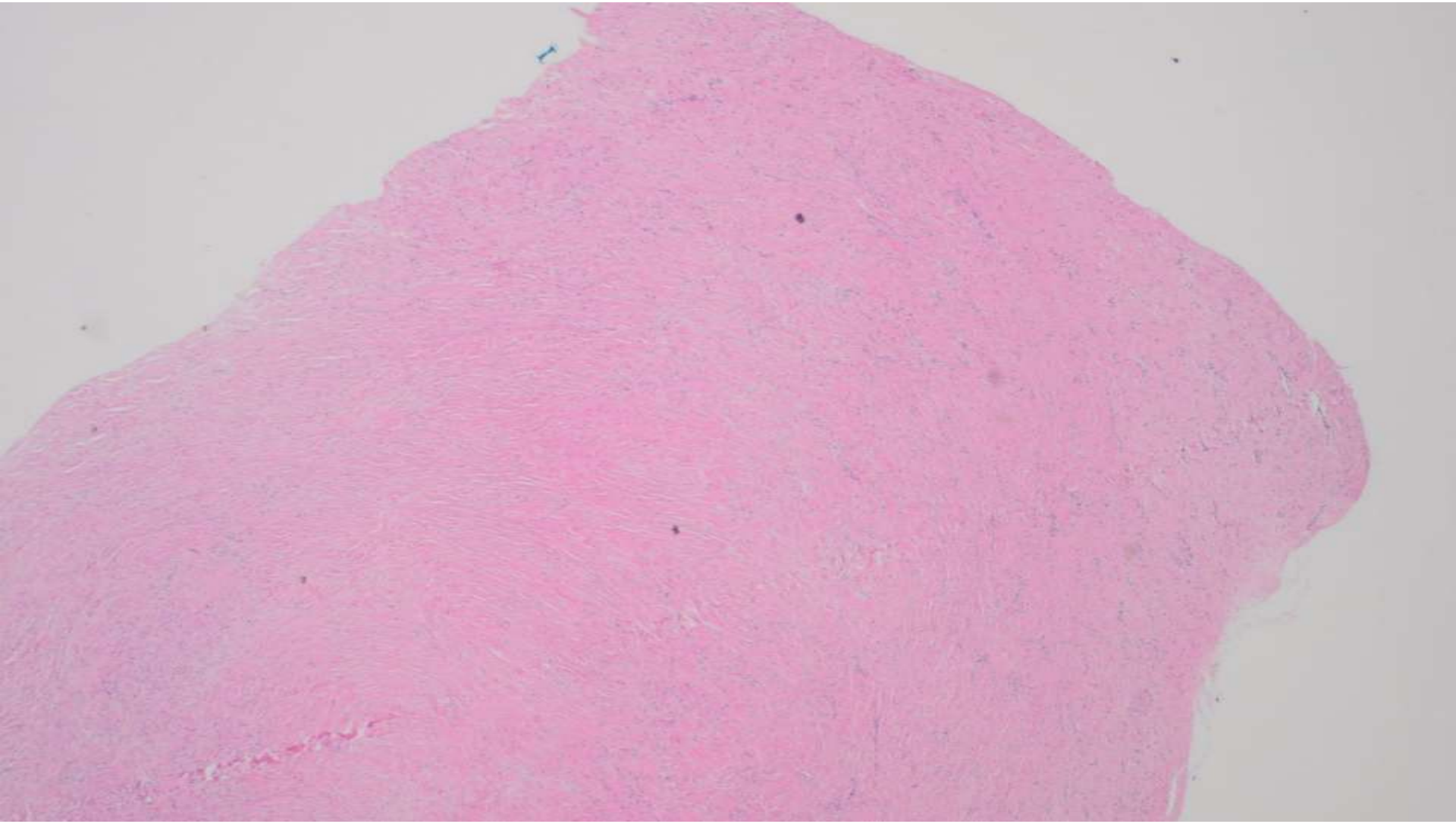
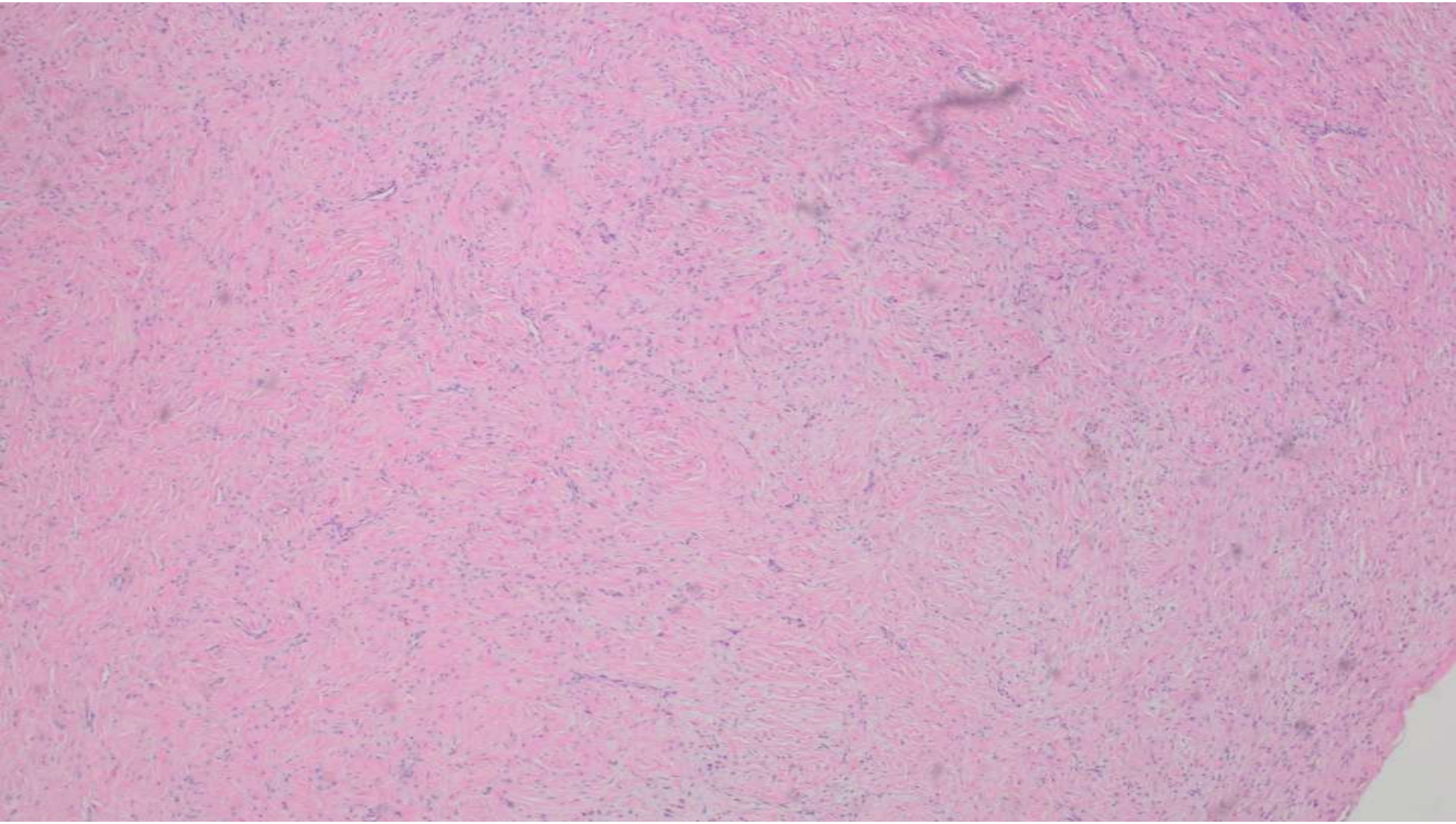
- Koster MJ, Kourelis T, Reichard KK, Kermani TA, Beck DB, Cardona DO, Samec MJ, Mangaonkar AA, Begna KH, Hook CC, Oliveira JL, Nasr SH, Tiong BK, Patnaik MM, Burke MM, Michet CJ Jr, Warrington KJ. Clinical Heterogeneity of the VEXAS Syndrome: A Case Series. Mayo Clin Proc. 2021 Oct;96(10):2653-2659. doi: 10.1016/j.mayocp.2021.06.006. Epub 2021 Sep 3. PMID: 34489099.

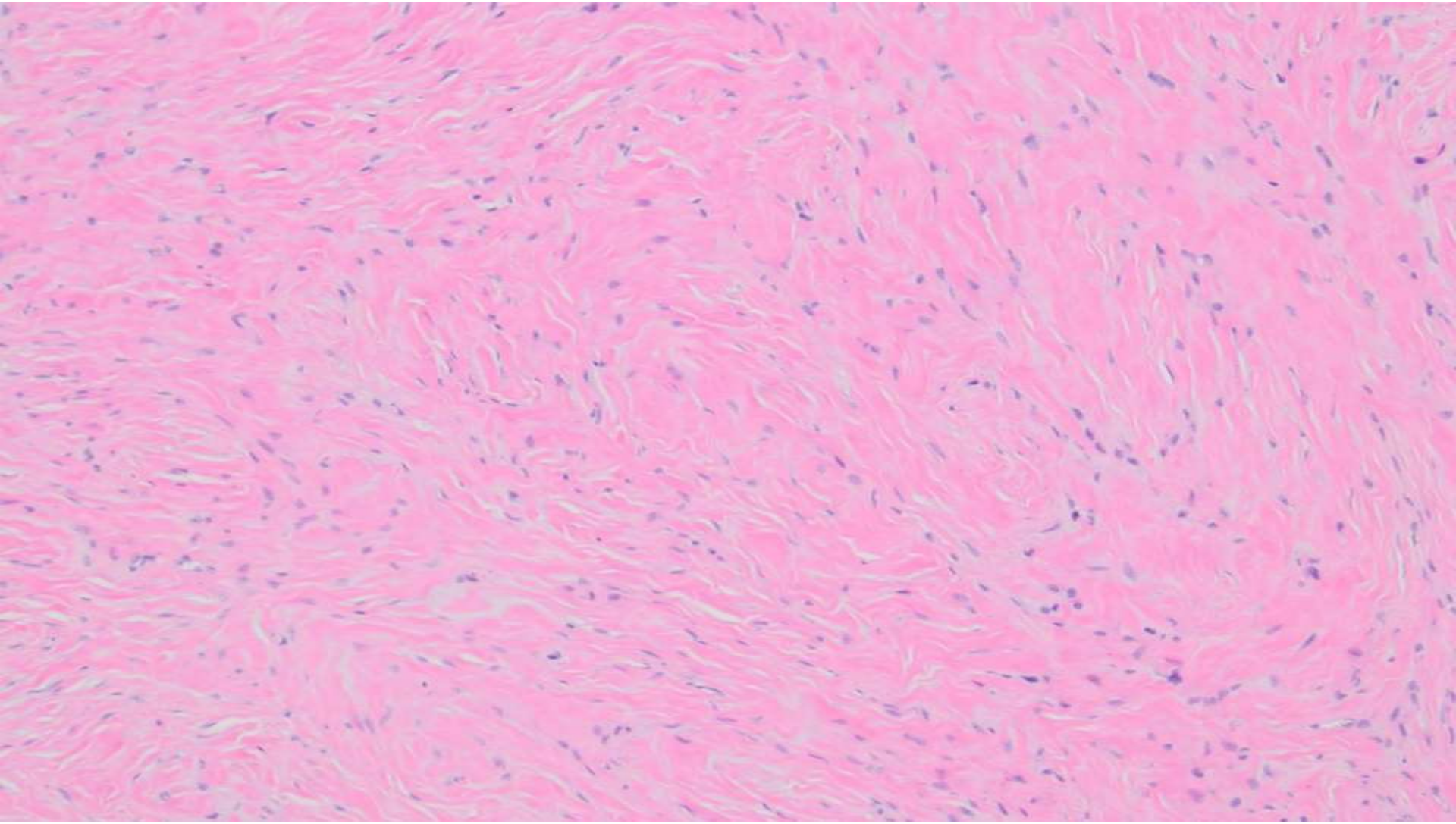
21-1202

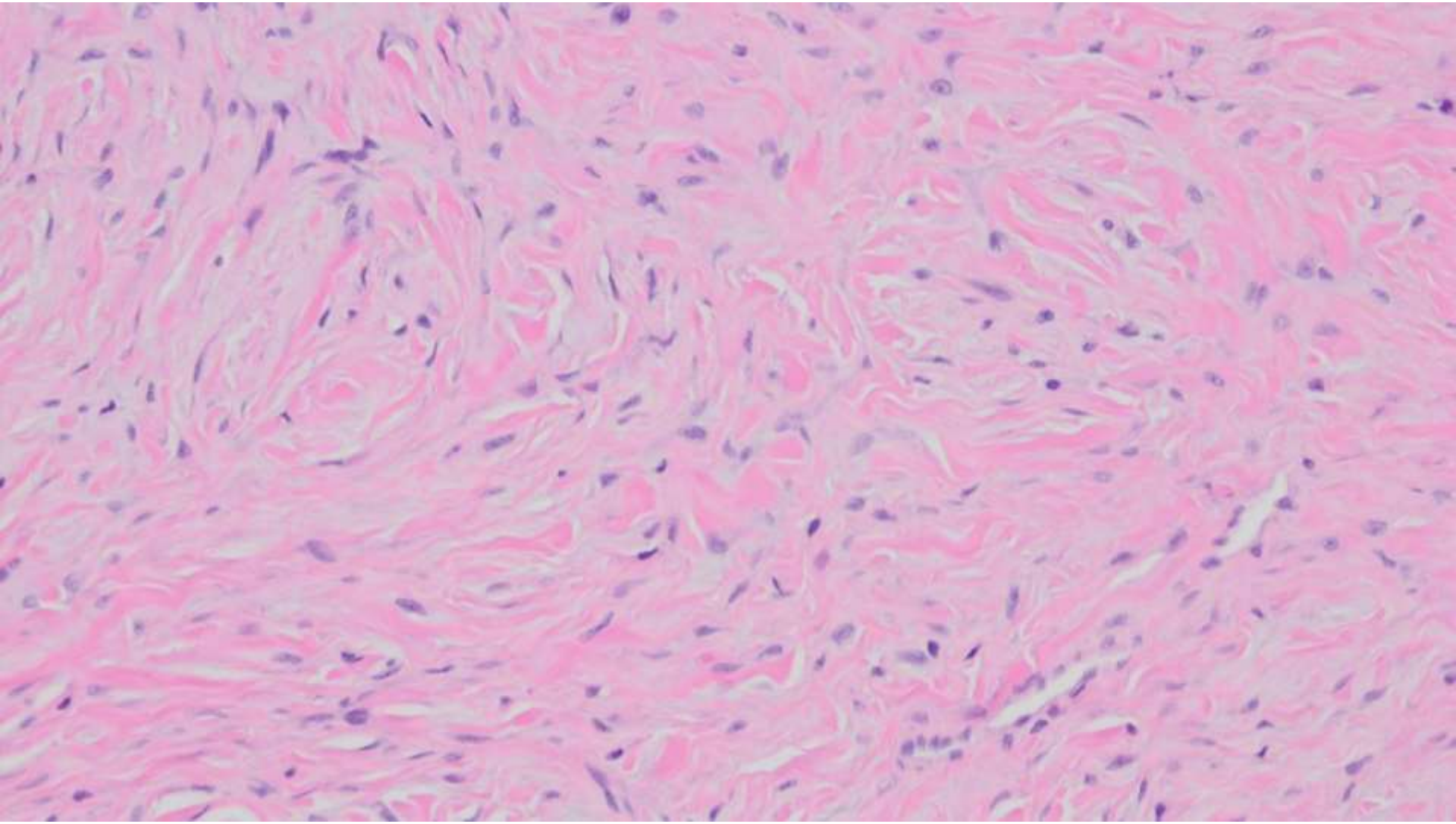
Andrew Bandy; CPMC

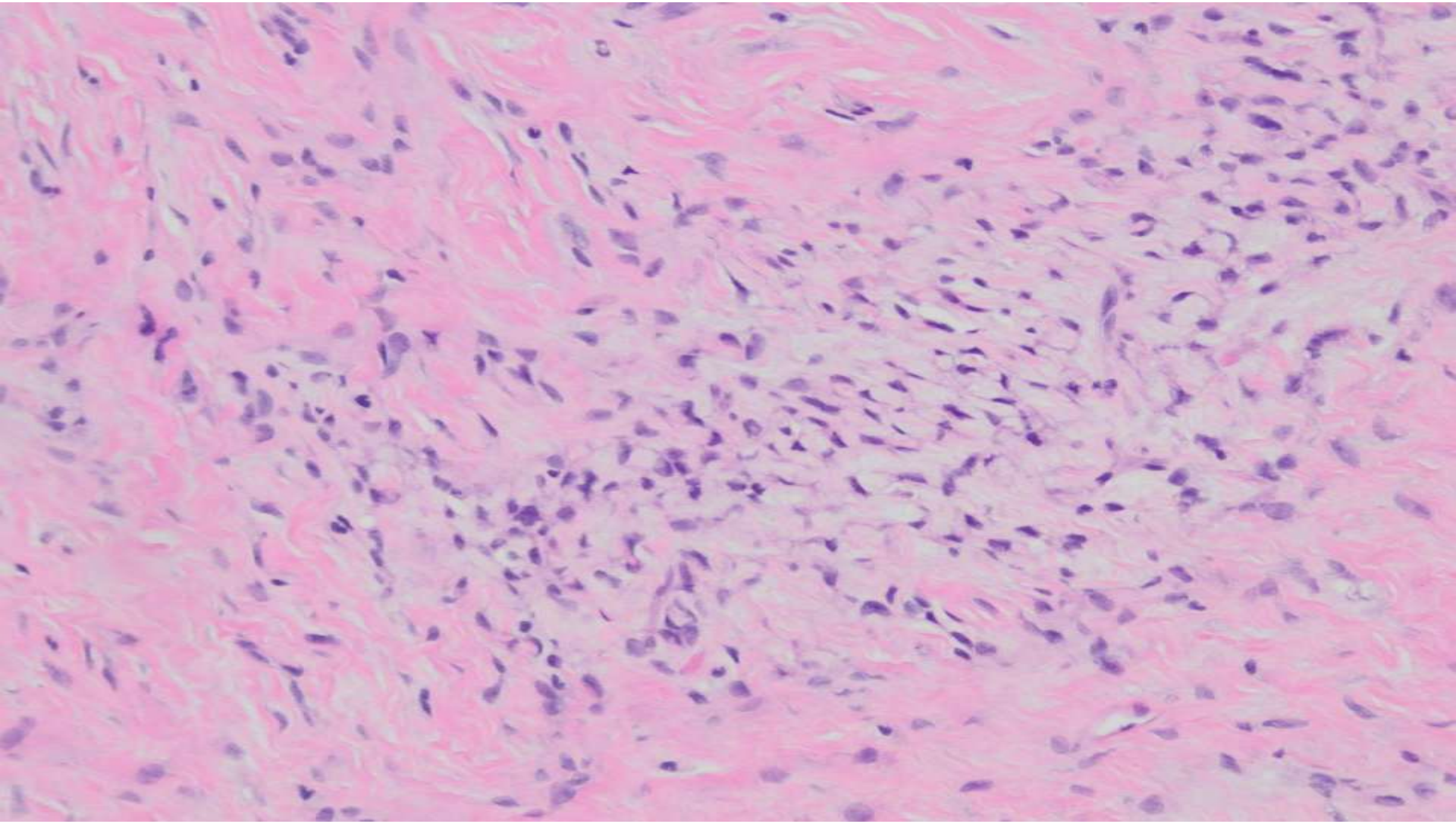
27-year-old F with 1.2cm well-circumscribed painless right long finger mass. Present for unknown period of time.





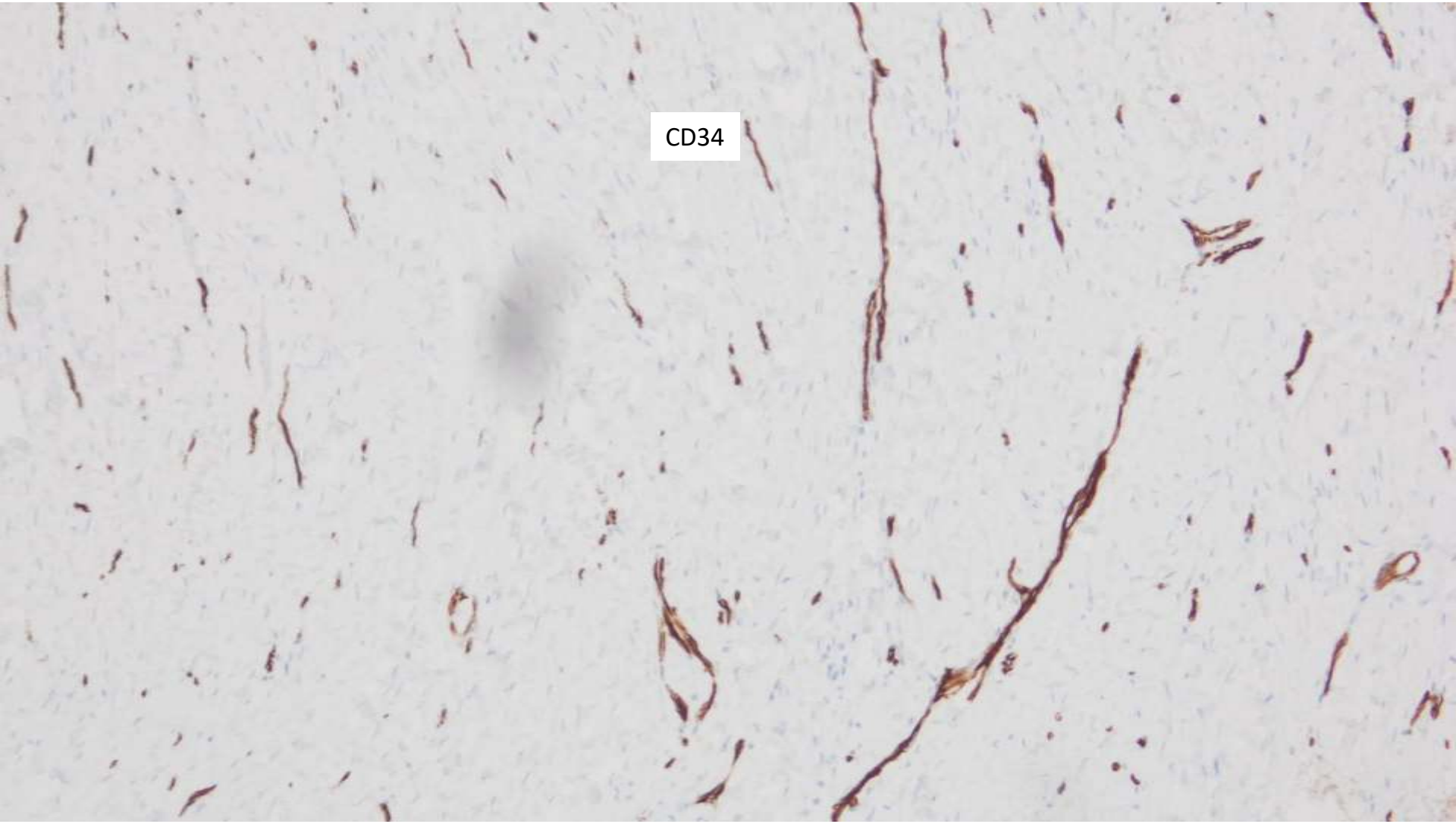


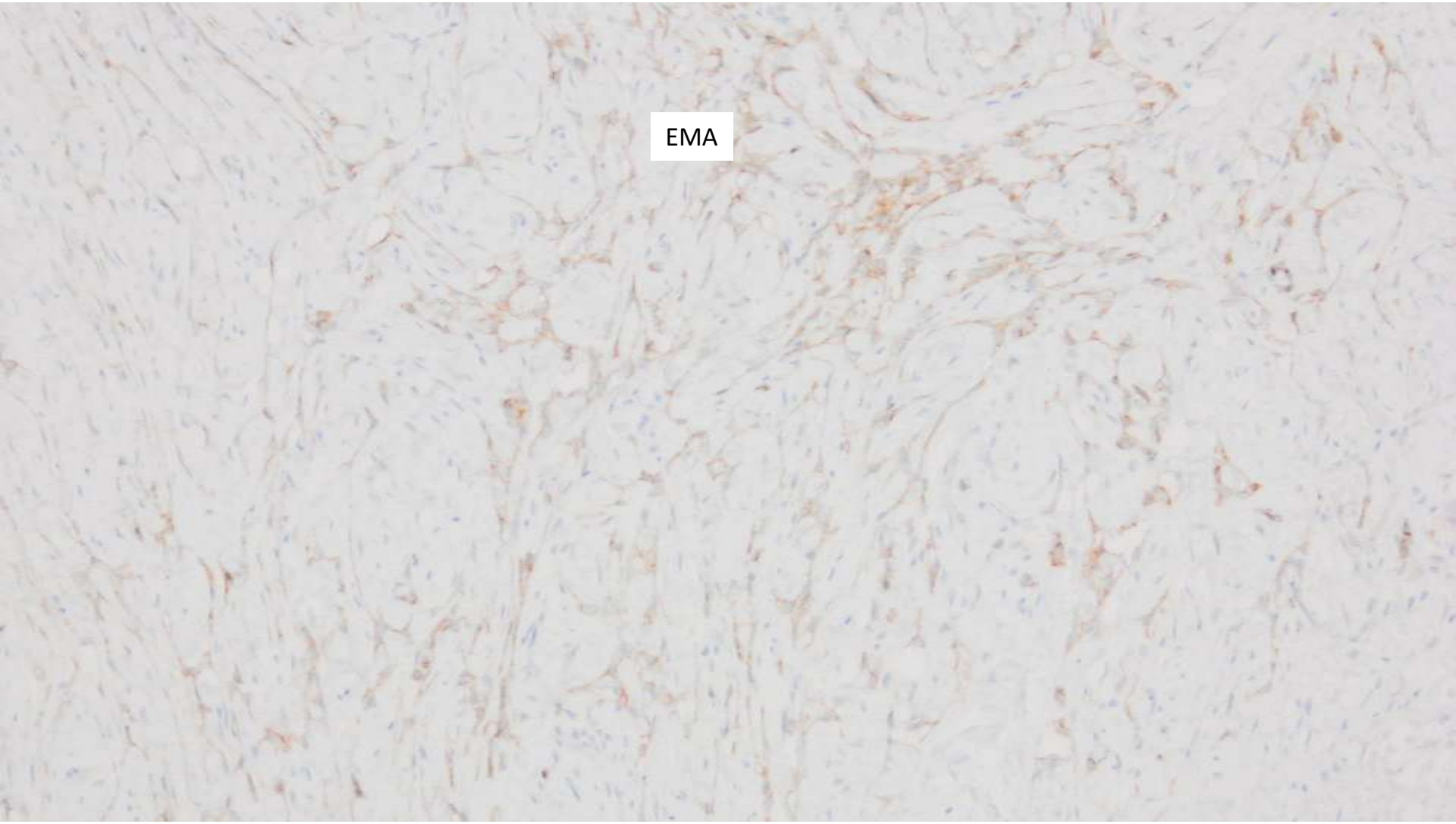


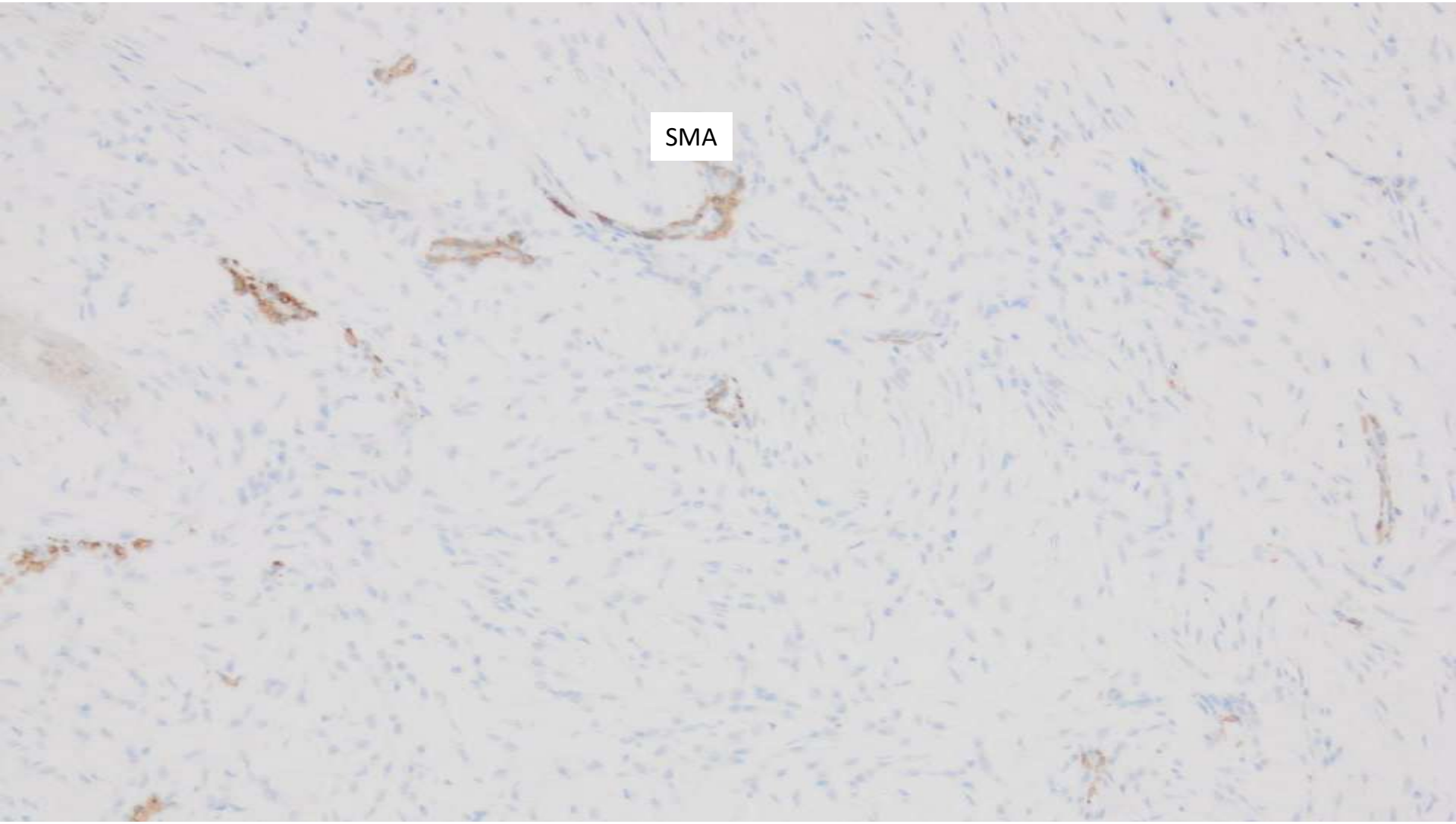


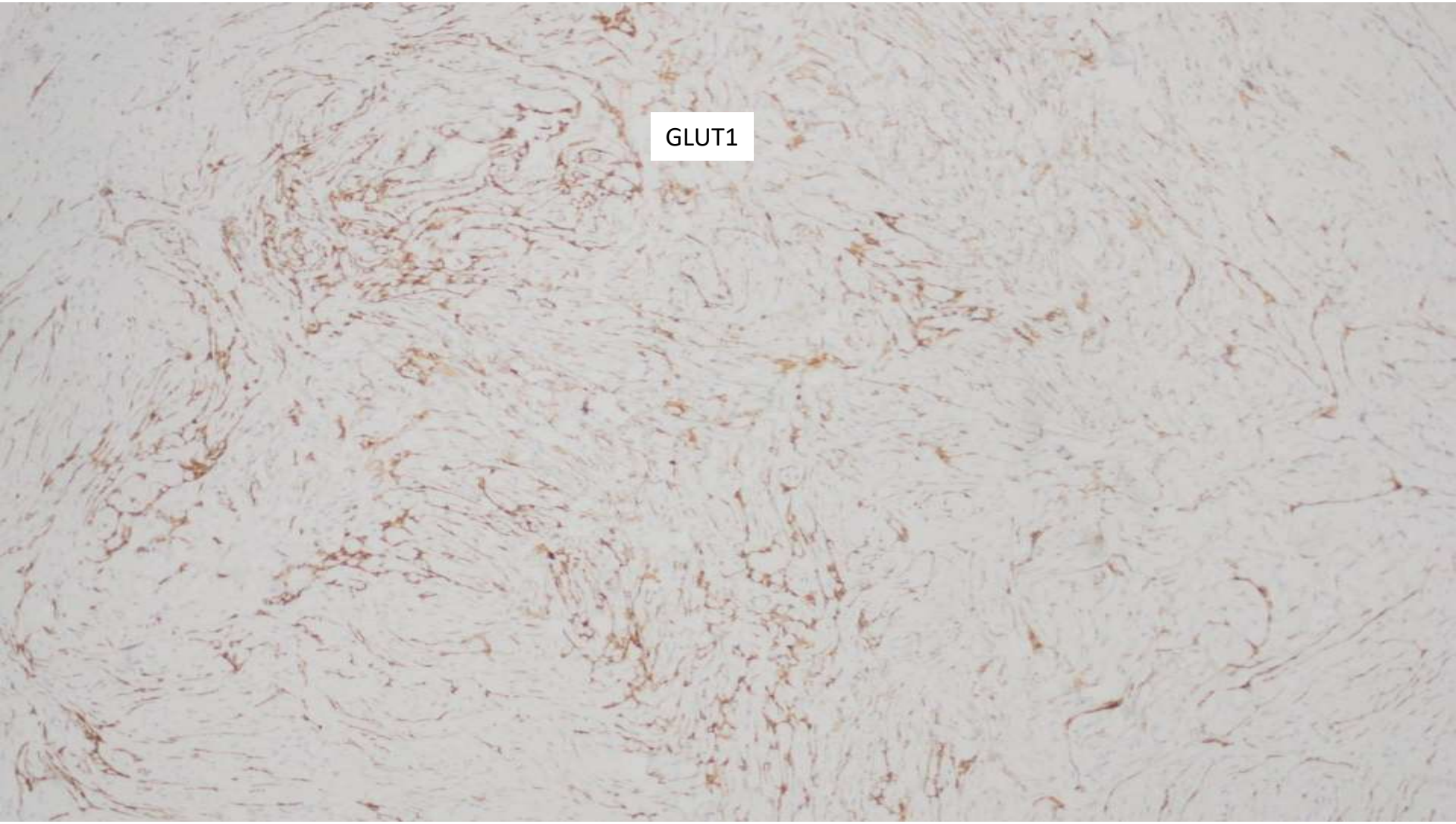
DDx

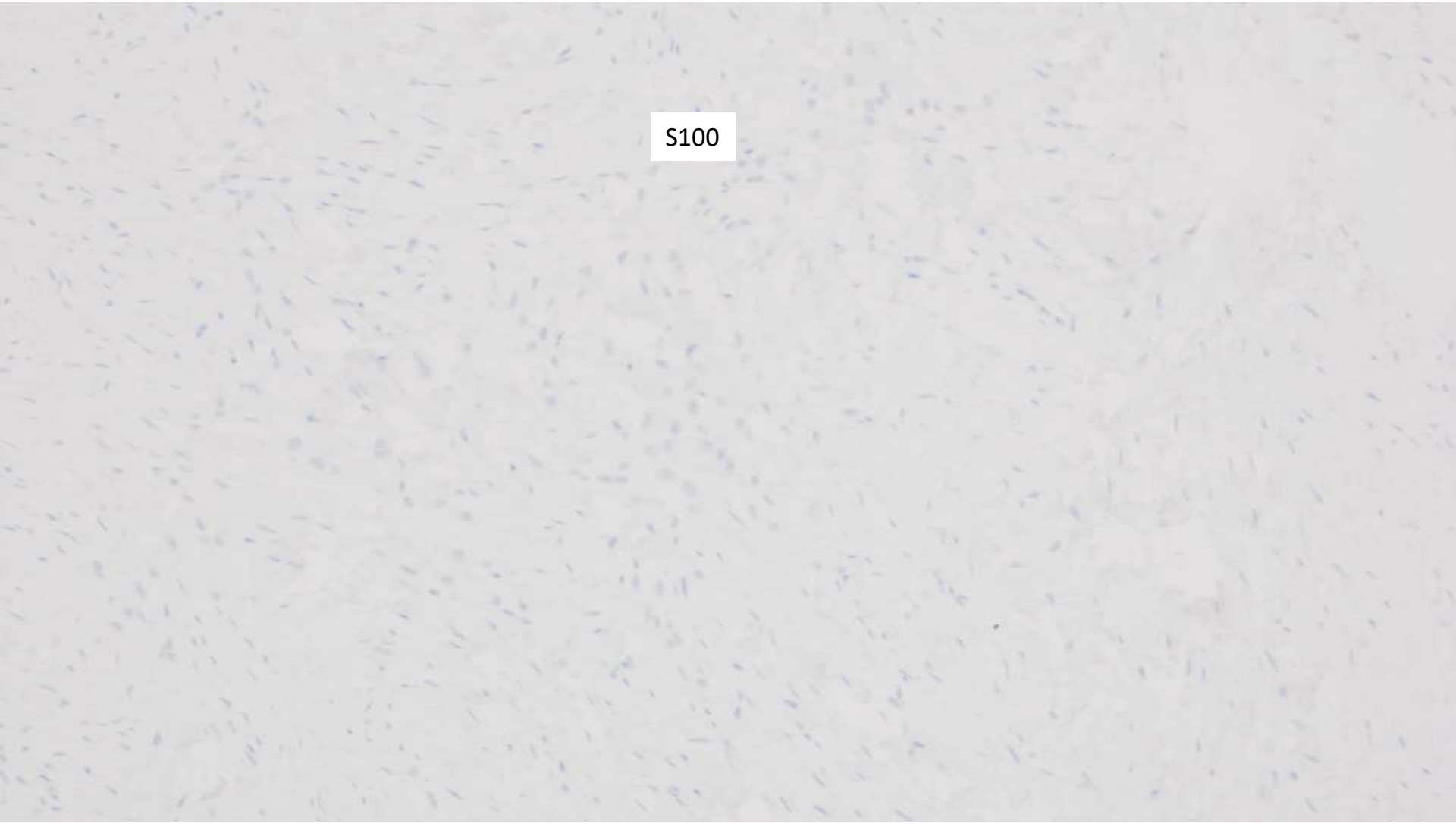
- Low-grade fibromyxoid sarcoma/sclerosing epithelioid fibrosarcoma
- Sclerosing perineurioma
- Sclerotic features within:
  - Other peripheral nerve sheath tumor (Schwannoma/neurofibroma)
  - Leiomyoma
  - Neurothekeoma
- Fibroma
- Superficial acral fibromyxoma

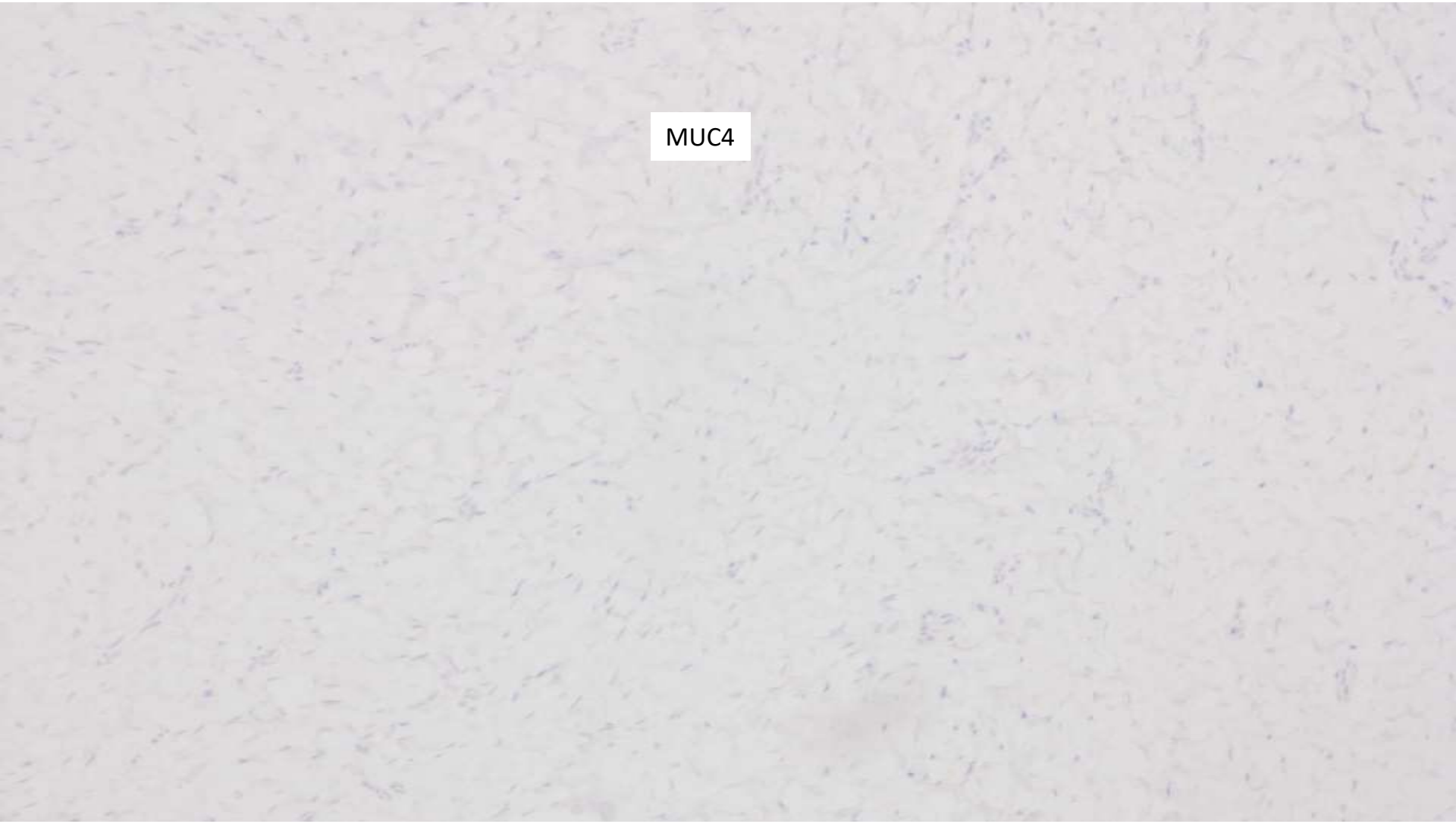

CD34


EMA


SMA


GLUT1


S100


MUC4

IHC Summary:

Positive: EMA, GLUT1

Negative: CD34, Sox10, S100, MUC4, desmin, SMA

Sclerosing Perineurioma

- Benign lesion derived from perineurial cells with predilection for hands of young adults
- Unclear if related to prior trauma or a true neoplasm
- Almost never recur
- Microscopic: Typically well-circumscribed with hypocellular collagenous/sclerotic matrix with scattered epithelioid or plump spindle cells (with frequent whorls/cords), ill-defined cell borders, inconspicuous nucleoli and absent/low mitotic activity
- Typical IHC profile: Positive for EMA, GLUT1, CD10, claudin1, collagen IV, +/-CD34

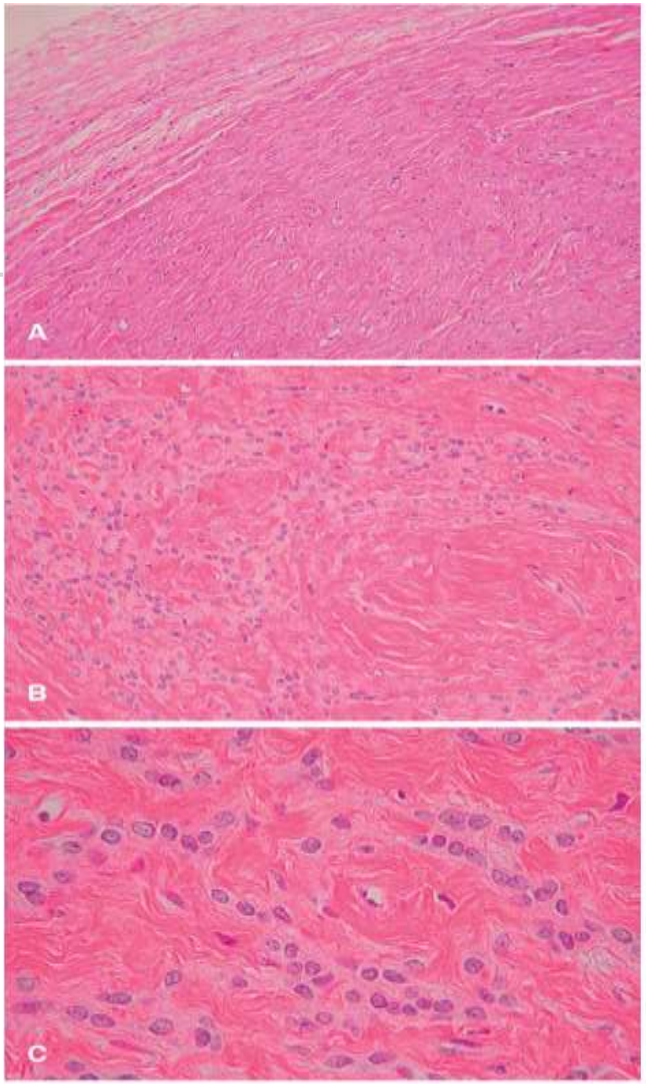
Virchows Arch (2003) 443:159–163
DOI 10.1007/s00428-003-0849-4

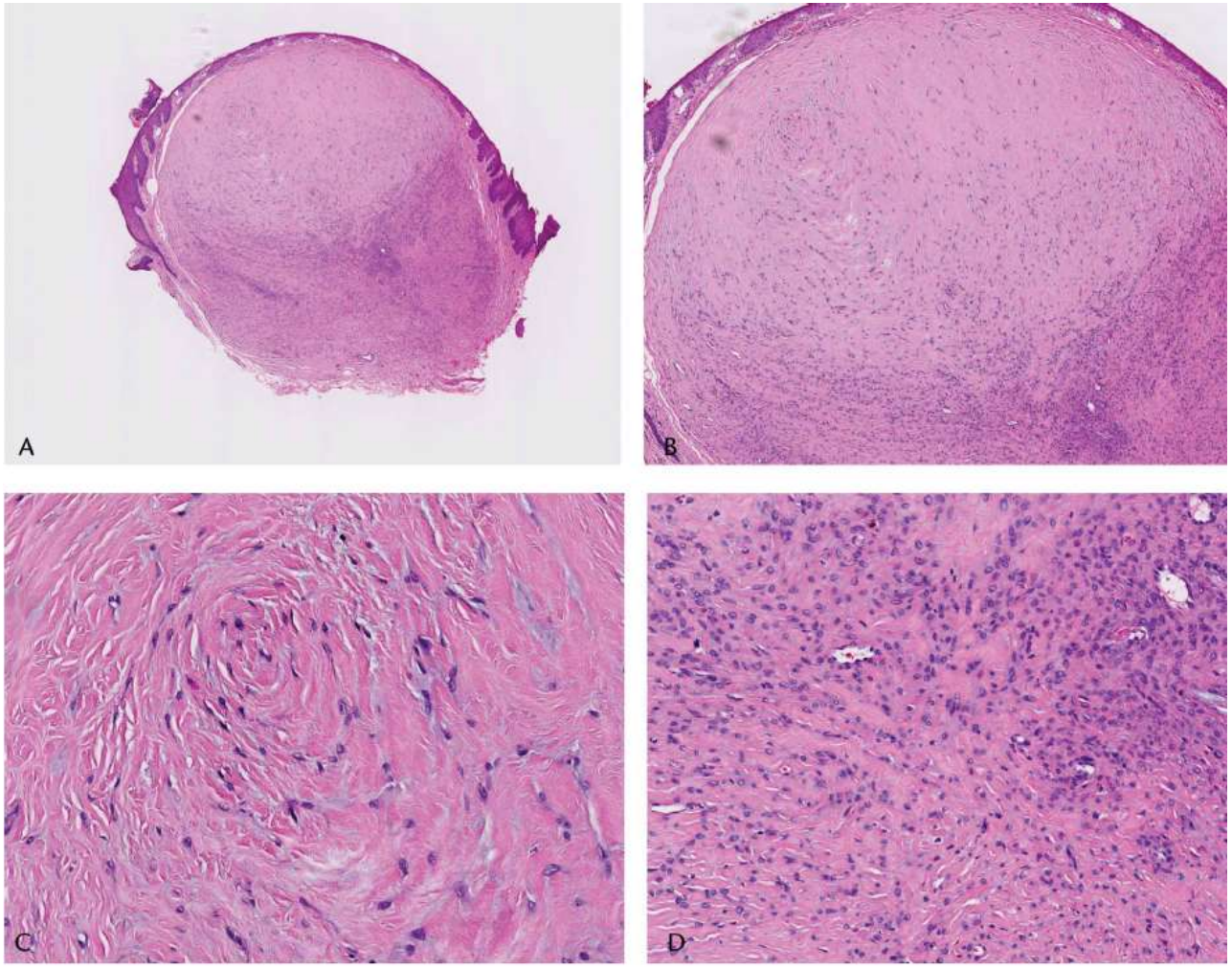
ORIGINAL ARTICLE

Umio Yamaguchi · Tadashi Hasegawa ·
Takanori Hirose · Kazunori Fugo ·
Tomoko Mitsuhashi · Michio Shimizu · Akira Kawai ·
Yasumasa Ito · Hirokazu Chuman · Yasuo Beppu

Sclerosing perineurioma: a clinicopathological study of five cases and diagnostic utility of immunohistochemical staining for GLUT1

Received: 5 February 2003 / Accepted: 21 April 2003 / Published online: 26 June 2003




A
B
C
D

References

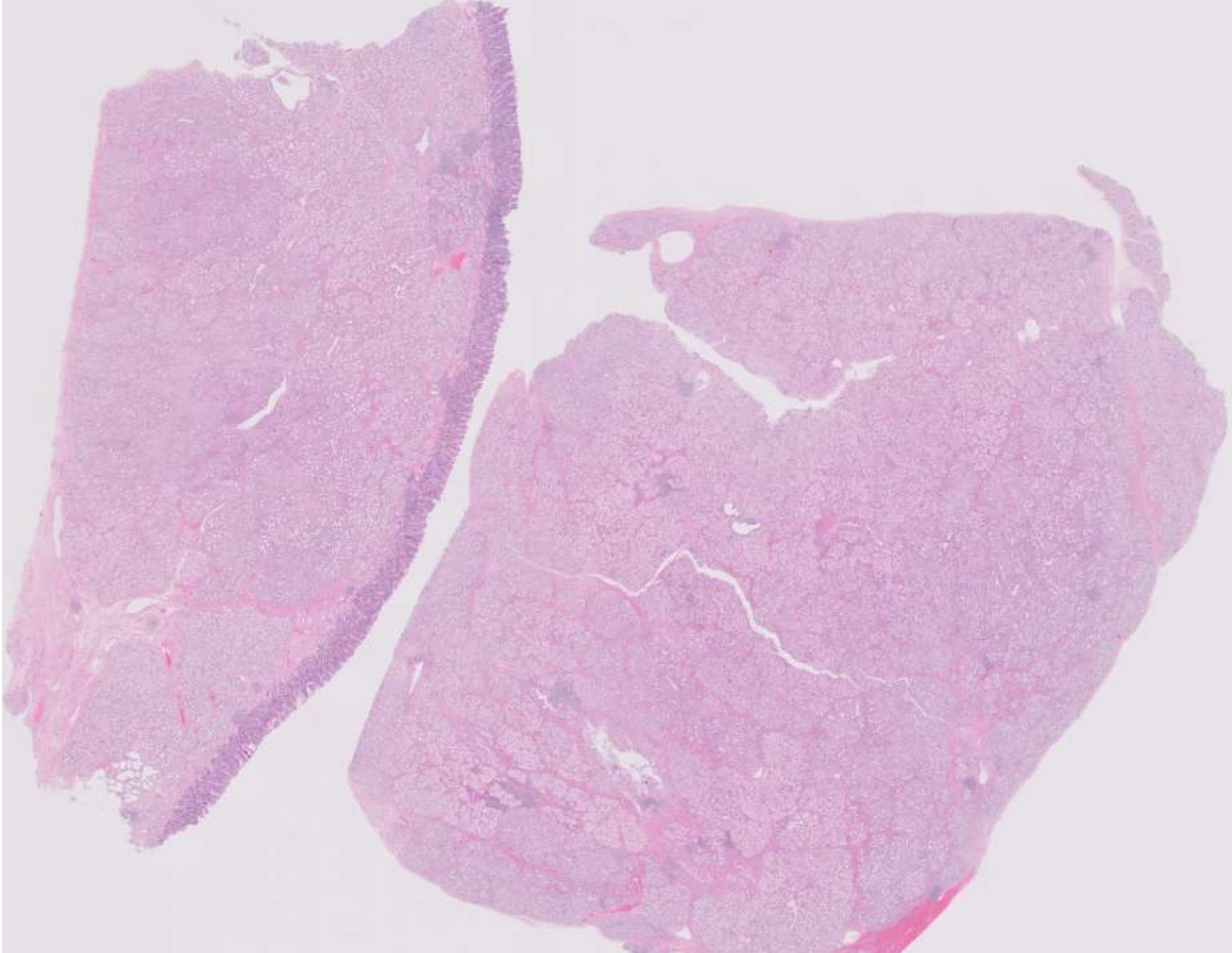
-Sclerosing perineurioma: a clinicopathological study of five cases and diagnostic utility of immunohistochemical staining for GLUT1. Virchows Arch (2003) 443:159–163

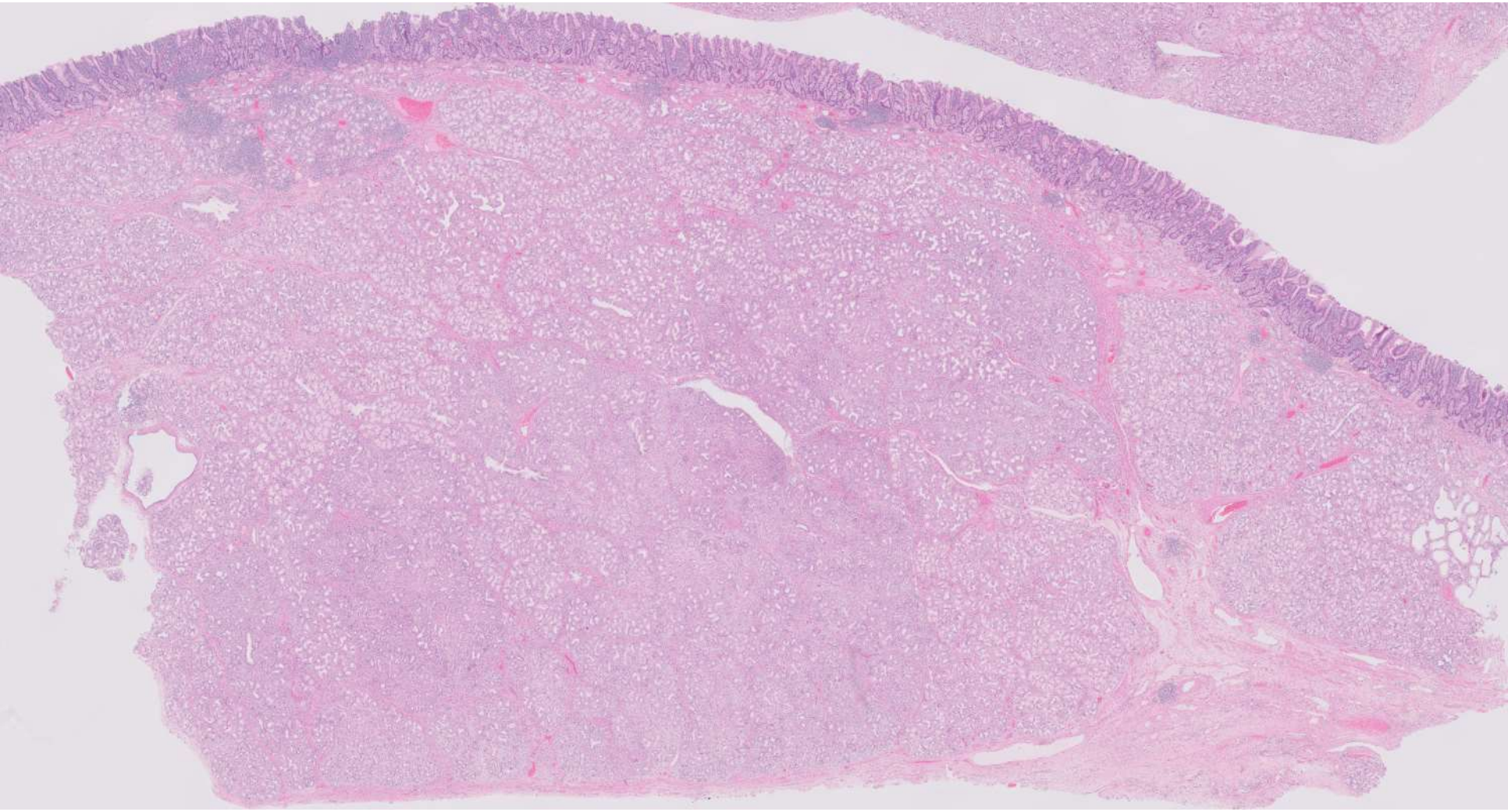
-A Clinicopathologic and Immunohistochemical Study of 7 Cases of Sclerosing Perineurioma. Am J Dermatopathol 2015;37:122–128

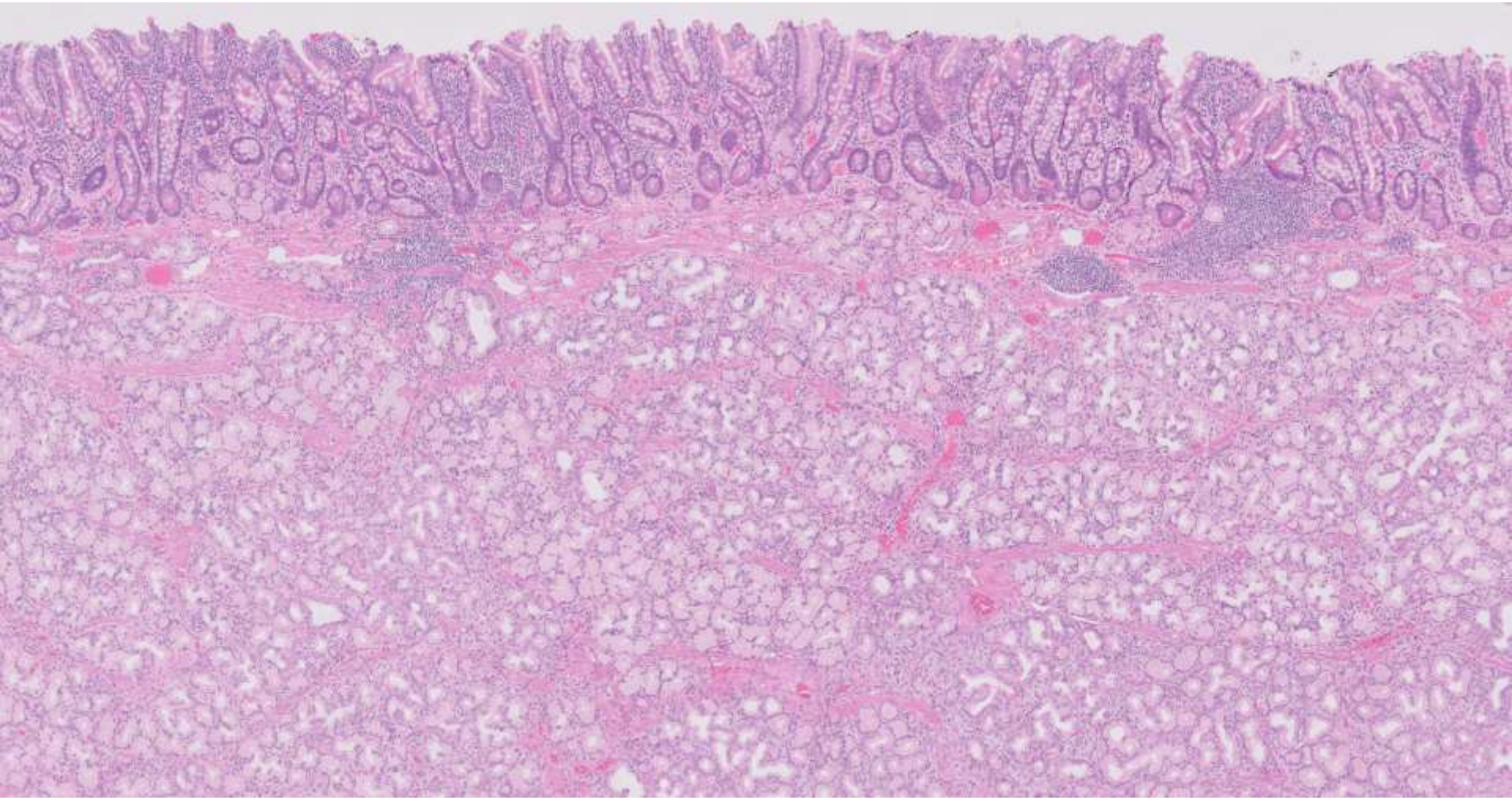
21-1203

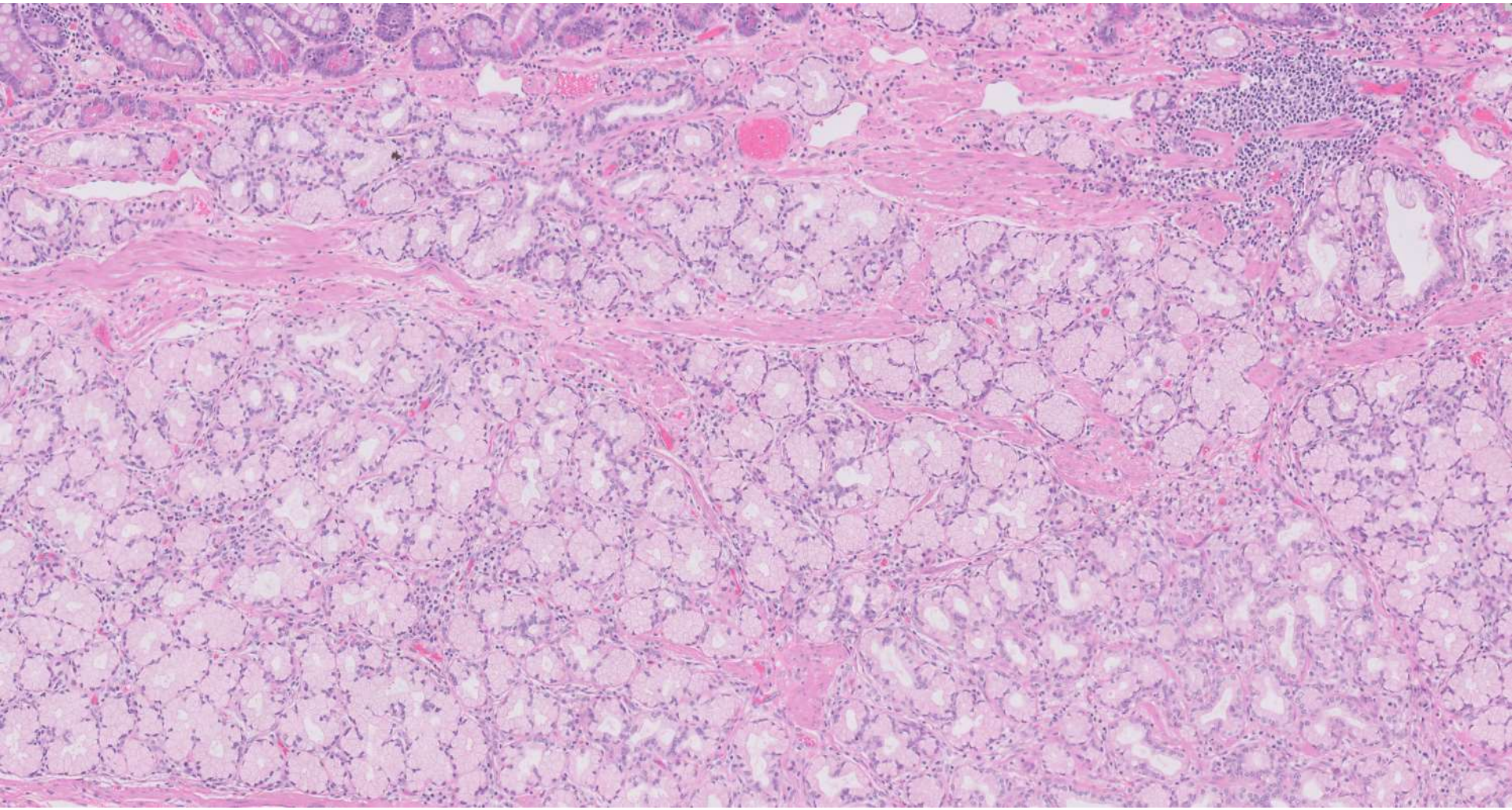
Diane Libert/David Bingham; Stanford

63-year-old F with 7.5cm mass arising in pylorus/1st portion of duodenum.

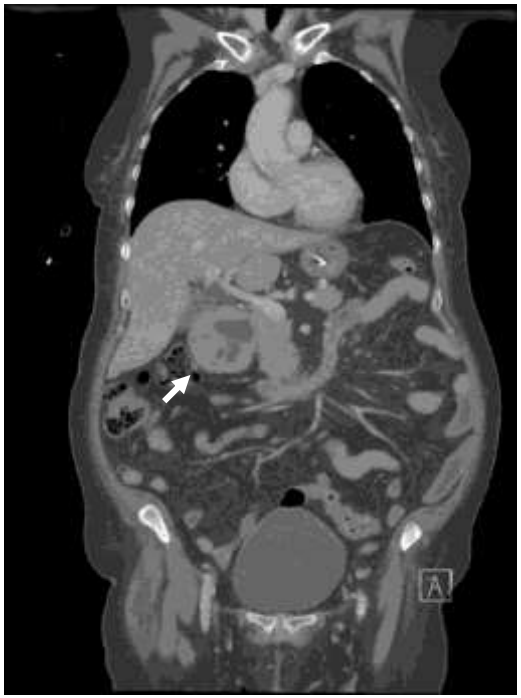


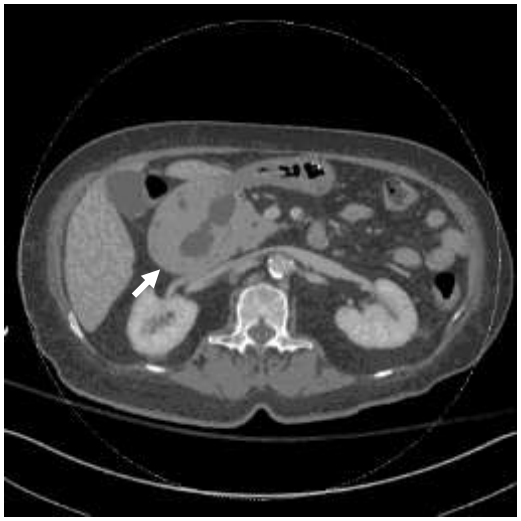


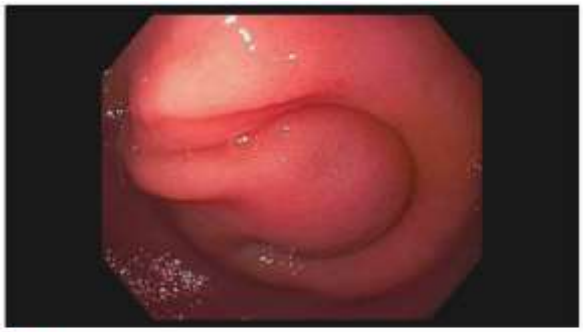




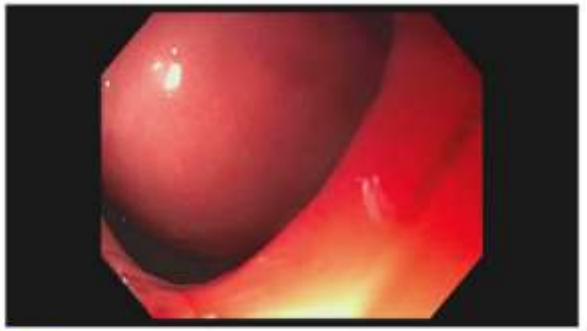
CT and EGD Procedural Images





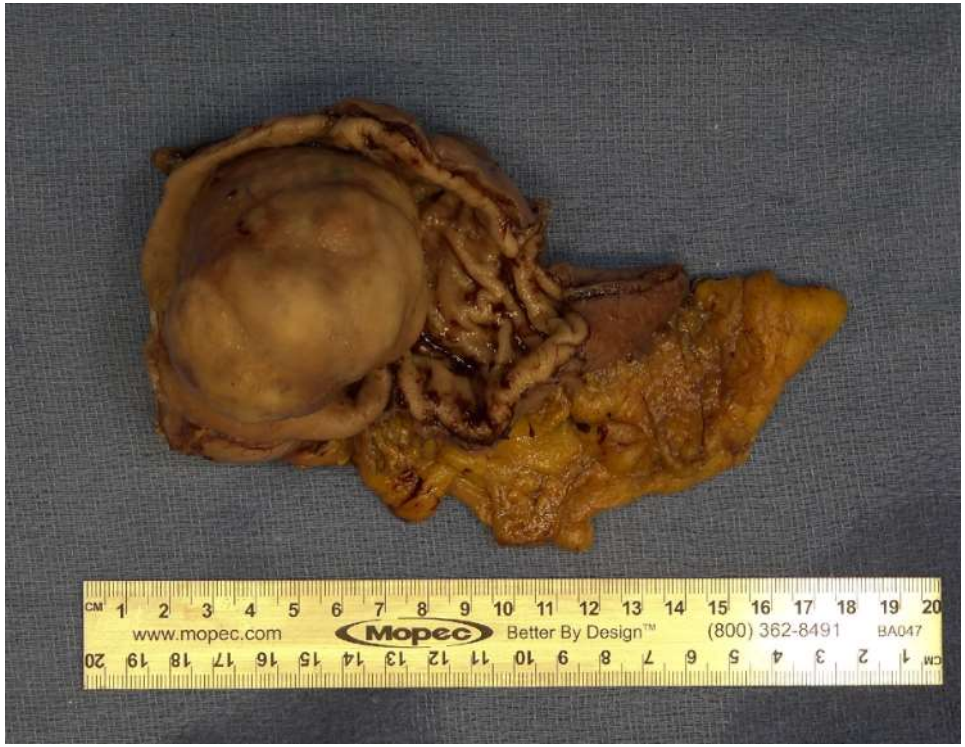


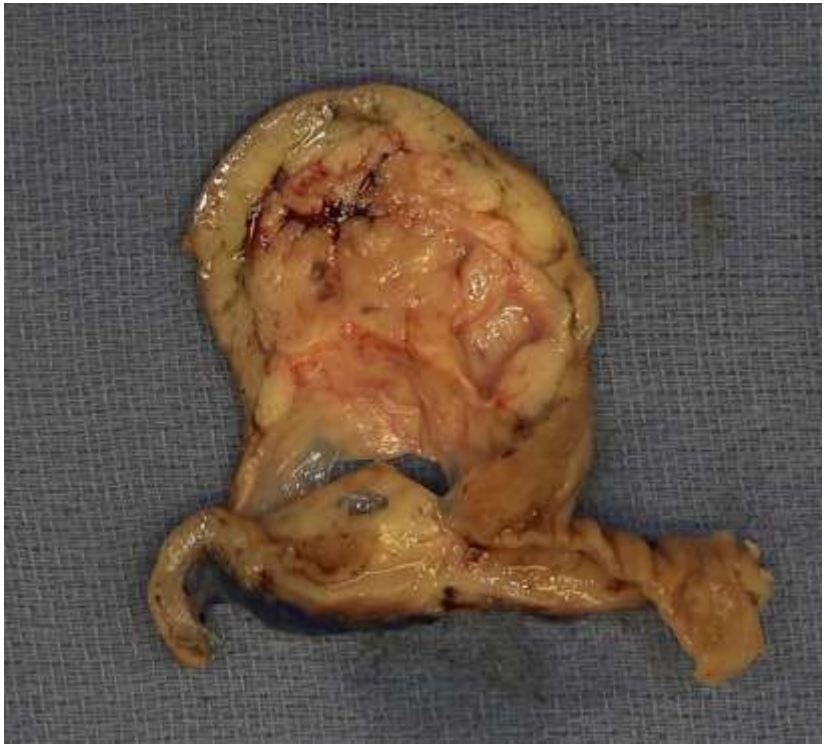
2 Pylorus



4 Duodenal Bulb

7.7 cm mass





Brunner gland hyperplasia/hamartoma

- Definitions:
  - Hamartoma: submucosal proliferation of Brunner's glands
  - vs. hyperplasia: no strict definition, size (1 cm)[1], presence of other features[2]
  - "Brunner gland adenoma" is not favored
- Epidemiology:
  - 5-10% of duodenal tumors[3]; 0.01% incidence[4]
  - 150 cases reported (2008)[5], 5 cases $\geq$ 7 cm (2019)[6]
- Characteristics:
  - Etiology unclear: hyperacidity, H. pylori infection[7]?
  - Most common in proximal duodenum
  - Histology: cystically dilated spaces, glands in fibromuscular stroma, admixed adipose tissue, smooth muscle, and/or lymphoid tissue
  - Prognosis: excellent, no reported cases of recurrence
- Endoscopic DDX: heterotopia, neuroendocrine tumor
- Pitfall: Delicate glandular cells may be crushed during biopsy
  - Mucin of Brunner glands is PAS-D positive

References

1. Rocco A, et. al. World J Gastroenterol. 2006 Mar 28;12(12):1966-8.
2. Zangara J, et. al. J Clin Gastroenterol. 1998 Dec;27(4):353-6
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4. Botsford TW, et. al. Am J Surg 1962; : 358–365.
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6. Yi L, et al. BMC Gastroenterol. 2019 Aug 23;19(1):151.
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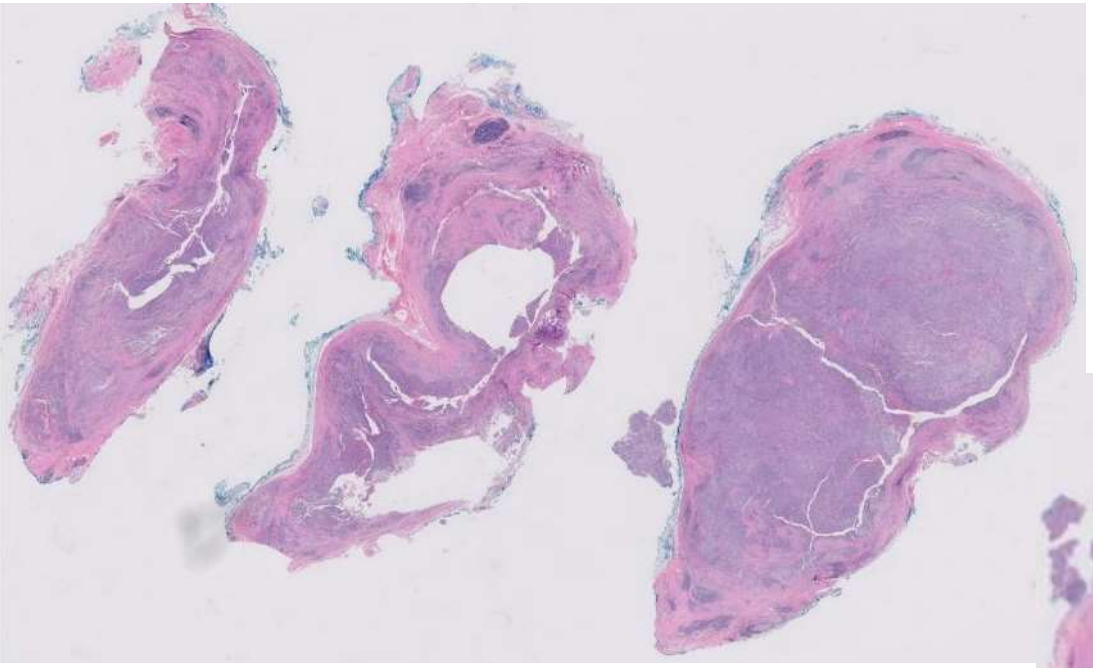
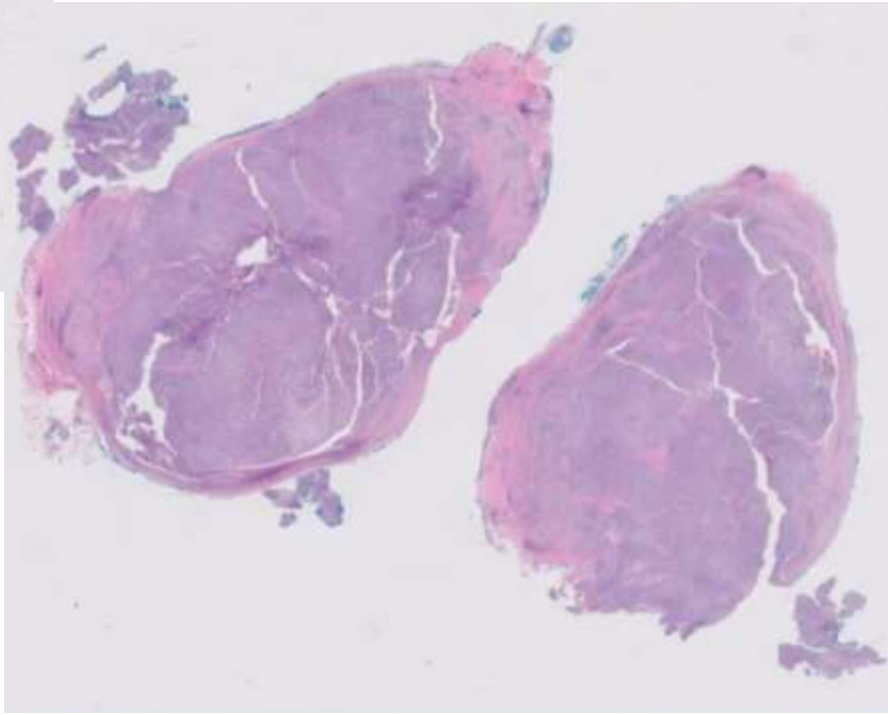
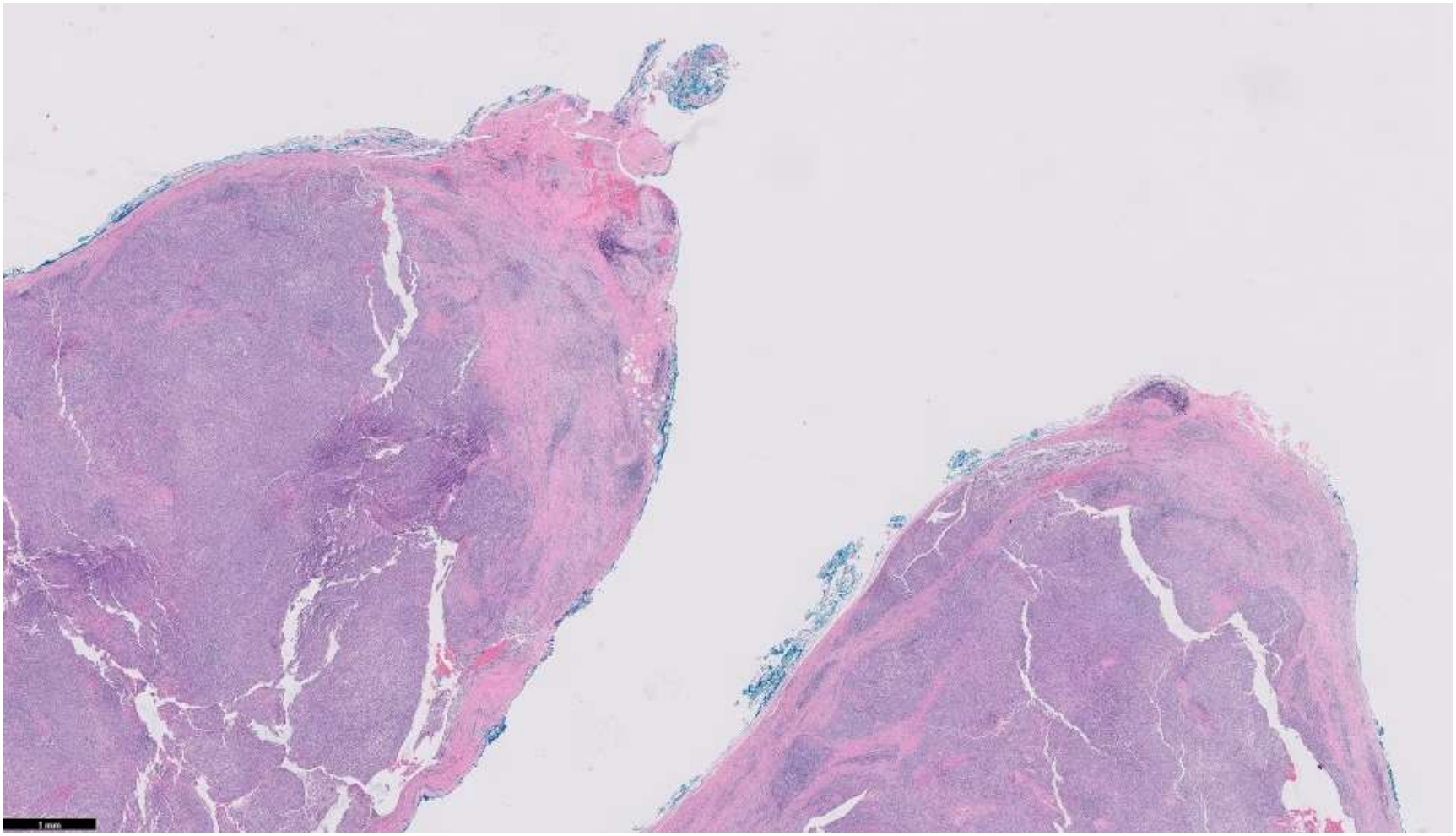
21-1204

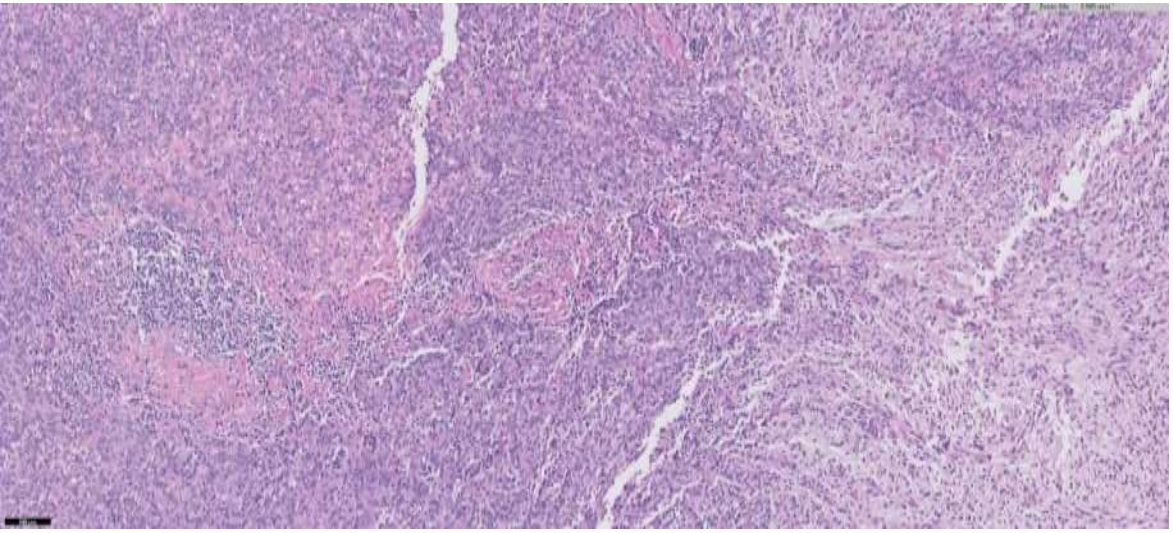
Amanda Borgen/Yue Peng; VA San Francisco; UCSF

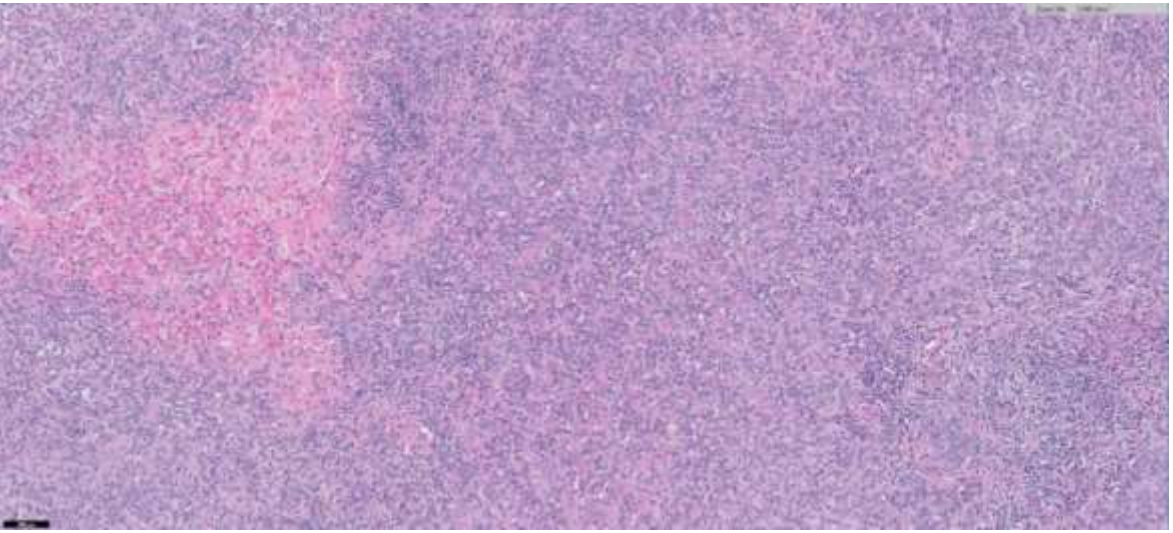
31-year-old M with 2.5cm firm, mobile, nontender subcutaneous forehead nodule present for 10 months.

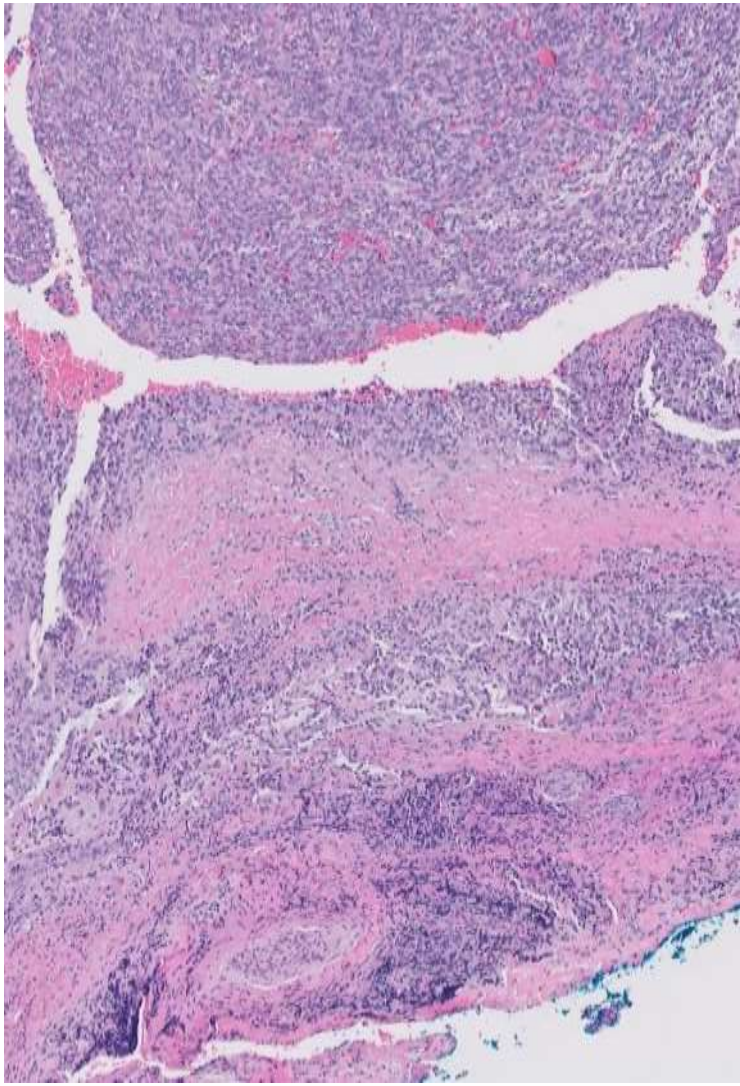


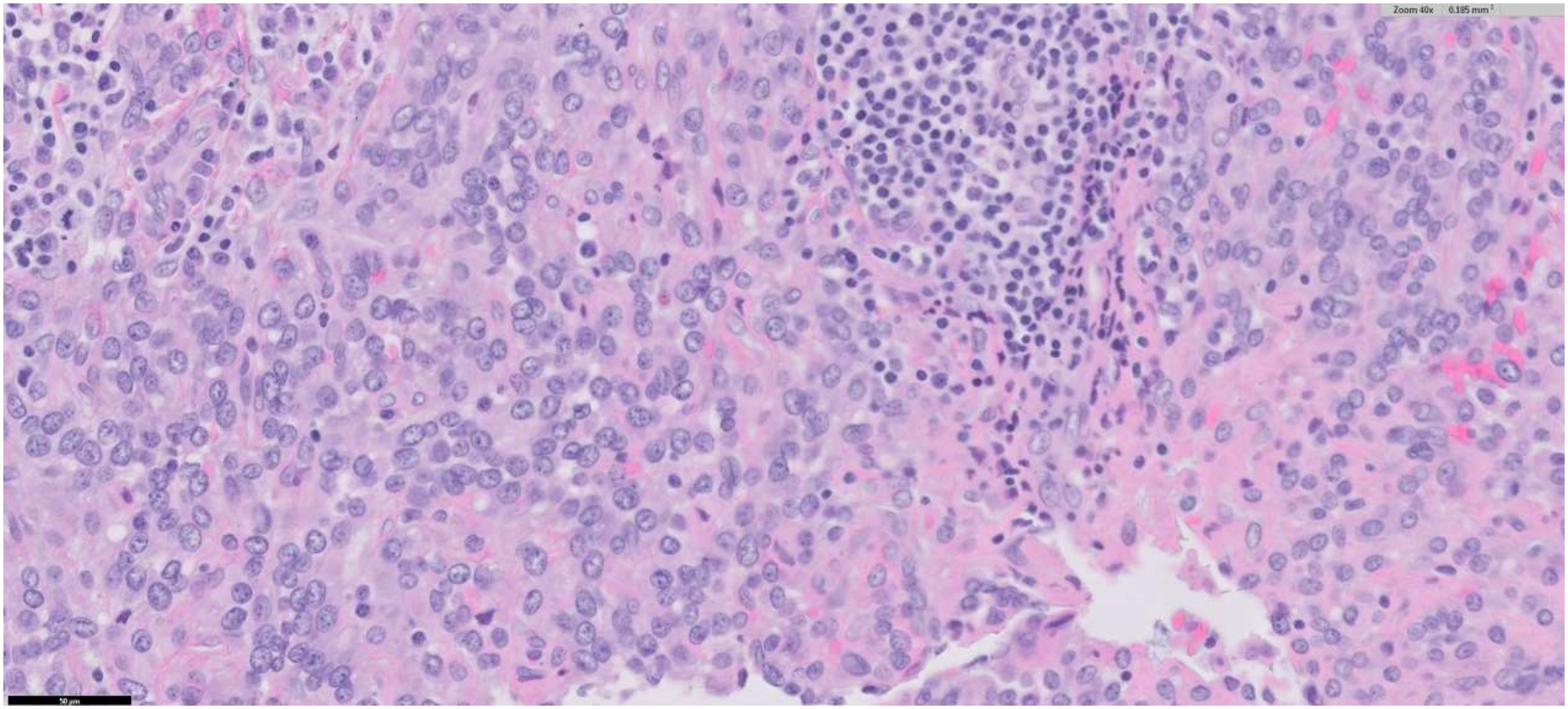



1 mm

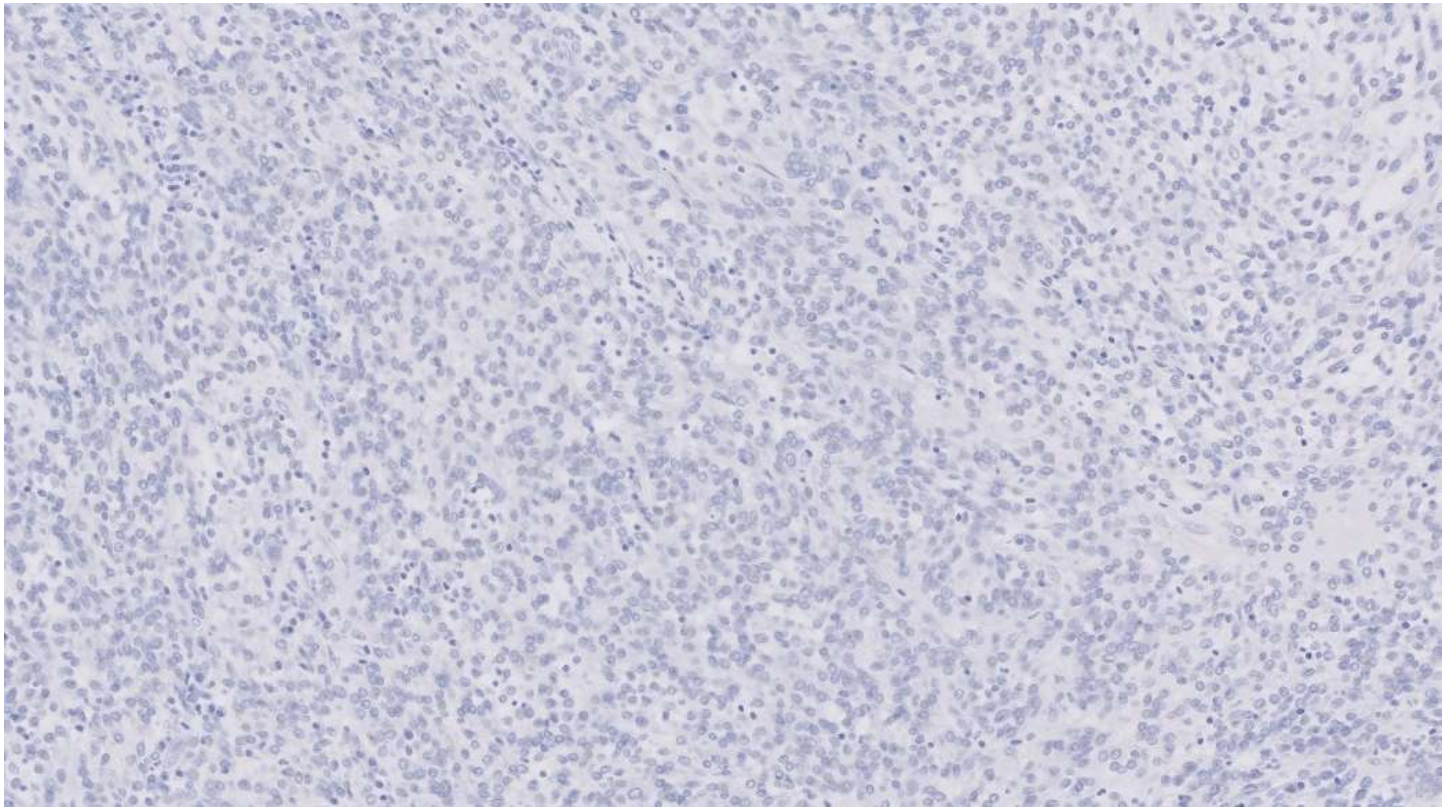




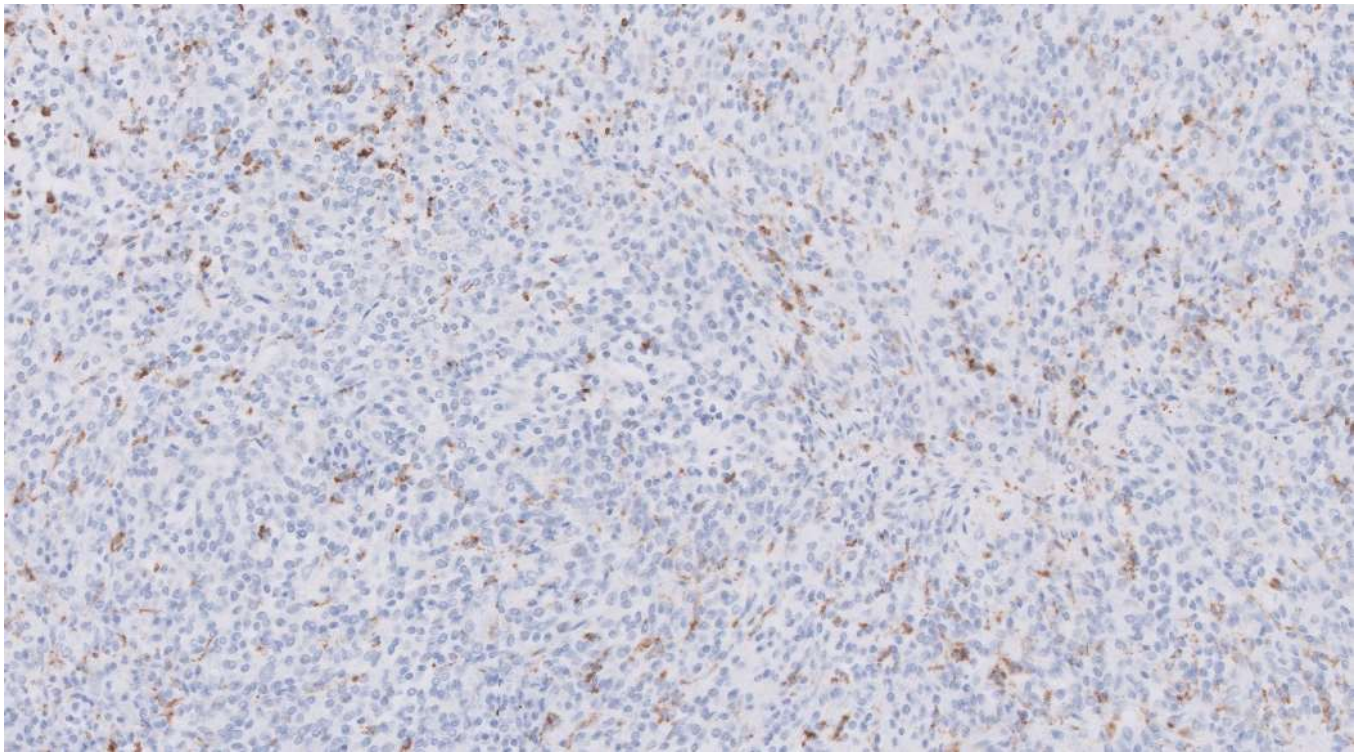



Zoom 40x
0.185 mm²
50 µm

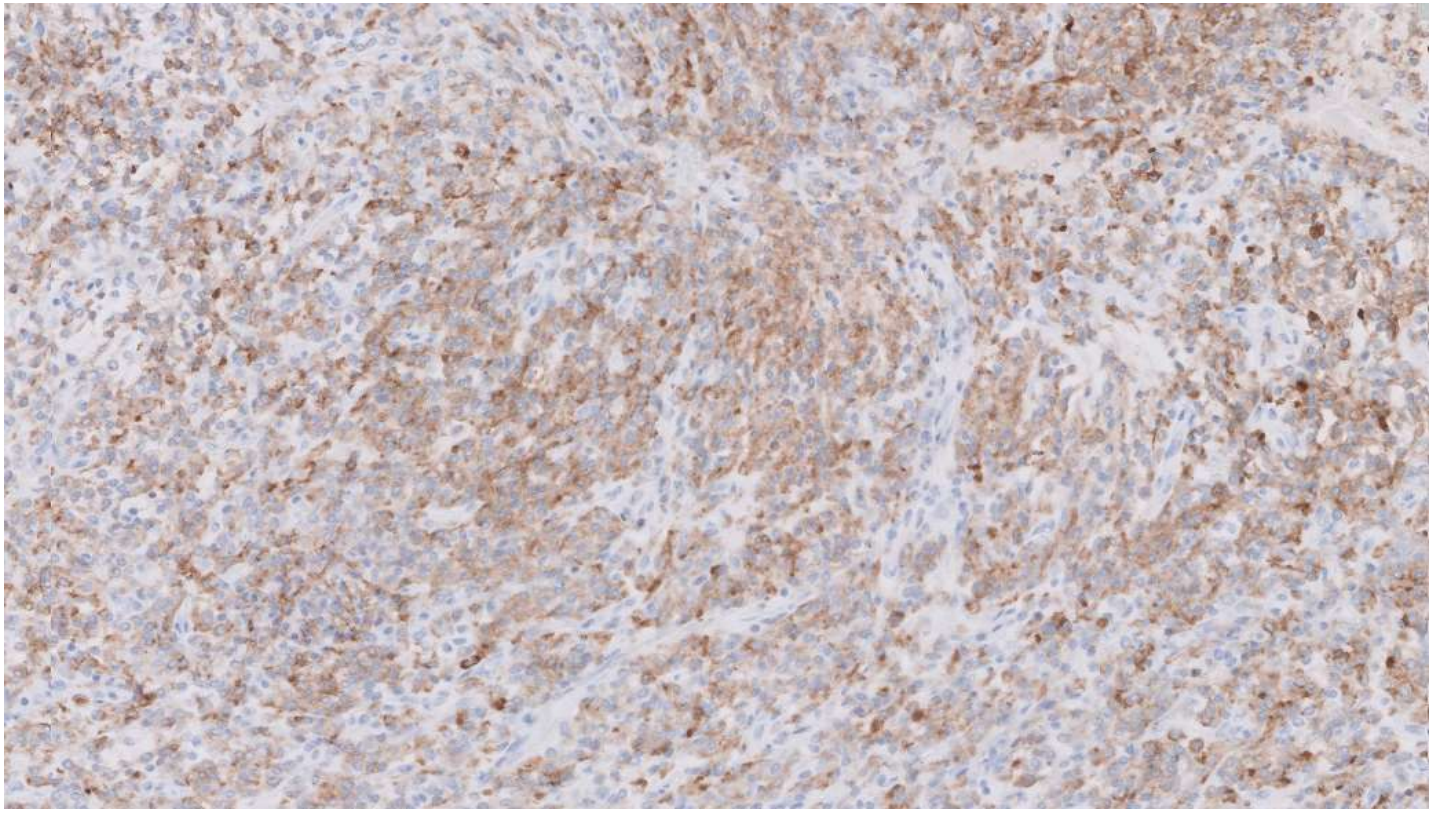
CK AE1/AE3



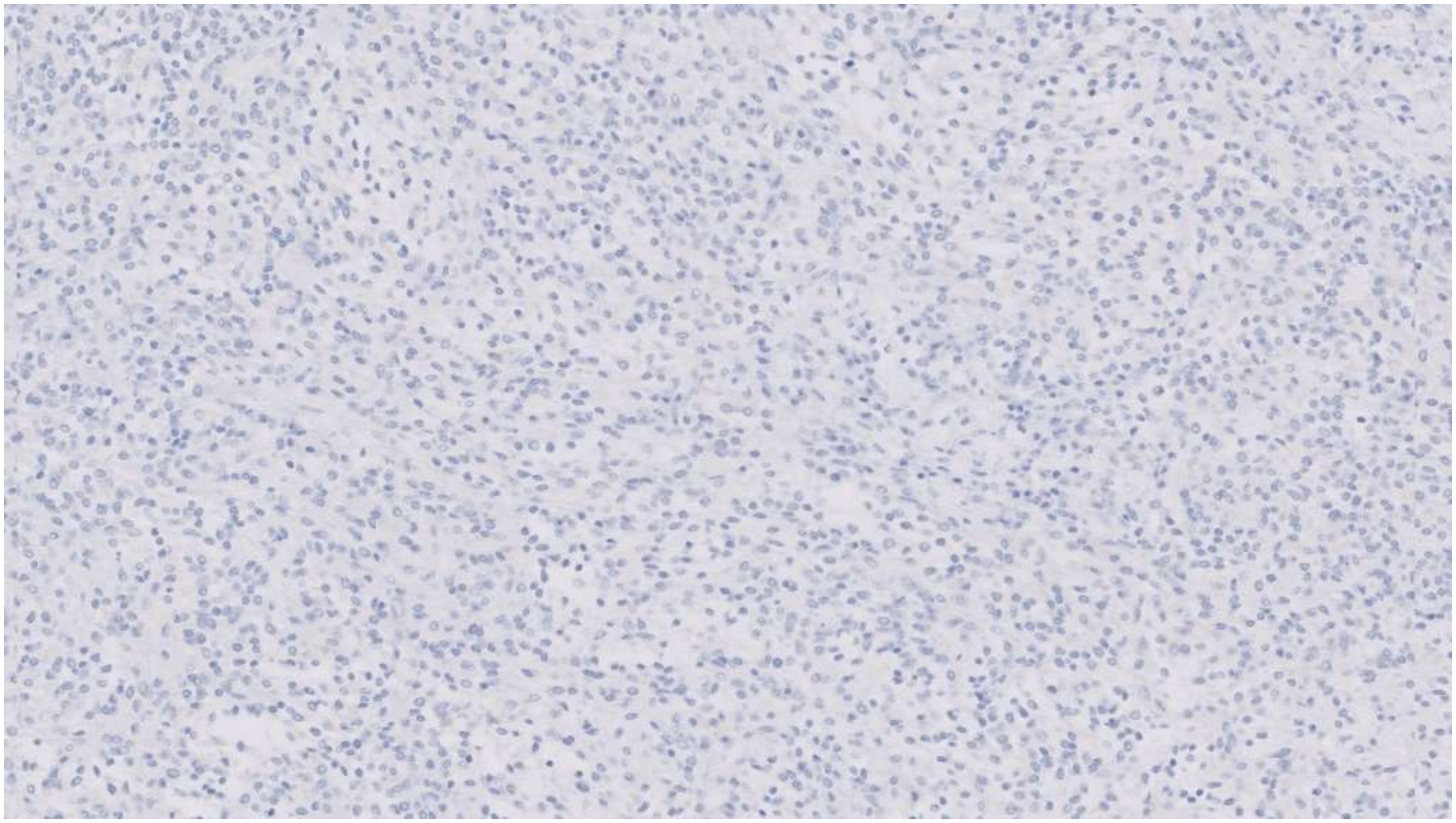
CD68



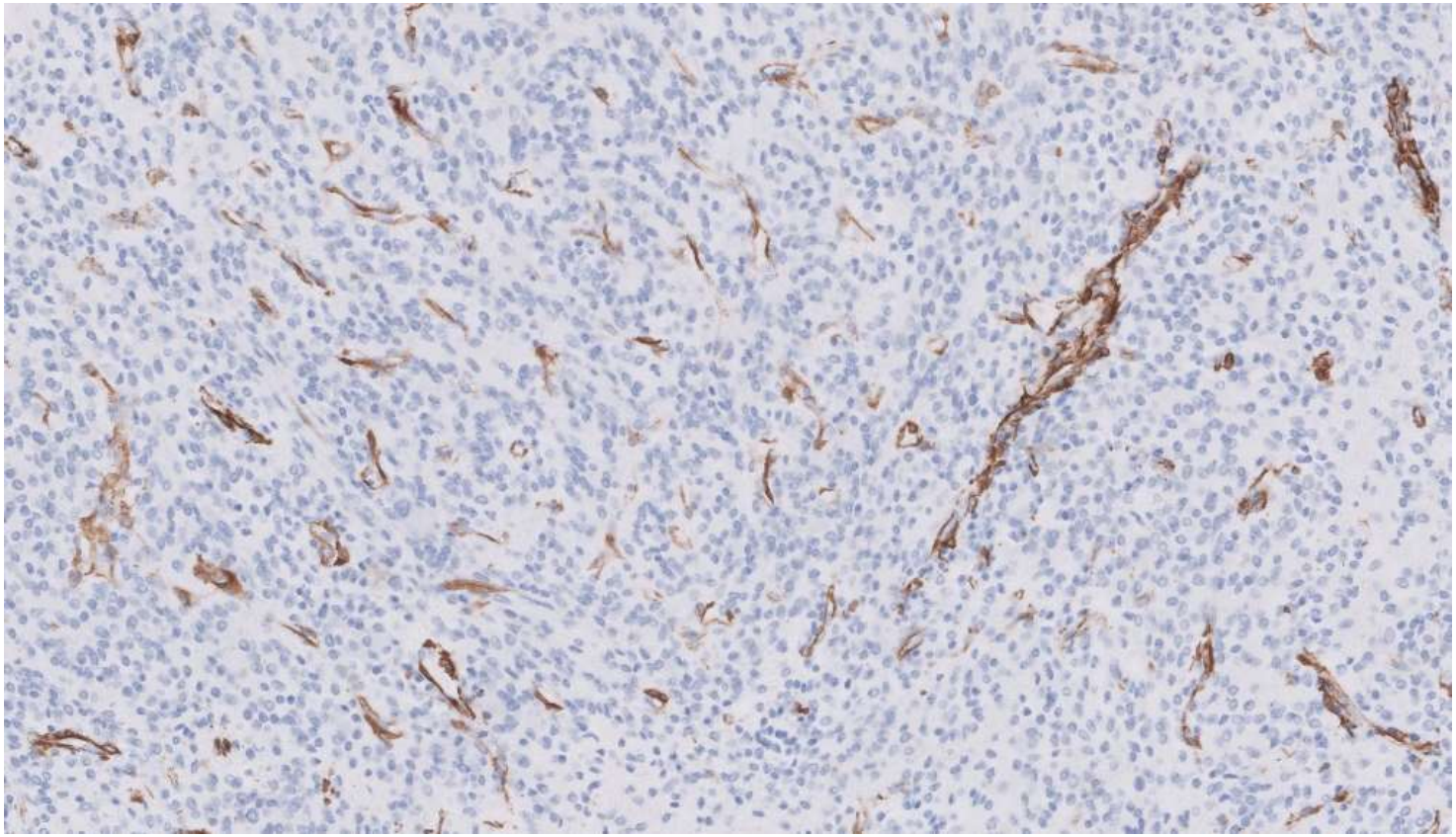
EMA



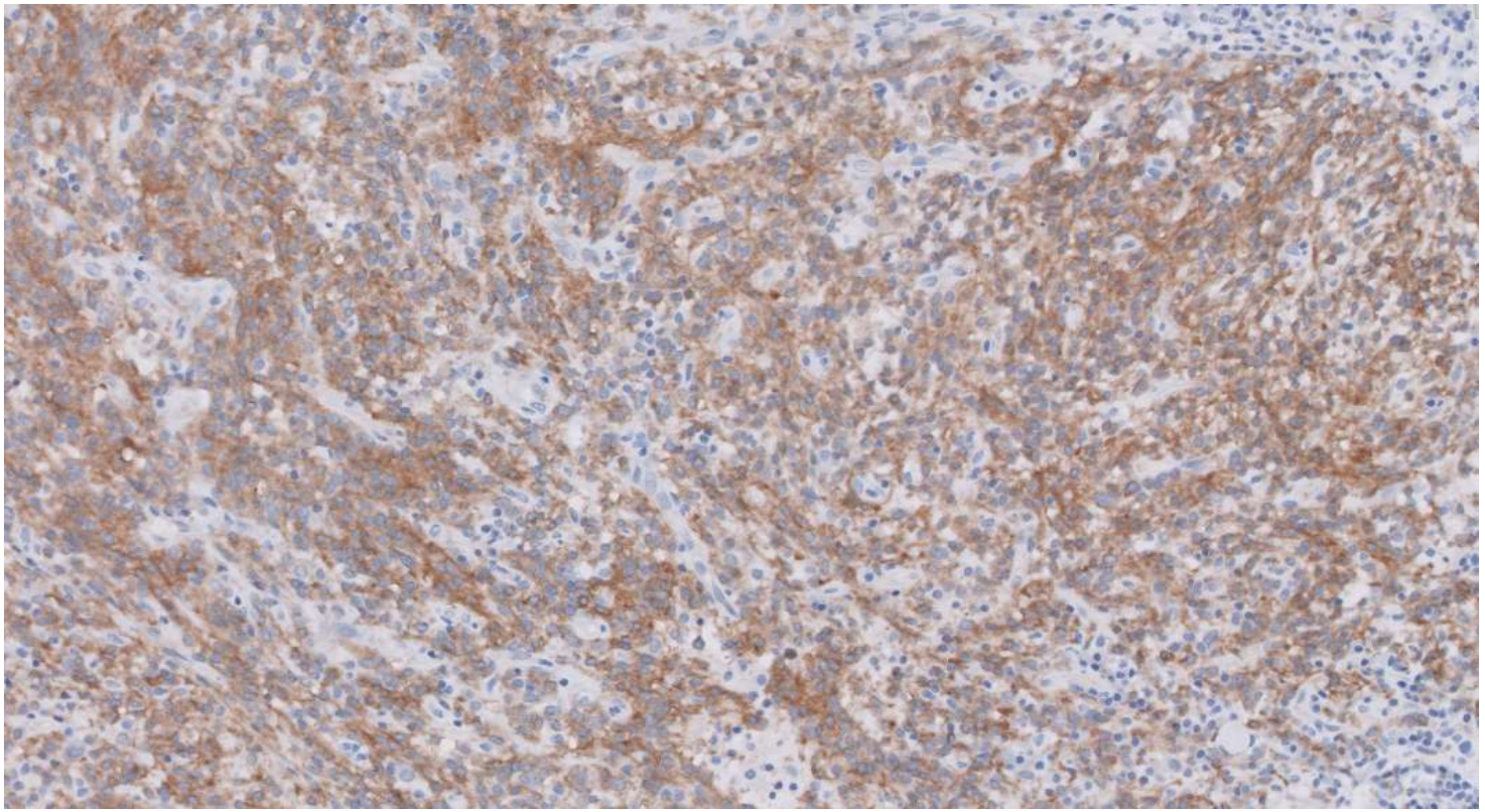
Desmin



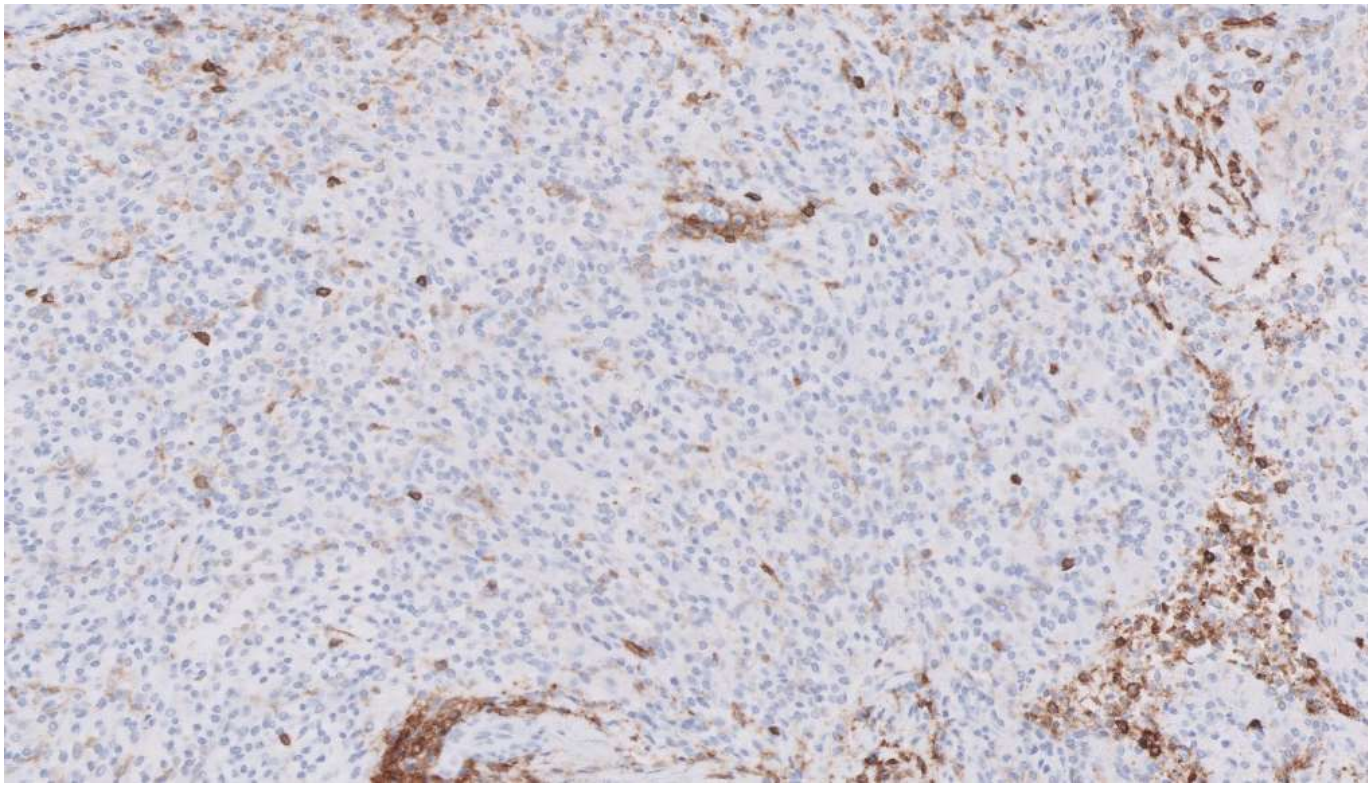
SMA



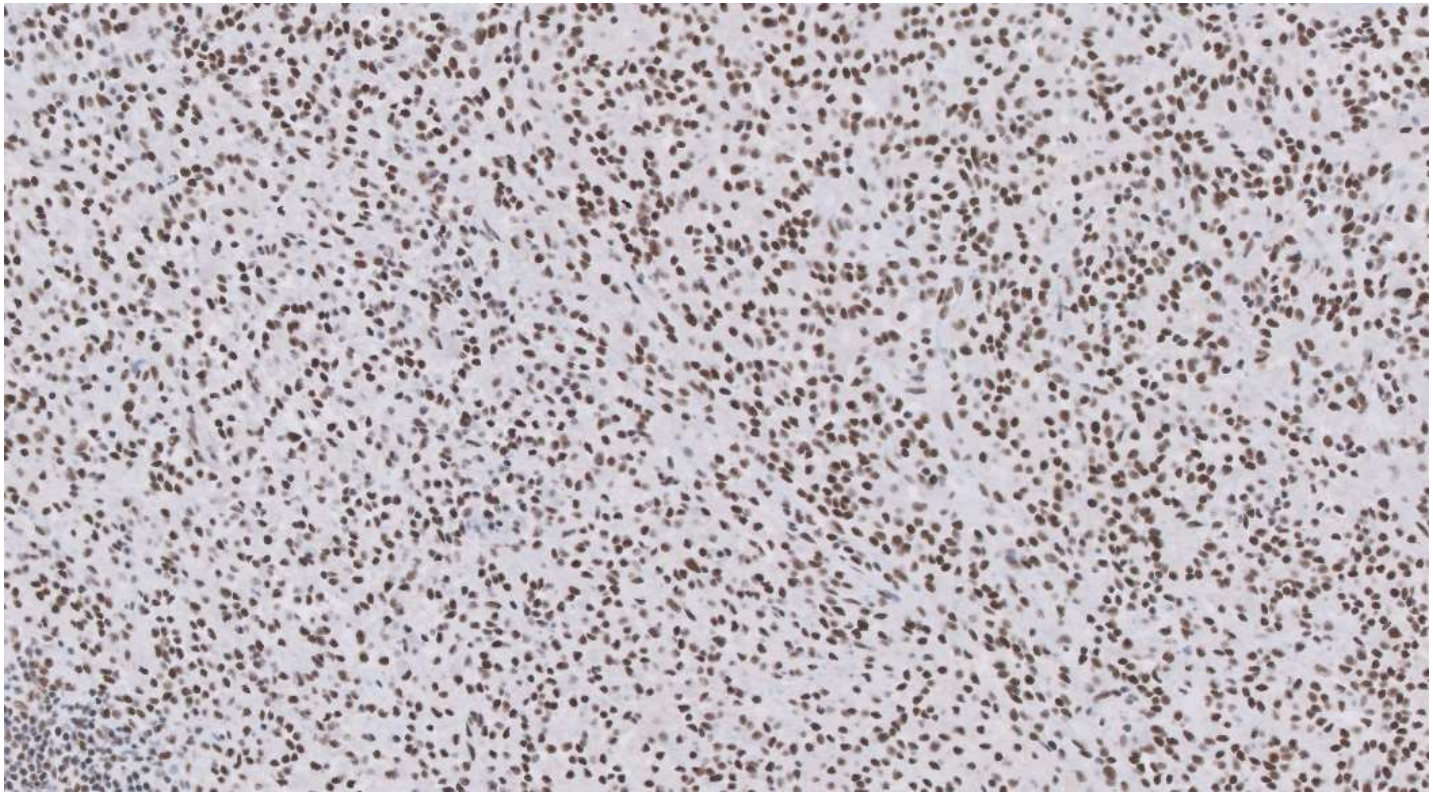
CD99



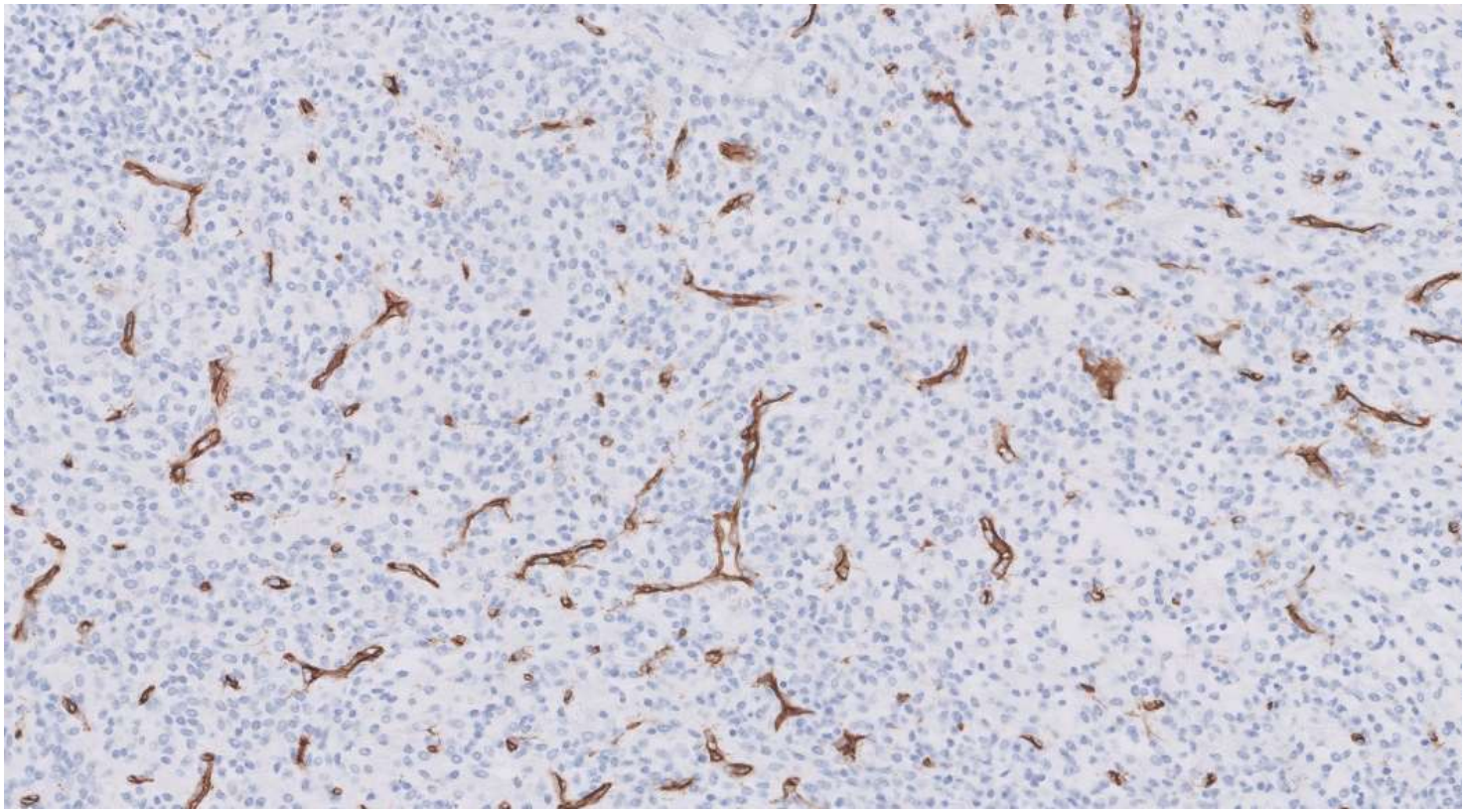
CD45



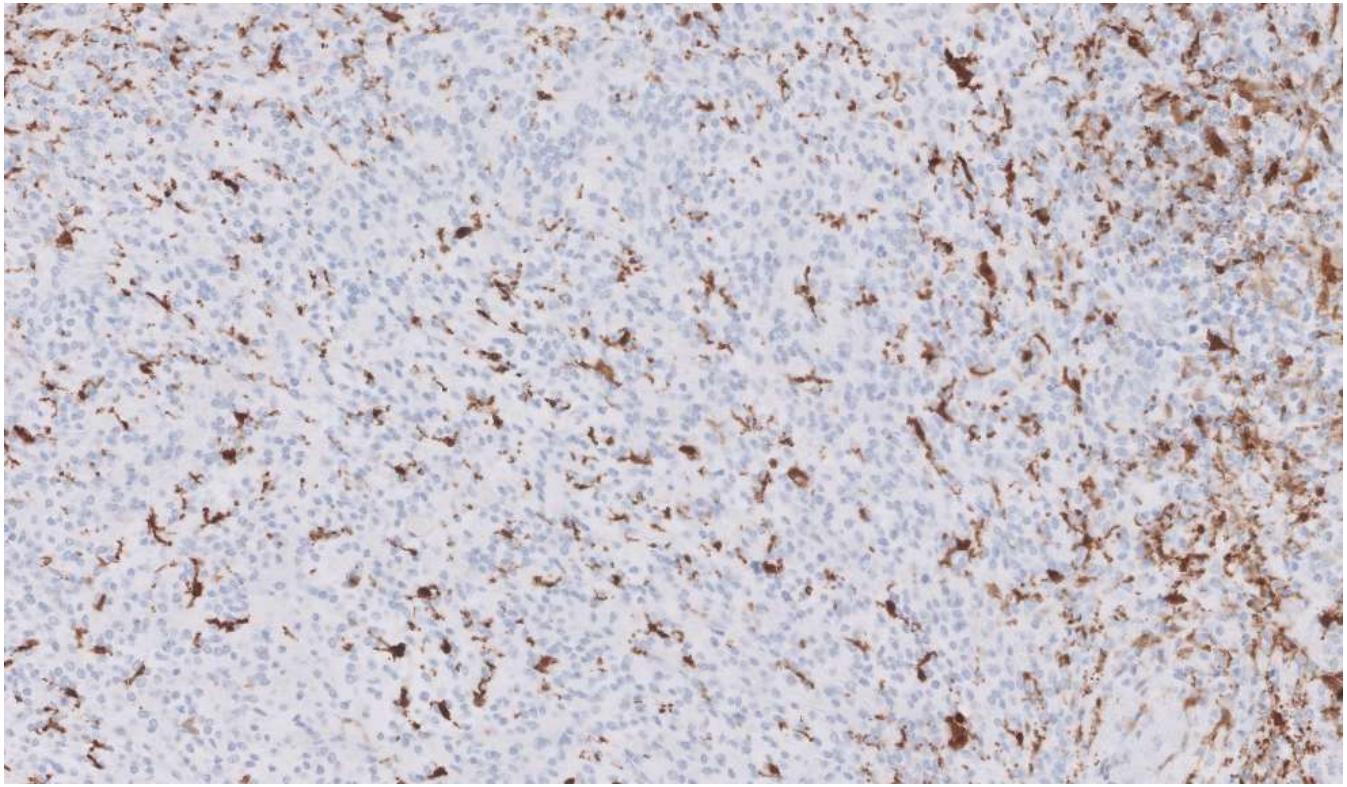
INI-1



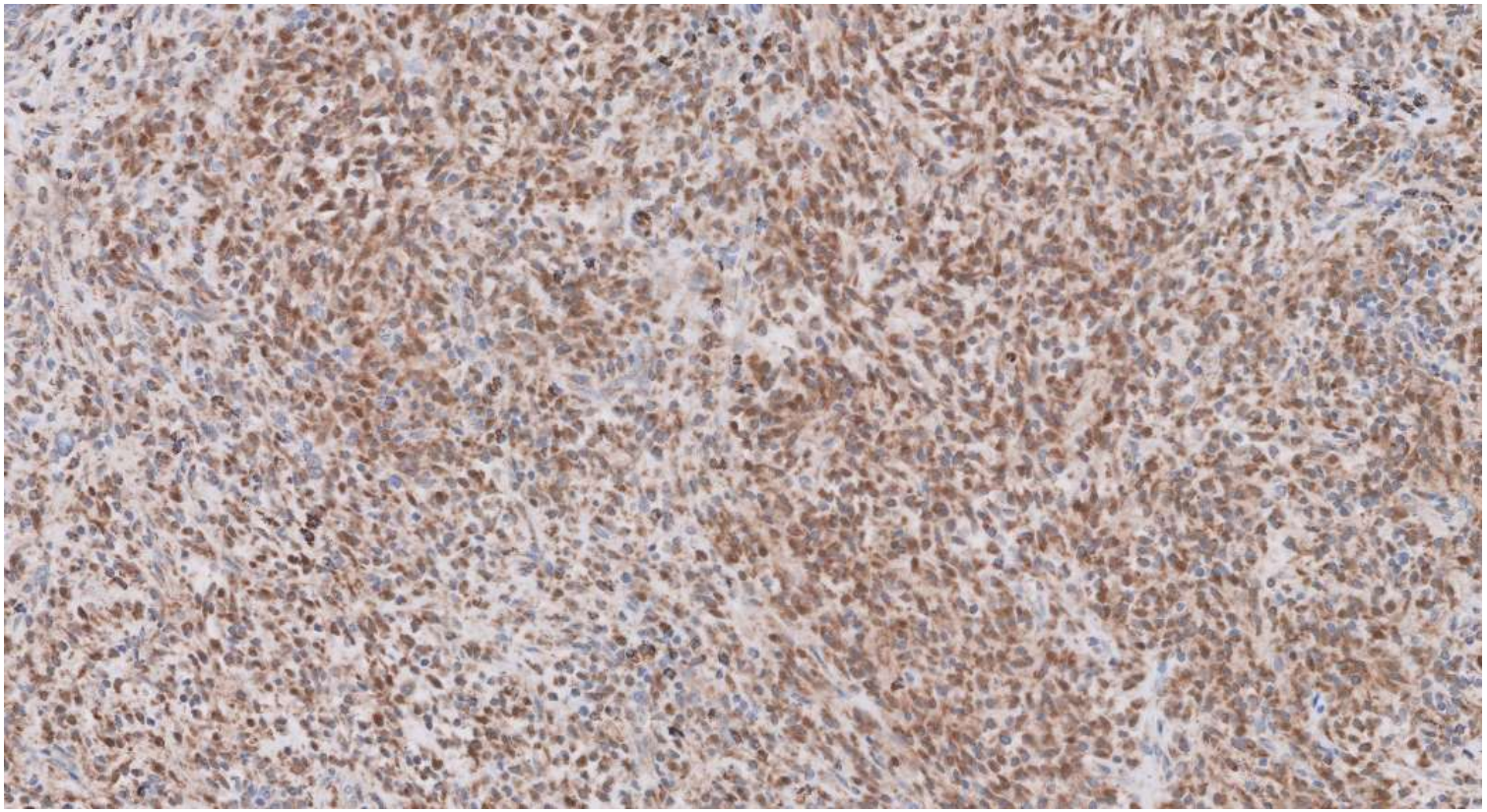
CD34



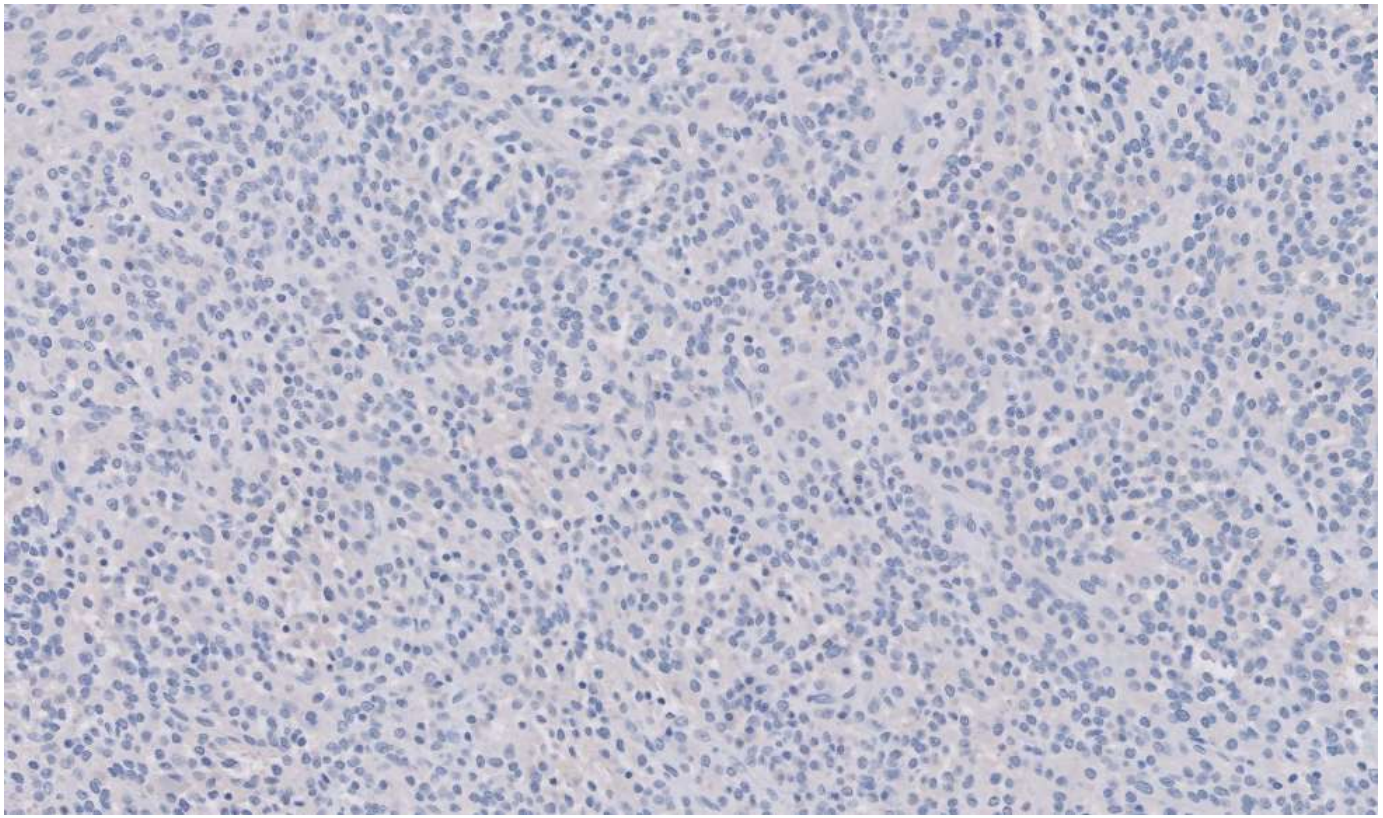
Factor 13a



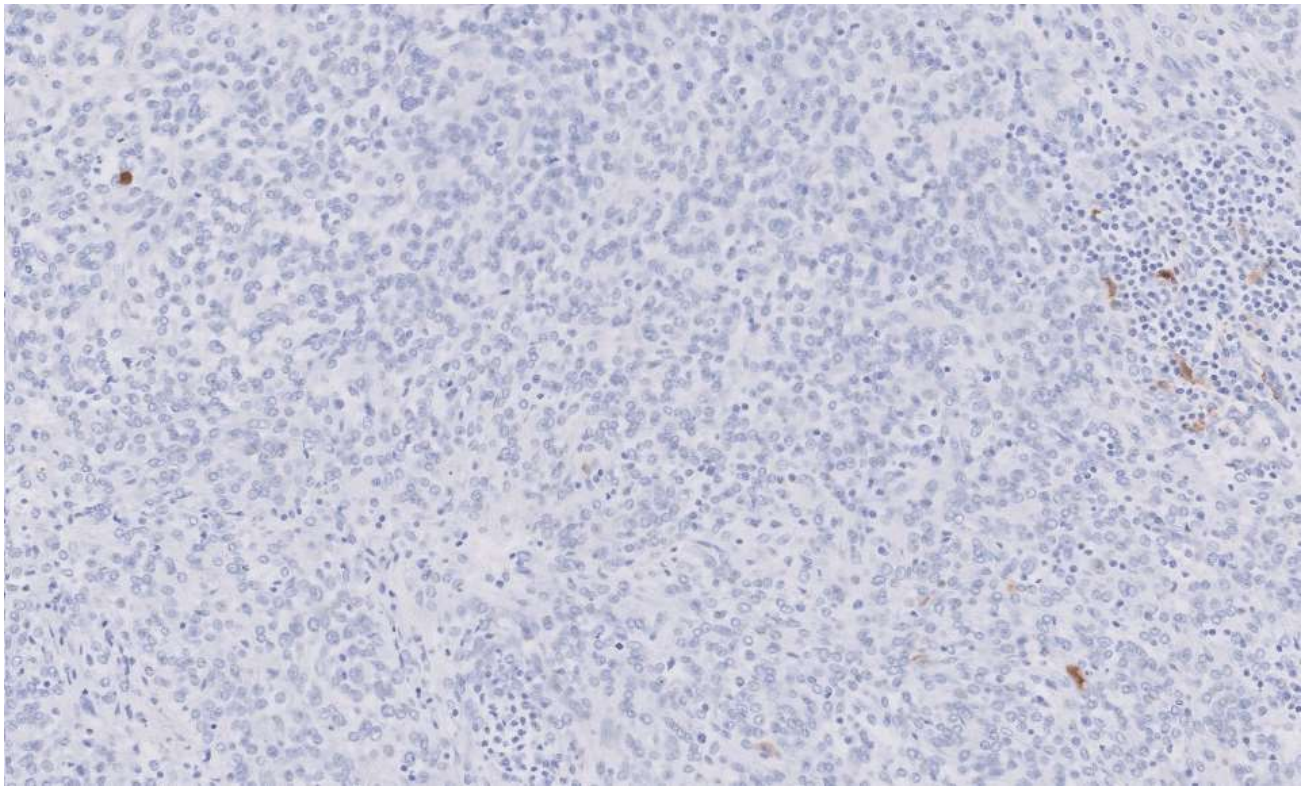
STAT6



MyoD1



S100



Immunohistochemistry summary

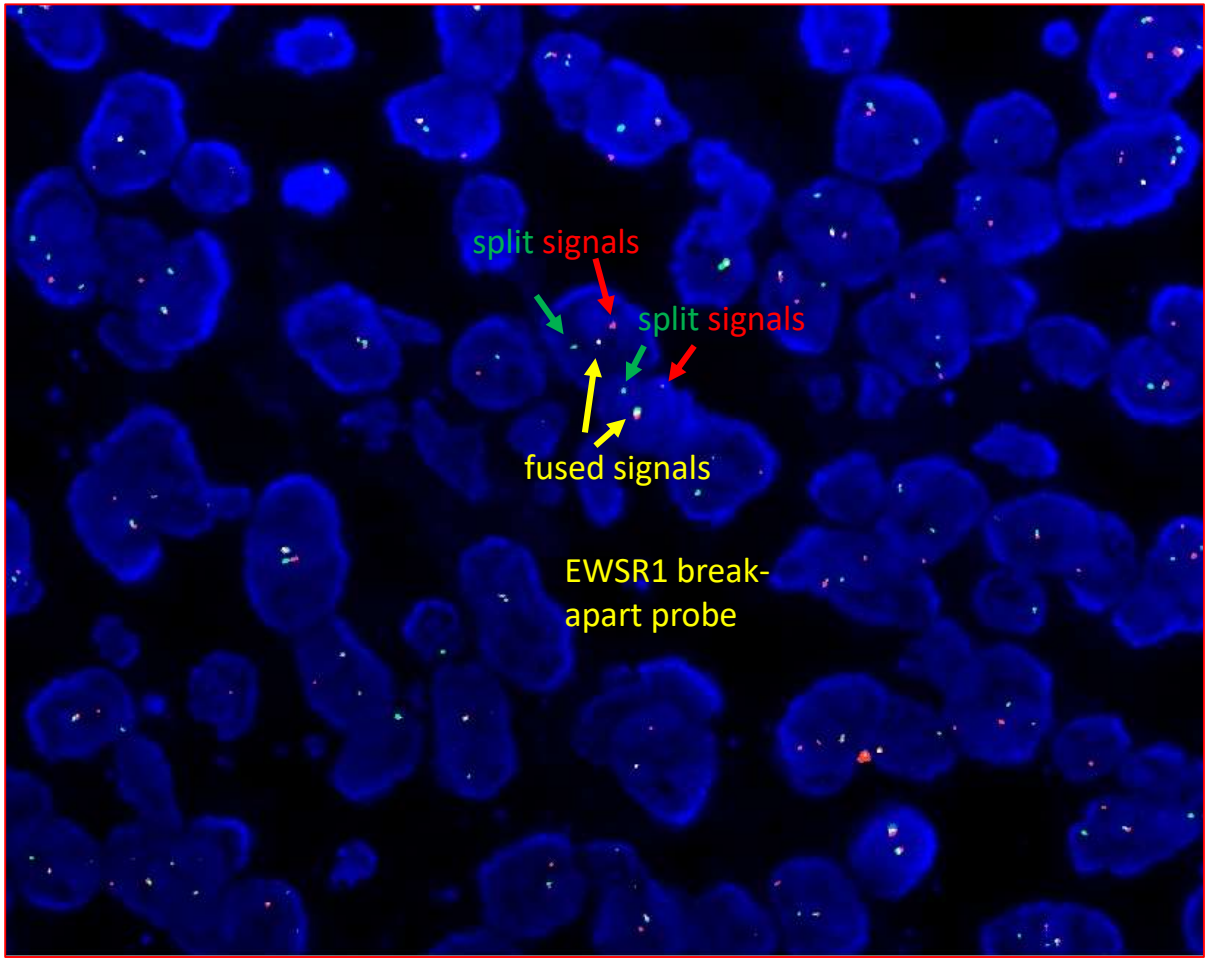
Positive	Negative
EMA	CK AE1/AE3
CD99	CD45
INI1 (retained, normal pattern)	S100 protein
CD68 (patchy)	Desmin
	SMA
	CD34
	Factor 13A
	STAT6 (no nuclear staining)
	MyoD1

Differential considerations

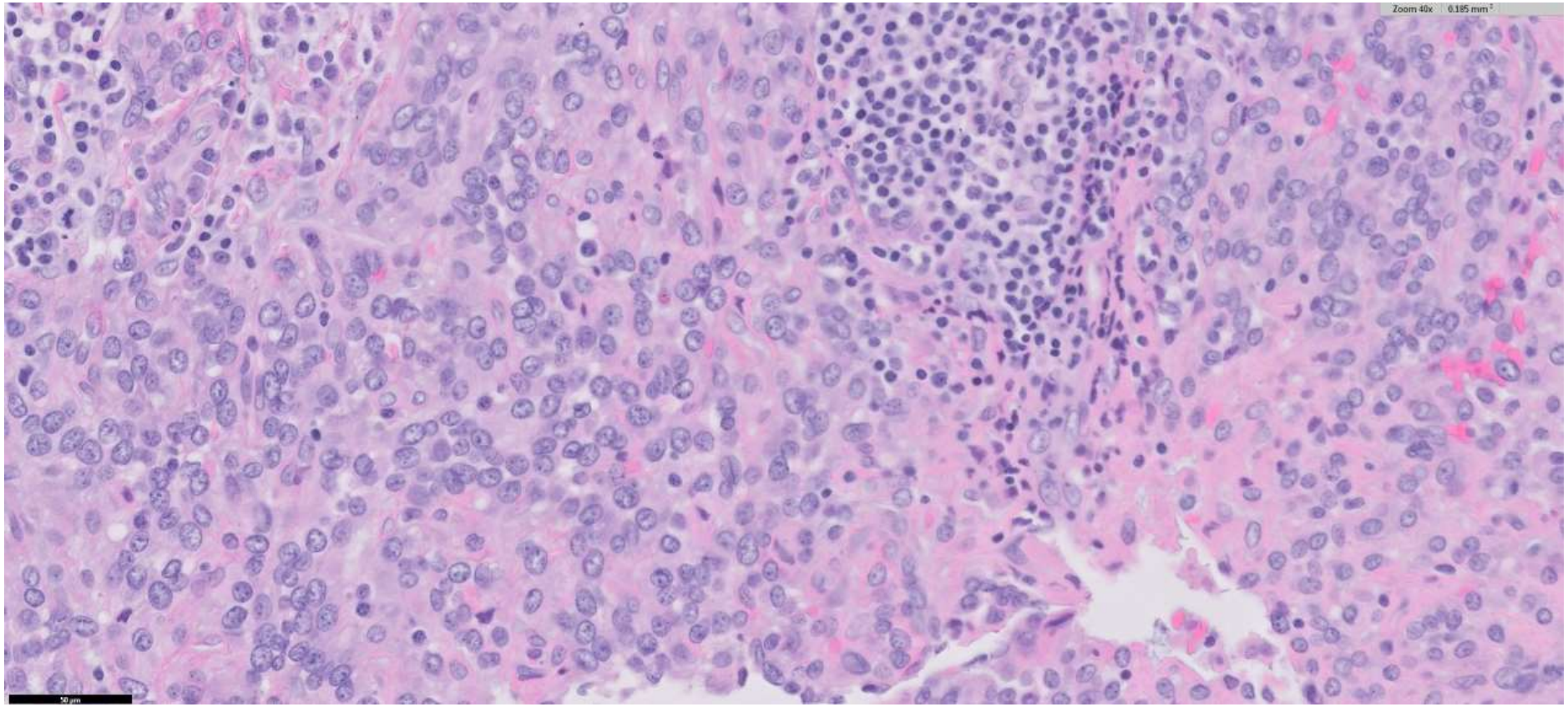
- Hematolymphoid and epithelial neoplasms ruled out
- EMA positive mesenchymal neoplasms:
  - Epithelioid sarcoma, but no keratin positivity
  - Soft tissue perineurioma
  - Follicular dendritic cell sarcoma
  - Sclerosing epithelioid fibrosarcoma
  - Angiomatoid fibrous histiocytoma
  - Synovial sarcoma
  - Soft tissue angiofibroma
- Other differential considerations:
  - Dermatofibroma/fibrous histiocytoma
  - Lymph node with metastatic tumor

Genetics

- Positive for *EWSR1* gene rearrangement
- Interphase FISH with the EWSR1 (22q12) break-apart probe
  - Fused red/green signals mark one intact 22q12 region
  - Split red/green signals indicate the presence of an EWSR1 gene rearrangement



Diagnosis: Angiomatoid Fibrous Histiocytoma (AFH)



AFH Clinical Features

- Rare
- Children and young adults (mean 20 years)
- Extremities, head and neck
- Most deep to fascia, rarely body cavities, intracranial
- Painless
- Slow growing
- Paraneoplastic syndrome:
  - Anemia, fever, weight loss
  - Mediated by IL-6, treatment role for anti-IL-6 antibody
- Intermediate malignant potential
  - Low local recurrence rates
  - Rare regional lymph node metastases

AFH Pathologic Features

- Well circumscribed, multinodular, less than 4 cm
- Thick fibrous pseudocapsule
- Dense lymphoplasmacytic cuff
  - May include germinal center formation and simulate a lymph node metastasis
- Central hemorrhage
  - May be lined by flattened tumor cells, not true vascular spaces
  - Hemosiderin or hematoidin deposition may be present
- Tumor cells in sheets, short fascicles or tentacles extending into lymphoid tissue
- Histiocytoid to myoid tumor cells
  - Round to oval nuclei with fine vesicular chromatin and inconspicuous nucleoli
  - Indistinct cell borders/syncytial appearance
- Scant stroma
  - Uncommonly myxoid change
- Usually minimal pleomorphism and mitotic activity

AFH Immunohistochemistry

- Positive stains:
  - **EMA ~50%**
  - **Desmin ~40%**
  - Rare: CD68, CD99, ALK, Calponin, CD34, CD21, keratin

AFH Molecular Genetics

- Most lesions have one of three characteristic translocations:
  - *EWSR1-CREB1* t(2;22)(q33;q12)
    - Most common
    - Also seen in clear cell sarcoma, gastrointestinal clear cell sarcoma-like tumor, and primary pulmonary myxoid sarcoma
  - *EWSR1-ATF1* t(12;22)(q13;q12)
    - Also seen in clear cell sarcoma, gastrointestinal clear cell sarcoma-like tumor, primary pulmonary myxoid sarcoma, and non-mesenchymal tumors (hyalinizing clear cell carcinoma of the salivary gland and clear cell odontogenic carcinoma).
  - *FUS-ATF1* t(12;16)(q13;p11)
    - First discovered, least common
- Caution: the fusions involving *FET* (*EWSR1*, *FUS*) and *CREB* (*ATF1*, *CREB1*, *CREM*) are not specific for AFH

Pearls and Pitfalls

- Combined clinical, morphologic and genetic features are key for recognition
  - EMA and desmin positivity helpful, but not sensitive or specific
  - Hematoidin is a useful clue, rare in other fibrohistiocytic tumors
  - Confirmation of *EWSR1* fusion may be necessary on small biopsies
- Central blood filled spaces can simulate hematoma, hemangioma, or a thrombosed vessel
  - Particularly challenging on cytology
- Dense lymphoplasmacytic cuff with fibrous pseudocapsule may be mistaken for a lymph node at low power
  - Absence of normal lymph node architecture such as subcapsular sinus and hilar vessels to distinguish AFH
- May be confused with **aneurysmal fibrous histiocytoma**
  - Similar/confusing nomenclature but completely distinct entity
  - Aneurysmal fibrous histiocytoma presents in older adults as cutaneous papule
  - Lacks pseudocapsule and lymphoplasmacytic cuff
  - Like all cutaneous fibrous histiocytomas, peripheral collagen trapping and associated epidermal changes

Acknowledgements

- Dr. Yue Peng
- Dr. Amir Qorbani
- Dr. Andrew Horvai

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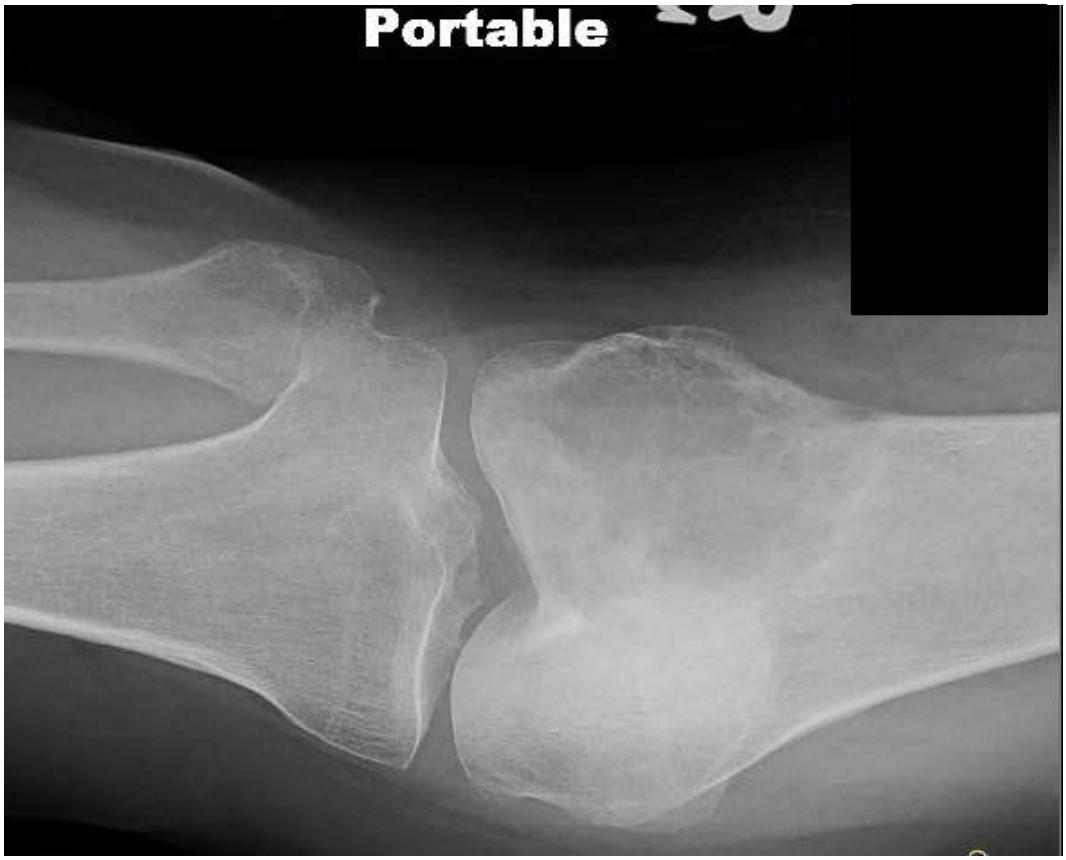
21-1205

Bonnie Balzer; Cedars-Sinai Medical Center

60-year-old F with no past medical history presents with right distal femur pain x5 months. Recent swelling and progressive pain leading to ambulatory difficulties.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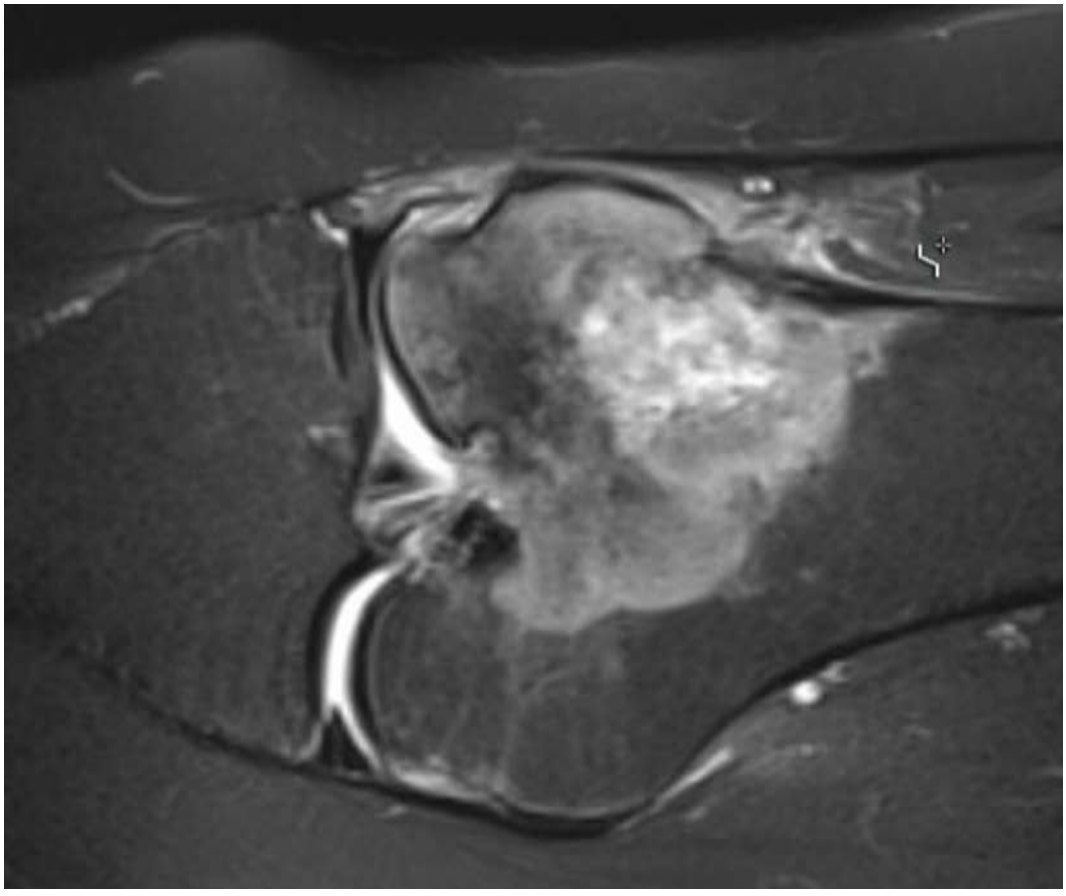

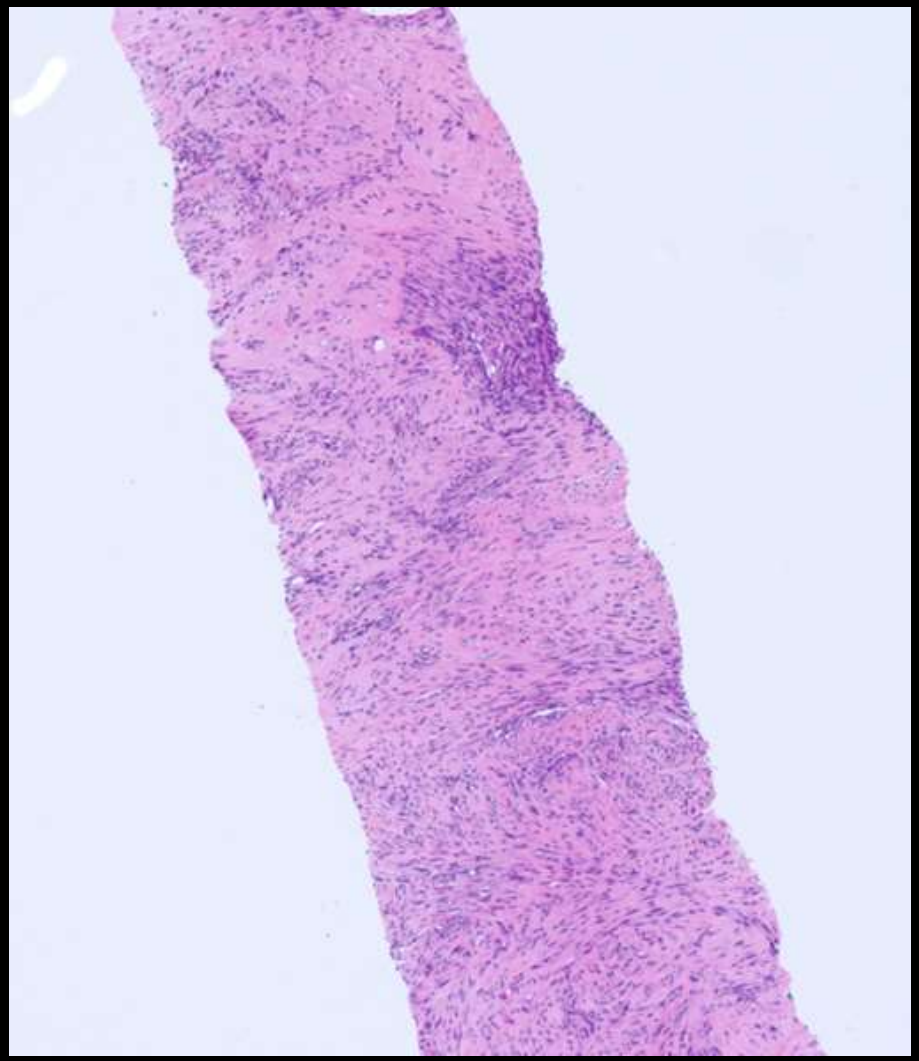

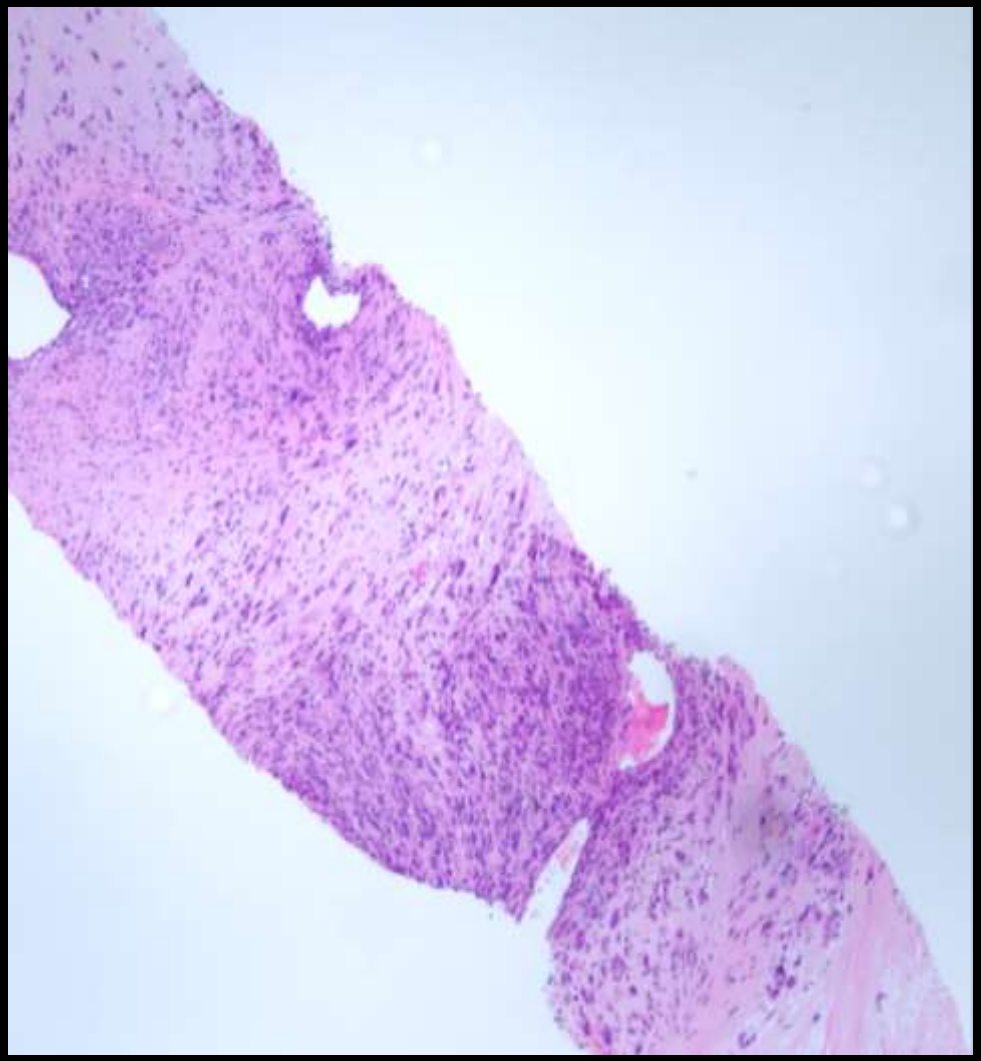

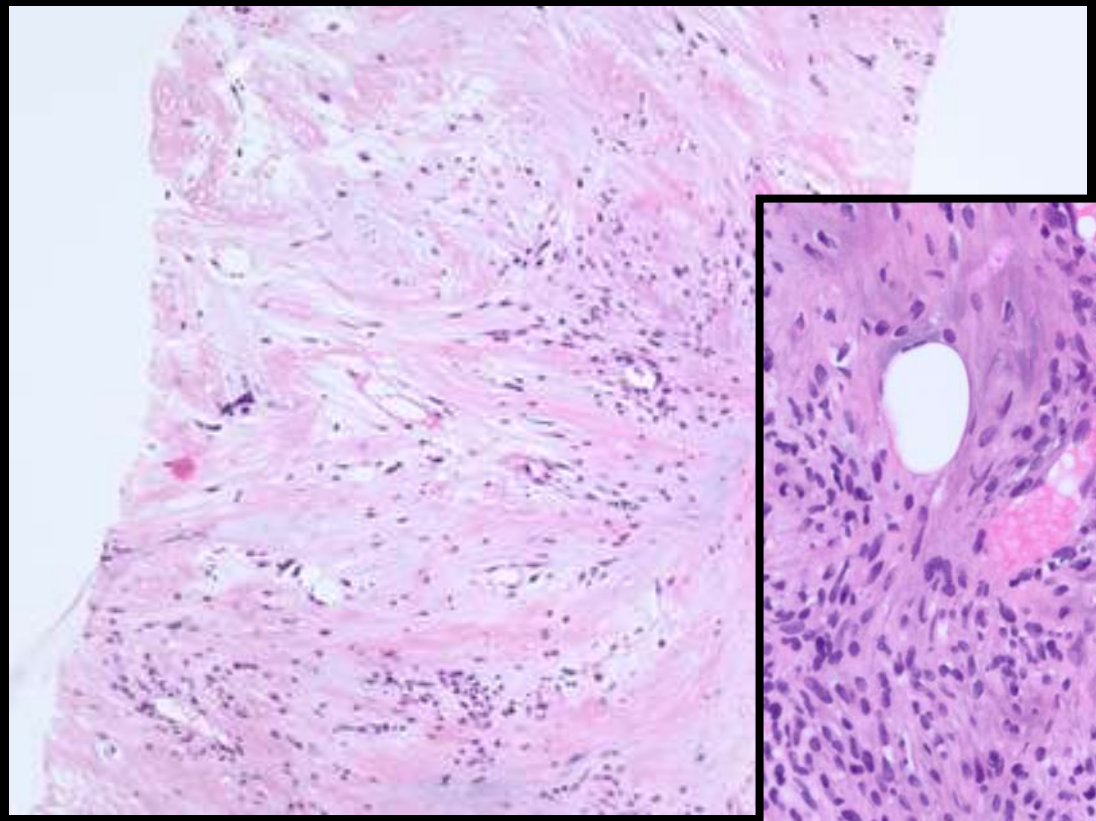

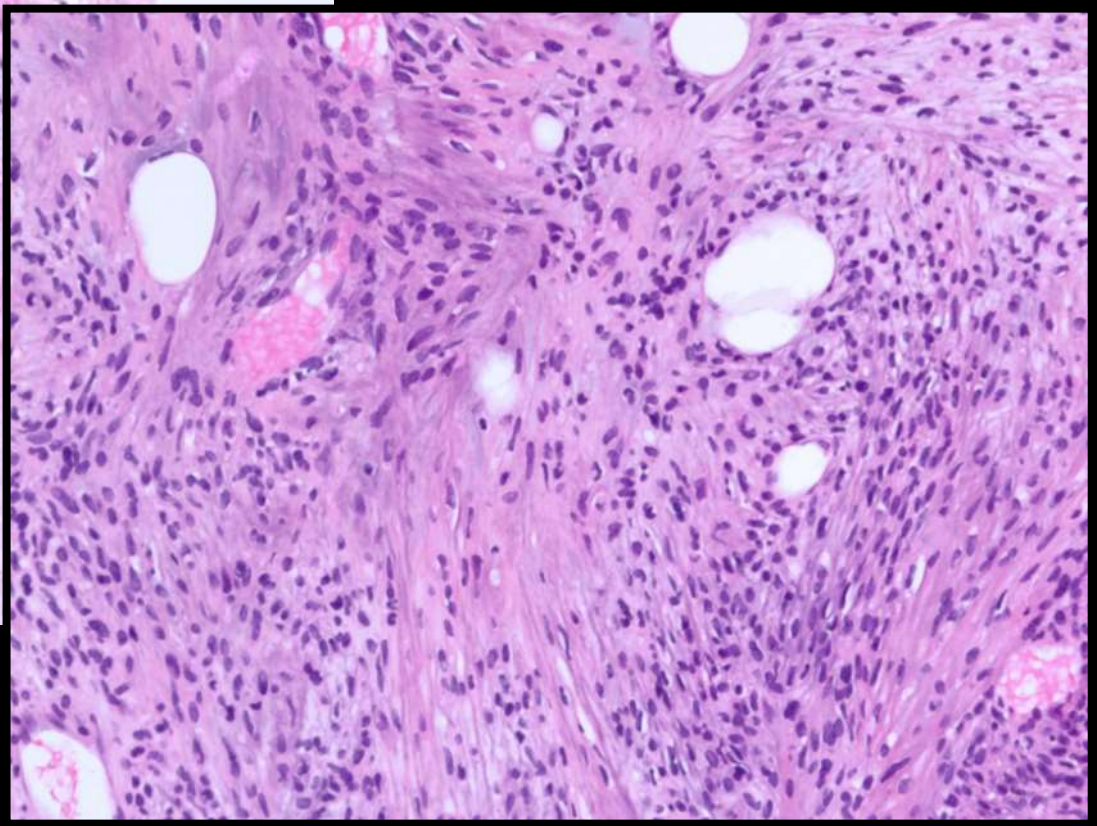

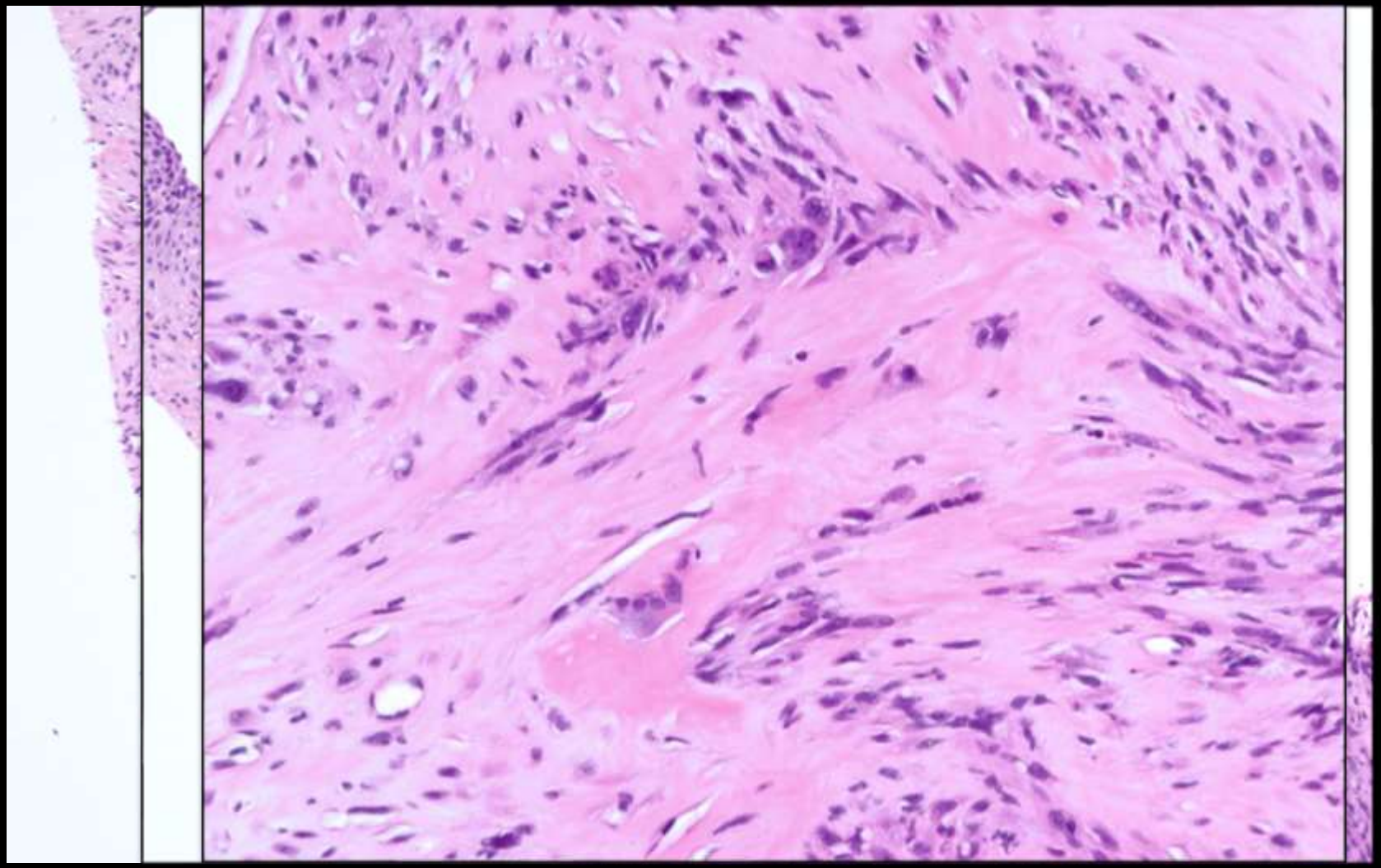

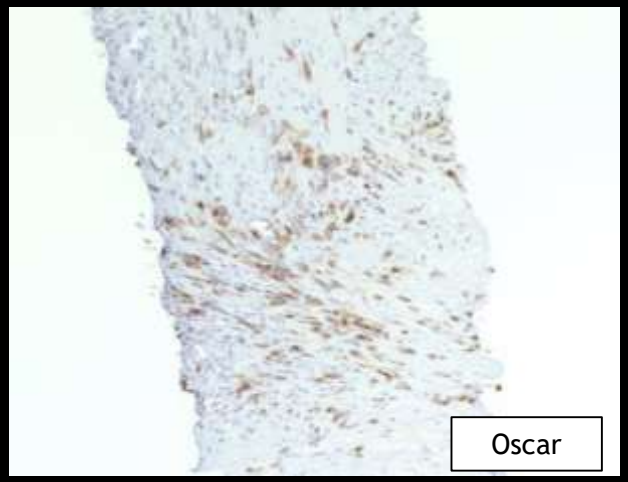
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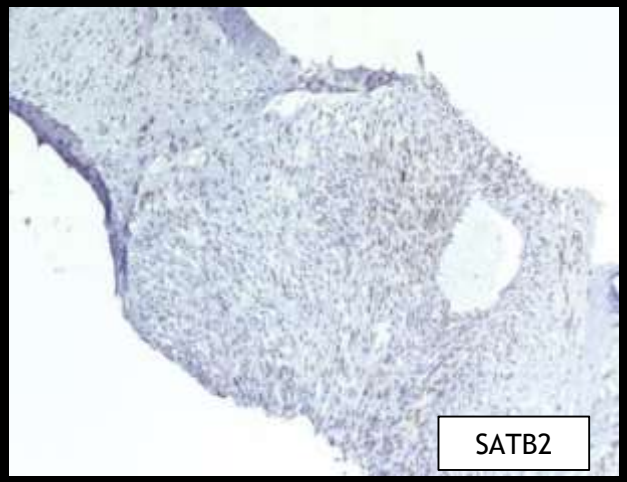
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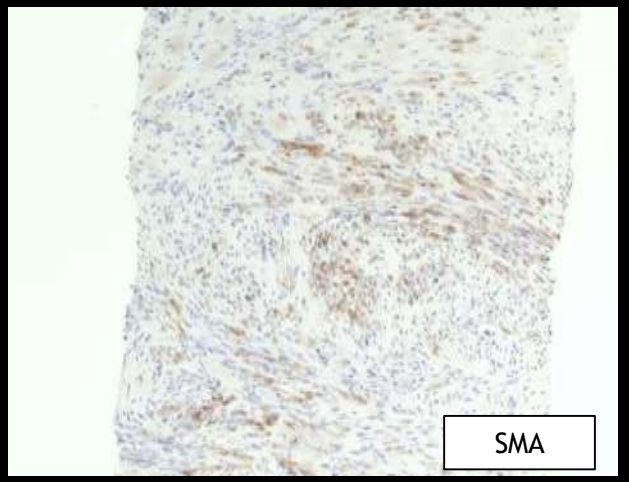
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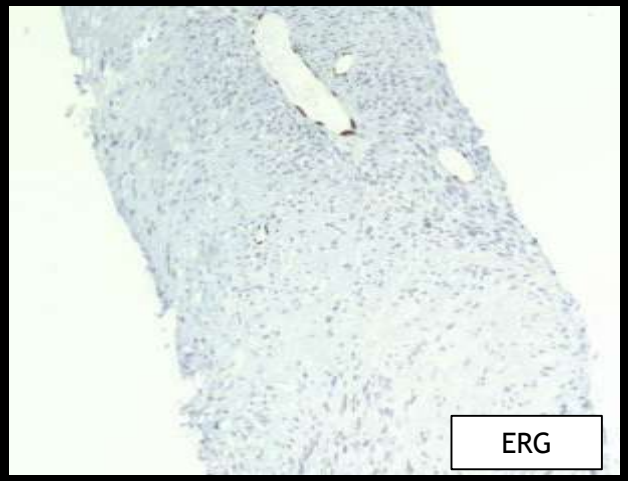
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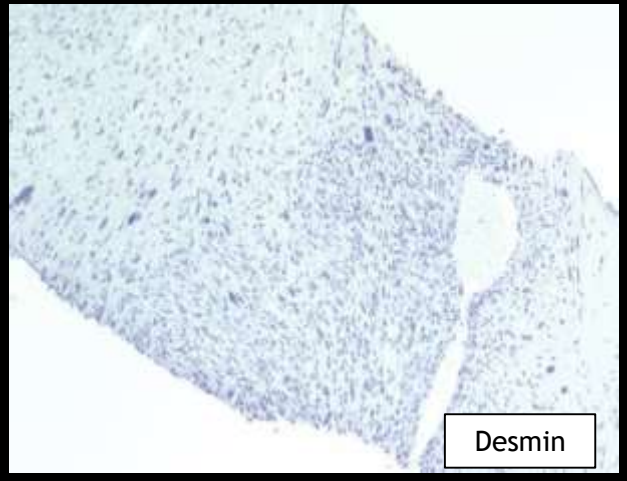
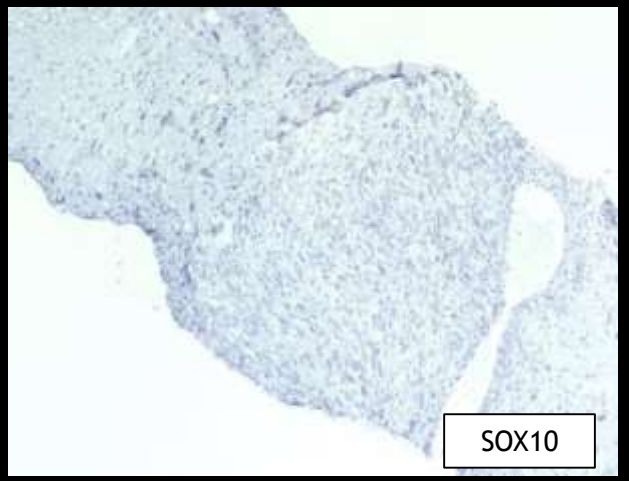

Desmin


SOX10

*** ADDENDUM ***
(9/21/2020)

CS - Comprehensive Cancer Panel

SPECIMEN INFORMATION

Specimen Type:	Bone biopsy sample	**Source:**	FEMUR

Percent Tumor Nuclei:	50
Clinical Indication:	High-grade spindle cell sarcoma

RESULT SUMMARY

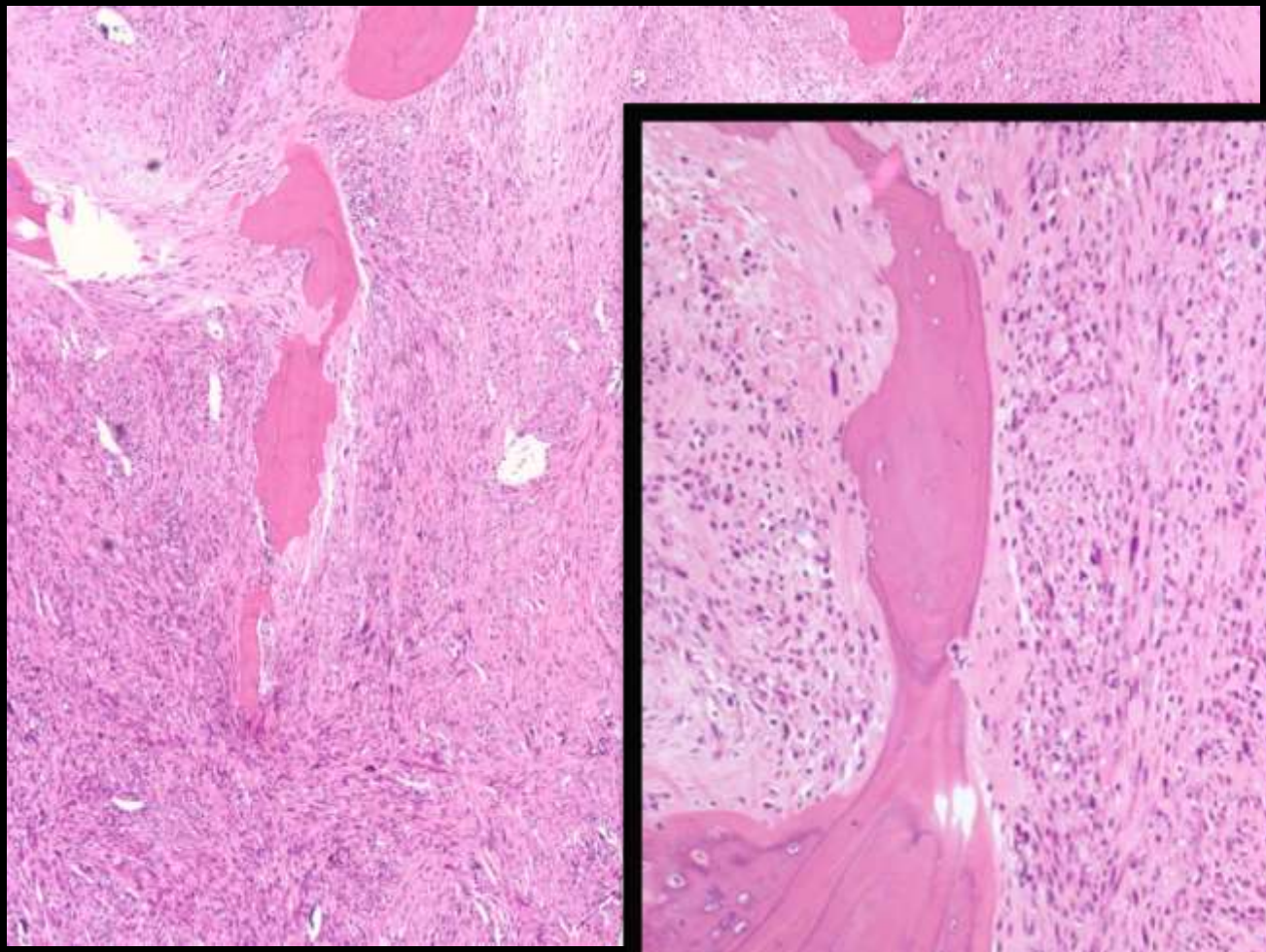
No clinically relevant results identified.

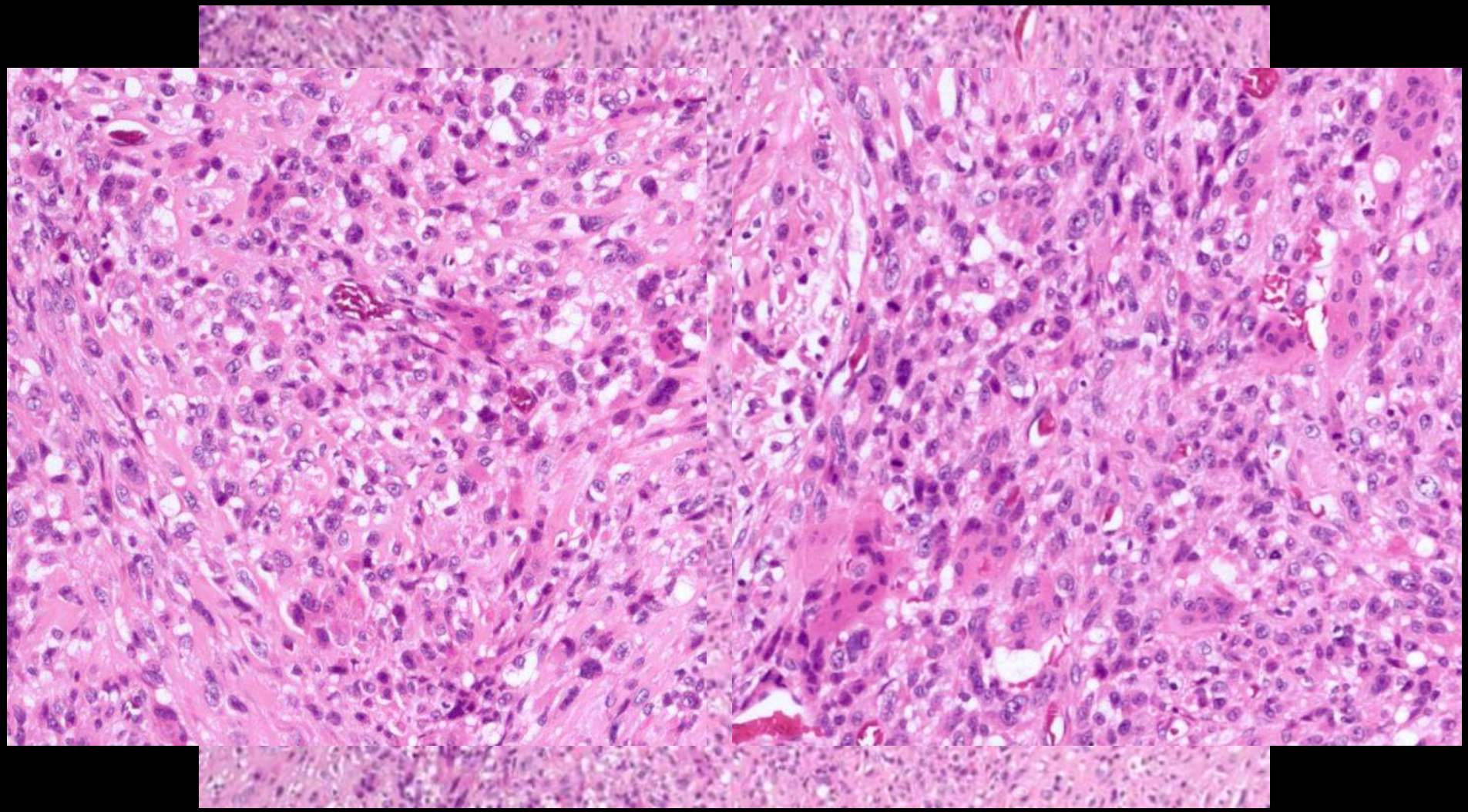
IMMUNOTHERAPY

TMB Low: 3 muts/Mb
Tumor mutational burden (TMB) is a measurement of the amount of nonsynonymous somatic mutations present within a tumor sample. Tumors that have low TMB are unlikely to respond to immunotherapy (PMID 28835386, 29657128, 30643254).

Microsatellite Instability (MSI) Not Detected.
Note: Testing was only performed on tumor tissue which can limit sensitivity of MSI detection. If clinically suspected, repeat analysis on matched tumor normal can be performed.


cm
1
2
3
4
5
Form 8119 (7/17)





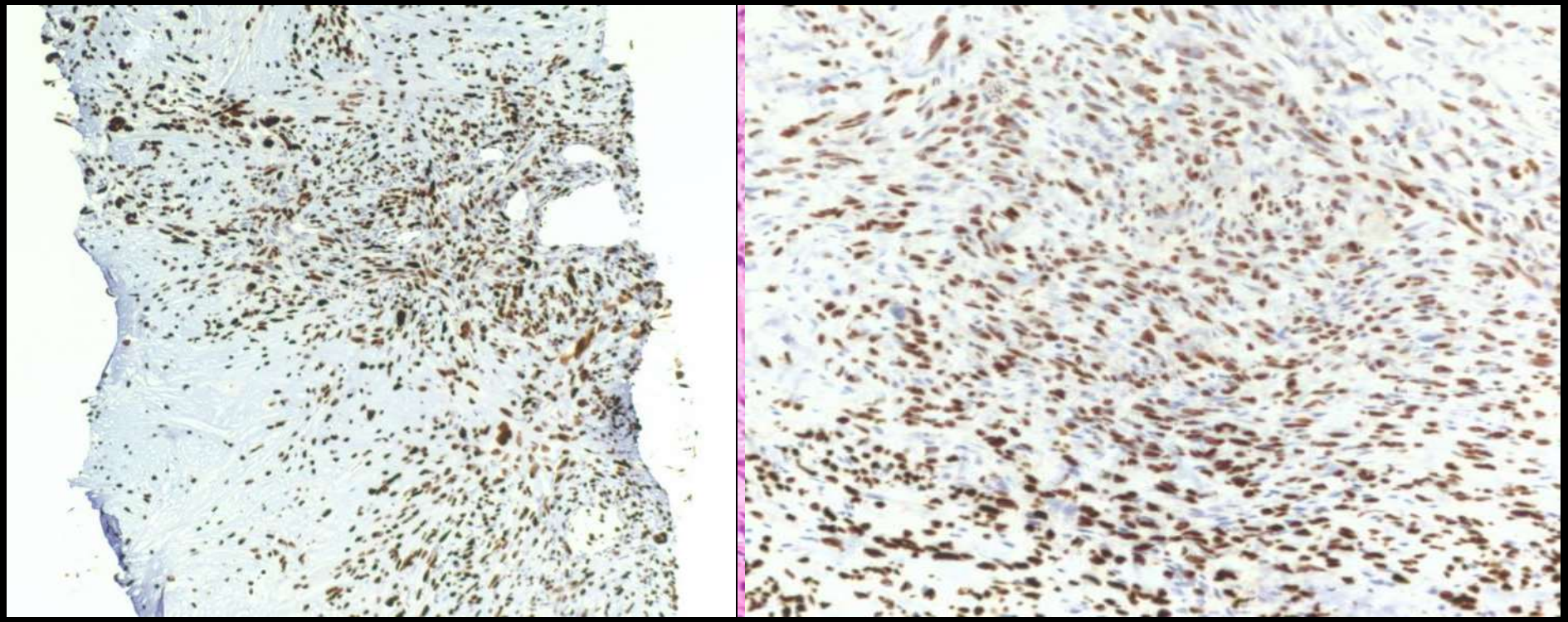
Diagnosis….

B. BONE, RIGHT DISTAL FEMUR, RESECTION:

- High-grade sarcoma, most consistent with malignant giant cell tumor of bone with osteosarcomatous differentiation (see synoptic report)

A&B. BONE, RIGHT FEMUR, BIOPSY:

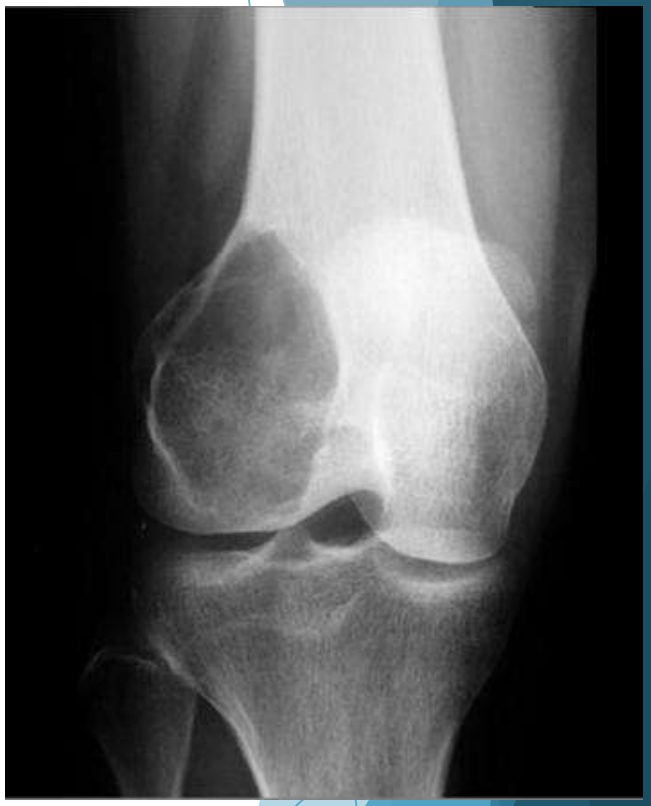
- High-grade spindle cell sarcoma, most consistent with malignant transformation in a giant cell tumor (malignant giant cell tumor of bone)



G34W

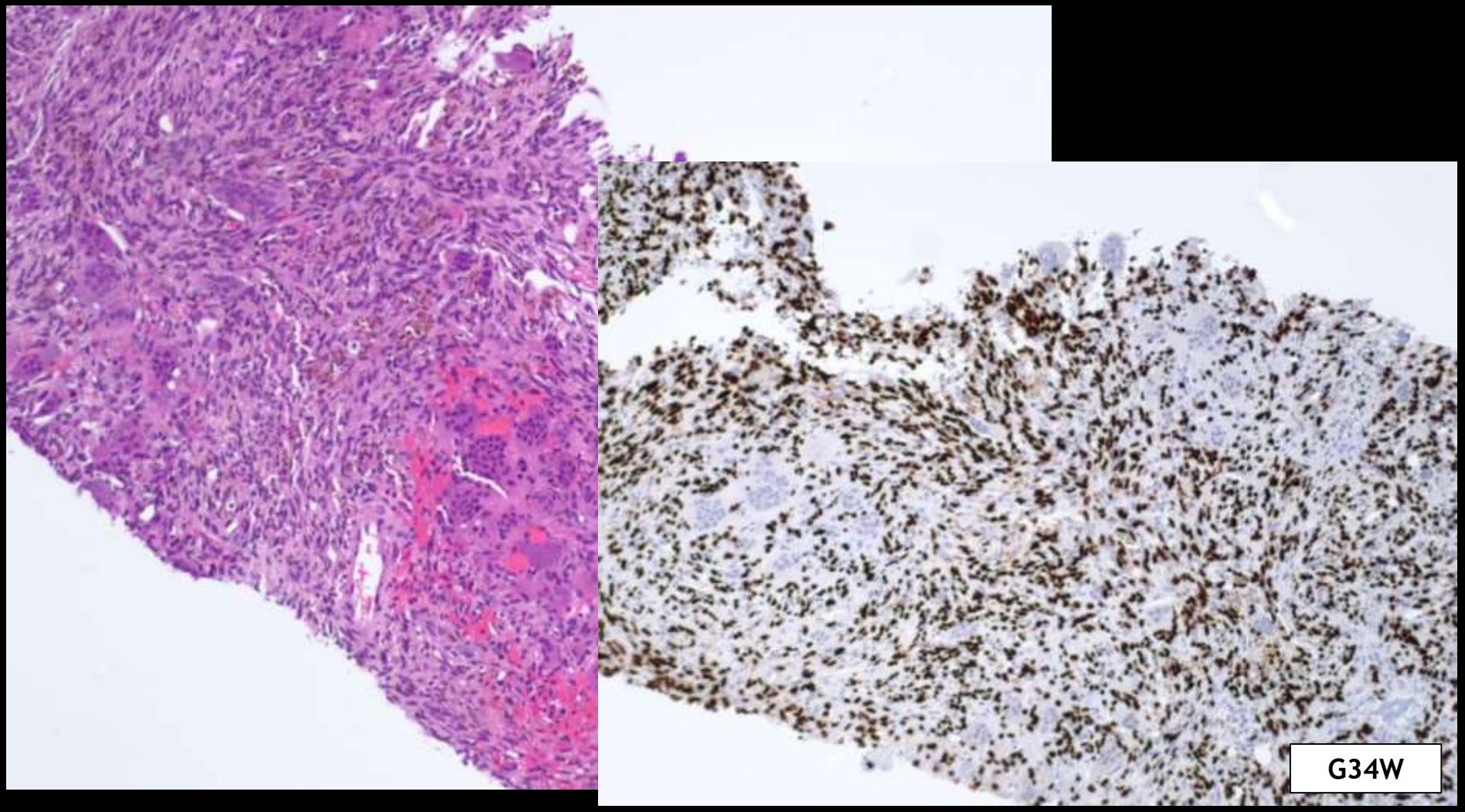
Giant Cell Tumor of Bone

- Accounts for ~5% of primary bone tumors
- Considered benign
  - Locally aggressive
  - Metastasis to lung
  - Rarely undergo malignant (sarcomatous) transformation
- More common in young and middle-aged adults
  - Slight female predominance
- Distal femur and proximal tibia are most common site
  - Epiphyseal → metaphyseal
- Lobulated, expansile osteolytic lesions “soap bubble” appearance



Giant Cell Tumor of Bone - Histology

- Demonstrates two distinct components:
  - Numerous osteoclast-like giant cells
    - Evenly distributed
    - Many nuclei
  - Mononuclear cells – neoplastic element
    - Spindled or round morphology
    - Osteoblastic in origin
- Histiocytes
- Vascular stroma with fibrosis/woven bone
- Acute hemorrhage and secondary aneurysmal bone cyst-like changes


G34W

Malignant Giant Cell Tumor of Bone

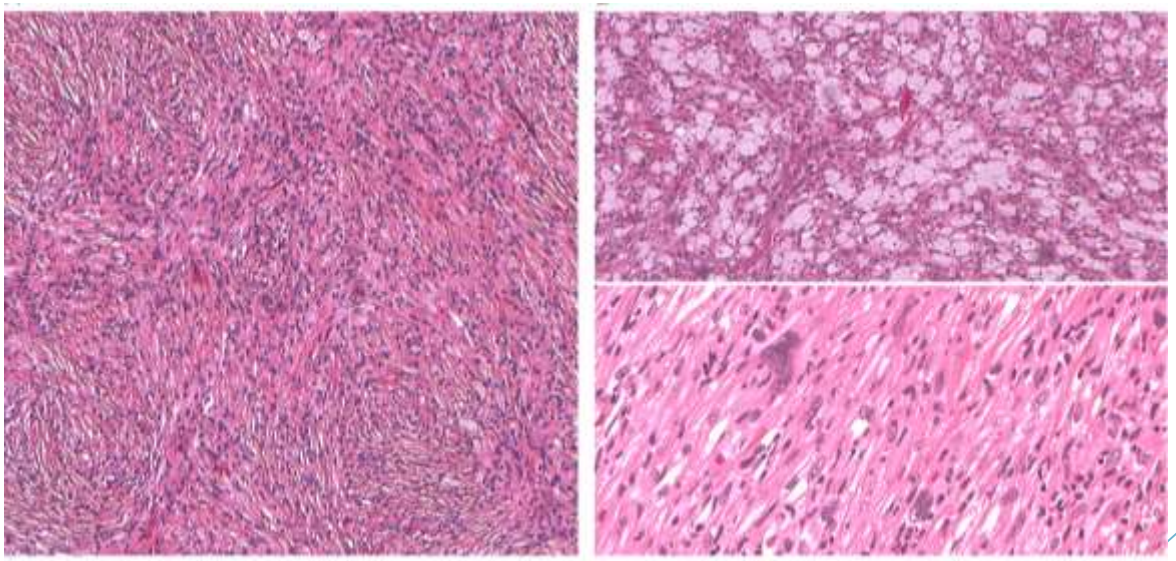
- Conventional giant cell tumor undergoes sarcomatous transformation
  - Osteosarcoma, fibrosarcoma or undifferentiated pleomorphic histology
- Considered primary or secondary
  - Primary = de novo
    - Sarcomatous component + conventional GCT histology
  - Secondary = occurs at site of previously treated GCT
    - Highest incidence with prior radiation therapy
    - Usually no conventional GCT component

Giant Cell Tumor of Bone – Treatment

- Surgical resection is standard first-line therapy
  - Curettage, en bloc resection or amputation
  - Success highly dependent on tumor location
- Radiotherapy is option for unresectable tumors
  - May be associated with secondary malignancy
- Systemic treatment
  - Bisphosphonates
    - Prevent bone resorption and inhibit osteoclast activity/promote apoptosis
  - Denosumab (human monoclonal antibody of RANKL)
    - Prevents RANK activation → maturation of osteoclasts

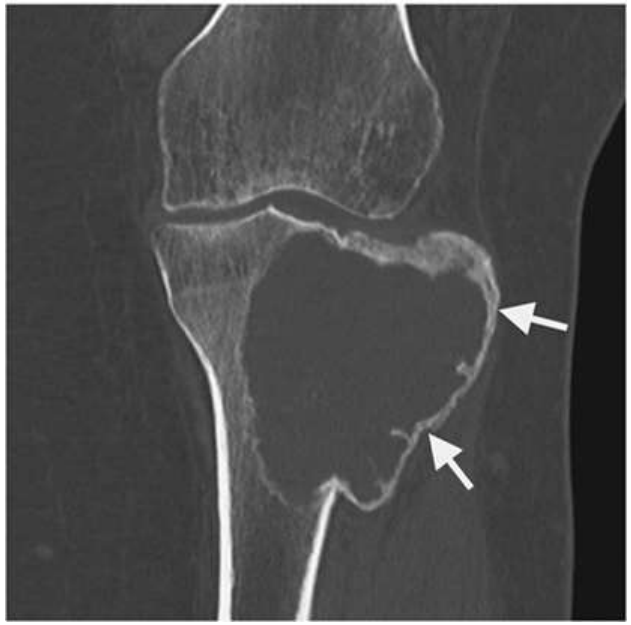
Giant Cell Tumor of Bone - Treatment

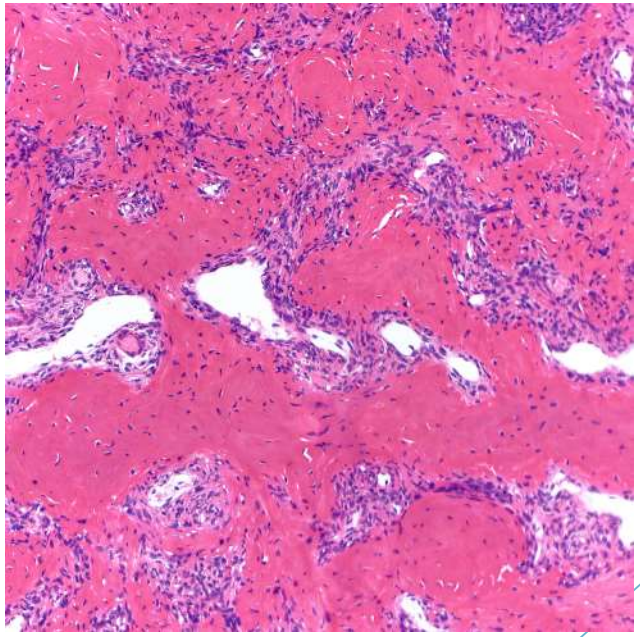
- Denosumab treated GCTs demonstrate altered morphology
  - Giant cell depletion
  - Altered cellularity
  - Fibrosis



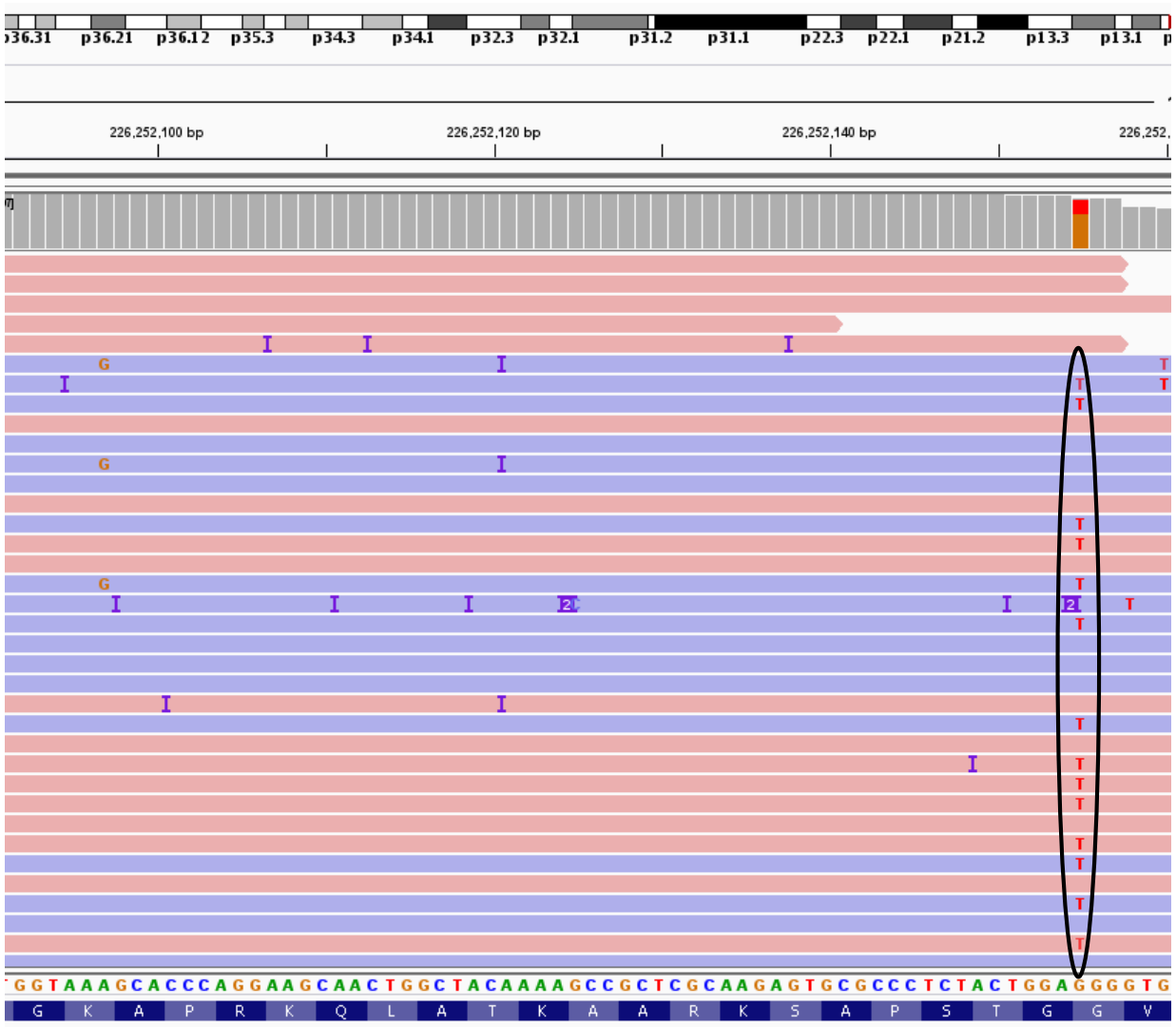
Giant Cell Tumor of Bone - Treatment

- Denosumab treated GCTs demonstrate altered morphology
  - New bone formation
    - Peripheral shell of reactive woven bone → diffuse





So why didn’t the NGS pick it up…..



G → T
Glycine (G) → Tryptophan (W)

*** ADDENDUM ***
(9/21/2020)

Amendment (12/2/2020): Repeat bioinformatic analysis revealed a missense mutation in H3F3A (p.G35W) that was inappropriately suppressed and not reported in the original study. An updated report containing the analysis of these findings is listed below with changes bolded and italicized.

CS - Comprehensive Cancer Panel

SPECIMEN INFORMATION			
Specimen Type:	Bone biopsy sample	**Source:**	FEMUR

Percent Tumor Nuclei:	50
Clinical Indication:	High-grade spindle cell sarcoma

RESULT SUMMARY

Variant Detected	FDA Approved Therapy Within Indication	FDA Approved Therapy Outside Indication	Resistance to Therapies	Guidelines	Clinical Trial Opportunity
H3F3A p.G35W ***30.5%***	***No***	***No***	***No***	***No***	***No***

Summary

- Giant cell tumor of bone is a benign but locally aggressive neoplasm
  - Rarely undergoes malignant transformation
- Composed of neoplastic mononuclear stromal cells + reactive giant cells
- Majority demonstrate driver mutations in histone H3.3 (*H3F3A*)
  - G34W or G34L
  - Recent development of antibody can be helpful
- Histones are proteins that are highly involved in gene expression
  - Exact mechanism of tumorigenesis is unknown
- Accurate diagnosis requires synthesis of clinical, histologic and molecular findings
  - Specific treatment options

References

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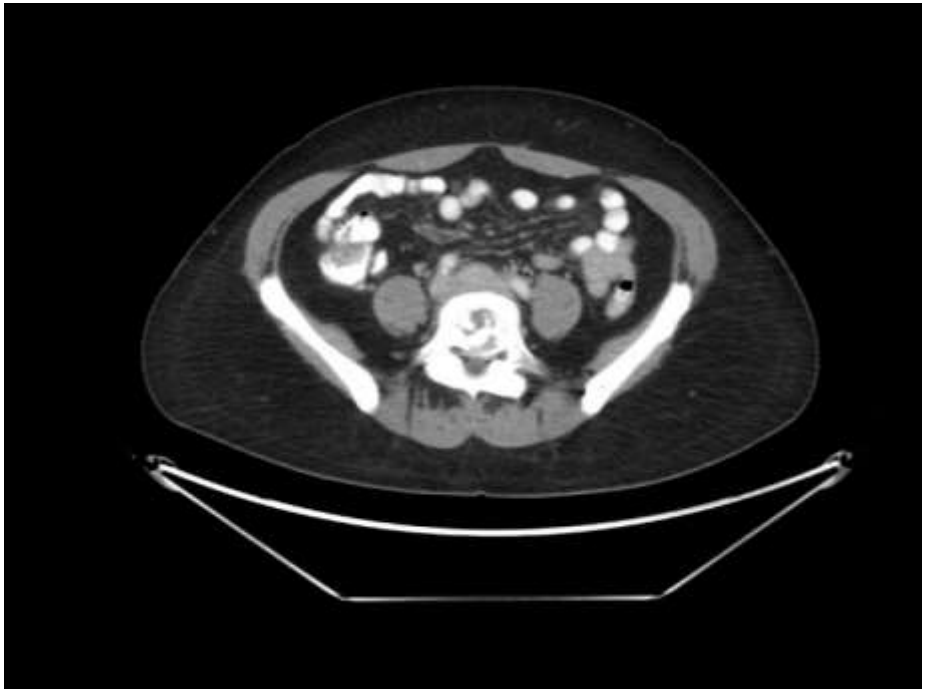
5. Treffel, M., Lardenois, E., Larousserie, F., Karanian, M., Gomez-Brouchet, A., Bouvier, C., ... & Rios, M. (2020). Denosumab-treated giant cell tumors of bone: a clinicopathologic analysis of 35 cases from the French Group of Bone Pathology. *The American Journal of Surgical Pathology*, *44*(1), 1-10.
6. Waldmann, T., & Schneider, R. (2013). Targeting histone modifications—epigenetics in cancer. *Current opinion in cell biology*, *25*(2), 184-189
7. Wojcik, J., Rosenberg, A. E., Bredella, M. A., Choy, E., Hornicek, F. J., Nielsen, G. P., & Deshpande, V. (2016). Denosumab-treated giant cell tumor of bone exhibits morphologic overlap with malignant giant cell tumor of bone. *The American journal of surgical pathology*, *40*(1), 72-80.

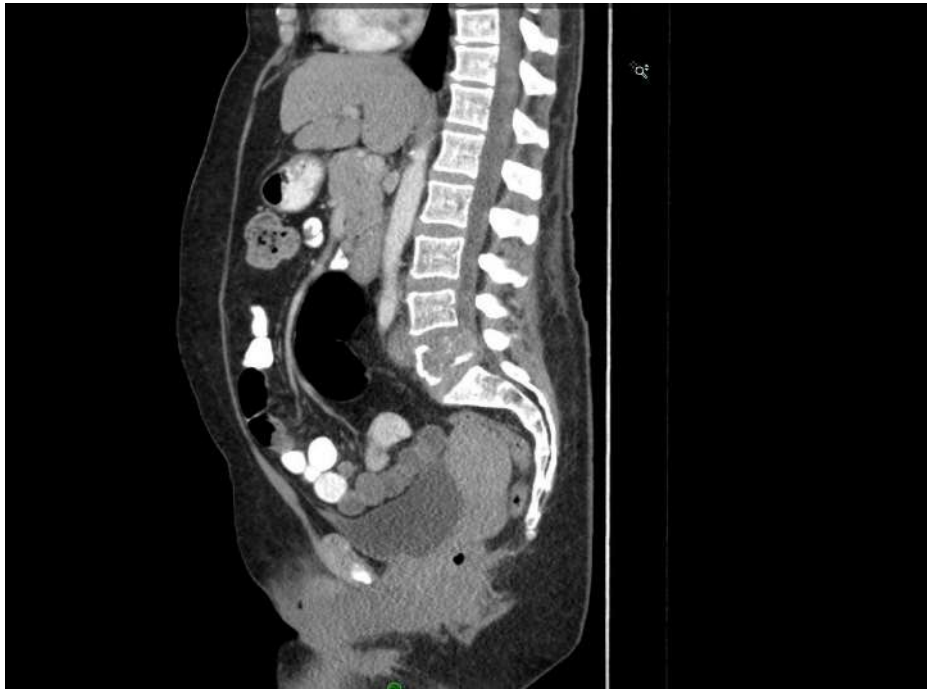
21-1206

Bonnie Balzer; Cedars-Sinai Medical Center

62-year-old F with lower back pain. Imaging showed L5 mass. Past medical hx: complex endometrial hyperplasia s/p curettage, 8.2mm RUL ground glass nodule, and stable 7mm liver lesion. Multiple core biopsies performed were non-diagnostic (rare keratin-positive cells, suspicious for carcinoma). Clinical course complicated by cord compression, and patient underwent emergency corpectomy.

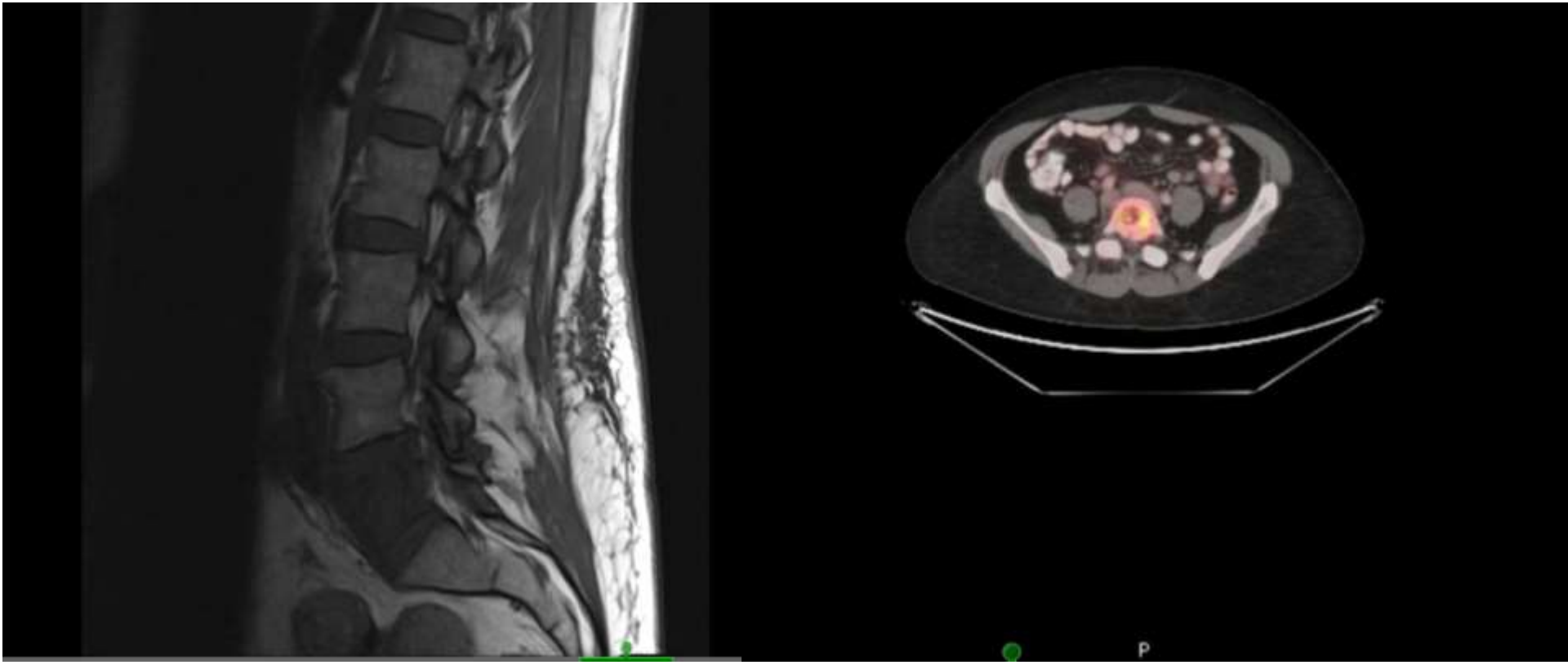
CT

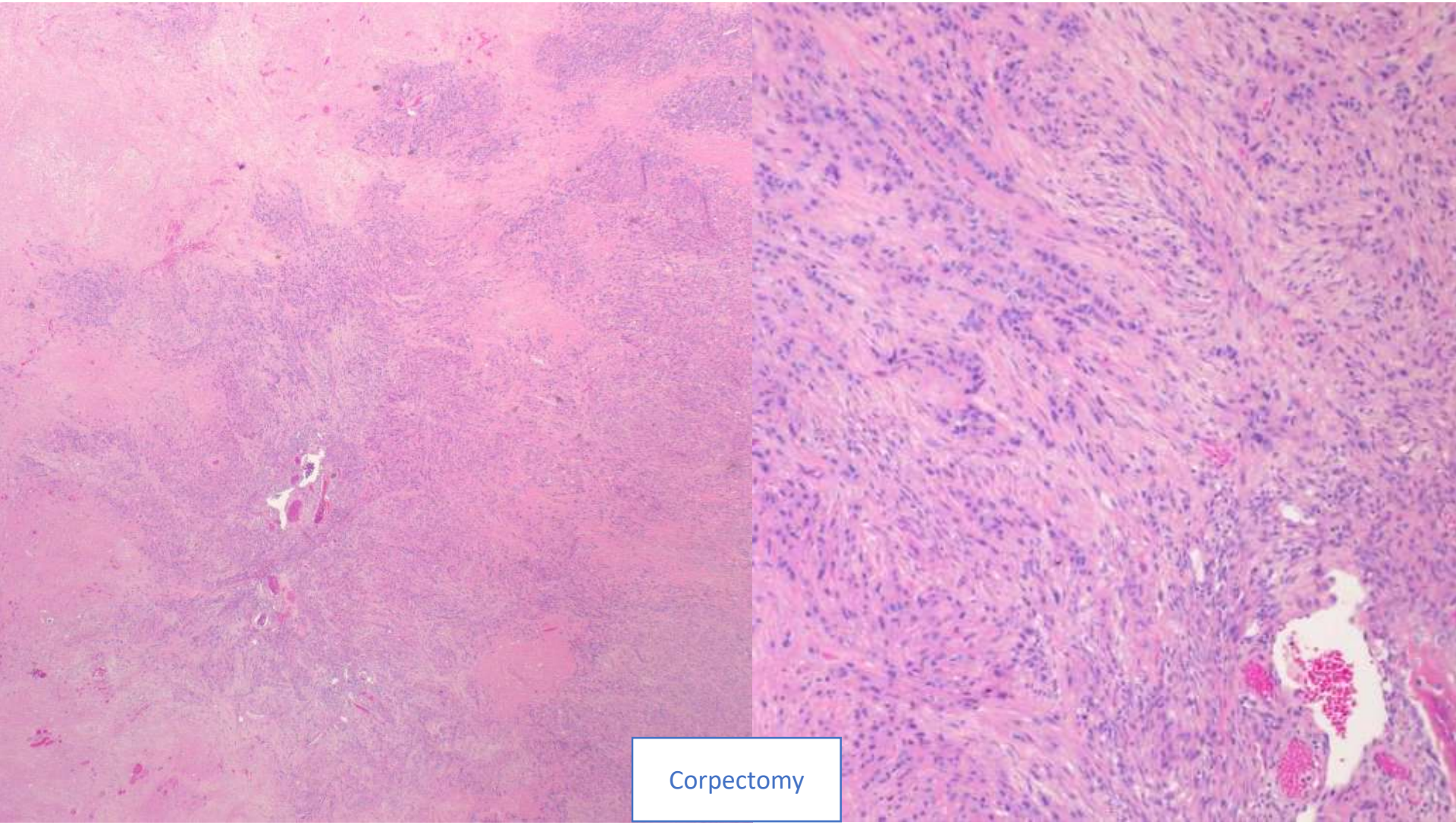




MRI

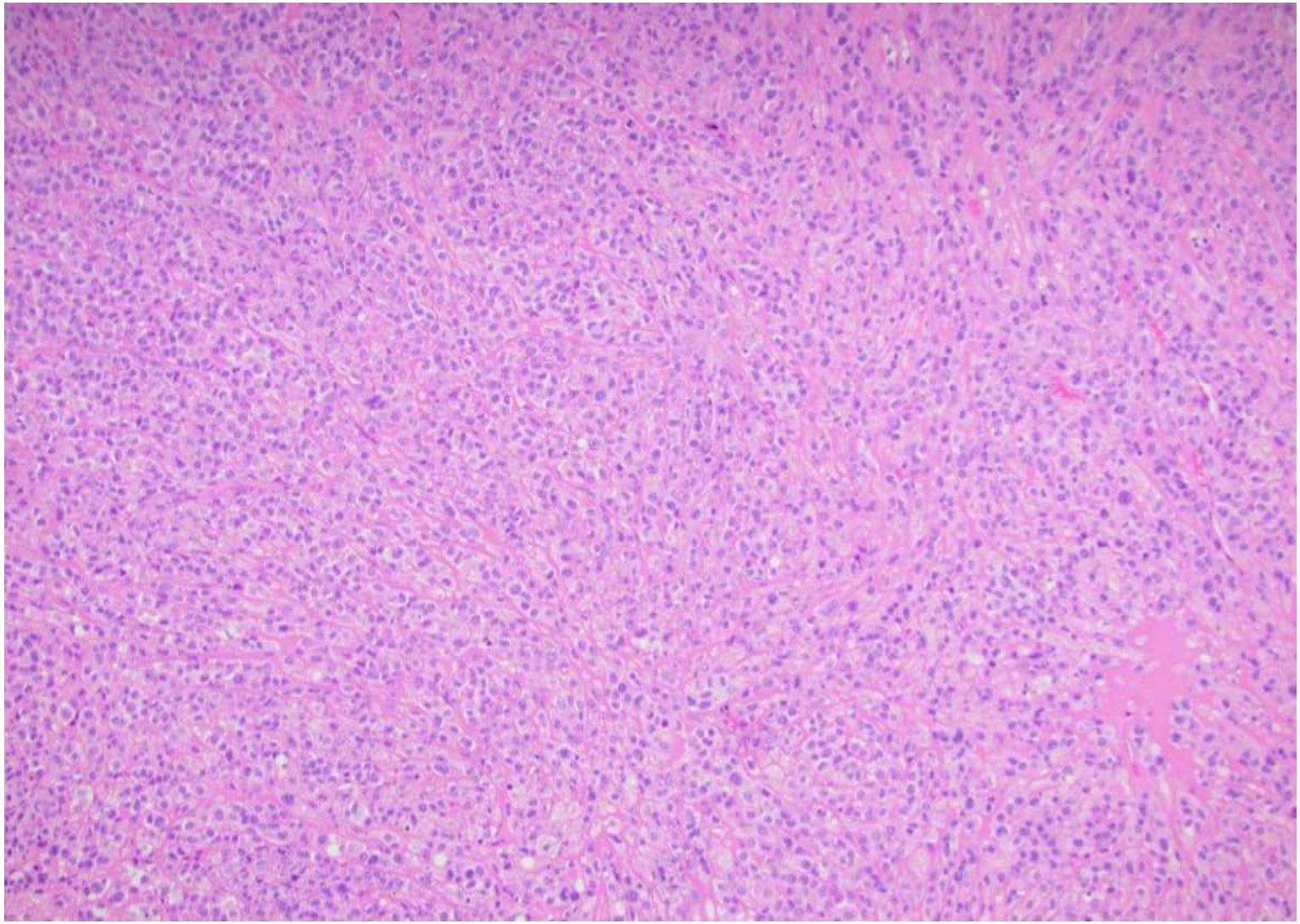
PET

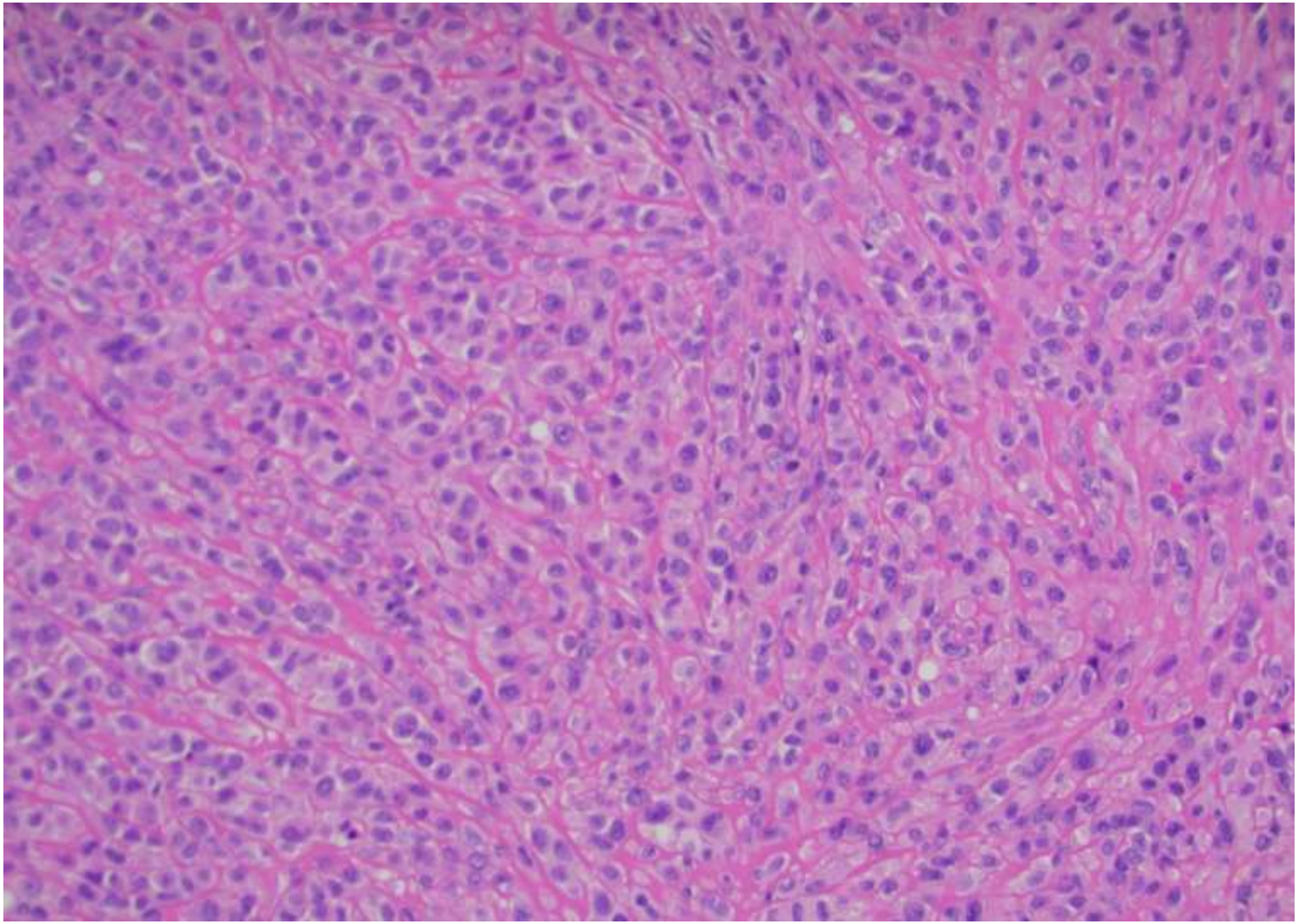


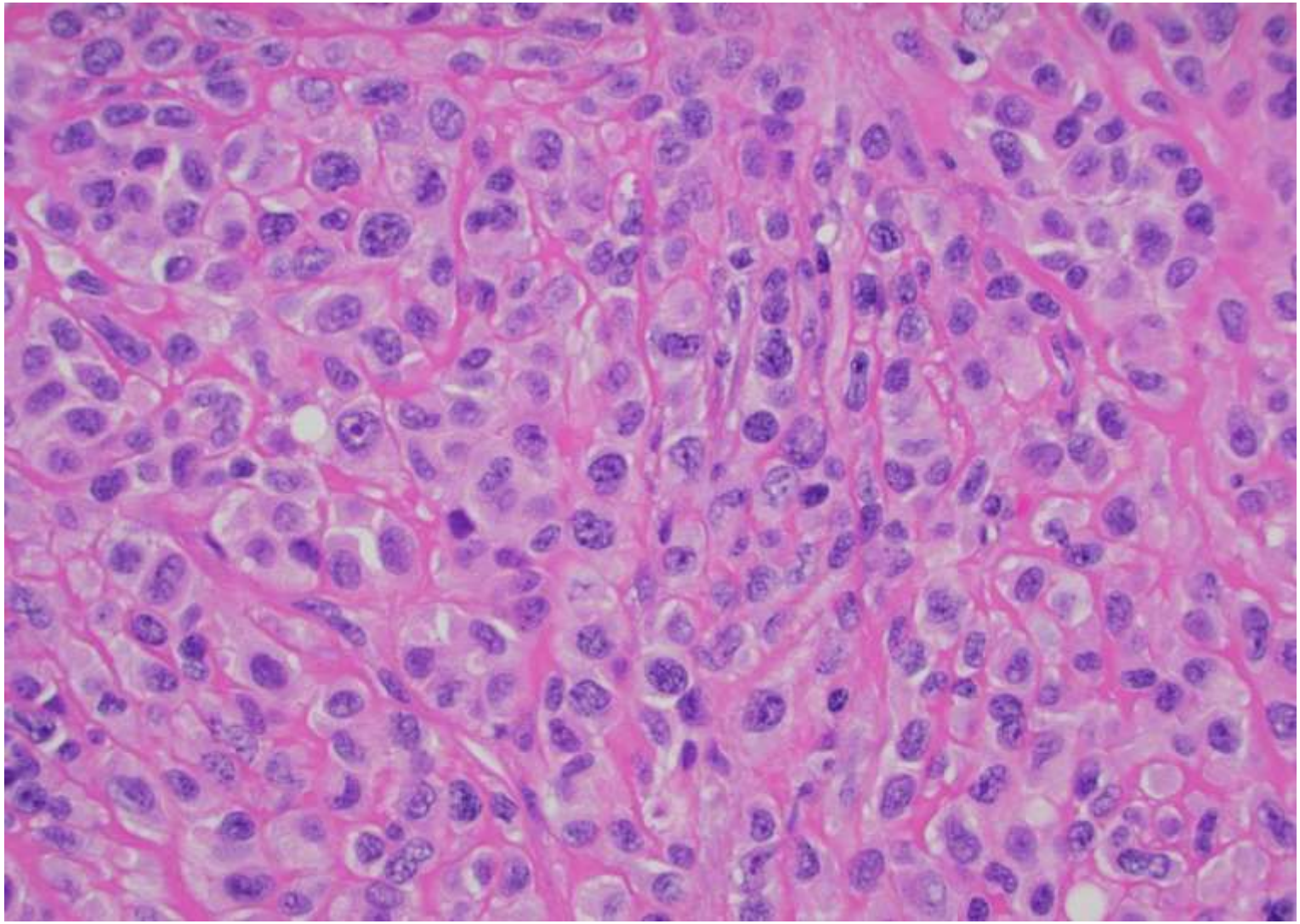


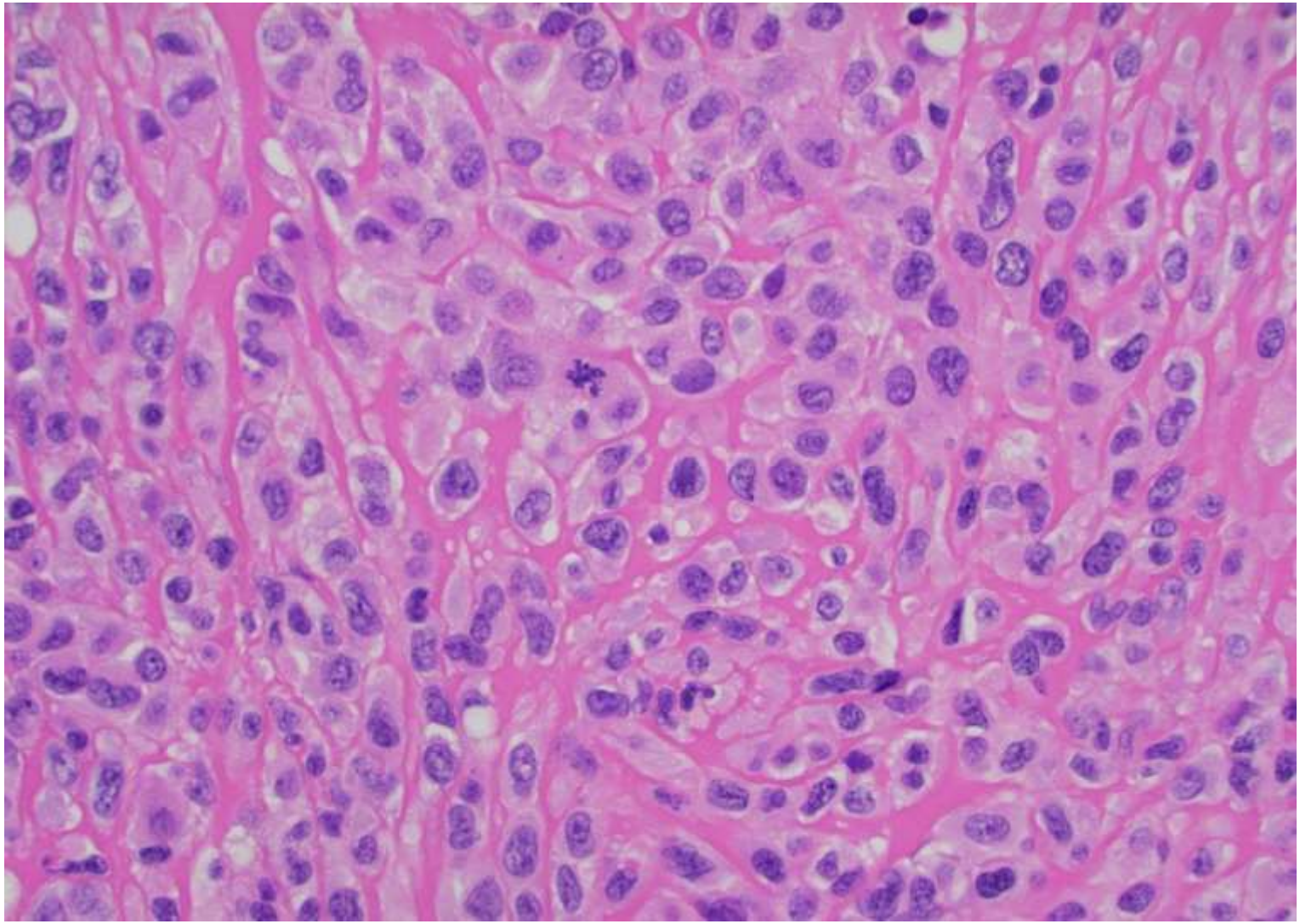
Corpectomy

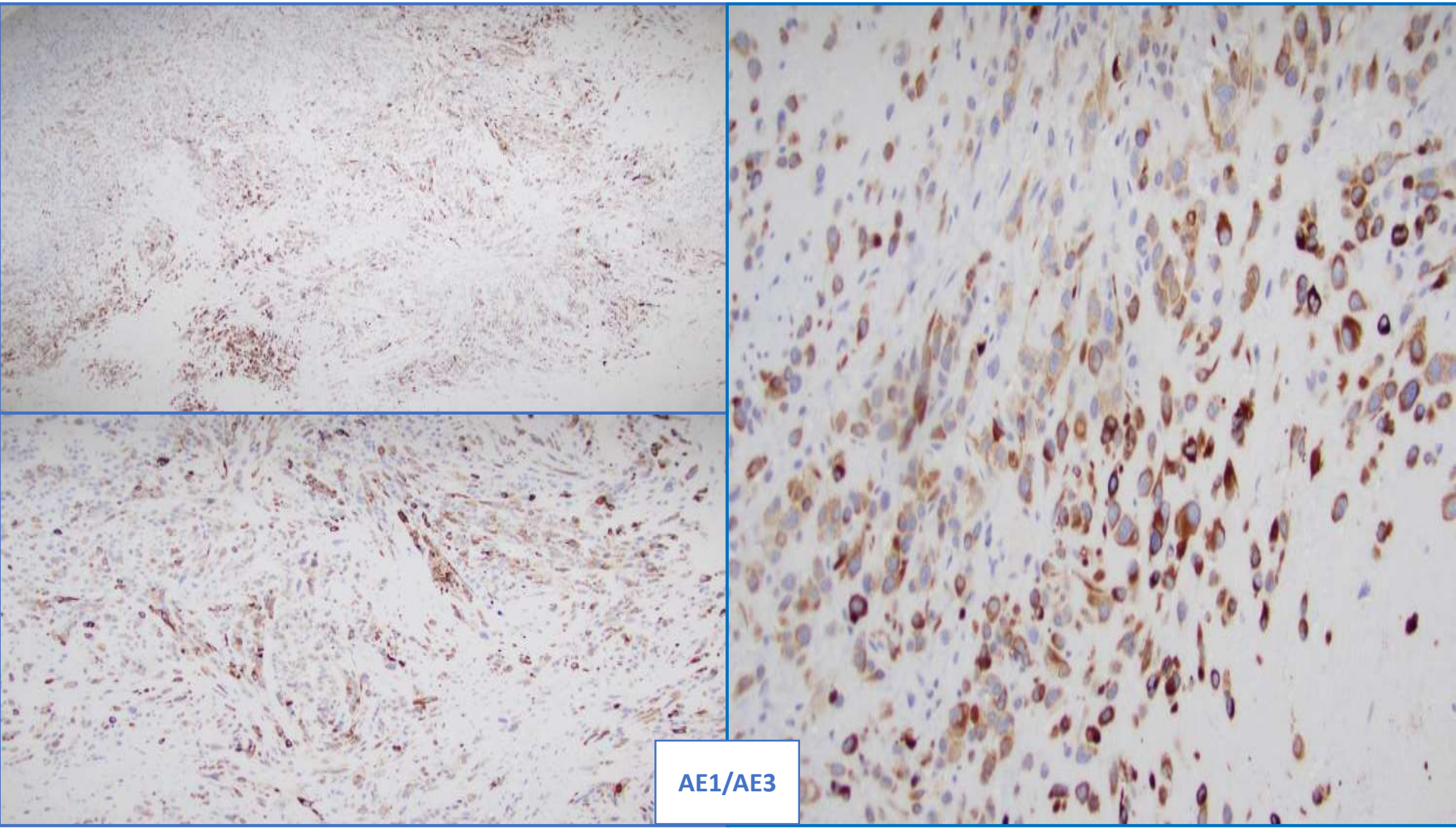
Corpectomy










AE1/AE3

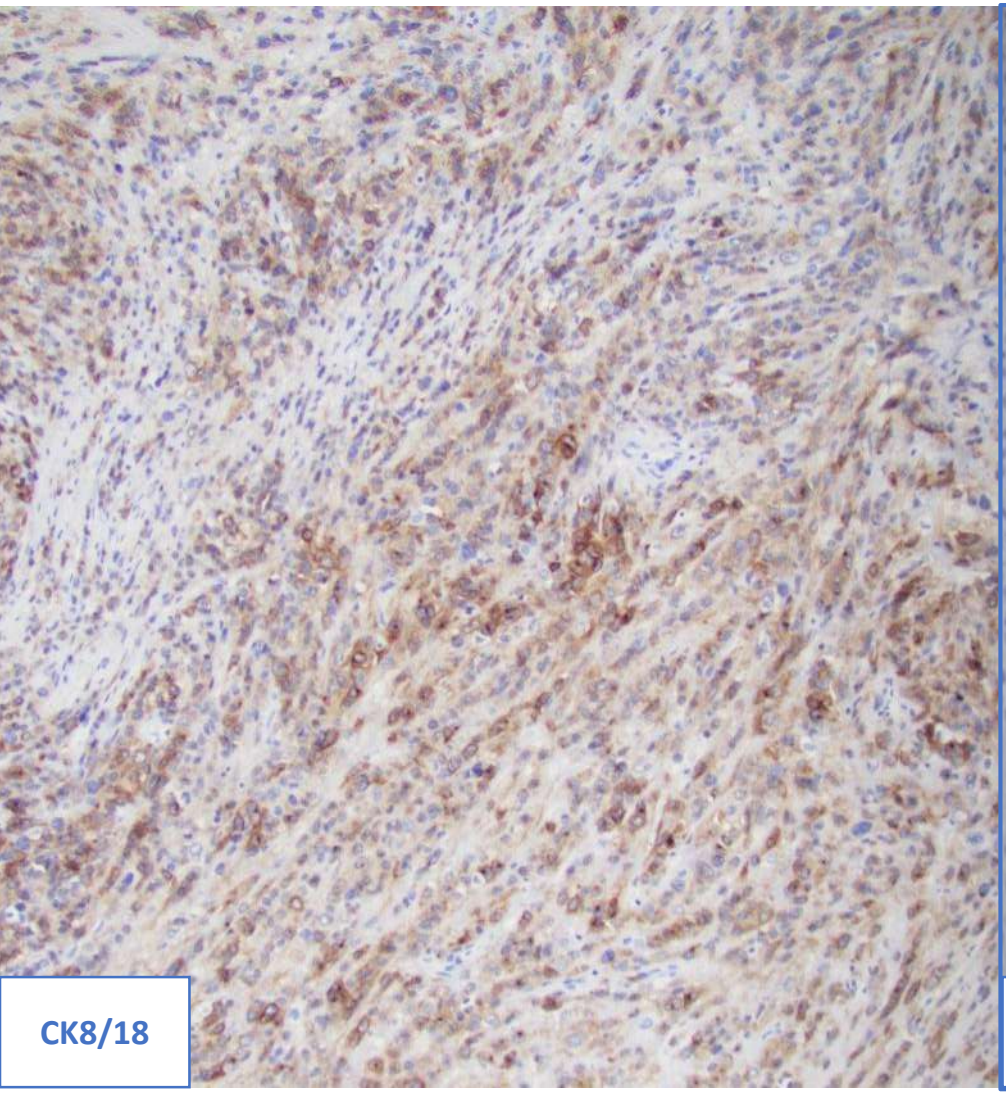
Ancillary studies

- Keratins: Multiple keratin mixes positive
  - CK7, CK20: Negative
- MDM2: Overexpressed
- Melanocytic markers (HMB45, Melan-A, SOX10, S100, BRAF): Negative
- Lineage markers (vascular, desmin, myogenin, actin): Negative
- Organ selective markers (PAX8, TTF, GATA3, SATB2, CDX2, etc.) Negative
- Fluorescence in situ hybridization:
  - Negative for MDM2 amplification
  - Negative for SYT rearrangement
  - Positive for EWSR1 rearrangement
- Next generation sequencing for partner: EWSR1-TFCP2 fusion detected

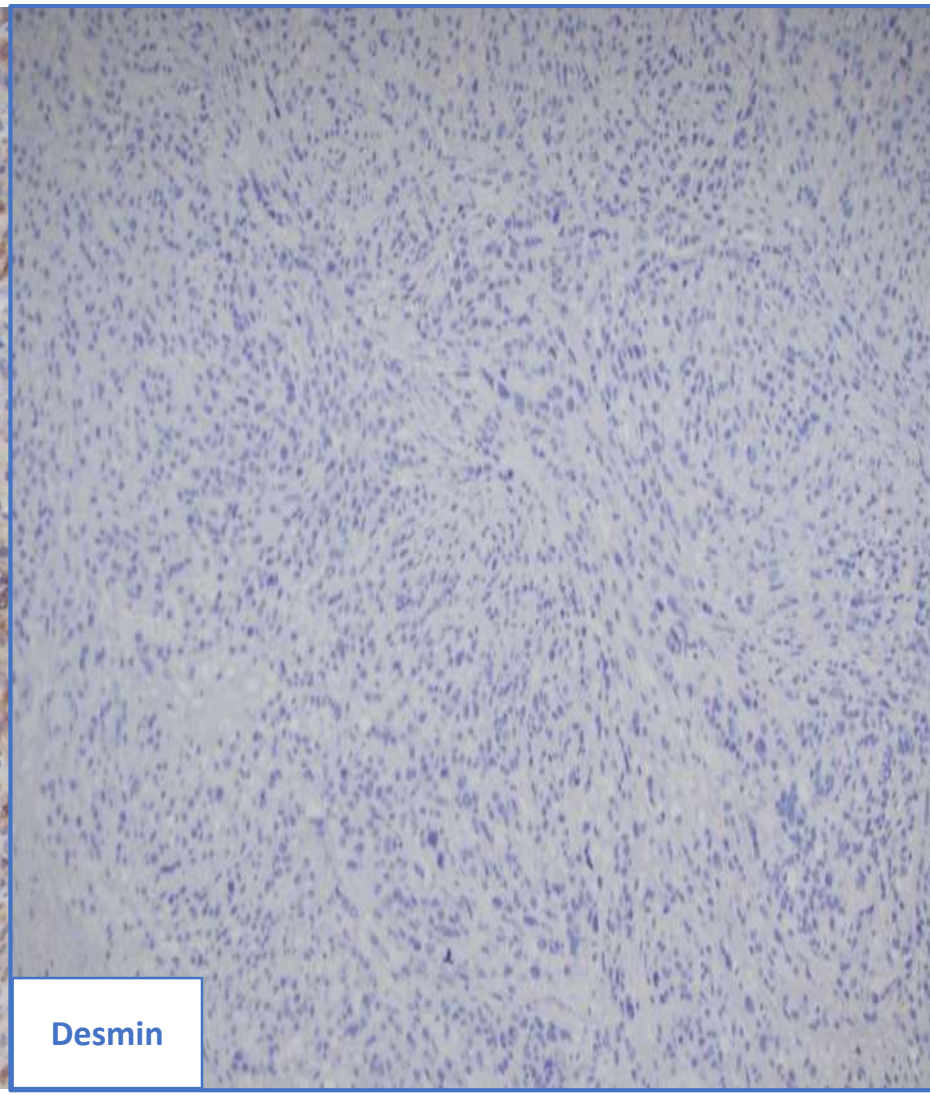
Differential diagnosis and final diagnosis:

- EWSR1 rearranged tumors of bone:
  - Myoepithelioma
  - Sclerosing epithelioid fibrosarcoma
  - Sclerosing intraosseous epithelioid rhabdomyosarcoma
- Metastasis (essentially excluded clinically and radiologically)

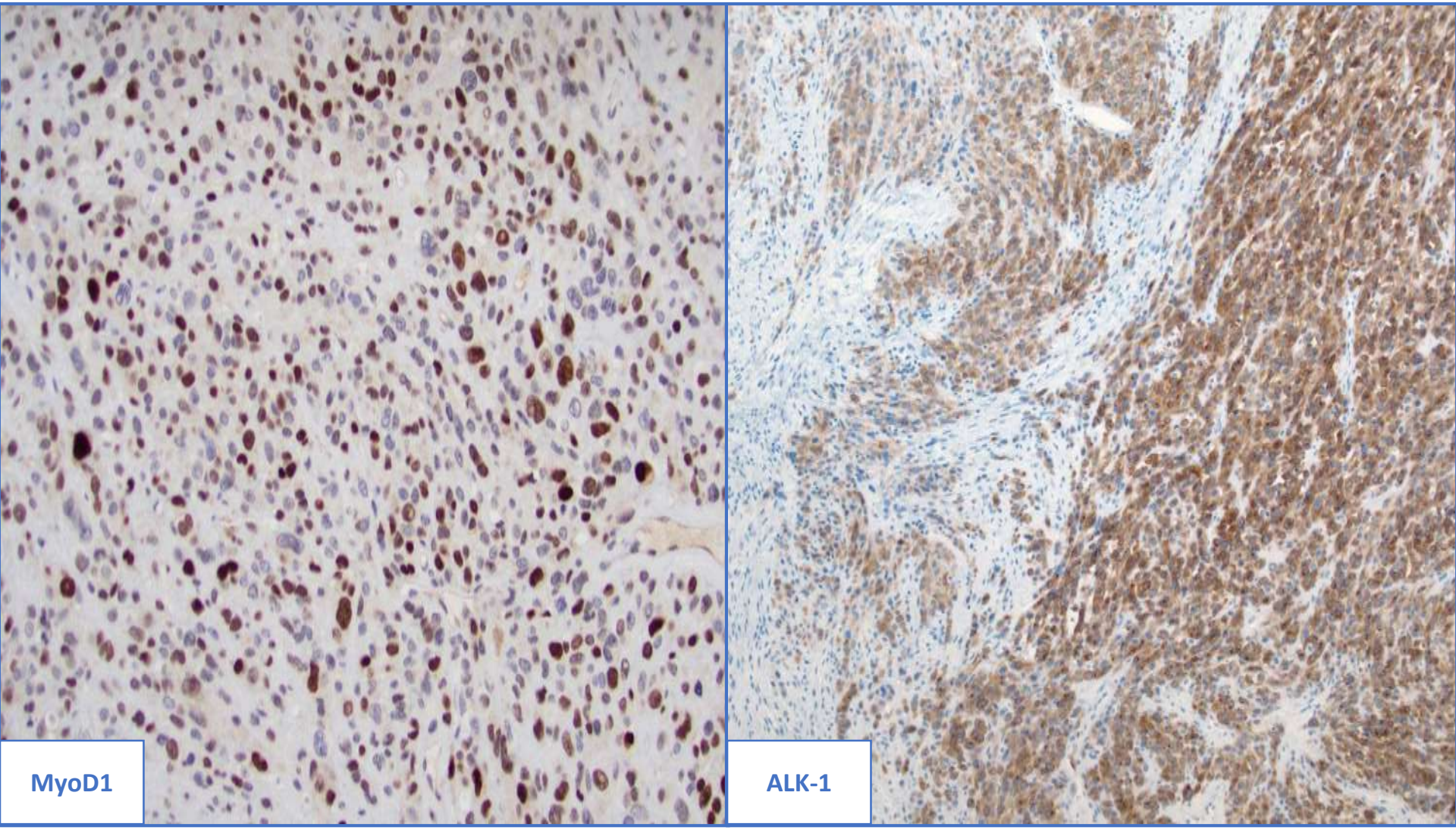
- Additional studies performed:
- Additional immunostains:
  - Myo-D1: Positive nuclear reactivity
  - ALK-1: Overexpressed (not rearranged)
- Final diagnosis: EWSR1-TFCP2 rearranged sarcoma of bone, consistent with sclerosing intraosseous epithelioid rhabdomyosarcoma
  - No desmin positivity (MSKCC concurred with diagnosis)



CK8/18



Desmin


MyoD1
ALK-1

Clinical follow up:

- **MANAGEMENT:**
  - Localized radiation therapy
  - vincristine, adriamycin, cyclophosphamide, alternating with ifosfamide and etoposide (Therapy for advanced bone and soft tissue sarcoma or Ewing sarcoma therapy), over 4 months with complications of neutropenic fevers, anemia cytopenias.

- **CLINICAL COURSE:**
  - Recurrent/progressive/metastatic disease: at 4 months: pelvic sidewall mass and adjacent anterior pelvic wall nodules 5 months: Pt was hospitalized for pancytopenia and back pain
  - US LEG showed an acute, nonocclusive thrombus in the common femoral vein. There is acute, occlusive thrombus in the deep femoral vein.
  - Started treatment on TAPUR study with Abemaciclib for CDK4 alteration with stable disease
  - Peritoneal sarcomatosis with ascites and chronic DVT, intractable pain
  - Deceased ~ 1 year from diagnosis

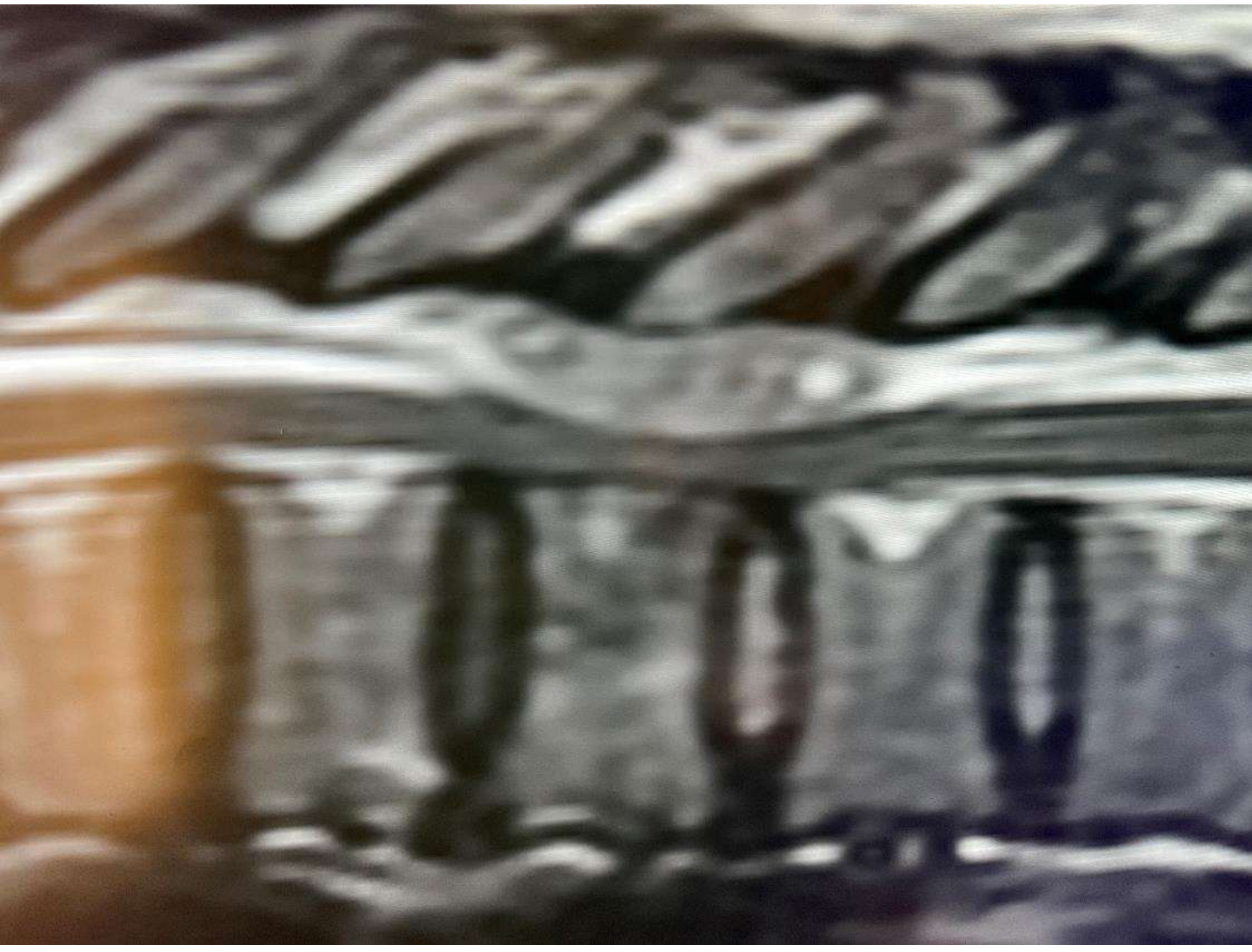
- **REFERENCES:**

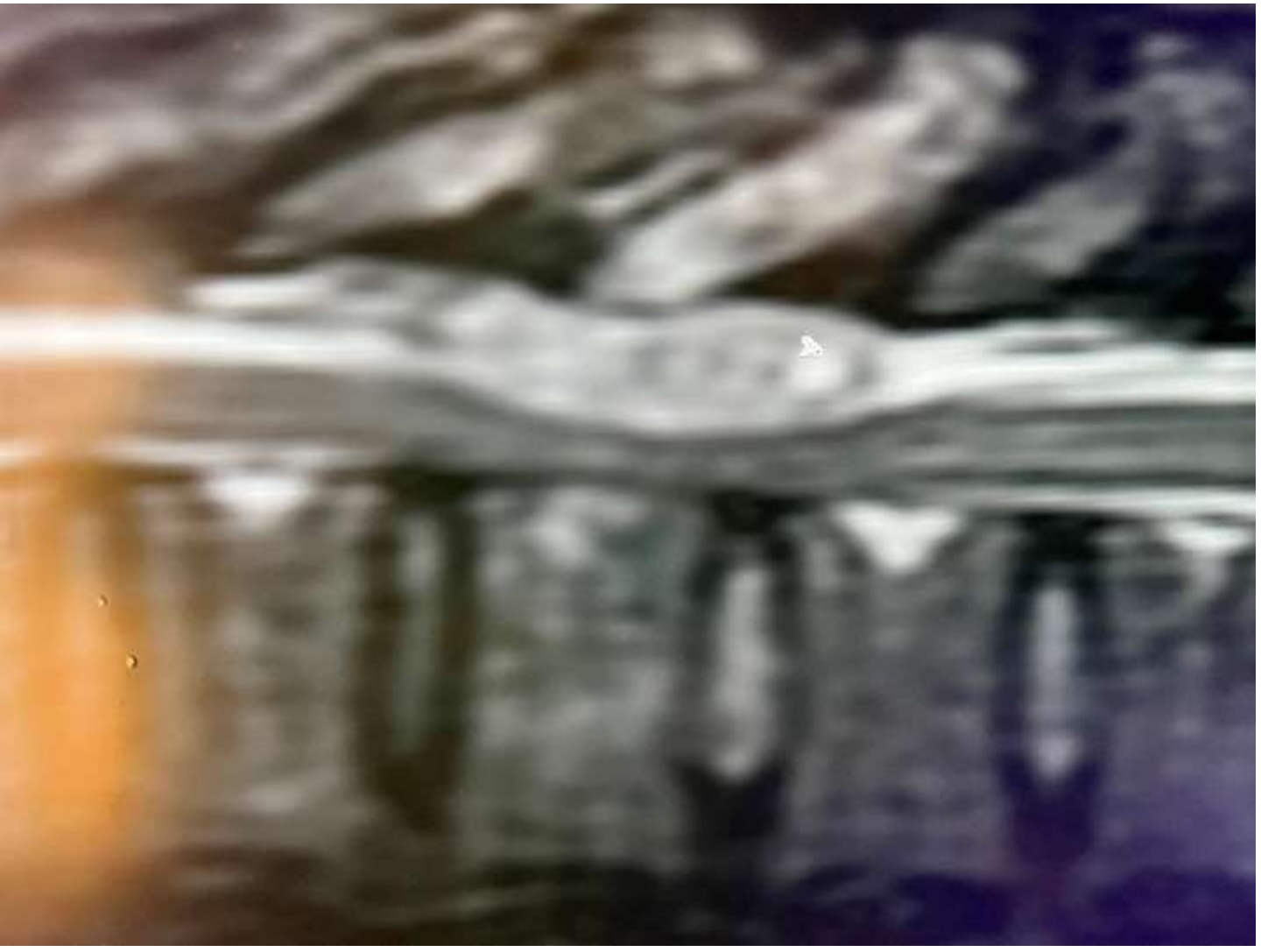
  - ***Am J Surg Pathol 2019;43:695–702.***
  - ***J. Pathol 2018; 245: 29–40***

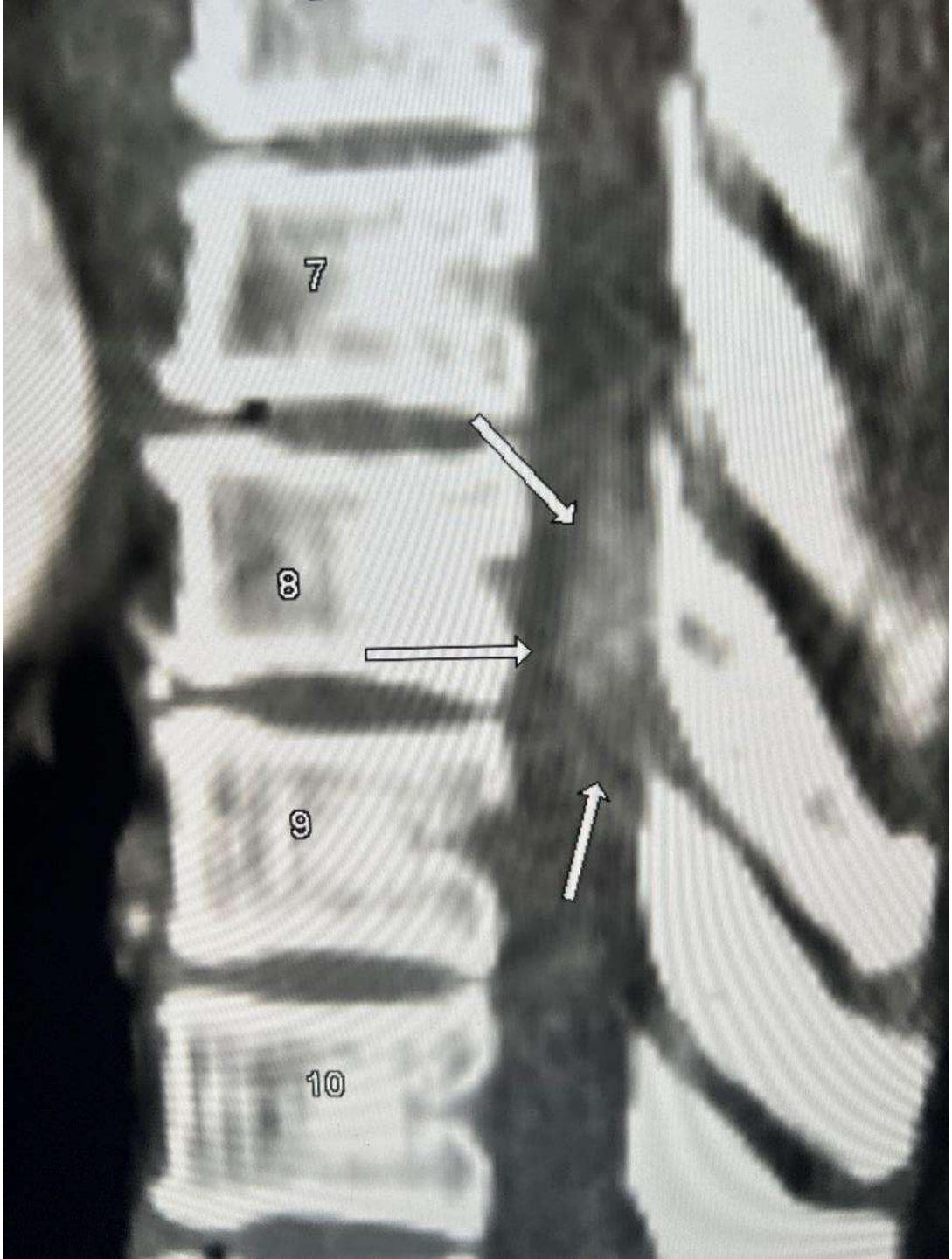
21-1207

Kanish Mirchia/Elizabeth Treynor; UCSF/Washington Hospital

46-year-old F in usual state of health, with 1 month recurrent mid back pain and subsequent urinary incontinence and paraparesis. Imaging showed T8 extramedullary mass with cord compression.



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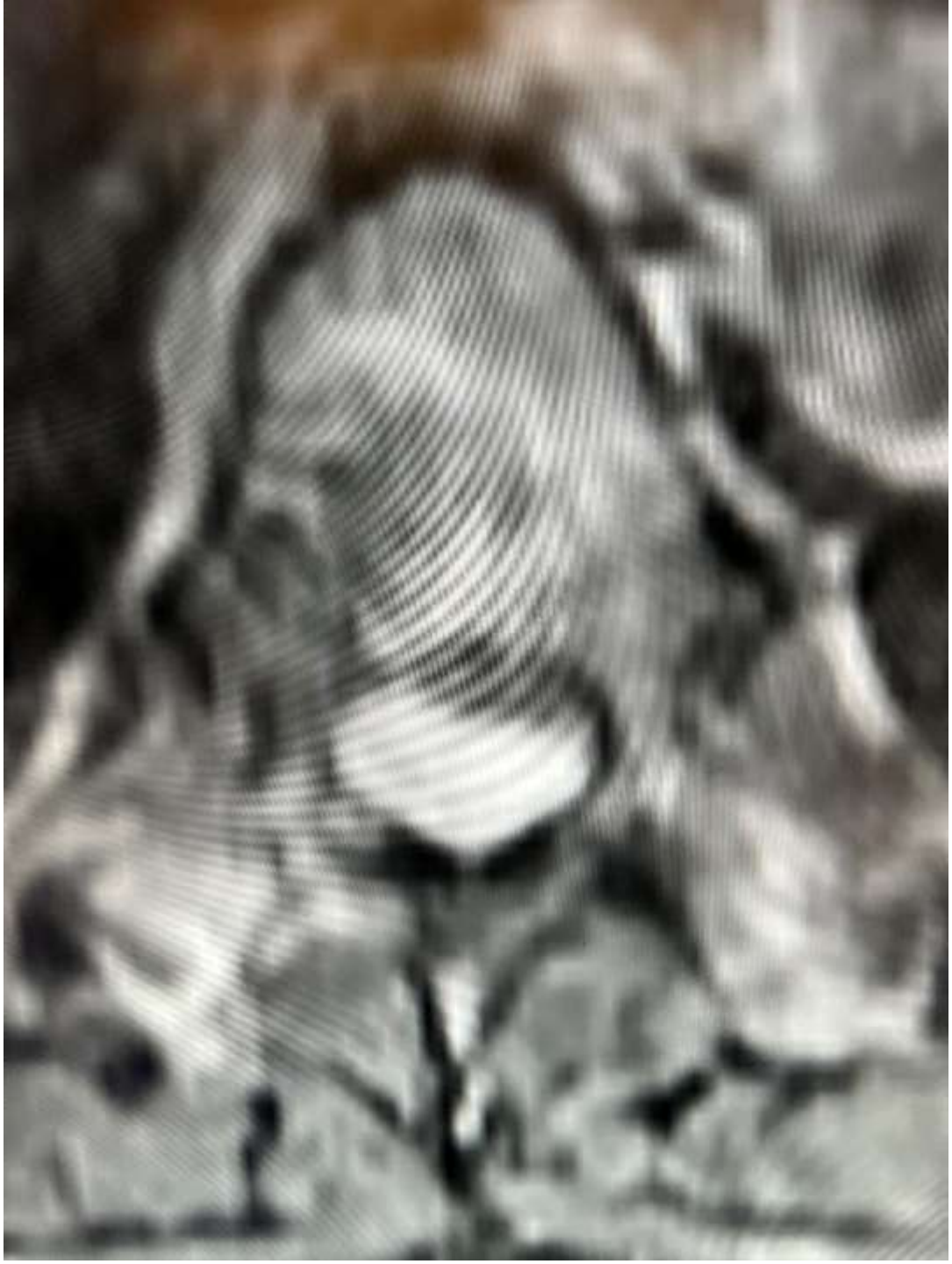
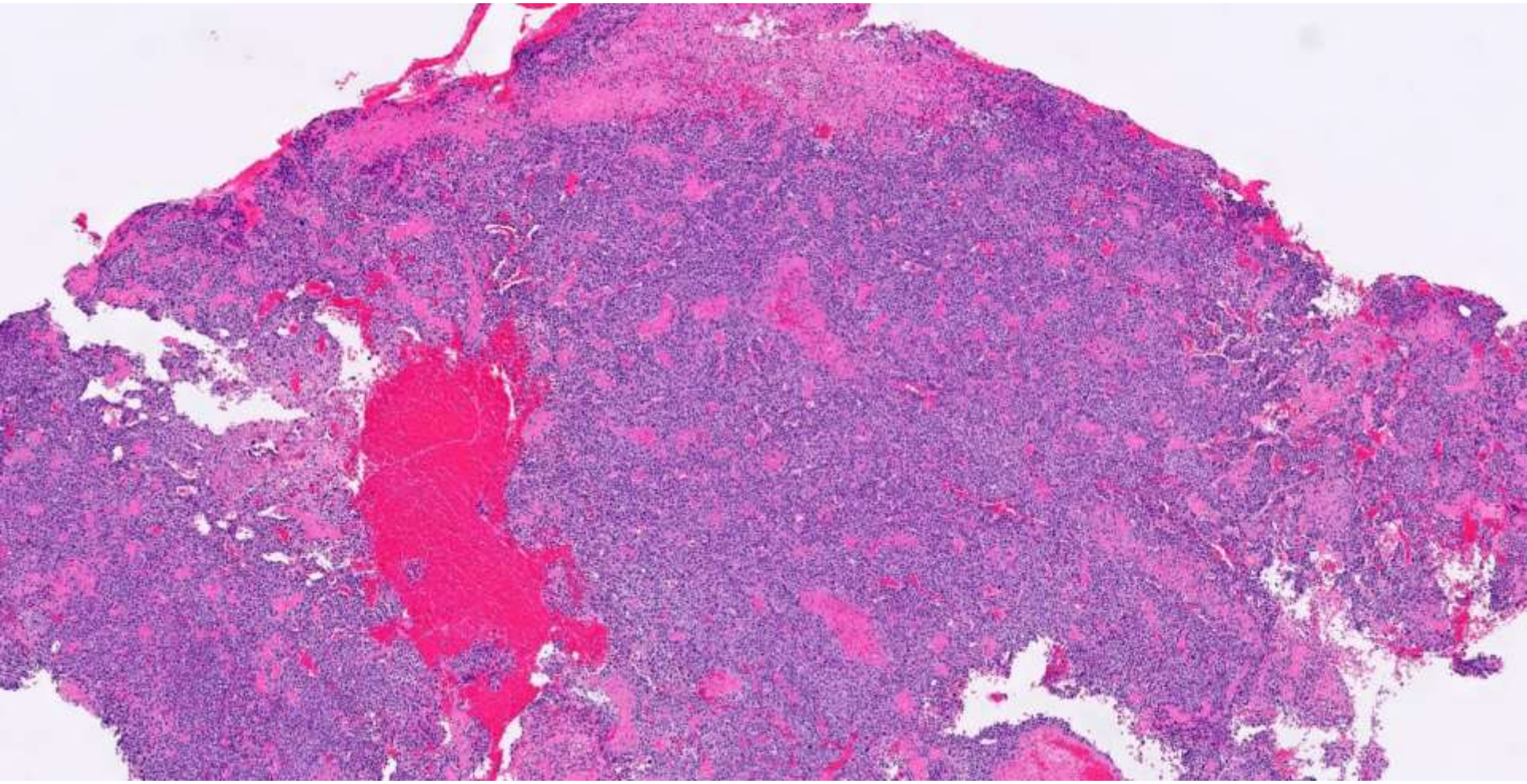
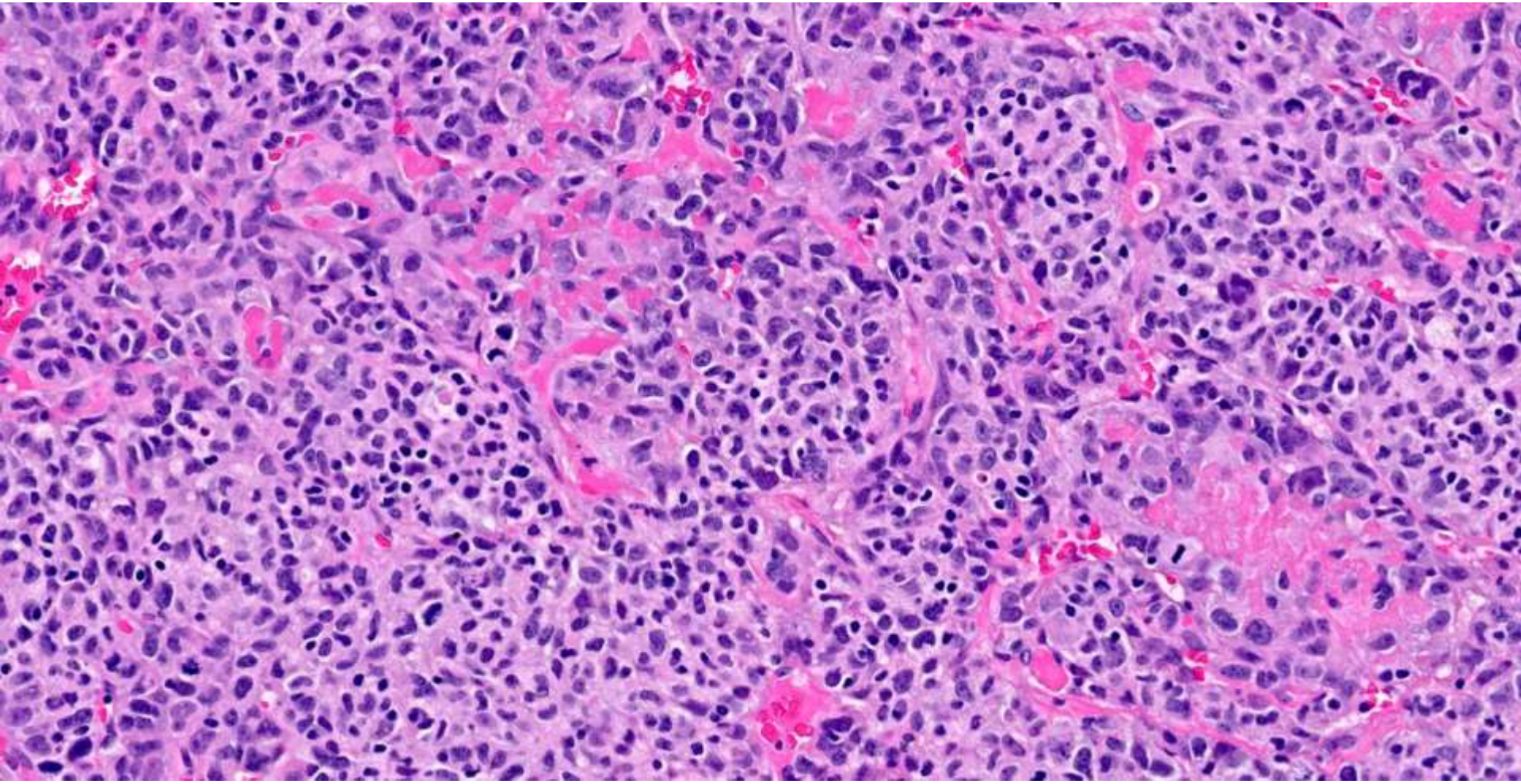
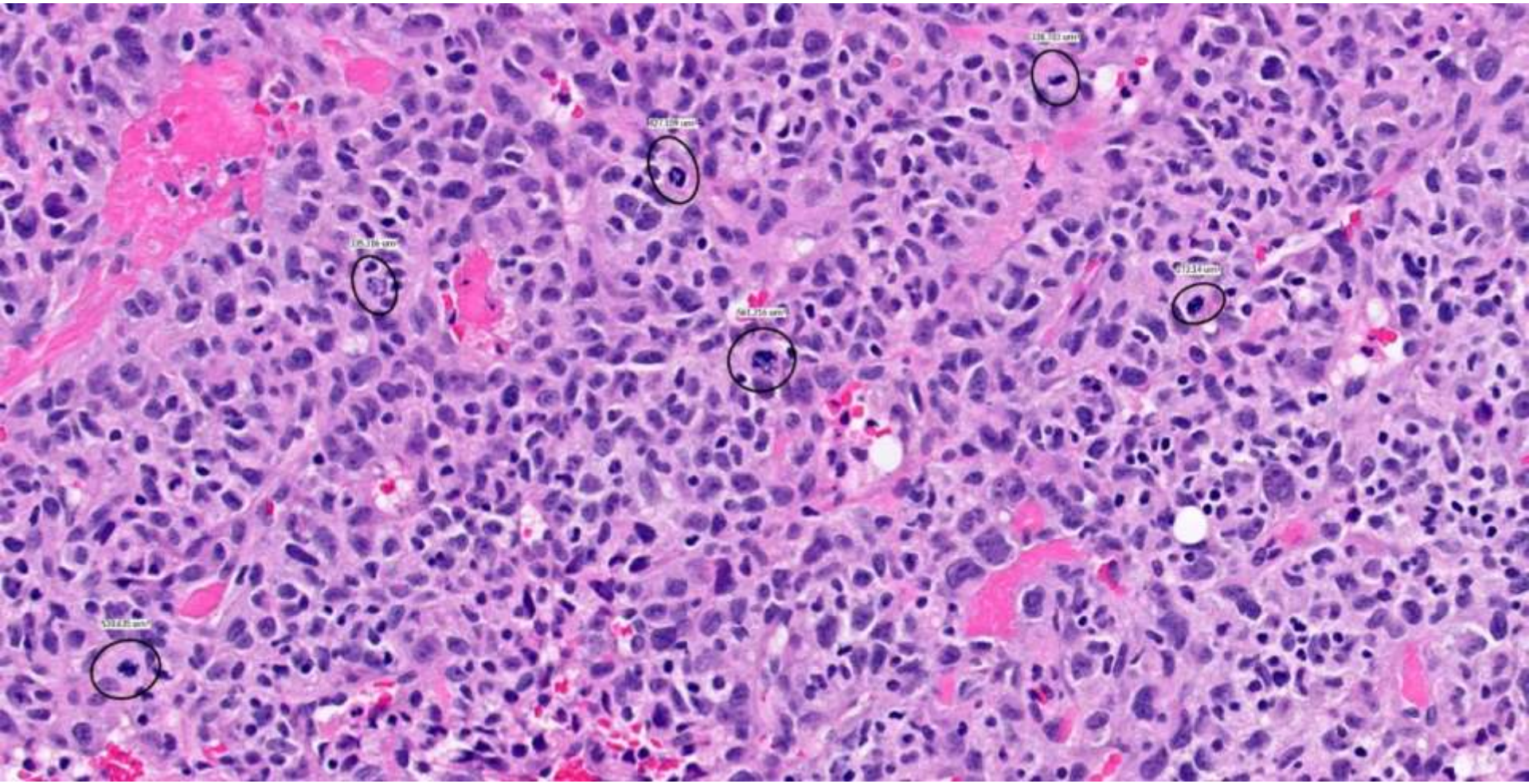
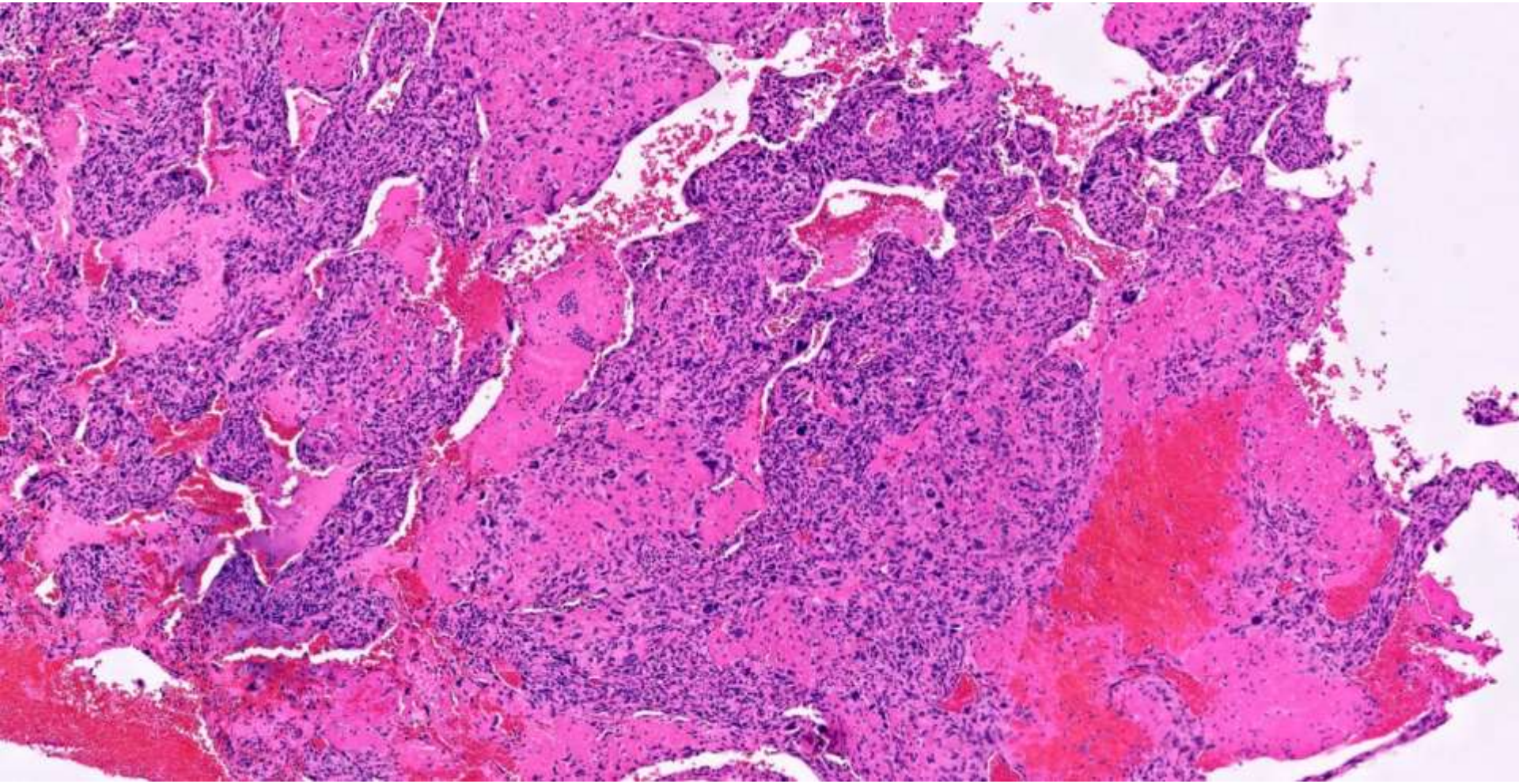
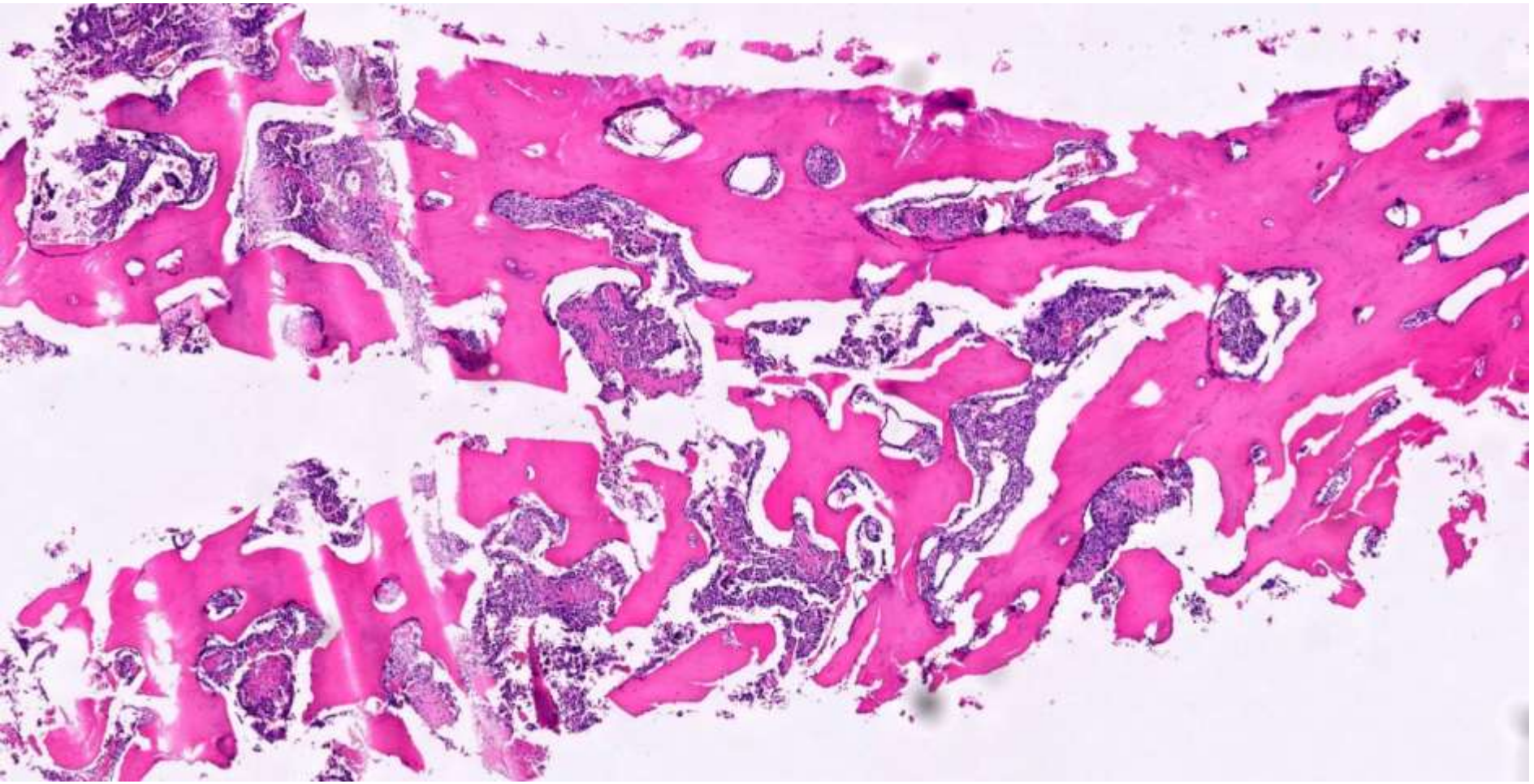












?Glial
?Neural

- GFAP
- SOX10
- S100
- Synaptophysin

?Ependymal

- GFAP
- EMA

?Carcinoma

- Pankeratin
- CK7
- CK20
- PAX8

?Vascular

- CD34
- ERG
- FLI1

?Hematopoeitic

- CD45
- CD20
- CD3
- CD68
- CD21
- CD23
- PAX5
- ALK
- MPO

?Others

- STAT6
- WT1
- CD99
- Desmin
- Myogenin
- MyoD1
- Arginase1

?Neural (again)

- Neurofilament
- H3K27me3
  - Partial loss of expression

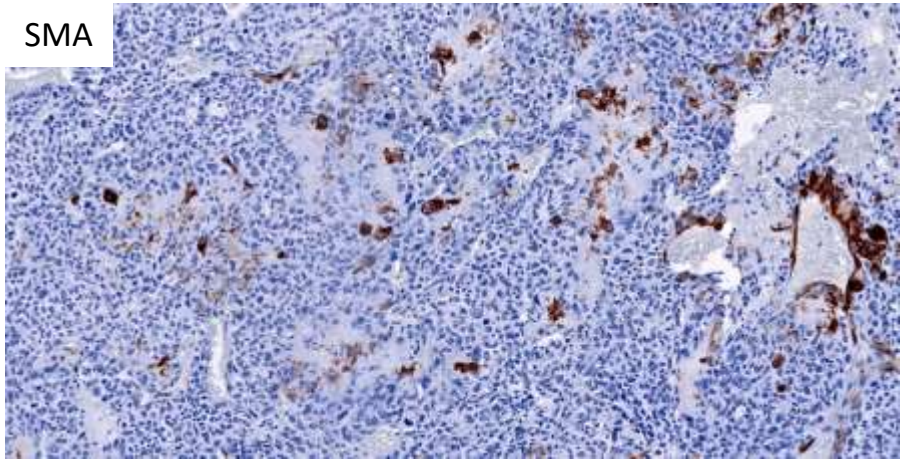
?Malignant PEComa

- HMB45
- MelanA

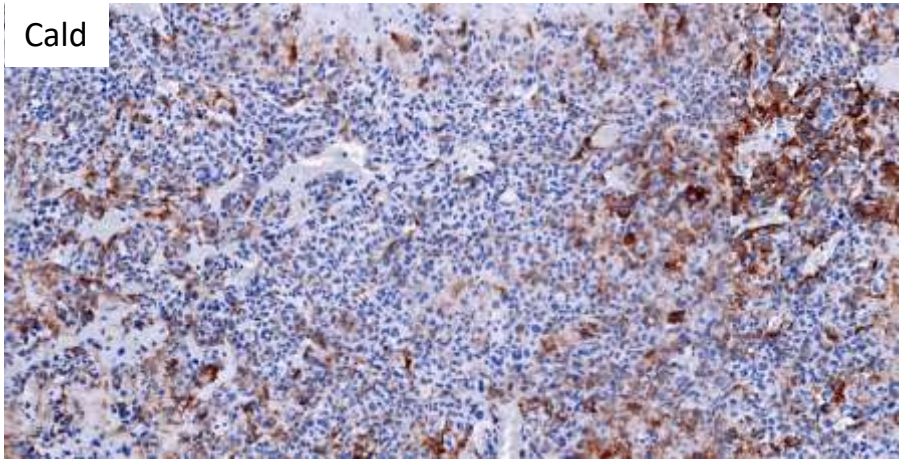
Malignant Glomus Tumor

- SMA
- Caldesmon

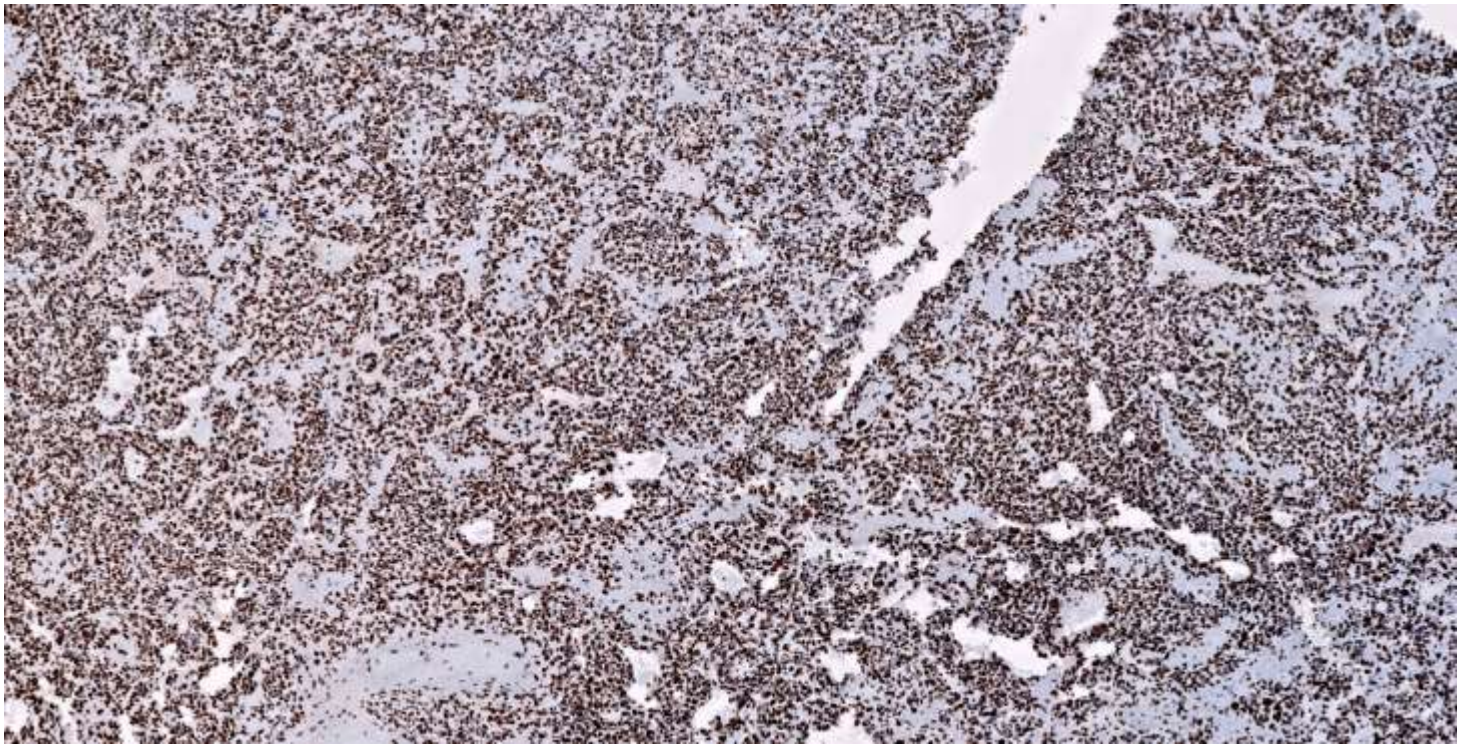
SMA



Cald

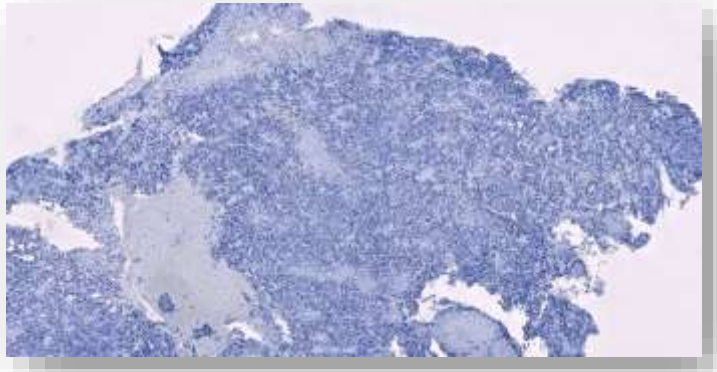


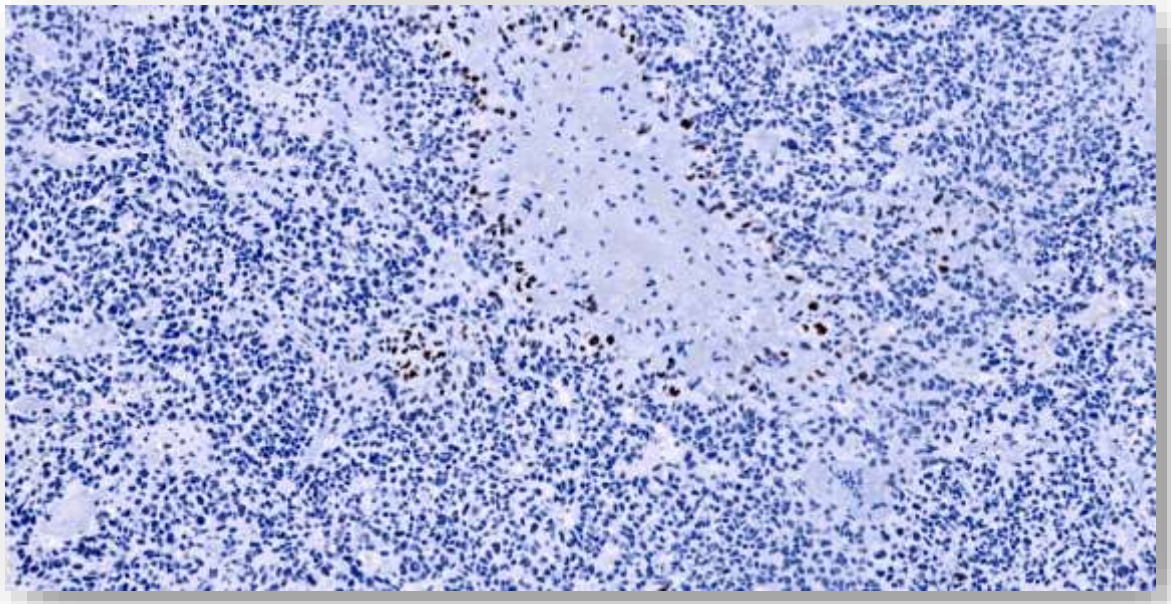
- INI1
  - Retained



Osteosarcoma

- SATB2





Malignant poorly differentiated neoplasm

NGS

- UCSF500

PATHOGENIC AND LIKELY PATHOGENIC ALTERATIONS				
VARIANT	**TRANSCRIPT ID**	**CLASSIFICATION**	**READS**	**MUTANT ALLELE FREQUENCY**
ATRX p.F2005fs	NM_000489.3	Pathogenic	796	32%
Chromosome 12q14q15 amplification	All	Pathogenic	~17.5x	N/A
Chromosome 11q13.3 amplification	All	Pathogenic	~5.0x	N/A
TP53 homozygous deletion	All	Pathogenic	N/A	N/A

- Copy number analysis
  - Copy gains and losses across the genome, involving whole chromosome and arm level changes.
- Amplification 11q13.3 including CCND1, FGF19, FGF4, and FGF3
- Amplification 12q14q15 including DDIT3, CDK4, HMGA2, MDM2, FRS2, and PTPRB.
- Homozygous / biallelic deletion of the TP53 tumor suppressor gene.
- ATRX is a chromatin regulator that functions as a member of the SWI/SNF helicase family that is inactivated in a wide-range of tumor types.
- CCND1 a regulator of the cell cycle, is amplified in various cancer types including breast, head and neck, and bladder cancers.
- CDK4 an intracellular kinase, is altered by amplification or mutation in various cancer types including lung, melanoma and bladder cancers.

MDM2

- “classic” *MDM2* amplified sarcomas
  - Dedifferentiated liposarcoma
  - Intimal sarcoma
  - Sclerosing rhabdomyosarcoma
  - Osteosarcoma (subtypes)

MDM2

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  - Osteosarcoma (subtypes)
    - MDM2
    - HMGA2
    - ATRX
    - TP53
    - CDK4
    - CCND1