AANP 2021 DIAGNOSTIC SLIDE SESSION CASE 1

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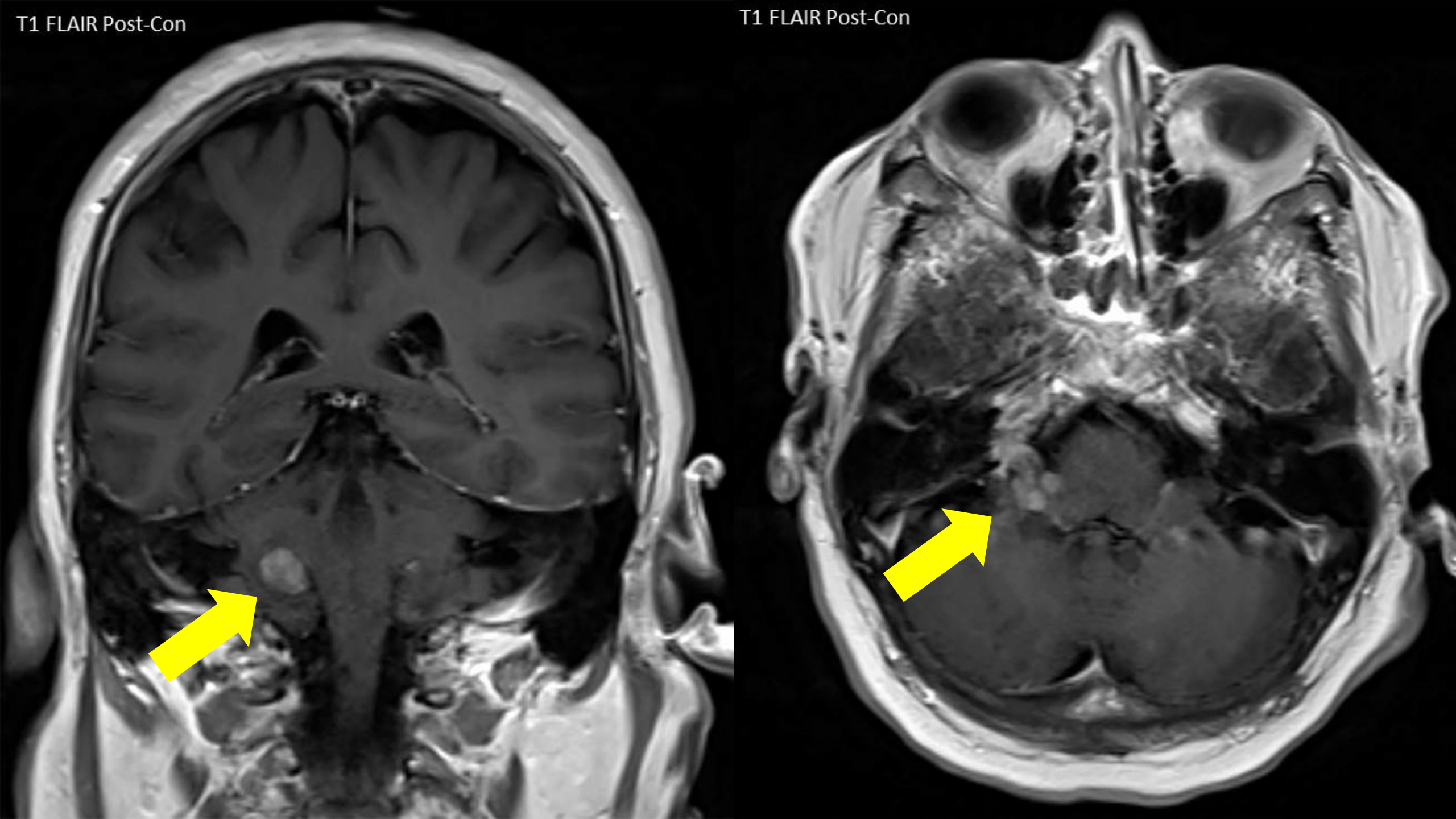
Clinical History:

- 60-year-old female with 3-year history of intermittent right-sided ear pain with subsequent hearing loss.
- Past medical history notable for multiple extracranial tumors (status post neck dissection and open-heart surgery).
- No known history of skin cancer.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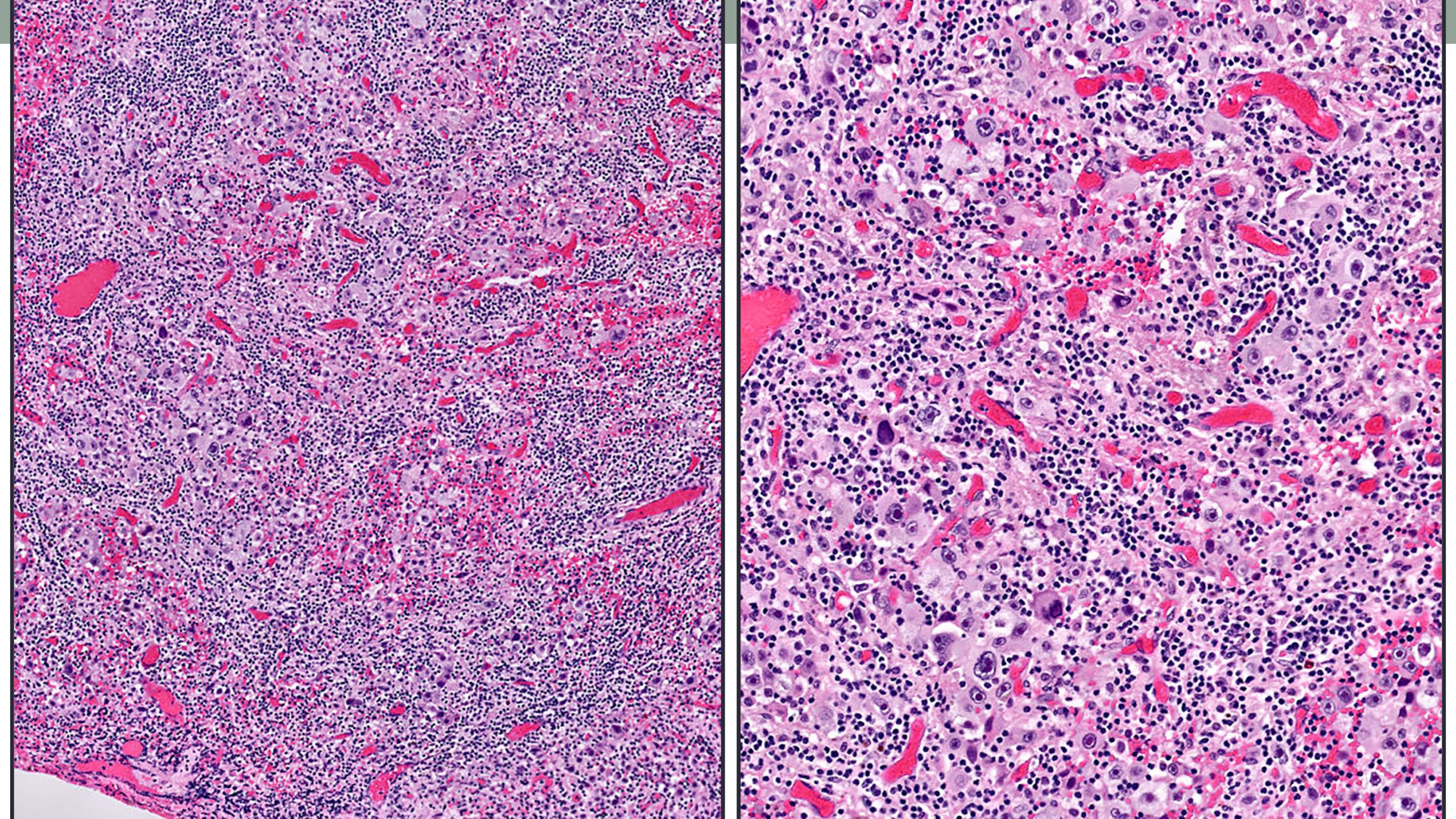
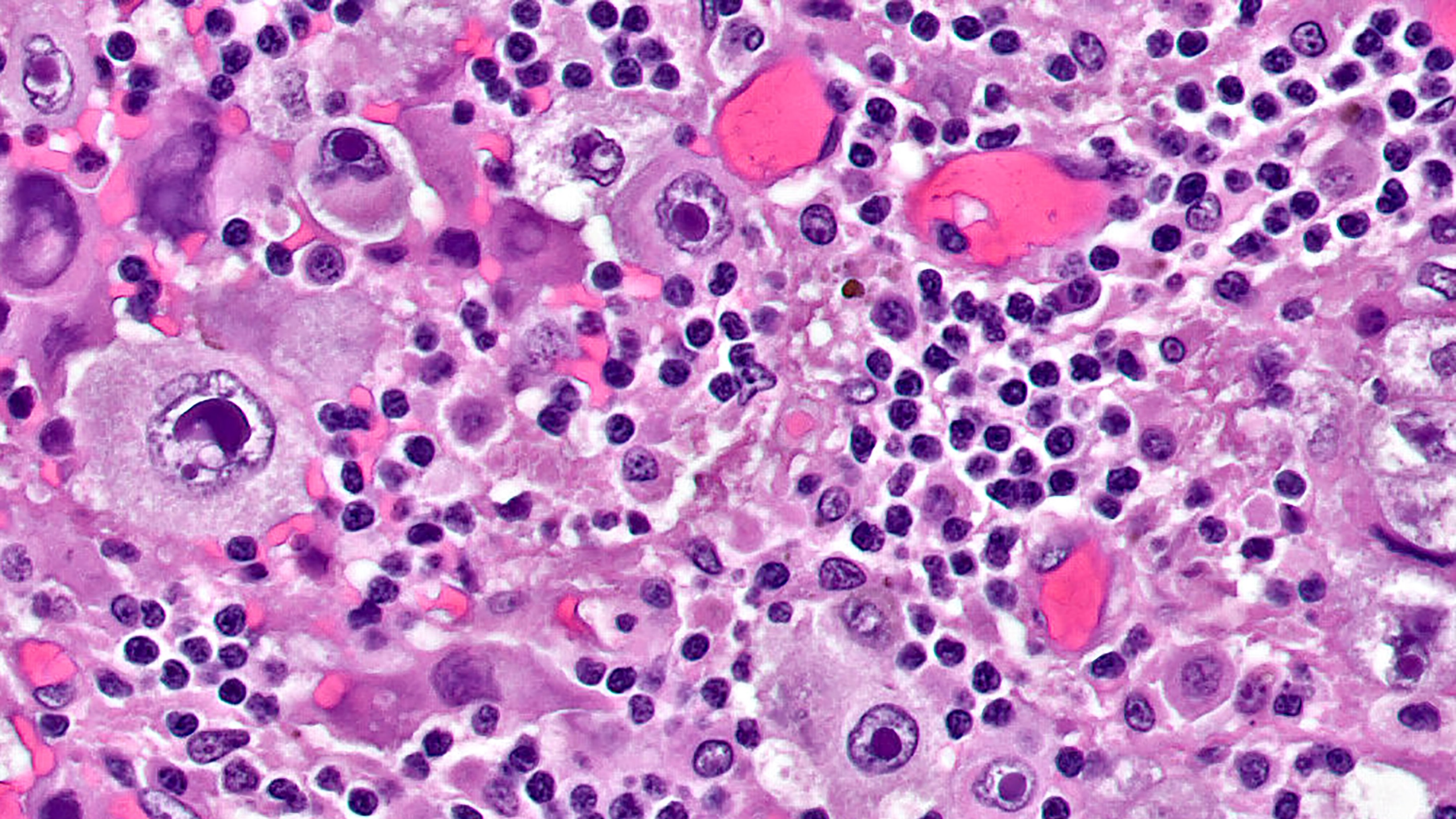
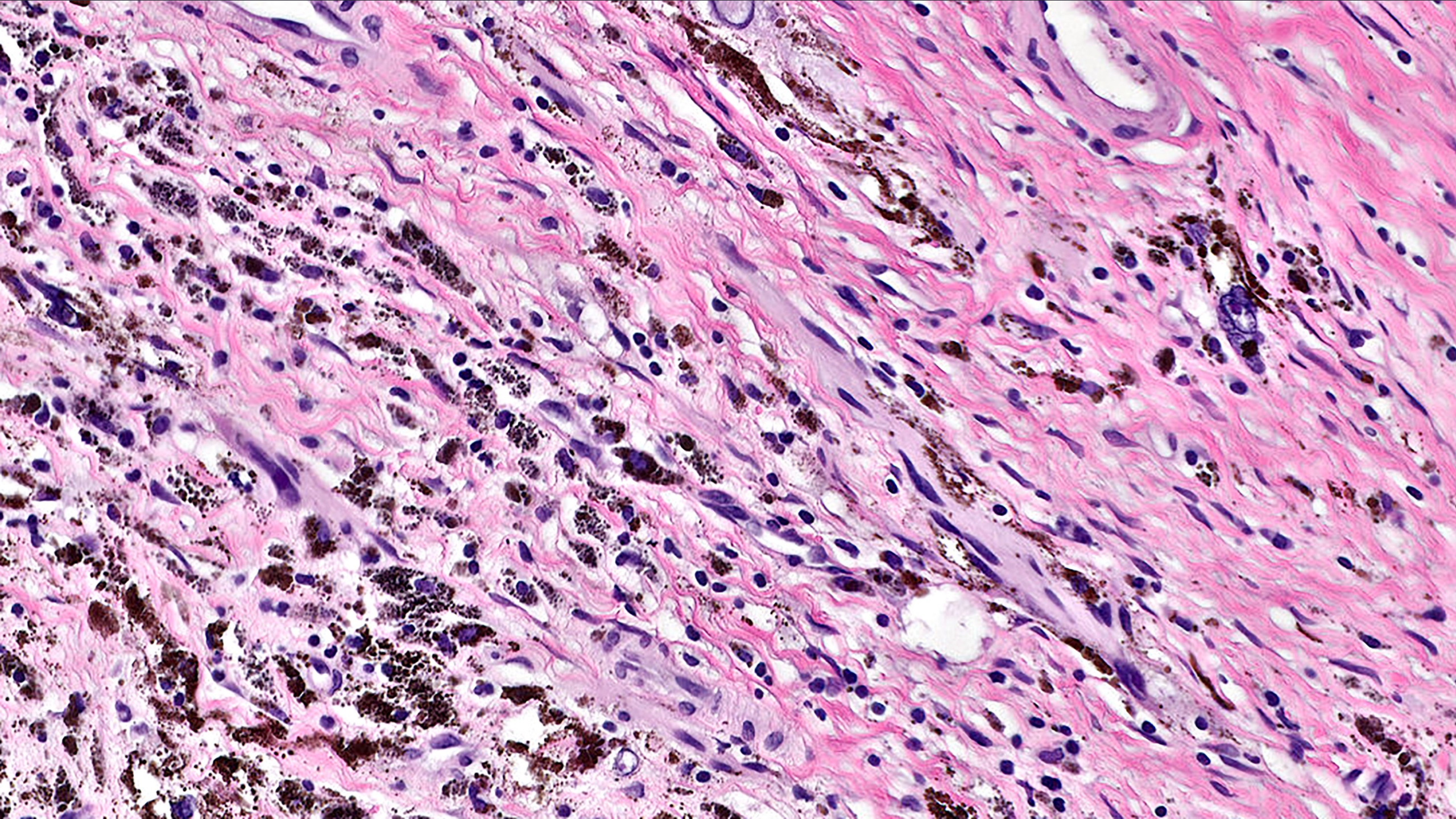




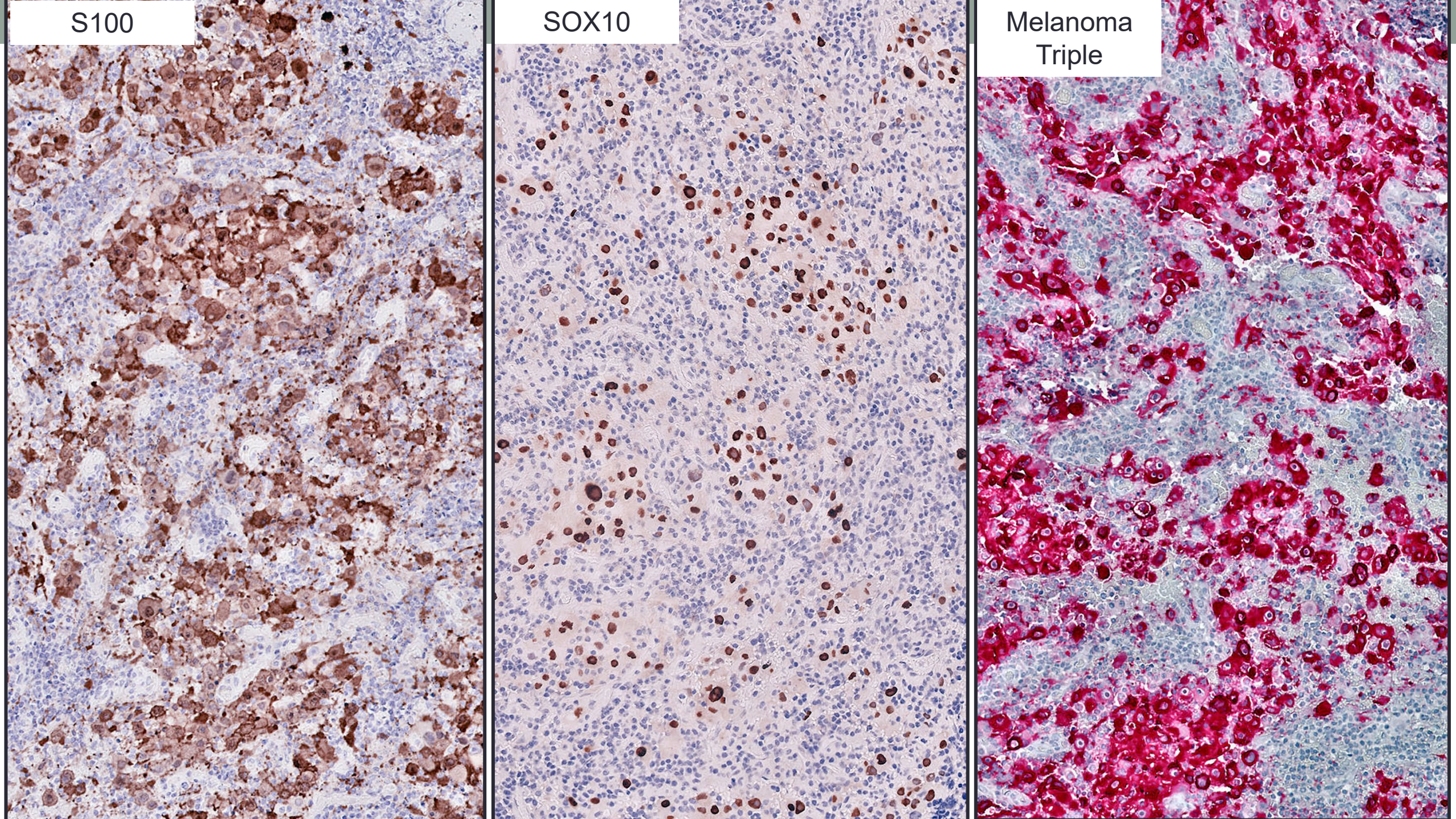


DISCUSSION:

- Differential?
- Additional studies?

Immunohistochemistry:

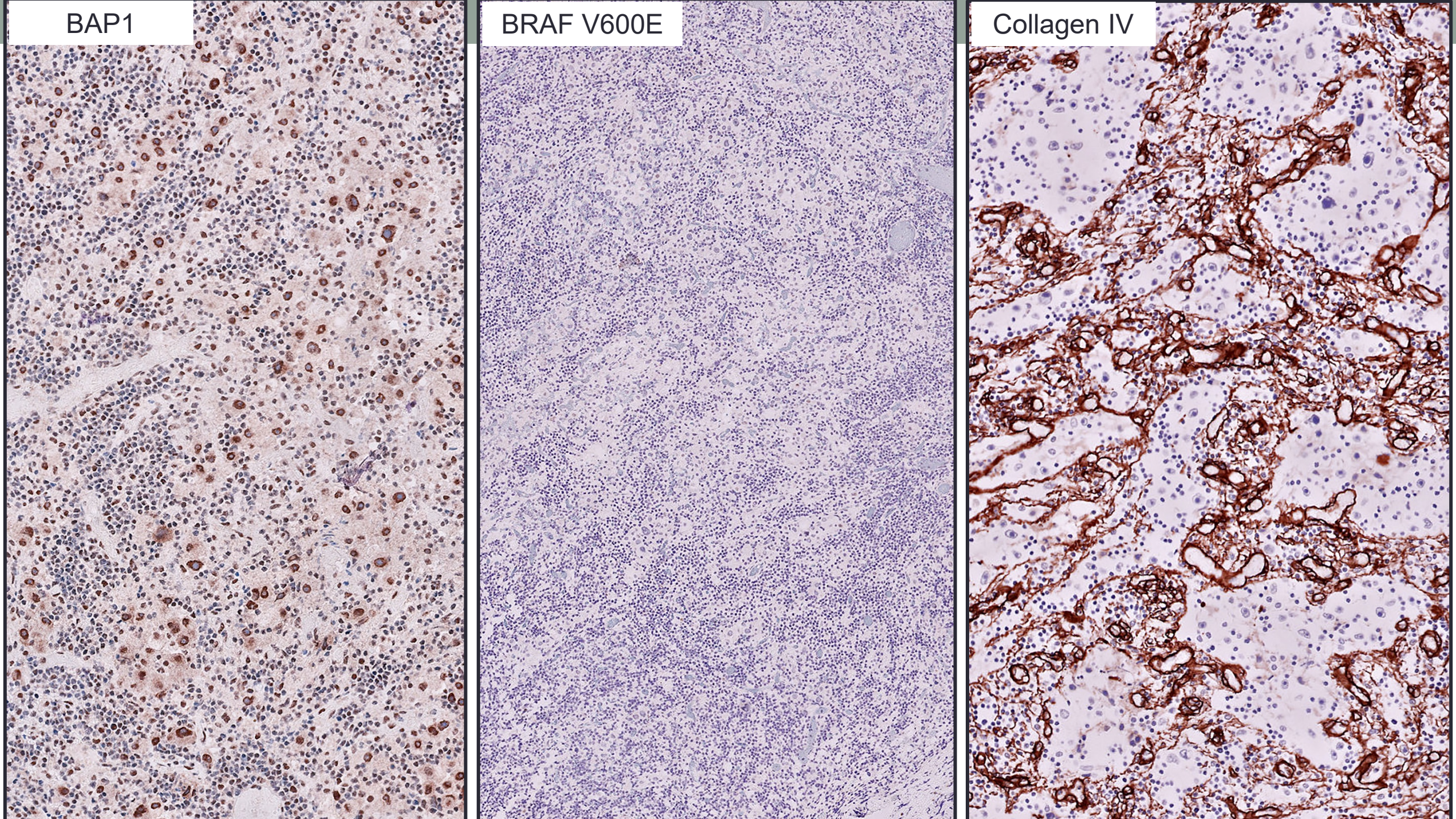
Stain	Expression in tumor cells
AE1/AE3	NEGATIVE
CK7	NEGATIVE
EMA	NEGATIVE
SMA	NEGATIVE
Caldesmon	NEGATIVE
Desmin	NEGATIVE
CD34	NEGATIVE
Synaptophysin	NEGATIVE
CD20	NEGATIVE


S100
SOX10
Melanoma
Triple

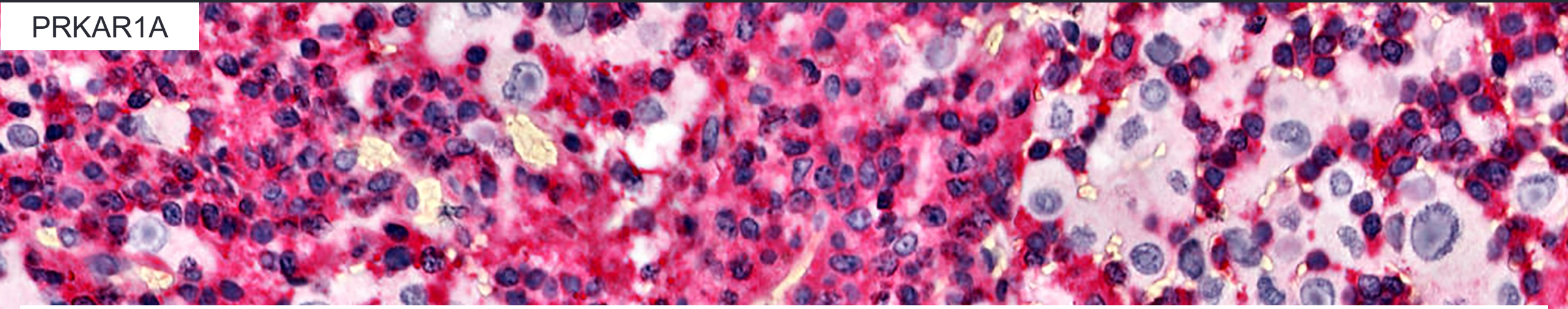
What next?

- Review clinical history:
  - No reported history of skin cancer
  - Multiple extracranial tumors (per clinical notes; no pathology reports available)
    - Benign “neck mass”
    - Cardiac myxoma

❖additional immunohistochemical and molecular testing


BAP1
BRAF V600E
Collagen IV

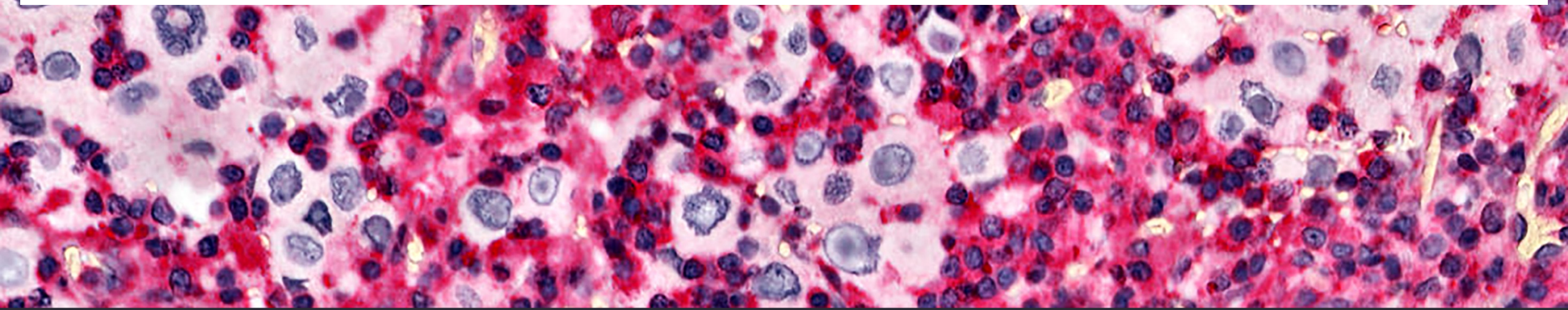
PRKAR1A



PATHOGENIC AND LIKELY PATHOGENIC ALTERATIONS

VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS	MUTANT ALLELE FREQUENCY
PRKAR1A p.R228*	NM_212472.2	Pathogenic	671	47%

'Reads' indicates the number of unique DNA molecules sequenced. 'Mutant Allele Frequency' indicates the percentage of the reads with the respective 'Variant' and is affected by the degree of normal cell contamination of the sample and whether the variant is fully clonal or subclonal. 'Pathogenic' and 'Likely Pathogenic' classifications are based on CCGL molecular pathologist/geneticist interpretation of data from somatic and germline databases and published literature. Variants classified as 'Possibly Pathogenic' have unknown significance but occur in genes or molecular pathways known to be recurrently altered in the tumor type.



DIAGNOSIS: MALIGNANT MELANOTIC NERVE SHEATH TUMOR (MMNST)

*Malignant melanotic nerve sheath tumor represents new nomenclature introduced in the 5th edition of the BST WHO 2020 (formerly melanotic schwannoma)

Malignant Melanotic Nerve Sheath Tumor

- Neoplastic melanin-producing cells with ultrastructural features of Schwann cells
  - Melan-A, HMB45, SOX10, S100 (+)
- Most often arises from spinal or autonomic nerves of adults
- Can follow an aggressive clinical course with frequent local recurrence (35%) as well as metastasis (44%)

- "CLASSIC" FEATURES:
  - High cellularity, lobules, fascicles
  - Spindle to Epithelioid cells
    - Macronucleoli ("Monster cells")
  - Pigmentation – variable or patchy
  - Thin-walled vessels
  - Lymphoplasmacytic infiltrate?
  - Psammoma bodies & "Adipocyte-like" cells

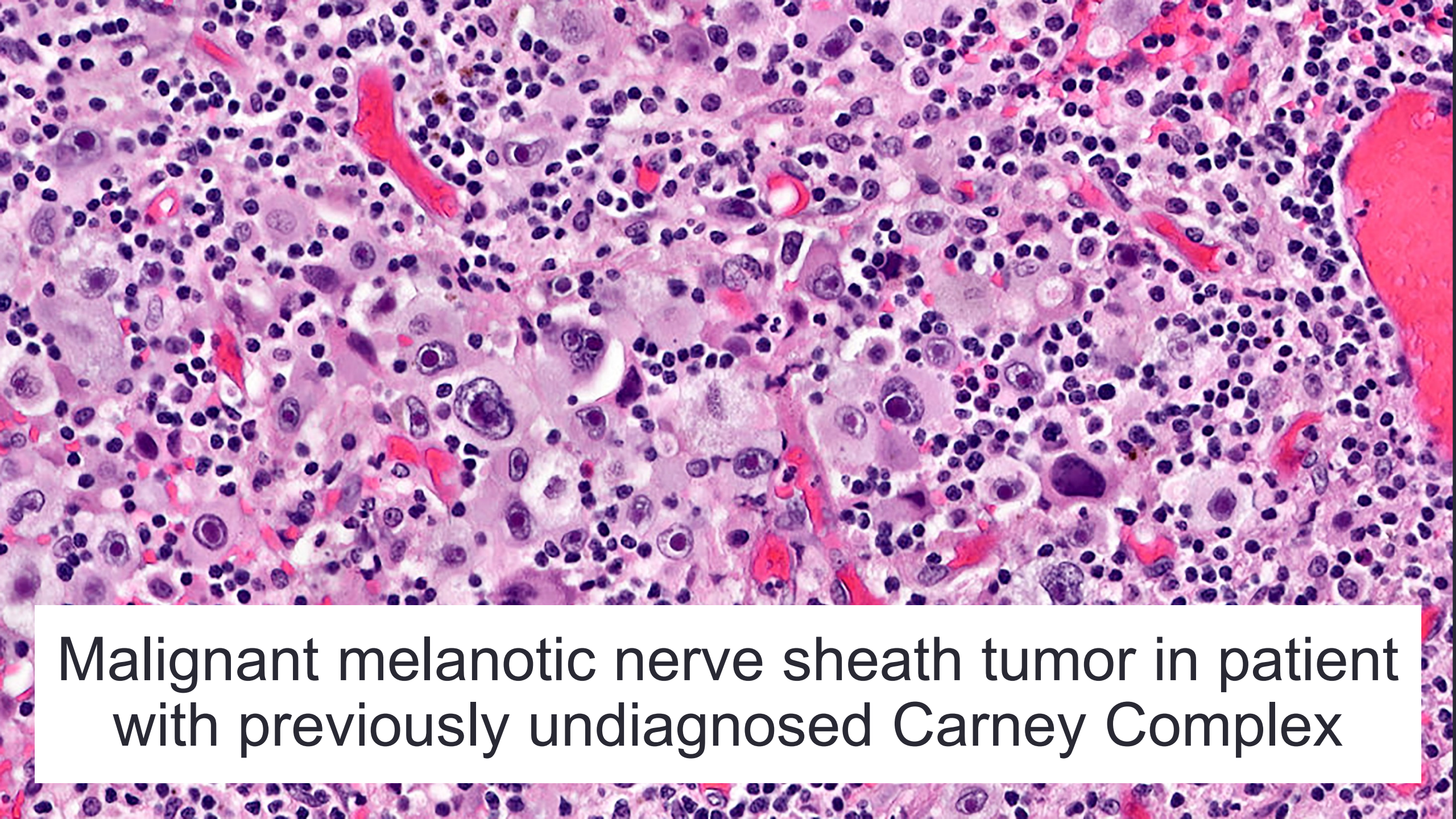
❖PRKAR1A inactivating mutations seen in Carney Complex

Carney Complex

- Association of myxomas, lentigines, and endocrine overactivity first reported by Dr. J. Aiden Carney in 1985.

Manifestation	Percentage
Spotty skin pigmentation	77
Heart myxoma	53
Skin myxoma	33
PPNAD [a]	26
LCCSCT [a]	33 (of male patients)
Acromegaly	10
PMS [a] *(MMNST)	10
Thyroid nodules or cancer	5
Breast ductal adenoma	3 (of female patients)

Diagnostic Criteria: 1) exhibit TWO of the manifestations below, or 2) exhibit ONE and meet one of the supplemental criteria
1. Spotty skin pigmentation with typical distribution
2. Myxoma (cutaneous or mucosal)
3. Cardiac Myxoma
4. Breast myxomatosis
5. PPNAD
6. Acromegaly d/t GH-producing adenoma
7. LCCSCT
8. Thyroid carcinoma
9. MMNST
10. Blue nevus, epithelioid (multiple)
11. Breast ductal adenoma
12. Osteochondromyxoma of bone
*SUPPLEMENTAL CRITERA:
1. Affected 1st-degree relative
2. Inactivating mutation of the PRKAR1A gene



Malignant melanotic nerve sheath tumor in patient with previously undiagnosed Carney Complex

References:

- Torres-Mora J, Dry S, Li X, Binder S, Amin M, Folpe AL. Malignant melanotic schwannian tumor: a clinicopathologic, immunohistochemical, and gene expression profiling study of 40 cases, with a proposal for the reclassification of "melanotic schwannoma". *Am J Surg Pathol*. 2014;38(1):94-105.
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