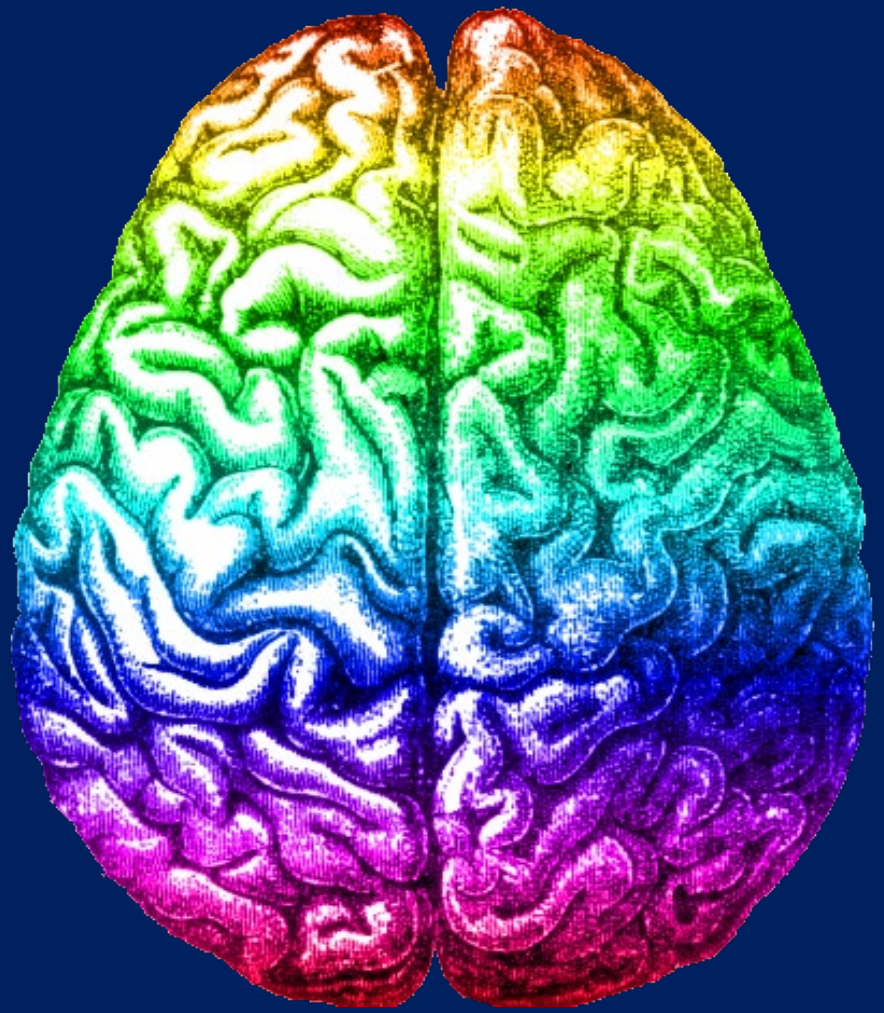
# Case 2023-1

Simmi Patel, MD

Thomas Pearce, MD PhD

University of Pittsburgh Medical Center

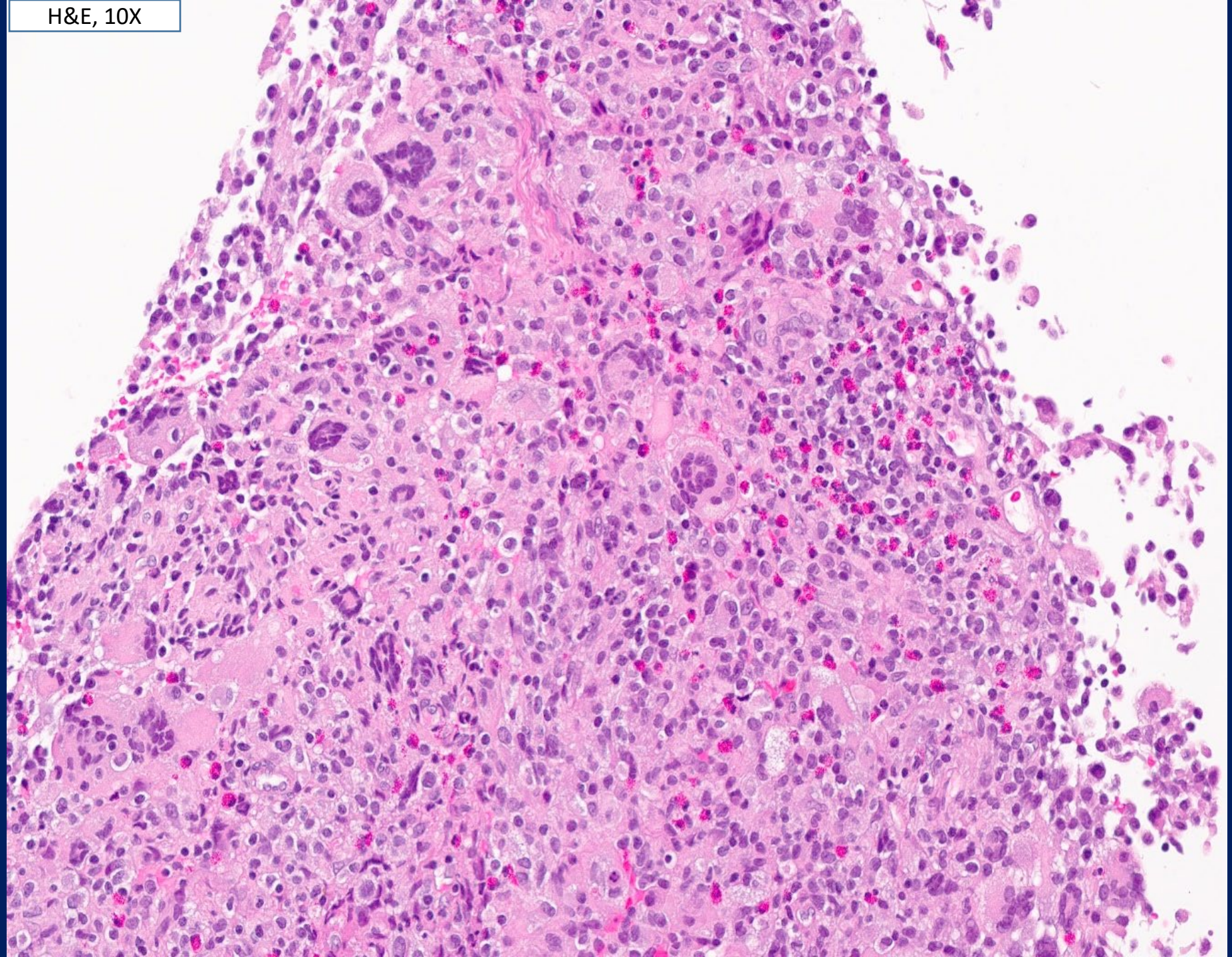


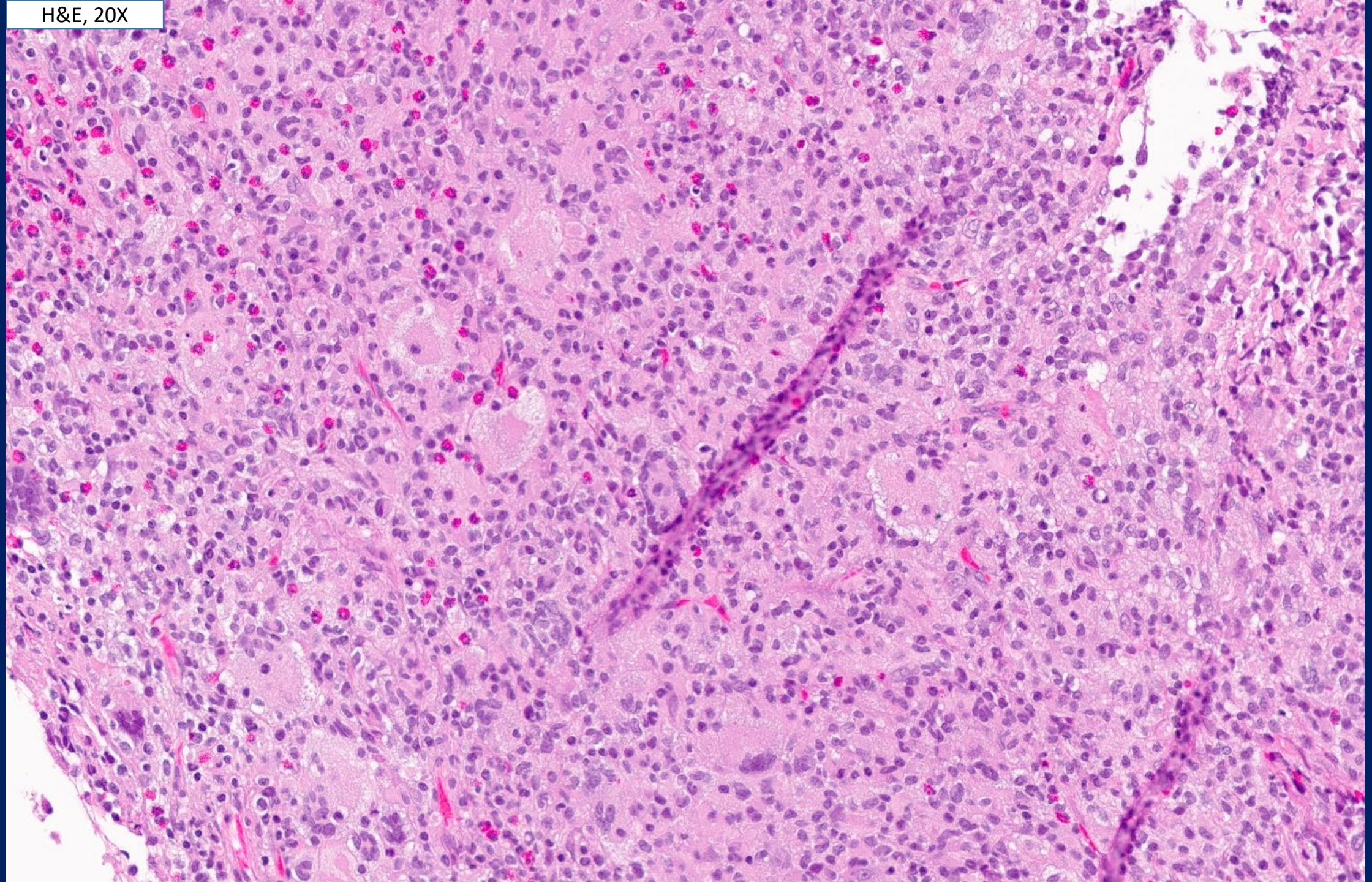
University of Pittsburgh

UPMC LIFE CHANGING MEDICINE

# Clinical history

- 54-year-old female with a past medical history of a pituitary adenoma  (gonadotroph) status post resection approximately two years prior, who now presents with a Meckel's cave/trigeminal nerve lesion.
- No other significant past medical history was contained in the medical records received at our institution for consultation.


H&E, 10X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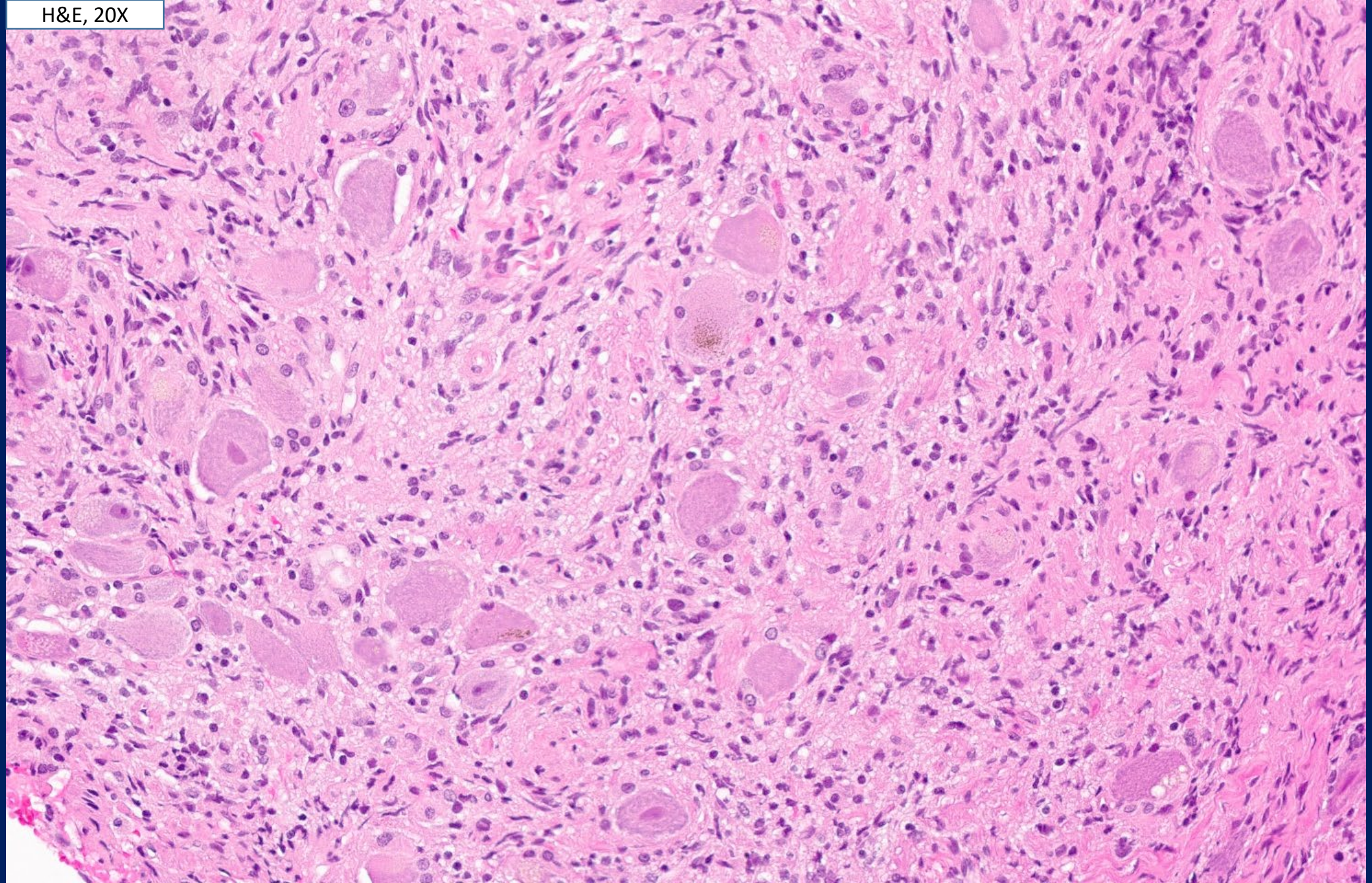
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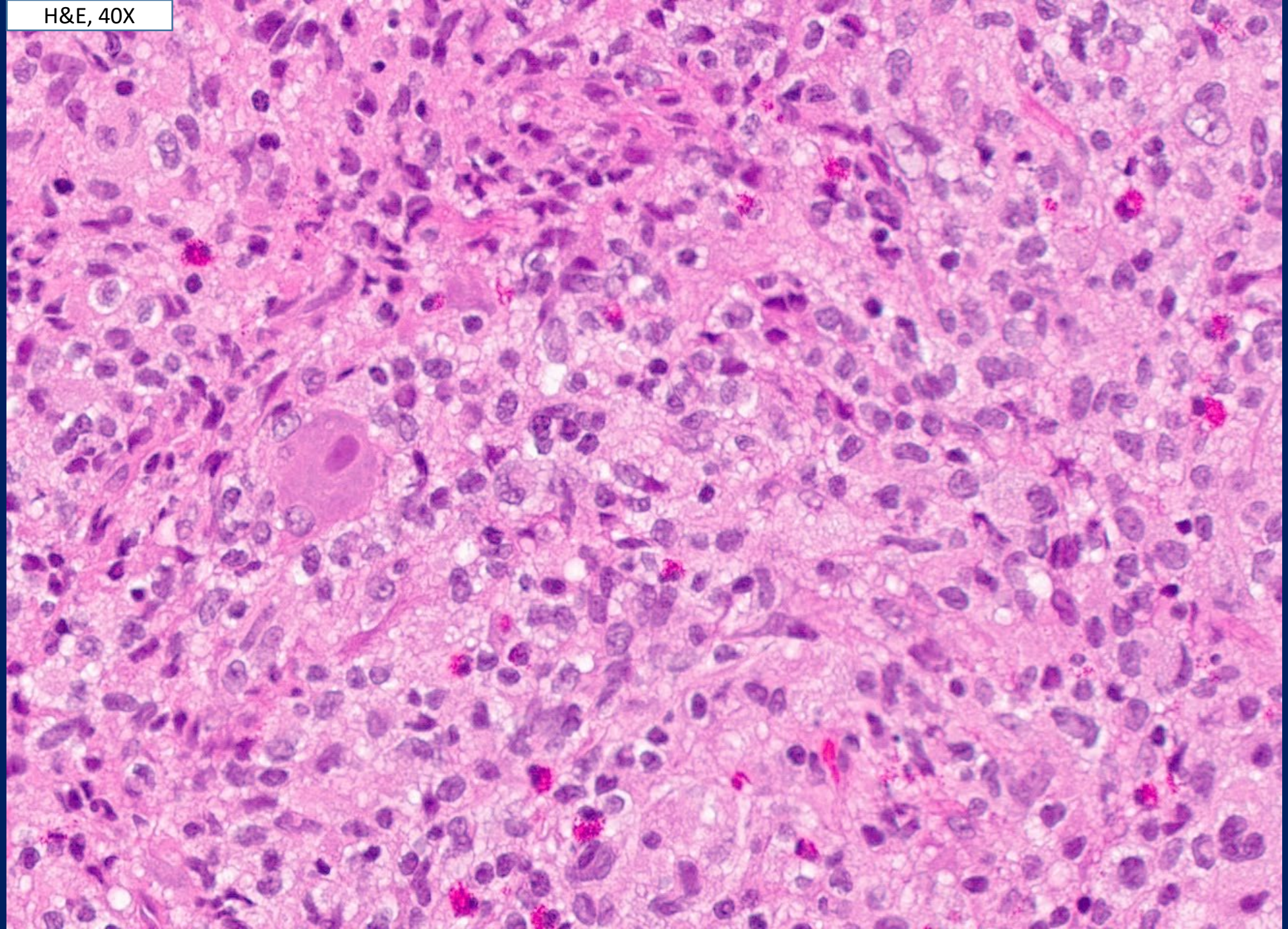
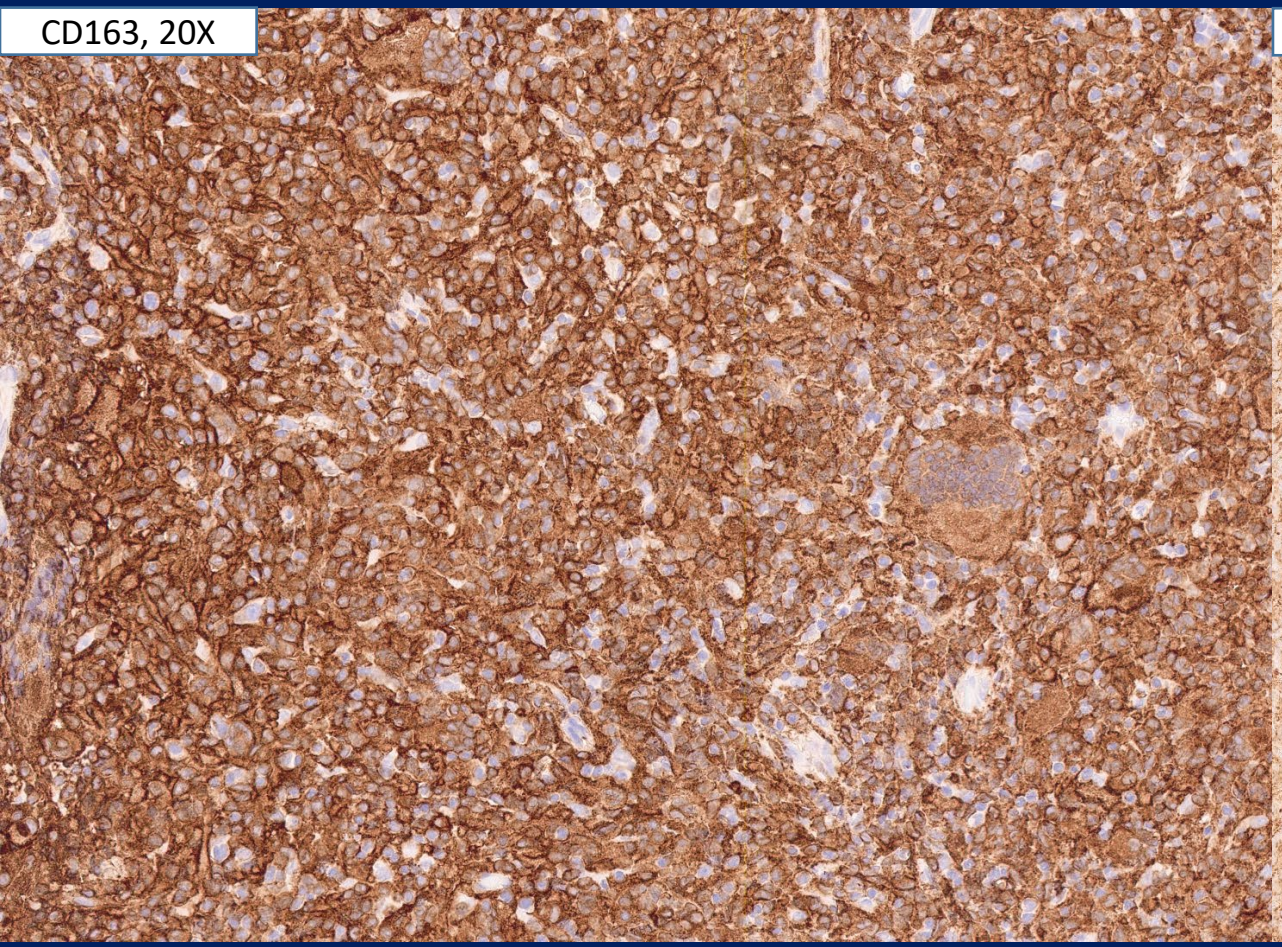
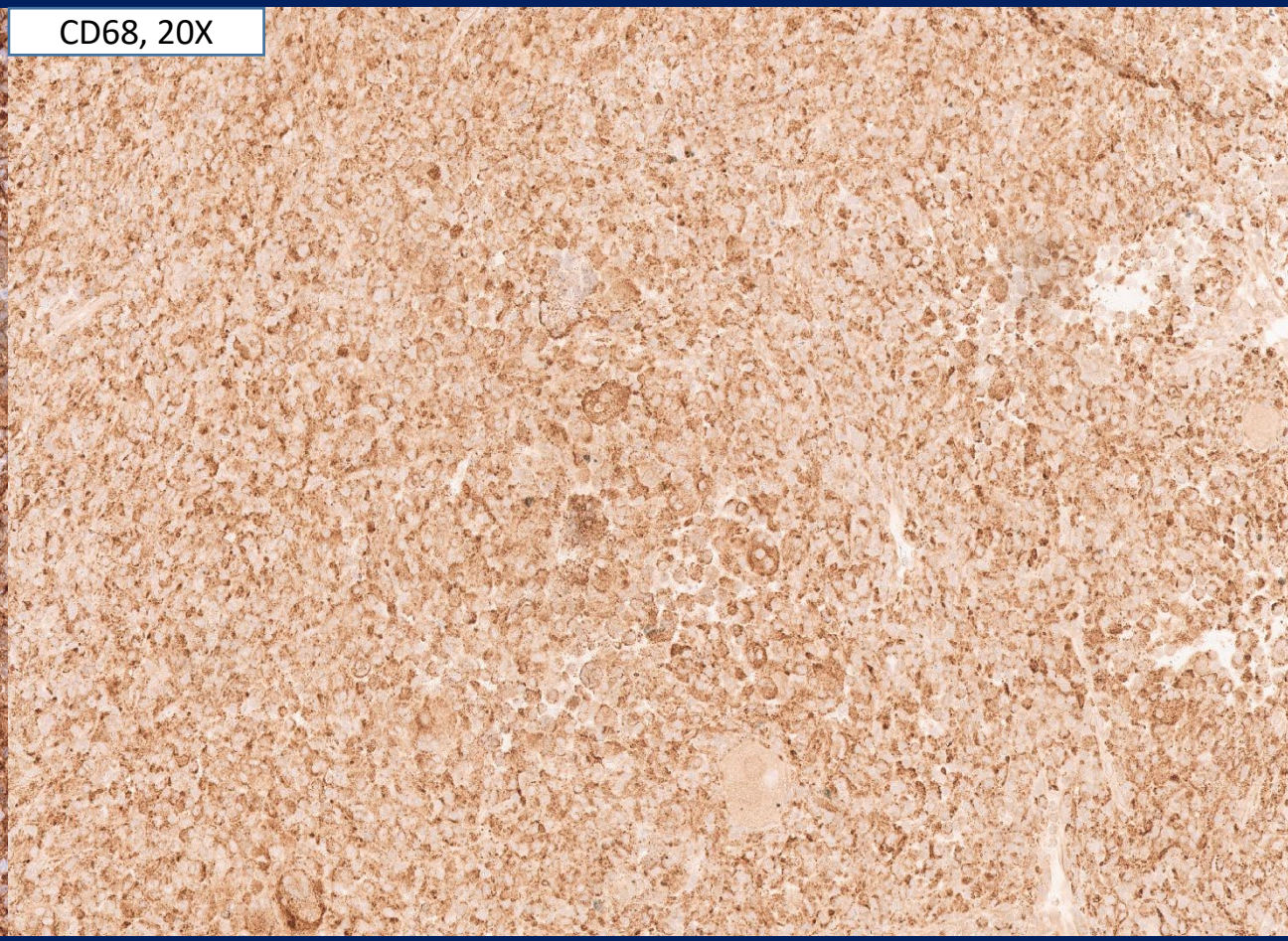

H&E, 40X

# Differential and workup?

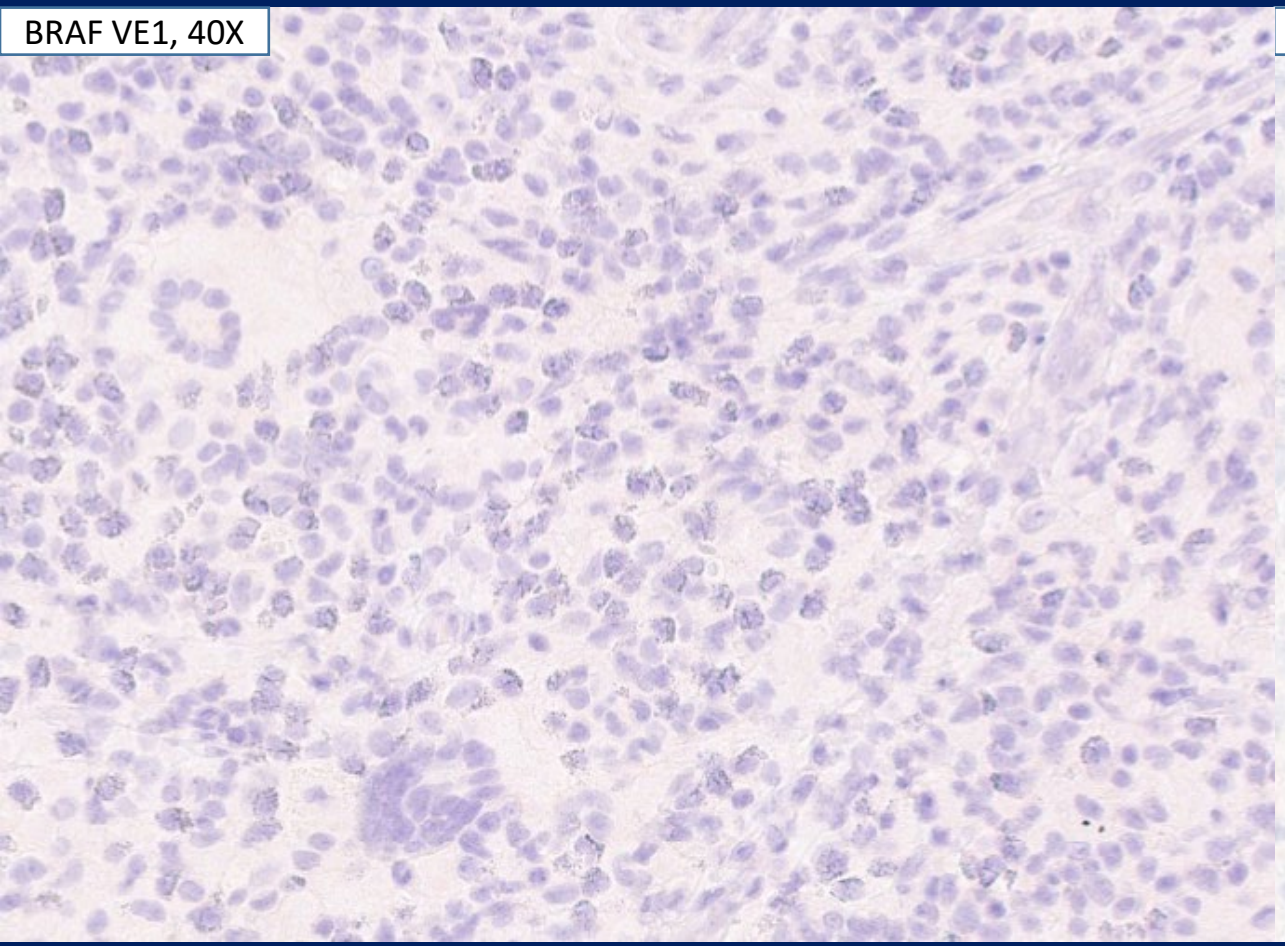
CD163, 20X



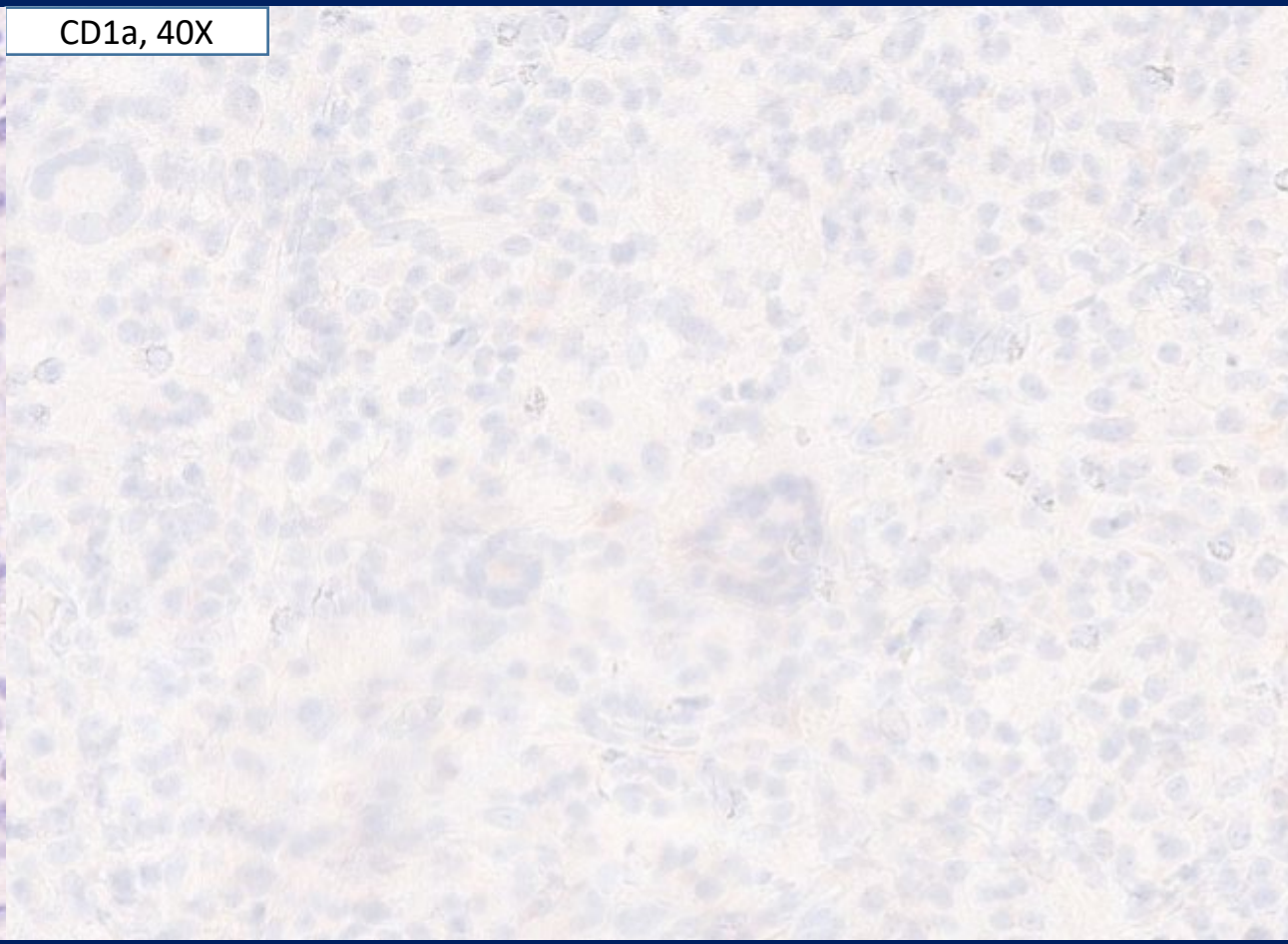
CD68, 20X



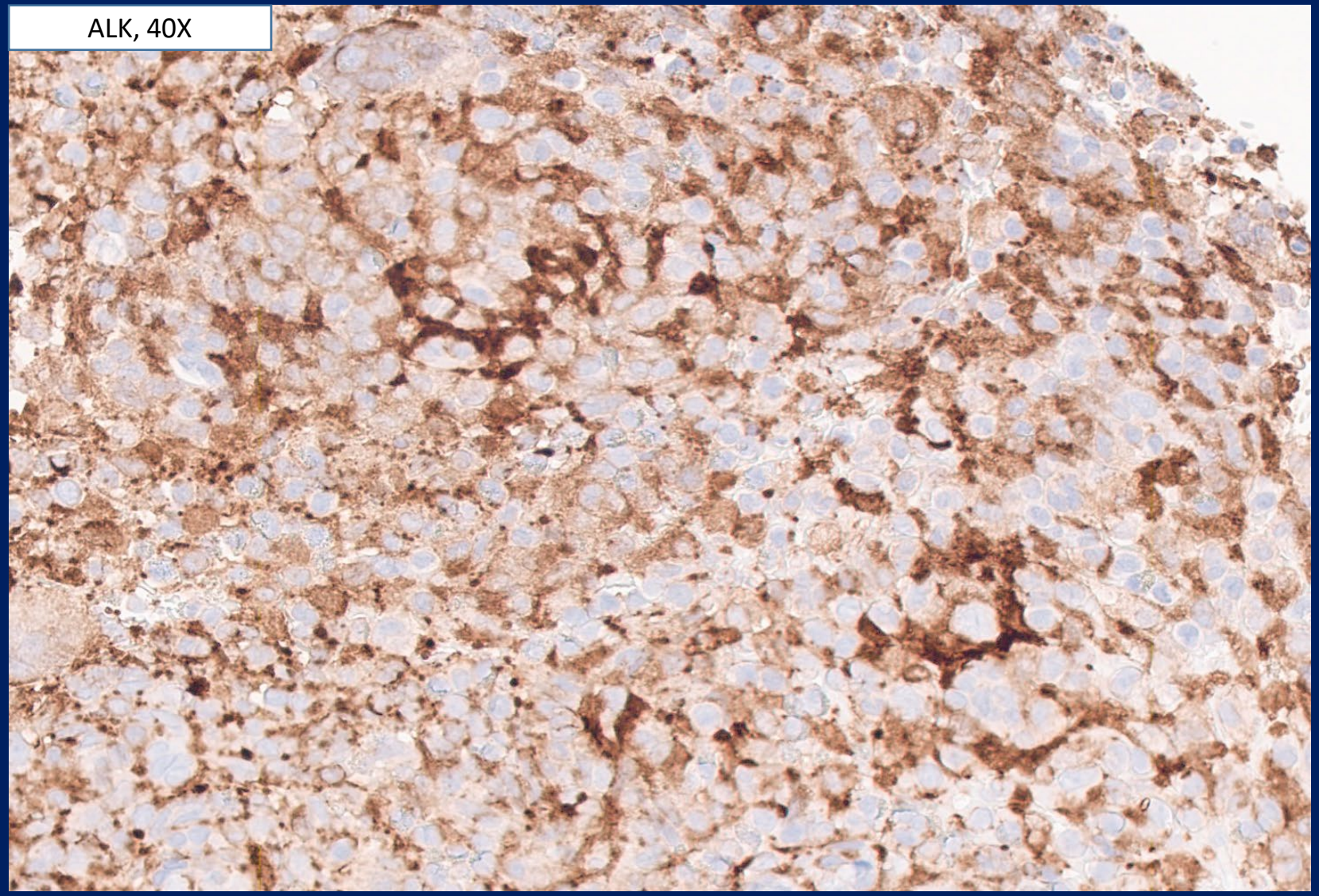
BRAF VE1, 40X



CD1a, 40X

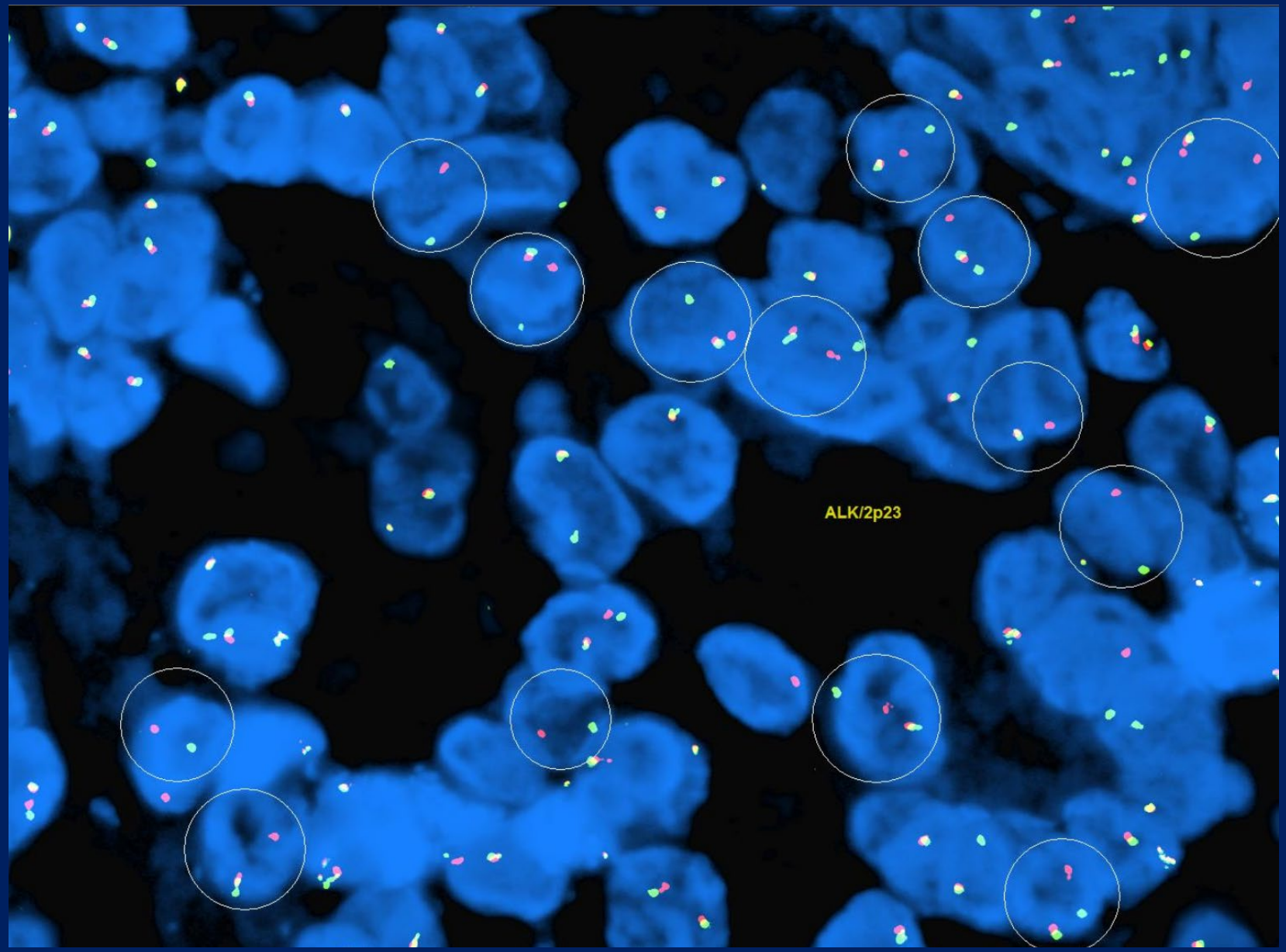


ALK, 40X



# FISH

- ALK rearrangement by FISH



# Final diagnosis

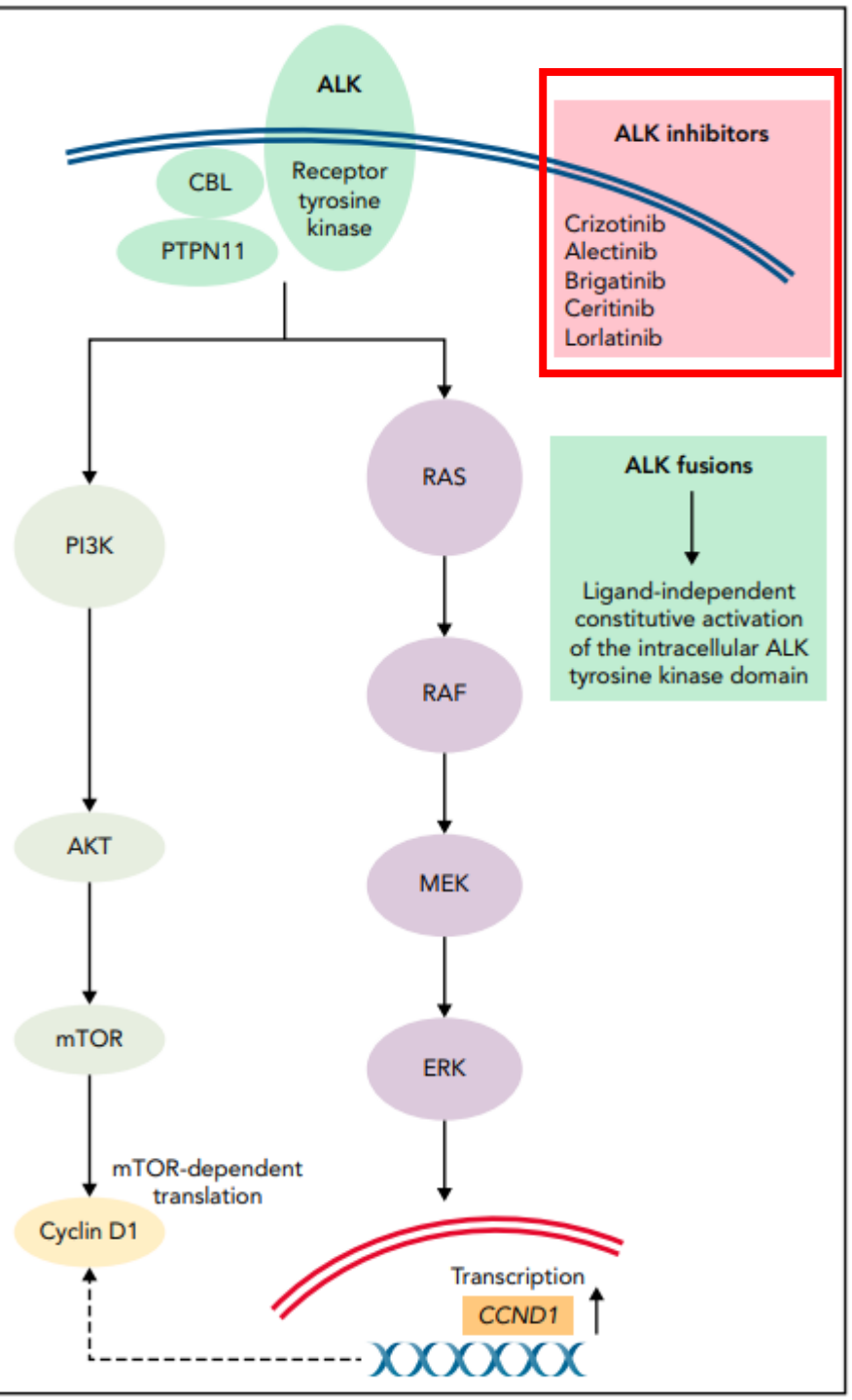
Cavernous sinus lesion and trigeminal nerve sheath, biopsy:

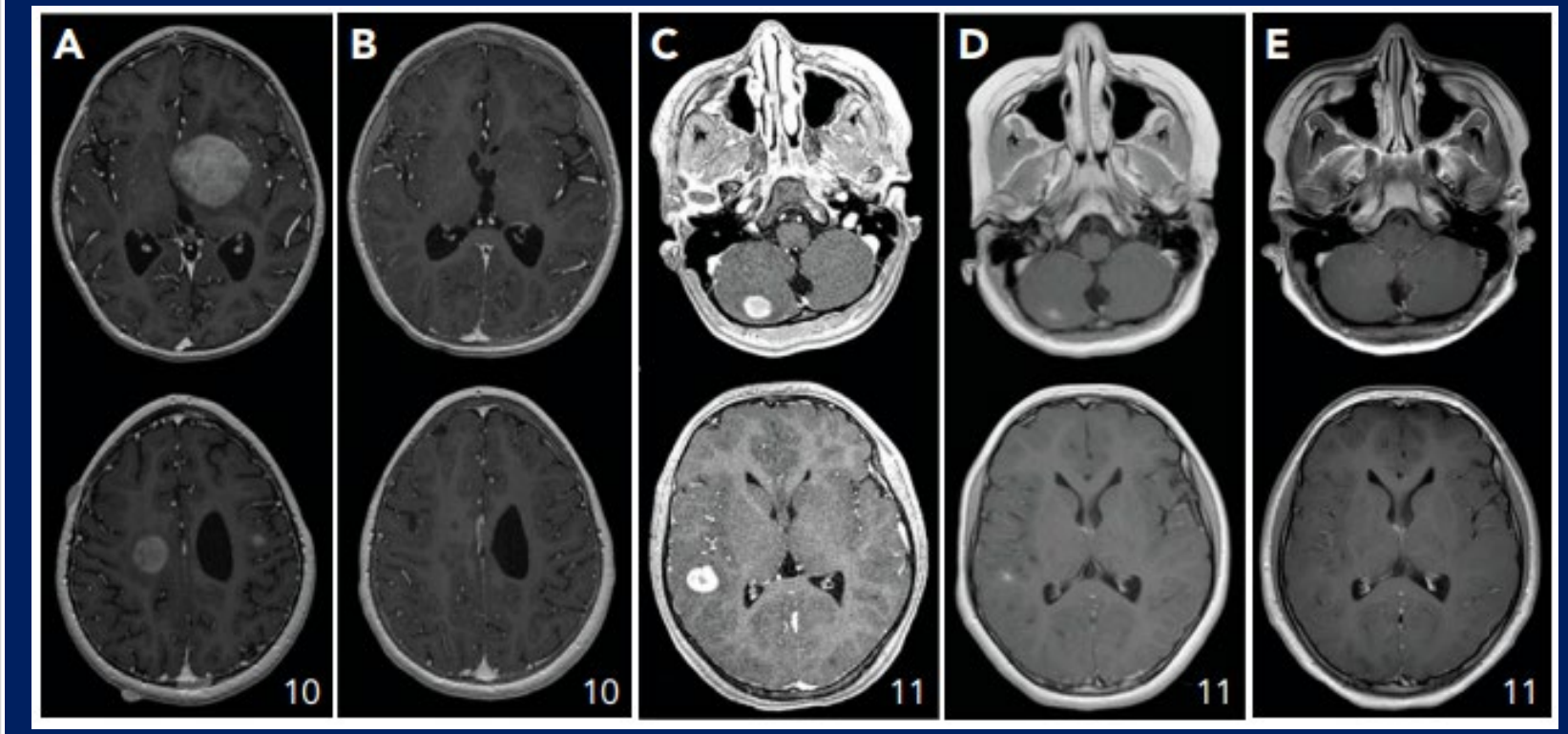
ALK-positive histiocytosis

# Classification

- Histiocytoses included in 2021 CNS WHO
  - Erdheim-Chester disease
  - Rosai-Dorfman disease
  - Juvenile xanthogranuloma
  - Langerhans cell histiocytosis
  - Histiocytic sarcoma
- New entity in 2022 Hematolymphoid WHO
  - ALK-positive histiocytosis

# Treatment implications




Kemps et al (2022) and Emile et al (2021)

# Discussion points

- ALK-positive histiocytosis is a newly-recognized histiocytic neoplasm lacking high-grade cytologic atypia and is characterized by ALK (anaplastic lymphoma kinase) immunoreactivity, usually due to *ALK* gene rearrangement.
  - Most commonly *KIF5B::ALK*
- The most comprehensive study to date (Kemps et al, 2022) documents 39 patients, including 31 children and 8 adults, with 41 years as the oldest.
  - 19 cases (49%) with nervous system involvement
- This lesion in a 54-year-old patient extends the clinical spectrum of intracranial ALK-positive histiocytosis described in recently published series by Chang et al. (2018), Lucas et al. (2019), Aoki et al. (2022), and Kemps et al. (2022)
- An integrated histologic and molecular approach is important for the diagnosis and treatment of histiocytic lesions.

| Entity | Histopathology | Immunohistochemistry | Molecular findings |
|---|---|---|---|
| Erdheim-Chester disease | • Lesion comprising of foamy histiocytes<br>• Touton giant cells<br>• Small lymphocytes, plasma cells and neutrophils<br>• Fibrosis | • Histiocytes are positive for: CD68, CD163, CD4, CD14, factor XIIIa and fascin; negative for CD1a and Langerin (CD207).<br>• ERK expression<br>• VE1: diffuse strong cytoplasmic staining | *BRAF* p.V600E mutations (~50% of cases), and other genetic alterations pertaining to the MAPK pathway. |
| Rosai-Dorfman disease | • Mixed inflammatory infiltrate: large pale histiocytes, numerous lymphocytes and plasma cells, and variable fibrosis. | • Histiocytes are positive for CD11c, CD68, CD163, fascin, and S100; negative for CD1a and CD207 (langerin).<br>• Expression of cyclin D1 | Suspected familial<br>RDD: SLC29A3 and TNFRSF6 germline mutation analysis. |
| Juvenile xanthogranuloma | • Lesion comprising of foamy histiocytes<br>• Lacking significant nuclear pleomorphism<br>• Touton giant cells | • Histiocytes are positive for: CD68, CD163, CD4, CD14, factor XIIIa and fascin; negative for CD1a and Langerin (CD207)<br>• ALK is negative. | Mutations of *CSF1R* and fusions involving an *NTRK* gene have been reported for peripheral juvenile xanthogranuloma. |
| Langerhans cell histiocytosis | • Langerhans cells and variable reactive macrophages, lymphocytes, plasma cells, and eosinophils. | • Neoplastic cells are positive for CD1a (surface), CD207 (also known as langerin; granular cytoplasmic), S100 (nuclear and cytoplasmic), and CD68; about 50–60% express BRAF p.V600E | *BRAF* p.V600E mutation |
| Histiocytic sarcoma | • Cellular, non-cohesive infiltrates of large, moderately pleomorphic, mitotically active histiocytes. | • Neoplastic cells are positive for histiocytic markers (e.g. CD68, CD163, lysozyme, CD11c, and CD14); variably positive for CD34; and negative for myeloid antigens, dendritic antigens, CD30, ALK, and other lymphoid markers. | Genes affecting the MAPK and mTOR pathway |
| ALK- positive histiocytosis | • Large oval (“epithelioid”) cells, foamy cells and spindle cells.<br>• Admixed touton giant cells | • Positive immunostaining for 2 or more histiocytic markers (CD163, CD68, CD14, CD4, lysozyme)<br>• Positive for ALK | ALK translocation |


Xochimilco, CDMX

# References


- Chang KTE, Tay AZE, Kuick CH, et al. (2018) ALK-positive histiocytosis: an expanded clinicopathologic spectrum and frequent presence of KIF5B-ALK fusion. *Mod Pathol,* 32(5):598–608.
- Huang H, Gheorghe G, North PE, Suchi M (2018) Expanding the Phenotype of ALK-positive Histiocytosis: A Report of 2 Cases. *Pediatr Dev Pathol,* 21(5):449–455.
- WHO Classification of Tumours Editorial Board. Haematolymphoid tumours [Internet; beta version ahead of print]. Lyon (France): International Agency for Research on Cancer; 2022. (WHO classification of tumours series, 5th ed.; vol. 11). Available from: https://tumourclassification.iarc.who.int/chapters/63.
- 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.
- Yuzuna Aoki, Masayuki Maeda, Seiya Kishi, et al. (2022) Central nervous system involvement of systemic ALK-positive histiocytosis with KIF5B-ALK fusion. *Radiology Case Reports*, 17(10): 3867-3870.
- Kemp et al (2022). ALK-positive histiocytosis: a new clinicopathologic spectrum highlighting neurologic involvement and responses to ALK inhibition, *Blood,* 139(2): 256-280.
- Lucas, CH.G., Gilani, A., Solomon, D.A. et al. (2019) ALK-positive histiocytosis with *KIF5B-ALK* fusion in the central nervous system. *Acta Neuropathol,* 138: 335–337.