DSS Case 8

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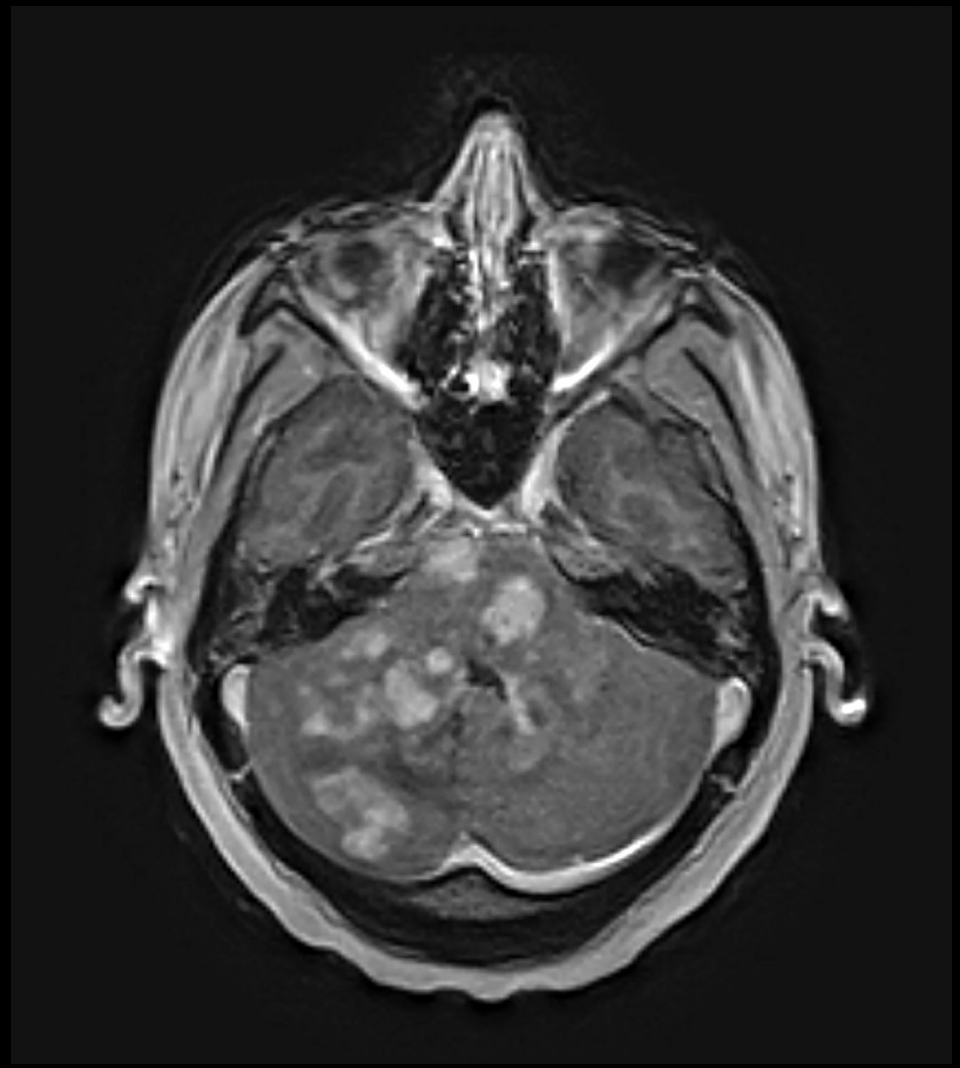
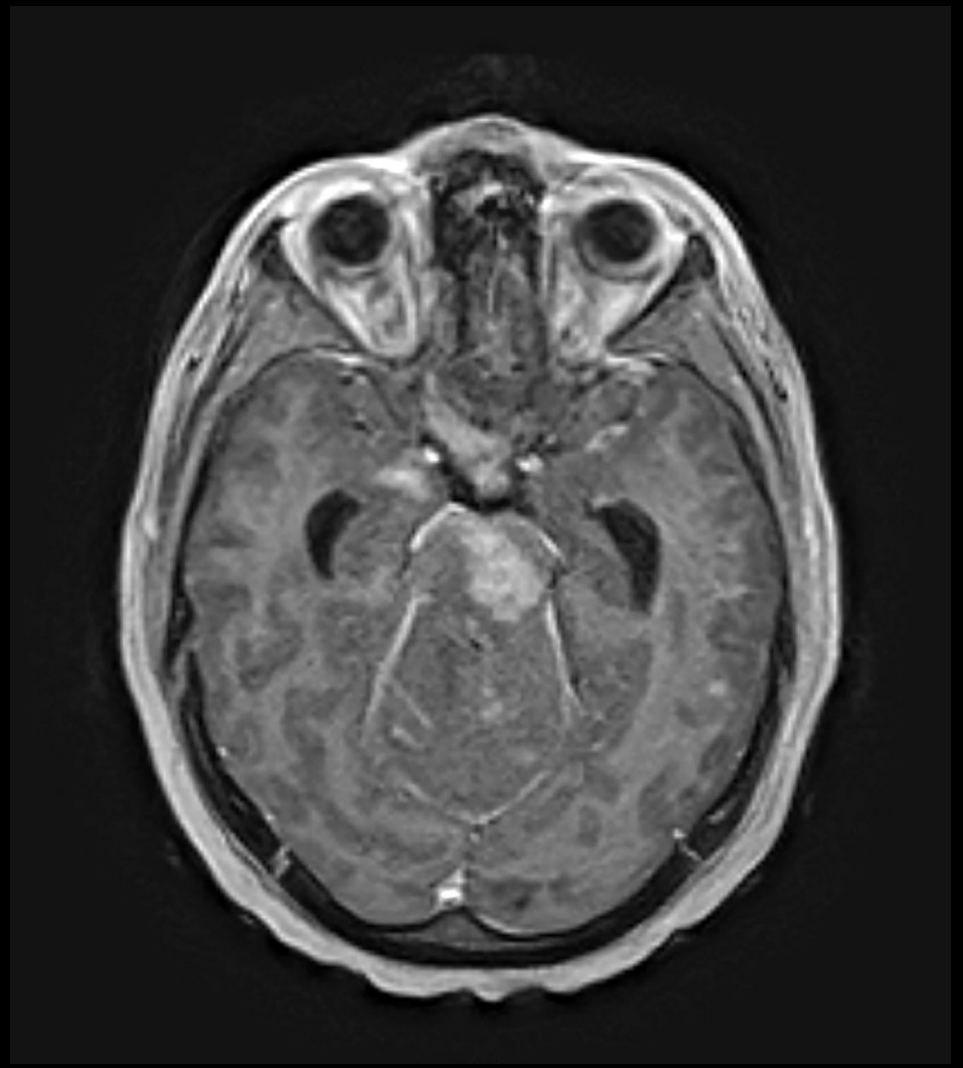
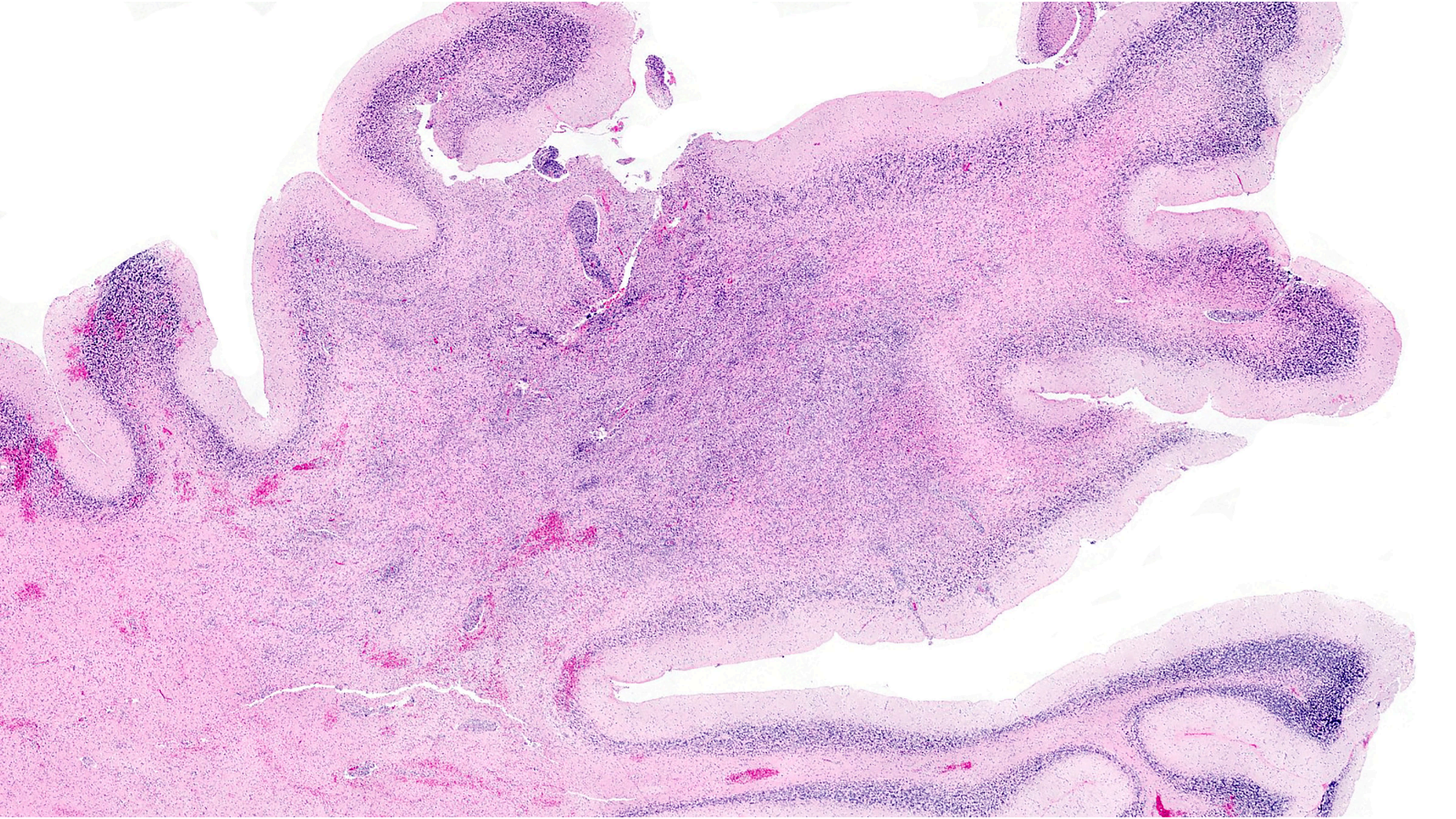
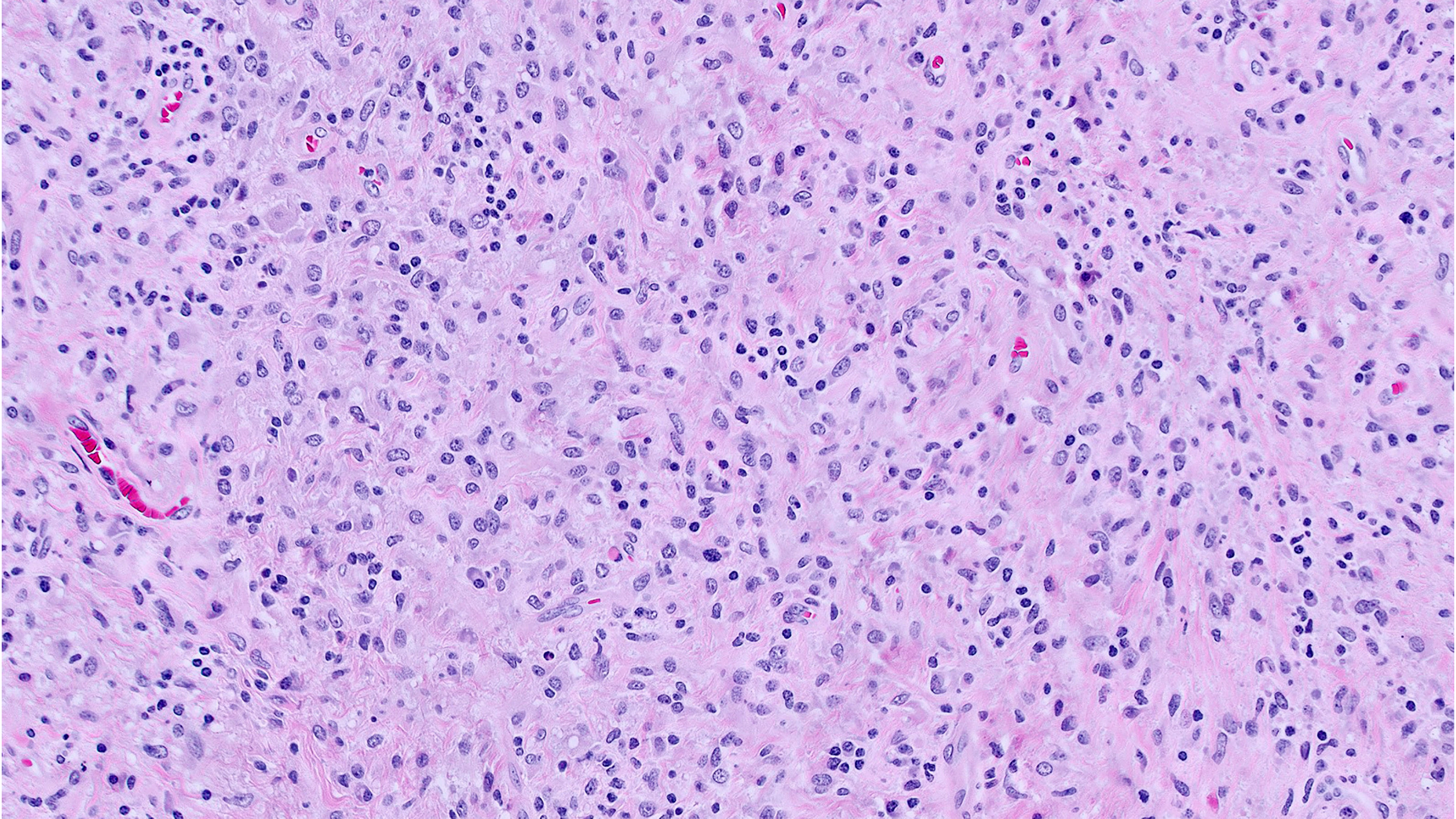
History

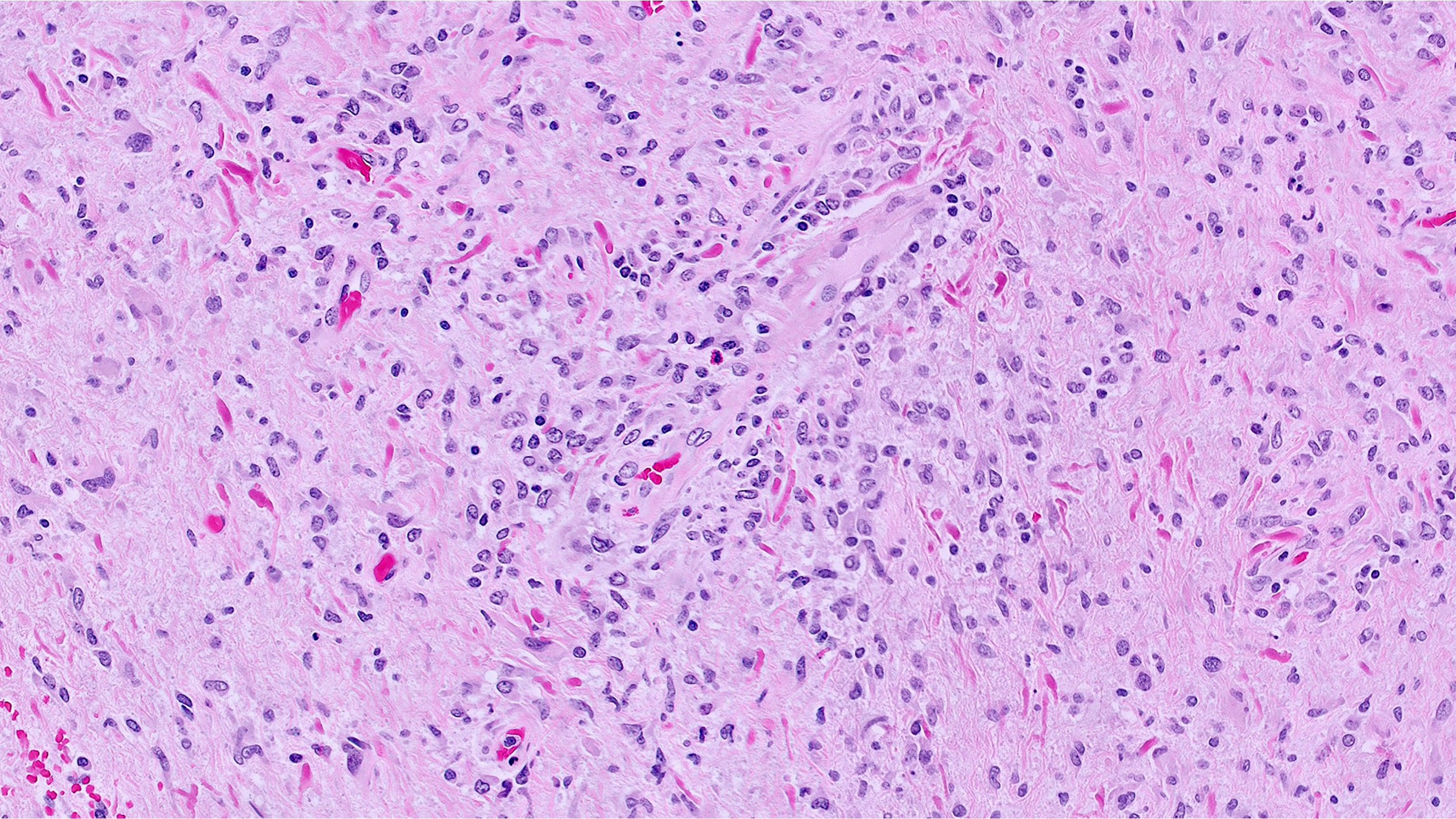
- 28-yo F with history of illicit drug use
- She presented with headaches and ataxia.
- MRI: multiple enhancing lesions in supratentorial and infratentorial brain, as well as the spinal cord.
  - The radiologic differential favored metastases, lymphoma, or infection.
- Bx of the cerebellar lesions.



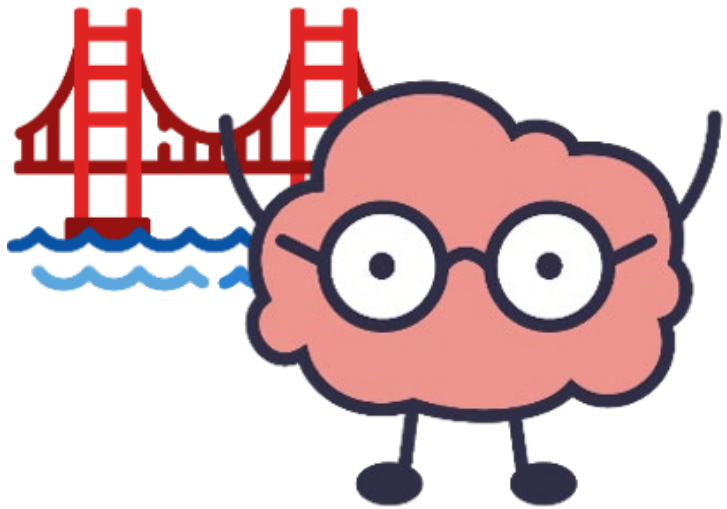






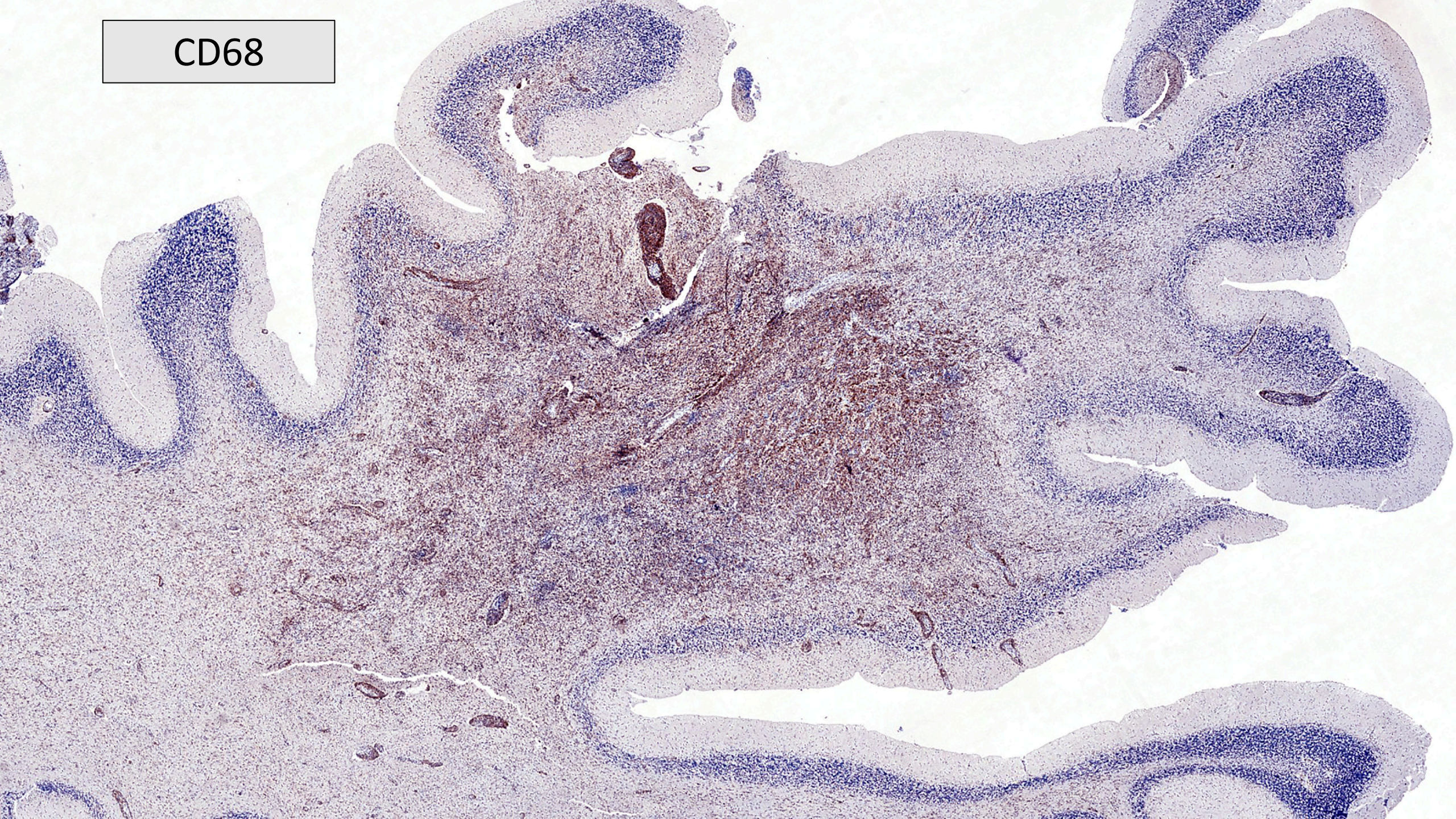


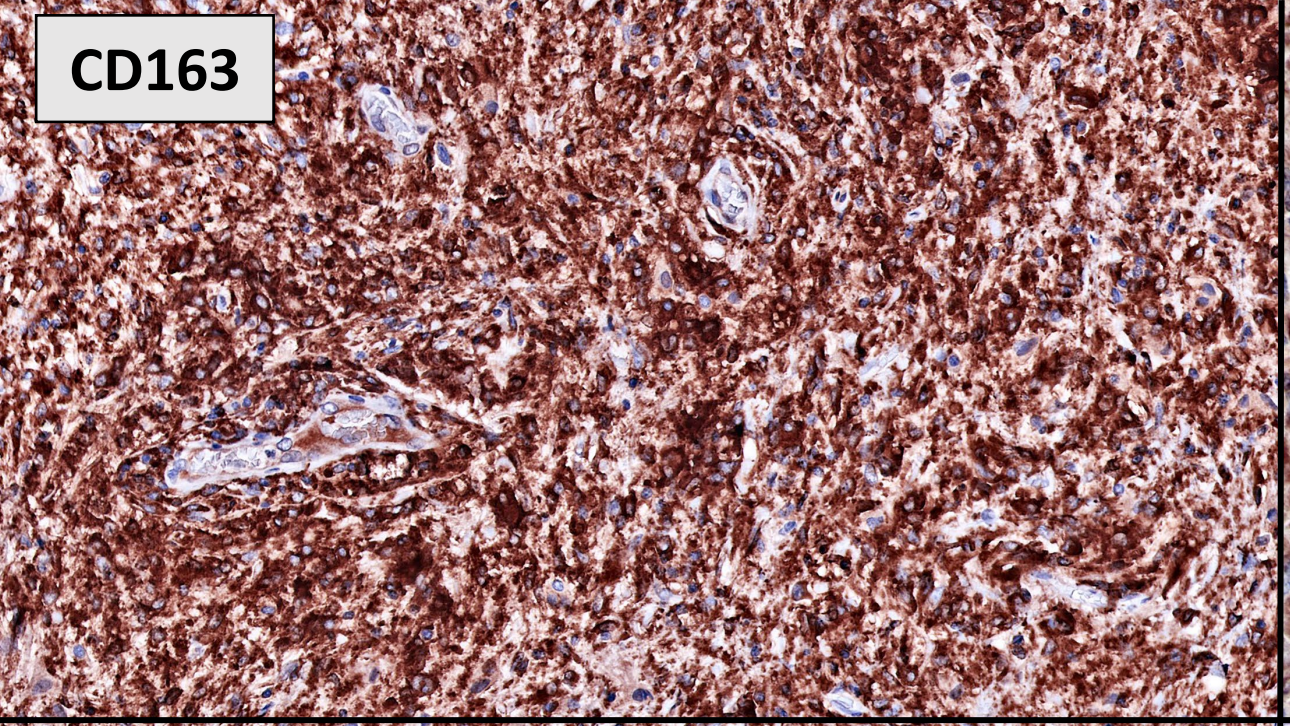
Differential?



Differential diagnosis

- Hematopoietic neoplasm (esp. Histiocytic):
  - Erdheim-Chester Disease
  - Langerhans cell histiocytosis
  - Rosai-Dorfman Disease
  - Histiocytic sarcoma
  - ALK-positive histiocytosis
  - Lymphomatoid granulomatosis
- Glial neoplasm:
  - Pilocytic astrocytoma
- Inflammatory:
  - Demyelinating disease
  - Neurosarcoidosis
  - IgG4-related disease
- Infection


CD68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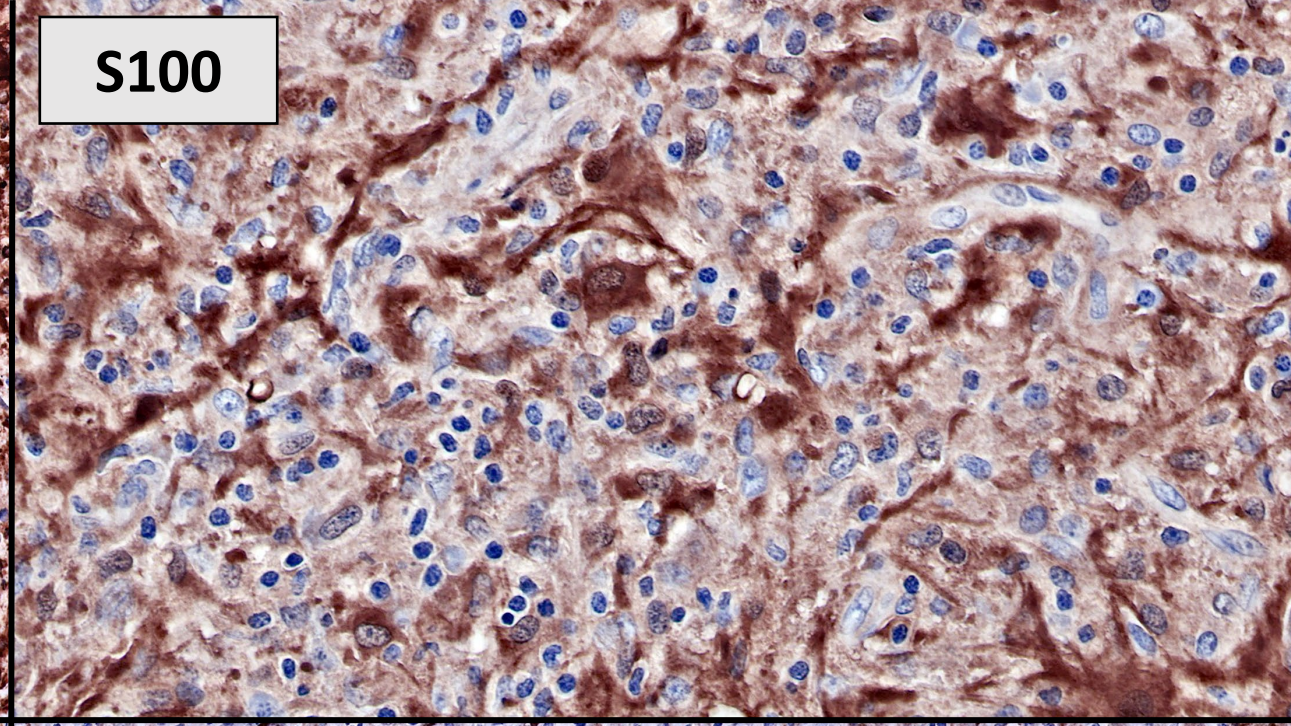
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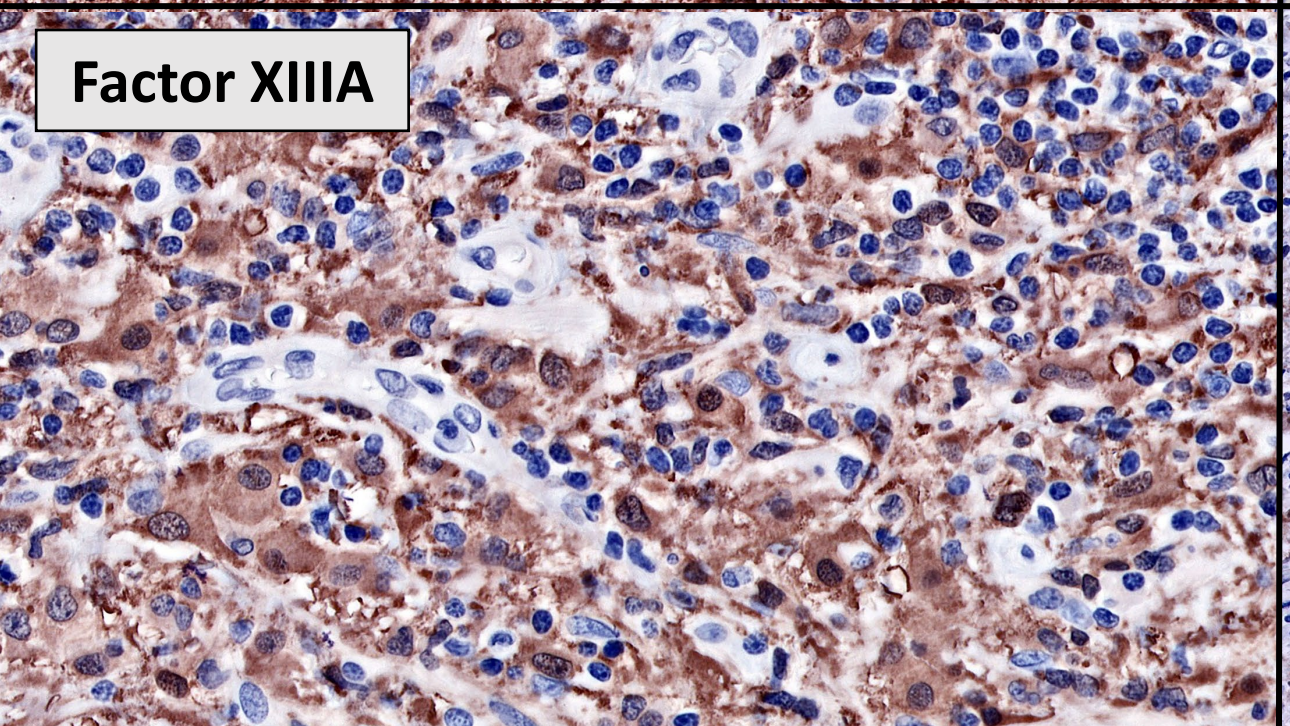
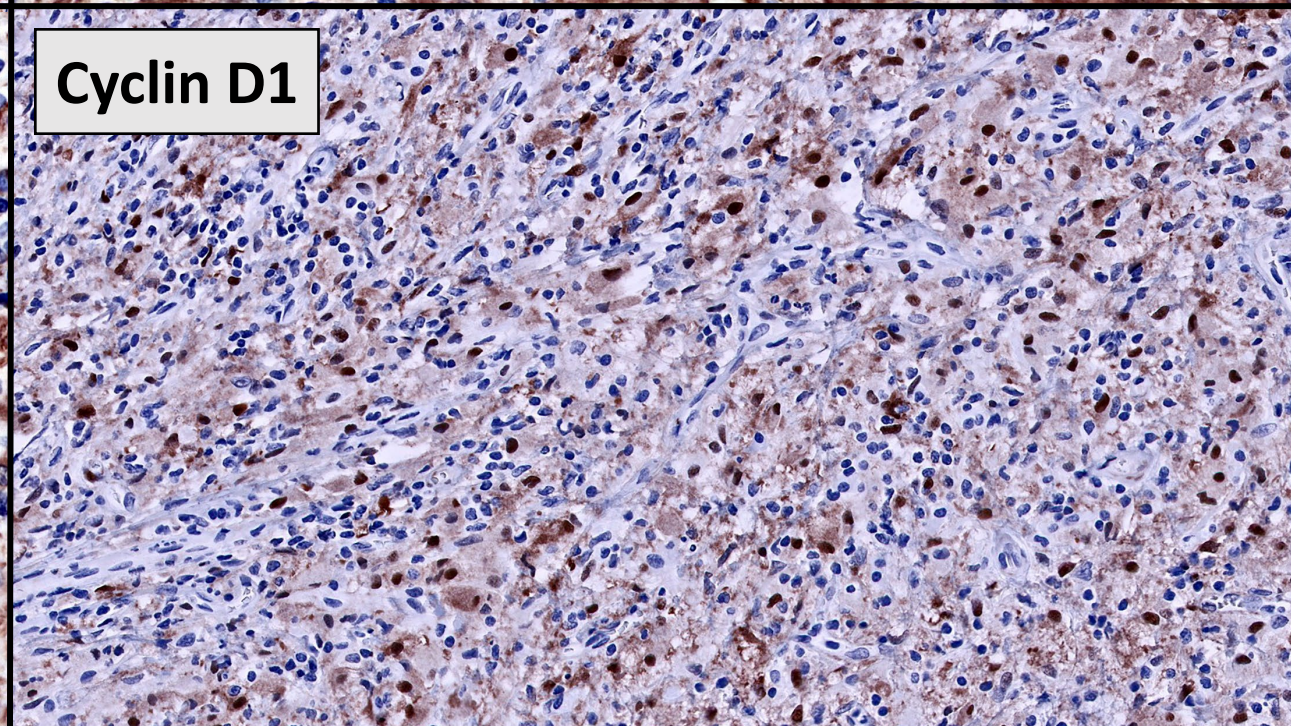

Factor XIIIA


Cyclin D1

Additional immunostains:

- CD1a: Negative.
- BRAF V600E: Negative.
- ALK: Negative.
- GFAP: Highlights piloid gliosis.
- CD3: Highlights scattered T-cells.
- CD20: Highlights scattered B-cells.
- LFB/PAS: Highlights loss of myelin within lesions.
- EBER ISH: Negative.
- GMS: Negative for fungal organisms.
- AFB: Negative for acid-fast bacilli.
- Ki-67: Labeling index ~5% (primarily highlights atypical histiocytes).

UCSF500 NGS analysis

PATHOGENIC AND LIKELY PATHOGENIC ALTERATIONS				
VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS	MUTANT ALLELE FREQUENCY
ARID1A p.Q1402*	NM_006015.4	Pathogenic	1756	14%
BRAF p.N486_P490del	NM_004333.4	Pathogenic	1116	18%

A pathogenic in-frame deletion was identified in BRAF, p.N486_P490del, occurring in exon 12. Also identified is a truncating nonsense mutation in the ARID1A tumor suppressor gene and member of the SWI/SNF chromatin-remodeling complex.

Chromosomal copy number analysis shows a balanced diploid genome without chromosomal gains, losses, or focal amplifications or deep deletions.

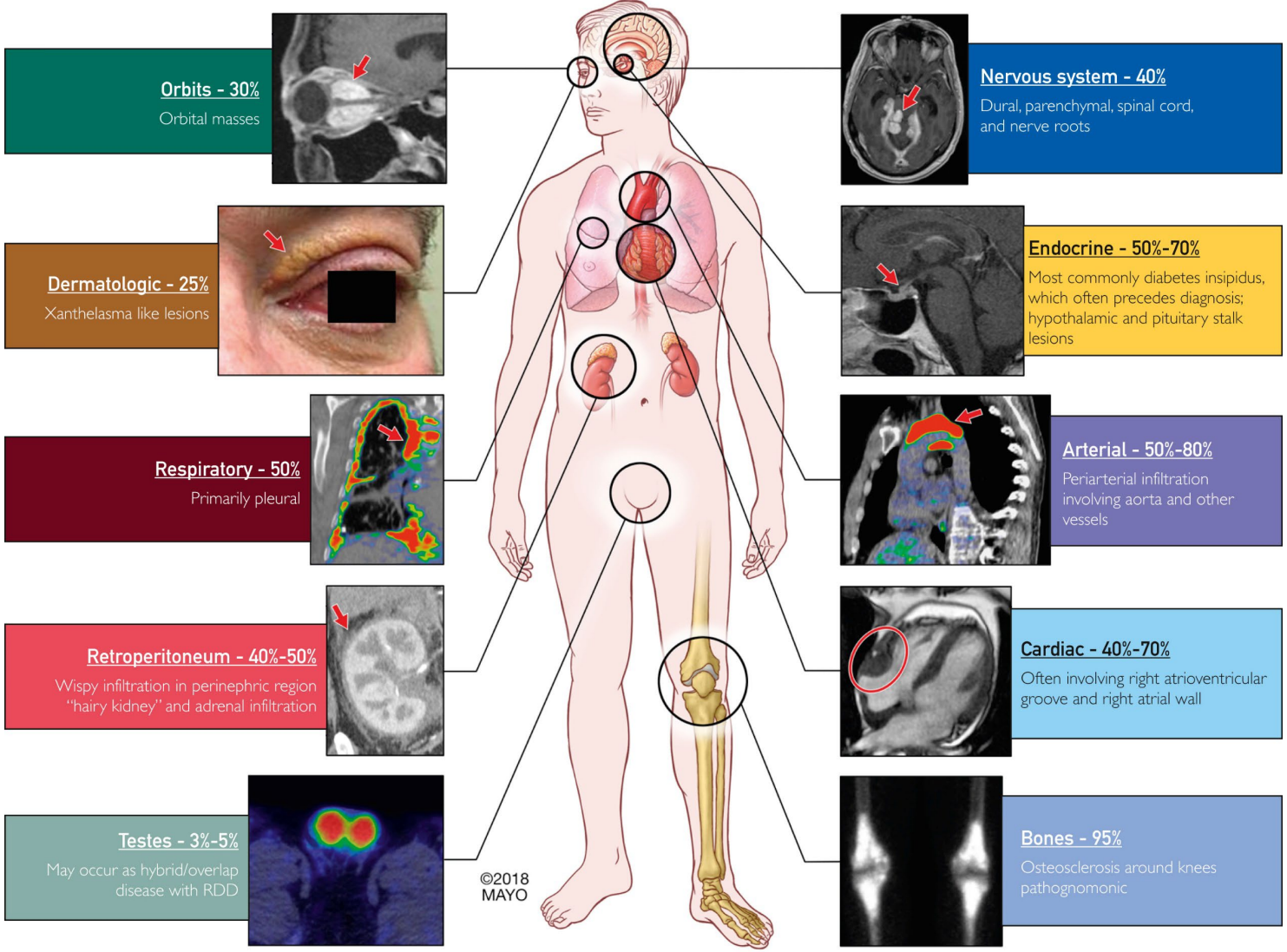
Final integrated diagnosis

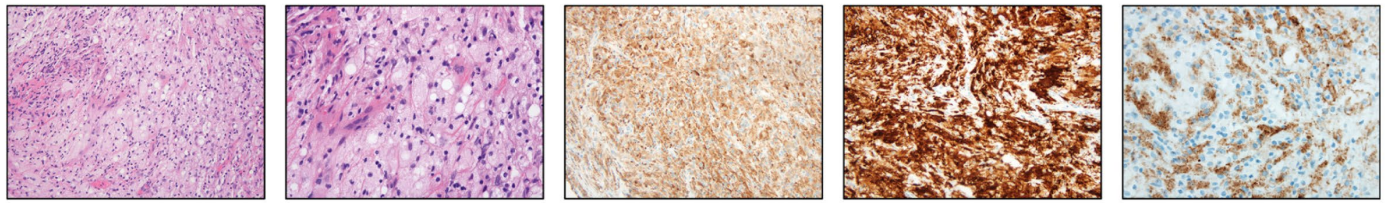
- Brain, cerebellar lesion, resection:
  - Histiocytic disorder; see comment.
- COMMENT:
  - Based on the histopathology, **Erdheim-Chester disease** is favored.
  - However, this diagnosis requires clinical correlation and nearly all histiocytic disorders have MAP kinase alterations.
  - Therefore, a more definitive diagnosis cannot be rendered based on the available data alone.

Follow-up

- ID work-up negative
- Serial MRIs showed progression of innumerable avidly enhancing supra- and infratentorial lesions with mass effect and tonsillar herniation
- MRI of the heart showed a myocardial signal abnormality at the mid-anteroseptal wall
- Chest CT showed interstitial lung opacities and bilateral cystic disease.
- Rx: chemotherapy and dexamethasone with improvement in existing lesions and no new lesions on follow-up.
- Discharged to outpatient rehab facility.

Erdheim-Chester Disease





Goyal G, et al; The Mayo Clinic Histiocytosis Working Group Consensus Statement for the Diagnosis and Evaluation of Adult Patients With Histiocytic Neoplasms: Erdheim-Chester Disease, Langerhans Cell Histiocytosis, and Rosai-Dorfman Disease. Mayo Clin Proc. PMID: 31472931.

Histiocytic disorders - Molecular

- The discovery of recurrent *BRAF*^{V600E} mutations or other activating MAPK pathway mutations led to designation of ECD, LCH, and RDD as histiocytic neoplasms.
  - BRAF p.V600E or other MAPK pathway mutations are present in majority of histiocytoses
    - BRAF in-frame deletion in this case is recurrent in other cancers and is a MAPK pathway activating event
    - Similar indels in BRAF exon 12 have been described in LCH
- Discovery of such alterations has therapeutic implications and led to the FDA approval of a drug (vemurafenib) for the treatment of *BRAF* V600–mutant ECD.
- ARID1A mutations have been reported in histiocytic sarcoma and aggressive LCH.

Table 17.1

Histiocytic Disorders

Disorder	Clinical Features	Localization	Histology	Special Studies [a]
Langerhans cell histiocytosis	Child (often <10 years old); DI	Skull tumor with secondary CNS spread Hypothalamus	Nuclear grooves or folds Eosinophil-rich infiltrate	$CD1a^+$, $S\text{-}100^+$; *BRAF* $V600E^+$ in subset; Birbeck granules on electron microscopy
Rosai-Dorfman disease	Mimics meningioma Systemic or CNS alone	Dural-based	Lobulated Emperipolesis Plasma cell–rich infiltrate	$S\text{-}100^+$, $CD1a^-$; mutations of *KRAS* or *MAP2K1* in subset
Juvenile xanthogranuloma	Infant/young child May have cutaneous or systemic disease	Meningeal, ventricular, parenchymal	Touton giant cells Spindled to foamy cells	Factor $XIIIa^+$, $S\text{-}100^\pm$, $CD1a^-$
Erdheim-Chester disease	Adult; bone, skin, lung disease DI; exophthalmos	Hypothalamus, pituitary, orbit, meninges, or CNS	Touton giant cells Spindled to foamy cells	Factor $XIIIa^+$, $S\text{-}100^\pm$, $CD1a^-$, *BRAF* $V600E^+$ in subset
Histiocytic sarcoma	Child or adult Systemic or CNS alone	Meningeal or parenchymal	Anaplastic features	$S\text{-}100^-$, $CD1a^-$

CNS, Central nervous system; *DI*, diabetes insipidus.

Perry A, Brat D, Practical Surgical Neuropathology: A Diagnostic Approach. 2nd ed.

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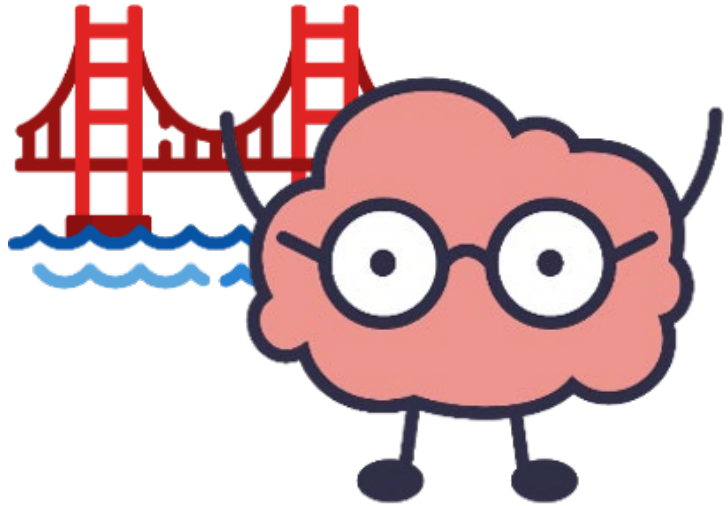

References

1. Goyal G, et al. Mayo Clinic Histiocytosis Working Group. The Mayo Clinic Histiocytosis Working Group Consensus Statement for the Diagnosis and Evaluation of Adult Patients With Histiocytic Neoplasms: Erdheim-Chester Disease, Langerhans Cell Histiocytosis, and Rosai-Dorfman Disease. Mayo Clin Proc. 2019 Oct;94(10):2054-2071. doi: 10.1016/j.mayocp.2019.02.023. Epub 2019 Aug 28. PMID: 31472931.
2. Goyal G, et al. Erdheim-Chester disease: consensus recommendations for evaluation, diagnosis, and treatment in the molecular era. Blood. 2020 May 28;135(22):1929-1945. doi: 10.1182/blood.2019003507. PMID: 32187362.
3. Razanamahery J, et al. Erdheim-Chester disease with concomitant Rosai-Dorfman like lesions: a distinct entity mainly driven by MAP2K1. Haematologica. 2020 Jan;105(1):e5-e8. doi: 10.3324/haematol.2019.216937. Epub 2019 May 23. PMID: 31123032; PMCID: PMC6939531.
4. Chen SH, et al. Oncogenic BRAF Deletions That Function as Homodimers and Are Sensitive to Inhibition by RAF Dimer Inhibitor LY3009120. Cancer Discov. 2016 Mar;6(3):300-15. doi: 10.1158/2159-8290.CD-15-0896. Epub 2016 Jan 5. PubMed PMID: 26732095
5. Chakraborty R, et al. Alternative genetic mechanisms of BRAF activation in Langerhans cell histiocytosis. Blood. 2016 Nov 24;128(21):2533-2537. doi: 10.1182/blood-2016-08-733790. Epub 2016 Oct 11. PMID: 27729324; PMCID: PMC5123197.