Case 2024-6

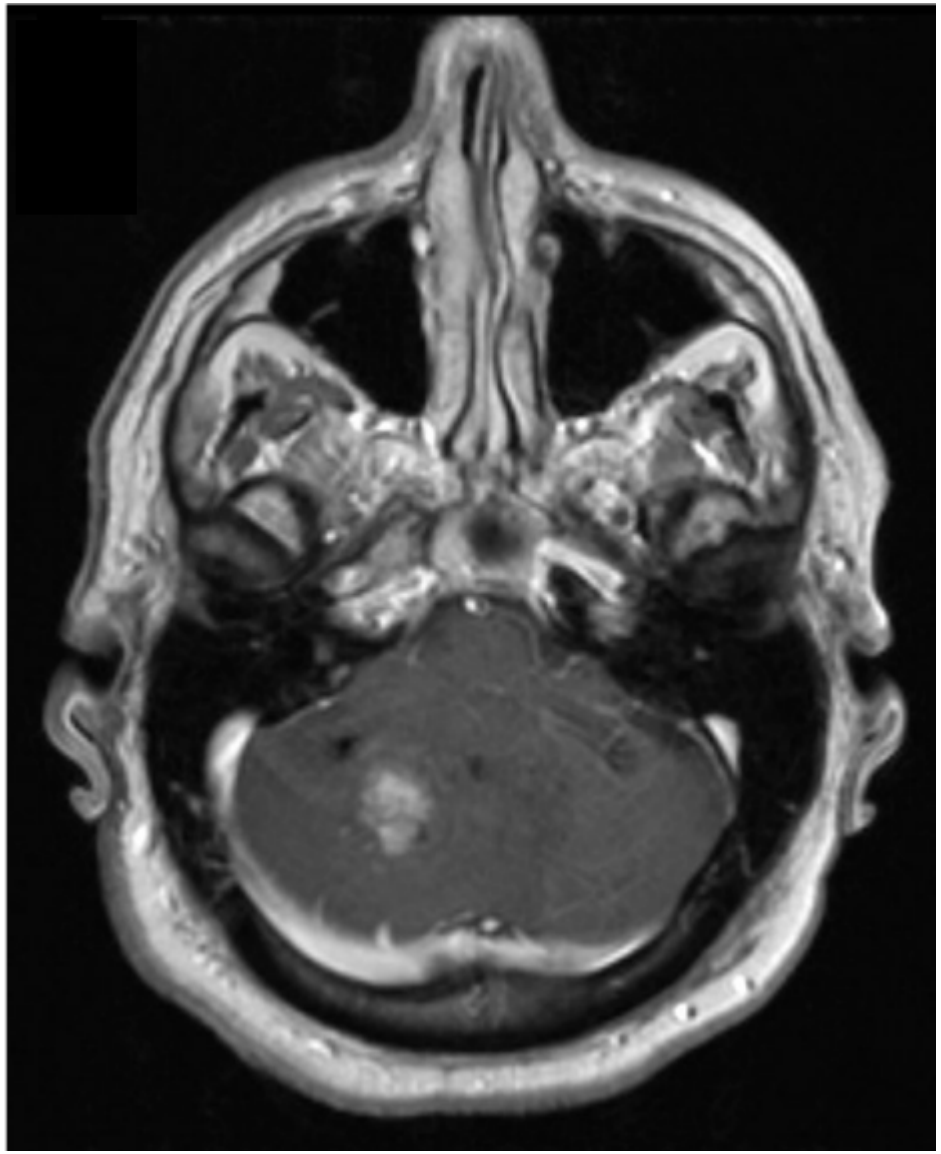
Diagnostic Slide Session

AANP 2024 Annual Meeting

Nicolas Kostelecky, MD and Craig Horbinski, MD PhD

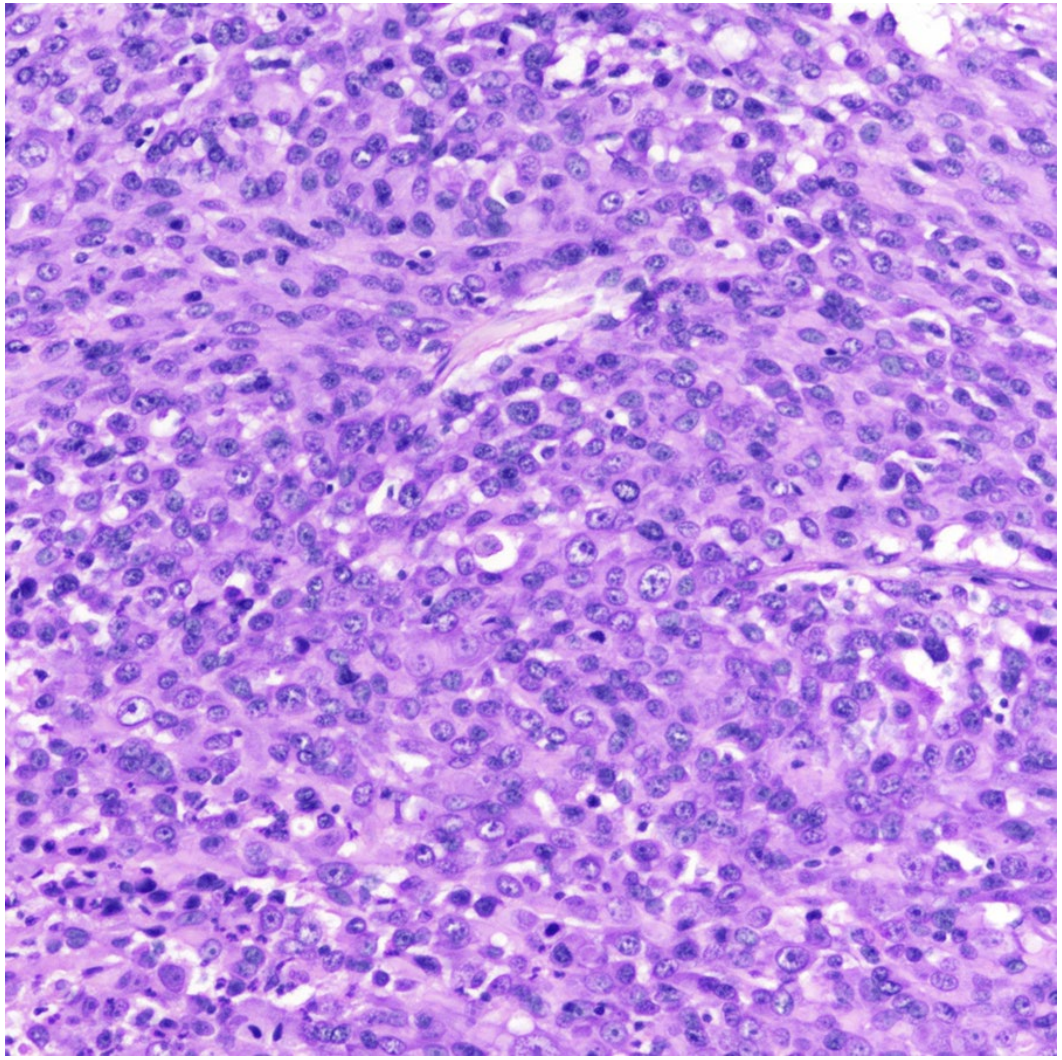
Clinical summary

- 68-year-old male patient
- Intractable vomiting and headache
- Cutaneous melanoma
  - Initially treated with immunotherapy (pembrolizumab)
- Metastatic melanoma to lymph nodes, lungs, and liver
  - Encorafenib (MAPK inhibitor) and binimetinib (MEK inhibitor)
- MRI→ heterogeneously enhancing 2.8 cm mass of the right cerebellum with edema and mass effect

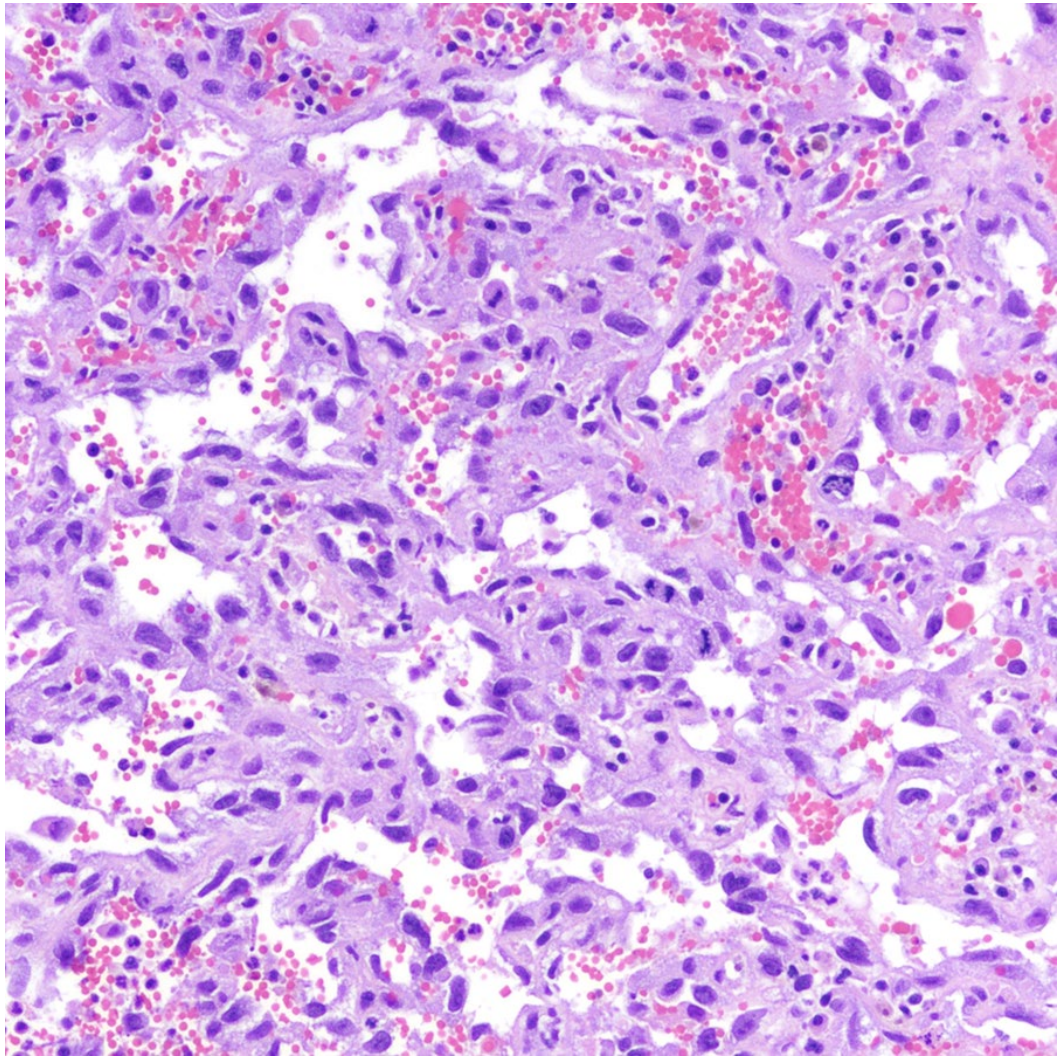


T1-weighted Magnetic Resonance Imaging with contrast of the patient’s right cerebellar tumor

Cutaneous Primary

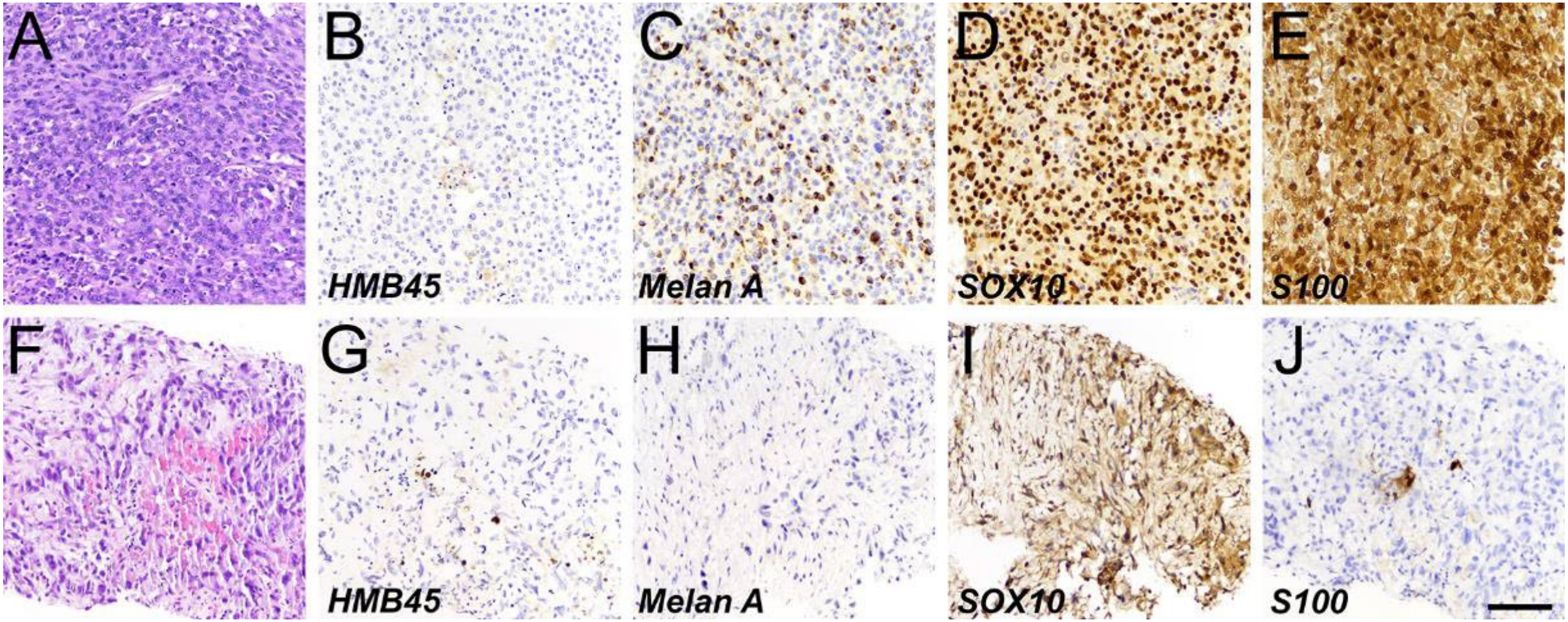


Cerebellar Lesion



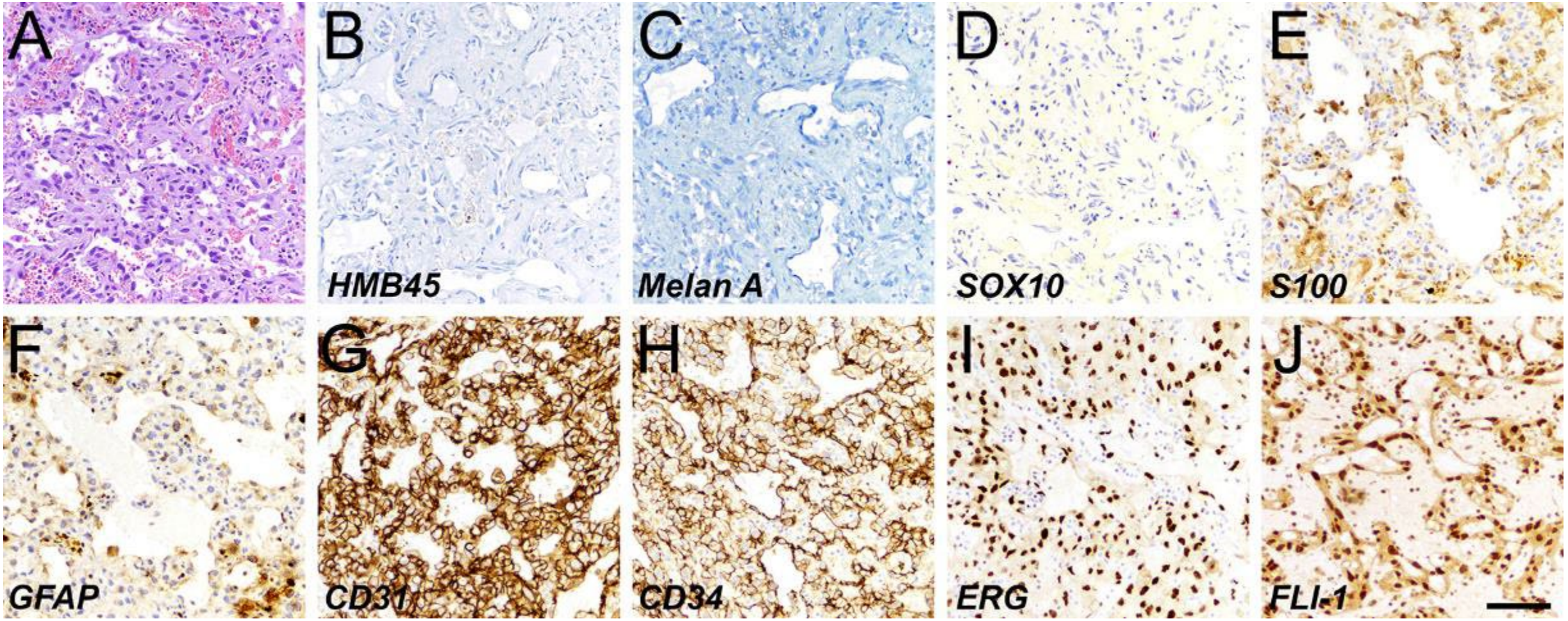
Discussion

Immunohistochemistry



(A-E) Primary cutaneous malignant melanoma
(F-J) Lymph node metastasis. Scale bar = 50 microns.

Immunohistochemistry



Cerebellar mass. Scale bar = 50 microns.

	NGS	Methylation profiling
Primary cutaneous site	**Pathogenic variants** - BRAF (V600E) - PTPRT (p.(R936*)) **Variants of Unknown Significance** - CARD11, EPHA7, FGF23, MAF, PIK3C2B, PREX2, PRSS1, SPTA1, TET1	Melanoma (score 1.0)
Lymph node metastasis	**Pathogenic variants** - BRAF (V600E) - PTPRT (p.(R936*)) **Variants of Unknown Significance** - CARD11, EPHA7, FGF23, MAF, PREX2, PRSS1, SPTA1, TET1, KEL	Not available (limited tissue)
Cerebellar mass	**Pathogenic variants** - BRAF (V600E) - PTPRT (p.(R936*)) **Variants of Unknown Significance** - CARD11, EPHA7, FGF23, MAF, PIK3C2B, PREX2, PRSS1, SPTA1, TET1	Angiosarcoma (score 0.87)

Diagnosis

- Transdifferentiation of melanoma into metastatic angiosarcoma

Prior literature

- **Only one other case like this in the literature**
- Kilsdonk et al., 2020
  - Cutaneous melanoma with lymph node metastases
  - Metastases had an angiosarcomatous component
  - Negative for MART-1, S100-protein, and Sox 10
  - Positive for ERG and CD31
- Conventional melanoma and the angiosarcomatous component had the same *NRAS* (p.(Gln61Arg) mutation
- Complete response to nivolumab immunotherapy

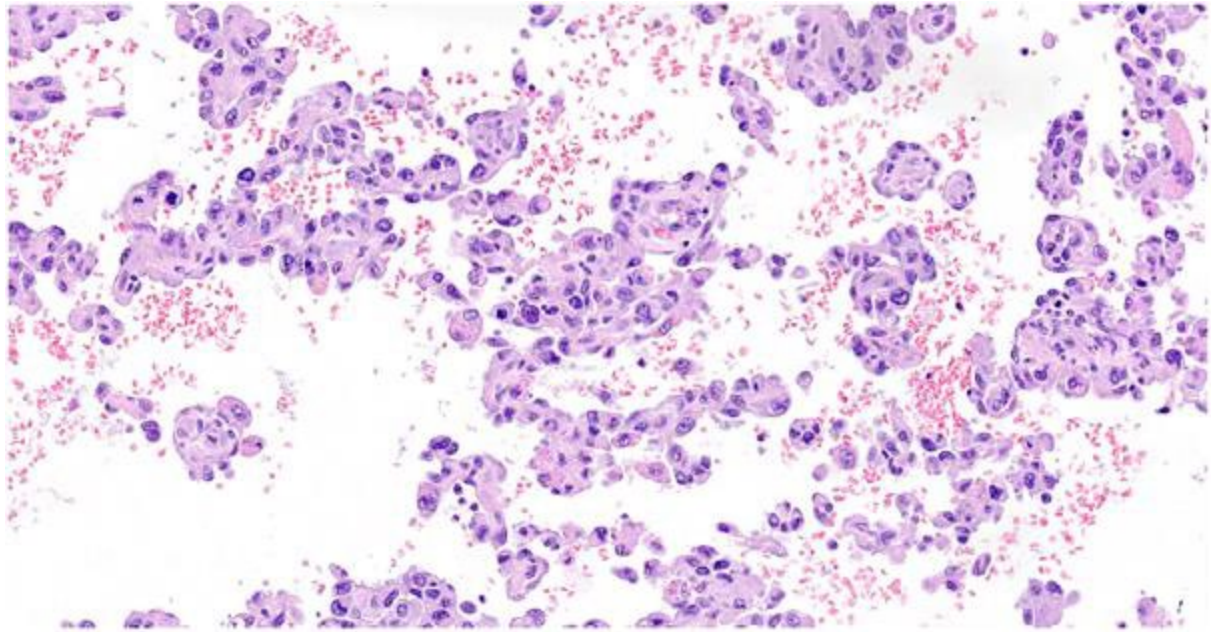


Figure 4: Kilsdonk et al. *J Cutan Pathol*.

Differential diagnosis: angiomatoid melanoma

- Still positive for melanoma markers
- Negative for vascular markers

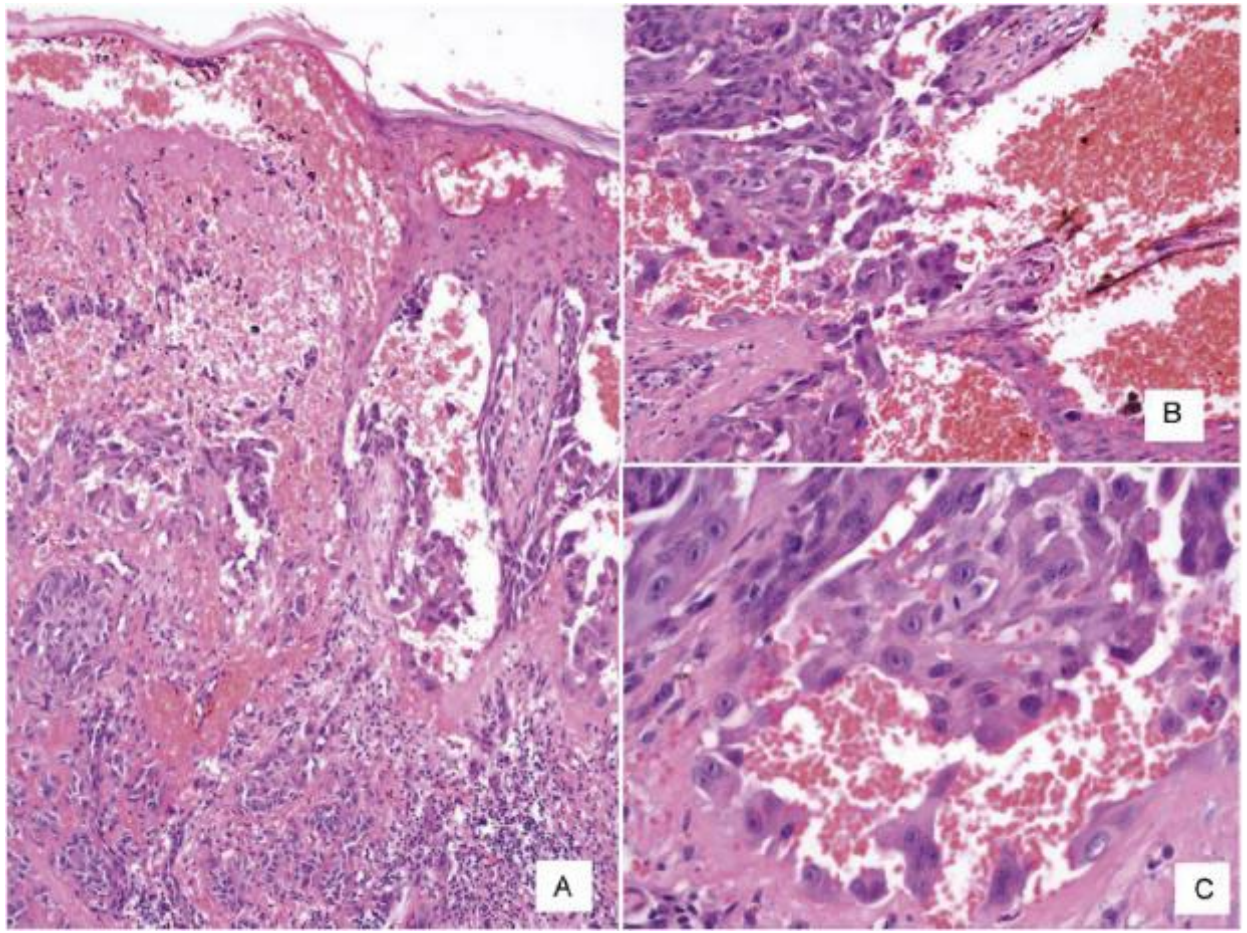
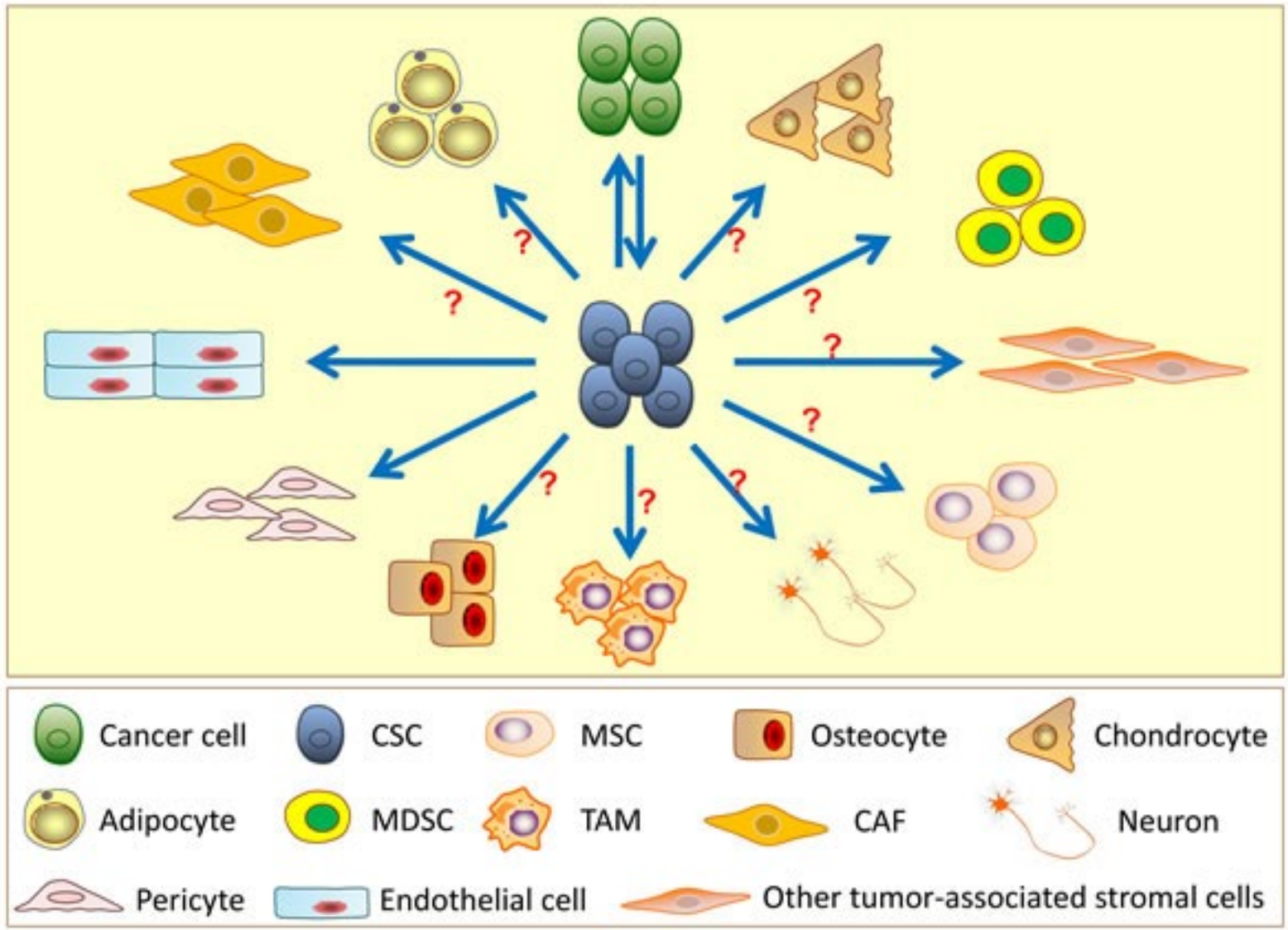


Figure 1: Ramos-Rodríguez et al. *Actas Dermo-Sifiliográficas*

Why does transdifferentiation happen?

- New microenvironment triggers an epigenetic shift?
  - Precedence in other cancers, e.g., stromal cells can change DNA methylation profile of pancreatic adenocarcinoma cells (PMID: 38734064)
- Immunotherapy or MAPK/ERK inhibitors causing transdifferentiation?
  - Leukemia→ immunotherapy→ histiocytic sarcoma (PMID: 37259821)
  - Lineage-specific inhibitors triggering neuroendocrine shift (PMID: 25758528, 30918106)



Oncotarget. 2015 Nov 24;6(37):39550-63.

Summary & outcome

- Diagnosing transdifferentiation requires:
  - Detailed medical history
  - Examination of prior specimens
  - Advanced molecular testing
- No cerebellar recurrences in the past 7 months

References

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