AANP Diagnostic Slide Session 2020

Case #9

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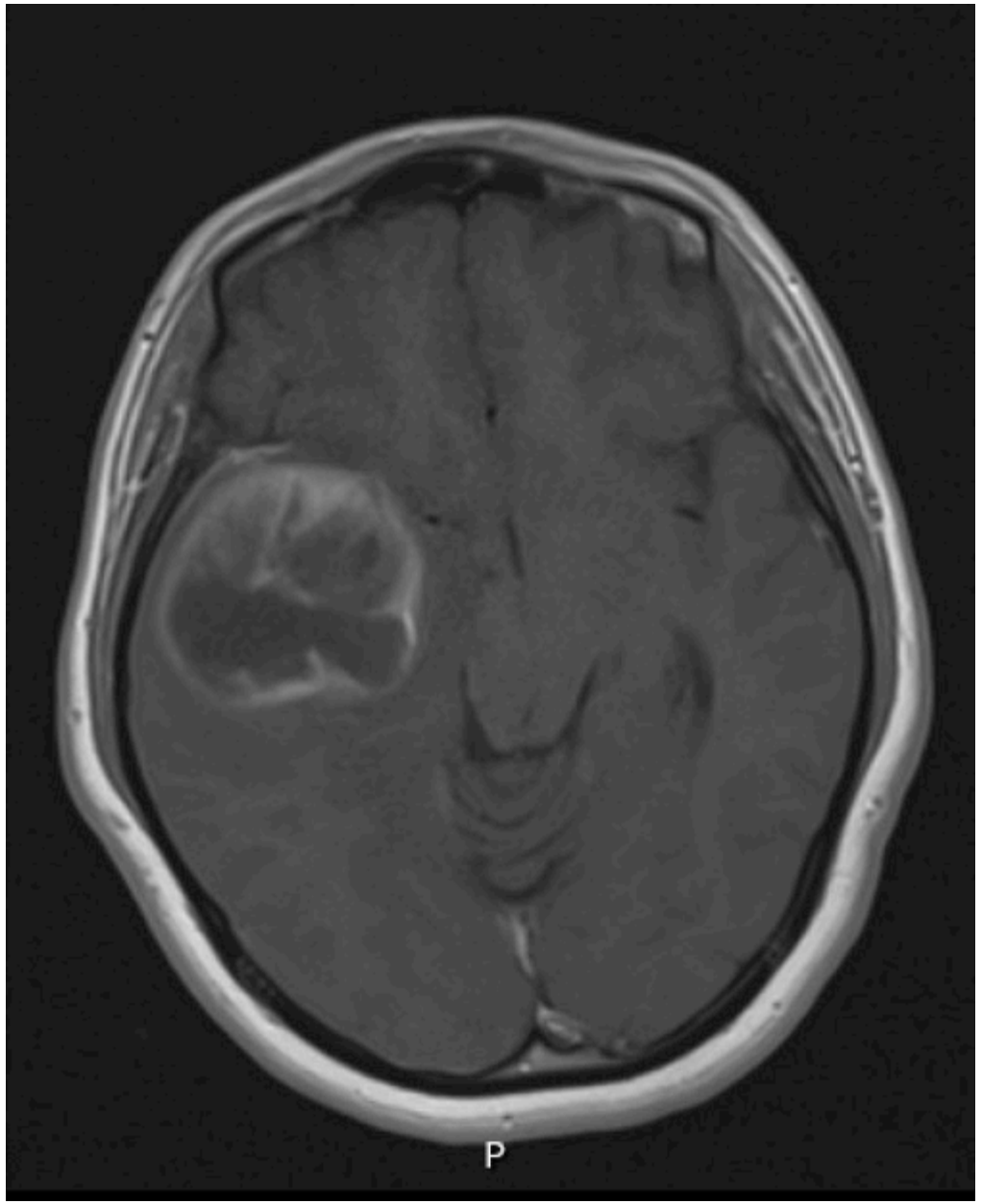
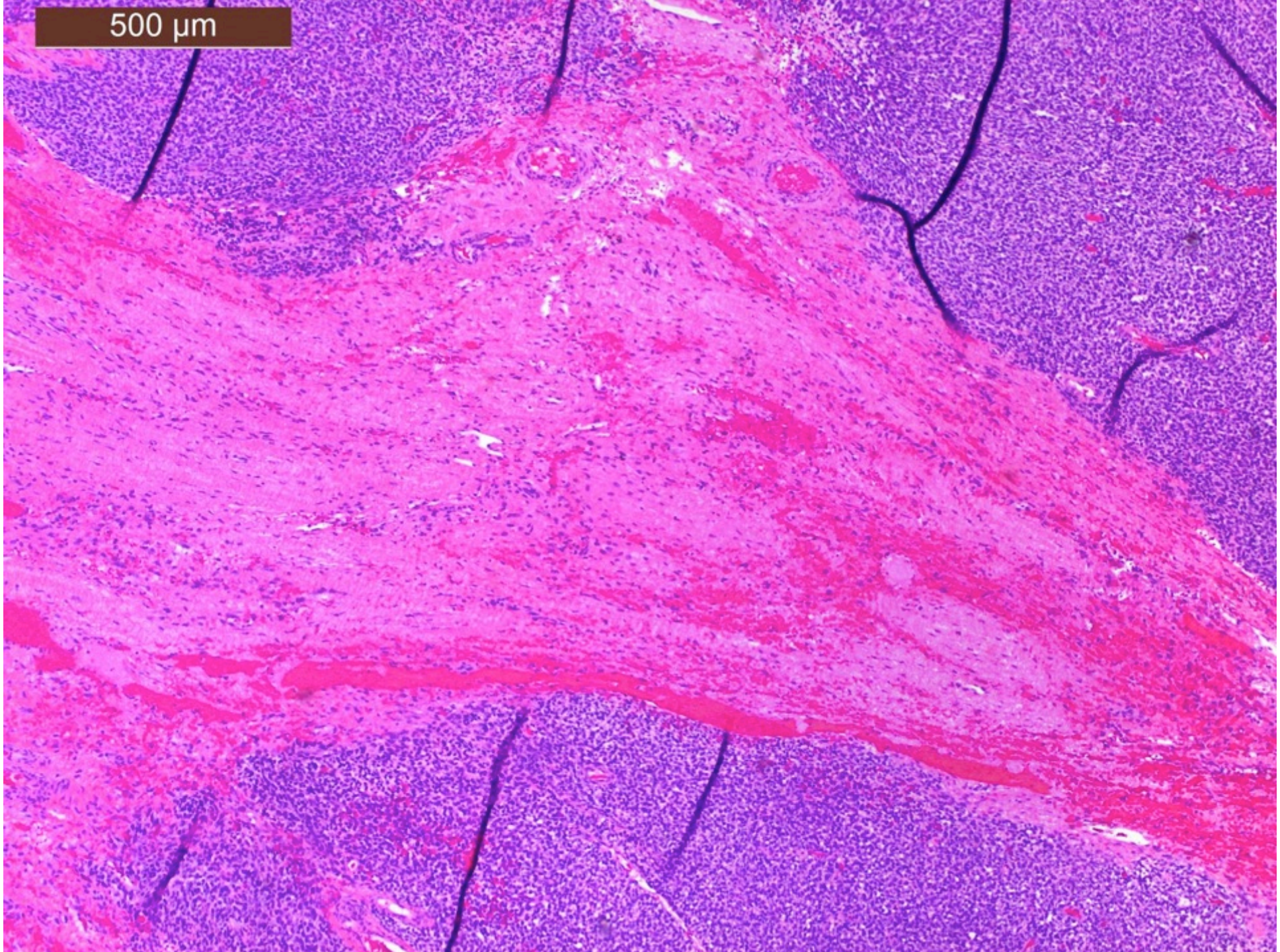
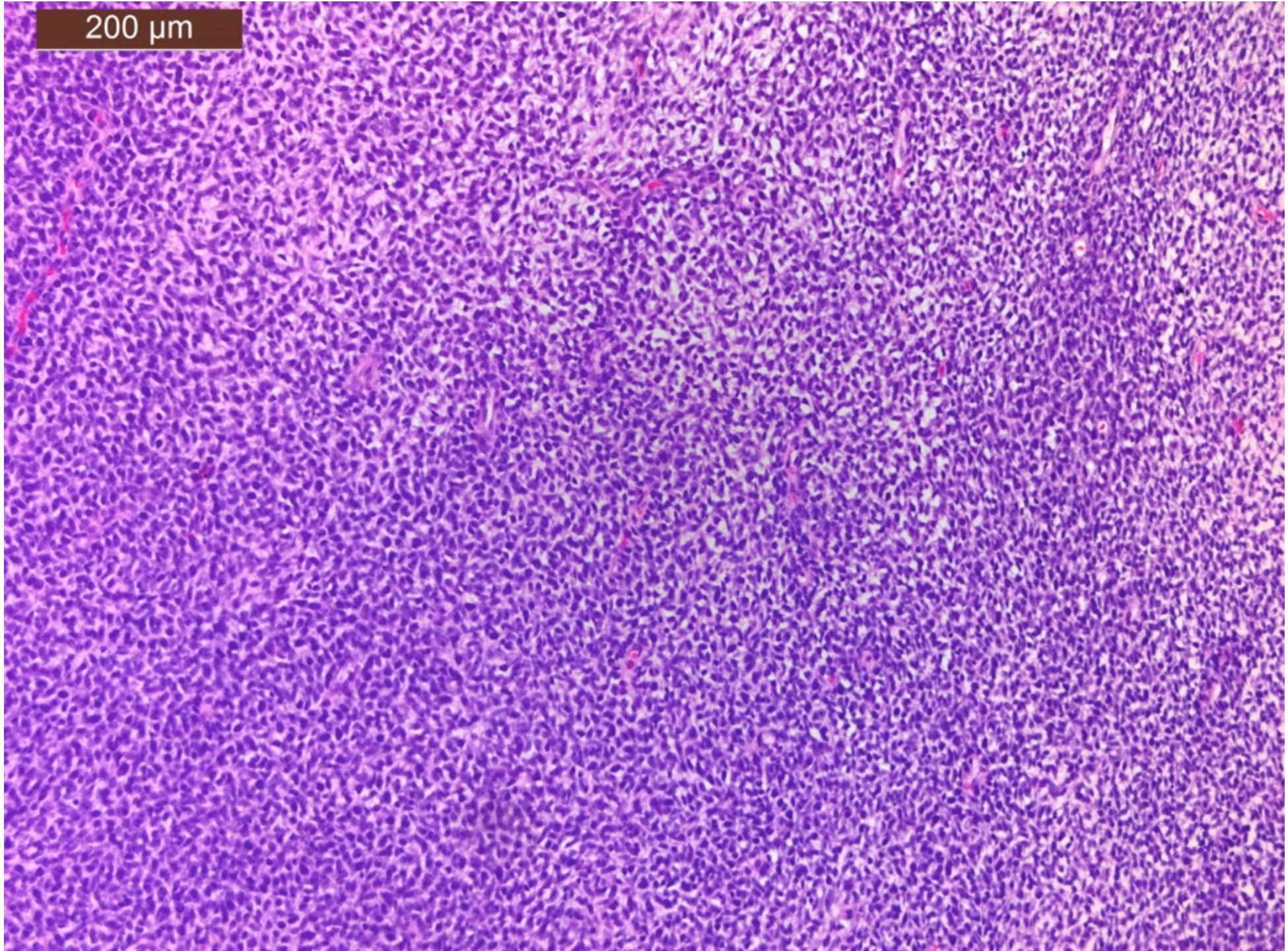
The authors have no disclosures

Clinical History

- 19 year-old female
- No significant past medical history
- Presented to an outside hospital (OSH) with 3 weeks of headaches that did not respond to medication
- Imaging showed a 6 cm right-sided temporal mass involving brain and meninges, of unclear origin




500 µm


200 µm

Differential Diagnosis?

Diagnostic Workup?

Differential Diagnosis

- High-grade glioma
- Medulloblastoma
- Anaplastic meningioma
- Solitary fibrous tumor
- Melanoma
- Lymphoma
- Sarcoma
- Metastatic poorly differentiated carcinoma
- Metastatic mesothelioma

IHC and FISH Results

Positive IHC	Negative IHC	Negative FISH
P53 (weak)	GFAP, OLIG-2, IDH1-R132H	EWSR1 (break-apart probe)
SSTR2	Synaptophysin	SYT
Pax-5	EMA	FUS
SATB2 (weak)	STAT-6	NUT
D2-40	S100, SOX-10, HMB-45, Melan-A, Tyrosinase	CIC
Ki-67 70%	CD68, CD3, CD5, CD20, CD79a, CD138, TdT, CD21, CD23, CD35, CD30, CD34, EBER(ISH)	BCOR
	Desmin, SMA, Nkx2.2, BCOR, TLE	
	AE1/3, ER, Pax-8	
	ALK	
	MUC-4	

Updated Differential Diagnosis?

Additional studies?

Differential Diagnosis

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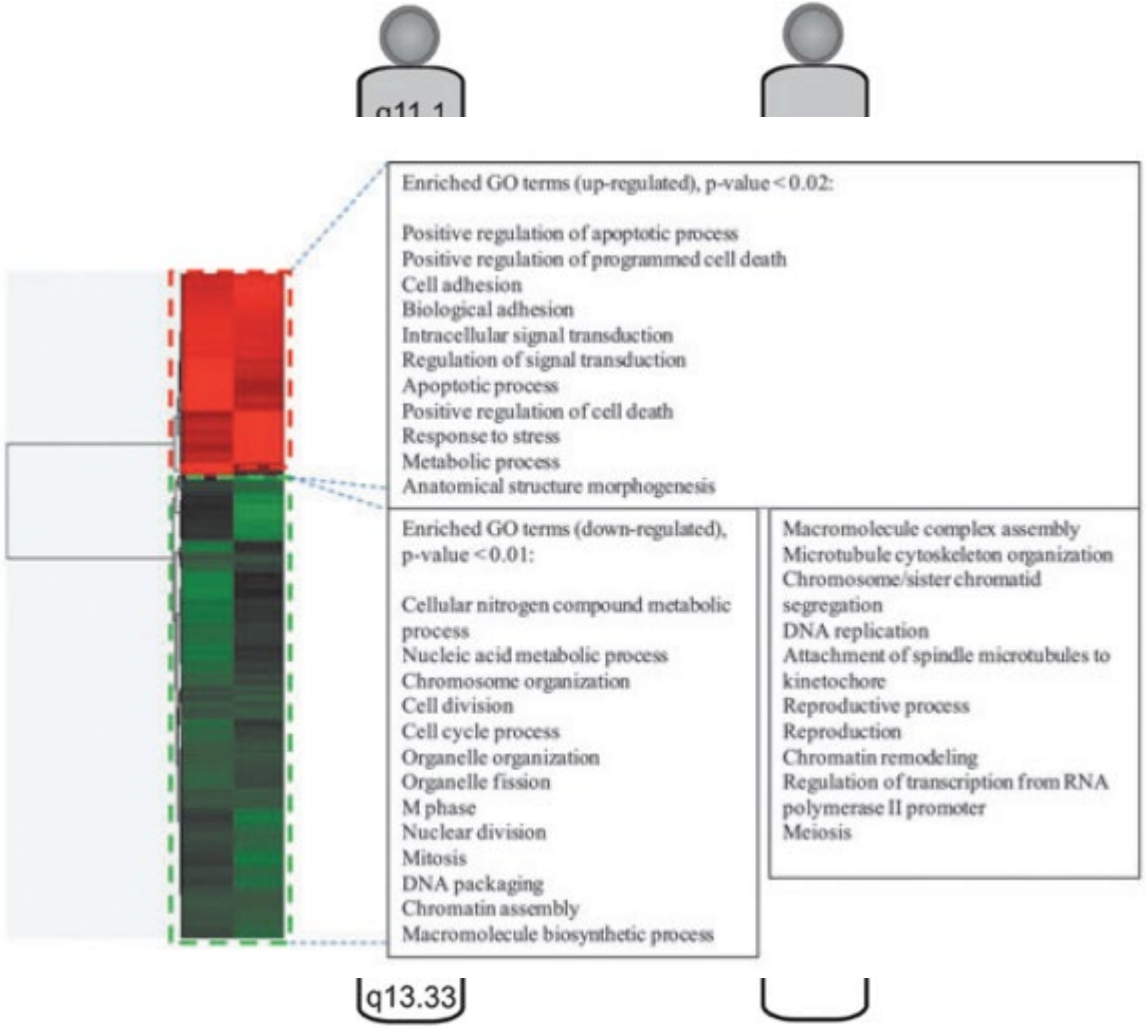
Next-generation Sequencing Results

- EWSR1-PATZ1 fusion
  - **Had not been detected by the FISH break-apart studies**

→Final diagnosis: “Malignant spindle and round cell neoplasm with EWSR1-PATZ fusion”

Discussion: EWSR1-PATZ1 fusion

- Intra-chromosomal rearrangement
  - In-frame fusion between activating N-terminal domain of EWSR1 and zinc finger domain of PATZ1
- PATZ1 is in close proximity (~2 Mb) to EWSR1 on chromosome 22
  - Submicroscopic intra-chromosomal paracentric inversion -> **may not be detected using FISH break-apart probes**
- Predicted to remove N-terminal repressor domain of transcription factor PATZ1 -> aberrant overexpression
- Implicated in maintenance of pluripotency in embryonic stem cells



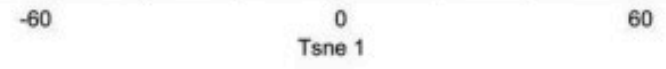
Ow et al., 2014

Bridge et al., 2019

Discussion: EWSR1-PATZ1 fusion

- Rare: few published cases
  - Predominantly sarcomas
  - Also pediatric/young adult primary CNS tumors
- Clinical features: no gender preference, wide age distribution, tendency to arise in chest wall
- Variable morphology
  - But share common features of fibrous stroma and component of spindle-shaped cells
- Variable immunophenotype
- But cluster together on differential expression analyses
  - Separate from other EWSR1-fused tumors: transcriptionally different entity

Case	Provisional diagnosis	Age/Sex	Biopsy site
Soft tissue			
1	Undifferentiated round cell sarcoma	35/F	Chest wall
2	Soft tissue myoepithelial neoplasm	53/M	Upper arm/Axilla
3	Undifferentiated low grade sarcoma	81/F	Post. cervical neck
4	Undifferentiated round cell sarcoma	11/F	Chest wall
5	Undifferentiated sarcoma, NOS	60/M	Chest wall
6	Alveolar rhabdomyosarcoma	19/F	Head and neck
7	Undifferentiated sarcoma, NOS	59/M	Lung
Brain			
8	Undifferentiated sarcoma, NOS	26/F	Brain
9	Primitive neuroectodermal tumor	21/M	Brain
10	Pleomorphic xanthoastrocytoma	13/M	Brain
11	Glioma	22/F	Brain



Bridge et al., 2019

Watson et al., 2018

Conclusions

- EWSR1-PATZ1 fusion tumors represent a biologically distinct entity from other EWSR1-fused tumors
- Consider EWSR1-PATZ1 fusion when:
  - Fibrous stroma and component of spindle-shaped cells
  - Unusual immunophenotype (particularly expressing neural/melanocytic and myogenic markers)
- May require next-generation sequencing or RT-PCR with specific primer sets
  - **Conventional FISH assay with EWSR1 break-apart probes may not detect fusion**

Update on Patient

- Treated as sarcoma rather than primary brain tumor
  - Although unclear site of origin
- Resection bed treated with adjuvant RT followed by cyberknife to recurrent enhancing nodules
- Now 2 months from completion of RT: current MRI shows no new or progressive neoplasm, and decreasing nodular enhancement
- Performance Status (ECOG): Grade 0 - Fully active, able to carry on all pre-disease performance without restriction
- Performance Status (Karnofsky): 100% - Normal. No complaints. No evidence of disease.
- Episodes of headaches and some difficulty with word finding but otherwise no complaints

References

- Bridge, J.A., et al. Clinical, pathological, and genomic features of EWSR1-PATZ1 fusion sarcoma. Modern Pathology, 2019, 32: 1593.
- Chougule, A., et al. Spindle and round cell sarcoma with EWSR1-PATZ1 gene fusion: A sarcoma with polyphenotypic differentiation. Am J Surg Pathol, 2019, 43: 220.
- Watson, S., et al. Transcriptomic definition of molecular subgroups of small round cell sarcomas. Journal of Pathology, 2018, 245: 29.

THANK YOU!