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ORIGINAL ARTICLE

Sarcomatous Meningioma: Diagnostic Pitfalls and the Utility of Molecular Testing

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Abstract

Anaplastic meningiomas can have a sarcomatous appearance on histology but true sarcomatous (metaplastic) differentiation is rare. These tumors follow an aggressive clinical course with recurrence and poor clinical outcomes. Due to significant overlap in morphology and immunohistochemical profiles, distinguishing between sarcomatous transformation of a meningioma and a true sarcoma can be challenging. Here, we outline potential diagnostic pitfalls and the utility of ancillary molecular testing in 3 patients diagnosed with sarcomatous meningiomas. We report loss of typical meningothelial markers in sarcomatous meningiomas. Ancillary molecular testing can support the diagnosis of sarcomatous meningioma when a molecular signature consistent with meningioma is seen, such as inactivation of the *NF2* gene. Recognition of this rare transformation in meningioma can prevent a misdiagnosis of a primary sarcoma, whether sporadic or radiation-induced from prior treatment of a more classic meningioma.

Key Words: Anaplastic, Meningioma, Molecular, Neuropathology, Sarcomatous.

INTRODUCTION

Anaplastic meningiomas are rare, comprising <5% of all meningiomas. They are considered World Health Organization (WHO) grade III and follow an aggressive clinical course associated with frequent local recurrences, increased potential for metastasis, and poor overall patient survival. The histologic criteria for anaplastic meningioma include brisk mitotic activity (i.e. >20 mitotic figures per 10 high-power fields) or frank anaplasia, defined as sarcoma-like, carcinoma-like, or melanoma-like histology (1). Frank sarcomatous (heterologous) change was one of the first histologic definitions for anaplastic meningioma in the original grading schemes proposed by Cushing and Eisenhardt, although they generally lacked the diagnostic tools during that era to distinguish sarcoma-like histology from true non-meningothelial/sarcomatous transformation (2). While most anaplastic meningiomas lose the classic histologic features of lower-grade meningiomas, true sarcomatous metaplasia (e.g. myogenic, chondroid, osteogenic, adipocytic, or angiomatous differentiation) in meningiomas is rarely observed (3). More commonly, sarcomatous neoplasms arising at sites of previously resected and irradiated meningiomas are often best categorized as radiation-induced sarcomas and can present across the spectrum of mesenchymal phenotypes. De novo primary sarcomas or metastatic sarcomas are rare but also need to be considered in the differential. Additional testing is often warranted to rule out considerations of the potential spectrum of malignancies in these cases.

Due to significant overlap in morphology and immunohistochemical profile with true sarcomas, distinguishing between sarcomatous meningioma and true sarcomas can be challenging. Here, we present 3 sarcomatous meningiomas with myogenic differentiation, highlighting diagnostic dilemmas and useful ancillary tests.

Patient #1

A 26-year-old woman presented with an extra-axial frontobasal tumor that extended into the sphenoid sinus and compressed the optic nerve. She underwent resection with pathologic examination revealing a cellular neoplasm with multiple appearances. The majority of the tumor was composed of pleomorphic spindled cells growing in fascicular and storiform configurations within a densely collagenous back-

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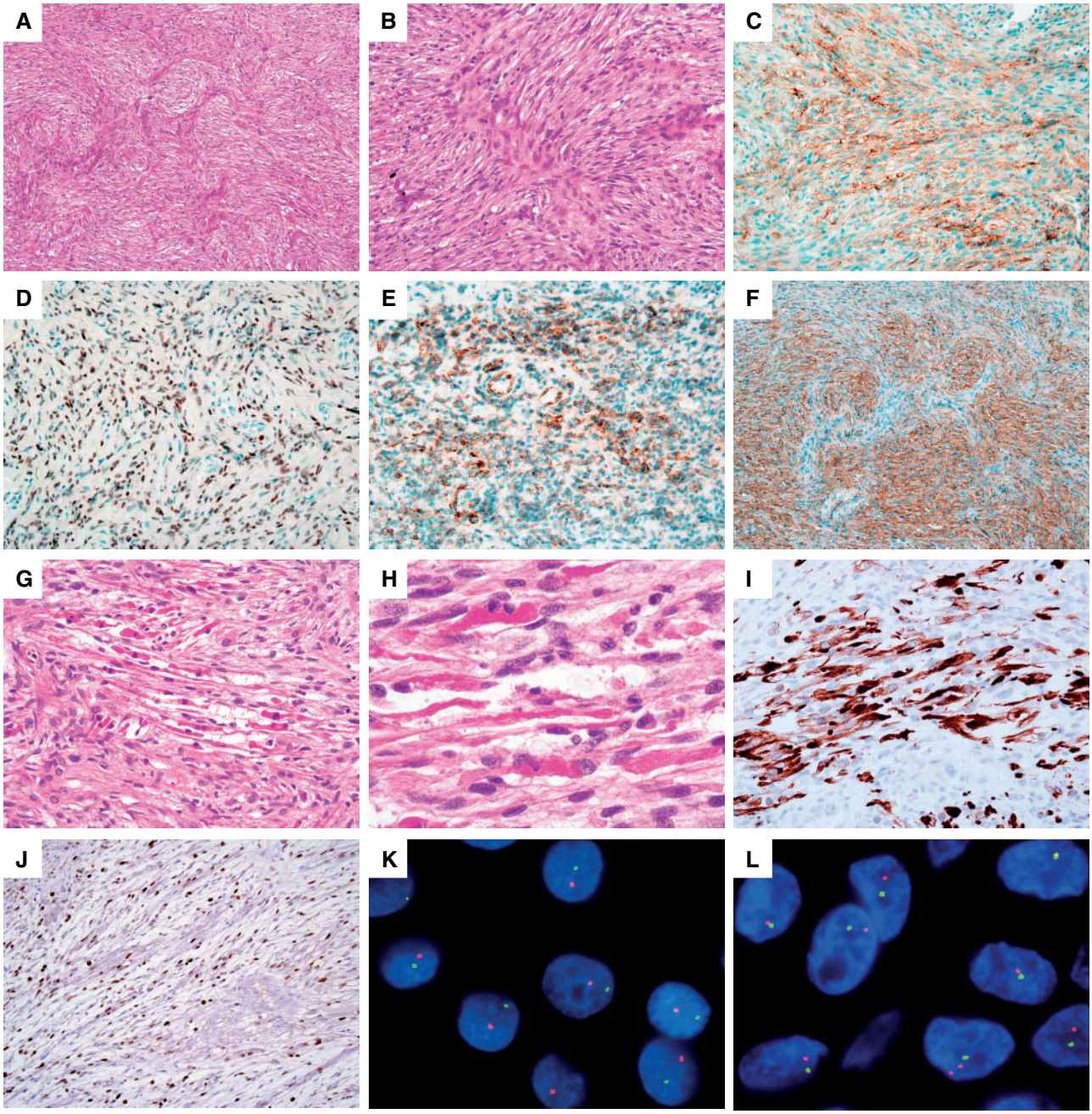


FIGURE 1. Patients #1 and #2. Low- **(A)** and high-magnification **(B)** microscopy from tumor #1 reveals pleomorphic spindled cells growing in fascicles, resembling fibrosarcoma. This tumor showed patchy positivity for EMA **(C)** and progesterone receptor **(D)**, as well as immunoreactivity against caldesmon **(E)** and SMA **(F)**. Low- **(G)** and high-magnification **(F)** microscopy from tumor #2 showed elongate cells with brightly eosinophilic cytoplasm resembling rhabdomyoblasts **(H)**. This tumor showed immunoreactivity against desmin **(I)** and myogenin **(J)**. FISH revealed losses of chromosome arms 1p and 14 q **(K**—green 1p32, red 14q32**)** as well as chromosome arm 22q **(L**—green BCR, red NF2**).**

ground (Fig. 1A, B), focally involving dura. In these sarcoma-like areas, the mitotic index reached up to 20 mitotic figures per 10 high-power fields. Patchy necrosis was also seen. Focally, the tumor showed more conventional features of a meningioma, including epithelioid cells with vague whorling architecture.

On immunohistochemical workup, the tumor was negative for somatostatin receptor 2A immunoreactivity (SSTR2A), showed patchy positivity for epithelial membrane antigen ([EMA], Fig. 1C) and progesterone receptor (Fig. 1D), and diffuse vimentin immunoreactivity. Additionally, both caldesmon (Fig. 1E) and smooth muscle actin ([SMA],

Fig. 1F) were positive in a large subset of tumor cells, supporting smooth muscle differentiation. Myogenin and desmin were negative in this case. Congruent with the mitotic index, the Ki-67 labeling index was elevated at 20%. The patient's clinical course was complicated by local recurrence 4 months after initial surgery. The histology of the recurrent neoplasm was similar to that of the original resection.

Patient #2

This patient was a 71-year-old woman who was found to have a dural-based right frontal mass. She underwent resection with pathologic examination revealing a cellular neoplasm with multiple appearances. Some areas resembled an atypical meningioma with meningothelial cells showing macronucleoli, focal sheeting architecture, and increased mitotic rate. These areas of more conventional meningioma transitioned into a sarcoma-like histology. The sarcomatous areas demonstrated anaplastic spindled cells arranged in intersecting fascicles. Focally, elongate cells with brightly eosinophilic cytoplasm and suggestions of cross striations were seen, resembling rhabdomyoblasts (Fig. 1G, H). The mitotic index in these areas reached up to 18 mitotic figures per 10 high-power fields.

Immunohistochemical stains showed patchy positivity for EMA in the area of conventional meningioma, but lack of staining in the sarcomatous component. SSTR2A was also negative for immunoreactivity in the sarcomatous component. Conversely, stains for desmin (Fig. 1I) and myogenin (Fig. 1J) were positive in the sarcomatous component, but negative in the meningothelial component, supporting divergent rhabdomyoblastic differentiation. The tumor was diffusely immunoreactive with vimentin. SMA was negative and the progesterone stain was mostly negative. The Ki-67 labeling index was elevated in both components, but highest in the sarcomatous component. Her clinical course was complicated by local recurrence 10 months after initial surgery. The histology of the recurrent neoplasm was purely sarcomatous.

Ancillary fluorescence in situ hybridization (FISH) testing was performed on both the original and recurrent tumor as previously described (4, 5). Both components of the original tumor showed deletions involving 1p, 14q, (Fig. 1K), and 22q (Fig. 1L). The sarcomatous component also demonstrated *CDKN2A* deletions in a subset of tumor cells. The recurrent tumor showed similar cytogenetic alterations as the sarcomatous component of the original tumor.

Patient #3

This patient was a 68-year-old woman who underwent subtotal resection of a posterior fossa atypical meningioma. She was subsequently treated with stereotactic radiosurgery. Surveillance imaging up to 3 years after initial resection demonstrated stable minimal residual tumor. However, 6 years after her initial resection, she developed worsening balance. Repeat imaging at that time showed an 8.9 cm heterogeneously enhancing mass occupying much of the posterior fossa (Fig. 2A). She underwent tumor resection. Intraoperatively, the tumor was markedly scirrhous and invaded portions of the cerebellar cortex. Pathologic examination of the recurrent tumor revealed a moderately cellular spindled to epithelioid neoplasm with tumor cells containing enlarged and pleomorphic elongate nuclei, prominent nucleoli, vesicular chromatin, and eosinophilic cytoplasm (Fig. 2B). The mitotic rate was moderately elevated, with up to 5 mitotic figures per 10 high-power fields. However, no histologic features of conventional meningioma were seen. Multiple areas of necrosis and extensive brain invasion were also noted (Fig. 2C).

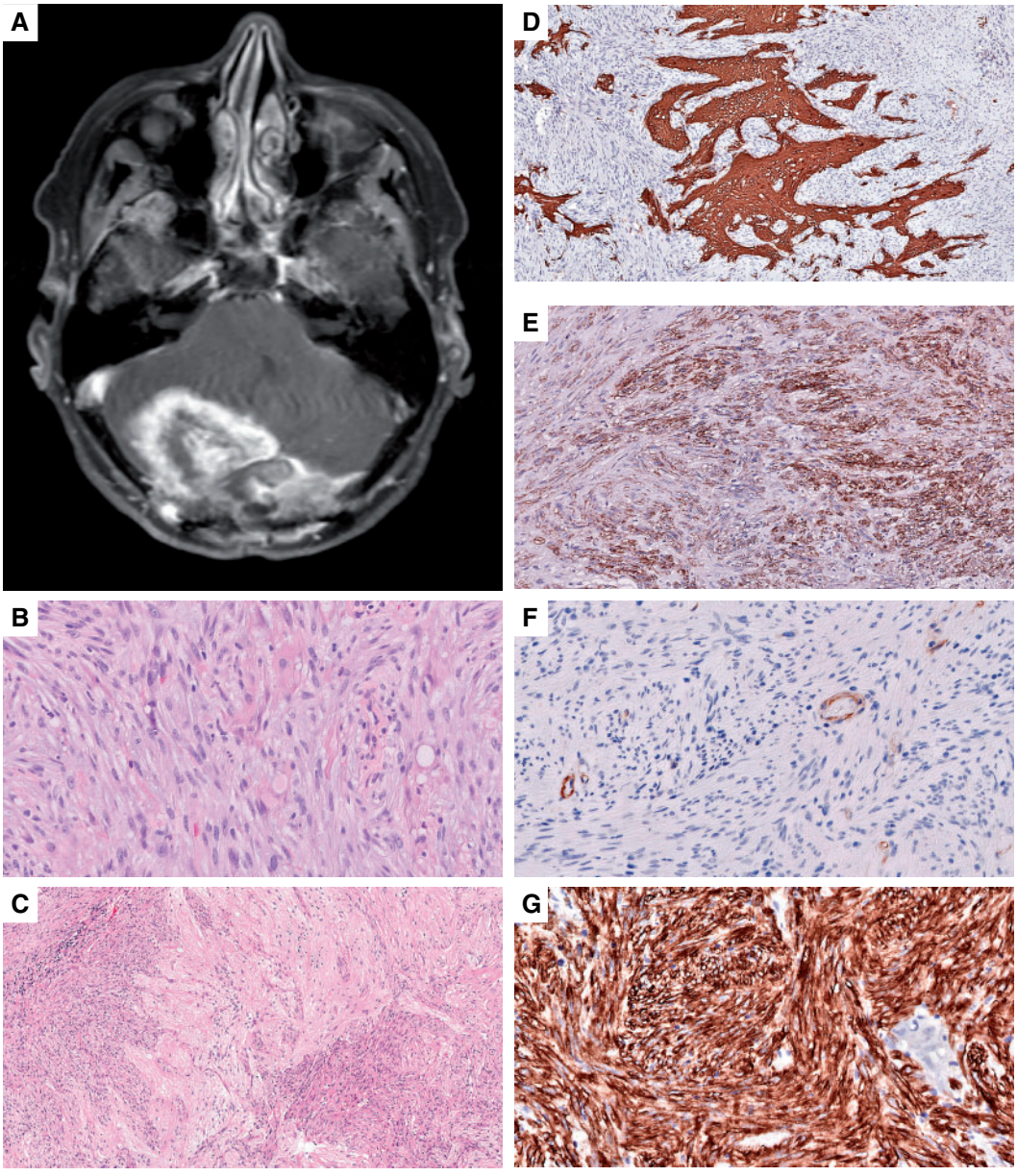
GFAP confirmed the extensive brain invasion with many areas of gliotic parenchyma entrapped deep within the tumor (Fig. 2D). The tumor showed patchy EMA positivity (Fig. 2E) but was negative for other meningioma markers, including SSTR2A (Fig. 2F) and progesterone receptor. SMA showed strong and diffuse positivity (Fig. 2G) and calponin was extensively positive, consistent with a smooth muscle lineage.

Next generation sequencing was performed on tumor tissue as previously described (6, 7). The findings included a pathogenic splice donor mutation in *NF2*, a hotspot activating mutation in the *TERT* promoter region, and a nonsense mutation in *BRCA1* (Fig. 2H). Additional copy number analysis demonstrated homozygous deletion of the *CDKN2A*/*CDKN2B* region at chromosome 9p21, as well as losses of 1p, 4p, proximal 4q, 6q, chromosome 9, 13q, chromosome 18, and 22q (containing *NF2*). No focal amplifications or chromosomal gains were identified.

DISCUSSION

Herein, we present 3 true sarcomatous meningiomas with myogenic metaplasia. All 3 patients in this series presented with a solitary intracranial mass without any reported history or evidence of a separate systemic malignancy. These rare tumors may occur sporadically or following prior radiotherapy in both younger and older adults, with a propensity for local recurrence over a short time interval. Some cases may appear entirely sarcomatous without any definite evidence of residual meningothelial differentiation. However, a subset of tumors displays areas of more conventional meningioma which may be seen adjacent to the sarcomatous foci. Of note, cytogenetic analysis of both the conventional and sarcomatous components in Patient #2 revealed a clonal relationship between the 2 elements with similar profiles of copy number changes, supporting a divergent evolution or dedifferentiation of the sarcomatous component from the meningothelial precursor lesion, rather than 2 separate neoplasms forming a collision tumor.

Heterologous differentiation was demonstrated through additional immunohistochemical studies. Of note, typical meningioma markers including EMA, SSTR2A, and progesterone receptor were either negative or not as strongly expressed in sarcomatous areas. While SSTR2A is generally a sensitive marker even in anaplastic meningiomas (8, 9), loss of expression can nevertheless be seen in cases with sarcomatous histology (as in all 3 cases reported here). In cases with loss of their meningothelial immunoprofile, identification of areas with conventional meningioma histology and/or genetic studies can aid in the accurate diagnosis of a sarcomatous meningioma.



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Chromosome	Position	Reference allele	Variant allele	Gene	Amino acid variant	cDNA variant	RefSeq transcript	Tumor sequencing reads	Tumor mutant allele frequency
chr5	1295228	G	A	TERT	n/a	c.-124C>T	NM_198253	1068	30
chr22	30038276	T	C	NF2	n/a	c.447+2T>C	NM_000268	367	48
chr17	41226499	C	T	BRCA1	p.W1508*	c.4524G>A	NM_007294	952	40

FIGURE 2. Patient #3. Postcontrast MR imaging of this patient with prior history of meningioma revealed an enhancing posterior fossa mass invading the underlying brain parenchyma **(A)**. The tumor was composed of spindled cells containing enlarged and pleomorphic elongate nuclei, prominent nucleoli, vesicular chromatin, and eosinophilic cytoplasm **(B)**. Multiple areas of brain invasion were seen **(C)**, which were highlighted on GFAP immunostain **(D)**. This tumor showed patchy positivity for EMA **(E)** and was negative for SSTR2A **(F)**. There was diffuse SMA positivity **(G)**. Next generation sequencing revealed alterations in *pTERT*, *NF2*, and *BRCA1* **(H).**

Radiation-induced sarcoma is the main differential consideration in cases of a new, rapidly expanding mass within the prior resection bed and prior irradiation field. In this scenario, molecular profiling may be necessary to differentiate a radiation-induced sarcoma from a sarcomatous meningioma. The most common cytogenetic alterations described in meningiomas is deletion of 22q, including the *NF2* locus. Other common meningioma-associated copy number changes include loss of 1p, 6q, 9p (including the *CDKN2A*/*CDKN2B* locus), 10, 14q, and 18q as well as gains of 1q, 9q, 12q, 15q, 17q, and 20q (4, 5). Additionally, mutations in the *TERT* promotor as well as homozygous deletion of *CDKN2A* have also been reported to be poor prognostic markers in meningioma (10–12); however, the latter feature is of limited diagnostic utility in the distinction from radiation-induced sarcoma since homozygous *CDKN2A* deletion is also commonly found (13). In contrast, alterations in *NF2* are uncommon in sarcomas (as are the common meningioma-associated chromosomal losses) but are the most frequent underlying driver mutations in meningioma, including anaplastic forms (14). Other mutations common in meningioma (such as *TRAF7*, *KLF4*, *AKT1*, *SMO, SUFU, POLR2A*) are not commonly found in sarcomas (15). Instead, molecular profiling in radiation-induced malignancies typically reveals a markedly aneuploid genome, often with numerous structural rearrangements secondary to double stranded DNA breaks (13, 16).

In summary, true sarcomatous meningiomas are exceptionally rare, but may be diagnostically challenging to distinguish from primary or radiation-induced sarcomas. In some of these cases, genomic profiling may therefore be necessary to distinguish between these disparate entities.

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