Intracranial Myxoid Mesenchymal Tumor/Myxoid Subtype Angiomatous Fibrous Histiocytoma: Diagnostic and Prognostic Challenges

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BACKGROUND AND IMPORTANCE: In the setting of intracranial neoplasms, EWSR1-cAMP Response Element-Binding Protein (CREB) transcription factor family fusions have been described in myxoid mesenchymal tumors, extremely rare entities with a close histopathologic and immunologic resemblance to myxoid subtype angiomatoid fibrous histiocytomas (AFH). Controversy exists on whether these central nervous system lesions are a subtype of myxoid AFH or a completely separate entity, which entitles a distinct clinical behavior and, consequently, a different approach to management. Upon review of the literature, only 14 cases of intracranial tumors harboring an EWSR1-CREB family fusion were identified, with only 3 cases presenting in middle-aged adults, none of which reported an EWSR1-CREB fusion mutation. Significant variability in reported radiographic and histopathological characteristics, as well as in clinical outcomes, was noted. Their similarity with other soft tissue tumors, added to the scarce information on its clinical behavior, represents a great diagnostic and therapeutic challenge to the treating physician.

CLINICAL PRESENTATION: We present a rare case of EWSR1-CREB mutated intracranial myxoid mesenchymal tumor/myxoid subtype AFH presenting as persistent headaches in a 36-yr-old woman with radiographic evidence of rapid growth and extensive vasogenic edema, for which she underwent surgical resection.

CONCLUSION: This represents a unique case of EWSR1-CREB mutated intracranial myxoid mesenchymal tumor presenting in adulthood, with evidence of aggressive behavior.

KEY WORDS: Intracranial myxoid mesenchymal tumor, Myxoid subtype angiomatous fibrous histiocytoma, EWSR1-CREB mutation, Surgical resection, Extra-axial

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EWSR1 is a protein involved in gene expression, cell signaling, and RNA processing.¹ Chromosomal translocations with transcription factor genes have been described in tumorigenesis.² cAMP Response Element-Binding Protein (CREB) is a transcription factor that induces plasticity.³ EWSR1-CREB fusions are commonly seen in the myxoid subtype of angiomatoid fibrous histiocytomas (AFH).^{1,3–7} In central nervous

system (CNS) neoplasms, this fusion has been described in intracranial myxoid mesenchymal tumors (IMMT). Controversy exists of whether they are a subtype of myxoid AFH or a separate entity.³

Upon literature review, only 14 cases were identified, with only 3 presenting in middle-aged adults, none of which reported an EWSR1-CREB fusion (Table).^{1–10} We describe an unique case of an EWSR1-CREB mutated intracranial tumor in a middle-aged adult presenting with evidence of rapid growth.

CLINICAL PRESENTATION

A 36-yr-old woman presented with new onset of headaches. Initial workup, including magnetic resonance imaging (MRI) without contrast of the

ABBREVIATIONS: ACA, anterior cerebral artery; AFH, angiomatoid fibrous histiocytoma; CMA, chromosomal microarray; CNS, central nervous system; CREB, cAMP Response Element-Binding Protein; IMMT, intracranial myxoid mesenchymal tumor; MRI, magnetic resonance imaging; SSS, superior sagittal sinus

VIDEO. Interhemispheric approach for resection of an intracranial myxoid mesenchymal tumor.

brain, was nonconclusive. Eight months later, her symptoms continued to progress; a new MRI with contrast revealed an interhemispheric contrast-enhancing mass. The patient was then referred to our institution, reporting worsening of her headaches, now occurring daily, associated with double vision, nausea, and vomiting. On physical examination, she had 4+/5 bilateral lower extremity weakness. In retrospect, the lesion was present on initial scan, which had grown considerably, with worsening vasogenic edema (Figure 1). In-house MRI redemonstrated an interhemispheric extra-axial mass measuring $1.9 \times 1.4 \times 1.5$ cm with extensive edema within the corpus callosum and frontal lobes, as well as splaying of the anterior cerebral arteries (ACAs) (Figure 1). Differential diagnoses included metastatic disease, hemangiopericytoma, and meningioma. Further workup, including whole-body positron emission tomography scan and thyroid biopsy, was negative for malignancy.

Given her symptomatology, tumor growth, and lack of diagnosis, surgical intervention for tumor resection and diagnosis was recommended.

Operative Details

An interhemispheric approach through a left-sided frontal craniotomy for tumor removal was performed (Video). Informed consent was obtained. The patient was positioned supine under general anesthesia. A linear bifrontal skin incision was made, followed by placement of a single burr hole posteriorly, turning the craniotomy flap across the superior sagittal sinus (SSS) and opening the dura in a U-shaped fashion (Figure 2). The operative microscope was then brought into the field.

After reaching the inferior edge of the Falx, the ipsilateral ACA was first identified, which we followed until we visualized the superior portion of the tumor, both frontal lobes, and the contralateral ACA (Figure 2). After proper identification of surrounding structures, we began to carefully dissect the tumor. The tumor was located inferiorly to the Falx, in between the ACAs, and anterior to the corpus callosum. No attachment to the Falx was seen, and a well-defined arachnoid plane was identified

for dissection, with no apparent infiltration of the adjacent pia or brain parenchyma.

Gross total resection was achieved with no complications and minimal blood loss. Papaverine was applied locally to the ACAs to prevent vasospasm. Dura was closed, bone flap secured, and skin sutured in a standard fashion. Postoperatively, the patient had complete resolution of her symptoms. MRI showed expected postsurgical changes with a small focal enhancement along the genu of the corpus callosum, concerning for residual tumor. At 3-mo follow-up, she remained neurologically intact. MRI showed gross total resection, with complete resolution of the previously noted enhancement, as well as the vasogenic edema (Figure 1). Follow-up with brain MRIs initially every 6 mo was recommended.

Pathology Result

On frozen section, tumor had spindle cell appearance with inconspicuous mitotic activity. On permanent sections, the tumor was noted to have a lobulated appearance with dilated vasculature and myxoid areas, with no evidence of brain invasion or necrosis (Figure 3). The cell morphology was compatible with a meningioma. However, classic features such as meningothelial whorls and psammoma bodies were not identified. By immunohistochemical staining, it had a low Ki67 labeling level. Smooth Muscle Antibody, desmin, paracellular reticulin, and STAT6 were negative, ruling out hemangiopericytoma. Given the extra-axial location, the low-grade features, and staining pattern, initial diagnosis consisted of a WHO grade I meningioma with odd morphologic appearance.

Due to the discordance between the clinical behavior and histopathology, it was further assessed with a chromosomal microarray (CMA) and a sequencing neuro-oncology gene panel. The gene panel revealed an EWSR1-CREM fusion (exon7: exon7), while CMA showed small focal losses on 22q11.23 and 22q12.1 (disrupting MN1 and CHEK2). These results, added to the clinical history, are most consistent with IMMT/myxoid-AFH.

DISCUSSION

EWSR1 has been described as the 5' fusion partner in gene rearrangements in various tumors, most frequently in sarcomas.^{1,11,12} Among CNS tumors, it has been reported in IMMT, ganglioglioma, high-grade glioma, and atypical teratoid/rhabdoid tumors.^{5,12,13} CREM has been observed as a 3' fusion partner in various tumors, including AFH and clear cell sarcoma.^{5,6}

IMMT was first proposed by Kao et al² in 2017 as a novel entity. However, due to similar histologic and immunophenotypic characteristics, controversy exists over whether these lesions are an intracranial variant of myxoid AFH. Bale et al³ reported the second series of this novel entity, with 3 pediatric cases. Additionally, 7 separate reports of intracranial myxoid-AFH have been reported.⁴⁻¹⁰ To the best of our knowledge, these 14 cases of

TABLE. Reported Cases of Intracranial Tumors Harboring EWSR1-CREB Family Fusion

Study	Case	Age	Sex	Location	Tumor size (greatest dimension in cm)	Radiographic characteristics	EWSR1-CREB family fusion	Pathological characteristics	Treatment protocol	EOR (biopsy, STR or GTR)	Time to recurrence (mo)
Dunham et al (2008) ⁵	1	25	M	Occipital	5.3	Contrast- enhancing, cystic component; partially encapsulated, focally hemorrhagic	EWSR1-ATF1	Multinodular, with pseudopseudomatoid spaces, pseudocapsule and lymphocyte cuffing	Surgical resection and close follow-up	GTR	–
Ochalski et al (2010) ⁸	1	35	M	Temporal/ extends to cerebellum	4 × 2 × 4	Hypointense rim surrounding tumor focus and minimal contrast enhancement with evidence of intratumoral hemorrhage	EWSR1-NR	Organizing hematoma with entrapped foci of a low-grade neoplasm composed of bland, round-to-oval nuclei with focal areas of moderate pleomorphism and a proliferative index of ~10%	Surgical resection and close follow-up. Surgical re-intervention for first 3 recurrences, combination therapy for subsequent recurrences (10 total)	GTR	13 ^a
Alshareef et al (2016) ⁴	1	58	F	CPA	4 × 4 × 5	Large, heterogeneous, extra-axial, centered in the right porous trigeminous, predominant cystic component	EWSR1-NR	Neoplastic cells exhibited epithelioid morphology with moderate amounts of pale, eosinophilic, and vacuolated cytoplasm. Ki-67 of <1%	Surgical resection and close follow-up	GTR	–
Kao et al (2017) ¹	1	15	F	Meningeal	NR	NR	EWSR1-CREB	Well-circumscribed with a multilobulated growth pattern	Surgical resection and close follow-up	GTR	–
	2	23	F	Meningeal (occipital)	NR	NR	EWSR1-CREB1				
	3	20	M	Brain (frontal)	NR	NR	EWSR1-CREB1				
	4	12	M	Brain (frontal)	NR	NR	EWSR1-ATF1				

TABLE. Continued											
Study	Case	Age	Sex	Location	Tumor size (greatest dimension in cm)	Radiographic characteristics	EWSR1-CREB family fusion	Pathological characteristics	Treatment protocol	EOR (biopsy, STR or GTR)	Time to recurrence (mo)
Bale et al (2018) ²	1	12	M	Posterior fossa	2.5 × 2.3 × 1	Lobulated, heterogeneous appearance, contrast enhancing, no tail sign present	EWSR1-CREB1	Epithelioid neoplasm composed of round-to-oval cells growing in short cords in a prominent myxoid background surrounded by a thin fibrous capsule	Surgical resection and close follow-up	GTR	–
	2	14	F	Intraventricular	3.8 × 3.6 × 3	Heterogeneous appearance, surrounding vasogenic edema and mass effect	EWSR1-CREB1	Epithelioid neoplasm composed of round-to-oval cells growing in short cords in a prominent myxoid background surrounded by a thin fibrous capsule	Surgical resection and close follow-up	GTR	–
	3	18	M	Midline/right frontal (Falx)	3 × 2 × 1.5	Contrast-enhancing, surrounding vasogenic edema, no definitive dural attachment	EWSR1-CREM	Epithelioid neoplasm composed of round-to-oval cells growing in short cords in a prominent myxoid background surrounded by a thin fibrous capsule	Surgical resection and close follow-up	GTR	–
Sciò et al (2018) ¹⁰	1	17	F	Frontal	5.9	Cystic lesion with surrounding vasogenic edema and contrast-enhancing nodule at the upper wall of the cyst	EWSR1-ATF1	Well-delineated, lobulated, solid to myxoid areas, as well as the branching vessels	Surgical resection and follow-up Radiation therapy to recurrence	GTR	20

TABLE. Continued

Study	Case	Age	Sex	Location	Tumor size (greatest dimension in cm)	Radiographic characteristics	EWSR1-CREB family fusion	Pathological characteristics	Treatment protocol	EOR (biopsy, STR or GTR)	Time to recurrence (mo)
Gareton et al (2018) ⁶	1	19	M	Dural (CPA) extends to cerebellum	NR	Predominantly cystic, significant perilesional edema	EWSR1-CREB	Small foci of necrosis and vascular proliferation, no pseudoangiomatoid spaces. Collagenous stroma, with marked myxoid areas and very few inflammatory infiltrates. Ki67 index of 10%	Surgical resection followed by 6 cycles of AP/Al type chemotherapy and radiation therapy to surgical cavity. Surgical resection for recurrence	GTR	120
Ghabari et al (2019) ⁷	1	58	F	Parafalcine/right parietal	1.6	Well-demarcated extra-axial lesion, homogeneous contrast enhancement, small dural tail	EWSR1-CREB1	Neoplastic cells had moderately pleomorphic nuclei, predominantly spindle in outline, with occasional plump and polygonal forms and eosinophilic cytoplasm. Mitotic rate of 4/10 HPFs	Surgical resection and close follow-up	STR	–
White et al (2019) ⁹	1	9	M	Interhemispheric/frontal arising from the falx	4.5 × 3.6 × 4.0	Extra-axial, heterogeneous contrast enhancement	EWSR1-CREB	Frequent hyalinized intratumoral vessels and apoptotic bodies, MI: 2 × 10 HPF Ki-67 Index 4% Desmin +	Surgical resection and follow-up. Radiation therapy to recurrence	GTR	6
Current case 2020											
	1	36	F	Interhemispheric/frontal	1.9 × 1.4 × 1.5	Extra-axial, contrast-enhancing, surrounding vasogenic edema, no dural attachment	EWSR1-CREB	EMA+, focal SSTR2+, Ki-67/MIB1 <2%	Surgical resection followed by close follow-up	GTR	–

CREB, cAMP Response Element-Binding Protein; GTR, gross total resection; HPF, high-power field; MI, mitotic index; NR, not reported; STR, subtotal resection.

^aReported mortality from the disease.

FIGURE 1. **A**, Axial T1-weighted MRI without contrast showing an anterior interhemispheric fissure mass at the moment of initial presentation. **B**, Sagittal T1-weighted MRI without contrast at the moment of initial presentation. **C**, Axial T2-weighted MRI at the moment of initial presentation. **D**, Axial T1-weighted MRI with contrast showing significant growth of the previously demonstrated interhemispheric contrast-enhancing mass 8 mo after initial presentation. **E**, Sagittal T1-weighted MRI with contrast of the brain showing significant growth of the previously demonstrated lesion. **F**, Axial T2-weighted MRI showing significant growth of the previously demonstrated lesion with extensive surrounding vasogenic edema within the corpus callosum and bilateral frontal lobes. **G**, Preoperative axial T1-weighted MRI with contrast re-demonstrating the interhemispheric mass, with extra-axial appearance and splaying of the bilateral anterior cerebral arteries. **H**, Preoperative sagittal T1-weighted MRI with contrast re-demonstrating the extra-axial, interhemispheric mass. **I**, Preoperative axial T2 fluid-attenuated inversion recovery (FLAIR)-weighted MRI showing significant vasogenic edema surrounding the lesion. **J**, Three-month postoperative T1-weighted MRI with contrast showing resection cavity without evidence of recurrent or residual tumor. **K**, Sagittal T1-weighted MRI with contrast 3-mo postoperatively demonstrating complete resolution of the enhancement at the genu of the corpus callosum. **L**, Axial T2 FLAIR-weighted MRI demonstrating complete resolution of the vasogenic edema 3 mo after surgical resection.

FIGURE 2. **A**, Intraoperative picture showing the left frontal craniotomy after removal of the bone flap, with visualization of the SSS (blue oval). **B**, Intraoperative picture showing the U-shaped dural flap based on the SSS. **C**, Operative microscope picture showing the tumor (green arrow) retracted by the suction and the ipsilateral anterior cerebral artery (blue arrow). **D**, Operative microscope picture showing the tumor (green arrow) and the branch of the contralateral ACA. **E**, Intraoperative picture showing the tumor removal en bloc (green arrow). **F**, Operative microscope showing the surgical cavity after removal of the tumor.

intracranial tumors harboring EWSR1-CREB fusions comprise all available cases in the literature.

Demographics of previously reported cases are consistent with a predilection to adolescence and young adulthood (Table). Two cases had a similar location to that in our case, described as interhemispheric frontal lesions in close relationship to the Falx; interestingly, all had the EWSR1-CREB mutation.^{3,9}

Data regarding clinical behavior are limited.^{7,9,14} Four cases showed local recurrence after gross-total resection.^{2,6,10} Ochalski et al⁸ reported the only case with multiple local recurrences (n = 10) and subsequent mortality from the disease. No distant metastasis has been described. The rapid growth observed in our

case suggested an aggressive behavior. However, 3 mo postoperative, there was no evidence of recurrence, with complete resolution of the vasogenic edema.

CONCLUSION

IMMT/myxoid AFH are extremely rare entities and represent a diagnostic and management challenge due to their rarity and close resemblance to other tumors. We present a unique case of an EWSR1-CREB mutated intracranial tumor presenting with radiographic evidence of rapid growth in a middle-aged adult.

FIGURE 3. **A**, Lower-power view of the lesion demonstrating lobulated appearance with dilated vasculature, with no brain invasion or necrosis present. **B**, Higher-power view of the lesion showing the spindle cell appearance with inconspicuous mitotic activity. **C**, Higher-power view of the lesion showing myxoid component. **D**, EMA stain positivity. **E**, STAT6 negative. **F**, Low level of Ki67 labeling. **G**, Desmin negative on tumor cells.

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