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A Case of Intracranial Mesenchymal Tumor, FET::CREB Fusion-positive, Diagnosed by Genomic Profiling with FoundationOne CDx

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Abstract

Intracranial mesenchymal tumor FET::cyclic adenosine monophosphate response element-binding fusion-positive is a soft tissue tumor with an extremely rare intracranial occurrence. Histological diagnosis is sometimes difficult, requiring confirmation of characteristic fusion genes. The patient was a 45-year-old male who presented with a chief complaint of pain and an abnormal sensation in the right trigeminal nerve area, in whom a neoplastic lesion in Meckel's cave was noted. The preoperative diagnoses included meningioma and schwannoma. The tumor was extirpated as much as possible, and the tumor tissue showed a high proliferative potential with rhabdoid features, raising the suspicion of a rhabdoid meningioma. However, immunostaining was positive for desmin and cluster of differentiation 99, suggesting the possibility of angiomatoid fibrous histiocytoma. For diagnosis, *Ewing sarcoma breakpoint region1 gene-cyclic adenosine monophosphate response element-binding 1* fusion and *Ewing sarcoma breakpoint region1 gene-activating transcription factor 1* fusion were examined at our institution, but were undetectable and did not lead to a diagnosis. Genomic profiling with FoundationOne CDx (Foundation Medicine, Cambridge, MA, USA) confirmed *Ewing sarcoma breakpoint region1 gene-cyclic adenosine monophosphate response element modulator* fusion and a diagnosis of intracranial mesenchymal tumor FET::cyclic adenosine monophosphate response element-binding fusion-positive was made. Diagnosis of intracranial mesenchymal tumor FET::cyclic adenosine monophosphate response element-binding fusion-positive requires both histological examination and confirmation of the fusion gene. Genomic profiling using the FoundationOne CDx is also useful when the fusion gene cannot be sufficiently confirmed at an individual's institution.

Keywords: intracranial mesenchymal tumor FET::CREB fusion-positive angiomatoid fibrous histiocytoma, intracranial myxoid mesenchymal tumor, *EWSR1-CREM* fusion, FoundationOne CDx

Introduction

Intracranial mesenchymal tumor (IMT) FET::cyclic adenosine monophosphate response element-binding (CREB) fusion-positive, is a recently recognized provisional entity in the 2021 World Health Organization (WHO) Classification of Tumors of the Central Nervous System.[1)] These are mesenchymal, tumors with a wide morphological spectrum.[2)] IMT FET::CREB fusion-positive occurs primarily in children and young adults and has previously been termed intracranial angiomatoid fibrous histiocytoma (AFH) or intracranial myxoid mesenchymal tumor (IMMT).[2)] The *FET* family (usually Ewing sarcoma breakpoint region1 gene [*EWSR1*] and less frequently fused in sarcoma [*FUS*]) gene rearrangements with *CREB* family genes (*CREB1*, *ATF1*, and *CREM*) have been identified to characterize a specific group of mesenchymal tumors called AFH and IMMT.[3,4)] AFH is a rare tumor that was first described approximately 40 years ago and accounts for approximately 0.3% of all soft tissue tumors.[5)] AFH is a neoplasm with intermediate malignant potential that occurs in the extremities of children and young adults.[6)] Histologically, AFHs may demon-

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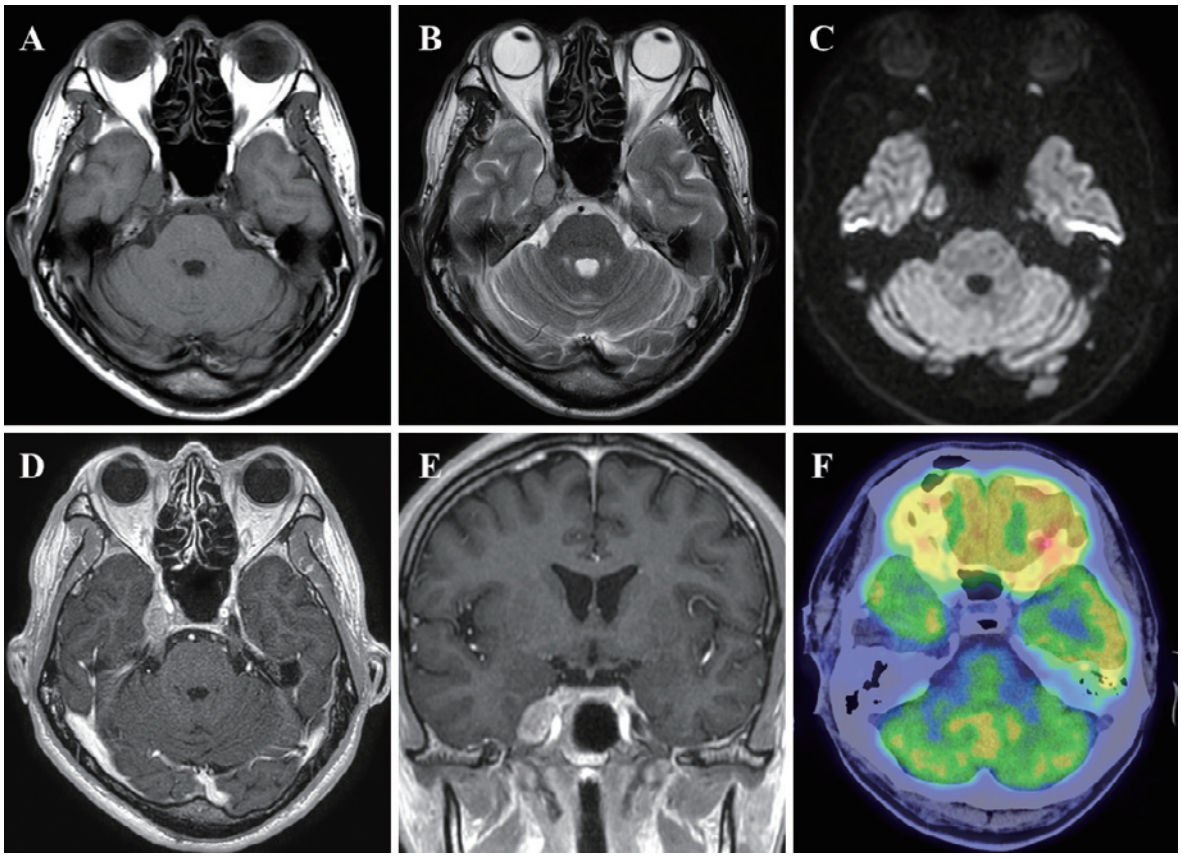

Fig. 1 Radiological findings. The tumor was observed in the Meckel's cave, and it showed as iso intensity on T1-weighted, T2-weighted, and diffusion-weighted images (A-C), and uniform enhancement on gadolinium contrast-enhanced MRI (D, E). No FDG accumulation was observed in positron emission tomography (F).
FDG: fluorodeoxyglucose; MRI: magnetic resonance imaging

strate a morphological spectrum, but representative features include a fibrous pseudocapsule, ovoid or pleomorphic cells, pseudoangiomatoid spaces, and lymphoplasmocytic cuffing.[7,8] Clear cells, small cell changes, and rhabdoid features are rare.[9] Intracranial AFH (iAFH) usually presents in young patients as either an intra- or extra-axial tumor that frequently displays prominent myxoid features and lacks lymphoid cuffing, which is unusual in AFH presenting in extracranial locations.[6] They contribute to a diverse group of mesenchymal tumors biologically characterized by oncogenic fusions between the *EWSR1* and members of the *CREB* gene family, notably *ATF1*, *CREB1*, and *CREM*.[10] Histologically, AFH is sometimes difficult to diagnose, but confirmation of the fusion gene can be diagnostic.[6] Genomic profiling is used to explore therapeutic options for the diagnosis and treatment of malignant tumors for which there is no standard treatment. In some cases, profiling results directly lead to treatment, whereas in others, they contribute to diagnostic confirmation. In this study, we report a case in which *ESWR1-CREM* fusion was confirmed and diagnosed using FoundationOne CDx (Foundation Medicine, Cambridge, MA, USA).

Clinical Summary

A 45-year-old man visited his dentist on December 2020 after experiencing an abnormal sensation in his right upper lip. In February X, he was treated with nerve blocks and oral medication at the Department of Anesthesiology of our hospital, but did not improve and was referred to our department after magnetic resonance imaging (MRI) showed a neoplastic lesion in the right middle cranial fossa. On admission, he experienced pain, an abnormal sensation on the right face, and hypesthesia of the right half of the tongue. No other symptoms of the cranial nerve were observed. Tumoral lesions were observed in the Meckel's cave, with isointensity on T1 weighted image (WI), T2WI, and diffusion-weighted images (Fig. 1A, B, C), and a uniform enhancement effect on gadolinium-enhanced T1WI (Fig. 1D, E). Fluorodeoxyglucose (FDG) positron emission tomography did not reveal any FDG accumulation (Fig. 1F). Considering trigeminal schwannoma and meningioma, a craniotomy was performed. Intraoperative findings revealed that the dura mater of the Meckel's cave was incised to identify the trigeminal nerve, which was enlarged by the tumor. A dark red tumor was present

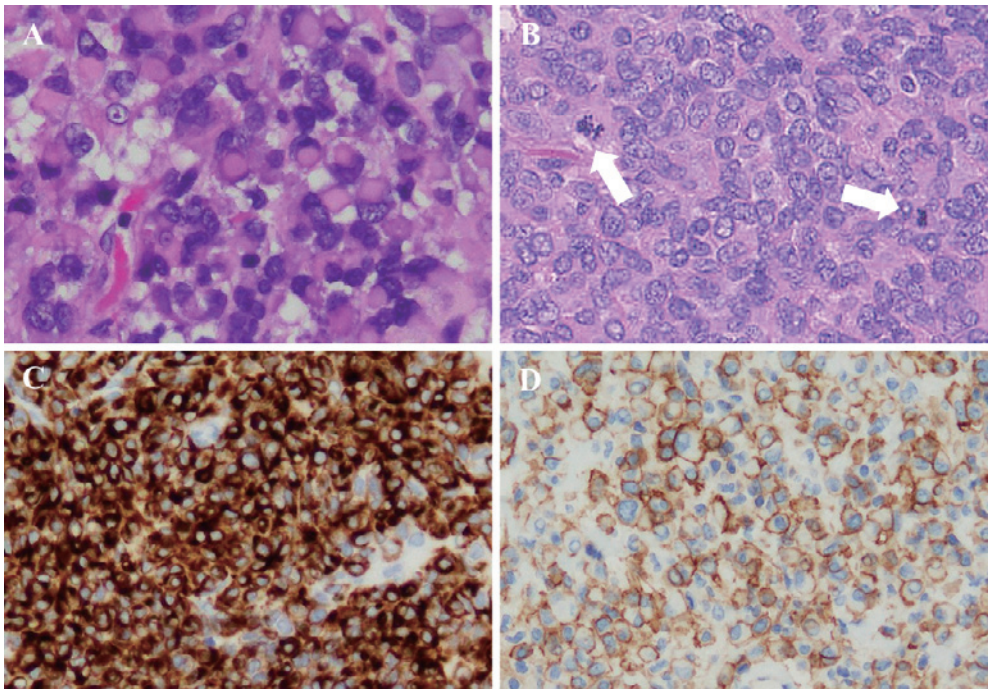

Fig. 2 Pathological findings. Rhabdoid cells with eosinophilic cytoplasmic inclusion are also present (A). Mitotic figures are occasionally found (up to 6 out of 10 high-power fields) (B). Tumor cells are diffusely positive for desmin (C) and CD99 (D).

within the trigeminal ganglion. The boundary between the tumor and the trigeminal nerve was indistinct, and the second and third branches of the trigeminal nerve, which were strongly attached to the tumor, were partially transected.

Pathological Findings

The section shows the proliferation of atypical round to polygonal cells with round or short, elongated nuclei in a haphazard fashion, accompanied by focal collagenous stroma and focal hyaline vascular changes. Rhabdoid cells with eosinophilic cytoplasmic inclusions were also observed (Fig. 2A). Mitotic figures were occasionally observed (up to 6 of 10 high-power fields) (Fig. 2B). Immunohistochemically, the tumor cells were diffusely positive for vimentin and focally positive for EMA, CK AE1/AE3, and synaptophysin, but negative for chromogranin A, STAT6, GFAP, and S-100 protein (Fig. 2B). The expression levels of INI-1 and BAP1 were retained. Desmin and CD99 were frequently detected in rhabdoid cells (Fig. 2C and D). The Ki-67 positive rate was approximately 13%. The morphological findings were consistent with rhabdoid meningioma; however, the desmin-positive findings were inconsistent with rhabdoid meningioma. Although iAFH was considered, no *EWSR1/CREB1* or *EWSR1/ATF1* fusion genes were detected by reverse transcription polymerase chain reaction. Although no clear histological diagnosis was made, rhabdoid meningioma was suspected morphologically, and 60 Gray radiotherapy administered over 30 fractions was administered. Since recurrence was expected thereafter, the patient was submitted to cancer genomic profiling at FoundationOne CDx for the purpose of considering future treatment. *EWSR1/CREM* fusion was identified as a genetic abnormality consistent with IMT, FET::CREB fusion-positive. Postoperatively, mild hypesthesia of the right face persisted, but the abnormal perception disappeared. The patient has been under observation for 36 months with no apparent recurrence.

Discussion

In this case, the tumor was located in the trigeminal nerve within Meckel's cave, and preoperative imaging revealed an enlarged trigeminal nerve. Based on the imaging findings, the differential diagnosis was trigeminal schwannoma or meningioma, whereas hematoxylin and eosin (HE) staining suggested rhabdoid meningioma. Rhabdoid meningioma is an uncommon, aggressive variant often showing high proliferation and other histologic features of malignancy, consistent with a WHO grade III tumor.[11-14] Given its high frequency of recurrence and aggressive behavior, patients with this tumor typically require aggressive clinical management and radiation.[15,16] In this case, HE staining showed proliferation of tumor cells similar to rhabdoid cells, suggestive of rhabdoid meningioma; however, immunostaining was positive for desmin, which is inconsistent with the immunohistological features of meningiomas. Furthermore, CD99 and Desmin were positive. Accordingly, the possibility of IMT, FET::CREB fusion-

Table 1 Literature-Based Case Summary

Age, median (range)		23 (5-79)
Sex, male:female		26:40
Location		
	extra axial	43
	intra axial	9
	ventricle	12
	cranial nerve	1
	spine	1
Histological diagnosis		
	AFH	12
	IMMT	39
	IMT, FET::CREB	15
Molecular Fusion		
	EWSR1-CREB	19
	EWSR1-CREM	20
	EWSR1-ATF1	19
	other	8
Ki-67, median (range)		10 (1-30)
Resection		
GTR		43
	*relapse late	*16/38
NTR		3
	relapse late	1/3
STR		8
	relapse late	8/8
PR		2
	relapse late	2/2
ND		10
Adjuvant therapy		
	RT	10
	GK	1
	CT	1
	RT+CT	2
Follow up period (months), median (range)		27 (1-158)
Outcome*		
	Alive and disease free	29
	Stable disease	3
	Alive with disease progression	7
	Alive and details unknown	11
	Died	4

*Only with documented postoperative course.
AFH: Angiomatoid fibrous histiocytoma, CT: Chemotherapy, GK: Gamma knife, GTR: Gross total resection, IMMT: Intracranial myxoid mesenchymal tumor, IMT, FET::CREB: Intracranial mesenchymal tumor, FET::CREB fusion positive, ND: Not described, NTR: Near total resection, PR: Partial resection, RT: Radiation therapy

positive was considered; however, a definitive diagnosis could not be made on histological examination alone. Notably, a previous report detailed a case in which a definitive diagnosis was made after confirming the presence of the fusion gene, which allows histological differentiation from rhabdoid meningioma.[6] Recurrent gene fusions involving *EWSR1* and the CREB family (*CREB1*, *ATF1*, and *CREM*) are well documented in AFH, with *EWSR1-CREB1* being the most frequent rearrangement,[7,17-21] followed by *EWSR1-ATF1*[22-24] and *EWSR1-CREM* fusions.[25,26] The presence of *EWSR1-CREB1* and *EWSR1-ATF* fusions was examined at our institution; however, the diagnosis could not be confirmed. Finally, *EWSR1/CREM* fusion was confirmed using FoundationOne CDx, confirming the diagnosis. In previous reports, there were cases in which the fusion gene could not be confirmed at one institution and the diagnosis was subsequently confirmed using next-generation sequencing at another institution.[6] Additionally, rare cases of sarcoma fusion-activated transcription factor 1 gene translocation (*FUS-ATF1*) have been reported.[23] Therefore, a wide range of fusion gene searches is necessary to confirm the diagnosis. FoundationOne CDx is a next-generation sequencing-based comprehensive genomic profiling test that can evaluate 324 cancer-related genes, including mutations, amplifications, deletions, and rearrangements in the entire coding region, along with the tumor mutation burden and microsatellite instability.[27] This foundation has led to treatment with tyrosine kinase inhibitors in a variety of carcinomas as a result of genomic profiling, and may also be useful in the diagnosis of IMT, FET::CREB fusion-positive. Genomic profiling tests currently covered by insurance in Japan include OncoGuide NCC Oncopanel System (Sysmex Corporation, Hyogo, Japan), GenMine TOP (Konika Minolta, Tokyo, Japan), and FoundationOne CDx. The number of genes analyzed in each test differed, and only FoundationOne CDx and GenMine TOP could detect *EWSR1-CREM* in this case. Therefore, the choice of genomic profiling test is also important.

Using the PubMed search engine, we searched for case reports of IMT, FET::CREB fusion-positive cases reported to date and compared this case with previous reports. The previous concept, in which AFH was diagnosed based on histological findings alone without a fusion gene search, was excluded. Currently, 66 cases, including this one, have been published (Table 1).[2-4,6,7,17,25,26,28-50] Of these, 12 patients had AFH, 39 had IMMT, and 15 had IMT, FET::CREB fusion-positive. Our patients had a relatively older age of onset, based on previous reports. Tumor localization was extra-axial in 42 cases and intra-axial in 9. In most previous reports, extra-axial tumors with an attachment site in the dura mater have been reported, but this case was rare because there was no obvious attachment site to the dura mater, and the tumor was located in the trigeminal nerve. The fusion gene pattern was *EWSR1-CREB1*, *EWSR1-ATF1*, *EWSR1-CREM*, *EWSR1-CREBL3*, *FUS-CREM*, and *EWSR1*-rearrangement (or fusion) in 19, 19, 20, 1, 1, and 6 cases, respectively. The most frequently reported fusion gene pat-

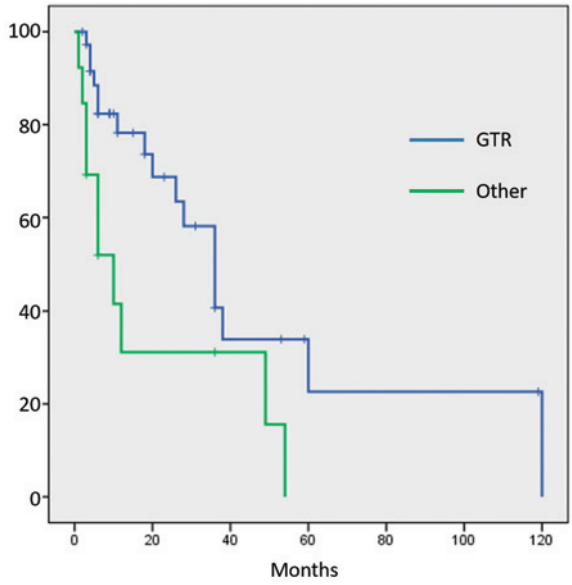

Fig. 3 Kaplan-Meier curves for PFS. Median PFS periods in GTR (n = 39) and other (n = 13) were 36 months (95% CI, 26.9-46.0) and 10 months (95% CI, 2.7-17.0), respectively. Patients with GTR had significantly longer PFS than other resection rates (p = 0.02, log-rank test).
CI: confidence interval; GTR: gross total resection; PFS: progression-free survival

terns in AFH were, in order, *EWSR1-CREB1*, *EWSR-ATF*, and *EWSR1-CREM*. However, in this study, the frequency of these 3 fusion genes did not change in IMT, FET::CREB fusion-positive. The *EWSR1-CREM* fusion in our case is not uncommon and should be recognized as being as common as other fusion patterns. Ki67 was described in 22 cases, with a mean and median of 9.6% and 10%, respectively. Of the 66 cases, postoperative follow-up was documented in 52, with gross total resection (GTR) in 39 and other resections (near-total resection [NTR], subtotal resection [STR], and partial resection [PR]) in 13. Of the 39 GTR cases, 30 were treated with surgical resection alone, of which 22 were recurrence-free and 17 had recurrence. The median follow-up period was 20.5 months. Salvage therapy for recurrent cases included reoperation in 4 patients, radiation therapy (RT) in 2, and stereotactic radiotherapy (SRS) in 2. In addition to GTR, RT and chemotherapy were administered in 7 cases, but all resulted in tumor recurrence. The median follow-up period was 48 months. Salvage therapy included surgery in 6 patients, RT in 4, SRS in 2, and crizotinib in one. Non-GTR included NTR, STR, and PR in 3, 8, and 2 cases, respectively. Adjuvant therapy included chemotherapy with ifosfamide, vincristine, adriamycin, carboplatin, and radiotherapy. Of the 13 patients who did not achieve GTR, 10 relapsed (76.9%), and the average follow-up was 33.2 months. Based on this tally, it should be recognized that the local recurrence rate in IMT, FET::CREB positive patients is much higher than the 15% rate previously reported for AFH. Additionally, when the time to recurrence was compared between the GTR and other groups using the Kaplan-Meier method and log-rank test, patients with GTR had a significantly longer time to recurrence (p = 0.02) (Fig. 3). Previous reports have shown that wide excision is important for improving prognosis and that complete wide resection is associated with better outcomes. The importance of GTR was also demonstrated in this study.[5] However, depending on the tumor location, the removal of the entire tumor may be difficult. In this case, the boundary between the tumor and the nerve was unclear in the trigeminal nerve in the cistern region, and it is possible that a portion of the tumor remained. We added RT in consideration of rhabdoid meningioma; however, there have been previous reports of postoperative radiation in some cases.[2,25] Postoperative irradiation or chemotherapy for curative treatment should also be considered in cases in which clear total resection is difficult.

Although our patient has not currently shown any recurrence, careful follow-up is required. The average age of patients with IMT, FET::CREB fusion-positive is 28.3 years, therefore, long-term postoperative tumor control is necessary for the patient's long life. Therefore, aggressive GTR acquisition through surgery and adjuvant therapy should be considered. The reported number of patients with IMT, FET::CREB fusion-positive was small, and further data collection is required.

Conclusion

We encountered a case of IMT FET::CREB fusion-positive that mimicked a rhabdoid meningioma. Diagnosis of IMT FET::CREB fusion-positive requires not only histological confirmation, but also confirmation of characteristic fusion genes. Fusion genes in AFH have multiple patterns, and genomic profiling using FoundationOne CDx is useful for diagnosis. IMT, FET::CREB fusion-positive is associated with a higher recurrence rate after GTR compared to known reports, requiring careful follow-up and consideration of adjuvant therapy.

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Ethical Approval

Informed consent was obtained from all individual participants.

Conflicts of Interest Disclosure

All authors have no conflict of interest.

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