Case report

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Intracranial mesenchymal tumor with FET::CREB fusion: diagnostic and therapeutic challenges in an adult patient: A case report

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Aims: To highlight the diagnostic and therapeutic challenges of intracranial mesenchymal tumors with FET::CREB fusion, emphasizing the role of molecular diagnostics and immunohistochemistry in accurate identification.

Case report: A 44-year-old male presented with seizures and chronic headaches. Brain MRI revealed a well-defined, enhancing lesion in the left frontal lobe with significant perilesional edema. Gross total resection was performed. Histopathological analysis showed round to oval, spindle, and epithelioid cells within a mucoid stroma, along with lymphoplasmacytic infiltration and prominent vasculature. Immunohistochemistry revealed positivity for EMA, CD99, and Desmin, while molecular testing confirmed the presence of EWSR1::CREB fusion. Adjuvant chemotherapy with temozolomide and irinotecan was administered.

Discussion: FET::CREB fusion-positive tumors, a molecular variant of angiomatoid fibrous histiocytoma, exhibit diverse morphological features resembling meningiomas or schwannomas. Accurate diagnosis relies on advanced molecular tools. Treatment primarily involves surgical resection, with adjuvant therapies tailored to the tumor's molecular profile.

Conclusion: Early and precise diagnosis using molecular studies is critical for guiding treatment decisions. Further research is needed to refine therapeutic strategies and explore targeted therapies for these rare tumors.

Keywords: *intracranial mesenchymal tumor; FET::CREB fusion; angiomatoid fibrous histiocytoma; EWSR1::CREB; CNS tumor; molecular diagnostics*

Introduction

Intracranial mesenchymal tumor, FET::CREB fusion-positive, is a recently recognized provisional entity in the 2021 WHO Classification of Tumors of the Central Nervous System [1]. These tumors are mesenchymal, non-meningothelial in nature, exhibiting a wide morphological spectrum. Mitotic activity is typically low (<5 mitoses/mm²), and the tumor architecture may range from syncytial or sheet-like to reticular or cord-like structures. The stroma is generally collagenous or myxoid. The defining diagnostic feature of these tumors is the fusion between a member of the FET RNA-binding protein family (EWSR1 or FUS) and a member of the CREB family of transcription factors (ATF1, CREB, or CREM). EWSR1::CREB fusion has been identified in angiomatoid fibrous histiocytoma and clear cell sarcoma [2,3]. Prior diagnostic terms such as "intracranial myxoid variant of angiomatoid fibrous histiocytoma" or "intracranial myxoid mesenchymal tumor with EWSR1::CREB family gene fusions" are no longer recommended. This report presents a case of an intracranial mesenchymal tumor, FET::CREB fusion-positive, located in the left frontal lobe of an adult patient.

Case report

A 44-year-old male patient presented with a history of one episode of seizure and chronic persistence headache for the past 10 years. Brain MRI with contrast showed a well-defined, lobulated lesion in the left frontal lobe, extending from the superior to the middle frontal gyrus, with intense enhancement and hyperperfusion. Significant perilesional edema was observed in the left frontal lobe, particularly in the perisylvian region, as well as in the genu and body of the corpus callosum. There was also a mass effect on the bilateral lateral ventricles (***Fig. 1***). The patient was started on oral steroids (dexamethasone) and antiepileptic medication (levetiracetam), resulting in significant improvement in the headache. Neurological examination was unremarkable.

The patient underwent a left frontal craniotomy, and gross total resection of the tumor was achieved.

The tumor was well delineated, with firm and rubbery consistency, consistent with the MRI findings (***Fig. 2***).

Postoperative imaging confirmed that a gross total resection had been achieved (***Fig. 3***).

Histopathological Findings

Microscopic examination of Hematoxylin and Eosin (H&E) - stained tissue sections revealed that the tumor was composed of round to oval, spindle, and epithelioid cells embedded in mucoid stroma. The tumor periphery showed a lymphoplasmacytic infiltrate. Amianthoid fibers-like collagen were observed at the tumor's

edge, along with microcystic changes and prominent vasculature. No marked cytological atypia, necrosis, atypical mitotic figures, or whorling patterns were noted (***Fig. 4***). Immunohistochemical staining revealed that the tumor cells were positive for EMA, CD99, and Desmin. However, they were negative for GFAP, Synaptophysin, S-100, CD-34, TTF-1, PR, and Pan-cytokeratin. These findings were consistent with an intracranial myxoid mesenchymal tumor.

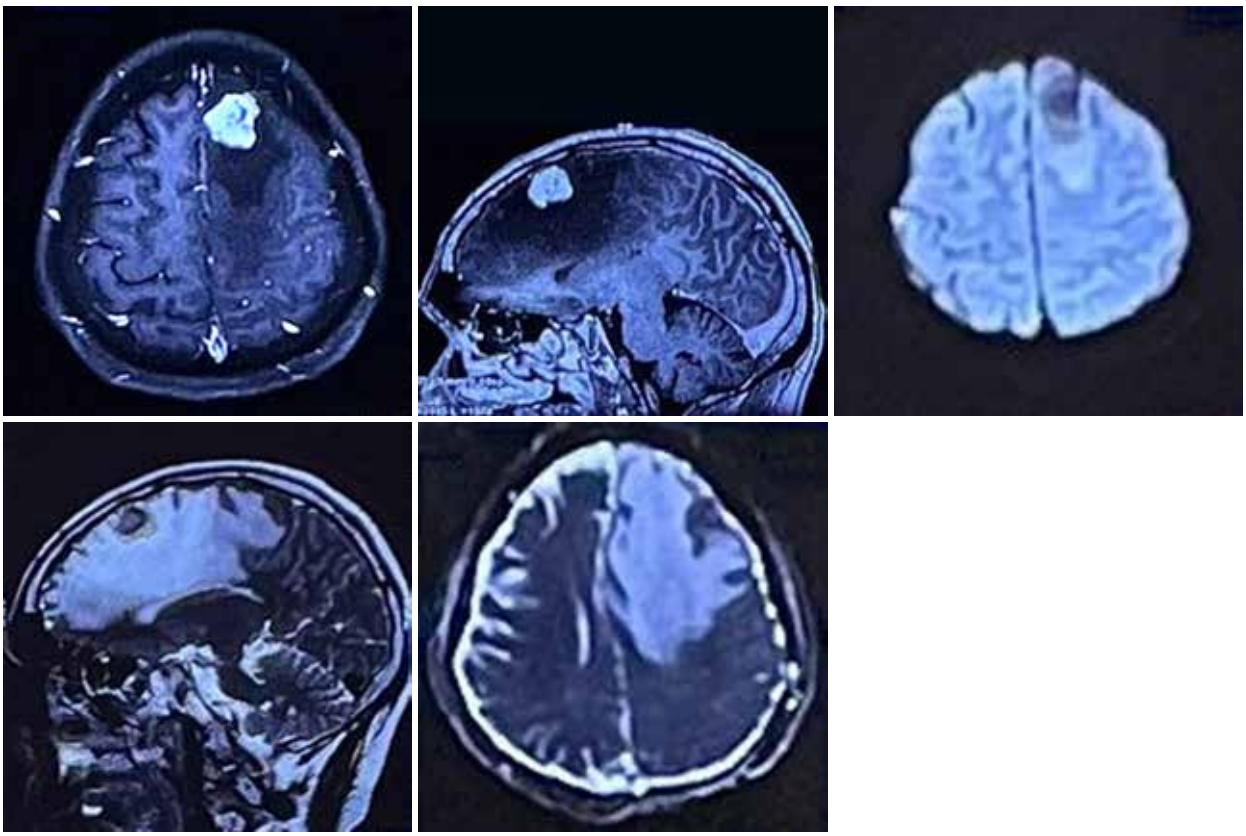

Fig. 1. MRI images show a well-defined, intensely enhancing lesion in the left frontal lobe (superior frontal gyrus and extending into the middle frontal gyrus) with hyperperfusion

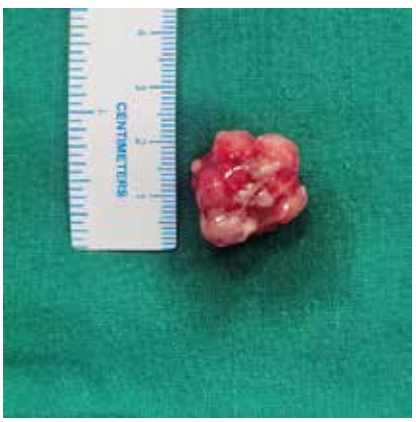

Fig. 2. Gross specimen of the excised tumor

This article contains some figures that are displayed in color online but in black and white in the print edition.

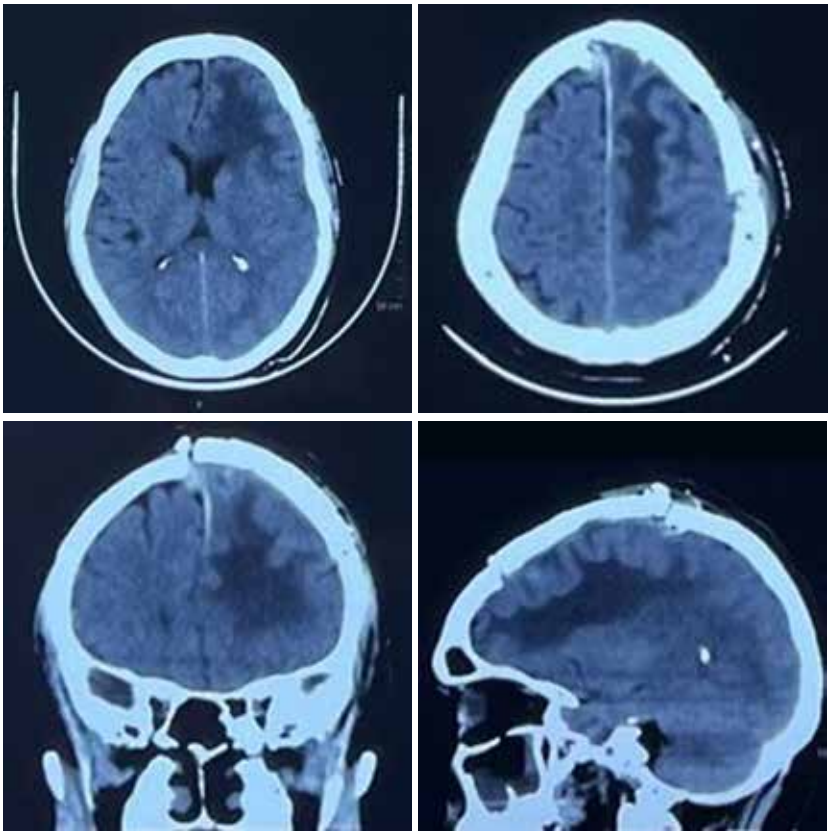

Fig. 3. Postoperative imaging

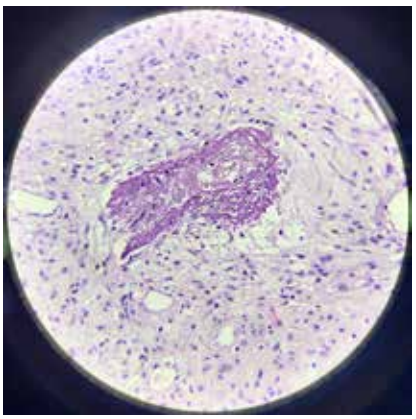

Fig. 4. Microscopic images of tumor sections showing round to oval and spindle to epithelioid cells embedded in mucoid stroma, with lymphoplasmacytic infiltrate, amianthoid fibers, microcystic changes, and prominent vasculature

Discussion

In 1979, Enzinger described angiomatoid fibrous histiocytoma (AFH) as a distinct fibrohistiocytic tumor, primarily affecting children and young adults, and resembling a vascular neoplasm [4]. AFH was included in the 2021 WHO CNS classification as an intracranial mesenchymal tumor [1]. Intracranial AFH is a rare primary CNS tumor, with the longest reported patient outcomes of up to five years and a median progression-free survival of 28 months 8 [3]. Patients with subtotal resections tend to experience local recurrence within 12 months [5].

Histologically, AFH is characterized by a multinodular proliferation of spindle-shaped or round cells with syncytial growth, forming bundles surrounded by a fibrous pseudocapsule, pericapsular lymphoplasmacytic cuffing, and pseudovascular spaces filled with blood. Desmin is often expressed, but myogenin or MyoD,

EMA, and CD68 are negative. Diagnosing AFH remains challenging due to its overlapping histological features with other tumors [2, 5].

Intracranial mesenchymal tumors with FET::CREB fusion represent a molecular variant of AFH. These tumors are often characterized by a collagenous stroma and dense intracellular matrix, which may resemble myofibroblastic tumors, poorly differentiated carcinomas, or meningiomas. Radiologically, these tumors typically show hypointense T1 signals and hyperintense T2 signals, with strong enhancement following gadolinium administration. Differential diagnoses include meningiomas and schwannomas, as these tumors may mimic extra-axial lesions with homogeneous contrast enhancement and a small dural tail on T1 fluid-attenuated inversion recovery (FLAIR) [2, 6].

Tauziède-Espariat et al. described 11 cases of CNS mesenchymal tumors with FET::CREB fusion. Of these, six were clustered with DNA methylation patterns, while the remaining five were similar to extra-CNS tumors such as angiomatoid fibrous histiocytomas, clear cell sarcomas, or solitary fibrous tumors [3]. These findings suggest that FET::CREB-fused intracranial tumors do not represent a single molecular entity, but rather a family of related tumors.

Treatment for intracranial mesenchymal tumors is primarily surgical, with complete resection being the goal. However, adjuvant therapies, including radiotherapy and chemotherapy (often sarcoma-based regimens), have been used in some cases [2, 7]. In our patient, the initial diagnosis was challenging, but following a comprehensive immunohistochemical panel and molecular analysis, the correct diagnosis of intracranial mesenchymal tumor, FET::CREB fusion-positive, was established. The patient subsequently received systemic chemotherapy, including temozolomide and irinotecan, tailored to sarcoma protocols, with good tolerability. The patient exhibited a favorable initial response to the sarcoma-based chemotherapy regimen, with good tolerability and no significant adverse effects noted during treatment. Follow-up MRI at 1 year postoperatively showed no evidence of tumor recurrence (***Fig. 5***).

Conclusion

This case highlights the importance of molecular studies and an extensive immunohistochemical workup in diagnosing rare CNS tumors, such as FET::CREB fusion-positive intracranial mesenchymal tumors. Early and accurate diagnosis is critical to guide treatment decisions, and personalized therapies based on molecular profiles may improve patient outcomes. Further studies and case reports will help refine treatment strategies and explore novel therapeutic options for these rare and complex tumors.

Disclosure

Consent

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for the publication of this case report and accompanying images. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

Ethical approval

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

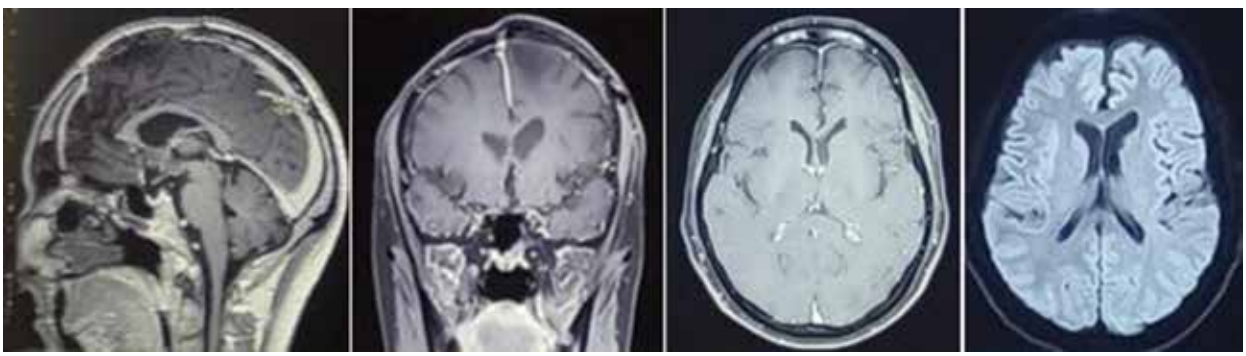

Fig. 5. One-year follow-up brain MRI showing no residual or recurrent lesion in the left frontal region following gross total resection of intracranial mesenchymal tumor with FET::CREB fusion

References

1. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, Hawkins C, Ng HK, Pfister SM, Reifenberger G, Soffietti R, von Deimling A, Ellison DW. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol. 2021 Aug 2;23(8):1231-1251. doi: 10.1093/neuonc/noab106
2. Antonescu CR, Dal Cin P, Nafa K, Teot LA, Surti U, Fletcher CD, Ladanyi M. EWSR1-CREB1 is the predominant gene fusion in angiomatoid fibrous histiocytoma. Genes Chromosomes Cancer. 2007 Dec;46(12):1051-60. doi: 10.1002/gcc.20491
3. Sloan EA, Chiang J, Villanueva-Meyer JE, Alexandrescu S, Eschbacher JM, Wang W, Mafra M, Ud Din N, Carr-Boyd E, Watson M, Punsoni M, Oviedo A, Gilani A, Kleinschmidt-DeMasters BK, Coss DJ, Lopes MB, Raffel C, Berger MS, Chang SM, Reddy A, Ramani B, Ferris SP, Lee JC, Hofmann JW, Cho SJ, Horvai AE, Pekmezci M, Tihan T, Bollen AW, Rodriguez FJ, Ellison DW, Perry A, Solomon DA. Intracranial mesenchymal tumor with FET-CREB fusion-A unifying diagnosis for the spectrum of intracranial myxoid mesenchymal tumors and angiomatoid fibrous histiocytoma-like neoplasms. Brain Pathol. 2021 Jul;31(4):e12918. doi: 10.1111/bpa.12918
4. Enzinger FM. Angiomatoid malignant fibrous histiocytoma: a distinct fibrohistiocytic tumor of children and young adults simulating a vascular neoplasm. Cancer. 1979 Dec;44(6):2147-57. doi: 10.1002/1097-0142(197912)44:6<2147::aid-cncr2820440627>3.0.co;2-8
5. Choi JH, Ro JY. The 2020 WHO Classification of Tumors of Soft Tissue: Selected Changes and New Entities. Adv Anat Pathol. 2021 Jan;28(1):44-58. doi: 10.1097/PAP.0000000000000284
6. Liu C, Liu Y, Zhao Y, Wei J, Ma Y, Liu Y, Huang J. Primary Intracranial Mesenchymal Tumor with EWSR1-CREM Gene Fusion: A Case Report and Literature Review. World Neurosurg. 2020 Oct;142:318-324. doi: 10.1016/j.wneu.2020.07.015
7. Garnier L, Fenouil T, Pissaloux D, Ameli R, Ducray F, Meyronet D, Honnorat J. Intracranial non-myxoid angiomatoid fibrous histiocytoma with EWSR1-CREB1 transcript fusion treated with doxorubicin: A case report. Mol Clin Oncol. 2021 Jul;15(1):131. doi: 10.3892/mco.2021.2293