

# Intracranial non-myxoid angiomatoid fibrous histiocytoma with *EWSR1-CREB1* transcript fusion treated with doxorubicin: A case report

LOUIS GARNIER<sup>1,2</sup>, TANGUY FENOUIL<sup>3,4</sup>, DANIEL PISSALOUX<sup>4,5</sup>, ROXANA AMELI<sup>6</sup>, FRANÇOIS DUCRAY<sup>1,2</sup>, DAVID MEYRONET<sup>2,3,7</sup> and JEROME HONNORAT<sup>1,2,8</sup>

<sup>1</sup>Department of Neuro-Oncology, East Group Hospital, Hospices Civils de Lyon, 69677 Lyon;

<sup>2</sup>Department of Clinical Sciences, Claude Bernard Lyon 1 University, 69008 Lyon; <sup>3</sup>Department of Pathology, East Group Hospital, Hospices Civils de Lyon, 69677 Lyon; <sup>4</sup>Department of Clinical Sciences,

Claude Bernard Lyon 1 University, INSERM U1052, CNRS UMR5286, Léon Bérard Center, Cancer Research Center of Lyon;

<sup>5</sup>Department of Biopathology, Léon Bérard Center, 69008 Lyon; <sup>6</sup>Department of Neuro-Radiology, East Group Hospital, Hospices Civils de Lyon, 69677 Lyon; <sup>7</sup>Cancer Research Center of Lyon, INSERM U1052, CNRS UMR5286,

Cancer Cell Plasticity Department, Transcriptome Diversity in Stem Cells Laboratory;

<sup>8</sup>Department of NeuroMyoGene Institute, INSERM U1217/CNRS UMR 5310, Lyon University, Claude Bernard Lyon 1 University, 69008 Lyon, France

Received July 3, 2020; Accepted October 21, 2021

DOI: 10.3892/mco.2021.2293

**Abstract.** Angiomatoid fibrous histiocytoma (AFH) is a rare soft tissue tumor that has only been reported in the central nervous system in case reports. After surgery, patients exhibit tumor recurrence. Pathological diagnosis of AFH remains difficult, especially in sites other than skin. AFH can harbor characteristic translocations implying that the Ewing sarcoma breakpoint region 1 gene (*EWSR1*) fuses with the transcription factor cyclic AMP response element binding (*CREB*) family genes. Doxorubicin is a chemotherapy that has previously been used successfully in two metastatic soft tissue AFH cases but never in intracranial AFH. The present report describes a case of an adult with a progressive classical intracranial non-myxoid AFH with *EWSR1-CREB1* transcript fusion 4 years after surgery. The patient was treated with doxorubicin as a single agent chemotherapy. This treatment resulted in a prolonged stable disease 15 months after treatment discontinuation. This is the first reported case of a treatment with doxorubicin in an adult with progressive intracranial AFH with *EWSR1-CREB1* transcript fusion which was sustained after treatment discontinuation.

## Introduction

Chromosomal translocations resulting in gene fusions are one mechanism underlying tumorigenesis, and some are more frequent in certain cancer entities. The Ewing sarcoma breakpoint region 1 gene (*EWSR1*), found on chromosome 22q12.2, has a tendency to fuse with the transcription factor cyclic AMP response element binding (*CREB*) family genes like *CREB1*, cAMP response element modulator (*CREM*), or activating transcription factor 1 (*ATF1*) (1,2). A group of neoplasms are associated with *EWSR1-CREB1* and/or *EWSR1-ATF1* gene fusions, including angiomatoid fibrous histiocytoma (AFH) but also, clear cell sarcoma, clear cell sarcoma-like tumor of the gastrointestinal tract, primary pulmonary myxoid sarcoma, hyalinizing clear cell carcinoma of the salivary gland, and soft tissue myoepithelial tumor (3). AFH is a rare soft tissue tumor described initially as 'angiomatoid malignant fibrous histiocytoma' by Enzinger in 1979 (4). It is now described as an indolent tumor with a favorable prognosis by the 2013 World Health Organization classification (5). It is a rare tumor of soft tissue (<0.5%) and mostly occurs superficially, in the extremities of children and young adults (6). Most AFHs are indolent, with a 15 percent regional recurrence rate and a metastatic rate <5%, most frequently involving regional nodes (7). Pathological diagnostic of AFH remain difficult, especially in other sites than skin. As immunohistochemical phenotype is not specific, molecular analysis is useful to confirm the diagnosis and distinguish this entity from likeness tumors. AFH is associated with 3 characteristic translocations: t(2;22)(q33;q12) *EWSR1/CREB1* being the most common, t(12;22)(q13;q12) *EWSR1/ATF1*, and t(12;16)(q13;p11) *FUS/ATF1* (3,8). The intracranial location represents a rare primary site, with six conventional AFH cases reported (9-13) and fifteen

---

*Correspondence to:* Dr Louis Garnier, Department of Neuro-Oncology, East Group Hospital, Hospices Civils de Lyon, 59 Boulevard Pinel, 69677 Lyon, France  
E-mail: garnier-louis@hotmail.fr

**Key words:** angiomatoid fibrous histiocytoma, Ewing sarcoma breakpoint region 1 gene, anthracycline, doxorubicin, central nervous system tumor, safety

myxoid AFH (14-23) described as a novel tumor entity. The *EWSR1/CREB1* fusion is reported in the myxoid variant but never in the classical non-myxoid component. None of the patients received chemotherapy for this lesion. Herein we describe a case of a classical intracranial non-myxoid AFH with *ESWR1-CREB1* transcript fusion treated with doxorubicin as a single agent chemotherapy, inducing a prolonged stable disease fifteen months after treatment discontinuation.

## Case report

**Clinical history and histological findings.** A 40-year-old male referred to the emergency department in 2012 for an intracranial hypertension syndrome with headaches and diplopia. Otherwise, his personal and familial medical clinical history was unremarkable. The magnetic resonance imaging (MRI) of the brain revealed a suspicious lesion of the splenium of the corpus callosum and the pineal region, with hypointense T1 signal, hyperintense T2 signal, and with strong enhancement following gadolinium administration. The lesion was associated with bi-parietal edema. Large increase in lipid and choline without apparent necrosis were showed on spectrometry. There was no sign of neoangiogenesis. The original diagnosis was thought to be lymphoma. He had three needle biopsies between 2012 and 2014 but none of them confirmed this diagnosis. He was then started on corticosteroids but the symptoms got worse with seizures, papillary edema, right homonymous hemianopsia, and agnostic alexia requiring a ventriculoperitoneal shunt. Finally, in March 2014, the patient underwent a left parieto-occipital craniotomy and a subtotal (60%) resection (Fig. 1). The surgical approach was decided because of the retrosplenial origin of the tumor and the inferior repulse of the deep venous system. Postoperatively, the patient maintained a right homonymous hemianopsia. He was started on radiation therapy for a total planned dose of 36 grays distributed into 20 sessions, but stopped after 12 sessions for his convenience (i.e. radiotherapy risks and consequences). Chemotherapy was not added to the treatment because of the lack of evidence of its benefits in this case.

From tumor specimens obtained after fine needle biopsy and after surgery, several formalin-zinc fixed paraffin-embedded (FFPE) blocks and Hematoxylin-Eosin-Saffron stained slides were submitted to histological examination after obtaining written informed and signed consent. It revealed a pathological tissue dominated by thick organized collagen fibers mixed with spindle or epithelioid cells. The nuclei were bland with open chromatin resembling those of macrophages or histiocytes (Fig. 2A and B). There was no pseudo syncytial growth pattern. The tumor exhibit large blood-filled pseudo-vascular spaces (Fig. 2A). Lympho-plasmocytic cuffs as well as thick fibrous pseudocapsule were not seen anymore compared to the second and third biopsy where they were respectively present (Fig. 2C and D). There was no myxoid feature nor necrosis, and no mitosis. Immunohistochemically was carried out on 4- $\mu$ m-thick FFPE tissue section using UltraView Ventana Universal DAB Detection Kit® (F. Hoffmann-La Roche AG, Switzerland). There was only cytoplasmic diffuse staining for desmin, patchy staining for EMA and CD68. The Ki-67 labeling index was low (<7%) (Fig. 3A-C). Fluorescence *in situ* hybridization (FISH)

analysis was performed on tumoral nuclei of paraffin embedded 4- $\mu$ m-sections using ZytoLight FISH-Tissue Implementation Kit with *EWSR1* Dual Color Break Apart Probe (Z-2096-50; ZytoVision), specific for *EWSR1* at 22q12.2. The number of orange and green dots were then counted (centromeric probe in 5' to the breakpoint and telomeric probe in 3' to the breakpoint, respectively), both into intron 4 of *EWSR1*, after DNA were counterstained with DAPI, using a fluorescence microscope. Fifty non-overlapping intact nuclei were examined for *EWSR1* rearrangement. Eighty percent of them presented in this case a split signal also called break apart signal meaning that separated orange and green dots or single orange dots were seen consistent with a *EWSR1* rearrangement (>20% of rearranged nuclei) (Fig. 3D). To look for its fusion partner, a retrotranscriptase-quantitative polymerase chain reaction was then performed in two different molecular departments on FFPE and frozen tissue and confirmed the presence of *EWSR1/CREB1* fusion transcript. Diagnosis of classical non-myxoid angiomatoid fibrous histiocytoma with the fusion transcript *EWSR1/CREB1* was made by the association of morphological, immunohistochemical and molecular data (5).

**Patient management and outcomes.** The patient was monitored for four years until MRI demonstrated tumor progression. The last MRI before progression in August 2017 showed a lesion of 35x28x29 mm.

On the MRI of April 2018, the lesion of the pineal region was heterogeneous and measure 40 mm of height, 27 mm of anteroposterior length, and 38 mm of width. It had a hypointense T1 signal, heterogeneous hyperintense T2 signal, and strong patchy enhancement following gadolinium administration. There were some cystic components, with the largest in the right anterior superior part with a diameter of 26 mm (Fig. 1). There was also peritumoral edema. At this time, surgical resection was considered too risky without possibility of complete removal and the patient could not be re-irradiated. The interdisciplinary tumor board decided to treat him as if he had a sarcoma-like tumor. In September 2018, as the tumor was still on progression (Fig. 1), he was started on intravenously doxorubicin 60 mg/m<sup>2</sup> every three weeks for a total of seven injections. Less than a month after treatment cessation, the patient was neurologically stable and brain MRI showed a <50% decrease in tumor size, considered as stable disease by the Response Assessment in Neuro-Oncology criteria (Fig. 1). Toxicities were measured by the Common Terminology Criteria for Adverse Events v5.0. The patient had a grade III constipation requiring a short-term hospitalization and a treatment with osmotic laxatives and mechanical removal. Otherwise, treatment was well tolerated; by the end, he had grade II alopecia, grade I asthenia, anorexia, and oral mycosis treated with oral bicarbonate. He had no feared anthracycline complication, meaning neither cardiac failure nor hepatotoxicity. Six months after stopping doxorubicin, he recovered from toxicities and MRI showed no signs of progression. Fourteen months after doxorubicin discontinuation in March 2020, MRI and neurological examination showed stable disease (Fig. 1). He still had some mild blurred vision and alexia. Although he was not cured from the disease, the tumor's progression was stopped and both his neuro-cognitive functions and quality of life were preserved.

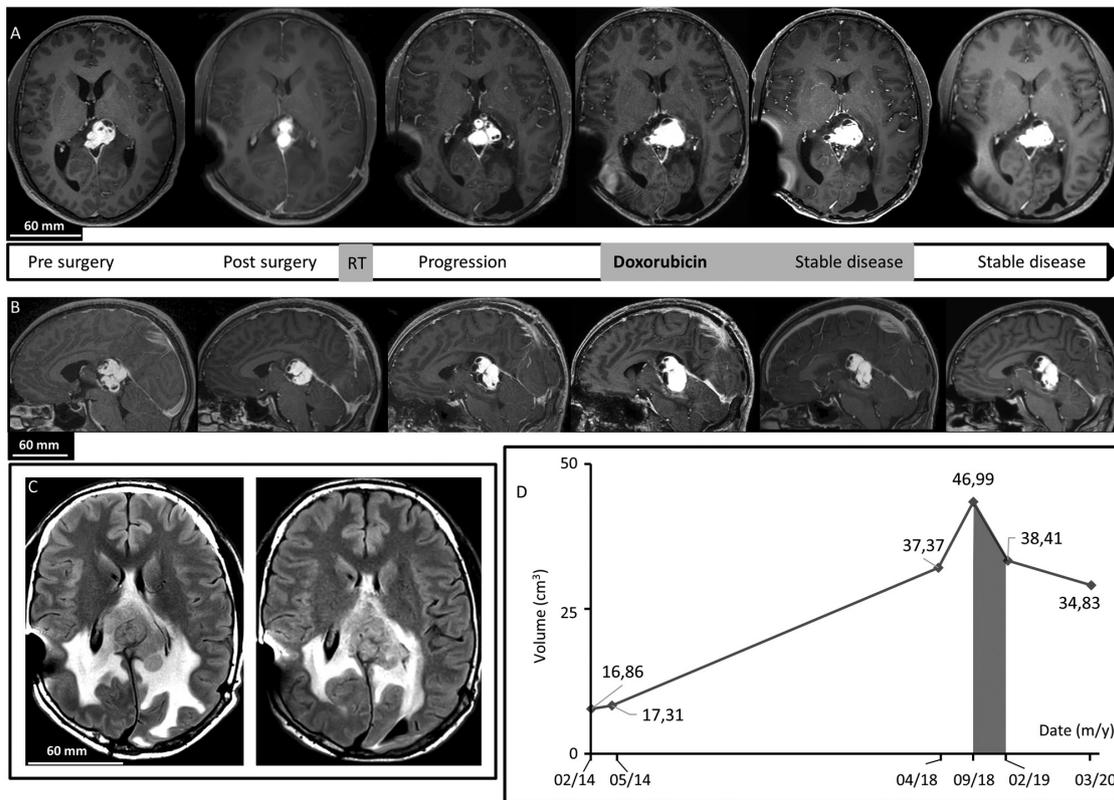


Figure 1. Brain MRI. (A) Axial after gadolinium injection T1-weighted imaging revealed dominant, patchy intense enhancing lesion of the splenium of the corpus callosum and the pineal region. In chronological order: Before surgery, after surgery showing residual tumor, 4 years after surgery demonstrating progression of the disease, at the beginning of Doxorubicin regimen treatment, just after treatment discontinuation confirming <50% decrease in tumor size, and last follow-up 15 months after treatment discontinuation demonstrating a stable disease. Note the cystic component. (B) Sagittal after gadolinium injection T1-weighted imaging revealed dominant, patchy intense enhancing lesion of the splenium of the corpus callosum and the pineal region before surgery, after surgery, 4 years after surgery, at the beginning of Doxorubicin treatment, after treatment, and at last follow-up. (C) Axial FLAIR T2-weighted images revealing peritumoral edema by large heterogeneous hyperintense signal before treatment with Doxorubicin and at last follow-up. (D) Diagram of evolution of tumor volume on MRI revealed a decrease during and after the Doxorubicin period (grey).

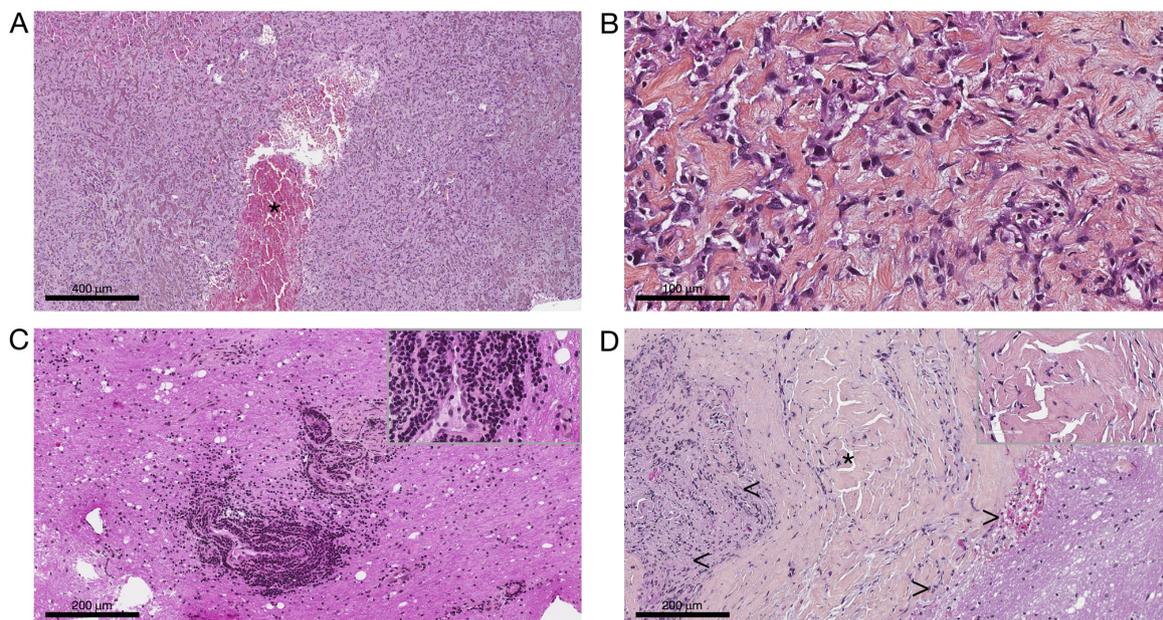


Figure 2. Pathological findings of tumor biopsy and resection. Characteristic histological features of angiomatoid fibrous histiocytoma from (A and B) both surgical specimen and (C and D) the biopsy sample. (A and B) Hematoxylin-Eosin-Saffron staining of surgical specimen. Original magnification, (A) x5 and (B) x40. Spindle-cell or epithelioid proliferation dispersed in thick organized collagen fibers with bland open chromatin nuclei. Note the blood-filled pseudo-vascular spaces (\*), which were lined by tumoral cells. (C and D) Hematoxylin-Eosin-Saffron staining of biopsy sample. Original magnification, x20. (C) Peripheral lymphocytic infiltrate corresponding to perivascular cuffs. (D) Thick pseudo-capsule (\*) lining tumor (<) and surrounding nervous tissue (>). The top right corner frame shows a 1.5X higher magnification (C and D).

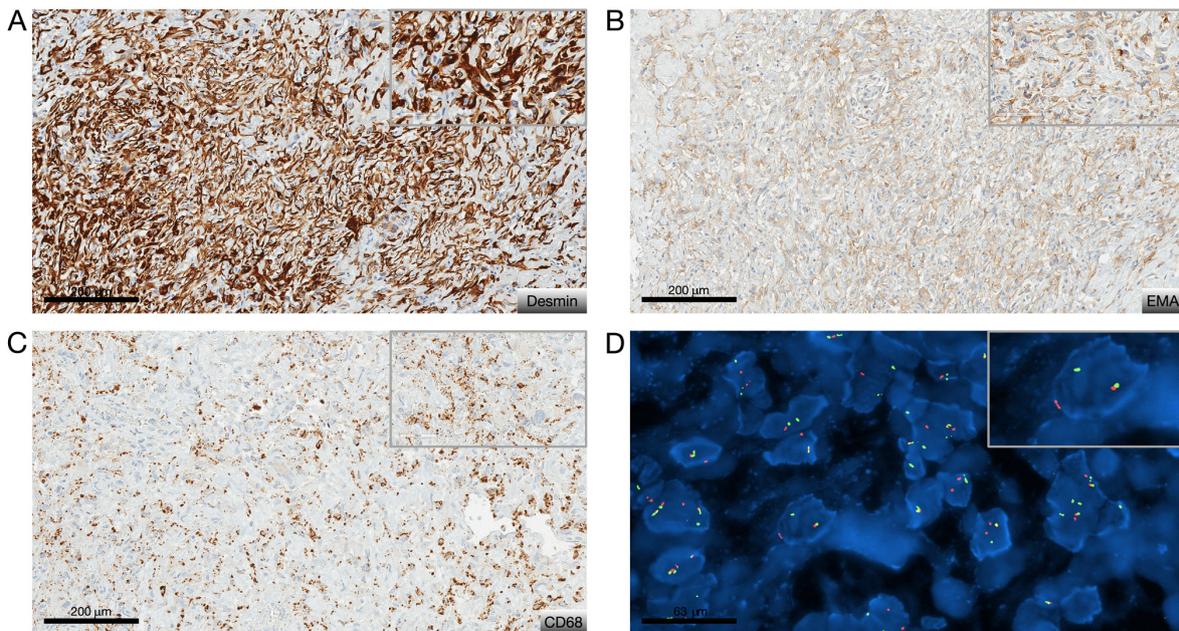


Figure 3. Immunohistochemical staining and FISH analysis results. Characteristic (A to C) phenotypical and (D) molecular features of angiomatoid fibrous histiocytoma. (A) Immunohistochemical view revealing diffusely positive staining for desmin (D33 clone; magnification, x20), (B) patchy staining for EMA (E29 clone; magnification, x20), and (C) CD68 (KP1 clone; magnification, x20). (D) FISH view revealing *EWSR1* rearrangement. Original magnification, x63. The top right corner frame shows a 1.5X higher magnification. EMA, epithelial membrane antigen; FISH, fluorescence *in situ* hybridization.

## Discussion

To our knowledge, this is the first case of a patient with classical non-myxoid intracranial AFH treated with single chemotherapy inducing prolonged stable disease. Even if the location is extremely rare, AFH was here confirmed by the integration of radiological, morphological and immunohistochemical data with the molecular analysis. The latter demonstrated the original *EWSR1-CREB1* fusion, heretofore only described in intracranial myxoid mesenchymal variant. Indeed, even if *EWSR1-CREB1* is the most frequently described fusion transcript in this entity (24), it is the first reported description in intracranial classical AFH. Most soft tissue AFH are indolent with 15 percent risk of local recurrence and less than 5 percent risk of metastases, predominantly to regional lymph nodes (7,25,26). It accounts for 0.3% of all soft tissue tumors and usually occurs in children and young adult (6). The intracranial location is extremely rare and only cases reports are described. This tumor has been reported in twenty-one previous instances: Six conventional AFH (9-13) and fifteen myxoid AFH (14-23). Characteristics of these tumors and their outcomes are listed in Table I. Unlike the present case, medium reported age at diagnosis is 26-year-old with a female predominance. Long-term outcomes (<1 year) are not available in 11 cases but the recurrence rate for the others is 60% (9-19,23). The scarcity of this location makes the diagnosis difficult. When utilizing imaging results, the most frequently established diagnosis is meningioma or lymphoma (12,18,23). Histologically, the diagnostic of intracranial AFH is difficult: The tumor is well delimited with lobulated or multinodular borders and thick fibrous pseudocapsule. In up to 80% of tumors, dense lymphoplasmacytic infiltrate or cuffs can be seen, resembling those of schwannoma. Multifocal hemorrhage is seen in most cases, forming blood-filled cystic spaces of variable size.

Mostly half of the AFHs express desmin, without positivity for myogenin or MyoD1. Many express EMA and CD68 (3). In our case, diagnosis was complicated due to repeated intracranial biopsy sampling of the tumor that not only gives little insights of its morphological characteristics but also induces changes in morphological features (like fibrosis, hemorrhage or tissue distortion). This tumor expressed desmin, EMA and CD68, which finally made us suspect AFH diagnosis and ask for the molecular analyses that confirmed it (25).

All the reports support gross total resection as the gold standard treatment at presentation and recurrence. Indeed there is a lack of proof regarding radiotherapy and chemotherapy. In metastatic soft tissue AFH, anthracycline based chemotherapy has previously been used successfully in two cases suggesting the likely usefulness of such treatment in patient with unresectable and/or metastatic disease (26,27). Also, one of the latest case reports of intracranial AFH suggests that use of chemotherapy as an adjuvant therapy could be considered if surgical resection was vain or deleterious to the patient (13). Actually, one patient was treated with 6 cycles of API/AI type chemotherapy but it was for a myxoid-variant AFH and after complete tumor removal. None of the patients presented in the cases was challenged with chemotherapy at tumor progression.

This case report confirms that the diagnostic of intracranial AFH can be problematic and a gross total resection, when possible, must be considered. Besides, an integrated approach using morphology, immunohistochemistry and molecular analysis is recommended to support the diagnosis of this rare entity. The potential relation with the myxoid component needs to be further studied. Treatments options after surgery for recurrent or progressive intracranial AFH, myxoid or not, are scarce and the optimal treatment sequence is unknown. Here we present the first case of intracranial conventional

**Table I. Comprehensive list of reported cases of angiomatoid fibrous histiocytoma (with myxoid component or not) and their treatment with reported outcomes.**

AFH	Authors	Age (years)/sex	Location	Symptoms/signs (clinical features)	MRI	Surgery	IHC	Genetic marker	Treatment post-surgery	Time to recurrence	Total follow up/recurrence	(Refs.)
Conventional AFH	Dunham <i>et al.</i> , 2008	25/M	Occipital lobe	Visual problems, headaches	Cystic component, heterogeneously enhancement	GTR	EMA <sup>+</sup> , desmin <sup>+</sup>	<i>EWSR1/ATF1</i>	None	NM	NM	(9)
	Ochalski <i>et al.</i> , 2010	35/M	Temporal lobe	Headaches, facial weakness	Minimal enhancement	GTR	Desmin <sup>+</sup> , EMA NM	Rearranged <i>EWSR1</i> gene	GKS <sup>a</sup>	0.8 months	49 months/multiple <sup>b</sup>	(10)
	Hansen <i>et al.</i> , 2015	17/F	Parieto-occipital lobe	Headaches	Heterogeneously enhancement, edema	GTR	EMA <sup>+</sup> , desmin <sup>+</sup>	Negative	None	NA	3 months/none	(11)
	Alshareef <i>et al.</i> , 2016	58/F	Porous trigeminus	Facial weakness	Heterogeneously enhancement, edema	GTR	NM	Rearranged <i>EWSR1</i> gene	None	NA	6 months/none	(12)
	Konstantinidis <i>et al.</i> , 2019	13/F	Frontal lobe	Headaches	Cystic component, enhancement, edema	GTR	Desmin <sup>+</sup> , EMA NM	<i>EWSR1/ATF1</i>	None	5 years (surgery)	11 years/yes	(13)
	Konstantinidis <i>et al.</i> , 2019	12/F	Frontal lobe	Visual problems, headaches	Cystic component, enhancement, edema	STR	EMA <sup>+</sup> , desmin <sup>+</sup>	<i>EWSR1/CREM</i>	None	28 months	28 months/yes	(13)
Myxoid mesenchymal AFH	Kao <i>et al.</i> , 2017	15/F	Meninges	NM	NM	NM	EMA <sup>+</sup> , desmin <sup>+</sup>	<i>EWSR1/CREM</i>	None	NA	17 months/none	(14)
	Kao <i>et al.</i> , 2017	23/F	Meninges (occipital)	NM	NM	NM	EMA <sup>+</sup> , desmin <sup>+</sup>	<i>EWSR1/CREB1</i>	None	NM	NM	(14)
	Kao <i>et al.</i> , 2017	20/M	Frontal lobe	NM	NM	NM	EMA <sup>+</sup> , desmin <sup>+</sup>	<i>EWSR1/CREB1</i>	None	NM	NM	(14)
	Kao <i>et al.</i> , 2017	12/M	Frontal lobe	Seizures	NM	NM	EMA <sup>+</sup> , desmin <sup>+</sup>	<i>EWSR1/ATF1</i>	None	NM	NM	(14)
	Bale <i>et al.</i> , 2018	12/M	Posterior cerebellar fossa	Headaches	Heterogeneously enhancement	STR	EMA <sup>+</sup> , desmin <sup>+</sup>	<i>EWSR1/CREB1</i>	None	NA	12 months/none	(17)
	Bale <i>et al.</i> , 2018	14/F	Intraventricular	Headaches, visual problems	Heterogeneously enhancement, edema	STR	EMA <sup>+</sup> , desmin <sup>+</sup>	<i>EWSR1/CREB1</i>	None	NA	12 months/none	(17)
	Bale <i>et al.</i> , 2018	18/M	Frontal lobe	Seizures	Enhancement, edema	STR	EMA <sup>+</sup> , desmin <sup>+</sup>	<i>EWSR1/CREM</i>	None	NA	12 months/none	(17)
	Sciot <i>et al.</i> , 2018	17/F	Frontal lobe	Hemiparesis, seizures	Cystic component, minimal enhancement	GTR	EMA <sup>+</sup> , desmin <sup>-</sup>	<i>EWSR1/ATF1</i>	RT after 2nd surgery	3 months (surgery and RT)	7 years/two	(16)
	Garetton <i>et al.</i> , 2018	19/M	Tentorium cerebelli	Seizures	NM	GTR	EMA <sup>+</sup> , desmin <sup>-</sup>	<i>EWSR1/CREM</i>	6 API/AI and RT	10 years	10 years/yes	(15)
	Spatz <i>et al.</i> , 2018	22/F	Occipital lobe	Visual problems, headaches, seizure	Heterogeneously enhancement, edema	STR	EMA <sup>+</sup> , desmin <sup>+</sup>	NM	None	NA	3 months/none	(23)
	Ghanbari <i>et al.</i> , 2019	58/F	Parafalcine	Seizure	Homogenous enhancement, edema	STR	EMA <sup>+</sup> , desmin <sup>+</sup>	<i>EWSR1/CREB1</i>	None	NA	3 months/none	(18)

Table I. Continued.

AFH	Authors	Age (years)/sex	Location	Symptoms/signs (clinical features)	MRI	Surgery	IHC	Genetic marker	Treatment post-surgery	Time to recurrence	Total follow up/recurrence	(Refs.)
	Gunnness <i>et al.</i> , 2019	32/F	Temporal lobe	Headaches	Cystic component, heterogeneously enhancement	STR	NM	NM	None	1 year (surgery)	2 years/yes	(19)
	White <i>et al.</i> , 2019	9/M	Frontal lobe	Fatigue, abulia	Cystic component, enhancement	GTR	Desmin <sup>4+</sup> , EMA NM	<i>EWSR1/CREM</i>	None	6 months (surgery and RT)	6 months/yes	(20)
	Ballester <i>et al.</i> , 2020	67/M	Temporal lobe	Aphasia, confusion	Cystic component, enhancement, edema	STR	EMA <sup>+</sup> , desmin <sup>+</sup>	<i>EWSR1/ATF1</i>	None	NA	3.5 months/none	(21)
	Komatsu <i>et al.</i> , 2020	53/F	Third ventricle	Headache, dizziness	Homogenous enhancement	STR	EMA <sup>+</sup> , desmin <sup>+</sup>	<i>EWSR1/CREB1</i>	GKS	NA	3 months/none	(22)

<sup>4</sup>GKS after 4 surgeries and then after 3 other surgeries; <sup>4</sup>died after 9 surgeries and 2 GKS. API, doxorubicin-ifosfamide-cisplatin-based regimen; AFH, angiomatoid fibrous histiocytoma; EMA, epithelial membrane antigen; F, female; GKS, gamma knife surgery; GTR, gross total resection; IHC, immunohistochemistry; M, male; NA, not applicable; NM, not mentioned; RT, radiotherapy; STR, subtotal resection.

AFH with *EWSR1/CREB1* fusion transcript, treated with doxorubicin at progression, inducing prolonged stable disease fourteen months after treatment discontinuation.

In conclusion, in the absence of gold standard management for such cases, the present case suggests that chemotherapy should be considered in intracranial AFH when surgery is not an option. Desmin staining and *EWSR1* gene fusions should be searched for in all cases possibly compatible with intracranial AFH especially in EMA positive spindle cell tumors without typical meningioma features. A single institute observational study is currently ongoing in Italy. All the medical records, radiological imaging, and histological slides are being reviewed to identify the best therapeutic approach (NCT03759327). Moreover, radiation therapy with or without chemotherapy combination (including doxorubicin) or targeted therapy before surgery are currently being explored for patients with newly diagnosed non-rhabdomyosarcoma soft tissue sarcomas (comprising AFH) (NCT02180867), which could give us clues to the best treatment for intracranial AFH patients.

### Acknowledgements

Not applicable.

### Funding

No funding was received.

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Authors' contributions

LG instructed and participated in the treatment of the patient, performed the literature search, and mainly wrote the manuscript. LG and TF created the figures and tables. JH and FD instructed and participated in the treatment of the patient. TF, JH and FD provided critical revisions of the manuscript for important intellectual content. TF, DM and DP carefully reviewed the pathological findings. RA carefully reviewed the radiology findings. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

The patient provided written informed consent prior to treatment.

### Patient consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

### Competing interests

The authors declare that they have no competing interests.

**References**

1. Lemaigre FP, Ace CI and Green MR: The cAMP response element binding protein, CREB, is a potent inhibitor of diverse transcriptional activators. *Nucleic Acids Res* 21: 2907-2911, 1993.
2. Gonzalez GA and Montminy MR: Cyclic AMP stimulates somatostatin gene transcription by phosphorylation of CREB at serine 133. *Cell* 59: 675-680, 1989.
3. Thway K and Fisher C: Tumors with EWSR1-CREB1 and EWSR1-ATF1 fusions: The current status. *Am J Surg Pathol* 36: 11, 2012.
4. Enzinger FM: Angiomatoid malignant fibrous histiocytoma. A distinct fibrohistiocytic tumor of children and young adults simulating a vascular neoplasm. *Cancer* 44: 2147-2157, 1979.
5. Antonescu CR and Rossi S: WHO Classification of Tumours of Soft Tissue and Bone. Vol 5. 4th edition. Fletcher CD, Bridge JA, Hogendoorn PC and Mertens F (eds). IARC, Lyon, pp204-205, 2013.
6. Saito K, Kobayashi E, Yoshida A, Araki Y, Kubota D, Tanzawa Y, Kawai A, Yanagawa T, Takagishi K and Chuman H: Angiomatoid fibrous histiocytoma: A series of seven cases including genetically confirmed aggressive cases and a literature review. *BMC Musculoskelet Disord* 18: 31, 2017.
7. Fanburg-Smith JC and Miettinen M: Angiomatoid 'malignant' fibrous histiocytoma: A clinicopathologic study of 158 cases and further exploration of the myoid phenotype. *Hum Pathol* 30: 1336-1343, 1999.
8. Huret JL: EWSR1 (Ewing sarcoma breakpoint region 1). *Atlas Genet Cytogenet Oncol Haematol* 15: 395-407, 2011.
9. Dunham C, Hussong J, Seiff M, Pfeifer J and Perry A: Primary Intracerebral angiomatoid fibrous histiocytoma: Report of a case with a t(12;22)(q13;q12) causing type 1 fusion of the EWS and ATF-1 genes. *Am J Surg Pathol* 32: 478-484, 2008.
10. Ochalski PG, Edinger JT, Horowitz MB, Stetler WR, Murdoch GH, Kassam AB and Engh JA: Intracranial angiomatoid fibrous histiocytoma presenting as recurrent multifocal intraparenchymal hemorrhage. *J Neurosurg* 112: 978-982, 2010.
11. Hansen JM, Larsen VA, Scheie D, Perry A and Skjøth-Rasmussen J: Primary intracranial angiomatoid fibrous histiocytoma presenting with anaemia and migraine-like headaches and aura as early clinical features. *Cephalalgia* 35: 1334-1336, 2015.
12. Alshareef MA, Almadidy Z, Baker T, Perry A, Welsh CT and Vandergrift WA III: Intracranial angiomatoid fibrous histiocytoma: Case report and literature review. *World Neurosurg* 96: 403-409, 2016.
13. Konstantinidis A, Cheesman E, O'Sullivan J, Pavaine J, Avula S, Pizer B and Kilday JP: Intracranial angiomatoid fibrous histiocytoma with EWSR1-CREB family fusions: A report of 2 pediatric cases. *World Neurosurg* 126: 113-119, 2019.
14. Kao YC, Sung YS, Zhang L, Chen CL, Vaiyapuri S, Rosenblum MK and Antonescu CR: EWSR1 fusions with CREB family transcription factors define a novel myxoid mesenchymal tumor with predilection for intracranial location. *Am J Surg Pathol* 41: 482-490, 2017.
15. Gareton A, Pierron G, Mokhtari K, Tran S, Tauziède-Espariat A, Pallud J, Louvel G, Meary E, Capelle L, Chrétien F and Varlet P: ESWR1-CREM fusion in an intracranial myxoid angiomatoid fibrous histiocytoma-like tumor: A case report and literature review. *J Neuropathol Exp Neurol* 77: 537-541, 2018.
16. Sciot R, Jacobs S, Calenbergh FV, Demaerel P, Wozniak A and Debiec-Rychter M: Primary myxoid mesenchymal tumour with intracranial location: Report of a case with a EWSR1-ATF1 fusion. *Histopathology* 72: 880-883, 2018.
17. Bale TA, Oviedo A, Kozakewich H, Giannini C, Davinemi PK, Ligon K and Alexandrescu S: Intracranial myxoid mesenchymal tumors with EWSR1-CREB family gene fusions: Myxoid variant of angiomatoid fibrous histiocytoma or novel entity? *Brain Pathol* 28: 183-191, 2018.
18. Ghanbari N, Lam A, Wycoco V and Lee G: Intracranial myxoid variant of angiomatoid fibrous histiocytoma: A case report and literature review. *Cureus* 11: e4261, 2019.
19. Gunness VR, Munoz I, González-López P, Alshafai N, Mikalkova A and Spears J: Intracranial angiomatoid fibrous histiocytoma with Hodgkin lymphoma. *Med J Malaysia* 74: 234-236, 2019.
20. White MD, McDowell MM, Pearce TM, Bukowinski AJ and Greene S: Intracranial Myxoid mesenchymal tumor with rare EWSR1-CREM translocation. *Pediatr Neurosurg* 54: 347-353, 2019.
21. Ballester LY, Meis JM, Lazar AJ, Prabhu SS, Hoang KB, Leeds NE and Fuller GN: Intracranial myxoid mesenchymal tumor with EWSR1-ATF1 Fusion. *J Neuropathol Exp Neurol* 79: 347-351, 2020.
22. Komatsu M, Yoshida A, Tanaka K, Matsuo K, Sasayama T, Kojita Y, Kanda T, Kodama Y, Itoh T and Hirose T: Intracranial myxoid mesenchymal tumor with EWSR1-CREB1 gene fusion: A case report and literature review. *Brain Tumor Pathol* 37: 76-80, 2020.
23. Spatz M, Nussbaum ES, Lyons L, Greenberg S, Kallmes KM and Nussbaum LA: Primary intracranial angiomatoid fibrous histiocytoma: A case report and literature review. *Br J Neurosurg*: Mar 15, 2018 (Epub ahead of print). doi: 10.1080/02688697.2018.1451823.
24. Antonescu CR, Dal Cin P, Nafa K, Teot LA, Surti U, Fletcher CD and Ladanyi M: EWSR1-CREB1 is the predominant gene fusion in angiomatoid fibrous histiocytoma. *Genes Chromosomes Cancer* 46: 1051-1060, 2007.
25. Thway K and Fisher C: Angiomatoid fibrous histiocytoma: The current status of pathology and genetics. *Arch Pathol Lab Med* 139: 674-682, 2015.
26. Ogden S, Harave S, McPartland J, Brennan B, Jeys L, Losty P and Pizer B: Angiomatoid fibrous histiocytoma: A case of local recurrence and metastases to loco-regional lymph nodes that responded to chemotherapy. *Pediatr Blood Cancer*: 64, 2017 doi: 10.1002/pbc.26376.
27. Bernini JC, Fort DW, Pritchard M, Rogers BB and Winick NJ: Adjuvant chemotherapy for treatment of unresectable and metastatic angiomatoid malignant fibrous histiocytoma. *Cancer* 74: 962-964, 1994.



This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.