Intracranial angiomatoid fibrous histiocytoma with EWSR1-CREB family fusions

DOI:

[10.1016/j.wneu.2019.02.107](https://doi.org/10.1016/j.wneu.2019.02.107)

Document Version

Accepted author manuscript

[Link to publication record in Manchester Research Explorer](#)

Citation for published version (APA):

Konstantinidis, A., Cheesman, E., O'Sullivan, J., Pavaine, J., Avula, S., Pizer, B., & Kilday, J. P. (2019). Intracranial angiomatoid fibrous histiocytoma with EWSR1-CREB family fusions: a report of two pediatric cases. *World Neurosurgery*. <https://doi.org/10.1016/j.wneu.2019.02.107>

Published in:

World Neurosurgery

Citing this paper

Please note that where the full-text provided on Manchester Research Explorer is the Author Accepted Manuscript or Proof version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version.

General rights

Copyright and moral rights for the publications made accessible in the Research Explorer are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

Takedown policy

If you believe that this document breaches copyright please refer to the University of Manchester's Takedown Procedures [<http://man.ac.uk/04Y6Bo>] or contact uml.scholarlycommunications@manchester.ac.uk providing relevant details, so we can investigate your claim.

Accepted Manuscript

Intracranial angiomatoid fibrous histiocytoma with *EWSR1-CREB* family fusions: a report of two pediatric cases

A. Konstantinidis, E. Cheesman, J. O'Sullivan, J. Pavaine, S. Avula, B. Pizer, J.P. Kilday

PII: S1878-8750(19)30518-2

DOI: <https://doi.org/10.1016/j.wneu.2019.02.107>

Reference: WNEU 11580

To appear in: *World Neurosurgery*

Received Date: 9 November 2018

Revised Date: 10 February 2019

Accepted Date: 10 February 2019

Please cite this article as: Konstantinidis A, Cheesman E, O'Sullivan J, Pavaine J, Avula S, Pizer B, Kilday J, Intracranial angiomatoid fibrous histiocytoma with *EWSR1-CREB* family fusions: a report of two pediatric cases, *World Neurosurgery* (2019), doi: <https://doi.org/10.1016/j.wneu.2019.02.107>.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Title:

Intracranial angiomatoid fibrous histiocytoma with *EWSR1-CREB* family fusions: a report of two pediatric cases

Authors:

A Konstantinidis^a, E Cheesman^{b, c}, J O'Sullivan^{d, e}, J Pavaine^{f, g}, S Avula^h, Pizer Bⁱ, JP Kilday^{a, b}

Author Academic Degrees

Dr. Konstantinidis = MBChB
Dr. Cheesman = MBChB, MRCPATH
Dr. O'Sullivan = BSc
Dr. Pavaine = MD, EDiNR, EDiPNR
Dr. Avula = FRCP, MRCPCH, MBBS
Prof. Pizer = MBChB, FRCPCH, PhD
Dr. Kilday = MBChB, MRCPCH, PhD

Affiliations:

- a. Department of Haematology/Oncology, Royal Manchester Children's Hospital, Oxford Road, Manchester, England, UK. M13 9WL
- b. Children's Brain Tumour Research Network (CBTRN), Royal Manchester Children's Hospital, Oxford Road, Manchester, England, UK; The Centre for Paediatric, Teenage and Young Adult Cancer, Division of Cancer Sciences, The University of Manchester, England, UK
- c. Department of Histopathology, Royal Manchester Children's Hospital, Oxford Road, Manchester, England, UK. M13 9WL
- d. Division of Evolution and Genomic Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, M13 9PL, Manchester, UK.
- e. Manchester Centre for Genomic Medicine, St. Mary's Hospital, Manchester University Foundation NHS Trust, Health Innovation Manchester, M13 9WL, Manchester, UK.

- f. Academic Unit of Paediatric Radiology, Royal Manchester Children's Hospital, Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Sciences Centre, Manchester, UK.
- g. Division of Informatics, Imaging & Data Sciences, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK
- h. Department of Neuroradiology, Alder Hey Children's Hospital, Eaton Road, Liverpool, L12 2AP.
- i. Department of Haematology / Oncology, Alder Hey Children's Hospital, Eaton Road, Liverpool, L12 2AP.

Corresponding author:

Dr. John-Paul Kilday, Department of Haematology/Oncology, Royal Manchester Children's Hospital, Oxford Road, M13 9WL Manchester, England, UK. E-mail: John-Paul.Kilday@mft.nhs.uk.

Telephone: 0044 (0)161 7018418; Fax 0044 (0)161 701 8410

Short Running Title:

Pediatric intracranial angiomatoid fibrous histiocytoma

Conflict of Interest Statement:

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Key words:

Pediatric; intracranial; angiomatoid; fibrous; histiocytoma

Funding:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Abbreviation List

AFH	= angiomatoid fibrous histiocytomas
CPA	= cerebellopontine angle
FISH	= Fluorescence in situ hybridization
FFPE	= Fresh frozen paraffin embedded
GKS	= Gamma knife radiosurgery
GTR	= gross total resection
L	= left
LHS	= Rim of low signal intensity
MRI	= Magnetic Resonance Imaging
NOS	= not otherwise specified
NTR	= near total resection
R	= right
RHS	= Rim of high signal intensity
RNA	= Ribonucleic acid
RT	= radiotherapy
RT-PCR	= Reverse Transcriptase Polymerase Chain Reaction

Abstract

Background

Intracranial angiomatoid fibrous histiocytomas (AFHs) are very rare tumors. Histologically, classical cases have been reported exclusively in adults with only myxoid variants identified in children. Here, we report the clinical presentation, treatment, biopsy and molecular test results for two children with classical intracranial AFH and combine this with a literature review of published intracranial AFH and AFH-like cases.

Case Description

Two pediatric females, presenting with abnormal neurological signs, were diagnosed with intracranial AFHs from histopathological analysis. No myxoid features were identified. Fluorescence in situ hybridization (FISH) and Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) testing demonstrated *EWS1-ATF1* and *EWS1-CREM* gene fusions respectively, verified by Sanger sequencing. Both patients underwent surgery only. The first child developed local recurrence five years from initial surgery. Following a further complete resection, this patient has remained recurrence-free over a subsequent six year follow-up period. The second patient has recently developed local multi-nodular recurrence 28 months after initial surgery and is awaiting surgical re-excision. No additional chemotherapy/radiotherapy has been administered to either patient.

Conclusions

This paper describes the first two cases of non-myxoid intracranial AFH in children; confirmed by molecular analysis. Our results suggest that a tumor spectrum incorporating classical and myxoid intracranial AFHs can occur in children and that gross total resection represents the treatment strategy of choice at diagnosis or following recurrence.

Introduction

First described almost 40 years ago ¹, angiomatoid fibrous histiocytomas (AFHs) are rare neoplasms with intermediate malignant potential, accounting for approximately 0.3% of soft tissue tumors ². They contribute to a diverse group of mesenchymal tumors biologically characterized by oncogenic fusions between the Ewing sarcoma breakpoint region1 gene (*EWSR1*) and members of the cAMP response element binding (*CREB*) gene family, notably *ATF1*, *CREB1* and *CREM* ³. The predominant fusion reported in AFHs is *EWSR1-CREB1*. Histologically AFHs may demonstrate a morphological spectrum but representative features include a fibrous pseudocapsule, ovoid or pleomorphic cells, pseudoangiomatoid spaces and lymphoplasmocytic cuffing ^{4,5}.

AFHs usually involve the limb extremities of adolescents and young adults with a median age at presentation of 14 years ². The brain has represented a very rare primary site, with only five ‘typical’ AFH adult cases reported to date ^{4,6-9} (Table 1). In the past two years, intracranial AFH-like tumors have been reported in both children and adults, characterized by increased vascularity, epithelioid cells and a prominent myxoid background ¹⁰⁻¹³. These myxoid lesions harbor novel *EWSR* – *CREB* family fusions (e.g. *EWSR1* – *CREM*) not identified in the aforementioned adult intracranial AFH cases, questioning whether they represent either a myxoid AFH variant or a novel tumor entity entirely.

We enhance knowledge of this tumor group further by reporting the first two pediatric cases of typical intracerebral AFH, confirmed by biological analysis, including one harboring the novel *EWS1* – *CREM* fusion previously associated only with the myxoid tumor variant. We discuss the management and prognostic implications of intracranial AFH and present a literature review of all published cases.

Case reports

Case 1

A 13-year-old girl presented with a three month history of intermittent frontal headaches. Examination at presentation identified horizontal nystagmus. Magnetic resonance Imaging (MRI) of the brain revealed an isolated, predominantly cystic, contrast-enhancing tumor in the right frontal lobe with a solid tumor nodule along its medial wall. Surrounding edema was detected with mild midline shift (Figure 1A / B). There was no evidence of metastatic disease.

The patient underwent craniotomy and macroscopic gross total tumor resection. Post-operatively, the patient made good recovery with no sequelae. Post-operative imaging (Figure 1C) demonstrated enhancement along the surgical margins which was thought to initially represent surgically induced enhancement of the dura.

Histological examination (Figure 2A – D) of the tumor confirmed a cystic lesion surrounded by a dense infiltrate of plasma cells and lymphocytes. Deep to this were nodular areas comprising sheets of ovoid cells with abundant eosinophilic cytoplasm and monomorphic nuclei. No myxoid features were evident. Immunohistochemistry revealed these cells were positive for Vimentin, CD99 and focally positive for desmin. Fluorescence-in situ hybridization demonstrated a *EWSR1-ATF1* gene fusion, which was confirmed by Sanger sequencing. Based on the composite findings, the diagnosis of intracerebral AFH was made.

Five years after the initial presentation, surveillance imaging detected a small enhancing nodule along the antero-inferior margin of the surgical cavity suggestive of tumor recurrence (Figure 1D). The patient underwent a second craniotomy with subsequent gross-total resection of the tumor. No adjuvant chemotherapy or radiotherapy was administered. Following this second resection, the patient has remained recurrence-free for six years with a good quality of life.

Case 2

A 12-year-old girl presented with a 4-month history of frontal headache and lower back pain. Other associated symptoms included blurred vision and intermittent vomiting. Neurological examination revealed a right pronator drift and expressive dysphasia. MRI evaluation of the neuraxis revealed an isolated homogeneously contrast-enhancing mass in the left frontal lobe with solid and cystic components incorporating a suspected hemorrhagic core (Figure 1; Case 2 A - D). There was significant mass effect with midline shift to the right. A subsequent full body MRI scan was negative. The patient underwent craniotomy, cyst fenestration and resection of a firm, dark purple tumor, with the surgical opinion of complete lesional excision. Following surgery, there was significant improvement in radiological appearances although the presence of small disease residuum could not be excluded (Figure 1; Case 2 E).

The histological examination of the lesion demonstrated a cystic lesion with a broad rim of tumor cells, with central necrosis (Figure 3A – D). The tumor was composed of sheets of large pleomorphic cells with abundant clear to eosinophilic cytoplasm and distinct cell membranes. The nuclei were relatively monomorphic, and mitotic activity was brisk. The tumor cells were strongly positive for CD99 and BCL2, and focally positive for desmin and EMA.

Targeted enrichment and sequencing was performed on RNA extracted from FFPE tumor tissue using the RecoverAll™ Total Nucleic Acid Isolation Kit for FFPE (Thermo Fisher Scientific, Waltham, MA, USA). Enrichment and library preparation was performed using the QIAseq Targeted RNAseq Human Oncology Panel kit (QIAGEN GmbH, Hilden, Germany) for Illumina, following the manufacturer's protocols. Sequencing was carried out on a NextSeq 500 sequencer (Illumina Inc, San Diego, CA, USA), following the manufacturer's protocols. A fusion between the EWS RNA binding protein 1 (*EWSR1*) and the cAMP responsive element modulator (*CREM*) was identified. Sanger sequencing of mRNA was used to confirm the fusion was between *EWSR1* NM_005243 exon 8 and *CREM* NM_001881 exon 3 (Figure 3E).

No adjuvant chemotherapy or radiotherapy was given to the patient. Other than known right-sided pre-operative optic atrophy, no other major neurological sequelae were noted in the post-operative period and the patient resumed normal activities at home and school where minor additional educational support was required. Despite being clinically well, recent surveillance imaging at 28 months following diagnosis has revealed an enhanced nodule of recurrent disease at the primary tumor site (Figure 1; Case 2F). Additional, less conspicuous nodules around the original resection site were also observed in other imaging planes. The patient is now awaiting second surgery with the objective again of achieving complete disease clearance.

Discussion

To our knowledge, these two cases represent the youngest patients reported with classical non-myxoid intracranial AFH. Both were confirmed by molecular analysis with one case demonstrating the novel *EWS1 – CREM1* fusion, hitherto only described in myxoid variant intracranial cases.

The typical histological appearance of AFH defines a predominantly cystic lesion with a central hemorrhagic/necrotic core¹⁴. Common features include a fibrous pseudo-capsule surrounded by a dense lymphoplasmocytic infiltrate, pseudoangiomatous spaces surrounded by tumor cells and a multi-nodular growth of histiocytoid syncytial cells^{1,4,5,14}. Immunohistochemically, there is positivity for mesenchymal sarcoma-specific markers such as desmin, CD99 and CD68^{15,16}. Histologically, our two intracranial AFH cases bear a closer morphological resemblance to this classical description also reported by others^{4,6-9} (Table 1), compared to the more recently defined myxoid variant (or potentially distinct myxoid entity), where increased vascularity, epithelioid cells and a prominent myxoid background are observed¹⁰⁻¹³. Both ‘classical’ and ‘myxoid’ AFHs described remain characterized molecularly by the presence of *EWSR1* fusions with either *ATF1*, *CREM* or *CREB1* partner genes.

This histological discrepancy between ‘classical’ and ‘myxoid’ groups may simply reflect the broad, subjective morphological spectrum that can be observed in AFH, underpinned by the lack of desmin

staining in 50% of cases¹¹, the absence of lymphoplasmocytic cuffing in approximately 20% of cases⁵, and contrasting reports of intralesional mitoses^{5,17}. In turn, this would imply the terms ‘classical’ and ‘myxoid’ are potentially misnomers, with all lesions instead belonging to a single nosocomial entity encompassing a histological spectrum of tumors sharing common *EWSR1* – *CREB* family fusions, irrespective of patient age. The molecular analysis of our patients’ tumors would support this, with Case 1 demonstrating the *EWSR1-ATF* fusion reported in classic and myxoid intracranial AFH, while Case 2 harbored the *EWSR1* – *CREM* fusion only ever observed in myxoid variant AFH.

Magnetic resonance imaging (MRI) remains the preferred imaging modality for diagnosis and follow-up. In keeping with previous extracranial AFH studies, our intracerebral cases support the findings of a mixed cystic/nodular lesion, hypointense on T1-weighted sequences^{18,19}. In both of our cases the tumors appear intra-axial but, as reported in other cases, the lesions are indeed extra-axial in origin⁹. A dural tail sign was identified in one of our cases (Case 1), a radiological feature observed in intracranial AFHs that can result in the misdiagnosis of alternative extra-axial lesions including meningiomas, schwannomas or meningeal hemangiopericytoma^{6,9}. Additional MRI findings can include the presence a fluid-fluid level and peritumoral edema^{18,19}. However, these signs lack specificity and can also be identified in association with other intracranial mass lesions e.g. cavernous malformations complicated by hemorrhage, rendering them supplementary rather than diagnostic.

Obtaining the correct diagnosis and therapy is important since AFHs are of intermediate malignant potential with published data suggesting local recurrence rates can occur in up to 15% of cases⁵. While long term follow-up data for affected patients with intracranial AFH is sparse, our cases and subsequent literature review would suggest that attempted gross total resection should represent the mainstay of treatment for disease control both at presentation and any subsequent recurrence should it occur. Indeed, our first case remains alive without disease 11 years following diagnosis, having had two tumor resections at both diagnosis and five years later at relapse. Our second case remains alive but has now developed local, multi-nodular recurrence just beyond two years from her initial diagnosis. She is awaiting repeat surgery, again with the objective of achieving complete tumor

removal. There appears no role for chemotherapy or radiotherapy from the little data that exists on review, as tumor relapse occurred in the two cases that have used these adjuvant therapies upfront. Nevertheless, given the paucity of data, it is likely that such adjuvant therapy would be considered if surgical excision proves unsuccessful or is deemed futile or deleterious to the patient.

Conclusion

We present two children with histologically classical non-myxoid intracranial AFH, tumors only previously described in adults. Both were confirmed by molecular analysis. One child's tumor harbored the *EWS1 – CREM1* fusion, hitherto exclusive to myxoid variant AFHs. Our cases and subsequent literature review suggest classical and myxoid-variant intracranial AFH may belong to an as yet unnamed lesional entity encompassing a histological spectrum of tumors that share *EWSR1 – CREB* family fusions. Our findings also support gross total tumor resection as the mainstay treatment at presentation or following recurrence.

Figure Legends:**Figure 1**

Case 1: Pre-operative axial T2 (Case 1 A) and post-contrast sagittal T1 (Case 1 B) MRI views demonstrate a 6 x 7cm predominantly cystic abnormality in the right frontal lobe with a peripheral solid nodule along its medial wall. There is enhancement of the margin and the solid component. There is evidence of a dural tail (white arrow; 1B). Edema in the surrounding brain parenchyma is evident with compression of the surrounding structures and mild midline shift. Post-operative, post contrast T1 axial imaging (Case 1 C) suggests complete resection of the tumor. Minimal linear enhancement along the surgical margins that was initially thought to represent surgically induced dural enhancement. However, follow-up axial imaging (Case 1 D) demonstrates a small enhancing nodule along the antero-inferior margin of the surgical cavity indicative of tumor recurrence (white arrow). This was resected and confirmed to be tumor.

Case 2: Pre-operative, axial T2 and post-contrast, axial T1 MRI brain views (Case 2 A and B respectively). A large 5 x 6cm, relatively well-demarcated lesion with solid and cystic components is seen in the left frontal lobe. Surrounding vasogenic edema results in midline shift to the right. The T2 image demonstrates an intralesional low-signal center, indicative of intrinsic hemorrhage, supported by histological appearances post resection (Figure 3). Axial diffusion weighted imaging (DWI; Case 2 C) and apparent diffusion coefficient imaging (ADC; Case 2 D) reveal that the most of the anterior solid and posterior cystic components of the lesion did not demonstrate diffusion restriction but an anterior, irregular ring of contrast-enhanced tumor tissue did show nodular diffusion restriction. The post-operative post-contrast T1 coronal view (Case 2 E) reveals improvement albeit the midline has not been re-approximated. Observed peri-resection increased signal change is in keeping with possible disease residuum. Follow-up post-contrast coronal imaging, two years following diagnosis, (Case 2 F) reveals an enhanced nodule of recurrent disease at the primary tumor site. Additional, less conspicuous nodules around the original resection site were also observed in other planes (not shown). The patient is now awaiting second surgery.

Figure 2:

Case 1: A – 10 x magnification – histological appearances were that of a cystic lesion in which the wall is composed of plasma cells and lymphocytes, with lymphoid follicle formation. No myxoid appearances were noted. Higher magnification (B – 40 magnification) revealed a nodular lesion composed of cells with abundant clear or eosinophilic cytoplasm. The proliferative index was around 5%. Tumor cells were positive for CD99 (C) and desmin (D). Fluorescence-in situ hybridization identified a *EWSR1-ATF1* fusion (Vysis, USA), subsequently confirmed by Sanger sequencing (not shown).

Figure 3:

Case 2: A – macroscopic appearances of the large, partly solid/cystic mass, measuring 4 x 5 x 3 centimeters and weighing 26 grams. On slicing, the cystic area contained blood clot. The solid areas were composed predominantly of relatively homogenous pale yellow, necrotic material with more viable, focal areas of myxoid-like tissue towards the periphery, forming a rim. B – 10 x magnification – The histology of the lesion was of a well-circumscribed, non-infiltrative lesion composed of sheets of large cells with abundant clear to eosinophilic cytoplasm with distinct cell membranes. As seen macroscopically, the tumor formed a rim surrounding a central area of hemorrhage and necrosis. There was focal chronic inflammation, but a prominent circumferential lymphoid infiltrate was not seen. The nuclei were round or elongated, and some contain a prominent nucleolus (C – 40 x magnification). Mitotic activity was brisk. Despite the suggestive macroscopic appearances, no myxoid features were noted in the lesion. Tumor cells were focally positive for desmin (D) and positive for CD99 (E). The proliferative index was approximately 15%. Targeted RNA sequencing of the lesion was performed (QIAGEN GmbH, Hilden, Germany; Illumina Inc, San Diego, CA, USA), identifying a fusion between the EWS RNA binding protein 1(*EWSR1*) and the cAMP responsive element modulator (*CREM*). Sanger sequencing of mRNA (F) was used to confirm the fusion was between *EWSR1* NM_005243 exon 8 and *CREM* NM_001881 exon 3.

References:

1. Enzinger FM. Angiomatoid malignant fibrous histiocytoma: a distinct fibrohistiocytic tumor of children and young adults simulating a vascular neoplasm. *Cancer*. 1979;44(6):2147-2157.
2. Huerter ME, Hammadeh R, Zhou Q, Riker AI. Recurrent angiomatoid fibrous histiocytoma: a case report and review of the literature. *Ochsner J*. 2014;14(3):441-444.
3. Paronetto MP. Ewing sarcoma protein: a key player in human cancer. *Int J Cell Biol*. 2013;2013:642853.
4. Dunham C, Hussong J, Seiff M, Pfeifer J, 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*. 2008;32(3):478-484.
5. Thway K, Fisher C. Angiomatoid fibrous histiocytoma: the current status of pathology and genetics. *Arch Pathol Lab Med*. 2015;139(5):674-682.
6. Alshareef MA, Almadidy Z, Baker T, Perry A, Welsh CT, Vandergrift WA, 3rd. Intracranial Angiomatoid Fibrous Histiocytoma: Case Report and Literature Review. *World Neurosurg*. 2016;96:403-409.
7. Hansen JM, Larsen VA, Scheie D, Perry A, Skjoth-Rasmussen J. Primary intracranial angiomatoid fibrous histiocytoma presenting with anaemia and migraine-like headaches and aura as early clinical features. *Cephalalgia*. 2015;35(14):1334-1336.
8. Ochalski PG, Edinger JT, Horowitz MB, et al. Intracranial angiomatoid fibrous histiocytoma presenting as recurrent multifocal intraparenchymal hemorrhage. *J Neurosurg*. 2010;112(5):978-982.
9. Spatz M, Nussbaum ES, Lyons L, Greenberg S, Kallmes KM, Nussbaum LA. Primary intracranial angiomatoid fibrous histiocytoma: a case report and literature review. *Br J Neurosurg*. 2018:1-3.
10. Bale TA, Oviedo A, Kozakewich H, et al. Intracranial myxoid mesenchymal tumors with EWSR1-CREB family gene fusions: myxoid variant of angiomatoid fibrous histiocytoma or novel entity? *Brain Pathol*. 2018;28(2):183-191.

11. Gareton A, Pierron G, Mokhtari K, et al. ESWR1-CREM Fusion in an Intracranial Myxoid Angiomatoid Fibrous Histiocytoma-Like Tumor: A Case Report and Literature Review. *J Neuropathol Exp Neurol*. 2018;77(7):537-541.
12. Kao YC, Sung YS, Zhang L, et al. EWSR1 Fusions With CREB Family Transcription Factors Define a Novel Myxoid Mesenchymal Tumor With Predilection for Intracranial Location. *Am J Surg Pathol*. 2017;41(4):482-490.
13. Sciôt R, Jacobs S, Calenbergh FV, Demaerel P, Wozniak A, Debiec-Rychter M. Primary myxoid mesenchymal tumour with intracranial location: report of a case with a EWSR1-ATF1 fusion. *Histopathology*. 2018;72(5):880-883.
14. Chen G, Folpe AL, Colby TV, et al. Angiomatoid fibrous histiocytoma: unusual sites and unusual morphology. *Mod Pathol*. 2011;24(12):1560-1570.
15. Marino-Enriquez A, Bovee JV. Molecular Pathogenesis and Diagnostic, Prognostic and Predictive Molecular Markers in Sarcoma. *Surg Pathol Clin*. 2016;9(3):457-473.
16. Parham DM. Immunohistochemical Markers of Soft Tissue Tumors: Pathologic Diagnosis, Genetic Contributions, and Therapeutic Options. *Anal Chem Insights*. 2015;10(Suppl 1):1-10.
17. Shi H, Li H, Zhen T, et al. Clinicopathological features of angiomatoid fibrous histiocytoma: a series of 21 cases with variant morphology. *Int J Clin Exp Pathol*. 2015;8(1):772-778.
18. Ajlan AM, Sayegh K, Powell T, et al. Angiomatoid fibrous histiocytoma: magnetic resonance imaging appearance in 2 cases. *J Comput Assist Tomogr*. 2010;34(5):791-794.
19. Li CS, Chan WP, Chen WT, et al. MRI of angiomatoid fibrous histiocytoma. *Skeletal Radiol*. 2004;33(10):604-608.

Table 1: Defined cases of primary classical intracranial AFH and myxoid, AFH variant tumors published in the literature

Study (year)	n	Patient Age	Patient gender	Location	Histopathology	Molecular fusion	Initial Therapy	Outcome
Present study (2018)	2	13 years 12 years	Female Female	R frontal lobe L frontal lobe	Classical AFH Classical AFH	<i>EWSR1-ATF1</i> <i>EWSR1-CREM</i>	Surgery (GTR) Surgery (NTR)	Relapse at 5 years – surgery GTR; ADF at 11 years total Relapse at 28 months – awaiting surgery
Bale <i>et al</i> (2018) ¹⁰	3	12 years 14 years 18 years	Male Female Male	Dural / cerebellum Intraventricular R frontal lobe	Myxoid AFH Myxoid AFH Myxoid AFH	<i>EWSR1-CREB1</i> <i>EWSR1-CREB1</i> <i>EWSR1-CREM</i>	Surgery (GTR) Surgery (GTR) Surgery (NOS)	Not available Not available Not available
Sciot <i>et al</i> (2018) ¹³	1	17 years	Female	L frontal lobe	Myxoid AFH	<i>EWSR1-ATF1</i>	Surgery (GTR)	Relapse at 20 months – surgery NTR and focal RT, followed by GTR for progression. ADF at 7 years total
Gareton <i>et al</i> (2018) ¹¹	1	19 years	Male	Dural (CPA) extending to cerebellum & extra-axial space	Myxoid AFH	<i>EWSR1-CREM</i>	Surgery (GTR) Chemotherapy Focal RT	Relapse at 10 years – GTR and focal repeat RT ADF at time of publication (approximately 10 years total)
Spatz <i>et al</i> (2018) ⁹	1	22 years	Female	R occipital lobe	Classical AFH	Not performed	Surgery x 2 (GTR)	No relapse. ADF at 3 months from diagnosis
Kao <i>et al</i> (2017) ¹²	4	12 years 15 years 20 years 23 years	Male Female Male Female	Frontal lobe Dural / extra-axial Frontal lobe Dural / extra-axial	Myxoid AFH Myxoid AFH Myxoid AFH Myxoid AFH	<i>EWSR1-ATF1</i> <i>EWSR1-CREM</i> <i>EWSR1-CREB1</i> <i>EWSR1-CREB1</i>	Not available Surgery (NOS) Not available Not available	Not available No relapse; ADF at 17 months from diagnosis Not available Not available
Alshareef <i>et al</i> (2016) ⁶	1	58 years	Female	CPA / middle cranial fossa	Classical AFH	<i>EWSR1</i> re-arrangement	Surgery (GTR)	No relapse; ADF at 3 months from diagnosis
Hansen <i>et al</i> (2015) ⁷	1	17 years	Female	Extra-axial / occipital lobes	Classical AFH	<i>EWSR1</i> re-arrangement	Surgery x 2 (GTR)	No relapse; ADF at 4 months from diagnosis
Ochalski <i>et al</i> (2010) ⁸	1	35 years	Male	L temporal lobe	Classical AFH	<i>EWSR1</i> re-arrangement	Surgery x 8 GKS x 2	Relapse at 13 months. Suffered multiple recurrences and died of disease at 4 years + 1 month from diagnosis
Dunham <i>et al</i> (2008) ⁴	1	25 years	Male	L occipital lobe	Classical AFH	<i>EWSR1-ATF1</i>	Surgery (GTR)	No relapse but written at time of initial surgery. ADF at time of publication (immediate post-operative period)

Key: n = number of cases, ADF = alive and disease free, R = right, L = left, GTR = gross total resection, NTR = near total resection, CPA = cerebellopontine angle, RT = radiotherapy, GKS = Gamma Knife Radiosurgery, NOS = not otherwise specified.

Case 1

Case 2