Case Report

Cranial angiomatoid fibrous histiocytoma: A case report and review of literature

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ABSTRACT

Background: Angiomatoid fibrous histiocytoma (AFH) is a rare low-grade soft-tissue tumor that typically arises from the deep dermal and subcutaneous tissue of the extremities in children and young adults. Intracranial AFH is exceedingly rare, and only four cases of primary AFH tumors have been reported to date.

Case Description: A 43-year-old male presented to our hospital with headaches, vision changes, and a known brain tumor suspected to be an atypical meningioma. After undergoing craniotomy for resection of the mass, the immunomorphologic features of the resected tumor showed typical features of AFH with ESWR1 (exon7) – ATF1 (exon 5) fusion.

Conclusion: AFH is a difficult tumor to diagnose with imaging and histologic studies. Thus, further knowledge is necessary – particularly of intracranial cases – to aid clinicians in its diagnosis and management.

Keywords: Angiomatoid fibrous histiocytoma, Craniotomy, Meningioma, Neuro-oncology

INTRODUCTION

Angiomatoid fibrous histiocytoma (AFH) is a rare, slow-growing, and low-grade soft-tissue tumor that typically arises from deep dermal and subcutaneous tissue of the extremities in children and young adults. The majority of these tumors present in the first three decades of life and account for 0.3% of all soft-tissue tumors. Intracranial AFH is rare, and currently, there are only four reports of primary intracranial AFH in the literature [Table 1].[3,7,10,11] These primary lesions are often misdiagnosed on imaging as atypical meningiomas or cavernous malformations, but a definitive diagnosis can be made through biopsy.[3] Extracranial AFH metastasizes in <1% of cases and generally follows an excellent overall clinical course with a recurrence rate of 15%.[5] Because these lesions rarely metastasize, the treatment of choice is excision with wide margins.

CASE DESCRIPTION

Patient case

A 43-year-old right-handed male with no significant medical history presented to our facility complaining of intermittent left-sided headaches associated with blurry vision in the right eye and

episodes of transient word finding difficulty for 1 year. The patient stated that he had lived in Saudi Arabia, where he was seen by a neurosurgeon who ordered a magnetic resonance imaging (MRI) of the brain which, as per the clinicians notes, showed an "atypical meningioma;" however, no images or official reports were available. The patient was started on levetiracetam 500 mg BID. He continued having headaches with no further episodes of blurry vision. Consequently, the patient presented to our emergency department for a second opinion. On physical examination, the patient was neurologically intact with no deficits. Computed tomography (CT) of the brain showed multiple ring-shaped lesions with significant perilesional vasogenic edema suspicious for abscesses or necrotic masses. The patient endorsed a 20 lb weight loss due to decreased appetite over the past year. Blood work revealed hemoglobin (Hb) of 10.8 g/dL as well as an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and prothrombin time.

The patient was admitted, and MRI of the brain showed an isointense T1 and hyper-intense T2 avidly enhancing extra-axial mass near the posterior edge of the tentorium cerebelli on the left side extending superiorly and inferiorly to the tentorium [Figure 1]. Multiple small cystic foci were
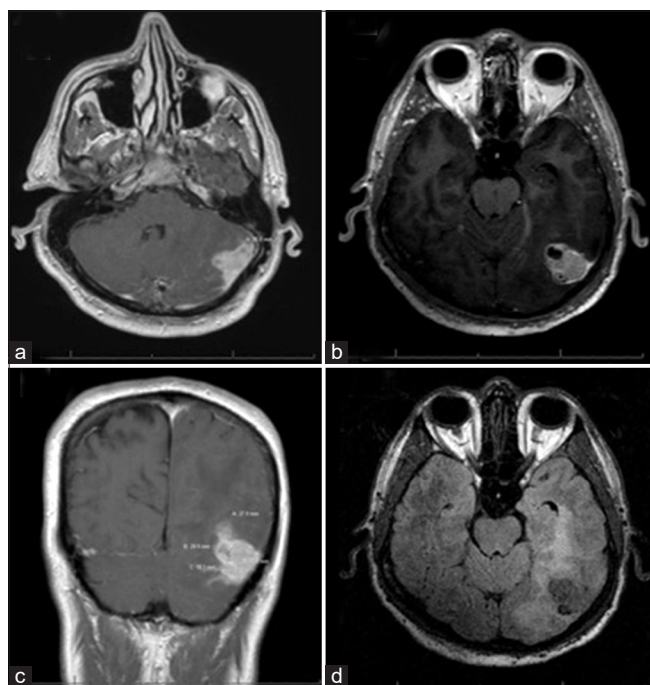

Figure 1: (a-d) Cranial angiomatoid fibrous histiocytoma. (a) T1 axial head magnetic resonance imaging (MRI). Homogeneously hypointense infratentorial 25.0 mm lesion; (b) T2 postcontrast MRI of the brain. Multilobulated enhancing mass at the lateral aspect of the tentorium on the left; (c) T1 coronal MRI of the brain. Homogenous lesion extending above and below the tentorium, possible occlusion of the transverse sinus as it is not visualized; (d) Axial FLAIR MRI of the brain.

visualized within the mass, and a large amount of vasogenic edema above and below the tentorium with mass effect and mild midline shift of the third ventricle to the right was appreciated. A CT angiogram of the brain was also performed showing obliteration of the left transverse sinus likely from the extra-axial mass extending on both sides of the left tentorium cerebelli. The patient was discharged a day later to follow-up in clinic to discuss surgical resection and was continued on levetiracetam 500 mg BID.

One month later, the patient underwent a left occipital and suboccipital craniotomy for resection of the mass. Using the navigation, two separate craniotomies were made, one above the transverse sinus and one below. The supratentorial opening demonstrated an obvious tumor that was adherent to the sinus. Although preoperative imaging suggested sinus occlusion, care was taken to not violate or injure the sinus due to preserved turgor suggesting continued flow. The supratentorial portion was 95% debulked with a small amount of residual abnormal tissue not resected due to firm adherence to the surrounding parenchyma and a large neighboring vein. The second craniotomy was opened infratentorially, and the tumor was resected between the supra and infratentorial compartments along the transverse sinus. Postoperatively, the patient remained intact with improvement in his headaches and blurry vision at 6-week follow-up with MRI demonstrating significant debulking with a small possible residual tumor in operative bed. A multidisciplinary tumor board recommendation was for repeat MRI in 6 months [Figure 2].

Microscopic examination revealed a dural-based multinodular tumor with a fibrous capsule [Figure 3]. The fibrous capsule showed chronic lymphohistiocytic inflammation (B cells, T cells, plasma cells, and a few eosinophils) with hemosiderin deposition. The neoplastic cells had a histiocytoid morphology with significant mitotic activity (up to 8/10 HPF) and MIB-1 proliferation index of 20%. No vascular spaces or myxoid areas were seen. The neoplastic cells were immunoreactive to vimentin, desmin, and cytokeratins (cam 5.2 and AE1/AE3, respectively)
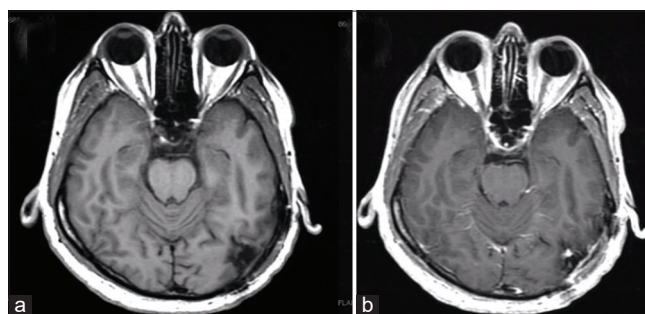

Figure 2: (a) Postoperative T1 precontrast magnetic resonance imaging and (b) T1 postcontrast MRI showing 95% debulking with a small focus of contrast enhancement anteriorly in operative bed suggesting possible residual tumor.

Table 1: Intracranial angiomatoid fibrous histiocytoma cases in medical literature with immunohistological features.

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S-100	+	N/A	-	+	-
CD68	+	+	-	+	N/A
EMA	+/-	N/A	N/A	+	+
Cytokeratin (CAM5.2)	-	N/A	N/A	+	+
Desmin	+	+	+	N/A	+
Vimentin	+	+	N/A	N/A	+
Mitoses	-	-	4/10 HPF	Ki67<1%	8/10 HPF
Lymphocyte Cuffing	+	+	+	+	+
Fibrous Capsule	+	+	+	+	+
	+	+	+	+	+
Rearrangement	EWS/ATF-1	Rearranged EWSR1	None	Rearranged EWSR1	EWSR1/AFT-1
Tumor Location	Left occipital lobe	Left temporal lobe	Parieto-occipital lobe	Right porous trigeminus	Left occipital and suboccipital lobe
Age/Sex	25, M	35, M	17, F	58, M	43, M
Reference	*Dunham et al.*, 2008	*Ochaleski et al.*,2010	*Hansen et al.*, 2015	*Alshareef et al.*, 2016	Current Case
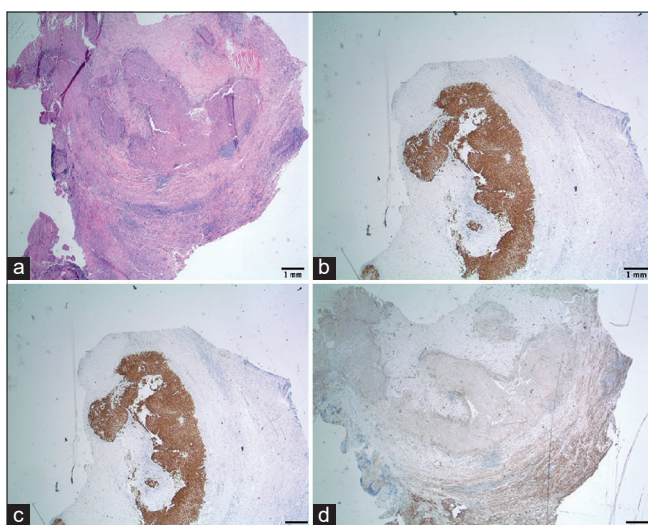
Figure 3: (a-d) Microscopic analysis of tumor specimen. (a) Pale histiocytoid tumor cells (lower half) with peripheral inflammatory response and hemosiderin deposition (hematoxylin and eosin), (b) and (c) the neoplastic cells are strongly and diffusely immunoreactive to desmin and Cam 5.2 (Immunoperoxidase), and (d) the neoplastic cells are negative for somatostatin receptor 2A.

and epithelial membrane antigen (EMA). The neoplastic cells were negative for somatostatin receptor 2A, Stat 6, PR, CD163, CD20, Pax-5, CD3, CD138, MyoD-1, S-100, Myogenin, MyoD1, CD21, and ALK [Figure 3]. The expressions of INI-1 by the tumor nuclei were retained. Archer Multiplex Solid tumor panel showed an in-frame EWSR1 (ex 7) – ATF1 (exon 5) fusion with breakpoints at chr 22:29683123 and chr12:51207793.

DISCUSSION

The first AFH diagnosis was made in 1979 by Enzinger; however, due to a growing number of reports, AFH is now characterized by the World Health Organization as a slow-growing tumor of uncertain differentiation with intermediate metastatic potential. These tumors range from 2 to 4 cm, but growth up to 10 cm has been reported.[8] Histologically, AFH is characterized as circumscribed, lobulated neoplasms composed of sheets of ovoid to spindle cells with a fibrous pseudocapsule, dense peripheral lymphoplasmacytic cuff, and blood-filled cystic cavities without an epithelial lining.[6,13,14] Due to secondary hemorrhage and inflammation, the rate of misdiagnosis is high. AFH lacks a specific immunophenotype, so immunohistochemical studies are not used to make the diagnosis; rather, they are used to support it. Although over half of AFH cases have desmin-positive cells with a dendritic morphology and it has been reported that there is a strong presence of hemosiderin-laden macrophages, these findings are also observed in other tumor types, and neither are specific for AFH.[5,11] The expression of EMA, CD99, CD68, smooth muscle actin, and calponin is also consistent, identifiable, yet nonspecific, features of AFH.[4]

Genetically, AFH is associated with three characteristic translocations: EWSR1-CREB1, EWSR1-ATF1, and FUS-ATF1.[12,16] The EWSR1-CREB1 fusion has been reported in 90% of cases, whereas the EWSR1-ATF1 fusion is more common in extrasomatic soft-tissue sites. The only other tumors with the known EWSR1-CREB1 and EWSR1-ATF1 translocations are clear cell sarcomas of soft tissues, osteoclast-rich tumors of the gastrointestinal tract, and hyalinizing clear cell carcinomas of the salivary gland.[5] Moreover, it has recently been reported by Ballester *et al.* that an intracranial myxoid mesenchymal tumor (IMMT) with EWSR1-CREB family gene fusion exists, which could represent a variant of AFH.[4] IMMT EWSR1-CREB lacks the characteristic morphologic features of AFH and has prominent myxoid changes, so it is uncertain whether this gene fusion is a variety of AFH or its own unique entity.[1,4]

Fluorescence *in situ* hybridization (FISH) and reverse transcription-polymerase chain reaction (RT-PCR) are useful in the diagnosis of AFH because they can detect characteristics that other methods miss. Thway *et al.* suggested that RT-PCR should be a first-line diagnostic tool due to its specificity for AFH and to use FISH as the second line to detect EWSR1 rearrangements in RT-PCR-negative cases that fit the criteria for AFH.[14] Proprietary multiplex PCR-based assays (like Archer® FusionPlex solid tumor panel) are increasingly being used in clinical practice to detect both known and novel fusions in solid tumors.

Intracranial AFH patients have reported symptoms of migraines, fatigue, vision changes, and seizures before the definitive diagnosis was made. In a report by Hansen *et al.*, a 17-year-old female patient suffered from migraines with auras and fatigue for 3 years until a change in her headaches prompted hospital referral and a subsequent MRI. The diagnosis of anemia and intracranial AFH was made, and after removal of the tumor, her headaches and anemia subsided.[10] In a case reported by Dunham *et al.*, a 25-year-old male presented with a 3–4 month history of headache and visual problems and two separate episodes of nausea and vomiting before a diagnosis of intracranial AFH.[7]

AFH patients often present with signs of uncontrolled IL-6 production, such as pyrexia, malaise, weight loss, anemia, elevated CRP, and night sweats.[15] One patient described by Villiger *et al.* presented with symptoms of uncontrolled IL-6, as well as an elevated CRP and ESR, and anemia.[15] The patient was started on tocilizumab, an IL-6 blocking agent, which resolved these symptoms.

Years after searching for the source of uncontrolled IL-6 production, it was discovered that what appeared to be a simple Baker's cyst in the knee was an AFH. The tocilizumab was stopped and after the tumor was removed, the patient's IL-6 related symptoms subsided.[15] Some authors suggest that the production of IL-6 or cytokines is an inherent property of the AFH tumor cells and is not related to the EWSR1-CREB1, EWSR1-AFT1, or FUS fusion variants.[9,2]

Our patient presented with headaches, vision changes, a 20-lb weight loss over 1 year, as well as anemia (Hb 10.8 g/dL), an elevated CRP of 5.7 (ref < 0.5 mg/dL), and an elevated ESR of 60 mm/h (ref < 15mm/h). One study suggests that these abnormal laboratory values are related to cytokine production by the tumor and parallel the disease course. This group studied a 17-year-old female with an upper extremity AFH who presented with, among other abnormal laboratory values, anemia, and an elevated CRP.[10] Because so few cases of AFH are reported, the correlation of lab values with the disease process is unclear. However, many of these abnormalities point to the paraneoplastic nature of this tumor.

Our tumor had most of the typical histopathologic features described in AFH, including multinodularity, fibrous capsule, peripheral inflammatory response, and hemosiderin deposition. Angiomatoid spaces or myxoid areas were absent. The immunoprofile was also typical except for the strong and diffuse immunoreactivity to cytokeratins. Although metastasis of AFH is rare, Costa *et al.* describe features of the tumor that may predict spread and recurrence. Irregular tumor borders, as well as tumors located on the head and neck, were associated with higher local recurrence rates, and the depth of the tumor was associated with a higher rate of subsequent metastasis.[6] Furthermore, other studies suggest that the levels of mitotic activity and atypia, genetic translocations, and immunohistochemical profiles were not correlated with the risk of recurrence.

As more cases are being reported in a variety of anatomical sites, the comparison can be made between tumors originating from somatic tissue and those originating outside somatic tissue. Chen *et al.* compared AFH tumors arising from various locations and found that the most significant differences between somatic and extrasomatic tumor origins are the age of the patients and the clinical outcomes.[5] The median age for patients with tumors arising outside somatic soft tissue was 35 years with only 26% of patients under age 20, whereas the median age for tumors originating from somatic soft tissue was 12–18 years with 80% of patients under age 20. Extrasomatic tumors tend to recur at a slightly higher rate of 33% compared with somatic tumors which recur at a rate of 11%. Lastly, tumors arising outside somatic soft-tissue display greater systemic inflammatory symptoms and are on average ~0.5 cm larger than their somatic tumor counterparts.[5]

AFH is difficult to diagnose for several reasons. Nodules of ovoid to spindle cells with blood-filled pseudoangiomatoid spaces and surrounding lymphoid cuff also present in other tumors. In addition, there is histological overlap with other lesions, lack of a specific immunophenotype, and increased occurrences in unusual extrasomatic sites.[14] The inflammation and hemorrhagic qualities of AFH can mimic other tumors. New fusions of unclear significance are being discovered and variants of AFH are still being classified. As more cases of intracranial AFH are reported, we can begin to recognize its patterns and pathognomonic features, which should lead to more expeditious diagnosis and treatment of this exceedingly rare condition.

CONCLUSION

AFH is a difficult tumor to diagnose with imaging and histologic studies. Thus further knowledge is necessary - particularly of intracranial cases - to aid clinicians in its diagnosis and management.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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