Intracranial angiomatoid fibrous histiocytoma presenting as recurrent multifocal intraparenchymal hemorrhage

Case report

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Angiomatoid fibrous histiocytoma (AFH) is a rare soft-tissue neoplasm that most commonly appears in the limbs, typically affecting children and young adults. The tumor has a propensity for local recurrence and recurrent hemorrhage but rarely for remote metastasis. To date, only 2 reports have documented an intracranial occurrence of the tumor (1 of which was believed to be metastatic disease). This is the second report of primary intracranial AFH. Additionally, hemorrhage from an intracranial AFH lesion has yet to be reported, and little is known about the radiographic characteristics and biological behavior of these lesions. In this report, the authors describe the case of a patient with recurrent hemorrhage due to primary multifocal intracranial AFH. Initially misdiagnosed as a cavernous malformation and then an unusual meningioma, the tumor was finally correctly identified when there was a large enough intact resection specimen to reveal the characteristic histological pattern. The diagnosis was confirmed using immunohistochemical and molecular studies. (DOI: 10.3171/2009.8.JNS081518)

KEY WORDS • angiomatoid fibrous histiocytoma • intracranial hemorrhage • sarcoma

First described by Enzinger4 in 1979, AFH is a rare soft-tissue sarcoma that infrequently recurs and rarely metastasizes. Clinically, the tumor most frequently arises within the subcutis or deep dermis of the extremities or trunk. Less commonly, it can develop in the head or neck regions. Usually, AFH affects adolescents or young adults in the 2nd or 3rd decade of life with most patients presenting with local tissue swelling or pain in the affected area. Constitutional symptoms such as fevers and nausea can occur in a minority of patients. Angiomatoid fibrous histiocytomas have been shown to have approximately a 1–5% rate of remote metastasis, warranting their classification as a low-grade malignant tumor.5 A wide local excision is the primary treatment modality, and a local recurrence rate of ~2–12% has been reported.1,3,5

Angiomatoid fibrous histiocytomas display characteristic microscopic and immunohistochemical features, allowing identification of this tumor type. Histologically, the tumor features sheets of histiocytoid cells admixed with organizing hemorrhage. Typically in an en bloc resection, these sheets of tumor cells and zones of hemorrhage are surrounded by a dense fibrous pseudocapsule with inflammatory cells. Because of the secondary hemorrhage and inflammation, the rate of misdiagnosis is high.5 Recently, genetic profiling has identified unique fusion genes thought to play an important role in sarcomagenesis of these tumors.1,7 These genetic markers can be used to help confirm the pathological diagnosis.

To date, there has been a single pathologically confirmed case of primary intracranial AFH.4 In addition, in a series of 108 patients diagnosed with AFH, one patient was presumed to have an intracranial metastasis; however, this was based on imaging findings alone.3 In the present report, the authors describe the second histologically confirmed case of multifocal intracranial AFH presenting with recurrent hemorrhages. In this particular case, the patient presented with multifocal recurrent hemorrhages. Although initially these tumors were misdiagnosed as cavernous malformations and then an unusual meningioma, the correct diagnosis was made after utilizing a combination of histological, immunohistochemical, and molecular features characteristic of AFH.

Case Report

First and Second Examinations. This 35-year-old

Abbreviations used in this paper: AFH = angiomatoid fibrous histiocytoma; FISH = fluorescence in situ hybridization.
man initially presented with progressively worsening headache that had developed over the preceding 2 weeks. On examination, he exhibited some mild right facial weakness but no other neurological deficits. A CT scan of the brain revealed an acute left posterior temporal intraparenchymal hemorrhage, measuring $4 \times 2 \times 4$ cm, with surrounding edema (Fig. 1A). Initial MR imaging showed a single $0.5 \times 0.5$–cm lesion, arising in the left mesial temporal area (Fig. 1B). On the T2-weighted images, we observed a thin rim of hypointensity consistent with hemosiderin surrounding the tumor capsule (Fig. 1C). Conventional angiography revealed no sign of vascular malformations or aneurysms (data not shown). In light of his stable clinical condition, the patient was managed

TABLE 1: Summary of surgical management and histopathological diagnosis*

<table>
<thead>
<tr>
<th>Procedure No.</th>
<th>Op Approach</th>
<th>Op Date</th>
<th>Follow-Up (mos)</th>
<th>Lesion Location</th>
<th>Pathological Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>lt temporal craniotomy</td>
<td>12/17/2004</td>
<td>0.8</td>
<td>lt pst temporal, lt sup cerebellum</td>
<td>neoplasm; organizing hematoma</td>
</tr>
<tr>
<td>2</td>
<td>lt retromastoid craniotomy</td>
<td>1/04/2006</td>
<td>13.4</td>
<td>lt sup cerebellum</td>
<td>proliferating meningothelium &amp; organizing hemorrhage</td>
</tr>
<tr>
<td>3</td>
<td>rt suboccipital craniotomy</td>
<td>9/21/2006</td>
<td>22</td>
<td>rt sup cerebellum</td>
<td>no specimen was analyzed</td>
</tr>
<tr>
<td>4</td>
<td>redo rt suboccipital craniotomy</td>
<td>2/08/2007</td>
<td>26.5</td>
<td>rt sup cerebellum</td>
<td>organizing granulation tissue</td>
</tr>
<tr>
<td>5</td>
<td>GKS</td>
<td>5/17/2007</td>
<td>29.8</td>
<td>lt pst temporal, lt sup cerebellum</td>
<td>NA</td>
</tr>
<tr>
<td>6</td>
<td>occipitoparietal craniotomy w/ Endoport</td>
<td>7/25/2007</td>
<td>32.1</td>
<td>lt pst temporal, lt sup cerebellum</td>
<td>AFH</td>
</tr>
<tr>
<td>7</td>
<td>redo lt retromastoid craniotomy</td>
<td>10/19/2007</td>
<td>34.9</td>
<td>lt sup cerebellum</td>
<td>AFH</td>
</tr>
<tr>
<td>8</td>
<td>redo lt temporal craniotomy w/ Endoport</td>
<td>8/4/2008</td>
<td>44.4</td>
<td>lt pst temporal, lt sup cerebellum</td>
<td>AFH</td>
</tr>
<tr>
<td>9</td>
<td>GKS</td>
<td>9/17/2007</td>
<td>45.8</td>
<td>lt pst temporal, rt sup cerebellum</td>
<td>NA</td>
</tr>
<tr>
<td>10</td>
<td>lt VP shunt</td>
<td>11/19/2008</td>
<td>47.9</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>11</td>
<td>redo lt retromastoid craniotomy</td>
<td>12/15/2008</td>
<td>48.8</td>
<td>lt sup cerebellum</td>
<td>dense fibrous tissue w/ chronic inflammation</td>
</tr>
</tbody>
</table>

* GKS = Gamma Knife surgery; NA = not applicable; pst = posterior; sup = superior; VP = ventriculoperitoneal.
conservatively and discharged with a working diagnosis of hemorrhage secondary to a cavernous malformation. He returned 2 weeks later with complaints of headache. Repeated imaging revealed enlargement of the previously documented hemorrhage and evidence that it extended through the tentorium into the left superior cerebellum.

**Initial Operation.** The patient underwent a left temporal craniotomy, and the hematoma was evacuated and the tumor debulked. Intraoperatively, we identified no major abnormal vascular channels, but the lesion appeared to originate from the tentorium with some extension into the infratentorial compartment. A gross-total resection was attempted. Pathological analysis showed fragments of an organizing hematoma with entrapped foci of a low-grade neoplasm composed of bland, round-to-oval nuclei with focal areas of moderate pleomorphism and a proliferative index of ~10%. Based on vimentin and weak, focal epithelial membrane antigen immunoreactivity, a tentative diagnosis of possible meningioma was made.

**Additional Operations.** Over a 49-month period, the patient experienced multiple intracranial recurrences. Tumor growth was identified within the left mesial temporal lobe as well as within the right cerebellopontine angle. A metastatic workup, including serial craniospinal MR imaging and whole-body CT scanning, did not reveal any evidence of tumor elsewhere. Furthermore, a number of hemorrhagic events associated with tumor growth were observed during this time. The recurrent hemorrhages were the result of residual tumor growth and de novo intratumoral bleeding. In total, the patient underwent a total of 8 open craniotomies for emergency clot evacuation and/or elective tumor debulking (Table 1). The patient also underwent 2 radiosurgical ablations in an attempt to gain local disease control and limit the need for additional open surgery. Despite these attempts, the patient died of progressive hydrocephalus due to recurrent hemorrhage after 49 months of clinical follow-up. What follows is an expanded discussion on the radiographic and histological characteristics of the tumor.

**Imaging Findings.** Imaging characteristics have not been previously described for intracranial AFH due to the paucity of reports. Using serial MR imaging, we characterized AFH imaging features (Fig. 2).

On precontrast T1-weighted MR imaging, AFH displayed loculations of T1 signal shortening that appeared isointense or slightly hyperintense compared with normal gray matter. Postcontrast T1-weighted imaging delineated aspects of the tumor capsule, but this modality has limited use when assessing recurrence (Fig. 2A and B); however, with tumor growth the enhancement did become more prominent (Fig. 2B inset). A characteristic MR feature of AFH, in our case, was the presence of a bubbly appearing mass on T2-weighted imaging (Figs. 2C and 3C) surrounded by a thin rim of hypointensity better seen on gradient echo scans and resulting from extracellular methemoglobin and hemosiderin.

**Histological, Immunohistochemical, and Genetic Findings.** Despite multiple open microsurgical evacuations and resections, a confirmatory diagnosis of AFH was not established until the sixth operation. The pathological diagnosis of AFH was made using combined data from histological sections, immunohistochemical stains, and the identification of a rearranged ESR1 gene investigated using FISH). Histologically, the classic features of AFH were not present collectively in the first several resection specimens because of the fragmented nature of the specimens. Each specimen showed predominantly organizing hemorrhage and glial scar with small foci of probable tumor. The later resection specimens did exhibit classic histological features of AFH including the following: 1) the presence of a fibrous pseudocapsule; 2) cellular foci of pleomorphic, hyperchromatic, histiocytoid cells; 3) focal areas of hemorrhage and pseudovascular, blood-filled spaces lacking an endothelial lining; and 4) a lymphohistiocytic inflammatory cuff surrounding the lesion (Fig. 3A and B). Furthermore, extensive hemosiderin and hematoidin pigment deposition was present with numer-
ous pigment-laden macrophages, which is also characteristic of AFH.

Immunohistochemical stains demonstrated strong, diffuse vimentin positivity in the cellular areas indicating a mesenchymal origin. The tumor was strongly desmin positive, as is seen in nearly 50% of AFH cases, suggesting myoid differentiation of the tumor. However, it was negative for most major skeletal muscle markers, including MYOD1, myoglobin, and myogenin. In the tumor cells, CD 68 was weakly positive, suggesting some degree of histiocytic differentiation (Fig. 3C–E).

**Discussion**

When it was first described in 1979, AFH was thought to be a histological subtype of malignant fibrous histiocytoma. The WHO subsequently reclassified AFHs as a distinct clinicopathological entity, a type of fibrous histiocytoma with an intermediate malignancy grade. However, due to the rarity of primary intracranial AFHs, the lesion was also not classified as a distinct pathological entity on the WHO 2007 CNS tumor list. Nevertheless, the diagnosis of AFH is made primarily by histological examination. Recent molecular studies have identified several chromosomal translocations that can be reproducibly seen in these lesions, thus aiding in the diagnosis. Two chromosomal translocations that were initially seen in AFHs are as follows: 1) fusion of ATF1 from chromosome 12q13 (a leucine-zipper transcription factor) with FUS from chromosome 16p11 (a TET family RNA binding protein); and 2) ATF1 to EWSR1 from 22q12 (also a TET family RNA binding protein). Additionally, Antonescu et al. identified a translocation between the EWSR1 gene and the CREBL1 gene and suggested that this fusion may be the most common in AFH. These translocations have been identified in several patients with AFH,
it should be noted that they are not entirely specific for this entity. The EWSR1/ATF1 fusion is also commonly seen in soft-tissue clear cell carcinomas, whereas the EWSR1/CREB1 fusion has also been described in clear cell sarcoma of the gastrointestinal tract.2 These findings suggest that the presence of the same translocation and fusion protein in 2 different precursor cells may explain the unique and varied phenotypes observed in AFH.

In our case, the tumor was subjected to FISH analysis with EWSR1 and FUS probes to access for possible EWSR1-ATF1, EWSR1-CREB1, and FUS-ATF1 translocations. The FUS Dual Color Break Apart probe showed no translocation in any of the 60 tumor cells analyzed. The EWSR1 Break Apart Rearrangement probe showed a complex pattern in 56 of the 60 cells involving the disruption of the EWS region and containing extra fusion signals. The remaining 4 cells exhibited a classic translocation pattern (Fig. 3F and G). Detection of this rearranged EWSR1 gene, in addition to the histological and immunohistochemical features, helped establish the diagnosis of AFH. Fresh tissue for RNA isolation would be necessary to definitively determine the exact fusion oncogene in this patient; these studies have not been performed to date.

Conclusions

We have reported the second case of primary multifocal intracranial AFH with recurrent hemorrhage. We discussed radiographic and histopathological findings as well as the clinical course and surgical management options to treat this unusual neoplasm. Although we suspect that more cases of intracranial AFH exist, classic histological features may not be seen in every resection specimen and a misdiagnosis of cavernous malformation may occur. Unfortunately, CT and MR imaging could not easily distinguish an AFH from a cavernous malformation. Similar to intracranial cavernous malformation, this AFH had a “popcorn” or “bubbly” appearance on T2-weighted imaging and often displayed a variable pattern of hemosiderin rim around the tumor. Therefore, an AFH was not considered and confirmatory molecular testing was not pursued, delaying the diagnosis. It follows, then, that without a high index of suspicion these lesions may be misdiagnosed. For this reason, correlation of the clinical, radiographic, and pathological features is essential to establish a timely definitive diagnosis. We recommend that the diagnosis of AFH be considered in cases of cavernous malformation in which the lesion recurs following resection. Furthermore, we recommend attempting a gross-total resection of the tumor, including its dural attachment, as this may reduce future hemorrhagic events.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

References