Meningeal angiosarcoma: a case report and review of the literature

Suqin Cai¹, Chunlin Wu¹, Sheng Zhang², Shanshan Cai¹, Xingfu Wang²

¹Department of Pathology, the Second Affiliated Hospital of Fujian Medical University, Quanzhou 362000, China; ²Department of Pathology, the First Affiliated Hospital of Fujian Medical University, Fuzhou 350005, China

Correspondence to: Xingfu Wang. Department of Pathology, the First Affiliated Hospital of Fujian Medical University, No. 20 Chazhong Road, Taijiang District, Fuzhou 350005, China. Email: wangxfu@fjmu.edu.cn; wangxfu@gmail.com.

Abstract: Primary angiosarcoma arising from the meninges is a rare form of malignant central nervous system (CNS) tumor. This study aimed to report the case of a 30-year-old female who presented with a 1-week history of worsening headache and numbness of the left limb. Neuroimaging revealed a broad based extra-axial mass occupying the right fronto-parietal area. The lesion showed a hypointense mixed intensity signal on T1 weighted image (WI) with flow voids, irregular necrotic areas, and peripheral enhancement on contrast, but a hyperintense mixed intensity signal on T2WI. Various histological patterns including sheets, small nests, cords, and sinus-like and primitive vessel-like structures were observed. Diffuse hemorrhage, necrosis, and cerebral parenchymal infiltration were also found in the tumor comprising spindle-shaped and epithelioid cells with marked atypia, abundant cytoplasm, and much of mitosis occurring. Tumor cells were positive for CD31, CD34, factor VIII (FVIII), FLI-1, CD117, ERG, and nestin. Furthermore, the MIB-1 labeling index was 10%. The patient underwent a total tumor resection with aggressive radiotherapy and chemotherapy, but had a tumor recurrence 5 months later. Compared with the previous one, the recurrent tumor from a second operation displayed almost the same morphological appearance and immune phenotype, with the MIB-1 labeling index rising up to 90%. Seven cases of meningeal angiosarcoma have been reported in the literature. A multidisciplinary treatment, such as a total tumor resection with radiotherapy or chemotherapy, is needed for primary angiosarcoma. The prognosis of patients with meningeal angiosarcoma remains poor considering the malignant nature of the tumor. It should be evaluated by more reported cases.

Keywords: Angiosarcoma; immunohistochemistry; meningeal sarcoma; pathology

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Introduction

Angiosarcoma is a malignant tumor that originates from vascular endothelial cells and mainly occurs in the head, face, liver, skin, and other soft tissues (1). However, primary angiosarcoma is extremely rare in the central nervous system (CNS). The epithelioid or spindle shaped tumor cells with pleomorphism show various “vasoformative” features (in cords or rudimentary, complex, anastomosing vascular channels). A primary angiosarcoma of CNS usually arises from the brain parenchyma, predominantly in the parietal lobe (2), and only a few arise from the meninges, as reported in the literature. This study reported a primary angiosarcoma arising from the meninges in an adult and reviewed relevant literature.

Case presentation

Clinical history and treatment

A 30-year-old woman was admitted to the neurosurgery department in October 2013. Without a history of head trauma or any other obvious causes, she complained of a week-long intermittent headache that worsened with the numbness of the left limb for 1 day. The neurological examination showed neck stiffness and positive Kernig’s sign. The general physical examination result was normal.
No history of hypertension, diabetes, and familial inherited disease was reported. She underwent a cesarean section 1 year ago with a good recovery after that.

A magnetic resonance imaging (MRI) scan of the brain revealed a well-demarcated mass that measured 3.5 cm × 3.0 cm × 2.0 cm in the right fronto-parietal area, next to the cerebral falx. A broad based extra-axial tumor with a positive dural tail sign showed a hypointense with dotted hyperintense signal on T1 weighted image (WI), which also revealed some irregular necrotic areas and flow voids with heterogeneous enhancement on contrast.

The T2WI revealed a hyperintense with dotted hypointense signal inside. A mixed intensity with multiple tortuous flow voids and an extensive edema belt of the peripheral brain parenchyma, which was pressed by the tumor, appeared on T2 fluid attenuation inversion recovery (Figure 1A,B,C).

During operation, a 3.5 cm × 3.0 cm × 2.0 cm lesion was found beside the longitudinal crack next to the cerebral falx. The tumor was highly vascular, fed by many arteries from the longitudinal crack and brain. The tumor was completely removed and subjected to a pathological examination. No obvious abnormal neurologic sign was found after surgery in this patient. After surgery, the patient was started on a 5-day inductive chemotherapy (temozolomide, TMZ, 240 mg per day) and then a cycle of radiotherapy (GTV-P65.8GY/28F). She underwent a consecutive 6-week concurrent radio-chemotherapy (TMZ 240 mg; GTV2-P58.8GY/28F) accompanied by a targeted drug bevacizumab (10 mg/kg), biweekly. Thereafter, the patient received TMZ (120 mg) and bevacizumab (10 mg/kg) biweekly, 4 times in total. Three months after the re-operation, showed multiple metastases in both lungs with bilateral pleural effusion. (Figure 1D,E,F).
after surgery, an MRI scan of the brain of the patient, who complained of recurrent headache and dizziness for a period of 2 months, revealed a bilateral intracranial space-occupying lesion located at the top of the frontoparietal section adjacent to the cerebral falx (Figure 1D). It was a recurrence of angiosarcoma confirmed by a second operation and the following pathological evaluation. The patient refused further radiotherapy and chemotherapy. Two months later, the patient returned with the chief complaint of headache for 3 days. Another MRI scan of the brain showed lesions similar to the previous ones (Figure 1E). The chest and back pain appeared 2 months later, and then a chest computed tomography (CT) scan revealed multiple pulmonary metastases with bilateral pleural effusion (Figure 1F). Palliative medications were given to the patient, but she finally was in a coma and passed away.

Pathological features
Grossly, the tumor nodule that measured 3.5 cm × 3.0 cm × 2.0 cm had soft texture with a crimson surface and cross-section. Microscopically, the tumor, covering the surface of the brain parenchyma, merged with the leptomeninges. Tumor cells showed various histological patterns such as sheets, nests, strips, blood sinus, and primitive vascular structures that were full of red blood cells and contained papillary structures inside the lumen that was lined by either spindle-shaped or epithelioid cells with marked atypia and unclear boundaries. The spindle-shaped tumor cells had fusiform and dark nuclei, whereas the epithelioid tumor cells had round or oval vesicular nuclei with basophilia, one to two small nucleoli, and shows 20 mitotic figures/10HPF. The tumor infiltrated the brain parenchyma with unclear boundaries, diffuse hemorrhage, and a large area of necrosis (Figure 2).

Immunohistochemical staining showed that the cells were positive for CD31 (Figure 3A), CD34, factor VIII (VIII), vimentin, FLI-1 (Figure 3B), CD117, Olig2, S-100, nestin (Figure 3C), and ERG (Figure 3D), but negative for synaptophysin (SYN), glial fibrillary acidic protein (GFAP),
D2-40, cytokeratin (CK), epithelial membrane antigen (EMA), progesterone receptor (PR), anaplastic lymphoma kinase (ALK), and CD30, desmin, and E-cadherin. The MIB-1 labeling index was 10%.

The pathological diagnosis was angiosarcoma.

Light gray tumor fragments (re-operation), which measured 6.0 cm × 6.0 cm × 2.0 cm, represented dark red soft tissue with hemorrhage and partly necrosis. the tumor had almost the same histopathology and immunophenotypes as the previous one, besides the extreme rise in the MIB-1 labeling index up to 90%.

The pathological diagnosis was angiosarcoma with massive necrosis.

Discussion

Primary intracranial angiosarcoma is a rare malignant tumor that occurs in each lobe of the brain, predominantly the parietal lobe, and is extremely rare in meninges. Approximately eight cases have been reported till date, including the one reported in this study. Of these cases, four cases were found in the brain, two in the spinal dura, another in the junction of pons and cerebellum, and the last one without clear position of the tumor (Table 1). These patients aged from 18 months to 60 years at diagnosis with a median age of 30 years, and included four males and two females with no gender information about the remaining two cases.

Clinical features

Primary angiosarcoma of CNS results in various neurological symptoms that depend on where the tumor appears and how fast it grows (2). Headache and vomiting, due to increasing intracranial pressure caused by the tumor, are the most common symptoms before a surgical resection of the tumor. If the nervous system is damaged by the tumor, corresponding neurological symptoms appear, such as seizures, numbness, and so forth.

Imaging studies can provide clues about meningeal angiosarcoma. MRI scans are characterized by irregular mixed intensity. T1WI reveals a heterogeneous hypointense signal with obvious hemorrhage, flow voids, and heterogeneous enhancement on contrast. Otherwise,
a heterogeneous hyperintense signal appears on T2WI. Although a dural tail sign can be seen in common meningeal tumors, including the meningeal angiosarcoma (3,4), all the aforementioned imaging characters can help distinguish it from other meningeal tumors.

**Origin and genetics**

The pathogenetic mechanism of angiosarcoma may be related to many vascular growth factors. Lots of studies suggested that vascular endothelial growth factor (VEGF) and its receptors can be overexpressed in angiosarcomas, especially highly concentrated VEGF-A with its receptors found in tissues of angiosarcoma (7). Lack of VEGFR-2 expression in tumor tissues could herald a worse prognosis (8). Angiosarcoma may also be associated with the abnormal expression of TP53 (7,9), Wilms’ tumor-1, and galectin-3 (10,11).

Studies have reported K-ras gene mutations in angiosarcoma of liver and cardiac tissue (12-14). Some researchers found that about 50% of angiosarcoma had positive C-kit gene expression, but showed no activating mutations on exon 11 (juxtamembrane domain) or 17 (tyrosine kinase domain) (15-17). Immunohistochemical analysis for CD117 was positive in this case. Common chromosomal abnormalities of angiosarcoma included trisomy 5; deletions on the short arm of chromosome 7; varied abnormalities on chromosomes 8, 20, and 22; and loss of chromosome Y (18).

**Pathological diagnosis**

Histopathologically, the primary diagnostic component is the presence of vasoformative structures in cords or rudimentary, complex, anastomosing vascular channels cords lined with epithelioid or fusiform tumor cells with marked atypia and hyperchromatic nuclei, in different sizes and shapes. The tumor cells display papillary patterns (4), blood sinus, or original blood vessels, which indicate well differentiation, whereas solid arrangement patterns suggest poor differentiation. In some cases, large areas of a tumor can be observed that are necrotic with neoplastic infiltration into the adjacent brain tissue. Immunohistochemistry tests reveal tumor cells strongly positive for some endothelial cell markers, such as CD31, CD34, and FVIII factor, but negative for GFAP and NeuN markers. In the last few years, FLI-1, with a high specificity, has had an important role in the diagnosis of angiosarcoma. Some other researchers found that angiosarcoma showed the positive expression of nestin, which increased with the grade of a tumor (19,20).

The diagnosis of angiosarcoma was mainly based on histologic features of vascular differentiation with definite cytologic pleomorphism and immunohistochemical characteristics. It needs to be differentiated from some other meningeal tumors such as malignant meningioma, melanomatous, or high-grade sarcomatoid

<table>
<thead>
<tr>
<th>Series</th>
<th>Sex</th>
<th>Age</th>
<th>Location</th>
<th>Therapy</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hackney et al. 2012</td>
<td>M; F</td>
<td>47; 35</td>
<td>Left sphenoid wing; the left retro-orbital infra-temporal</td>
<td>Partial surgical resection, chemotherapy, radiotherapy</td>
<td>Unknown; alive 18 months</td>
</tr>
<tr>
<td>Guode et al. 2008</td>
<td>F</td>
<td>16</td>
<td>Cerebellopontine angle</td>
<td>Total surgical resection</td>
<td>Alive 6 months</td>
</tr>
<tr>
<td>Mena et al. 1991</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Meninges</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Russell et al. 1989</td>
<td>Unknown; F</td>
<td>1.5; 6</td>
<td>The anterior cranial fossa dura; dorsal dura of the upper cervical and low brainstem</td>
<td>Unknown; unknown</td>
<td>Unknown; unknown</td>
</tr>
<tr>
<td>Kristoferitsch et al.</td>
<td>M</td>
<td>60</td>
<td>Thoracic spinal dura</td>
<td>Unknown</td>
<td>3 weeks</td>
</tr>
<tr>
<td>Present</td>
<td>F</td>
<td>30</td>
<td>Right frontal top</td>
<td>Total surgical resection, chemotherapy, radiotherapy</td>
<td>9 months</td>
</tr>
</tbody>
</table>

F, female; M, male.
patterns but without expressing CD31 and FVIII factor. The solitary fibrous tumor/hemangiopericytoma also featured the typical well-differentiated antler-shaped branching vessels with the uneven thickness of walls without expressing CD31 and FVIII factor. In gliosarcomas, mesenchymal and glial differentiation can be found, while it is absent in the case of angiosarcoma. Another important differential diagnosis includes metastatic angiosarcoma to the CNS that often has a history of primary tumors.

**Treatment and prognosis**

Primary treatment for angiosarcoma is surgical resection. An adjuvant radiotherapy or chemotherapy may yield some effects in a subset of patients when total resection of a tumor is hardly achieved. Temozolomide is effective for sarcoma (21), particularly as an option for CNS sarcomas because it can pass through the blood-brain barrier. Bevacizumab, as a VEGF inhibitor, has been used successfully in some recurrent glioblastomas (22). However, its effect on primary CNS angiosarcoma has not been reported. In most instances, combination chemotherapy has not been confirmed any more effective than single-agent therapy (21). Although radiation therapy is reported to be effective against angiosarcoma of the bone or metastatic cerebral angiosarcoma, findings on the effectiveness of radiotherapy against primary cerebral angiosarcomas are still controversial (5). Prognosis is poor considering the malignant nature of the tumor. In the series reported by Mena et al. (2), the median survival time in the five patients was 8 months, and the tumors were located in the cerebral hemispheres. Among the primary CNS angiosarcomas, primary meningeal angiosarcomas are even rarer. Only seven cases have been reported in the literature. The prognosis of the meningeal angiosarcoma is very poor.

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**Footnote**

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

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