Multifocal primary central nervous system angiosarcoma: illustrative case

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BACKGROUND Angiosarcoma is a malignant mesenchymal tumor derived from vascular endothelial cells in which a primary intracranial origin is extremely rare. Most previous reports of primary central nervous system (CNS) angiosarcoma have been solitary cases.

OBSERVATIONS The authors report a case of primary CNS angiosarcoma that caused the development of multiple disseminated cerebral hemorrhagic lesions within a short period of time. This rapid progression of symptoms resulted in the death of the patient. During surgery, several nodules suggestive of a tumor were removed from just below the surface of the brain, mixed into the hematoma. A pathological examination revealed atypical cells mimicking blood vessels in the subarachnoid space that were positive for specific vascular endothelial markers.

LESSONS In this case, multifocal angiosarcoma occurred on the brain surface and ventricles, suggesting cerebrospinal fluid dissemination. If multiple cerebral hemorrhages are found on the brain surface, multifocal angiosarcoma should also be considered.

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KEYWORDS primary central nervous system angiosarcoma; malignant mesenchymal tumor; subarachnoid space; nodule; dissemination

Angiosarcoma is a malignant mesenchymal tumor that originates from endothelial cells, with an overall prognosis that remains poor. Angiosarcoma arising in the head, neck, breast, liver, heart, bone, and spleen have been reported frequently.1 However, primary angiosarcoma of the central nervous system (CNS) is very rare, with only a few cases reported previously.2-10 Moreover, the majority of cases reported thus far have been sporadic. Angiosarcoma has a very poor prognosis, so early diagnosis and intervention are critical. Here, we report an extremely rare case of multifocal primary CNS angiosarcomas that were difficult to diagnose and treat.

Illustrative Case

A 72-year-old male presented to another hospital with progressive left hemiparesis. The patient had no history of cancer and no family history of the disease. Computed tomography (CT) performed at another hospital revealed multiple cerebral hemorrhages localized to the sulcus (Fig. 1A). Enhanced T1-weighted magnetic resonance imaging (MRI) revealed a nodular shadow in the hematoma with a slightly enhancing margin but no enhanced nodules, including nonbleeding lesions (Fig. 1B). A nodular lesion with hemorrhage was also observed on the surface of the ventricle (Fig. 1C). Gamma Knife surgery was performed on nine brain lesions at another hospital because multiple metastatic brain tumors were suspected. Subsequently, an excisional biopsy of the largest lesion in the right frontal lobe was performed. Nonetheless, no primary origin of the tumor was diagnosed, and the primary cancer site remained unknown when a whole-body examination was performed.

One and one-half months later, the patient was transferred to our hospital. The patient’s symptoms and diffusion-weighted imaging (DWI) findings were intractable and progressive (Fig. 1D). Whole-body enhanced CT was repeated at our hospital but again failed to identify a primary site of cancer origin. Whole-body 201thallium (201-Tl) scintigraphy was performed to search for the primary tumor and was negative.

A craniotomy for biopsy of a new lesion in the right occipital lobe was performed to avoid effects of Gamma Knife irradiation.

ABBREVIATIONS 201Tl = 201thallium; CNS = central nervous system; CT = computed tomography; DWI = diffusion-weighted imaging; FDG-PET = positron emission tomography with 18fluorodeoxyglucose; MRI = magnetic resonance imaging.

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Significant bleeding on the brain surface was observed with incision of the dura mater. Multiple feeders and elastic hard red nodules were identified on the cortical surface. Each nodule was removed (Fig. 2A). A histopathological examination demonstrated diffuse tumor cell proliferation within nodules. A tumor pathology mimicking that of a vascular structure was observed, suggesting malignant transformation of vascular endothelial cells (Fig. 2B). On one hand, tumor cells were positive for CD31 and specific vascular endothelial markers ERG (Fig. 2C) and S1PR1 (Fig. 2D). On the other hand, CD34 and D2-40 were negative. Tumor cells had spread into the subarachnoid space (Fig. 3). On the basis of the patient's clinical examination and histopathological findings, the tumor was diagnosed as angiosarcoma.

There is no evidence of the efficacy of standard chemotherapy for the treatment of CNS angiosarcoma. Therefore, whole-brain radiotherapy (30 Gy/10 fractions) in combination with steroids was administered. However, treatment efficacy was poor, and DWI MRI revealed an increase in the number of hemorrhagic tumors, including in the posterior cranial fossa (Fig. 1E and F), corresponding to disease progression. The performance status scores of the patient gradually declined, and he died 4 months after disease onset.

**Patient Informed Consent**

The necessary patient informed consent was obtained in this study.

**Discussion**

Angiosarcoma, a subtype of soft-tissue sarcoma, is an aggressive and malignant endothelial cell tumor of vascular or lymphatic origin. Angiosarcoma arises in the head and neck, breast, lung, liver, heart, bone, or spleen and tends to metastasize to other parts of the body. Metastatic angiosarcoma has a hematogenous mechanism, with many cases of brain metastasis reported. However, there have been few reports of cases of primary CNS angiosarcoma. Hoshiai et al. reported radiation therapy–induced angiosarcoma. Balamurali et al. reported Thorotrast-induced primary cerebral angiosarcoma.

However, other reports did not mention the cause of intracranial onset. Angiosarcoma is caused by chromosomal abnormalities in endothelial cells and environmental factors such as chronic lymphedema, trauma, radiation therapy, and chemical exposure. In our case, there was no family history and living history; therefore, the cause is unknown.

**Observations**

Intracerebral angiosarcoma is highly hemorrhagic, often presenting with intracranial hemorrhaging. Consequently, patients are at risk of rebleeding and recurrence. The tumor tends to present as a well-demarcated, heterogeneous, moderately to strongly enhancing lesion with vasogenic edema. Although few other cases have mentioned nodules, in our case, a nodule was found in the hematoma on enhanced T1-weighted imaging (Fig. 1B). Notably, a
Few prior case reports have revealed imaging findings indicative of nodules.2,4,7,15 Follow-up MRI revealed multiple hemorrhagic nodules (Fig. 1D–F), which may have comprised the metastatic dissemination of the angiosarcoma. Unfortunately, follow-up enhanced MRI was not possible because of the patient’s gadolinium allergy.

Cavernous hemangioma and metastatic brain tumor present imaging features very similar to intracranial angiosarcoma. Cavernous angioma appears as mixed hyperintense and hypointense signals on T1 and T2 sequences, surrounded by a rim of hypointense signals on the T2 sequence. Cavernous angioma was not identified on enhanced MRI, and the presence of peripheral edema was unclear. Similar to the present case, multiple cavernous angiomas have multiple, spotty, low-intensity lesions indicated on T2*-weighted images. However, there is a large difference between the pathologies of multiple cavernous angiomas and CNS angiosarcoma. Importantly, rebleeding in patients with multiple cavernous angiomas is slow, whereas rebleeding in primary CNS angiosarcoma progresses rapidly.2,4

Metastatic brain tumors that frequently cause intracranial hemorrhaging include choriorcinomas, thyroid cancers, melanomas, and renal cell carcinoma.16 Lung cancer can also cause hemorrhagic metastases. Metastatic brain tumors were first considered in our patient because they are both sporadic and multifocal and occur at a higher prevalence. The possibility of metastatic brain tumors prompted a repeat whole-body contrast-enhanced CT examination; however, no abnormal lesions in any organ were found. It is difficult to distinguish metastatic brain tumors from angiosarcoma in the early stages. Positron emission tomography with 18fluorodeoxyglucose (FDG-PET) is useful and highly sensitive for systemic screening of metastatic brain tumors, including angiosarcoma. On one hand, FDG-PET should have been performed in this case; however, the Japanese public healthcare system does not allow FDG-PET during hospitalization. On the other hand, whole-body 201Tl scintigraphy was performed to search for the primary tumor and was negative in this case.20 201Tl scintigraphy has been reported to be useful for systemic malignant tumor screening of mammary gland, thyroid, lung, lymph node, and bone and soft tissue tumors.17,18 Its sensitivity is reported to be 94%.18 201Tl scintigraphy is considered to be comparable to FDG-PET when used in combination with whole-body contrast-enhanced CT. Therefore, we diagnosed primary CNS angiosarcoma.

Metastatic CNS angiosarcoma is significantly more common than primary CNS angiosarcoma. Therefore, it is important to search for the primary origin of angiosarcoma throughout the body. However, much of the older literature does not describe extracranial examination. Those literatures may confuse primary CNS angiosarcoma with metastatic CNS angiosarcoma. We summarized the literature that clearly excluded extracranial angiosarcoma in the text and described extracranial examination methods in Table 1.2,5–10 (some not listed examination methods).

According to the World Health Organization classification (2020) of tumors (soft tissue and bone tumors), CD31 and ERG are typically positive in the diagnosis of angiosarcoma with high sensitivity and specificity. Similarly, S1PR1 has been reported to be a highly sensitive and useful marker for angiosarcoma.19

This is a very rare case of multifocal primary CNS angiosarcoma presenting with multiple dissemination on admission. There have been some reports of multiple metastatic intracranial angiosarcomas from other systemic organs.12,15 These metastatic lesions are usually located deep in the brain lobe.2,12 On one hand, hematogenous metastasis is considered to be the cause of metastatic angiosarcoma. On the other hand, solitary primary CNS angiosarcoma has been the only type reported previously, indicating that it may not undergo hematogenous metastasis. In our case, lesions were observed in the brain sulcus from an early stage. Therefore, lesions invaded the brain surface and intraventricular space. A histopathological examination of our patient revealed that the tumor cells were mainly distributed in the subarachnoid space. Thus, angiosarcoma first occurred in the subarachnoid vessels, not vessels of the cerebral
parenchyma. Subsequently, the disease was diffusely disseminated via the cerebrospinal fluid.

There is currently no effective therapy for primary CNS angiosarcoma. Resection is essential, with radio- and chemotherapy performed after surgery. Systemic angiosarcoma has been treated with doxorubicin and paclitaxel.\(^\text{10-20}\) Primary CNS angiosarcoma has not been effectively treated with chemotherapy. In contrast, there is a report of treatment using temozolomide and bevacizumab,\(^\text{3}\) which may be promising treatment options. Bevacizumab is undergoing phase II trials and has reported some efficacy and safety.\(^\text{21}\) However, clear evidence has yet to be established, and phase III trials are expected.

In conclusion, we report a case of multifocal primary CNS angiosarcoma that clearly excluded extracranial angiosarcoma. Therapy was not possible. Radiation therapy alone was administered, which was mostly ineffective. The prognosis of primary CNS angiosarcoma is very poor, with reviews suggesting that life expectancy ranges from several months to about 3 years.\(^\text{2,3,5-7}\) Prognosis may be worsened in patients with multiple cases, as was observed in our patient.

**Lessons**

In conclusion, we report a case of multifocal primary CNS angiosarcoma that was difficult to diagnose and treat. Angiosarcoma should be considered as a differential diagnosis when multiple hemorrhagic brain tumors are observed.

**References**


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**TABLE 1. Summary of case reports of primary CNS angiosarcoma that clearly excluded extracranial angiosarcoma**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs)/Sex</th>
<th>Location</th>
<th>Solitary/Multiple Hemorrhage</th>
<th>Therapy</th>
<th>Overall Survival</th>
<th>Extracranial Exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balamurali et al., 2009(^1)</td>
<td>68/M</td>
<td>Rt parietal lobe</td>
<td>Solitary</td>
<td>+</td>
<td>Surgery (biopsy)</td>
<td>12 mos</td>
</tr>
<tr>
<td>Baldovini et al., 2013(^2)</td>
<td>54/M</td>
<td>Septum pellucidum</td>
<td>Solitary</td>
<td>+</td>
<td>Surgery</td>
<td>2 mos</td>
</tr>
<tr>
<td>Hoshiai et al., 2015(^3)</td>
<td>65/M</td>
<td>Rt temporal lobe</td>
<td>Solitary</td>
<td>+</td>
<td>Surgery &amp; radiotherapy &amp; chemo</td>
<td>13 mos</td>
</tr>
<tr>
<td>La Corte et al., 2015(^4)</td>
<td>35/F</td>
<td>Lt frontal lobe</td>
<td>Solitary</td>
<td>+</td>
<td>Surgery &amp; radiotherapy &gt;37 mos &amp; chemo</td>
<td>FDG-PET, whole-body CT</td>
</tr>
<tr>
<td>Gao et al., 2019(^5)</td>
<td>68/M</td>
<td>Lt hemisphere</td>
<td>Multiple</td>
<td>+</td>
<td>Surgery</td>
<td>4 wks</td>
</tr>
<tr>
<td>Mhatre et al., 2021(^6)</td>
<td>25/M</td>
<td>Meninges (Lt parietal)</td>
<td>Solitary</td>
<td>–</td>
<td>Surgery &amp; radiotherapy &gt;4 mos</td>
<td>NL</td>
</tr>
<tr>
<td>Kuang et al., 2023(^7)</td>
<td>73/M</td>
<td>Meninges (rt occipital)</td>
<td>Solitary</td>
<td>+</td>
<td>Surgery &amp; radiotherapy</td>
<td>9 mos</td>
</tr>
<tr>
<td>Present case</td>
<td>72/M</td>
<td>Diffuse cerebrum &amp; ventricle</td>
<td>Multiple</td>
<td>+</td>
<td>Surgery &amp; radiotherapy</td>
<td>4 mos</td>
</tr>
</tbody>
</table>

chemo = chemotherapy; NL = not listed; US = ultrasound examination; + = yes; – = no.


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

**Author Contributions**
Conception and design: Hirai, Tao. Acquisition of data: Hirai, Tao, Nishimura, Nakazaki. Analysis and interpretation of data: Hirai, Tao. Drafting the article: Hirai, Nishimura. Critically revising the article: Nishimura. Reviewed submitted version of manuscript: Hirai, Tao, Nishimura. Approved the final version of the manuscript on behalf of all authors: Hirai. Administrative/technical/material support: Hirai, Nishimura. Study supervision: Hirai, Uno.

**Supplemental Information**
**Previous Presentations**
This work was previously presented as an oral presentation at the Japanese Neurosurgical Society Chugoku-Shikoku Branch Scientific Meeting in Ehime, Japan, on April 3, 2022.

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