



Case Report

Therapeutic options for primary meningeal angiosarcoma: A case report

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ABSTRACT

Background: Primary angiosarcoma (AS) of the central nervous system (PACNS) is an extremely rare malignancy. The meninges represent an uncommon site of origin of PACNS. This report describes a recurrent meningeal PACNS treated with surgery, radiotherapy, stereotactic radiosurgery, and paclitaxel at different stages of the disease.

Case Description: A 36-year-old Asian male presented to our facility with a 4-month history of worsening headaches and complete right homonymous hemianopia. Neuroimaging revealed a left occipital lobe hematoma with an underlying left tentorial tumor. After subtotal resection, neuropathological examination revealed features of a malignant endothelial cell AS. He received a course of adjuvant radiation therapy but experienced disease progression. He subsequently received additional stereotactic radiosurgery followed by weekly paclitaxel. Magnetic resonance imaging during the course of treatment revealed stable disease until patient died following another progression of his tumor.

Conclusion: This case of a meningeal PACNS highlights the importance of considering this entity in the face of a malignant lesion presenting with intracranial hemorrhagic activity. Our observations suggest that the use of paclitaxel provided a modest clinical response in PACNS, highlighting the need to consider a combined approach structured mainly on surgery and radiotherapy. Stereotactic radiosurgery appears to be a promising treatment option.

Keywords: Hemangiosarcoma, Meninges, Vascular neoplasms

INTRODUCTION

Angiosarcomas (AS) are malignant vascular neoplasms representing <1% of all sarcomas.^[9] The majority of AS originate at cutaneous sites (60%) and other soft tissues; the region of the head and neck is the most affected.^[9,15] The management of AS remains difficult due their inherent complex evolution. In an effort to raise awareness and suggest treatment options for this entity, we report a case of a primary meningeal AS treated with surgery, radiotherapy, stereotactic radiosurgery, and paclitaxel at different stages of the disease; a review of the literature looking for similar cases was done by searching PubMed.

CASE DESCRIPTION

A 36-year-old Asian male presented to our facility with a 4-month history of worsening headaches and complete right homonymous hemianopia. He had a medical background of the

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left occipital, intracranial cerebral hematoma 2 years before the current event, the etiology of which was never found. The ensuing computed tomography (CT) and magnetic resonance imaging (MRI) scans revealed a left occipital lobe hematoma with an underlying left tentorial tumor, suggesting the presence of a cavernous angioma [Figure 1]. The patient had a craniotomy in an attempt for gross total resection; however, the intraoperative findings indicated tumor invasion of the falx cerebri as well as the cerebral cortex resulting in a subtotal resection. An early postoperative MRI was not performed. Postoperative CT did not report significant findings. Yet according to the surgical report, no major bleeding was reported during and after surgery despite of the vascular nature of these tumors.

After maximal safe resection (subtotal resection), the histopathological examination demonstrated the presence of spindle cells forming masses with branching ecstatic vasculature and focal collagenous regions, with up to 20 mitoses per ten high power fields. Further immunohistochemical studies showed strong immunoreactivity for CD31, CD99, and Fli-1 with a few scattered S100 positive cells but negative for CD34, EMA, desmin, muscle-specific actin, and Bcl-2; the latter findings were suggestive of meningeal sarcoma with angiosarcomatous features, ultimately assessed as a malignant endothelial cell sarcoma/AS [Figure 2 and Table 1].

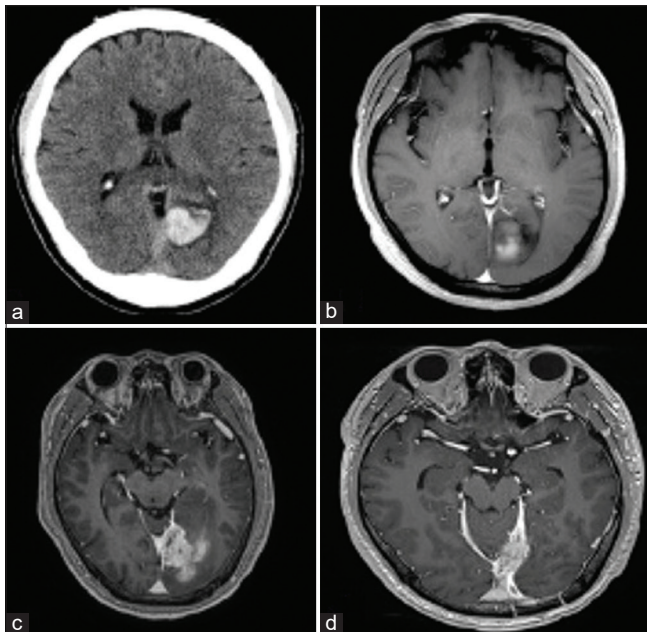


Figure 1: Initial presentation of a left occipital lobe intraparenchymal hemorrhage. (a) Head computed tomography without contrast. (b) Axial T1-weighted magnetic resonance imaging (MRI) with contrast. (c) Axial T1-weighted MRI with contrast revealing a left tentorial extra-axial enhancing mass with parenchymal hemorrhage. (d) Baseline axial T1 with contrast before initiation of paclitaxel.

Nevertheless, in view of the complex morphology, location and patterns of infiltration of this tumor, further efforts were made toward a broad differential diagnostic panel. We screened our patient with a next generation sequencing platform performed at Foundation Medicine (Cambridge, USA). Two diagnostic panels were performed (FoundationOne and Foundation heme assay), analyzing 236 genes, 47 introns from 19 genes rearrangements for solid tumors including non-small cell lung cancer, colorectal, breast, ovarian, and Melanoma, and 405 DNA genes, 31 introns from rearrangements, 265 RNA genes, gene fusion for hematologic tumors including leukemias, myelodysplastic syndrome, myeloproliferative neoplasm, acute myeloid leukemia, and acute lymphoblastic leukemia, respectively. Both of these tests were negative for identifying any genomic alterations with therapeutic implications. Gliosarcoma, a new variant of IDH-wildtype glioblastoma based on the WHO 2016 classification characterized by a biphasic tissue pattern with alternating areas displaying glial and mesenchymal differentiation was also considered. Further molecular analysis did not detect the presence of O6-methylguanine-DNA methyltransferase promoter methylation.

Still eager to elucidate the origin of this tumor, the patient was referred to the MD Anderson Cancer Center for a new pathology review. The reviewed immunohistochemistry proved positive for CD31, focally positive for factor VIII and S100 and negative for CD34, BCL2, EMA, actin, and desmin [Table 1]. The final conclusion from this second institution was a meningeal sarcoma, the WHO Grade III. Of note, a concurrent PET scan showed a solitary pulmonary nodule assessed to be an infectious process or a malignancy; due to its complex location, the nodule was not biopsied. Not showing clinical signs of extracranial disease, it was decided that the patient should stay on follow-up by a clinical oncologist.

Following diagnosis, he received a 7-week course of adjuvant intensity-modulated radiation therapy (45 Gy in 15 fractions

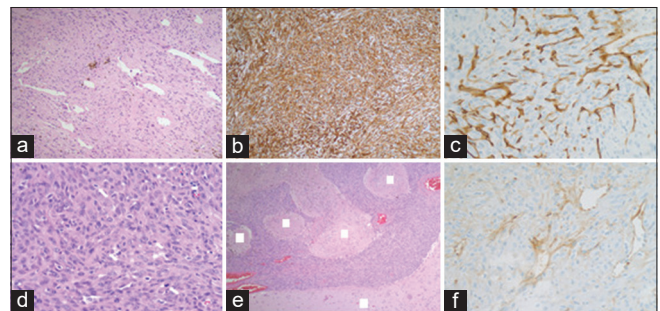


Figure 2: Neuropathological findings. (a) H&E abnormal blood vessels. (b) CD31 immunoreactive. (c) CD34 abnormal blood vessels. (d) H&E four mitoses in one high power field. (e) H&E brain invasion (squares). (f) Factor VIII faint membrane staining, abnormal blood vessels, and tumor cells.

Table 1: Immunohistochemical analysis.

Initial report	Further reports
Spindle cells forming cellular masses	Meningeal sarcoma, WHO Grade III
Branching ecstastic vasculature	CD31 immunoreactivity
Focal collagenous regions	Factor VIII immunoreactivity
Up to 20 mitoses per 10 HPF	S100 immunoreactivity
Up to 4 mitoses per HPF	Negative for CD34, BCL2, EMA, actin, and desmin
Abnormal blood vessels by H&E	
CD34 abnormal blood vessels	
CD31 immunoreactivity	
CD99 immunoreactivity	
Fli-1 immunoreactivity	
Brain invasion by H&E	
Factor VIII faint membrane staining	
Tumoral cells	

followed by a 14.4 Gy boost in eight fractions); however, the tumor progressed 8 months later as evidenced on a follow-up MRI. He was subsequently treated with linear accelerator-based stereotactic radiosurgery (Novalis Tx, 25 Gy in 5 fractions), followed by weekly paclitaxel (90 mg/m²) days 1, 8, and 15 in 4 weeks cycle. He completed seven cycles and tolerated well except for alopecia and mild peripheral neuropathy. He retained a Karnofsky Performance Status of 90% and continued working full time at his particular time. After completing eight cycles of paclitaxel, the patient started having worsening headaches and head pressure sensation that improved with the addition of dexamethasone; MRI studies showed a significant volume increase of the lesion with intratumoral hemorrhage within the limits of the left tentorium, further extending into the cerebellum; paclitaxel was then discontinued. A left occipital craniotomy was completed and pathology revealed a residual/recurrent malignant meningioma with reactive changes consistent with treatment effect. Patient was not eligible for inclusion to sarcoma specific trials due to the history of intracranial hemorrhage and lack of safety data in CNS involvement. The patient died following a massive cerebral hemorrhage. The previously reported lung nodule remained stable throughout follow-up; the patient died 21 months following diagnosis.

DISCUSSION

AS may involve the central nervous system (CNS) as metastatic lesions or as primary neoplasms, metastatic origin being the most common. Primary AS of the CNS (PACNS) is a rare condition, accounting for 1–2% of all primary intracranial tumors.^[7] In the context of metastatic intracranial

disease with AS histology, the most common primary site is the heart, specifically the right atrium. Metastatic lesions in the brain do not show an established topographic pattern; however, they are usually multiple and hemorrhagic.^[15] In this context, the complication rates of hemorrhage are not clearly established.

In the past 43 years, 33 cases of PACNS have been reported in the medical literature;^[8,9,13-15] only eight of these are meningeal [Table 2]. To the best of our knowledge, this report illustrates the ninth case of a meningeal PACNS. PACNS usually arise from the brain parenchyma (81%) and the meninges (16%); interestingly, the parietal lobe has been described as the location of preference.^[9] PACNS is recognized as highly vascular tumors with aggressive patterns of local infiltration; chemotherapy, and radiation treatment have limited efficacy.^[11] Unlike our case, complete surgical excision may provide recurrence free interval for more than 2 years even without adjuvant chemotherapy or radiation. Negative prognosis has been associated to extracranial metastatic disease, with a median life expectancy of 8 months;^[15] the most common sites of metastatic activity are the lungs, bone, and soft tissues.^[9] PACNS is more common in men and can be found in patients of all ages,^[9,15] similarly to what was found in cases of meningeal PACNS. The clinical course is characterized by a rapid progression of symptoms caused by hemorrhagic lesions, as it was the case in our patient. Furthermore, from an imaging perspective, PACNS is often difficult to differ from cavernous angiomas.^[9]

Because of the heterogeneous nature of the lesions, several immunohistological markers had been used, including CD31, CD34, and factor VIII. The first two are expressed in epithelioid vascular tumors, CD31 being the most accepted. Other described markers are vimentin, S100, HMB-45, MIB-1, UEA-1, and GFAP; particularly useful in making differential diagnosis with sarcoma, hemangioblastoma, solitary fibrous tumor, hemangioendothelioma, cavernous angioma, and carcinoma metastases, or epithelioid melanoma.^[9,10] In our case, the initial immunohistochemistry showed CD31 and Fli-1 while the second review reported positivity for S100 and factor VIII.

The low frequency of patients affected by this entity and the great variability of histological subtypes make it unlikely for clinical trials to be conducted; in view of the latter, evidence pointing to optimized therapeutic interventions remains severely precluded. The United Kingdom guidelines for the management of sarcoma recommend surgery with wide resection margins as standard treatment in patients with localized disease. In our patient, gross total resection was problematic due to the aforementioned anatomical constraints. For patients with partial resection, intermediate or high grade tumors, neoadjuvant, or adjuvant radiotherapy is recommended.^[5] Of note, the radiotherapy dose delivered

Table 2: Cases of primary meningeal angiosarcoma.

Author	Sex	Age	Background	Clinical features	Diagnosis	Location	Biomarkers	Treatment	Survival (months)
Kristoferitsch <i>et al.</i> (1986) ^{[8]a}	M	60 years	Smoker, generalized vascular disease, chordotomy	Progressing paraparesis, complete sensory loss with T1 level, hyperreflexia, Right Babinski's sign	Cervical myelogram, autopsy, pathology	Thoracic and upper lumbar spinal cord	Positive for Factor VIII and GFAP	-	1
Russel <i>et al.</i> (1989) ^[13]	F	6 years	ND	ND	ND	Brainstem	ND	ND	ND
Mena <i>et al.</i> (1991) ^[10]	M	1 year	ND	ND	ND	Anterior fossa	ND	ND	ND
	ND	ND	ND	ND	Pathology	ND	ND	Resection	ND
Kirk <i>et al.</i> (1992) ^[7]	F	2 weeks	Product of a twin pregnancy	Macrocephaly, progressive irritability, vomit, tense fontanelle, right proptosis	Cranial sonography, CT of the Brain, Head MRI, pathology	Right temporal region	-	Total resection	>26
Hackney <i>et al.</i> (2012) ^[6]	F	35 years	Caucasian	Left eye irritation, exophthalmos with blurred vision	Neuroimaging, pathology	left retro-orbital infra-temporal area	Positive for CD31	Subtotal resection, radiotherapy, bevacizumab	>24
	M	47 years	Caucasian	Acute onset of visual loss in the left eye, subtle memory problems and word-finding difficulties	Neuroimaging, pathology	left sphenoid wing	Positive for CD31	Subtotal resection, radiotherapy, temozolomide, and bevacizumab	ND
Sakai <i>et al.</i> (2014) ^{[14]b}	M	33 years	Asian, NF2, bilateral schwannomas in the CPAs and multiple tumors in cranial nerves and spinal cord	4-year history of left hearing loss and left facial palsy	Neuroimaging, pathology.	Left CPA	80% of the lesion was positive for CD31, podoplanin and negative for CD31, factor VIII and S100. 20% of the lesion was weak positive for EMA, positive for PgR. Negative for cytokeratin AE1/AE3, CK CAM5.2 and S100	Resection, gamma knife in lesion of the right CPA	27

(Contid...)

Table 2: (Continued).

Author	Sex	Age	Background	Clinical features	Diagnosis	Location	Biomarkers	Treatment	Survival (months)
This case	M	36 years	Asian, history of left occipital, intracranial cerebral hematoma	4-month history of worsening headaches and complete right homonymous hemianopia	Neuroimaging, pathology	Left occipital lobe	Positive for CD31 and Fli-1, focally positive for factor VIII and S100. Negative for CD34, BCL2, EMA, actin and desmin	Subtotal resection, IMRT 45 Gy in 15 fractions followed by a 14.4 Gy boost in 8 fractions, SRS 25 Gy in 5 fractions, paclitaxel (90mg/m2) eight cycles	21

ND: No data, F: Female, M: Male, GFAP: Glial fibrillary acidic protein, CT: Computed tomography, MRI: Magnetic resonance imaging, NF2: Neurofibromatosis type 2, CPA: Cerebellopontine angle, IMRT: Intensity-modulated radiation therapy, SRS: Stereotactic radiosurgery. ^aThe patient did not accept the surgery. ^bThe lesions in the bilateral CPAs was reported as angiosarcoma arising in schwannoma. A third injury in Left CPA was diagnosed as mixed angiosarcoma and meningioma.

to our patient was biologically similar to those recommended by such guidelines (60-66 Gy in 1.8-2.0 Gy/fraction).

Although treatments for PACNS are not standardized, some studies showed that paclitaxel and bevacizumab are active against AS.^[1,11,12] Regimens for soft-tissue sarcoma recommend paclitaxel as an alternative to doxorubicin.^[12] In a Phase II randomized clinical trial paclitaxel showed disease-free survival rates of 74% and 45% at 2 and 4 months, respectively, in patients with advance AS or metastatic disease and was not candidates to surgery.^[11] Another clinical trial evaluated the efficacy of bevacizumab in patients with AS, reporting a median progression-free survival of 3 months. Ray-Coquard *et al.*^[12] compared paclitaxel as monotherapy versus paclitaxel and bevacizumab and found a median overall survival of 19.5 months for monotherapy and 15.9 months for combined therapy. In our patient, paclitaxel was used based on the immunohistochemical features of AS. Bevacizumab was not considered due to history of the previous cerebral hemorrhage.

Studies evaluating the efficacy and safety of chemotherapy for the treatment of AS have been performed in tumors with extracranial localization. For intracranial AS, chemotherapy does not appear to be effective, since most medications do not penetrate the blood-brain barrier.^[2] In the case of paclitaxel, therapeutic concentrations in the brain are often very low. *In vitro*, paclitaxel access to the CNS is limited by mechanisms in which the p-glycoprotein participates. *In vivo*, in human glioblastoma tumor cells implanted in the CNS of mice, paclitaxel did not show effect on tumor size reduction,^[3] suggesting that the use of paclitaxel in our patient may have had a limited therapeutic effect. Overall, there is not enough clinical evidence to support the use of Taxanes in patients with PACNS; indeed, we found no reported cases of meningeal PACNS treated with paclitaxel. However, we identified one case of meningeal PACNS treated with bevacizumab, and another case treated with bevacizumab and temozolomide.^[6]

The blood-brain barrier is indeed a crucial issue for PACNS, even after a possible increase of the permeability after high-dose radiation.^[2] Stereotactic radiosurgery improves local control rates in patients with sarcomas. In a series of 21 cases with sarcomatous intracranial metastases treated with stereotactic radiosurgery (either as initial, maintenance, or rescue therapy), a local control rate of 88% was observed with a median of 4 months.^[4] Extrapolating the above findings to PACNS, radiosurgery might well be considered in selected cases. Furthermore, the possible synergistic effects of concurrent radiation and systemic treatment should not be forgotten;^[6,9] in that case, we could hypothesize on the real effects of adding selected systemic treatment to radiosurgery. Yet until further evidence is presented on the subject, we submit to the reader that the combination of surgery, IMRT-

based radiotherapy, and stereotactic radiosurgery played a major role on the overall survival.

CONCLUSION

This case of a meningeal PACNS highlights the importance of considering this entity in the face of a malignant lesion presenting with intracranial hemorrhagic activity. Our observations suggest that the use of paclitaxel provided a modest clinical response in PACNS, highlighting the need to consider a combined approach mainly structured mainly on surgery and radiotherapy. In this context, stereotactic radiosurgery appears to be a promising treatment option. The development of clinical research evaluating the efficacy of systemic agents in the context of PACNS is necessary, taking into account the limitations of drug distribution in the microenvironment of the CNS.

Declaration of patient consent

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

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Conflicts of interest

There are no conflicts of interest.

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