Title: Metastatic Cardiac Angiosarcoma to the Lung, Spine, and Brain: A Case Report and Review of the Literature

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Abstract

Background: Metastatic angiosarcoma to the brain is a rare entity without an established management protocol.

Case description: The authors describe a case of primary cardiac angiosarcoma with a rare brain metastasis in an adult. This patient underwent successful resection of his brain metastasis and was initiated on only chemotherapy for his systemic disease. The patient did not develop local recurrence. A review of primary and metastatic CNS angiosarcoma, its pathologic features, clinical disease course, treatment strategies and genomics is also described.

Conclusions: Angiosarcomas are rare tumors that remain difficult to treat. Gross total resection of a CNS metastasis is recommended prior to the initiation of adjuvant chemotherapy or radiation therapy. Close follow-up is still required given the propensity for these tumors to continue metastasis. Future treatments may be developed based on the genomics of angiosarcomas.

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2. Introduction

CNS angiosarcoma is a rare entity with a described incidence of less than 1% of all sarcomas.\(^1,2\) Here we describe a case of an adult that presented with a brain hemorrhage with multiple tumors involving the right atrium of the heart, lung, and spine. The patient was ultimately diagnosed with metastatic angiosarcoma after craniotomy and was initiated on systemic chemotherapy. Our purpose is to describe this case and review the literature on primary CNS and metastatic angiosarcoma.
3. Case Report

3.1. History

A 63 year old male presented to our emergency room with new right arm weakness and a hemorrhagic mass in his left frontal lobe on CT. The brain MRI revealed a 2 centimeter heterogeneously-enhancing, well demarcated left frontal lesion with surrounding vasogenic edema. (Figure 1) Several additional punctate contrast enhancing lesions as well as FLAIR-signal abnormality were present supra- and infratentorially. A CT-chest-abdomen and pelvis demonstrated multiple pulmonary nodules, a right atrial appendage mass, and a right T10 pathologic transverse process fracture. A lung core biopsy of a pulmonary nodule did not confirm a diagnosis, but did demonstrated atypical spindle cells with increased mitotic figures. Given the new neurologic deficit and the lack of diagnostic tissue, the patient underwent a left frontal craniotomy for tumor resection.

3.2. Neurosurgical Operation and Pathology

At surgery, the tumor was noted to have black coloration with distinct margins and firm consistency. It was easily identified and removed en-block to avoid hemorrhage. Pathologic evaluation was significant for a tumor composed of anastomosing vascular channels lined with malignant endothelial cells. Areas of necrosis, and hemorrhage were also present. The tumor cells were positive for CD31 and CD34 with immunohistochemistry. (Figure 2) The CNS tissue matched the lung biopsy tissue and represented metastatic angiosarcoma. Given the propensity of angiosarcomas to originate from the right atrium, his right atrial mass was presumed to be the primary source.

3.3. Post-operative Course

The patient regained strength in his right upper extremity post-operatively. The cardiothoracic surgery team was consulted and did not recommend resection of his right atrial appendage mass. He was ultimately discharged to an acute rehabilitation facility on post-operative day 7. Gemcitabine,
docetaxel and bevacizumab chemotherapy was initiated and he underwent a total of 7 cycles over 10 months. Radiation therapy to the T10 metastasis was performed 4 months post-operatively. A 3 and 7-month body CT-scan and MRI of the brain demonstrated interval size decreases of the lung metastasis and no additional brain metastasis. However, a repeat brain MRI at 10 months demonstrated new sub-centimeter brain metastasis in the right frontal lobe. The patient decided to continue monitoring this lesion while on chemotherapy and remains alive 12 months after surgery.

4. Discussion

We describe a case of a cardiac angiosarcoma with multiple metastasis to the lung, spine, and brain.

Primary and metastatic CNS angiosarcomas are a rare malignancy with an incidence rate less than 1%. Described risk factors for angiosarcoma include vinyl chloride, irradiation, chemotherapy, arsenic and thorotrast-contrast. In published case reports of angiosarcoma of the CNS, the clinical presentation is often rapid onset of neurologic deficits with intracranial hemorrhage. The propensity of angiosarcomas to hemorrhage is underscored by a report of surgical resection that required 12 units of packed red blood cell and plasma transfusions.

Systemic angiosarcomas originate from endothelial cell of arteries, veins, or lymphatic channels. Similarly, primary CNS angiosarcomas originate from the mesenchymal elements of the brain. The pathologic features of angiosarcomas consist of malignant spindle cells lining vascular channels with hemorrhage and necrosis. The endothelial origin of angiosarcomas is often confirmed with Factor VIII-related antigen, CD34 and/or CD31 immunohistochemistry. Electron microscopy often shows tumors cells with irregular-nuclei, rich endoplasmic reticulum, pinocytic vesicles and projections into the vascular lumen. Weibel-Palade bodies can also be identified within the endothelial cells on electron microscopy. Our patient’s tissue pathology was consistent with the diagnosis of metastatic angiosarcoma (Figure 2).
For metastatic CNS angiosarcoma, Shweikeh et al reported an average patient age of 42.3 years with 70% male predominance.\(^2\) Primary sites of disease have included the heart, aorta, femur, placenta, spleen, liver and scalp.\(^7\) The most common primary site of angiosarcomas with CNS metastasis is the right atrium of the heart (35% of reported cases).\(^8\) The most common metastasis sites are the cervical lymph nodes, lung, liver and spleen.\(^7\) In our patient, we suspect that the primary site was the right atrial mass, with metastatic spread to the lung and brain.

The diagnosis of angiosarcoma is grim. Reported overall 2-year and 5-year survival following a diagnosis of angiosarcoma is 17% and 12%, respectively.\(^2,7\) In a case series of 8 patients with primary CNS angiosarcoma, mean survival was 8 months.\(^11\) Merimsky et al describe three cases of primary CNS angiosarcoma with survival of 2.5, 5 and 20 months.\(^3\) Similar poor mortality rates have been described with metastatic CNS angiosarcoma with an average overall survival of 4.8 months after diagnosis.\(^2,3,34,37,38,40\) Despite this, case reports of long-term survivors following craniotomy have been reported.\(^4,11,15,22,23\) A recent paper demonstrated spontaneous regression of metastatic angiosarcoma.\(^42\)

Gross total resection has been recommended as first-line treatment for both primary and metastatic CNS angiosarcoma given the propensity of these tumors to recur.\(^15,30\) Adjuvant treatment options include chemotherapy, radiation therapy and local brachytherapy. However, a standardized protocol has not been established. Moreover, a review of 99 cases of angiosarcoma demonstrated that often no treatment for these patients was undertaken.\(^7\) One reason may be because gross total resection is often difficult given the size and multiplicity of these tumors, as well as their propensity to hemorrhage.\(^13,42\) Secondly, sarcomas are radioresistant. Mean survival following whole brain radiation for CNS sarcomas is 3 months.\(^13\) Stereotactic radiosurgery is also minimally effective for sarcomas.\(^43,44\) Finally, use of chemotherapy agents such as paclitaxel, gemcitabine, bevacizumab, sorafenib, and docetaxel have been used against angiosarcoma.\(^42,45-49\) However, angiosarcomas have been partially resistant to these chemotherapies, with most reported time-to-progression remaining under 12 months and overall survival ranging from 6 to 15 months.\(^42,45-49\) These data
reflect the difficulty in treating angiosarcoma. Regardless, using each of these treatment modalities in combination has been recommended given the tumor’s malignant features.\textsuperscript{15,22,28}

Genomic studies of angiosarcoma have been reported. Zhrebker et al reported a case of a 56 year old male with metastatic angiosarcoma who underwent postmortem whole exome sequencing. They discovered the patient had a KDR mutation, a vascular-specific tyrosine kinase receptor, resulting in its overactivation.\textsuperscript{50} KDR mutations in angiosarcoma patients has been reported to have a 10% incidence and the whole exome sequencing study supported the potential clinical efficacy of a KDR inhibitor.\textsuperscript{51} Other genomic studies have demonstrated an upregulation of p53, Ras, BRCA, PTEN, and MYC in angiosarcomas.\textsuperscript{52,53} Morphoproteomic studies of angiosarcoma patients demonstrated constitutive activation of (1) the signal transducer and activator of transcription (STAT3) pathway, (2) the ras/Raf kinase/extracellular signal-regulated kinase (ERK) pathway, (3) the hypoxia pathway, (4) the sonic hedgehog pathway, and (5) the mechanistic target of rapamycin (mTOR) pathway.\textsuperscript{52,54} While these studies provide insight into the different oncogenic pathways utilized by angiosarcomas, the multiplicity of these pathways underscore the difficulty in effectively treating these tumors.

5. Conclusion

CNS angiosarcoma is a rare and aggressive disease that is resistant to chemotherapy and radiation therapy. Genomic studies of angiosarcoma suggest its uses multiple oncogenic pathways to promote its growth. Here, we present a patient with a primary cardiac angiosarcoma and extensive metastatic angiosarcoma with CNS involvement. Our patient underwent surgical resection of his CNS lesion and adjuvant chemotherapy, which is consistent with prior literature recommendations. Our patient remains alive 12 months after craniotomy without local tumor recurrence.
6. Bibliography


**Figure Legends**

*Figure 1-* T1 and T1-post-contrast sequences demonstrate a heterogeneous enhancing mass in the left middle frontal lobe. The Head CT demonstrates hemorrhage within the mass.

*Figure 2-* H&E stain at 4x demonstrates multiple vascular channels with areas of necrosis. The tumor cells were positive for CD31 and CD34 with immunohistochemistry.
Highlights

- We describe a patient with metastatic angiosarcoma to the brain who underwent craniotomy and chemotherapy and remains alive 1 year after diagnosis.
- Metastatic CNS angiosarcoma is a rare entity with no standardized treatment regimen.
- Gross total resection of metastatic CNS angiosarcoma is recommended prior to adjuvant therapy, although close follow-up is still required given the propensity of these tumors to recur locally.