Case Report

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Primary cerebral angiosarcoma: a case report

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Introduction and importance: Central nervous system sarcomas are rare tumors of mesenchymal origin. Angiosarcomas are an even rarer subtype with poor prognosis and no consensus regarding therapeutic approach.
Case presentation: This article presents the case of a 50-year-old Palestinian female patient with a history of treated breast cancer who presented to the emergency room with a tonic-clonic seizure. Brain computed tomography showed a cerebral space-occupying lesion managed with craniotomy and gross tumor resection. Histopathology revealed an epithelioid cerebral angiosarcoma. The patient was treated with concurrent chemoradiotherapy with temozolomide resulting in the resolution of the tumor as well as symptoms and complaints.
Clinical discussion: Primary cerebral epithelioid angiosarcoma is a highly malignant tumor of an unknown etiology. The patient history of breast created an additional challenge, as recurrence with metastasis had to be excluded. Signs of blood product degradation are an important radiological feature. According to existing literature, gross tumor resection followed by concurrent chemoradiotherapy offers the best approach and outcome.
Conclusion: Cerebral angiosarcoma is a rare disease with a challenging therapeutic approach due to the scarcity of available literature. It should be included in the differential diagnosis of space-occupying lesions, especially in those with a history of exposure to radiotherapy. Immunohistochemistry is key for diagnosis. Surgical resection followed by concurrent chemoradiotherapy is associated with a longer disease-free survival when compared to either option alone.

Keywords: angiosarcoma, brain tumor, case report, concurrent chemoradiotherapy, rare neoplasm

Introduction

Primary intracranial sarcomas are uncommon malignant tumors comprising ~1–2% of all primary intracranial neoplasms. These tumors arise from mesenchymal elements in the brain and meninges. Angiosarcomas account for a small portion of vascular tumors; most of them arise in the skin and soft tissue[1]. Brain angiosarcomas are extremely rare, with only a handful of cases reported in the literature. Prognosis is generally poor, with only occasional long survivors[2]. To improve our understanding of this rare entity, we report a case of cerebral angiosarcoma arising in the left frontal lobe and left occipital lobe of a 50-year-old woman.

HIGHLIGHTS

- Primary epithelioid cerebral angiosarcoma is a very rare entity, with only a few cases found in the literature.
- It is often difficult to differentiate between primary angiosarcoma and cavernous hemangioma due to similar radiologic features.
- Radiologists and neurosurgeons should be aware of this rare entity. Histopathology is key diagnosis.
- There is no consensus regarding the approach to this rare entity and whether radiation alone or concurrent chemoradiation offers a better outcome.
- The prognosis is usually poor.

Case presentation

A 50-year-old Palestinian woman arrived accompanied by her family members to the emergency room in May 2022 due to repetitive, rhythmic, uncontrolled movements associated with a loss of consciousness of 5 min in duration. This episode, which was the first of its kind, resolved spontaneously upon arrival at the hospital. The patient had been completely free prior to this event, with no headache, dizziness, double vision, or tinnitus. She is a married housewife with four children. She had a history of breast cancer treated in 2005 with mastectomy, chemotherapy followed by radiotherapy, then adjuvant hormonal therapy for 10 years. The patient had no relevant drug history; she had no known drug or food allergy. Her family history was free of malignancy; she had no history of smoking, alcohol, or drug abuse. A review of the systems disclosed no relevant symptoms.

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Physical examination showed a well-looking female; her height was 167 cm, her weight was 82, and she had a body mass index of 29.4. Her vitals were within normal limits. The neurological exam was unremarkable. Her routine lab workup was unremarkable too. Brain computed tomography (CT) showed a left frontal lobe space-occupying lesion (SOL). Magnetic resonance imaging (MRI) was obtained for better characterization and revealed an enhancing left frontal intra-axial lesion with slight heterogeneity that is mainly hypointense on both T1 and T2, showing blooming artifact on susceptibility-weighted imaging (SWI), mostly related to degraded blood products, with surrounding vasogenic edema. These radiological features were nonspecific, and the differential diagnosis at that time included hemorrhagic metastasis, cavernoma, or hemorrhagic glioma. In fact, angiosarcoma was not expected. MRI is shown in Figure 1.

Whole-body CT showed no evidence of breast cancer recurrence or any other suspicious lesions, which made metastasis less likely. Tumor markers, including CA (cancer antigen) 15-3 and CEA (carcinoembryonic antigen), were negative.

The patient was referred to the care of the neurosurgery team, and a diagnosis of a primary brain tumor was made. She was operated under general anesthesia by the attending neurosurgeon in charge of a district general hospital. A wide frontoparietal craniotomy was performed after the dura was opened, and a corticotomy as well. Macroscopically total surgical excision was made without any incident. The patient was extubated the next day, and the follow-up was good. Her postoperative course was smooth without complications. Her neurological exam was unremarkable with no deficit. Grossly, the excised tumor consisted of a small black irregular mass measuring $1.3 \times 1 \times 0.7$ cm. Histopathology revealed low-grade well-differentiated angiosarcoma with retiform architecture, tumor cells were positive for CD31, focally positive for CD34 and FL-1 but negative for pan-CK, CK7, TTF1, estrogen/progesterone receptors (ER/PR), human epidermal growth factor receptor-2 (HER2) neu immune stains. Histopathology slides are shown in Figure 2.

The patient was referred to our hospital to continue her management and treatment. On presentation, the patient was conscious, alert, and oriented with no special complaints; her Glasgow Coma Scale was 15/15, cranial nerves were intact, her muscle tone was normal, and her power was 5/5 in all four limbs. Her Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) score was 0. Routine labs and tumor markers were ordered, disclosing normal results, CA 15-3 was 19.65 U/ml, and CEA 0.972 ng/ml (negative). Brain MRI was repeated (roughly 4 months following the operation). It showed postoperative changes at the site of the previously mentioned lesion in the left frontal lobe; however, a newly seen mass is noted in the left occipital lobe, revealing a heterogeneous intensity on T1 and T2 of mainly high signal with a halo and foci of low signal, surrounded by vasogenic edema, showing blooming artifact on SWI and demonstrating subtle minimal peripheral enhancement after the administration of intravenous (i.v.) contrast. Angiosarcoma was at the top of differential diagnosis. The image is shown in Figure 3.

Brain MRI was reviewed by the neurosurgery team of an affiliated hospital. Their opinion was that the SOL in the occipital

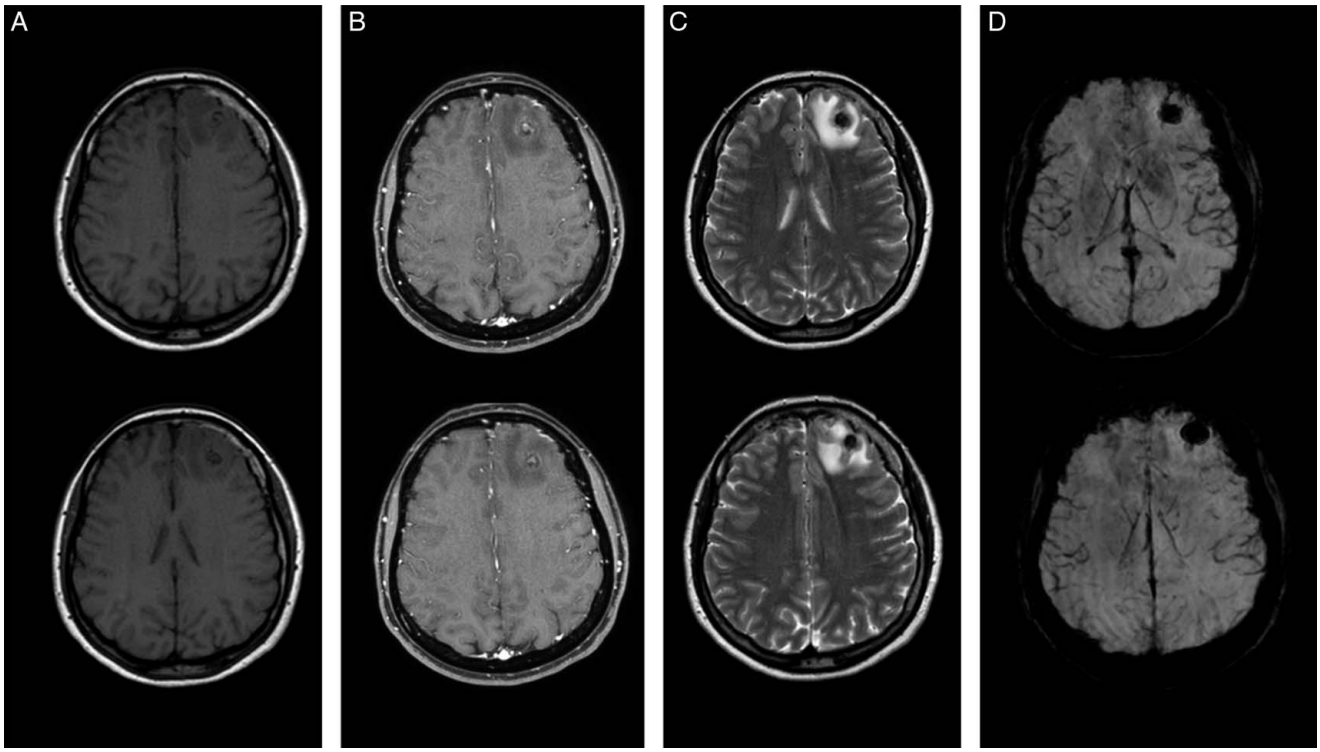

Figure 1. Axial T1-weighted images before (A) and after (B) intravenous contrast administration demonstrate a relatively well-defined left frontal lesion, showing slightly heterogeneous, mainly hypointense signal with peripheral and central punctate hyperintensities, revealing thin peripheral almost complete ring and avid central enhancement. On T2-weighted images (C), the lesion appears markedly hypointense with mild heterogeneity and surrounded by vasogenic edema. The lesion shows blooming artifact on susceptibility-weighted images (D).

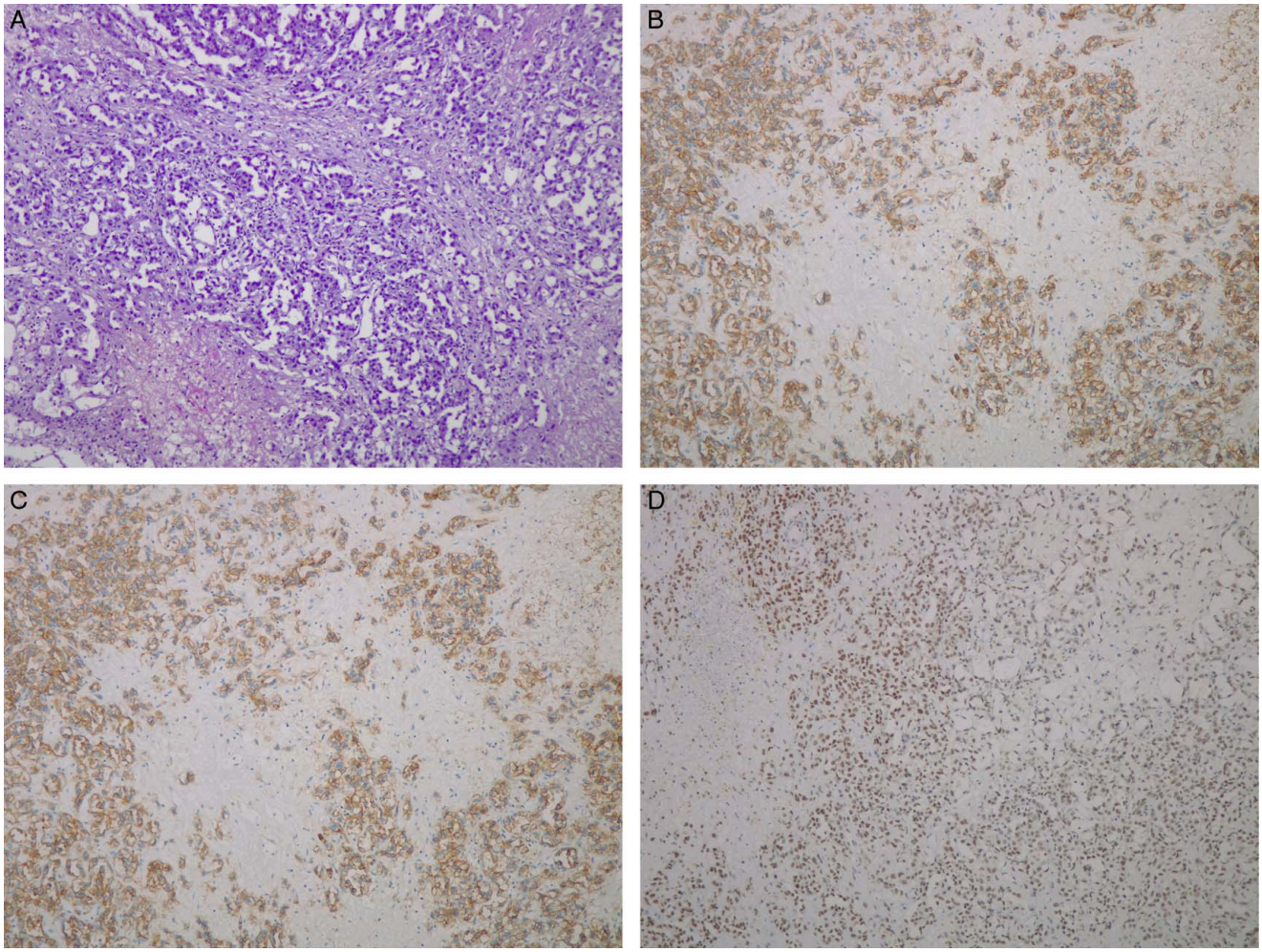

Figure 2. (A) Hematoxylin and eosin (H&E) stain of the space-occupying lesion (SOL) excised from the frontal lobe. 10 × magnification of the excised tumor shows low-grade, well-differentiated angiosarcoma with retiform architecture of epithelioid subtype. (B) Immunohistochemistry (IHC) showing CD31 positive cells. (C) IHC showing CD34 positive cells. (D) IHC showing FL-1 focally positive neoplastic cells.

lobe needed to be excised, so she underwent another craniotomy under general anesthesia, the neurosurgery attending in charge assisted by the senior resident. The skin of the left occiput was excised in a linear pattern, subcutaneous tissue and periosteum were dissected, a burr hole was made, and a bone cutter was used to open the bone flap. The dura was opened in a C-shape. A yellowish tissue was seen, excised, and sent for pathology; an underlying dark, bluish tumor was seen with dark blood, sent for pathology. The tumor was grossly excised, reaching the tentorium, falx cerebri, and recess of the torcula. Hemostasis was assured, then the dura was approximated, and cranioplasty was done using bone cement. Subcutaneous tissue and skin were closed, and dressing was applied.

The histopathology of the tumor resembled that of the first tumor. The case was discussed by the multidisciplinary team at the weekly tumor board, who made a joint decision and started the patient on adjuvant concomitant chemoradiation with temozolomide, 75 mg/m^2 once daily. Her radiotherapy regimen consisted of 2 grays (Gy) of radiotherapy over 27 fractions via volumetric art therapy (VMAT) for a total of 54 Gy with daily temozolomide. She was not completely adherent to her chemotherapy regimen, as she felt she improved after receiving the first week of radiotherapy. Her course was complicated by grade I mucositis; no significant treatment-associated adverse effects were observed.

The patient was evaluated after 4 months of finishing treatment. She was doing well and returned to her daily life activities without limitations, her neurological exam was normal, and ECOG-PS score was 0. MRI showed postoperative changes with no evidence of mass occupying lesions or abnormal pattern of enhancement. The image is shown in Figure 4.

Regarding her perspective, the patient was pleased with her management at our hospital. She now takes care of her old mother. She is performing her daily life functions without hindrance.

This case has been reported in line with the SCARE (Surgical Case REport) criteria[3].

Discussion

Epithelioid angiosarcomas are rare, highly malignant vascular endothelial cell tumors. They can be found anywhere in the body, mainly in deep soft tissues. Primary cerebral epithelioid

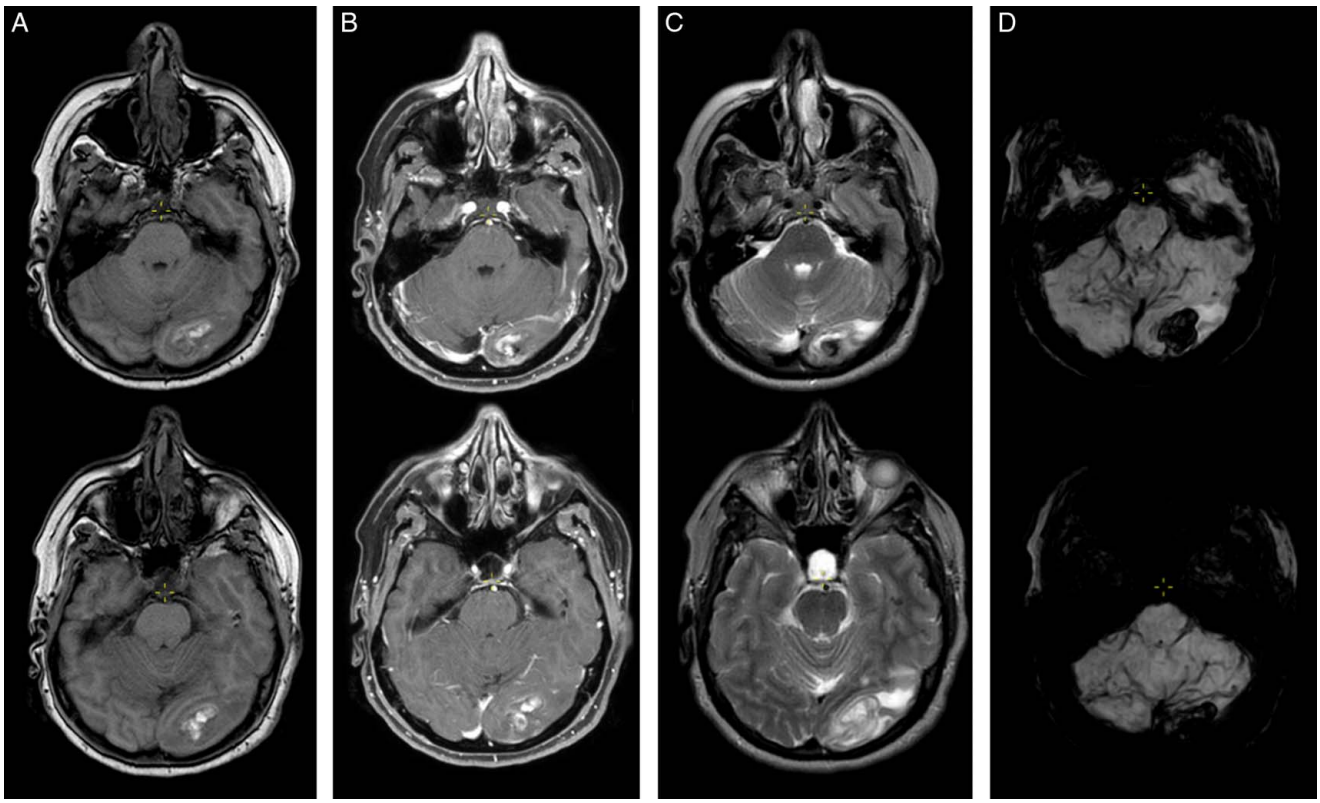

Figure 3. Aaxial T1-weighted images before (A) and after (B) intravenous contrast administration demonstrate a relatively well-defined left occipital lesion, showing slightly heterogeneous mainly high signal with a halo and foci of low signal, revealing subtle eccentric peripheral enhancement. On T2-weighted images (C), the lesion appears heterogeneous of both high and foci of low signals surrounded by vasogenic edema. The lesion shows blooming artifact on susceptibility-weighted images (D).

angiosarcoma is extremely rare; four cases have been reported in the literature thus far (Table 1)[4–7].

The etiology of epithelioid cerebral angiosarcoma is still unknown; they are more predominant in males compared to females. Risk factors for the development of angiosarcoma include exposure to vinyl chloride, thorotrast contrast, radiation therapy, chronic lymphedema, and familial syndromes, such as neurofibromatosis type 1[1,7]. Radiation exposure is one of the

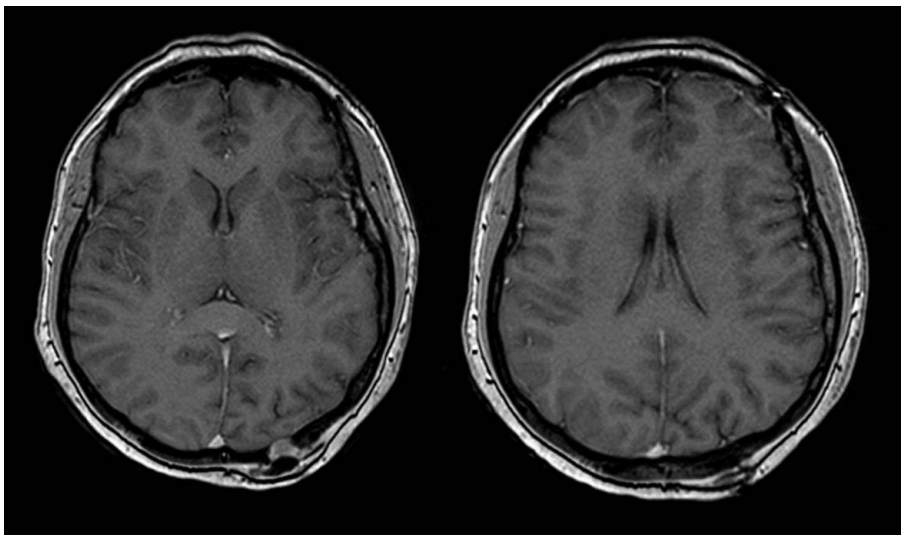

Figure 4. Evidence of left frontal and left occipital resected tumors with postoperative changes. Stable left frontal and left temporal lesions in comparison with the previous study. No evidence of new lesions. No previous lesion progression.

Table 1

Details of cases of primary cerebral epithelioid angiosarcoma.

Case author (year)	Sex	Age (year)	Location	Time of onset	Tumor stroke	IHC	Therapy	Metastasis	Outcome
Fuse *et al.*[4]	M	39	R parietal lobe	2 weeks	No	CD31 (+), CK (+), vimentin (+)	S+RT	No	Death after 29 months
Baldovini *et al.*[5]	M	54	Septum pellucidum	3 days	Yes	CD31 (+), FVIII (+), CK (+) Ki-67 index higher	S	No	Death after 2 months
La Corte *et al.*[6]	F	35	L frontal lobe	Unknown	Yes	CD31 (+), CD34 (+) vimentin(+), Ki-67 (20%)	S + RT + CT	No	Still alive at 37 months
Kuang, *et al.*[7]	M	73	R occipital lobe	1 month	Yes	CD31 (+), ERG (+), Fli-1(+) CK (+), Ki-67 (40%)	S+RT	No	Death after 9 months
Our case	F	50	L frontal lobe, L occipital lobe	Sudden with no preceding symptoms	No	CD31 (+), CD34 (+), vimentin (+), FL-1 (+)	S + CRT	No	Still alive at 14 months

CRT, concurrent chemoradiotherapy; CT, chemotherapy; F, female; IHC, immunohistochemistry; L, left; M, male; R, right; RT, radiotherapy; S, surgical.

most common risk factors for angiosarcoma. We describe a case of cerebral angiosarcoma with a distant history of breast cancer treated with chemotherapy followed by radiation therapy to the breast presenting with abnormal movement. Brain MRI revealed a SOL in the left frontal lobe; the patient underwent left frontal craniotomy with resection of the left frontal lesion, and histopathology revealed angiosarcoma. Postoperative MRI revealed another left occipital SOL, so another craniotomy was performed, and the excised lesion showed the same pathology. CT of the chest, abdomen, and pelvis was negative for malignancy. It is established that exposure to external beam radiotherapy increases the risk of angiosarcoma in the future. The proposed mechanism by which radiation induces the development of angiosarcoma is that the effect of ionizing radiation directly affects oncogenes, leading to mutation and genome instability[8]. Our patient's exposure to radiation did not include a brain radiation field as it was directed to the chest, so the location of her angiosarcoma cannot be explained by prior radiation exposure. Although rare, further investigation is warranted to increase our knowledge regarding the development of angiosarcoma.

Clinical manifestations of cerebral angiosarcoma depend on its anatomical location, and neurologic symptoms might be exacerbated by intralesional hemorrhage. Rapid growth leading to increased intracranial pressure can lead to rapid deterioration. Radical surgical excision is recommended due to the high rate of recurrence. Radiation therapy is beneficial for good disease local control; however, response to chemotherapy is generally poor. The prognosis is usually poor. Some reports show up to 3 years of survival. Due to the rarity of the disease, there is no consensus regarding adjuvant therapy. According to the literature, patients treated with concurrent chemotherapy with radiotherapy showed a mean survival period of 25 months, longer than those receiving surgery alone without adjuvant therapy[9]. Given her history of breast cancer, our patient was suspected to have a metastatic disease rather than a primary tumor. However, whole-body CT scans and tumor markers failed to detect a site of primary tumor other than the brain tumor, three sets of histopathology performed at three different centers, taken from the frontal and occipital lesions, agreed on the rare pathology. The patient received adjuvant concurrent chemotherapy with radiation.

Several immunohistological markers of epithelial angiosarcoma were described, including CD31, CD34, and factor VIII. The first two are expressed in epithelioid vascular tumors, with CD31 being the most accepted. Other markers include vimentin, S100, HMB-45, MIB-1, UEA-1, and GFAP, which are useful for differentiating angiosarcoma from sarcoma, hemangioblastoma, hemangioendothelioma, solitary fibrous tumors, cavernous angioma, metastatic carcinoma, and epithelioid melanoma[10]. In our case, initial immunohistochemistry showed CD31 and CD34, the second look was positive for vimentin, the third look was positive for FLI-1.

There are no common radiological features to identify cerebral angiosarcoma. In some cases, T1-weighted and T2-weighted images showed heterogeneous signal intensities with mild enhancement, which indicates the presence of multistage blood degradation components. Variable T1 and T2 signals can be seen depending on the age of the bleeding. In other cases, T1-weighted images showed low signal intensity with high signal spots with heterogeneous enhancement and some necrosis. Surrounding edema was observed in most cases. The differential diagnosis of

such findings lies with hemorrhagic lesions, including cavernous malformation, glioblastoma, and metastasis[9,11].

In conclusion, primary cerebral angiosarcomas are difficult to diagnose, especially in the presence of a prior history of malignancy. Radiologists and neurosurgeons need to strengthen their understanding of the disease, which most likely presents as heterogenous, well-demarcated, moderately-to-strongly enhancing lesions with signs of intralesional bleeding. Histopathology is key for diagnosis. Concomitant chemoradiotherapy offers the best survival benefit in such cases. To our knowledge, this case represents the first reported Palestinian case. More research is required to reach a consensus regarding the most effective approach toward such cases.

Ethical approval

Ethical approval is not required for case reports at the Augusta Victoria Hospital.

Consent

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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Author contribution

H.A. and M.B.: conceived the idea; H.A., M.B., M.R., M.F., and F.A.: collected the data; H.A. and M.R.: wrote the original draft of the manuscript. All authors reviewed and approved the manuscript.

Conflicts of interest disclosure

The authors declare that they have no conflicts of interest.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

Hasan Arafat.

Data availability statement

The data that support the findings of this study are available from the corresponding author, Hasan Arafat, upon reasonable request.

Provenance and peer review

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