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Title

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Journal

Dermatology Online Journal, 30(2)

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Publication Date

2024

DOI

10.5070/D330263590

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Peer reviewed

Angiosarcoma: hiding in plain sight

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Abstract

Angiosarcoma is a rare, aggressive soft-tissue sarcoma of endothelial origin that necessitates early recognition, diagnosis, and treatment. The most commonly reported presentation consists of violaceous patches and plaques on the head and neck of elderly white men, with fewer reports affecting patients with Skin of Color. Most cases of angiosarcoma are idiopathic and tend to recur locally with early metastasis, conferring a poor prognosis. We report a case of an 83-year-old Fitzpatrick skin type IV man who presented with a large violaceous-to-black mamillated plaque on the frontotemporal scalp that was clinically highly suggestive of cutaneous angiosarcoma. However, unrevealing histopathology complicated our diagnostic process and delayed management. Immunohistochemistry was invaluable in determining the diagnosis of angiosarcoma. Our case highlights the aggressive nature of cutaneous angiosarcoma, necessitating close clinicopathologic correlation to confirm the diagnosis and initiate treatment.

Keywords: cutaneous angiosarcoma, dermatooncology, dermatopathology, medical dermatology, skin of color

Introduction

Soft tissue sarcomas comprise less than 1% of malignancies and angiosarcomas account for 2% of soft tissue sarcomas [1,2]. Angiosarcomas can occur anywhere in the human body, forming neoplastic vascular channels, with 60% arising in the skin and

superficial soft tissues. The most commonly reported presentation is a purple lesion on the head and neck (50% of cutaneous angiosarcomas), particularly on the scalp. It carries a poor prognosis owing to local recurrence and early metastasis. Proportionally, angiosarcoma affects more elderly white men compared to those with Skin of Color [1-3]. The most common form of cutaneous angiosarcoma is idiopathic, though cases of post-irradiation or surgical angiosarcoma have been reported in patients with chronic lymphedema of the extremities [2]. We present a patient with cutaneous angiosarcoma of the scalp and face that was a diagnostic challenge owing to the patient's background skin tone as well as multiple nondiagnostic pathologic specimens. This required a persistent high index of suspicion to arrive at the definitive diagnosis and avoid unnecessary treatment delays.

Case Synopsis

An 83-year-old Fitzpatrick skin type IV man with multiple comorbidities was admitted to the hospital for failure to thrive and was noted to have a large violaceous-to-black neoplasm located on the left frontal scalp that had been growing for two months. He had been told it was a bruise after multiple punch biopsies of the area showed dermal hemorrhage. A head computed tomography scan showed signs suggestive of malignancy with fixation to the temporalis muscle and no erosive changes to the underlying calvarium.



Figure 1. Clinical appearance of the 15cm×10cm violaceous-to-black mammillated plaque on the left frontotemporal scalp and lateral forehead at the time of incisional biopsy.

Dermatology consultation examination revealed a large violaceous-to-black mammillated plaque measuring 15cm×10cm on the left frontotemporal scalp and lateral forehead (**Figure 1**). There were additional areas of macular purpura surrounding the tumoral plaque, as well as a few scattered areas of heme crusts within the plaque. The initial differential diagnosis included angiosarcoma, melanoma, Kaposi sarcoma, or cutaneous metastasis of a non-cutaneous tumor. Given the strong clinical suspicion of cutaneous angiosarcoma, small shave biopsies were obtained at the peripheral edge of the tumor because of the risk of hemorrhage and lack of access to an electrosurgical device in the inpatient setting. Initial histopathology, which was identical to the three prior punch biopsies read by multiple dermatopathologists prior to admission, demonstrated dermal hemorrhage without evidence of malignancy (**Figure 2**).

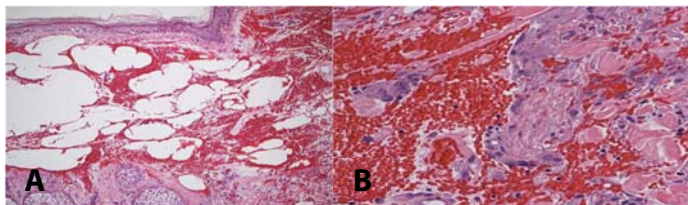


Figure 2. H&E histopathology. **A)** Low power photomicrograph from initial shave biopsy demonstrates empty spaces, hemorrhage, and no well-formed vessels, 4×. **B)** Higher power photomicrograph from initial shave biopsy shows a few atypical cells suggestive of endothelial origin, 40×.

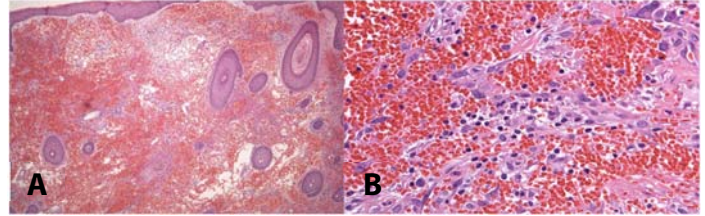


Figure 3. H&E histopathology. **A)** Low power photomicrograph from incisional biopsy reveals extensive dermal hemorrhage and no well-formed vasculature, 4×. **B)** Higher power photomicrograph from incisional biopsy demonstrates discontinuous endothelial cell lined spaces; note the mitosis in the center, 40×.

After hospital discharge, clinical suspicion led the team to perform a 3.5cm×2.5cm incisional biopsy in the dermatology clinic of the tumoral plaque in the temporal area with depth to the temporalis fascia (**Figure 3**). This was read by three tertiary dermatopathology and soft tissue centers, who again noted extensive dermal hemorrhage on histopathology. Some small aggregates of atypical cells with focal vasoformative architecture that were diffusely positive for CD31 (**Figure 4**), multifocally positive for ERG, and negative for CD34 on immunohistochemical staining were now noted, leading to a diagnosis of poorly differentiated cutaneous angiosarcoma. The patient underwent wide local excision and adjuvant radiotherapy but eventually developed metastases to the brain, lung, and vertebrae. He died 13 months after the initial inpatient consultation owing to metastatic disease.

Case Discussion

Angiosarcoma is a rare endothelial sarcoma with an aggressive course and poor prognosis because of the propensity for both local recurrence and distant metastases. Although the tumor can occur anywhere

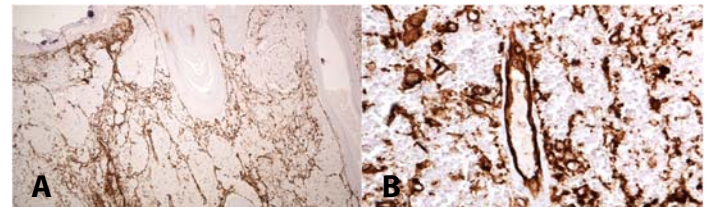


Figure 4. **A)** Low power CD31 immunohistochemistry highlights large, cavernous spaces with endothelial cell marking, 4×. **B)** CD31 immunohistochemistry demonstrates a normal vessel in the middle surrounded by round, atypical endothelial cells with fenestrated vascular spaces, 40×.

in the body, there is a marked predilection for the skin and soft tissues [4]. Angiosarcoma is subdivided into five major subtypes: cutaneous angiosarcoma, soft-tissue angiosarcoma, lymphedema-associated angiosarcoma, primary-breast angiosarcoma, and radiation-induced angiosarcoma [1]. Cutaneous angiosarcoma is typically idiopathic, is reported most in elderly men with an average age of 73, and usually spreads hematogenously [5]. The most common metastasis sites are the lung and brain, with other less common sites including the liver, spleen, and bone [6, 7]. In our case, the patient had distant metastases to his lungs, brain, and vertebrae.

Cutaneous angiosarcoma can present as a single or multiple violaceous-to-red patches, nodules, or plaques that often ulcerate and bleed. Clinically, they can appear as a bruise and be mistaken for other benign lesions and histopathologically they can mimic other pathologies leading to delayed diagnosis [1]. Mentzel et al. reported a case of angiosarcoma that clinically resembled rosacea [8]. Shehan et al. reported a case resembling Kaposi sarcoma both clinically and histopathologically [9]. Other mimicking skin conditions include scarring alopecia, rhinophyma, and ecchymosis [10, 11, 12]. Beyond the various clinical presentations of cutaneous angiosarcoma, cases in patients with Skin of Color are seldomly reported in literature; this added another layer of diagnostic complexity to our case.[3]. Having angiosarcoma in the clinical differential diagnosis in darker-skinned patients is important, particularly for head and neck lesions, especially as red-purple lesions may appear different in this population. Along with a thorough history and physical examination, biopsy and imaging studies can help determine the diagnosis and extent of metastasis [12].

Angiosarcoma is an infiltrative, non-encapsulated neoplasm. [1]. Morphologically, the differences between angiosarcoma and other benign proliferative tumors are obvious with the presence of neoplastic vasoformative cells. Abnormal, pleomorphic, malignant endothelial cells seen in angiosarcoma can be rounded, polygonal, fusiform, or epithelioid, with a wide histologic spectrum that ranges from well-differentiated to poorly differentiated variants [6]. Well-differentiated

cutaneous angiosarcomas are composed of well-defined irregular vascular channels lined by flat endothelial cells that retain some normal function [7, 14]. As the tumor becomes more aggressive, the architecture becomes more distorted with poorly-differentiated and ill-defined vascular spaces. The aberrant cells form papillary projections intraluminally instead of a single endothelial blood vessel lining. Poorly differentiated angiosarcomas are less common in the skin and may appear like other sarcomas or carcinomas; they form continuous sheets of epithelioid morphology with areas of hemorrhage and necrosis. Although some angiosarcomas contain vasoformative areas, confirming the diagnosis, others display pleomorphic spindled or epithelioid cells with a high mitotic index and poor vascular lumen formation [1, 14]. Our case showed mostly hemorrhagic findings with no clear vasoformative component, with one small section in the deep dermis showing small aggregates of cytologically atypical, spindled, or round cells with focal vasoformative architecture consistent with poorly differentiated cutaneous angiosarcoma.

Owing to the histopathologic variations of angiosarcoma, immunohistochemistry is important to confirm the diagnosis. Angiosarcoma is positive for CD34, CD31, *Ulex europaeus* agglutinin 1, and vascular endothelial growth factor, [1]. In our case, the tumor was positive for CD31 and negative for CD34. Additionally, staining for erythroblast transformation specific related gene (*ERG*) was positive in our case. Erythroblast transformation specific related gene is a protooncogene that is a sensitive marker for endothelial differentiation expressed in vascular cancers. Sullivan et al. showed that *ERG* and CD31 staining showed 100% sensitivities for angiosarcoma with significant correlation. The two markers demonstrated higher sensitivity than CD34. Therefore, CD31, in conjunction with *ERG*, can help confirm the diagnosis of angiosarcoma [15].

Because of its low incidence, there are no standard guidelines for treating angiosarcoma. Treatment options most widely reported include surgery, radiotherapy, and chemotherapy. Radical surgery with wide excisional margins is the treatment of

choice for local disease. However, achieving negative margins may be challenging owing to the infiltrative and multifocal nature of the cancer [1]. As a result, the risk of local recurrence is between 30-100%. Adjuvant radiotherapy is added after surgical resection and has been shown to improve mortality. Head and neck tumors are especially challenging owing to the complex anatomy which facilitates metastatic spread [6]. Chemotherapy, including anthracyclines and taxane drug classes, is primarily used in metastatic disease, though data on their efficacy is limited. The prognosis of angiosarcoma is poor, with a 5-year survival rate of 33.5%, highlighting the importance of early recognition [1]. Our patient did not have problems with access to care, but because of his darker skin, a diagnosis of cutaneous angiosarcoma was not actively pursued by his other medical providers until he presented to us with more advanced disease. A meta-analysis identified poor prognostic factors, including increasing age, tumor size (lesions larger than 5cm yielding poorer prognosis), margin status, and cancer site [16]. Primary scalp cutaneous angiosarcoma was shown to have increased mortality rates compared to facial lesions. It was posited that hematogenous spread of cancer cells through the venous communicating system via the emissary veins could explain this increased mortality risk [17].

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Conclusion

Cutaneous angiosarcoma is a rare, aggressive malignancy requiring early recognition, diagnosis, and treatment. Numerous clinical variations exist, posing challenges to diagnosis, particularly in patients with Skin of Color. Although our initial clinical impression highly suggested cutaneous angiosarcoma, unrevealing histopathologic examinations from multiple specimens read by multiple dermatopathologists consistently yielded dermal hemorrhage without malignancy, which delayed our diagnosis. Incisional biopsy was critical to obtain enough tissue for a definitive diagnosis. Poorly differentiated or poorly vasoformative cutaneous angiosarcoma is a diagnostic challenge, often requiring multiple biopsies and discussions with dermatopathology; immunohistochemistry is invaluable in such cases to identify well-associated biomarkers. Our case highlights the aggressive nature of cutaneous angiosarcoma, necessitating early clinical recognition and close clinicopathologic correlation to confirm the diagnosis and prevent treatment delays.

Potential conflicts of interest

The authors declare no conflicts of interest.

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