Cutaneous Angiosarcoma With Skin Metastases and Persistent Bloody Pleural Effusions

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Cutaneous angiosarcoma is a rare aggressive malignancy of vascular origin that usually arises in the scalp or face of elderly men. We describe a case of primary cutaneous angiosarcoma with skin metastases and presumed metastases to the lung in a 58-year-old man who presented with persistent bloody pleural effusions, an asymptomatic nontraumatic red patch on the forehead of 2 to 3 months' duration, and a pair of purpuric papules on his left mid back of unknown duration. Cutaneous metastases of angiosarcoma are uncommon. Spontaneous persistent bloody effusions without hemoptysis are distinctly uncommon, and pleural fluid cytology is repeatedly negative in lung or pleural angiosarcoma, making it difficult to diagnose without tissue biopsy.

Cutis. 2012;89:129-132.

Angiosarcoma is a rare, aggressive, malignant vascular tumor accounting for only 1% to 2% of all soft tissue sarcomas, and sarcomas themselves account for less than 1% of all malignancies.[1] Angiosarcoma arises from endothelial cells of small vessels, hence the historic term *malignant angioendothelioma*.[2] Unlike most sarcomas, angiosarcoma has a predilection for skin and soft tissues but also can occur in the breast, spleen, and liver. The cutaneous form of angiosarcoma that primarily affects the face and scalp of elderly males was described by Jones[2] in 1964 and is characterized by a locally aggressive course and a poor prognosis because of a high potential for metastasis.[3] Insidious in onset, the clinical appearance can be quite variable and oftentimes rather innocent, resembling nothing more than a spreading bruise. Common sites of metastatic spread include the lungs, liver, spleen, and bone, with the lungs being the most common. Cutaneous metastases of angiosarcoma are exceedingly rare. Spontaneous persistent bloody effusions, especially when seen without hemoptysis, are particularly rare and force one to consider uncommon etiologies such as underlying parenchymal and malignant lung disease.

We present a case of cutaneous angiosarcoma with metastases to the skin and presumed metastases to the lung masquerading as bilateral bloody pleural effusions.

Case Report

A 58-year-old man presented to Columbia University Medical Center, New York, New York, in April 2007 with persistent bloody pleural effusions and an expanding asymptomatic red forehead lesion. He had a history of asthma and chronic obstructive pulmonary disease. He was admitted to an outside hospital in February 2007 for presumed pneumonia after 3 weeks of worsening shortness of breath. His workup revealed a large, bloody, exudative pleural effusion with negative pleural fluid cytology and cultures. The patient was transferred to Columbia University Medical Center in April 2007 for further workup and management that included large bilateral pleural effusions and possible lytic rib lesions, continuous sanguineous chest tube drainage, and treatment with intravenous antibiotics for presumed pneumonia.

On examination, in addition to the purpuric targetoid patch on his forehead (Figure 1), similar less conspicuous lesions were present on the forehead and in the hairline of the anterior scalp, which were believed to be satellite lesions. According to the patient, the lesion on his forehead was present for approximately 2 to 3 months prior to presentation and appeared to be gradually enlarging. A pair of purpuric papules

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The authors report no conflict of interest.

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were noted on his left mid back (Figure 2), but we were unable to obtain a history because the patient was unaware of their presence. Our initial differential diagnosis for the forehead lesion included hemorrhage secondary to trauma, Kaposi sarcoma, angiosarcoma, and opportunistic infection. The differential diagnosis of the purpuric papules on the back was broadened to include cutaneous metastases, pyogenic granulomas, sarcoidosis, and necrotizing vasculitis.

Skin biopsies from the forehead lesion and 1 of the papules on the back revealed ectatic anastomosing endothelial-lined vascular spaces permeating between collagen bundles in the dermis (Figure 3A). Prominent endothelial cells with minimal atypia protruding into the vascular spaces were seen on higher power (Figure 3B). Immunohistochemical stains of the skin biopsy specimens were negative for human herpesvirus 8. The histologic differential diagnosis for both lesions included Kaposi sarcoma, primary and metastatic angiosarcoma, targetoid hemosiderotic hemangioma, and epithelioid hemangioendothelioma.

Further workup included negative human immunodeficiency virus testing. He was scheduled to undergo video-assisted thoracoscopy for visualization of the lungs and tissue biopsy. With a rapidly declining respiratory status and persistent bloody effusions, the patient's condition acutely deteriorated and thoracoscopy with tissue biopsy were delayed. He died shortly thereafter and the family refused autopsy. We suspect that the etiology of the persistent bloody pleural effusions was metastatic angiosarcoma to the lungs with the primary site being the forehead.

Comment

Cutaneous angiosarcoma is an aggressive malignant vascular tumor that has a predilection for the skin of the face and scalp in the absence of radiation or lymphedema. Typically it occurs during the sixth and seventh decades of life and is more common in men. It tends to develop in 3 clinical settings: on the scalp or face of elderly white men, described by Jones[2] in 1964 and referred to as senile angiosarcoma; associated with postmastectomy lymphedema and known as Stewart-Treves syndrome; and postirradiation angiosarcoma that develops in irradiated skin.[4]

Although the tumor arises from endothelial cells, it is still not entirely clear if it is derived from lymphatic or blood vessels. Upregulation of vascular endothelial growth factor and the angiopoietin 2 gene, *ANGPT2*—2 factors involved in angiogenesis—has been found in tumor cells of cutaneous angiosarcomas.[1] Additionally, the absent expression of vascular endothelial cadherin on

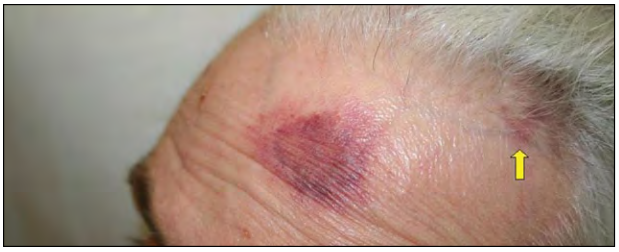

Figure 1. Purpuric targetoid patch on the patient's forehead and in the hairline of the anterior scalp (arrow).

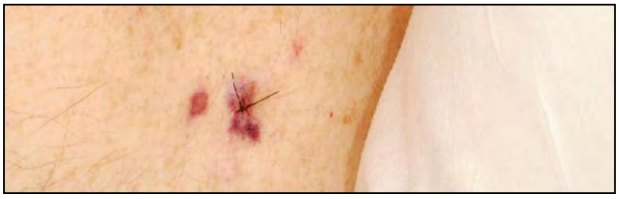

Figure 2. Pair of purpuric papules on the patient's left mid back.

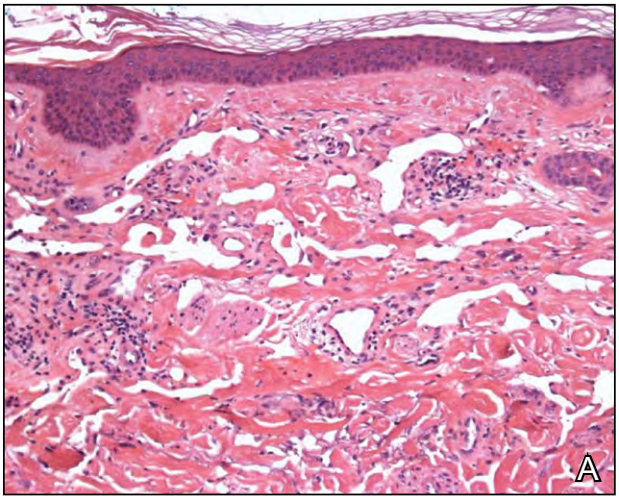

Figure 3. Ectatic anastomosing endothelial-lined vascular spaces permeating between collagen bundles in the dermis (A)(H&E, original magnification ×10). Prominent endothelial cells protruding into the vascular spaces seen on higher power (B)(H&E, original magnification ×40).

endothelial junctions could be associated with diminished cell-to-cell adhesiveness, possibly promoting local invasion and metastases.[5]

Even as the etiology continues to remain unclear, the most frequent association with angiosarcoma of the scalp is prior radiation, with a mechanism that may be related to mutations in the tumor protein p53 gene, *TP53*.[6] Because few nonwhite patients have been reported with angiosarcoma, actinic damage related to excessive UV exposure has been proposed as a possible risk factor.[7] Trauma also has been considered a possible causative agent, but trauma seems more likely to be the reason the lesion is noticed by the patient.[4]

Fifty percent of cutaneous angiosarcomas occur on the head and neck. The clinical appearance is quite variable. Insidious in onset, they frequently appear clinically innocent, resembling a spreading bruise, which is deceiving because they typically have an aggressive course. The lesion may be single or multifocal; bluish or violaceous; and may consist of nodules, plaques, or flat infiltrating areas that can occasionally bleed or ulcerate. The lesions are asymptomatic in most patients. The primary tumor often is more extensive than is apparent on physical examination, and the interval between the onset of symptoms and diagnosis can range from 0 to 12 months.

Multifocal lesions and extensive local growth are seen in approximately half of patients.[8] There is a tendency for spread through the dermis manifesting as satellitosis. It has been postulated that multiple lesions on presentation may be due to a delay in the clinical diagnosis of scalp angiosarcoma, which allows the lesions to progress unfettered, resulting in an eventual worse prognosis.[8] Our patient had multiple foci of disease at presentation; the lesions in the hairline and on the right side of the forehead were likely satellite lesions. Small, scattered, subtle lesions help remind us how important it is to perform a complete meticulous skin examination.

Angiosarcoma is a difficult diagnosis to make, even for experienced pathologists, because of its rarity and complex histology. The tumors contain a proliferation of ramifying and anastomosing vascular channels lined with atypical endothelial cells that dissect through collagen bundles and other surrounding structures. The tumor usually extends well beyond the limits of the apparent clinical lesion, leading to poorly defined margins. The histologic grade is based on the degree of differentiation of the vascular spaces and the degree of cytologic atypia in the lining of endothelial cells.

Although there is no immunohistochemical stain that is pathognomonic for angiosarcoma, the diagnosis may be supported by a finding of positivity for certain vascular and endothelial cell markers such as factor VIII–related antigen, ulex europaeus, CD31, and CD34.[9] The most sensitive and specific marker for endothelial differentiation is CD31; CD34 is less sensitive but not at all specific. von Willebrand factor is not sensitive and only somewhat specific, and ulex europaeus agglutinin 1 is a little sensitive and not specific.

Cutaneous metastases of sarcomas in general are very uncommon. They make up only 3.1% of all cutaneous metastases of cancers in men and 1.6% of all cutaneous metastases of cancers in women.[10] Only 4 case reports of primary cutaneous angiosarcoma with cutaneous metastases have been described[6,11-13] and there have been descriptions of 2 cases of cardiac angiosarcomas metastasizing to the skin,[13-23] 7 cases of aortic angiosarcomas presenting with cutaneous metastasis,[24-29] and 1 case of mediastinal angiosarcoma spreading to the finger.[30]

The overall prognosis for patients remains dismal with a reported 5-year survival rate of approximately 10% to 20%.[4,14,15] Cutaneous angiosarcomas commonly are diagnosed late in the course of the disease. A poor prognosis has been associated with an initial misdiagnosis, advanced age at presentation, multifocal nature of lesions at presentation, lesions greater than 5 cm in greatest dimension, lesions that initially cannot be surgically resected, and lesions with greater depth of invasion.[16]

Angiosarcoma has a tendency for metastasis via lymphatic or hematogenous routes. The rate of regional nodal involvement, stated to be 20% to 30%, is higher than most other sarcomas.[3] Most of the recorded metastases of angiosarcomas are at distant sites and occur late in the course of the disease. Common sites of distant spread include the lungs, liver, spleen, and bone, with the lungs being the most common.[4] Thin-walled, cystic pulmonary lesions and pneumothorax caused by pulmonary metastases are characteristic. Cerebral metastases are uncommon, but direct extension of the tumor through the skull has been reported.[4,17]

The rarity of spontaneous, bilateral, intractable bloody effusions without hemoptysis forces one to consider serious underlying parenchymal lung disease, including coagulation disorders, primary vascular disorders, and malignancy. Primary or metastatic lung or pleural angiosarcoma must be in the differential diagnosis. Primary angiosarcoma of the lung and pleura is extremely rare with only 31 cases of pleural origin, 4 cases of pulmonary tissue origin, 2 cases of tracheal origin, and 1 case of pulmonary artery origin reported.[18-20,31-35] The lungs are the primary sites for angiosarcoma metastasis, and the face and head are the most common primary origin for angiosarcoma lung metastasis.[21] Pleural metastases of angiosarcoma

are much less common. In the case of primary or metastatic lung or pleural angiosarcoma, pleural fluid cytology is either nonspecific or repeatedly negative and it is difficult to make a diagnosis without tissue biopsy,[22] as was the case with our patient.

The present case is reported to highlight the rarity of cutaneous angiosarcoma metastasizing to skin and the importance of maintaining a high index of suspicion for malignancy when presented with bilateral spontaneous bloody pleural effusions. The physician should be aggressive to biopsy any persistent atypical scalp lesion but also to biopsy the lung and/or pleura even with negative pleural fluid cytology in the case of unexplained persistent hemothoraces.

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