

Angiosarcoma Complicating Systemic Sclerosis: A Case Report

Margaret A. Fonder, MD; Deborah K. Douglas, MD

GOAL

To understand angiosarcoma to better manage patients with the condition

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the association of angiosarcoma and systemic sclerosis as well as other disease manifestations.
2. Discuss the role of vascular endothelial growth factor in the development of angiosarcoma.
3. Identify commonly employed modes of treatment for angiosarcoma.

CME Test on page 474.

This article has been peer reviewed and approved by Michael Fisher, MD, Professor of Medicine, Albert Einstein College of Medicine. Review date: May 2008.

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Albert Einstein College of Medicine and Quadrant HealthCom, Inc. Albert

Einstein College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Albert Einstein College of Medicine designates this educational activity for a maximum of 1 AMA PRA Category 1 Credit™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This activity has been planned and produced in accordance with ACCME Essentials.

Drs. Fonder and Douglas report no conflict of interest. The authors report no discussion of off-label use. Dr. Fisher reports no conflict of interest.

Cutaneous angiosarcoma is a rare malignant vascular tumor with a poor prognosis, most commonly affecting elderly white men. Diagnosis usually is delayed because the tumor has a highly variable and often innocuous presentation. Cutaneous angiosarcoma has been associated with a number of conditions and factors, including chronic lymphedema, prior radiation therapy, exposure to

chemicals, and vascular malformations. We report the case of a 40-year-old black man with systemic sclerosis (SSc) who developed a cutaneous angiosarcoma in an area of sclerodermatous scalp. We propose that vascular endothelial growth factor (VEGF) overexpression in sclerodermatous skin may predispose a patient to the development of vascular tumors, such as angiosarcoma. Because early diagnosis and treatment positively impact survival outcome in patients with angiosarcoma, it is essential that physicians recognize the association of angiosarcoma and SSc and maintain a low threshold for performing a biopsy when suspicious lesions are present on sclerodermatous skin.

Cutis. 2008;81:468-472.

Accepted for publication March 2, 2007.

Dr. Fonder is an intern in internal medicine, Greater Baltimore Medical Center, Maryland. Dr. Douglas is former Assistant Professor, Johns Hopkins Bayview Medical Center, Baltimore.

The authors report no conflict of interest.

Correspondence: Margaret A. Fonder, MD (margofonder@gmail.com).

Angiosarcoma is a rare malignant vascular tumor that is localized to the skin or superficial soft tissue in 60% of cases.^{1,2} More than half of cutaneous angiosarcomas arise on the head or neck.^{2,3} Skin lesions may be difficult to diagnose early because of their highly variable and often seemingly innocuous appearance^{1,4}; it is not uncommon for there to be extensive local spread and/or distant metastases by the time angiosarcoma is diagnosed. Cutaneous angiosarcoma typically affects elderly patients and is more common in men.^{1,4} It is relatively rare in black individuals.^{1,3} Classic presentation is an erythematous or violaceous lesion arising on the scalp of an elderly white man.^{1,4}

Cutaneous angiosarcoma has well-documented associations with a number of conditions and factors, including chronic lymphedema, prior radiation therapy, and exposure to chemicals such as thorotrast and vinyl chloride.^{1,4} In addition, there are several reported cases of malignant transformation to angiosarcoma of otherwise benign vascular lesions such as hemangiomas.⁵ To date, there is only one reported case of cutaneous angiosarcoma arising in association with scleroderma on the face of a 77-year-old white woman with systemic sclerosis (SSc).⁶ We report the case of a 40-year-old black man with SSc who developed a cutaneous angiosarcoma in an area of sclerodermatous scalp.

Case Report

A 40-year-old black man with a 5-year history of SSc involving the skin, lungs, and esophagus developed a painful nodule in a sclerodermatous plaque on the scalp (Figure 1). The patient's medical history was remarkable for Raynaud phenomenon, with recurrent digital ulcerations, a restrictive ventilatory defect, chronic dysphagia, and gastroesophageal reflux disease, as well as diffuse thickening and tightening of the skin, all related to his SSc. Serologic tests revealed antinuclear antibodies (titer ≥ 640) with a homogeneous nucleolar pattern and high levels of anti-Scl-70 antibodies. Anticentromere and anti-DNA antibodies were absent. His only medications were esomeprazole magnesium (40 mg daily) and amlodipine besylate (5 mg daily).

On physical examination, there was a 1.8-cm faintly erythematous nodule with overlying excoriations and crust on the right anterior parietal scalp. The remainder of the physical examination was notable for diffusely tight, firm, shiny skin involving the scalp, face, neck, chest, arms, hands, and groin. There were areas of depigmentation in several of the scleroderma plaques as well as multiple fingertip ulcerations.

On initial evaluation, the scalp lesion was diagnosed as a skin abscess not requiring further

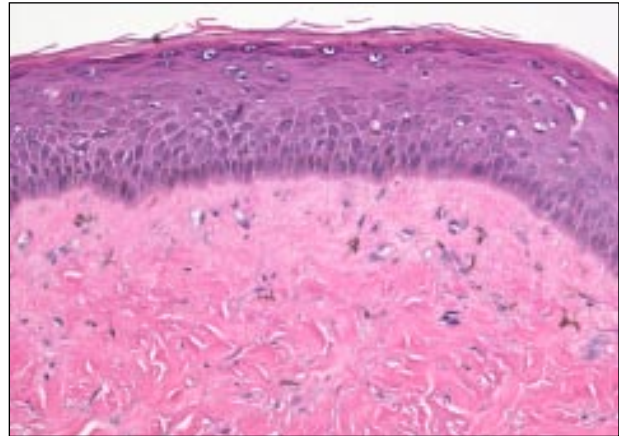


Figure 1. A biopsy specimen of a sclerodermatous plaque on the scalp revealed extensive dermal fibrosis and absence of adnexal structures (H&E, original magnification $\times 64$).

intervention. It continued to grow and cause discomfort, eventually necessitating surgical excision. Because of its anatomic position and the extremely taut nature of the surrounding sclerodermatous scalp, the mass was excised only partially so that primary closure would be possible. Histologic evaluation of the 2.5 \times 1.5-cm surgical specimen revealed an epithelioid-type high-grade angiosarcoma composed of cells that were positive for CD31 and CD34 (endothelial cell markers) on immunohistochemical stain (Figure 2). A wide excision of the lesion was then performed. Intraoperatively, the tumor was observed to have involved the galea and pericranium, necessitating removal of full-thickness soft tissue and adjacent bone (Figure 3). The scalp excision defect was closed with a split-thickness skin graft.

Microscopic examination of the excised tissue revealed extensive invasion of the dermis, perineural tissue, and deep skeletal muscle by angiosarcoma. Both circumferential and deep margins of the surgical specimen were involved by tumor. Tumor size was estimated at 9.5 cm. Computed tomographic (CT) scans of the chest, abdomen, and pelvis revealed a moderately dilated esophagus and moderate diffuse, hazy, ground glass pattern radiodensities of the bilateral lung bases consistent with SSc but no lesions suggestive of metastasis.

The extensive local tissue involvement by tumor dictated radiation therapy to the area. Treatment was delayed, however, by failure of the skin graft to completely heal. The open wound was subsequently surgically debrided and closed with an allograft. This second graft began to successfully heal, but an enlarging subcutaneous mass at its anterior border soon developed. Results of a biopsy revealed recurrent angiosarcoma. This lesion grew quickly to encompass over half of the patient's forehead,

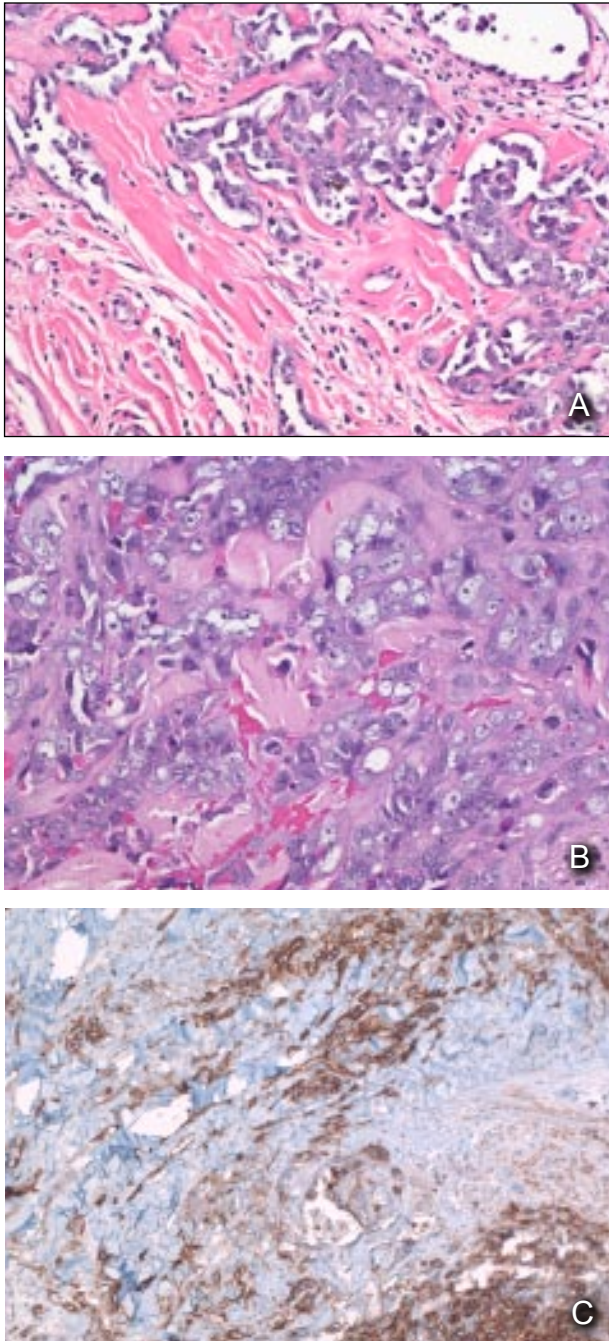


Figure 2. Histologic evaluation of the surgical specimen showed an epithelioid cellular lesion forming both large irregular channels as well as small, poorly formed vascular channels with extravasated red blood cells. The endothelial cells lining these irregular cleftlike spaces are enlarged and atypical, with prominent nucleoli, cellular pleomorphism, and mitoses. In some areas, these malignant cells have proliferated, forming papillary tufts and solid sheets (H&E, original magnifications $\times 64$ [A] and $\times 100$ [B]). Immunohistochemical staining was diffusely positive for the endothelial cell marker CD34 (original magnification $\times 40$) (C). Staining also was positive for CD31. Tests for epithelial and melanoma markers as well as synaptophysin and chromogranin stains were negative.

as well as the nasal root, causing severe periorbital edema and conjunctival congestion. Daily radiation therapy totaling 5000 cGy to the upper face and frontal, parietal, and occipital scalp was initiated.

Soon after, the patient was hospitalized for methicillin-resistant *Staphylococcus aureus* bacteremia thought to have originated from a skin infection near the tumor. He also complained of worsening sharp right retroauricular and left hip pains. Results of a punch biopsy of the right posterior auricular scalp revealed recurrent angiosarcoma, and a CT-guided biopsy specimen of the left iliac bone revealed metastatic angiosarcoma. Magnetic resonance imaging of the pelvis and lower extremities showed bone marrow lesions involving the left ischium, left anterior superior iliac spine, and femoral necks of both legs. Palliative radiation therapy to the left iliac bone was initiated for symptom control.

Given the extensive metastatic spread, systemic paclitaxel chemotherapy (100 mg/m^2 weekly [3 of 4 weeks]) was administered through a central venous port. Soon after completing the first round of chemotherapy, the patient was hospitalized with a polymicrobial infection of his partially healed scalp wound including *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and group B streptococci. He was treated with levofloxacin (500 mg daily for 10 days). An abdominal CT scan showed that the patient had a lesion in the right posterior inferior lobe of the liver suggestive of metastatic angiosarcoma. Several weeks after discharge, he presented to the emergency department of an outside hospital complaining of worsening dysphagia and purulent material draining from his central venous port. Shortly thereafter, he died, with sepsis as the presumed cause of death.

At autopsy, there were multiple large scalp ulcerations extending to bone. The skin was diffusely firm and taut. Serial sectioning of the liver demonstrated a somewhat hemorrhagic-appearing dark red-brown lesion measuring 3 cm in the right posterior lobe, composed microscopically of diffusely infiltrating metastatic angiosarcoma confirmed by CD31 immunostain. Additionally, there were multifocal microabscesses of the heart, lungs, kidneys, spleen, and skin of the face and neck.

Comment

Systemic sclerosis, or scleroderma, is a chronic systemic disease characterized by widespread fibrosis of the skin and internal organs, vasculopathy, and autoimmunity.^{7,8} Black individuals are affected more frequently than white individuals and tend to have an earlier age of disease onset, greater tendency for severe disease, and overall worse prognosis.⁹ Patients



Figure 3. Scalp excision defect showing removed portions of periosteum and cranium.

with SSc have a 2.6% to 8.7% risk of malignancy in general, with lung cancer and squamous cell carcinoma (arising in affected pulmonary or skin tissue) among the most commonly associated neoplasms.^{10,11} To our knowledge, we describe the second reported case of SSc-associated angiosarcoma.

Systemic sclerosis is thought to arise from altered endothelial cell function and blood vessel reactivity occurring in association with inflammation and autoimmunity. The earliest disease manifestations are generally vasculature related, with most patients developing Raynaud phenomenon before manifesting signs and symptoms of overt sclerosis.^{7,8} Characteristic nail fold capillaroscopy findings in patients with SSc include enlarged capillaries, busy capillary formations, microhemorrhages, and variable capillary loss.⁷

Patients with SSc have increased serum and skin levels of vascular endothelial growth factor (VEGF), a key mediator of angiogenesis that induces differentiation, proliferation, and migration of endothelial cells.⁷ Endothelial cell VEGF receptors are up-regulated in SSc as well. This chronic overexpression of VEGF is thought to account for the chaotic vessel morphology observed on nail fold capillaroscopy.⁷ We hypothesize that elevated levels of VEGF in sclerodermatous skin may also predispose one to the development of angiosarcoma. Studies have shown that the proliferating cells in angiosarcoma overexpress VEGF messenger RNA, VEGF protein, and VEGF receptors, suggesting that VEGF may spur the development and invasion of neoplasia.¹²⁻¹⁴ Furthermore, Arbiser et al¹³ found that overexpression of human VEGF in immortalized endothelial cells

was sufficient to convert them from benign hemangiomas to malignant angiosarcomas.

Cutaneous angiosarcoma can assume a variety of clinical appearances, including bruise-like lesions, dusky plaques, chronic edema or cellulitis, ulcerated nodules, infectious-appearing lesions, and scarring alopecia.¹⁻⁴ Tumor tissue usually extends far beyond the apparent borders of the lesion and frequently invades underlying soft tissue and bone. Thus, patients often have advanced disease at the time of diagnosis.¹⁻⁴

Angiosarcoma prognosis is generally poor, with reported 5-year survival rates ranging from 10% to 35%.^{1,2} Surgical excision, extended-field radiotherapy, and/or paclitaxel chemotherapy are commonly employed modes of treatment,^{1,4,15,16} though even with these interventions, local tumor recurrence and distant metastases are common. Importantly, early diagnosis positively correlates with prolonged survival.^{3,4}

Conclusion

We present a case of cutaneous angiosarcoma arising in an area of SSc-affected skin. We suspect that the co-occurrence of these 2 diseases may be related to interconnected underlying pathophysiology. Because early diagnosis can positively impact prognosis, physicians should maintain a high index of clinical suspicion and low threshold for performing a biopsy when suspicious lesions are present on sclerodermatous skin.

Acknowledgment—We thank Frederick M. Wigley, MD, for his detailed clinic and procedure notes.

REFERENCES

1. Mark RJ, Poen JC, Tran LM, et al. Angiosarcoma: a report of 67 patients and a review of the literature. *Cancer*. 1996;77:2400-2406.
2. Morgan MB, Swann M, Somach S, et al. Cutaneous angiosarcoma: a case series with prognostic correlation. *J Am Acad Dermatol*. 2004;50:867-874.
3. Holden CA, Spittle MF, Jones EW. Angiosarcoma of the face and scalp, prognosis and treatment. *Cancer*. 1987;59:1046-1057.
4. Hausteil UF. Angiosarcoma of the face and scalp. *Int J Dermatol*. 1991;30:851-856.
5. Rossi S, Fletcher CD. Angiosarcoma arising in hemangioma/vascular malformation: report of four cases and review of the literature. *Am J Surg Pathol*. 2002;26:1319-1329.
6. Puizina-Ivić N, Bezić J, Marasović D, et al. Angiosarcoma arising in sclerodermatous skin. *Acta Dermatovenerol Alp Panonica Adriat*. 2005;14:20-25.
7. Distler O, Distler JH, Scheid A, et al. Uncontrolled expression of vascular endothelial growth factor and its receptors leads to insufficient skin angiogenesis in patients with systemic sclerosis. *Circ Res*. 2004;95:109-116.
8. Abraham DJ, Varga J. Scleroderma: from cell and molecular mechanisms to disease models. *Trends Immunol*. 2005;26:587-595.
9. Reveille JD. Ethnicity and race and systemic sclerosis: how it affects susceptibility, severity, antibody genetics, and clinical manifestations. *Curr Rheumatol Rep*. 2003;5:160-167.
10. Leandro MJ, Isenberg DA. Rheumatic diseases and malignancy—is there an association? *Scand J Rheumatol*. 2001;30:185-188.
11. Rosenthal AK, McLaughlin JK, Gridley G, et al. Incidence of cancer among patients with systemic sclerosis. *Cancer*. 1995;76:910-914.
12. Amo Y, Masuzawa M, Hamada Y, et al. Serum concentrations of vascular endothelial growth factor in angiosarcomas with and without p53 gene mutation. *Acta Derm Venereol*. 2002;82:373-374.
13. Arbiser JL, Larsson H, Claesson-Welsh L, et al. Overexpression of VEGF 121 in immortalized endothelial cells causes conversion to slowly growing angiosarcoma and high level expression of the VEGF receptors VEGFR-1 and VEGFR-2 in vivo. *Am J Pathol*. 2000;156:1469-1476.
14. Zietz C, Rössle M, Haas C, et al. MDM-2 oncoprotein overexpression, p53 gene mutation, and VEGF up-regulation in angiosarcomas. *Am J Pathol*. 1998;153:1425-1433.
15. Fata F, O'Reilly E, Ilson D, et al. Paclitaxel in the treatment of patients with angiosarcoma of the scalp or face. *Cancer*. 1999;86:2034-2037.
16. Skubitz KM, Haddad PA. Paclitaxel and pegylated-liposomal doxorubicin are both active in angiosarcoma. *Cancer*. 2005;104:361-366.

DISCLAIMER

The opinions expressed herein are those of the authors and do not necessarily represent the views of the sponsor or its publisher. Please review complete prescribing information of specific drugs or combination of drugs, including indications, contraindications, warnings, and adverse effects before administering pharmacologic therapy to patients.

CONFLICT OF INTEREST STATEMENT

The Conflict of Interest Disclosure Policy of Albert Einstein College of Medicine requires that authors participating in any CME activity disclose to the audience any relationship(s) with a pharmaceutical or equipment company. Any author whose disclosed relationships prove to create a conflict of interest, with regard to their contribution to the activity, will not be permitted to present.

The Albert Einstein College of Medicine also requires that faculty participating in any CME activity disclose to the audience when discussing any unlabeled or investigational use of any commercial product, or device, not yet approved for use in the United States.

The staff of CCME of Albert Einstein College of Medicine have no conflicts of interest with commercial interest related directly or indirectly to this educational activity.