

Brittany Carter^{1*}, Christine Jaworsky²
and Monte Fox³

¹Western Reserve Hospital, Ohio University Heritage College of Osteopathic Medicine, Detroit, USA

²Department of Dermatology, Case Western Reserve University School of Medicine, University of Pennsylvania, Cleveland, USA

³Western Reserve Hospital, Summa Akron City, Cleveland Clinic Akron General, Case Western Reserve School of Medicine, Cuyahoga Falls, USA

Dates: Received: 11 August, 2016; Accepted: 26 August, 2016; Published: 27 August, 2016

***Corresponding author:** Brittany Carter, DO, Resident, Western Reserve Hospital, Ohio University, Heritage College of Osteopathic Medicine, 3670 Woodward Avenue, #414 Detroit, MI 4820, USA, Tel: 313-585-6927; E-mail: carter.brittanyd@gmail.com

www.peertechz.com

ISSN: 2455-8605

Keywords: Cutaneous angiosarcoma; Epithelioid angiosarcoma; Systemic sclerosis

Case Report

Systemic Sclerosis Associated Angiosarcoma: A Case Report and Review of the Literature

Abstract

Cutaneous angiosarcoma is an uncommon malignant vascular tumor with a highly variable presentation. It most commonly occurs on the head and neck of elderly Caucasian men, while less commonly on the skin of persons with pre-existing conditions or cutaneous lesions. To date, only three reports of angiosarcoma arising on the head and neck of individuals with systemic sclerosis exist in the literature. We report the fourth case: a 58 year-old African-American female with systemic sclerosis who developed an epithelioid subtype of cutaneous angiosarcoma on the right elbow, rather than the head and neck region.

Abbreviations

PET: Positron Emission Tomography

Introduction

Cutaneous angiosarcoma is an uncommon malignant vascular tumor with a highly variable presentation. It has a predilection for elderly Caucasian men, with 50% of tumors occurring primarily on the head and neck [1]. Cutaneous angiosarcomas may also occur in sites with chronic lymphedema, areas of prior radiation therapy, and in association with vascular and peripheral nerve sheath tumors [1]. Review of the literature reveals three reports of angiosarcoma arising on the head and neck of those with concomitant systemic sclerosis. There is also one report of angiosarcoma and morphea arising in a site of irradiation. We report a fourth case of angiosarcoma occurring in a patient with coexistent systemic sclerosis. Our patient has an epithelioid variant of angiosarcoma, which presented on the right elbow as an innocuous-appearing cutaneous lesion. We discuss therapeutic options and prognosis in patients with both diseases.

Case Report

A 58 year-old African-American woman was referred to dermatology from rheumatology in January of 2016 for evaluation of a “wart-like lesion with skin breakdown” on the right elbow. Her past medical history was significant for progressive systemic sclerosis, end stage renal disease on hemodialysis, essential hypertension, fibromyalgia, osteochondropathy, and adhesive capsulitis of the shoulder. Surgical history was noncontributory. Her social history was negative for use of tobacco, alcohol, or recreational drugs.

Review of the patient’s records shows that in January 2015 rheumatology documented drainage from the right elbow. Cultures were positive for methicillin-sensitive staphylococcus aureus. She had started on twice-daily trimethoprim-sulfamethoxazole and warm

soaks empirically, and continued for 10 days. Improvement was noted in February 2015, only to worsen soon thereafter. Concerns for possible non-infectious etiologies such as calciphylaxis and/or calcium deposits were raised. Conservative treatment continued through December 2015. At that time, further irritation, cutaneous breakdown and a new verrucous-appearing area were noted.

On presentation in dermatology, the patient’s main complaint was dry skin. Physical examination revealed an asymptomatic friable, verrucous plaque with central ulceration located on the right elbow (Figure 1). The remainder of her physical examination was notable for diffusely taut, shiny skin of the face (Figure 2), neck, trunk, upper, and lower extremities. There was superimposed generalized xerosis. Firm yellowish nodules were seen overlaying the fingers, wrists, and elbows, suggestive of calcinosis cutis. Severe contractures involving finger, wrist, elbow, and shoulder joints showed a reduced range of motion.

Shave biopsy of the suspicious growth showed an ulcerated exophytic nodule with overlying papillomatous spongiotic acral epithelium (Figure 3). The dermis contained variably sized aggregates of monotonous appearing basophilic staining epithelioid cells with individual cell necrosis, mitotic activity and focal prominent nucleoli.



Figure 1: A friable, verrucous plaque on the right elbow.

Such aggregates approximated the epidermal undersurface however, did not appear to arise from the epidermis (Figure 4). Occasional collections showed epithelioid cells lining papillomatous projections and cribriform structures (Figure 5 a,b). Within the deeper dermis, pleomorphism and cytologic atypia were more notable (Figure 6). Immunohistochemical stains showed tumor cells to be negative with Melan-A, AE1/AE3, and CK20. They marked strongly with CD31 and D2-40 (Figure 7 a,b), indicating vascular and lymphatic lineage. These findings are consistent with an atypical vascular neoplasm, and the diagnosis of epithelioid angiosarcoma.

The patient was referred to hematology-oncology for further evaluation and management. PET imaging demonstrated areas of



Figure 2: Characteristic taut, bound down skin with loss of skin markings in a patient with systemic sclerosis.

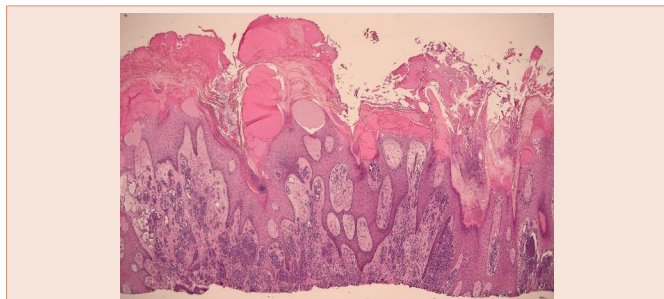


Figure 3: Shave biopsy at 4x magnification reveals an ulcerated exophytic nodule with overlying papillomatous spongiotic acral epithelium.

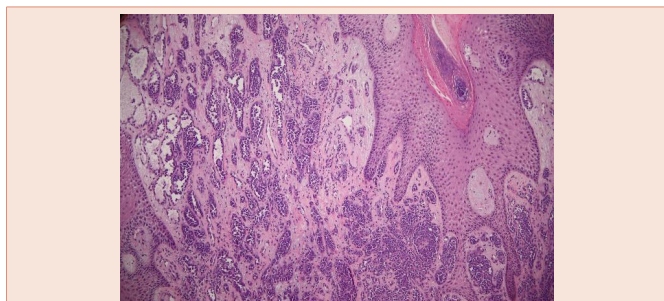


Figure 4: 10x magnification of variably sized aggregates of monotonous appearing basophilic staining epithelioid cells with individual cell necrosis, mitotic activity and focal prominent nucleoli, approximating the epidermal undersurface, but not arising from the epidermis.

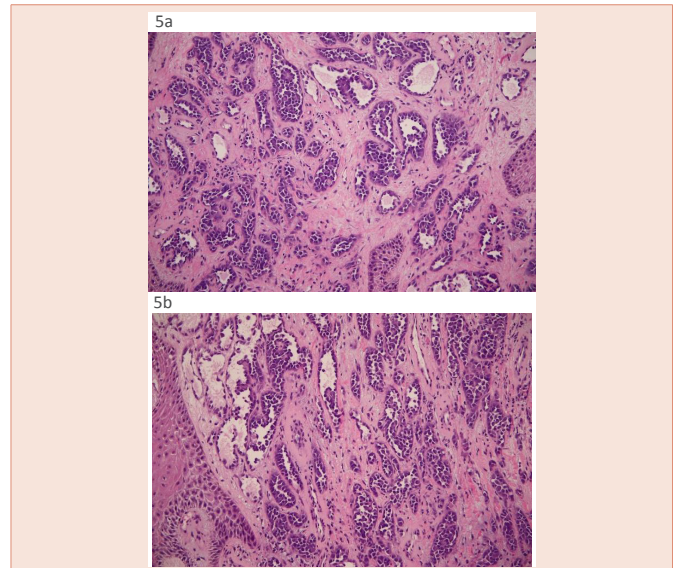


Figure 5a,b: 20x magnification of epithelioid cells lining papillomatous projections and cribriform structures.

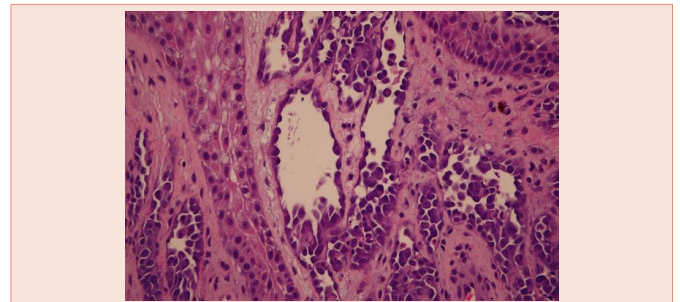


Figure 6: Pleomorphism and cytologic atypia seen at 40x magnification.

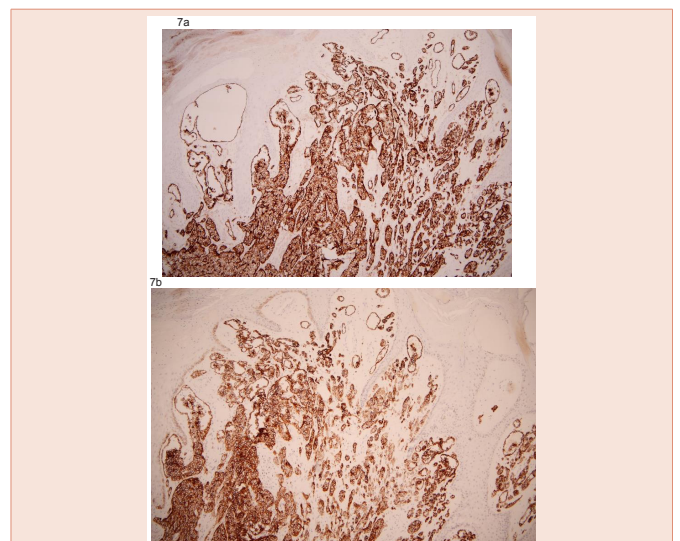


Figure 7a,b: Positive stains of immunohistochemical markers CD31 (a) and D2-40 (b) at 10x magnification.

abnormal radiotracer accumulation in the right elbow, as well as within the proximal right upper extremity, and right axilla. There was no evidence of metastases to the lungs, liver, adrenal glands, or skeleton.

Hematology-oncology noted that the likelihood for disease control was small, even with surgical intervention. The use of radiotherapy was also thought to be of limited utility because of her underlying scleroderma. Therefore, palliative chemotherapy with paclitaxel was suggested. Her wound care regimen was conservative, and consisted of washing twice daily with soap and water, followed by a topical over-the-counter antibiotic for prophylaxis.

The patient reported a visible reduction in the size of the right elbow angiosarcoma during a follow-up telephone encounter in June of 2016. She also denied any unwanted side effects from chemotherapy.

Discussion

Angiosarcoma is variably referred to as malignant hemangioendothelioma, hemangiosarcoma, and lymphangiosarcoma in the literature. It is an uncommon malignant neoplasm of endothelium, accounting for less than 1% of all sarcomas. Although it may occur at any location in the body, it has a predilection for the skin and superficial soft tissue [2,3]. Cutaneous angiosarcomas account for one half of all angiosarcomas [3] and have variable presentations [4]. The three main clinico-pathological subtypes of cutaneous angiosarcoma include: idiopathic/primary cutaneous angiosarcoma of the head and neck, angiosarcoma arising in the setting of chronic lymphedema, and post-irradiation angiosarcoma [1]. A miscellaneous category is acknowledged due to a number of other skin conditions and factors cited to be associated with the development of angiosarcoma [1]. This includes, but not limited to, angiosarcomas arising in pre-existing benign vascular tumors, benign and malignant peripheral nerve sheath tumors, exposure to chemicals, adjacent to foreign body material, in the vicinity of arteriovenous fistulas in renal transplant patients, or in association with rare genetic syndromes [1,5]. As in our patient, there is often delay in diagnosis since such tumors frequently have an innocuous clinical appearance. Often, there is extensive local spread with or without distant metastases at the time of diagnosis [4].

Primary cutaneous angiosarcoma, the most common clinical form, usually occurs after the seventh decade, with a strong predilection for Caucasians compared to individuals of African or Asian descent. Approximately a 2:1 male: female ratio exists [1-3]. Most lesions in this category appear as an ill-defined bruise-like area with indurated borders involving the upper part of the face or scalp. Edema may be present [2]. Advanced lesions are elevated, nodular, and occasionally ulcerated [3]. Angiosarcoma associated with lymphedema most often occurs within 10 years of a mastectomy, following the diagnosis of breast carcinoma. One or more firm violaceous coalescing nodules or an indurated plaque superimposed on brawny, nonpitting edema of the affected extremity may be seen. Ulceration and serosanguineous discharge are seen in late lesions [3]. Post-irradiation angiosarcomas appear as infiltrative plaques or nodules in or near the area of tissue irradiated [2].

The diagnosis of angiosarcoma is confirmed histologically and appears similar in all of the three main subtypes.¹ Well-differentiated areas display a network of sinusoidal vessels lined by a single layer of endothelial cells with slight to moderate nuclear atypia. Such cells exhibit an infiltrative pattern, splaying collagen bundles and groups of adipocytes. In less well-differentiated areas, the endothelial cells with more pronounced nuclear pleomorphism and mitotic form confluent sheets and line papillary projections. In poorly differentiated areas, luminal formation may be non-apparent and mitotic activity may be high, mimicking other high-grade sarcomas, carcinoma or melanoma. Hemorrhage and blood-filled cavities may be present [2]. Immunohistochemical studies are useful in establishing the lineage of the tumor and excluding other neoplasms. Vascular and lymphatic markers, CD 31 and D2-40 respectively, confirm the nature of the tumor [3].

Highly aggressive angiosarcomas with an epithelioid appearance occasionally occur in the skin, however, show a predilection for the limbs [6]. Our patient's epithelioid angiosarcoma evolved on the right elbow. This histologic variant shows large rounded cells with prominent eosinophilic nucleoli. The only morphologic evidence of vascular differentiation may be the presence of occasional intracytoplasmic vacuoles. Cytokeratin positivity is present in about one-third of epithelioid angiosarcomas [7,8], making distinction from carcinoma problematic. Using both CD34 and CD31, nearly all angiosarcomas, even poorly differentiated ones, can be identified. CD31 (platelet-endothelial cell adhesion molecule) appears to be the more sensitive and more specific antigen for endothelial differentiation [2,3]. The distinction between malignant tumors showing blood vessel differentiation (angiosarcoma) and those showing lymphatic differentiation (lymphangiosarcoma) has often been unclear in the past. With the advent of the marker D2-40, a selective marker of lymphatic endothelium, a more reliable distinction can be made [1,9]. Our patient's tumor was negative for both CK20 and AE1/AE3, as well as a melanocytic marker, but marked strongly with both CD31 and D2-40 (Figure 7 a,b), confirming a vascular and lymphatic lineage.

In 2008, Weiss and colleagues reviewed 69 cases of sporadic cutaneous angiosarcoma. Increased mortality was observed in older patients and in those whose tumors occurred on the trunk and extremities as compared with those of the head and neck cases. Necrosis and epithelioid features also correlated with increased mortality. Clinical extent, resectability, and margin status are also important determinants of outcome, as reported in several studies [3]. These features are, however, less significant as tumor size increases [1]. Tumor size is a strong predictor of outcome in all angiosarcomas [3]. Approximately one-half of angiosarcomas are less than 5 cm at the time of presentation. Such tumors have a significantly better prognosis than those larger than 5 cm at the time of diagnosis [3].

Sclerodermatous skin prohibited total excision of an angiosarcoma on the temporal scalp of a 77 year-old Caucasian female with systemic sclerosis, reported by Puizina-Ivic et al. [5], Fonder et al. discussed similar obstacles occurring in the case of a 40 year-old African-American male with systemic sclerosis and an angiosarcoma on the scalp. Their patient initially had only a partial

excision due to the anatomic location of the angiosarcoma and the extremely taut nature of the surrounding sclerodermatous scalp. The excision defect was eventually closed with a split-thickness skin graft. Radiation was delayed due to failure of the skin graft to completely heal. This necessitated debridement. A second graft was placed during repeat closure. The angiosarcoma recurred at the periphery and treated with daily radiation. The area later became secondarily infected. The angiosarcoma eventually metastasized warranting palliative chemotherapy, predisposing the patient to more infections and eventually passing due to sepsis [4]. Kubota et al. reported the third case of cutaneous angiosarcoma that developed in a patient with systemic sclerosis. Their patient was a 67 years old woman. Multiple granulomatous tumors grew rapidly within sclerotic skin on her scalp [10].

General consensus holds that treatment for localized disease includes surgical excision with wide margins [2,3], but obtaining negative margins can be difficult.¹ Even with negative margins by histologic examination, the recurrence rate and chance of metastatic disease are high and the prognosis is extremely poor. This is likely due to the disease often times being multifocal [2]. Fewer than 15% of cases survive 5 years [2]. Most long-term survivors receive early radical ablative surgery [2]. Adjunct radiotherapy may be combined with surgery [3], for palliative purposes, but does not improve survival [2]. There is no conclusive evidence to support the use of adjuvant chemotherapy for localized disease after surgery and radiation [3]. Cytotoxic chemotherapy, which includes the use of anthracyclines, ifosfamide, and taxanes (i.e. paclitaxel), is the primary treatment for metastatic angiosarcoma [3].

In our patient, surgical intervention was not offered due to the potential for incomplete closure of a post-operative defect. Furthermore, radiation to the site was thought to be potentially more harmful than beneficial. Given metastasis demonstrated on PET scan, the age of the patient, associated comorbidities, location of the tumor, and the aggressive subtype, palliative chemotherapy was most appropriate. Of note, our patient's tumor was not associated with the AV fistula placed for dialysis, which was located in her left subclavian system.

The three prior reports of angiosarcoma arising in the setting of systemic scleroderma arose on the head and neck region. Our patient differed in that her tumor arose on an extremity and was epithelioid in subtype. Although clinical presentations of angiosarcomas in sclerodermatous skin vary, it is common for lesions to be initially mistaken for soft tissue infections. This was the case with our patient, who was referred to dermatology when a verrucous plaque with ulceration developed on the elbow. Lack of response to conservative

measures and maintaining a low threshold for biopsy in the proper clinical setting may allow for a more timely diagnostic assessment.

Conclusion

We add a fourth report of angiosarcoma arising in a patient with systemic sclerosis to the literature. Unlike prior patients, our patient had an epithelioid subtype of tumor, which presented on an extremity rather than the head and neck area. Early diagnosis and treatment of angiosarcoma positively impacts survival. It is especially important in those with concomitant systemic sclerosis, where the underlying disease complicates wound healing and presents difficulties in adequately eradicating even localized tumor burden. A high index of suspicion for lesions presenting on sclerodermatous skin, and a low threshold for performing biopsies are necessary to allow for early diagnosis and potentially effective therapy.

Acknowledgement

The authors wish to thank Dr. Christopher Fletcher for his assistance in confirming the histopathological diagnosis.

References

1. Patterson JW (2016) "Vascular Tumors." Weedon's Skin Pathology. Elsevier 1069–1115.
2. Paula EN, Kincannon J (2012) "Vascular Neoplasms and Neoplastic-like Proliferations." *Dermatology*. Elsevier 114: 1915–1941.
3. Goldblum John R, Andrew L Folpe, Sharon W Weiss (2014) "Malignant Vascular Tumors." *Enzinger and Weiss's Soft Tissue Tumors*. Elsevier 703–732.
4. Fonder MA, Douglas DK (2008) "Angiosarcoma Complicating Systemic Sclerosis: A Case Report." *Cutis* 81: 468–472.
5. Puizina-Ivić N, Bezić J, Marasović D, Gotovac V, Carija A, et al. (2005) Angiosarcoma Arising in Sclerodermatous Skin." *Acta Dermatovenerol Alp Pannonica Adriat* 14: 20–25.
6. Suchak R, Thway K, Zelger B, Fisher C, Calonje E, et al. (2011) Primary cutaneous epithelioid angiosarcoma: a clinicopathological study of 13 cases of rare neoplasm occurring outside the setting of conventional angiosarcomas and with predilection for the limbs. *Am J Surg Pathol* 35: 60-69.
7. Gray MH, Rosenberg AE, Dickersin GR, Bhan AK (1990) Cytokeratin expression in epithelioid vascular neoplasms. *Hum Pathol* 21: 212-217.
8. Meis-Kindblom JM, Kindblom LG (1998) Angiosarcoma of soft tissue: a study of 80 cases. *Am J Surg Pathol* 22: 683-697.
9. Kahn HJ, Bailey D, Marks A (2002) Monoclonal Antibody D2-40, a New Marker of Lymphatic Endothelium, Reacts with Kaposi's Sarcoma and a Subset of Angiosarcomas. *Mod Pathol* 15: 434–440.
10. Kubota N, Fujisawa Y, Nakamura Y, Tanaka R, Saito A, et al. (2015) Angiosarcoma of the Scalp in a Patient with System Sclerosis. *The Journal of Dermatology* 42: 102–104.

Copyright: © 2016 Carter B. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Citation: Carter B, Jaworsky C, Fox M (2016) Systemic Sclerosis Associated Angiosarcoma: A Case Report and Review of the Literature. *Int J Dermatol Clin Res* 2(1): 014-017. DOI: 10.17352/2455-8605.000015