

Angiosarcoma in a Patient With Congenital Nonhereditary Lymphedema

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Angiosarcoma is an uncommon but aggressive tumor of endothelial origin that may occur in the upper extremities of patients with postmastectomy lymphedema (Stewart-Treves syndrome) as well as in other regions. We present an unusual case of angiosarcoma associated with congenital nonhereditary lymphedema in an 18-year-old man. Our case underscores the need for a careful clinical examination and shows the importance of appropriate sampling and thorough pathologic examination of suspicious areas to exclude the presence of a malignant process.

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Various cutaneous tumors associated with chronic lymphedema have been described, including angiosarcoma.¹ Angiosarcomas are rare malignant tumors that show a mixed vascular and lymphatic phenotype and account for less than 1% of all sarcomas. Cutaneous angiosarcoma has several subtypes, including idiopathic, lymphedema-associated, and postirradiation types. Regions of the body with long-term sun exposure, such as the head or neck, are the most common sites of idiopathic angiosarcoma. Cases of chronic lymphedema-associated angiosarcoma tend to be iatrogenic¹ and largely occur in patients who have undergone a radical mastectomy with lymph node dissection (Stewart-Treves syndrome). The diagnosis may be delayed because of a benign appearance of the lesion and a lack of consistency in clinical presentations. We report a case of angiosarcoma in an 18-year-old man with congenital nonhereditary lymphedema.

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Case Report

An 18-year-old man with a history of unilateral congenital lymphedema of his right lower extremity presented to the dermatology department with purpuric discoloration and increased swelling of skin on the chronically edematous, distal portion of his right ankle and instep. A prior diagnosis of congenital lymphedema was rendered at the age of 2 years when lymphoscintigraphy showed the absence of lymph vessels. He had no family history of lymphedema. He had been diligent with the use of compression garments throughout his childhood and adolescence, though severe edema persisted and progressed. He was hospitalized several times due to episodes of recurrent cellulitis followed by lichenification and progressive hyperkeratosis.

Physical examination showed several ill-defined erythematous to violaceous papules and nodules around the medial aspect of his right ankle and instep (Figure 1), raising suspicion of a de novo vascular neoplasm. A 4-mm punch biopsy was performed. Histologic examination of the lesion showed an atypical dermal vascular proliferation with features resembling retiform hemangioendothelioma with multiple



Figure 1. Congenital nonhereditary lymphedema and numerous erythematous to violaceous plaques with lichenification and hyperkeratosis on the right ankle and instep.

superficial and deep dilated blood vessels lined with atypical, round, hobnailed endothelial cells involving the base of the biopsy specimen (Figure 2). No tumor necrosis or mitotic figures were identified. On immunohistochemistry, the atypical endothelial cells were positive for CD31 and FLI-1 (friend leukemia virus integration 1 transcription factor) but were negative for human herpesvirus 8 and monoclonal antibody D2-40. At 18 years of age, he underwent a below-the-knee amputation of his right lower extremity. The cutaneous plaques were associated with underlying superficial and deep hemorrhagic infiltrating tumor nodules within the skin and subcutaneous tissue on gross examination of the amputation specimen (Figure 3).

Histopathologic examination showed an ill-defined, deeply invasive tumor with a dissecting vasoformative pattern. The tumor predominantly consisted of racemose vascular channels lined with a multilayering of large pleomorphic and hyperchromatic tumor cells (Figures 4A and 4B). There were solid areas of mixed spindled and epithelioid cells, tumor necrosis, and brisk mitotic activity. Retiform hemangioendotheliomalike

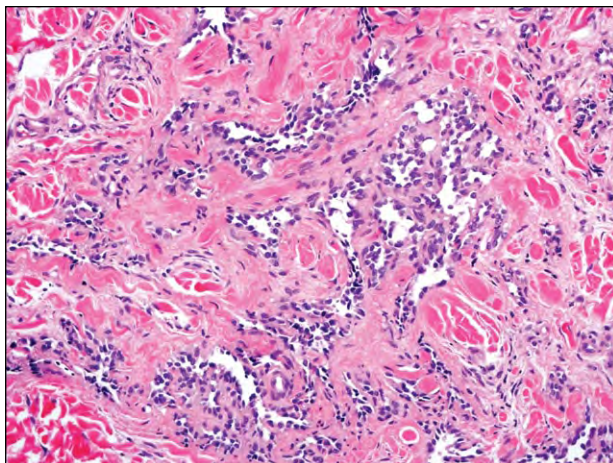


Figure 2. Angiosarcoma resembled retiform proliferation of relatively low-grade appearing, hobnailed endothelial cells and perivascular fibrosis (H&E, original magnification $\times 200$).

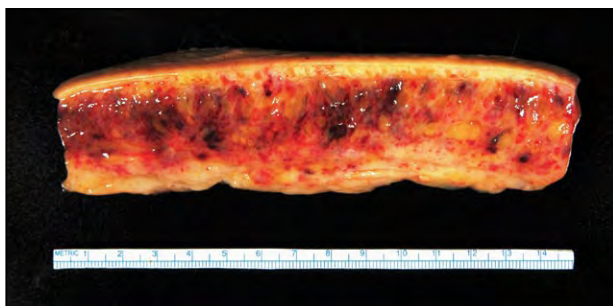


Figure 3. Following amputation, a hemorrhagic infiltrating tumor within the skin and subcutaneous tissue was noted.

areas with striking lymphedema were identified in the superficial dermis. Tumor cells also exhibited positivity

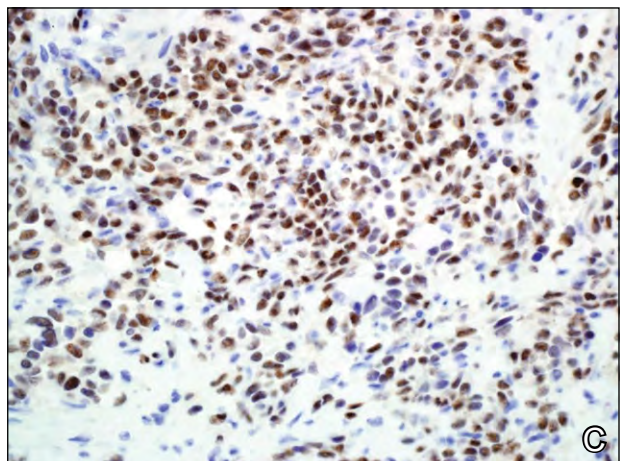
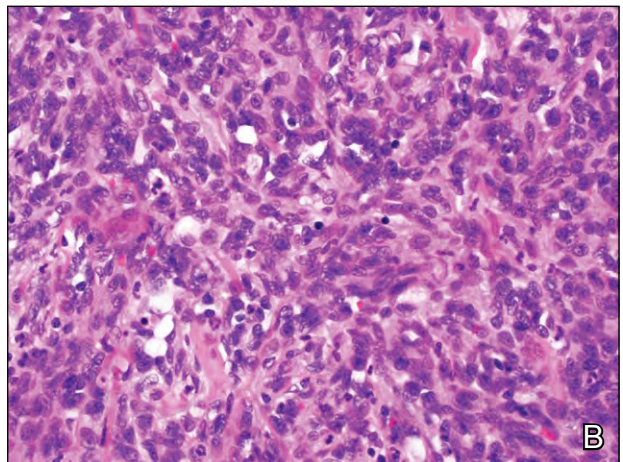
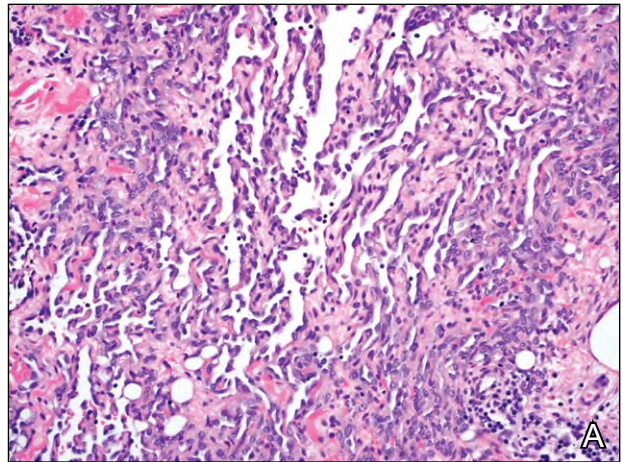


Figure 4. Histology revealed large, markedly pleomorphic, hyperchromatic tumor cells with dissecting vasoformative (A) and solid growth pattern (B)(H&E; original magnifications $\times 200$ and $\times 400$, respectively). Immunostaining for FLI-1 (friend leukemia virus integration 1 transcription factor) showed diffuse staining of angiosarcoma tumor cells (C)(original magnification $\times 400$).

for FLI-1 (Figure 4C) and CD31. Staining for human herpesvirus 8 and D2-40 was negative.

A diagnosis of angiosarcoma was rendered and an above-the-knee amputation was subsequently performed because of positive resection margins in the deep tissues. He completed 4 cycles of doxorubicin and ifosfamide and 4 months of paclitaxel on a weekly basis. He experienced no toxicities. The patient continues to be disease free 3.5 years after initial diagnosis and treatment.

Comment

Angiosarcoma is an aggressive tumor arising from the endothelium of blood vessels or lymphatic channels and accounts for less than 1% of all soft tissue sarcomas.¹ These tumors have been classified as being of endothelial or lymphatic origin (lymphangiosarcoma), though this distinction is controversial. There are 2 prevailing theories regarding the histogenesis of these neoplasms. The first theory involves a pathway of undifferentiated stem cells that proliferate with varying degrees of differentiation toward blood vessel endothelium. The second theory involves a pathway of multicentric hyperplasia containing lymphatic venular anastomoses with elements of both lymphatic and blood vessel endothelium.¹

Angiosarcoma may develop on any region of the body, but skin and superficial soft tissues most commonly are affected.¹ Various conditions are known to be associated with the development of cutaneous angiosarcoma, including sun exposure, chronic lymphedema, irradiation, trauma, and exposure to certain chemicals (eg, thorium dioxide). Idiopathic angiosarcoma on the scalp and face of older men represents the most common form of the disease in the superficial skin and soft tissues. The lesion exhibits varied clinical presentations including nonspecific edema, patches resembling ecchymosis, crusted plaques, and dusky or ulcerating satellite nodules.

Cutaneous angiosarcomas may be subdivided into 2 clinical subsets of cases associated with lymphedema and cases not associated with lymphedema. Most lymphedema-associated cases involving the upper extremities have occurred 10 to 20 years following radical mastectomy (Stewart-Treves syndrome). The pathogenesis in this particular subtype is poorly understood, though several hypotheses have been formulated. These tumors are believed to arise from proliferating endothelial cells, stimulated by a systemic carcinogen or chronically raised hydrostatic pressure.^{2,3} Impaired local immunity also may play a role, as many of these tumors occur in the upper extremities after lymph node dissection for breast cancer. Furthermore, inadequate lymphatic drainage in affected areas impairs the trafficking of lymphocytes and Langerhans cells,

potentially predisposing these populations of cells to angiosarcoma.⁴

Lymphedema may be caused by several other disease processes, and angiosarcoma arising in these processes likewise is uncommon. Prior radiotherapy or infestation (filariasis) can result in chronic lymphedema of the lower extremity. Less frequently the lymphedema may be congenital, as in the case of our patient. Congenital lymphedema may be hereditary or sporadic/nonhereditary. In the hereditary forms, the edema may present at birth or in early childhood (Milroy disease) or between the first decade and late puberty (Meige disease). Milroy disease and Meige disease are considered to be phenotypically distinct entities.⁵ The molecular alteration in Milroy disease localizes to the *fms*-related tyrosine kinase 4 gene, *FLT4* (also known as *VEGFR3*), whereas the genetic defect in Meige disease has yet to be identified.^{6,7} Nonhereditary forms of lymphedema may manifest at birth or later in life. Furthermore, the idiopathic form of lymphedema that occurs in early adolescence has been referred to as lymphedema praecox. However, it is classified as lymphedema tarda when the lesion develops after the age of 35 years.

Angiosarcoma arising in congenital nonhereditary lymphedema is rare and tends to involve the extremities of adults. Based on a PubMed search of articles indexed for MEDLINE using the terms *angiosarcoma and congenital lymphedema* or *non-hereditary lymphedema*, there have been 16 individually confirmed cases (excluding our patient) described in the English-language literature.^{5,8-22} Overall, angiosarcoma has been reported in 9 males and 7 females. The age at diagnosis ranges from 2 to 85 years (mean, 41.5 years). However, angiosarcoma tends to occur in the adult population, with only 3 cases found in pediatric patients,^{10,11,21} and shows a predilection for the extremities. Fifteen of 16 cases involved the upper or lower extremity, and 1 case involved the pubic region.

Therapeutic strategies for this form of angiosarcoma are similar to other sarcomas and based on a combination of prompt surgical ablation associated with irradiation and chemotherapy with the intent of complete eradication of the tumor. However, the prognosis often is dismal despite the use of aggressive therapy. Although targeted therapies have yet to be developed for these tumors, a mutation in the vascular-specific KDR (kinase insert domain receptor) in some patients with breast angiosarcoma lends promise to the possibility for tumor-specific treatments.²³

The histologic appearance of angiosarcoma is similar in all clinical settings including congenital nonhereditary lymphedema, varying from hemangioma-like to poorly differentiated sarcoma with hemorrhagic background. The histologic hallmark of angiosarcoma

is the presence of anastomosing vascular channels that dissect dermal collagen. Atypical endothelial cells with prominent hyperchromatic nuclei and mitotic figures also are demonstrated. Higher-grade angiosarcomas often show multilayering, more endothelial tufting, prominent nuclear atypia, brisk mitotic activity, and extensive solid areas without obvious vascular differentiation. Tumor necrosis and extensive hemorrhage often are present. Immunohistochemical analysis may assist in establishing a diagnosis of angiosarcoma.

In our patient, the lesion contained a spectrum of both well-differentiated and poorly differentiated histologic patterns of angiosarcoma. The differential diagnosis of retiform hemangioendothelioma initially was considered due to the presence of atypical hobnailed endothelial cells. Similar histologic features also were documented by Alessi et al²⁴ involving the upper extremities of a 55-year-old man. The most helpful histologic features in this differential diagnosis were the growth pattern and nuclear grade of the lesion. Angiosarcoma typically shows a higher nuclear grade, increased mitotic activity, and a diffusely infiltrative growth pattern. It also lacks the fibrosis typically present in retiform hemangioendothelioma.

Conclusion

We emphasize that cutaneous angiosarcomas are less frequently seen in children and young adults, and vigilance of the possibility of cutaneous angiosarcoma with congenital lymphedema is important. Clinical suspicion should alert the physician to perform a biopsy of unusual hemorrhagic patches or nodules in lymphedematous tissue to establish an early definitive histologic diagnosis and facilitate appropriate therapy.

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