Diffuse Dermal Angiomatosis of the Breast

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Background: Diffuse dermal angiomatosis is rare and usually considered a variant of reactive angioendotheliomatosis. It generally involves the extremities of patients with severe vascular disease and other comorbidities. Two patients with breast involvement have been described; however, neither had a relevant medical history or a vaso-occlusive disorder, but both had large pendulous breasts, and 1 was positive for IgM anticardiolipin and antinuclear antibodies.

Observations: A 53-year-old woman had a reticulated, erythematous plaque with superficial ulceration and underlying tender nodules on her left breast. She had a history of cardiovascular disease and was a heavy smoker. Biopsy of the lesion showed diffuse proliferation of additional endothelial cells and small bland vessels within the papillary and upper reticular dermis. Angiography showed almost complete occlusion of the subclavian artery proximally. Diffuse dermal angiomatosis was diagnosed. With isotretinoin therapy, the lesions improved. One month later, after percutaneous subclavian arterial revascularization, the lesion resolved completely. A literature review suggested that a history of heavy smoking, in addition to a history of vascular disease, may be important in the pathogenesis of diffuse dermal angiomatosis.

Conclusions: Clinical acumen is crucial to diagnose diffuse angiomatosis of the breast. Appropriate treatment to alleviate hypoxia may improve the patient's condition.

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Diffuse dermal angiomatosis (DDA) is a rare skin condition that commonly presents as erythematous, violaceous, indurated plaques on the lower extremities of patients with severe peripheral vascular disease. The lesions are often ulcerated and tender. The condition is usually considered a variant of reactive angioendotheliomatosis. Since its first description by Krell et al in 1994, a total of 8 cases of DDA have been reported in the English-language literature (Table). Involve ment of the breast is rare, having been reported in only 2 patients. Neither of these patients had a relevant medical history or a vaso-occlusive disorder, but both had large pendulous breasts. Although the 2 cases demonstrated histologic features that are typical of DDA, it has been suggested that they may have resulted from traumatic ulceration of fat-rich areas, with subsequent angiogenesis. Herein, we describe a classic presentation of DDA of the breast and discuss its management.

A 53-year-old woman presented with a 3-month history of tenderness and focal ulceration of the left breast. The area involved measured $4 \times 3$ cm and demonstrated reticulated erythematous induration and focal ulceration (Figure 1). Deeper tender nodularity was also observed. The patient's medical history included coronary artery disease with coronary artery bypass grafting performed 10 years earlier, familial type II hyperlipidemia, angina, fibromyalgia, and osteoporosis. She also had a family history of coronary artery disease. At the time of presentation, she was taking multiple medications, including valsartan (Diovan, 80 mg/d), metoprolol succinate (Toprol XL, 50 mg/d), atorvastatin (Lipitor, 40 mg/d), ezetimibe (Zetia, 10 mg/d), clopidogrel (Plavix, 75 mg/d), aspirin (81 mg/d), folic acid (800 µg/d), bumetanide (1 mg/d), diazepam (1000 mg/d), and calcium with vitamins daily.

Initial laboratory tests included a complete blood cell count, blood chemistry panel, lipid panel, coagulation studies, and determination of antinuclear, antiphospholipid, and anticardiolipin antibody levels. Except for a mild increase in the leuk-
kocyte count, with mild lymphocytosis, and a slight increase in the erythrocyte sedimentation rate, all results were within normal limits.

A punch biopsy specimen was obtained from the lesional area of the left breast. Examination of the specimen showed diffuse proliferation of additional endothe-
Diffuse proliferation of spindle-shaped endothelial cells with focal small, bland vessel formation in full thickness of the dermis, extending to superficial panniculus (hematoxylin-eosin); B, higher magnification shows proliferating endothelial cells (hematoxylin-eosin); and C and D, CD31 staining highlights diffuse proliferating endothelial cells in the dermis (original magnification ×40 [A] and ×200 [B-D]).

Because of her angina pectoris and left arm claudication, angiography was performed and showed almost complete occlusion of the left subclavian artery proximally, with a subclavian “steal” phenomenon (Figure 3A). A stent was placed in the proximal left subclavian artery, and circulation was restored (Figure 3B). One month after the procedure, the lesion on the left breast completely resolved.

Although DDA was described initially in 1994 as a variant of reactive cutaneous angioendotheliomatosis, it was recently recognized as a distinct clinical pathologic entity in the spectrum of cutaneous reactive angiomatoses. All the reported cases of DDA have involved women (age range, 28-63 years), with most of them in their 50s (Table). At presentation, lesions vary from a solitary erythematous patch to an indurated plaque surrounded by dusky erythema. Ulceration and tenderness are common. The sites most affected are the extremities, especially the upper thigh area. Comorbid conditions in-
clude cardiovascular disease, hypertension, and diabetes mellitus. Severe peripheral vascular disease has been noted in most cases.

The distinctive histopathologic feature of DDA is diffuse proliferation of endothelial cells between collagen bundles, instead of within the vascular lumina, which is often observed in reactive angioendotheliomatosis. Small vascular lumina formed by spindle-shaped endothelial cells with vacuolated cytoplasm occur throughout the full thickness of the dermis. The histopathologic differential diagnosis includes benign conditions such as acroangiodermatitis and malignant conditions such as Kaposi sarcoma and low-grade angiosarcoma. Acroangiodermatitis has a clinical presentation similar to that of DDA and often presents as slow-growing, red-vio-

laceous, brown, or dusky macules, papules, or plaques on the lower extremities. Histologically, however, it is not characterized by a diffuse proliferation of endothelial cells between collagen bundles in the interstitium of the dermis, as in DDA. Instead, there is often a slight prolif-

eration of endothelial cells, with the formation of new thick-walled vessels in a lobular pattern in the papillary dermis. The lack of appreciable atypia within the proliferating cells, the pattern of growth of the DDA lesion, and the negative results on staining for human herpesvirus 8 readily differentiate DDA from malignant forms of vascular tumors, including Kaposi sarcoma and angiosarcoma, even though some of the clinical findings may be similar.

Involvement of the breast by DDA is rare. Thus far, 2 cases have been described that demonstrated typical histologic features of DDA. However, both of the patients involved lacked a relevant medical history, including a history of a vaso-occlusive disease process. It is possible, as suggested by some authors, that both patients had traumatic ulcerations of fat-rich areas in their large pendulous breasts and that subsequent angiogenesis was responsible for a DDA-like histologic picture. The case report of DDA by Kutzner et al lends support to this hypothesis. They described a 43-year-old woman who had a brownish, livid, rapidly evolving lesion of DDA above a surgical scar. The lesion had developed after 20 kg of fatty tissue had been removed from the lower abdominal wall. It regressed within 12 weeks, and the patient was disease free 4 years later. Potentially, other mechanisms may be involved in the evolution of DDA. It is possible that along with vaso-occlusive disease, an underlying coagulopathy may have a role in pathogenesis. Thus far, 1 patient with DDA-like lesions has been described who was positive for antinuclear and IgM anticardiolipin antibodies.

Our patient had the classic medical history for DDA, including a personal and family history of coronary artery disease and a medical history of triple bypass surgery, hyperlipidemia, and peripheral vascular disease. The management of DDA requires improving underlying tissue hypoxia and ischemia status. The most efficient method for accomplishing this improvement is revascularization of the affected area. Corticosteroid therapy was used in 1 patient, and the lesion completely resolved after 2 months. Our patient had noted improvement with isotretinoin therapy, which was reported to be effective in 1 patient, possibly because of its antiangiogenesis effect. After the blockage of the subclavian artery was identified and treated with percutaneous stent placement in our patient, her skin lesions resolved entirely.

Figure 3. A, Angiogram showing severe stenosis of proximal left subclavian artery; B, with percutaneous stent placement, normal flow was restored.

It is notable that our patient and nearly all the others described in the literature had a history of heavy smoking. Smoking is a well-recognized risk factor for cardiovascular disease. Free radicals in cigarette smoke are responsible for endothelial dysfunction, decreased levels of high-density lipoprotein, increased levels of low-density and very-low-density lipoproteins, and abnormal platelet function. Cigarette smoking is one of the most
important factors for the development of peripheral arterial disease. Smoking increases the risk of peripheral arterial disease by several-fold and is a more influential pathogenetic factor for this disease than for coronary artery disease. In an animal study, smoking increased vascular endothelial growth factor gene expression in pulmonary arteries. Our patient had a history of familial type II dyslipidemia, which also may have contributed to the vascular endothelial cell proliferation of her skin condition.

In summary, we describe a distinctive case of DDA involving the breast. Diffuse dermal angiomatosis is a rare condition in the spectrum of reactive angiomatoses. Many comorbid conditions exist in patients with DDA. Accurate clinical evaluation of a patient’s vascular status and education about smoking cessation are critical, because appropriate treatment to alleviate hypoxia may be therapeutically effective.

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