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Diffuse dermal angiomatosis of the breast: an emerging entity in the setting of cutaneous reactive angiomatoses

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Abstract New and emerging types of cutaneous vascular (capillary) proliferations have been described or better categorized in the last few years. They include reactive angioendotheliomatosis, acroangiodermatitis (pseudo-Kaposi sarcoma), diffuse dermal angiomatoses, intravascular histiocytosis, glomeruloid angioendotheliomatosis, and angiopericytomatosis (angiomatosis with cryoproteins). Clinically, they are characterized by multiple, red violaceous, and purpuric patches and plaques, sometimes evolving toward necrosis and ulceration with a wide distribution but a propensity to involve the extremities. Histologically, they are characterized by different patterns of intravascular or extravascular lobular or diffuse hyperplasia of endothelial cells, pericytes, and sometimes histiocytes. Although these angioproliferations can histologically have a pseudoangiosarcomatous pattern, they are reactive in that they originate from the (sub)occlusion of vascular lumina by different localized or systemic disorders. The vascular proliferation stops after the inducing hypoxic stimulus has been withdrawn. Among them, diffuse dermal angiomatosis of the breast is a variant of diffuse dermal angiomatosis involving middle-aged women with macromastia, obesity, smoking, and vasculopathic disorders, considered a distinct disorder in the spectrum of cutaneous reactive angiomatoses. It presents with reticulated erythematous to purple patches with sometimes a tendency to ulcerate and bleeding, appearing on large, pendulous breasts. The pathogenesis is related to tissue hypoxemia resulting from subclinical torsion, compression, and increased venous hydrostatic pressure due to the macromastia, aggravated by the associated ischemic conditions such as hypertension and diabetes. There is no evidence-based therapy, but reduction mammoplasty is a viable treatment option. This should be evaluated in all patients who fail conservative therapy.

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Introduction

The umbrella term “cutaneous reactive angiomatoses” was introduced in 2003 to include uncommon angioproliferative (capillary) conditions of the skin, which present with variable
clinical aspects and involve patients with a variety of underlying systemic diseases. Histologically, these conditions are characterized by different patterns of intravascular or extravascular lobular or diffuse hyperplasia of endothelial cells, pericytes, and sometimes histiocytes, mostly throughout the dermis. The first condition to be described in this setting was reactive angioendotheliomatosis (REA). Although its initial histologic report appeared in 1958, the term “angioendotheliomatosis” was coined by Josef Tappeiner (1909-1996) and Lilly Pfleger (1909-1992) from Vienna in 1963. Originally, two variants of angioendotheliomatosis were considered: (1) benign or reactive angioendotheliomatosis; (2) malignant angioendotheliomatosis. Additional reports, however, revealed that malignant angioendotheliomatosis corresponds to intravascular, angiotropic lymphoma and should be distinguished from the benign, reactive form.

REA is a rare disorder that affects women and men equally (F:M = 1:1.3). It has been reported in all age groups, from a 3-month-old infant to an 88-year-old adult (median age 60 years). The clinical features are characterized by erythematous or purple-brownish macules and papules or purpuric plaques and occasionally ulcerated lesions. The extremities are the most common site of involvement, but the lesions have a wide distribution. REA has been especially associated with infectious and autoimmune diseases, inflammatory and occlusive vasculopathies, and hemo-lymphoproliferative disorders.

Histopathologically, there is a proliferation of endothelial cells within the lumina of dermal vessels with intravascular thrombi. Different stimuli can possibly lead to vessel (sub) occlusion, local hypoxia, and subsequently synthesis of angiogenic cytokines, which induce endothelial cell proliferation.

Diffuse dermal angiomatosis (DDA) was reported as a variant of REA in two cases in 1994, but it has more recently been considered as a distinct disorder in the spectrum of REA. DDA is a condition typically seen in adults, and most reported cases have been in middle-aged women. The clinical lesions are indistinguishable from those of REA, in the absence or presence of intraluminal thrombi. Mitotic figures are rare, but cellular atypia is absent. There is an associated background of slight to moderate inflammatory infiltrate made of CD3 lymphocytes with rare CD20-positive cells, plasma cells, and sometimes eosinophils. Calciphylaxis with calcification of subcutaneous vessels, microthrombi, and tissue necrosis may be a feature in patients with chronic renal failure. Immunohistochemistry for factor XIIIa, CD34, ERG, and CD31 stain highlights the endothelial proliferation.

Clinical features

DDA of the breast is a unique clinicopathologic entity in the spectrum of cutaneous reactive angiomatoses, because the triggers and the clinical setting are not entirely the same as DDA involving other areas of the body. DDA of the breast is characterized by enlarging, reticulated, erythematous to purple patches (Figure 1) sometimes with a tendency to ulcerate and bleed. Patients often complain of pain at the sites of ulceration. The lesions are usually bilateral and occur exclusively in young to middle-aged women, aged between 20 and 62 years (mean age 46.6 years), associated with large pendulous breasts (in 75.0% of all the cases in the literature, in 5 cases with a history of breast reduction surgery), overweight, with frank obesity, and smoking. There may be an association with coronary artery disease, hypertension, surgery/trauma, diabetes, calciphylaxis, and the antiphospholipid syndrome.

Histopathology

On histologic grounds, DDA is characterized by a diffuse extravascular proliferation of mostly endothelial cells and rare pericytes interstitially arranged between the collagen bundles throughout the full thickness of the reticular dermis with only minimal or absent intravascular proliferation. In some areas, the proliferating cells, which may show a spindle-shaped appearance and a vacuolated cytoplasm, form small vascular channels. There may be scattered extravasated erythrocytes with hemosiderin in the stroma and intraluminal thrombi. Mitotic figures are rare, but cellular atypia is absent. There is an associated background of slight to moderate inflammatory infiltrate made of CD3 lymphocytes with rare CD20-positive cells, plasma cells, and sometimes eosinophils. Calciphylaxis with calcification of subcutaneous vessels, microthrombi, and tissue necrosis may be a feature in patients with chronic renal failure. Immunohistochemistry for factor XIIIa, CD34, ERG, and CD31 stain highlights the endothelial proliferation.

Fig. 1 Diffuse dermal angiomatosis of the breast. Reticulated erythematous to violaceous patches involving both large pendulous breasts.
<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients/mean age, y</th>
<th>History and clinical features</th>
<th>Obesity</th>
<th>Smoking habits</th>
<th>Comorbidities</th>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>McLaughlin et al., 17, 2001</td>
<td>1/28</td>
<td>Large pendulous breasts</td>
<td>na</td>
<td>Current smoker</td>
<td>No relevant medical history</td>
<td>Isotretinoin 80 mg/day</td>
<td>Dramatically improved after 2 months; patient lost to FU</td>
</tr>
<tr>
<td>Pichardo et al., 20, 2002</td>
<td>1/47</td>
<td>Large pendulous breasts</td>
<td>na</td>
<td>na</td>
<td>IgM anticardiolipin antibodies</td>
<td>Low-dose aspirin and pentoxifylline</td>
<td>Improved with aspirin and pentoxifylline</td>
</tr>
<tr>
<td>Yang et al., 21, 2006</td>
<td>1/53</td>
<td>na</td>
<td>na</td>
<td>Current smoker</td>
<td>Hyperlipidemia, coronary artery disease, peripheral artery disease with unilateral subclavian artery occlusion</td>
<td>Isotretinoin 40 mg/day; subclavian artery revascularization</td>
<td>Markedly improved with isotretinoin; completely resolved after revascularization</td>
</tr>
<tr>
<td>Quatresooz et al., 22, 2006</td>
<td>1/46</td>
<td>Obesity</td>
<td>Current smoker</td>
<td>Hypertension, hyperlipidemia, unilateral humeral artery thrombosis without underlying hypercoagulable state</td>
<td>Oral corticosteroids</td>
<td>Markedly improved with oral corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Villa et al., 27, 2008</td>
<td>1/20</td>
<td>Large pendulous breasts</td>
<td>Overweight</td>
<td>Former smoker</td>
<td>No relevant medical history</td>
<td>Reduction mammaplasty</td>
<td>Completely resolved; no recurrence 4 months PO</td>
</tr>
<tr>
<td>Adams et al., 23, 2012</td>
<td>1/59</td>
<td>Large pendulous breasts; reduction mammaplasty</td>
<td>na</td>
<td>Current smoker</td>
<td>Hypertension, hyperlipidemia, cerebrovascular accident, COPD</td>
<td>Isotretinoin 100 mg/day</td>
<td>Improved with isotretinoin</td>
</tr>
<tr>
<td>Sanz-Motilva et al., 24, 2014</td>
<td>3/57.6 (57-59)</td>
<td>Large pendulous breasts (3)</td>
<td>Overweight (2)</td>
<td>Current smokers (3)</td>
<td>Hypertension, hepatic cirrhosis, basal ganglia hematoma (1); monoclonal gammopathy (1); breast cancer treated with unilateral mastectomy and lymphadenectomy, hepatic cirrhosis due to hepatitis B treated with liver transplant (1); Takayasu arteritis with bilateral subclavian artery occlusion and secondary stroke, hypertension (1); peripheral artery disease (1); multiple thromboembolic events, but no hypercoagulability found (1)</td>
<td>Smoking cessation (3)</td>
<td>Completely resolved after 6 months (1) and 12 months (2), respectively, without additional specific therapy</td>
</tr>
<tr>
<td>Tollefson et al., 19, 2014</td>
<td>5/51 (47-58)</td>
<td>Large pendulous breasts (5); reduction mammaplasty (3)</td>
<td>na</td>
<td>Current smoker (1); former smokers (2)</td>
<td>Subclavian artery revascularization (1); isotretinoin 80 mg/day (1)</td>
<td>Improved after revascularization (1); markedly improved with isotretinoin (1)</td>
<td></td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients/ mean age, y</th>
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<th>Comorbidities</th>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reusche et al., 2015</td>
<td>22/48.4 (20-62)</td>
<td>Large pendulous breasts (13); reduction mammaplasty (1)</td>
<td>Overweight or obesity (22); obesity class II (15)</td>
<td>Current smokers (6); former smokers (5)</td>
<td>No relevant medical history except for breast reduction surgery (2)</td>
<td>Isotretinoin (2); pentoxyfylline (2); pentoxyfylline and nifedipine (1); aspirin (1); reduction mammaplasty (1); mastectomy (1)</td>
<td>Improved with isotretinoin (2), recurrence when taken off therapy (2); improved but not resolved with pentoxyfylline (2); pentoxyfylline and nifedipine not effective (1); improved but not resolved with aspirin (1); completely resolved after breast surgery (2), no recurrence after 20 months of FU</td>
</tr>
<tr>
<td>Galambos et al., 2017</td>
<td>1/51</td>
<td>Large pendulous breasts</td>
<td>Obesity class II (BMI 35.0)</td>
<td>Current smoker</td>
<td>Hypertension</td>
<td>Isotretinoin 40 mg/day; bilateral reduction mammaplasty with excision of involved areas</td>
<td>Isotretinoin not effective; completely resolved after breast surgery; no recurrence after 4.5 months and 2.5 years of FU</td>
</tr>
<tr>
<td>Galambos et al., 2015</td>
<td>1/52</td>
<td>Large pendulous breasts</td>
<td>Obesity class I (BMI 34.7)</td>
<td>Current smoker</td>
<td>Hypertension</td>
<td>Smoking cessation; bilateral reduction mammaplasty with excision of involved areas</td>
<td>Smoking cessation without positive effect; completely resolved after breast surgery; no recurrence after 3 months of FU PO</td>
</tr>
<tr>
<td>Frikha et al., 2018</td>
<td>1/71</td>
<td>Large pendulous breasts with livedoid patches, necrosis and ulceration</td>
<td>na</td>
<td>No</td>
<td>Cardiovascular disease</td>
<td>Isotretinoin, surgery (mastectomy)</td>
<td>No recurrence after 30 months-follow-up</td>
</tr>
<tr>
<td>Hui et al., 2018</td>
<td>1/49</td>
<td>Erythematous, weeping lesion with focal ulceration</td>
<td>na</td>
<td>na</td>
<td>Hypertension, diabetes, HCV-related cirrhosis, anasarca</td>
<td>na</td>
<td>na</td>
</tr>
</tbody>
</table>

FU, follow-up; na, not available; PO, post operation; PY, pack-years; COPD, chronic obstructive pulmonary disease; BMI, body mass index; HCV, hepatitis C virus.
that characterize lymphatic differentiation of endothelia is negative. The newly formed vessels are surrounded by α-SMA-positive pericytes, indicating the benign nature of this vascular proliferation. Immunohistochemistry for human herpesvirus-8 (HHV-8) is negative. Linear and granular deposits of immunoreactants along endothelial cells and at the dermal-epidermal junction in lesional skin have been observed in two patients with DDA. DDA is probably the most common form of cutaneous reactive angiomatosis, as the term “REA” has been used to describe cases with histological features more consistent with DDA.

**Pathogenesis**

The pathogenesis of cutaneous reactive angiomatoses is not clear. All the variants including REA and DDA have been consistently associated with systemic conditions in which occlusive or subocclusive inflammatory vasculopathic processes occur in the vascular tree. The intravascular or extravascular proliferation of the endothelial cells is involved in the subsequent recanalization of the thrombotic vessel or in the formation of new vessels to restore an adequate blood circulation under the stimulus of endothelial growth factor induced by ischemia. The former condition produces an intravascular growth pattern that is histologically seen as REA when the lumen is filled with endothelial cells, whereas the extravascular hyperplasia of endothelial cells causes the histologic picture of DDA.

In diffuse dermal angiomatosis of the breast (DDAB), tissue hypoxemia can be induced by subclinical torsion, compression, and increased venous hydrostatic pressure related to enlarged pendulous breasts. In obese women, impairment in pulmonary function due to the obstructive sleep apnea syndrome and/or obesity hypoventilation syndrome may increase the local tissue hypoxia. These patients often present with associated systemic occlusive vasculopathies such as cardiovascular disorders and diabetes or with smoking habits that aggravate the ischemic status.

**Differential diagnosis**

On clinical grounds, necrotizing (leukocytoclastic) vasculitis could be considered; however, typical microscopic features of leukocytoclastic vasculitis including fibrinoid necrosis with perivascular infiltrate of neutrophils and nuclear dusts are lacking. In one case, DDA mimicked inflammatory carcinoma of the breast in the clinical and radiologic examinations, but again histopathology distinguished the two conditions.

The histopathologic differential diagnosis of DDAB mainly includes well-differentiated cutaneous angiosarcoma, postradiation atypical vascular lesion, and patch/plaque-stage Kaposi sarcoma. Angiosarcoma is characterized by an atypical proliferation of irregular vascular channels lined by multilayering endothelial cells with mitoses lacking an outer layer of α-SMA-positive pericytes. Postradiation atypical vascular

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**Fig. 2** Histopathology. (A) Diffuse proliferation of bland endothelial cells between collagen bundles in the upper and middle dermis forming small capillary vessels. (B) Close-up of endothelial cells and small capillary vessels. (C) The endothelial cells and the small vessels are immunoreactive for CD31.
Conclusions

DDAB is more common than previously believed, the breast presumably being the most commonly involved site in DDA. DDAB should be considered as a unique, emerging clinicopathologic entity within the spectrum of cutaneous reactive angiomasoses. It typically involves middle-aged women, presenting with macromastia, obesity, smoking habits, and often some risk factors for (sub)occlusive vasculopathies. The histopathology is characterized by a diffuse extravascular proliferation of endothelial cells throughout the full thickness of the reticular dermis with new small vessel formation. Weight control and tobacco cessation are important supporting measures in its management, as well as treatment of the associated (sub)occlusive vasculopathic disorders. Although many medical therapies have been used to lessen the manifestations of the disease, there is no therapy that has been proven really effective. Isotretinoin and other agents have been used with variable results. Reduction mammoplasty, though not fully proven, is a viable treatment option in patients who fail conservative therapy.

Therapy

The measures to improve the underlying relative ischemia and tissue hypoxemia are mandatory to heal DDAB. One therapeutic approach is to educate patients about weight control and smoking cessation, as well as treatment of other cardiovascular risk factors such as hypertension, diabetes, or hyperlipidemia. In one report of three patients, complete healing occurred after 1 year of smoking cessation and no additional therapy. 

A workup to exclude calciphylaxis involving the breasts or a hypercoagulable state is advisable in patients with end-stage kidney failure or a history of thromboembolic episodes. Although many medical therapies have been used to lessen the manifestation of the disease, there is no treatment that has proven effective in managing it. Isotretinoin has been used with variable results. Clinical improvement has mainly been attributed to the antiangiogenic effects of retinoids, but some patients who obtained complete healing with isotretinoin had a recurrence, when treatment was discontinued; moreover, teratogenic risk and side effects limit its use in women. Other medical therapies such as pentoxifylline, nifedipine, or aspirin have provided equivocal success anecdotally. Antibiotics for occult infections and oral corticosteroids for their suppressive effect on neangiogenesis have also been used in those rare cases with no apparent underlying pathology. Reduction mammoplasty is a viable treatment option. It should be evaluated in all patients who fail conservative therapy, although DDAB developed in five previously reported women with macromastia after breast reduction surgery. In two patients in whom a subclavian artery occlusion was present, DDAB developed in an infant. A review of the literature.

References


Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.


