



UNICA

UNIVERSITÀ
DEGLI STUDI
DI CAGLIARI



Università di Cagliari

UNICA IRIS Institutional Research Information System

This is the Author's [*accepted*] manuscript version of the following contribution: (author name, title, publisher, ecc)

Ferrelì C, Atzori L, Caputo V, Rongioletti F.

Diffuse dermal angiomatosis of the breast: an emerging entity in the setting of cutaneous reactive angiomatoses. Clin Dermatol. 2021 Mar-Apr;39(2):271-277.

The publisher's version is available at:

cod. DOI: 10.1016/j.clindermatol.2020.10.004. Epub 2020 Oct 16. PMID: 34272021

When citing, please refer to the published version.



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

Caterina Ferreli, MD^a, Laura Atzori, MD^{a,*}, Valentina Caputo, MD^b, Franco Rongioletti, MD^a

^aUnit of Dermatology, Department of Medical Sciences and Public Health, Dermatology Clinic, University of Cagliari, Cagliari, Italy

^bUnit of Pathology, Grande Ospedale Metropolitano Niguarda, Milan, Italy

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 angiomatosis, 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 The vascular proliferation stops after the inducing hypoxic stimulus has been withdrawn.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.

© 2020 Elsevier Inc. All rights reserved.

Introduction

The umbrella term “cutaneous reactive angiomatoses” was introduced in 2003 to include uncommon angioproliferative (capillary) conditions of the skin, which present with variable

* Corresponding author.

E-mail address: atzoril@unica.it (L. Atzori).

clinical aspects and involve patients with a variety of underlying systemic diseases.¹ 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 1958,² the term “angioendotheliomatosis” was coined by Josef Tappeiner (1909-1996) and Lilly Pfleger (1909-1992) from Vienna in 1963.³ 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.⁴

REA is a rare disorder that affects women and men equally (F:M = 1:1.3). It has been reported in all age groups,⁵ from a 3-month-old infant⁶ 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.⁷

Histologically, 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.^{1,5}

Diffuse dermal angiomatosis (DDA) was reported as a variant of REA in two cases in 1994,⁸ but it has more recently been considered as a distinct disorder in the spectrum of REA.^{1,9} DDA is a condition typically seen in adults, and most reported cases have been in middle-aged women. The clinical lesions are indistinguishable from REA with violaceous, purpuric, and occasionally ulcerated plaques mainly on the lower extremities or abdomen of patients with peripheral vascular atherosclerotic disease. In general, any medical condition that can lead to ischemia could cause DDA. It has also been reported on the forearm secondary to iatrogenic arteriovenous fistulas in the setting of chronic hemodialysis or in patients with comorbidities such as hypertension, diabetes, calciphylaxis, obesity, and smoking.¹⁰⁻¹⁶ The lesions may be asymptomatic or painful.

Histopathologically, DDA displays a diffuse interstitial proliferation of bland endothelial cells and pericytes forming small caliber vessels within the superficial layers of the papillary and reticular dermis. It differs from REA, where the endothelial proliferation is seen inside the capillary lumina.^{1,12,16} In 2001 the first case of DDA involving the breast in a woman was published,¹⁷ followed by additional case reports and a few case series,^{9,18,19} making the breast the most commonly involved site.

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.⁹ There may be an association with coronary artery disease, hypertension, surgery/trauma, diabetes, calciphylaxis, and the antiphospholipid syndrome.¹⁷⁻²⁷ (See Table 1.)

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 (Figure 2A).⁹⁻²³ In some areas, the proliferating cells, which may show a spindle-shaped appearance and a vacuolated cytoplasm, form small vascular channels (Figure 2B). 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 reduced kidney function. Immunohistochemistry for factor XIIIa, CD34, ERG, and CD31 stain highlights the endothelial proliferation (Figure 2C). D2-40/podoplanin

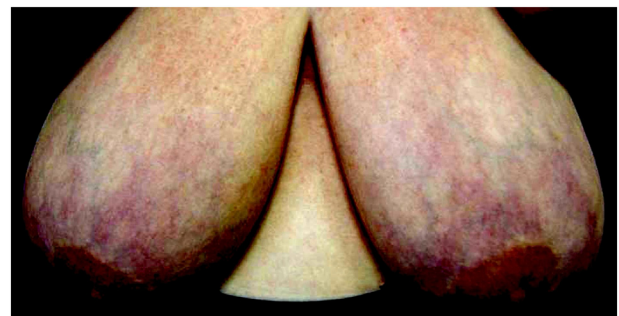


Fig. 1 Diffuse dermal angiomatosis of the breast. Reticulated erythematous to violaceous patches involving both large pendulous breasts.

Table 1 Main characteristics of women with diffuse dermal angiomatosis of the breast reported in the literature (updated from ref. ⁹)

Reference	No. of patients/ mean age, y	History and clinical features	Obesity	Smoking habits	Comorbidities	Management	Follow-up
McLaughlin et al., ¹⁷ 2001	1/28	Large pendulous breasts	na	Current smoker	No relevant medical history	Isotretinoin 80 mg/day	Dramatically improved after 2 months; patient lost to FU
Pichardo et al., ²⁰ 2002	1/47	Large pendulous breasts	na	na	IgM anticardiolipin antibodies	Low-dose aspirin and pentoxifylline	Improved with aspirin and pentoxifylline
Yang et al., ²¹ 2006	1/53	na	na	Current smoker	Hyperlipidemia, coronary artery disease, peripheral artery disease with unilateral subclavian artery occlusion	Isotretinoin 40 mg/day; subclavian artery revascularization	Markedly improved with isotretinoin; completely resolved after revascularization
Quatresooz et al., ²² 2006	1/46	na	Obesity	Current smoker	Hypertension, hyperlipidemia, unilateral humeral artery thrombosis without underlying hypercoagulable state	Oral corticosteroids	Markedly improved with oral corticosteroids
Villa et al., ²⁷ 2008	1/20	Large pendulous breasts	Overweight	Former smoker	No relevant medical history	Reduction mammoplasty	Completely resolved; no recurrence 4 months PO
Adams et al., ²³ 2012	1/59	Large pendulous breasts; reduction mammoplasty	na	Current smoker	Hypertension, hyperlipidemia, cerebrovascular accident, COPD	Isotretinoin 100 mg/day	Improved with isotretinoin
Sanz- Motilva et al., ²⁴ 2014	3/57.6 (57-59)	Large pendulous breasts (3)	Overweight (2)	Current smokers (3)	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)	Smoking cessation (3)	Completely resolved after 6 months (1) and 12 months (2), respectively, without additional specific therapy
Tollefson et al., ¹⁹ 2014	5/51 (47-58)	Large pendulous breasts (5); reduction mammoplasty (3)	na	Current smoker (1); former smokers (2)	Takayasu arteritis with bilateral subclavian artery occlusion and secondary stroke, hypertension (1); peripheral artery disease (1); multiple thromboembolic events, but no hypercoagulability found (1);	Subclavian artery revascularization (1); isotretinoin 80 mg/day (1)	Improved after revascularization (1); markedly improved with isotretinoin (1)

(continued on next page)

Table 1 (continued)

Reference	No. of patients/ mean age, y	History and clinical features	Obesity	Smoking habits	Comorbidities	Management	Follow-up
Reusche et al., ¹⁸ 2015	22 ² /48.4 (20-62)	Large pendulous breasts (13); reduction mammoplasty (1)	Overweight or obesity (22); obesity class II (15)	Current smokers (6); former smokers (5)	no relevant medical history except for breast reduction surgery (2) No relevant medical history (22)	Isotretinoin ³ (2); pen- toxifylline (2); pentoxi- fylline and nifedipine (1); aspirin (1); reduc- tion mammoplasty (1); mastectomy (1)	Improved with isotretinoin (2), recurrence when taken off therapy (2); improved but not resolved with pentoxifylline (2); pentoxifylline 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
Galambos et al., ⁹ 2017	1/51	Large pendulous breasts	Obesity class II (BMI 35.0)	Current smoker	Hypertension	Isotretinoin 40 mg/day; bilateral reduction mammoplasty with excision of involved areas	Isotretinoin not effective; completely resolved after breast surgery; no recurrence after 4.5 months and 2.5 years of FU PO
Galambos et al., ⁹ 2015	1/52	Large pendulous breasts	Obesity class I (BMI 34.7)	Current smoker	Hypertension	Smoking cessation; bilateral reduction mammoplasty with excision of involved areas	Smoking cessation without positive effect; completely resolved after breast surgery; no recurrence after 3 months of FU PO
Frikha et al., ²⁵ 2018	1/71	Large pendulous breasts with livedoid patches, necrosis and ulceration	na	No	Cardiovascular disease	Isotretinoin, surgery (mastectomy)	No recurrence after 30 month- follow-up
Hui et al., ²⁶ 2018	1/49	Erythematous, weeping lesion with focal ulceration	na	na	Hypertension, diabetes, HCV- related cirrhosis, anasarca	na	na

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.

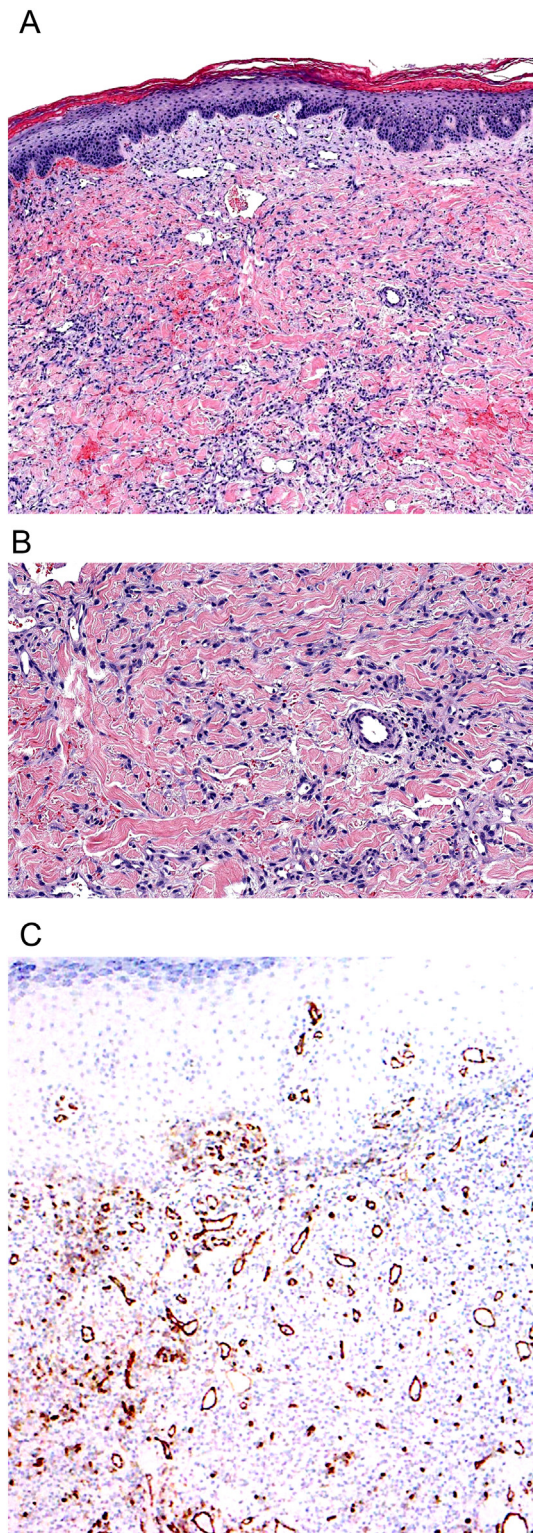


Fig. 2 Histopathology. (A) Diffuse proliferation of bland endothelial cells between collagen bundles in the upper and middle dermis forming small capillary vessels. (B) Close-up of endothelial cells and small capillary vessels. (C) The endothelial cells and the small vessels are immunoreactive for CD31.

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.²² DDA is probably the most common form of cutaneous reactive angiomas, as the term “REA” has been used to describe cases with histological features more consistent with DDA.²⁸

Pathogenesis

The pathogenesis of cutaneous reactive angiomas 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.^{1,17,23} 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.⁹ These patients often present with associated systemic occlusive vasculopathies such as cardiovascular disorders and diabetes or with smoking habits that aggravate the ischemic status.^{18,19,23}

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.²⁶

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

lesion usually shows irregular, dilated vascular spaces more than extravascular single cell proliferation, and D2-40/podoplanin expression is positive in the endothelial cells. A frank spindle cell proliferation, irregular slitlike lumen formation with the “promontory sign,” an inflammatory infiltrate rich of plasma cells, and a positive immunostaining for HHV-8 is useful to distinguish Kaposi sarcoma from DDAB.

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.^{9,18,19,29} In one report of three patients, complete healing occurred after 1 year of smoking cessation and no additional therapy.²⁴

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.^{9,17–19} Clinical improvement has mainly been attributed to the antiangiogenic effects of retinoids,³⁰ 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.³¹ Other medical therapies such as pentoxifylline, nifedipine, or aspirin have provided equivocal success anecdotally.⁹ Antibiotics for occult infections and oral corticosteroids for their suppressive effect on neoangiogenesis have also been used in those rare cases with no apparent underlying pathology.¹ 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.^{18,19,23} In two patients in whom a subclavian artery occlusion was present, revascularization with stent placement resulted in substantial improvement.^{19,21}

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 angiomatoses.¹ 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.

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.

References

- Rongioletti F, Rebora A. Cutaneous reactive angiomatoses: patterns and classification of reactive vascular proliferation. *J Am Acad Dermatol* 2003;49:887-896.
- Gottron HA, Nikolowsky W. Extrarenale Lohlein-Herdnephritis der Haut bei Endocarditis. *Arch Klein Exp Dermatol* 1958;207:156-176.
- Tappeiner J, Pfleger L. Angioendotheliomatosis proliferans systemisata: ein klinisch pathohistologisch neues Krankheitsbild. *Hautarzt* 1963;14:67-70.
- Wick MR, Rocamora A. Reactive and malignant angioendotheliomatosis: a discriminant clinicopathologic study. *J Cutan Pathol* 1988;15:260-271.
- McMenamin ME, Fletcher CD. Reactive angioendotheliomatosis: a study of 15 cases demonstrating a wide clinicopathologic spectrum. *Am J Surg Pathol* 2002;26:685-697.
- Brazzelli V, Baldini F, Vassallo C, et al. Reactive angioendotheliomatosis in an infant. *Am J Dermatopathol* 1999;21:42-45.
- Nikam B, Shah S, Kale M, et al. Reactive angioendotheliomatosis as a presenting cutaneous manifestation of Hughes syndrome. *Lupus* 2015;24:1557-1561.
- Krell JM, Sanchez RL, Solomon AR. Diffuse dermal angiomatosis: a variant of reactive cutaneous angioendotheliomatosis. *J Cutan Pathol* 1994;21:363-370.
- Galambos J, Meuli-Simmen C, Schmid R, et al. Diffuse dermal angiomatosis of the breast: a distinct entity in the spectrum of cutaneous reactive angiomatoses - clinicopathologic study of two cases and comprehensive review of the literature. *Case Rep Dermatol* 2017;9:194-205.
- O'Connor HM, Wu Q, Lauzon SD, et al. Diffuse dermal angiomatosis associated with calciphylaxis: a 5-year retrospective institutional review. *J Cutan Pathol* 2020;47:27-30.
- Touloei K, Tongdee E, Smirnov B, et al. Diffuse dermal angiomatosis. *Cutis* 2019;103:181-184.
- Ferreli C, Atzori L, Pinna AL, et al. Diffuse dermal angiomatosis: a clinical mimicker of vasculitis associated with calciphylaxis and monoclonal gammopathy. *G Ital Dermatol Venereol* 2015;150:115-121.
- Kim S, Elenitsas R, James WD. Diffuse dermal angiomatosis: a variant of reactive angioendotheliomatosis associated with peripheral vascular atherosclerosis. *Arch Dermatol* 2002;138:456-458.
- Sriphojanart T, Vachiramon V. Diffuse dermal angiomatosis: a clue to the diagnosis of atherosclerotic vascular disease. *Case Rep Dermatol* 2015;7:100-106.
- Crickx E, Saussine A, Vignon-Pennamen MD, et al. Diffuse dermal angiomatosis associated with severe atherosclerosis: two cases and review of the literature. *Clin Exp Dermatol* 2015;40:521-524.

16. Requena L, Farina MC, Renedo G, et al. Intravascular and diffuse dermal reactive angioendotheliomatosis secondary to iatrogenic arteriovenous fistulas. *J Cutan Pathol* 1999;26:159-164.
17. McLaughlin ER, Morris R, Weiss SW, et al. Diffuse dermal angiomatosis of the breast: response to isotretinoin. *J Am Acad Dermatol* 2001;45:462-465.
18. Reusche R, Winocour S, Degnim A, et al. Diffuse dermal angiomatosis of the breast: a series of 22 cases from a single institution. *Gland Surg* 2015;4:554-560.
19. Tollefson MM, McEvoy MT, Torgerson RR, et al. Diffuse dermal angiomatosis of the breast: clinicopathologic study of 5 patients. *J Am Acad Dermatol* 2014;71:1212-1217.
20. Pichardo RO, Lu D, Sanguenza OP, et al. What is your diagnosis? Diffuse dermal angiomatosis secondary to anticardiolipin antibodies. *Am J Dermatopathol* 2002;24:502-503.
21. Yang H, Ahmed I, Mathew V, et al. Diffuse dermal angiomatosis of the breast. *Arch Dermatol* 2006;142:343-347.
22. Quatresooz P, Fumal I, Willemaers V, et al. Diffuse dermal angiomatosis. A previously undescribed pattern of immunoglobulin and complement deposits in two cases. *Am J Dermatopathol* 2006;28:150-154.
23. Adams BJ, Goldberg S, Massey HD, et al. A cause of unbearably painful breast, diffuse dermal angiomatosis. *Gland Surg* 2012;1:132-135.
24. Sanz-Motilva V, Martorell-Calatayud A, Rongioletti F, et al. Diffuse dermal angiomatosis of the breast: clinical and histopathological features. *Int J Dermatol* 2014;53:445-449.
25. Frikha F, Boudaya S, Abid N, et al. Diffuse dermal angiomatosis of the breast with adjacent fat necrosis: a case report and review of the literature. *Dermatol Online J* 2018;24:13030.
26. Hui Y, Elco CP, Heintz NF, et al. Diffuse dermal angiomatosis mimicking inflammatory breast carcinoma. *Breast J* 2018;24:196-198.
27. Villa MT, White LE, Petronic-Rosic V, et al. The treatment of diffuse dermal angiomatosis of the breast with reduction mammoplasty. *Arch Dermatol* 2008;144:693-694.
28. Vacharathit V, Billings SD, Kirksey L. Resolution of reactive angioendotheliomatosis in an arteriovenous fistula with innominate vein angioplasty. *J Vasc Access* 2018;19:94-97.
29. Messner B, Bernhard D. Smoking and cardiovascular disease: mechanisms of endothelial dysfunction and early atherogenesis. *Arterioscler Thromb Vasc Biol* 2014;34:509-515.
30. Lingen MW, Polverini PJ, Bouck NP. Retinoic acid induces cells cultured from oral squamous cell carcinomas to become antiangiogenic. *Am J Pathol* 1996;149:247-258.
31. Karadag AS, Parish LC, Lambert WC. Isotretinoin in retrospect. *Clin Dermatol* 2017;35:335-339.