Diffuse Dermal Angiomatosis

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PRACTICE **POINTS**

- Diffuse dermal angiomatosis is commonly reported in patients with hypoxic comorbidities such as smoking or vascular disease as well as in women with large pendulous breasts.
- Effective treatments include control of comorbidities, revascularization, withdrawal of the offending agent, steroids, and isotretinoin.

Diffuse dermal angiomatosis (DDA) is a benign and rare acquired, cutaneous, reactive, vascular disorder. We report a rare case of a 43-year-old man who presented with a large (15-cm diameter), indurated, hyperpigmented plaque covering the left buttock for 6 years. This report further discusses DDA with a review of the literature, including its classification, epidemiology, pathophysiology, etiology, histopathology, differential diagnosis, and current therapeutic approaches.

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Diffuse dermal angiomatosis (DDA) is a rare acquired, cutaneous, reactive, vascular disorder that was originally thought to be a variant of cutaneous reactive angiomatosis (CREA) but is now considered to be on the spectrum of CREA. This article will focus on DDA and review the literature of prior case reports with brief descriptions of the differential diagnosis.

Case Report

A 43-year-old Haitian man presented to the clinic with a lesion on the left buttock that had developed over the last 6 years. The patient stated the lesion had been enlarging over the last several months. Upon examination, there was a large (15-cm diameter), indurated, hyperpigmented plaque covering the left buttock (Figure 1). The patient reported no medical or contributory family history. Upon review of systems, he described a burning sensation sometimes in the area of the lesion that would develop randomly throughout the year.

Three biopsies were performed, which revealed a collection of slightly dilated blood vessels with normal-appearing endothelial cells occupying the mid dermis and deep dermis (Figure 2). Immunohistochemical stains with antibodies were directed against human herpesvirus 8 (HHV-8), CD31, CD34, the cell surface glycoprotein podoplanin, Ki-67, and smooth muscle actin antigens, with appropriate controls. The vessel walls were positive for CD31, CD34, and smooth muscle actin, and negative for HHV-8 and podoplanin; Ki-67 was not increased. These histologic findings were consistent with a diagnosis of DDA. A detailed history was taken. The cause of DDA in our patient was uncertain.

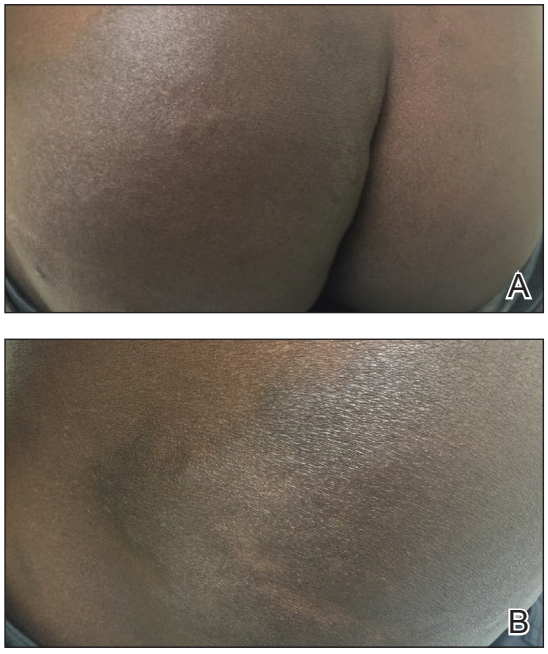

FIGURE 1. A 15-cm, indurated, hyperpigmented plaque covering the left buttock. A, Posterior view. B, Lateral view.

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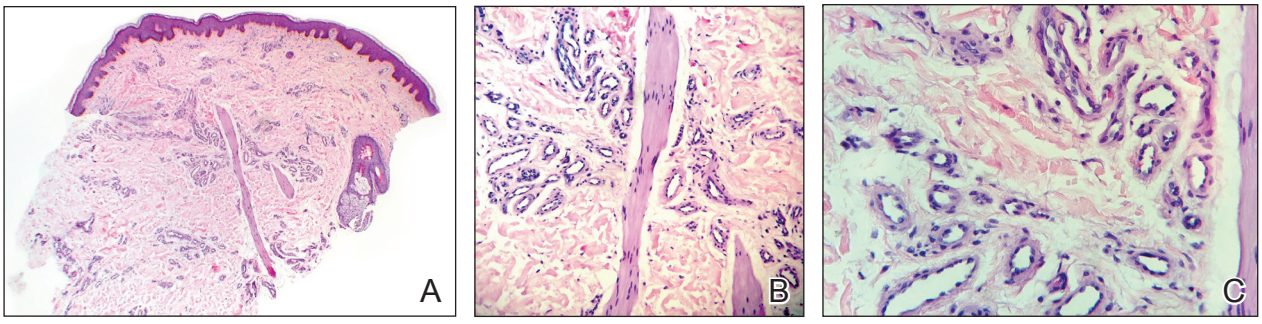

FIGURE 2. A, Biopsy of the patient's left buttock showed a diffuse interstitial proliferation of vascular structures and dilated lumen in the papillary and reticular dermis (H&E, original magnification ×4). B and C, Higher magnification showed well-differentiated endothelial cells forming small vascular structures with intraluminal erythrocytes (H&E, original magnifications ×20 and ×40).

Comment

Classification and Epidemiology—Diffuse dermal angiomatosis is a rare acquired, cutaneous, reactive, vascular disorder first described by Krell et al[1] in 1994. Diffuse dermal angiomatosis is benign and is classified in the group of cutaneous reactive angiomatoses,[2] which are benign vascular disorders marked by intravascular and extravascular hyperplasia of endothelial cells that may or may not include pericytes.[2] Diffuse dermal angiomatosis was originally described as a variant of CREA, which is characterized by hyperplasia of endothelial dermal cells and intravascular proliferation.[3] However, DDA has more recently been identified as a distinct disorder on the spectrum of CREA rather than as a variant of CREA.[2] Given the recent reclassification, not all physicians make this distinction. However, as more case reports of DDA are published, physicians continue to support this change.[4] Nevertheless, DDA has been an established disorder since 1994.[1]

Vascular proliferation in DDA is hypothesized to stem from ischemia or inflammation.[5] Peripheral vascular atherosclerosis has been associated with DDA.[6] The epidemiology of DDA is not well known because of the rarity of the disease. We performed a more specific review of the literature by limiting the PubMed search of articles indexed for MEDLINE to the term *diffuse dermal angiomatosis* rather than a broader search including all reactive angioendotheliomatoses. Only 31 case reports have been published[1,3-32]; of them, only adults were affected. Most reported cases were in middle-aged females. A summary of the demographics of DDA is provided in the Table.[1,3-32]

Pathophysiology—The pathophysiology of DDA remains unclear. It has been hypothesized that ischemia or inflammation creates local hypoxia, leading to an increase in vascular endothelial growth factor with subsequent endothelial proliferation and neovascularization.[5] Rongioletti and Robora[2] supported this hypothesis, proposing that occlusion or inflammation of the vasculature creates microthrombi and thus hypoxia. Afterward, histiocytes are recruited to reabsorb the microthrombi while hyperplasia of endothelial cells and pericytes ensues.[7] Complete resolution of skin lesions following revascularization provides support for this theory.[8]

Etiology—Diffuse dermal angiomatosis is a rare complication of ischemia that may be secondary to atherosclerosis, arteriovenous fistula, or macromastia.[9-11] In DDA of the breasts, ulcerations of fatty tissue occur due to trauma in these patients who have large pendulous breasts, causing angiogenesis resembling DDA

Summary of Published Case Reports of Diffuse Dermal Angiomatosis[1,3-32]

Parameter	Review of Literature
Total no. of patients	73
Average age, y	49.5
Race, n	
White	6
Black	3
Asian	1
Not listed	63
Sex	
Male	16
Female	52
Not listed	5
Locations,[a] n	
Breasts (large, pendulous)	38
Thighs	7
Abdomen	6
Arms	6
Legs	5
Buttocks	2
Trunk	1

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TABLE. (CONTINUED)

Parameter	Review of Literature
Medical history, n	
Smoker	42
Overweight	24
Vascular disease[b]	17
PVD	7
Hyperlipidemia	3
CVD	2
Cutis marmorata telangiectatica congenita	1
Wegener granulomatosis	1
Hypertension	15
ESRD/CKD	5
Fistula	5
Calciphylaxis	4
Diabetes mellitus	4
Monoclonal gammopathy	4
Atrial fibrillation	2
Anticardiolipin antibodies	1
Recent administration of IV trabectedin for the treatment of myxoid liposarcoma	1
Thrombosis	1
Unknown	1
Treatment efficacy	
Control of comorbidities	Effective
Revascularization	Effective
Withdrawal of offending agent	Effective
Isotretinoin	Mostly effective
Steroids	Mixed results
Reduction mammoplasty	Mixed results

Abbreviations: PVD, peripheral vascular disease; ESRD, end stage renal disease; CKD, chronic kidney disease; CVD, cardiovascular disease; IV, intravenous.
[a]Some patients reported multiple locations.
[b]Some patients reported multiple vascular diseases.

histologically.[2] One case of DDA was reported secondary to relative ischemia from cutis marmorata telangiectatica congenita,[12] whereas another case highlighted Wegener granulomatosis as the cause of ischemia.[7] There also have been reported cases associated with calciphylaxis and anticardiolipin antibodies.[13] In general, any medical condition that can lead to ischemia can cause DDA. Comorbid conditions for DDA include cardiovascular disease, hypertension, diabetes mellitus, and most often severe peripheral vascular disease. Many patients also have a history of smoking.[14] Diffuse dermal angiomatosis rarely presents without underlying comorbidity, with only 1 case report of unknown cause (Table).

Presentation, Histopathology, and Differential Diagnosis—Cutaneous reactive angiomatosis disorders present the same clinically, with multiple erythematous to violaceous purpuric patches and plaques that can progress to necrosis and ulceration. Lesions are widely distributed but are predisposed to the upper and lower extremities.[2] The differential diagnosis of DDA includes CREA, acroangiodermatitis (pseudo–Kaposi sarcoma), or vascular malignancies such as Kaposi sarcoma and low-grade angiosarcoma.[7]

In DDA, lesions may be painful and sometimes have a central ulceration.[15] They often are associated with notable peripheral vascular atherosclerotic disease and are mainly found on the lower extremities.[12,16] Histologically, DDA presents as a diffuse proliferation of endothelial cells between collagen bundles. The endothelial cells are distributed throughout the papillary and reticular dermis and develop into vascular lumina.[17] Furthermore, the proliferating endothelial cells are spindle shaped and contain vacuolated cytoplasm.[14]

Acroangiodermatitis, or pseudo–Kaposi sarcoma, presents as slow-growing, erythematous to violaceous, brown, or dusky macules, papules, or plaques of the legs.[14] Histologically, acroangiodermatitis presents with relatively less proliferation of endothelial cells found intravascularly rather than extravascularly, as in DDA, forming new thick-walled vessels in a lobular pattern in the papillary dermis.[14]

Vascular malignancies, such as Kaposi sarcoma and angiosarcoma, may present similarly to DDA. Kaposi sarcoma, for example, presents as erythematous to violaceous patches, plaques, or nodules found mostly on the extremities.[7] Histologically, spindle cells and vascular structures also are found but in a clefting pattern representative of Kaposi sarcoma (so-called vascular slits).[7] Diffuse dermal angiomatosis and vascular malignancies can further be distinguished based on atypia of the proliferations and staining for HHV-8.[7,14] Lastly, DDA differs from vascular tumors in that vascular tumors are reactive to locations of occluded vessels, with vascular proliferation ceasing once the underlying cause of hypoxia is removed.[2]

Treatment—There is no standard treatment of DDA.[7] Treatment of the underlying cause of ischemia is the primary goal, which will cause the DDA to resolve in most cases. Stenting, removal of an arteriovenous fistula, or other forms of revascularization may be warranted.[1,5,6,10,17,29,30]

Reported medical therapies for DDA include systemic or topical corticosteroids used for their antiangiogenic properties with varying results.[7] Isotretinoin also has been used, which has been found to be effective in several

cases of DDA of the breast, though 1 study reported a subsequent elevated lipid profile, requiring a decrease in dosage.[14,15,27,31]

Most interestingly, a study by Sanz-Motilva et al[16] demonstrated that control of comorbidities, especially smoking cessation, led to improvement, which highlights the importance of incorporating nonpharmacotherapy rather than initiating treatment solely with medication. The Table summarizes treatments used and their efficacy.

Conclusion

Diffuse dermal angiomatosis is associated with medical conditions that predispose an individual to ischemia. Although rare, DDA can present as painful and visibly disturbing lesions that can affect the daily life of afflicted patients. By reporting the few cases that do arise and reviewing prior cases and their treatments, physicians can consider DDA within the differential diagnosis and identify which treatment is most efficient for a given patient. For all DDA patients, strict control of comorbidities, especially smoking cessation, should be incorporated into the treatment plan. When DDA affects the breasts, isotretinoin appears to provide the best relief. Otherwise, treatment of the underlying cause, revascularization, withdrawal of the offending agent, or steroids seem to be the best treatment options.

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