Diffuse dermal angiomatosis with clinical features simulating calciphylaxis in the setting of end-stage renal disease

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INTRODUCTION

Reactive angioendotheliomatosis refers to a group of benign disorders characterized by intravascular or extravascular endothelial hyperplasia without cytologic atypia.[1] Diffuse dermal angiomatosis is a rare, acquired, and typically localized form of reactive angioendotheliomatosis. Vascular hyperplasia in diffuse dermal angiomatosis results from ischemia or inflammation that upregulates vascular endothelial growth factor.[2] Diffuse dermal angiomatosis can also be observed in the setting of atherosclerosis, which can result in embolization to distant vessels supplying the skin.[3] Clinically, diffuse dermal angiomatosis presents as erythematous, violaceous, and purpuric patches or plaques.[1] Extensive disease can result in central ulceration, necrosis, and subsequent widespread involvement.[1] Calciphylaxis is a life-threatening vasculopathy characterized by necrosis resulting from calcification of arterioles in the subcutis, most commonly observed in the setting of end-stage renal disease.[4] Rarely, diffuse dermal angiomatosis has been observed in association with calciphylaxis.[4,5] Herein, we present a case of diffuse dermal angiomatosis in the setting of end-stage renal disease, with clinical features simulating calciphylaxis.

CASE REPORT

A 63-year-old woman with secondary hyperparathyroidism and end-stage renal disease presented with several painful indurated nodules with purpura and ulceration on the thighs (Fig 1). An initial punch biopsy result demonstrated a proliferation of vascular channels of various size, which were lined by endothelia without cytologic atypia. The vessels dissected collagen throughout the dermis (Fig 2). Given the clinical context, a wider incisional biopsy with ample sampling of the subcutis was promptly recommended to exclude calciphylaxis. However, histopathology once again demonstrated a similar reactive vascular proliferation, and multiple-level sections were scrutinized. Von Kossa stain failed to identify vascular, interstitial, or perieccrine calcification or calcified elastic fibers. Verhoeff-Van Gieson stain failed to identify fragmented or thickened elastic fibers in the septae. The patient had 2 sets of radiographic imaging conducted 3 months apart, both of which demonstrated widespread atherosclerotic calcifications in the pelvis and thighs within large arteries. This was consistent with known end-stage renal disease. There was no evidence of a netlike pattern of calcification in the soft tissue to suggest calciphylaxis.

DISCUSSION

Considered a reactive vascular proliferation in response to tissue hypoxia, diffuse dermal angiomatosis is well described in association with peripheral vascular disease, macromastia and obesity, severe atherosclerosis, and smoking. It may also be observed in the setting of end-stage renal disease and may clinically simulate causes of retiform purpura and ulceration, including vasculitides, vasculopathies, and calciphylaxis. Vavricka et al[5] reported 9

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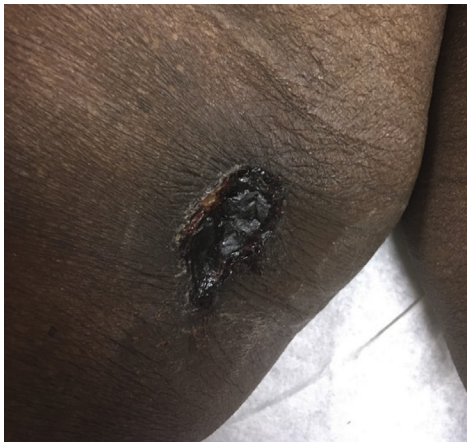

Fig 1. Purpuric nodule with ulceration on the thigh.

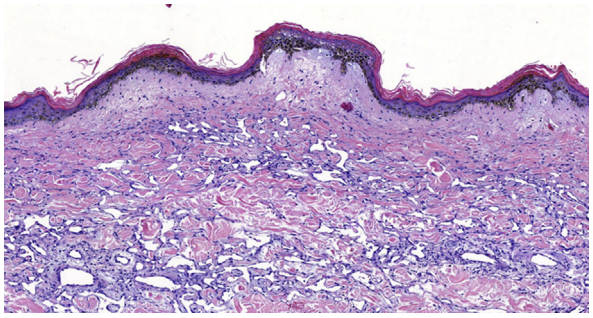

Fig 2. Proliferation of vascular channels of varying size, lined by endothelia without cytologic atypia and dissecting the dermis. (Hematoxylin-eosin stain; original magnification: ×200.)

cases of diffuse dermal angiomatosis associated with calciphylaxis. In all cases, histopathologic features of both diffuse dermal angiomatosis and calciphylaxis were present. The case described herein is unique in that diffuse dermal angiomatosis was associated with clinical features of calciphylaxis in the context of end-stage renal disease, but without diagnostic histopathologic or radiologic evidence of arteriolar calcification. In this case, severe atherosclerotic disease was likely the major contributing factor to end-stage renal disease and diffuse dermal angiomatosis.

In cases with overlapping clinical features, diffuse dermal angiomatosis and calciphylaxis can be distinguished with histopathology, special stains, and radiography. Calciphylaxis is a life-threatening condition that requires prompt management, in comparison to the indolent nature of diffuse dermal angiomatosis.[6] Nonulcerating calciphylaxis is associated with a 33% mortality rate in 6 months, and mortality is higher for patients with ulcerating disease.[7] For this reason, it is important to promptly distinguish these entities.

The classic histopathologic feature of diffuse dermal angiomatosis is a proliferation of small-caliber vessels lined by cytologically bland endothelia, with a dissecting appearance in the papillary and reticular dermis.[1] However, this pattern may also be observed as a reactive phenomenon overlying calciphylaxis, in response to tissue hypoxia.[4] More commonly in calciphylaxis associated with diffuse dermal angiomatosis, the reactive neovascularization is overwhelmed by ischemia, resulting in frank tissue necrosis.[4] In subtle cases of calciphylaxis that lack arteriolar calcification, perieccrine calcification, thrombotic vasculopathy, and fat necrosis with lipophages can support the presumptive diagnosis and management of calciphylaxis in time-critical settings or when larger incisional biopsies are not feasible because of comorbidities or severe pain.[8] Nondiagnostic sampling in calciphylaxis is not uncommon. Special stains are also helpful in differentiation of diffuse dermal angiomatosis from calciphylaxis. Von Kossa and alizarin red can detect interstitial or vascular calcium deposition in subtle cases.[9]

It has been postulated that patients with calciphylaxis may first develop diffuse dermal angiomatosis-like changes when ischemia is still low grade.[5] This may indicate impending development of frank calciphylaxis because of worsening ischemia. If this is the case, prompt management of low-grade ischemia may prevent development of life-threatening sequelae. A stepwise approach for distinction of diffuse dermal angiomatosis from calciphylaxis in the context of end-stage renal disease is presented (Fig 3).

Management of both diffuse dermal angiomatosis and calciphylaxis focuses on cessation of vascular ischemia or inflammation.[1] In diffuse dermal angiomatosis, revascularization often results in resolution.[10] Underlying causes of tissue hypoxia—peripheral vascular disease, atherosclerosis, smoking, and macromastia—should be addressed.[2,10] Vascular surgery may be considered to improve arterial blood flow. Well-established guidelines for the management of calciphylaxis are lacking, but the consensus is that a multidisciplinary approach is required. Wound management can be approached with surgical debridement, hyperbaric oxygen therapy, or negative-pressure dressings.[9] Given the severe pain associated with calciphylaxis, narcotic analgesics are often required.[9] Medical management is based on stabilization of calcium, phosphorous, and parathyroid hormone levels; hemodialysis; optimization of nutrition; and surveillance for superinfection, with prompt institution of directed antimicrobial therapy.[9]

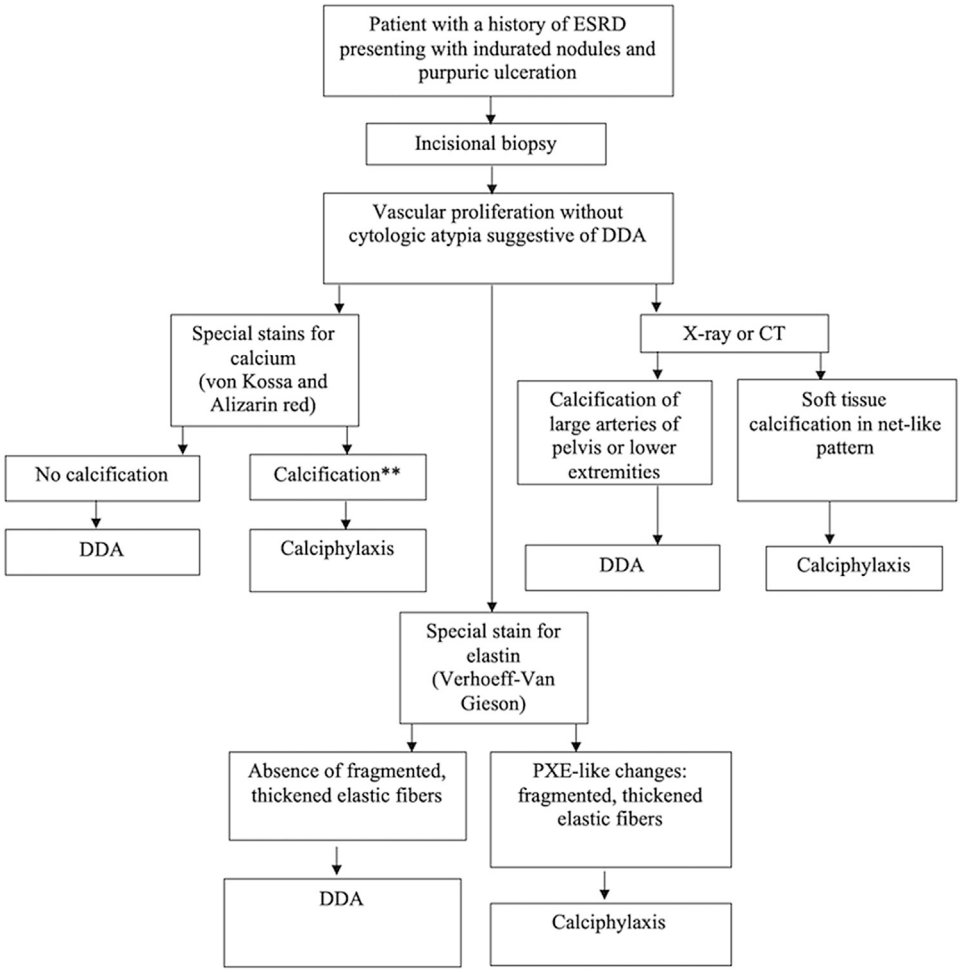

Fig 3. Suggested approach for evaluation of patients with end-stage renal disease who present with features of diffuse dermal angiomatosis. *CT*, Computed tomography; *DDA*, diffuse dermal angiomatosis; *ESRD*, end-stage renal disease; *PXE*, pseudoxanthoma elasticum. **Arteriolor, perieccrine, intersititial, or elastic fiber calcification.

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