A unique clinical and histologic presentation of catastrophic systemic calciphylaxis in a nonuremic patient with systemic lupus erythematosus

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INTRODUCTION

Calciphylaxis, or calcific uremic arteriolopathy, is a rare disorder characterized by calcium deposition in both dermal and subcutaneous adipose tissue as well as in small vessels. It leads to thrombosis, ischemia, and cutaneous necrosis.[1] Calciphylaxis is typically seen in the setting of end-stage renal disease, but it has been increasingly reported in patients with preserved renal function and patients with systemic lupus erythematosus (SLE).[2-6] We report an unusual, highly aggressive, and rapidly progressive case of fatal nonuremic calciphylaxis with atypical clinical and histopathologic features in a patient with SLE.

Abbreviation used:

SLE: systemic lupus erythematosus

CASE REPORT

A 25-year old African-American woman with an 18-month history of SLE presented with a progressive skin eruption of 2 weeks' duration. Her SLE was complicated by class I lupus nephritis, arthritis, and anemia that were adequately controlled with hydroxychloroquine, mycophenolate mofetil, and prednisone. Her serum blood urea nitrogen/creatinine ratio had been normal for many months prior.

Physical examination found 2 distinct primary lesion morphologies. Numerous linear, round, oval, and geometric, skin-colored and yellow-to-brown indurated papules and thin plaques were seen on the trunk and upper extremities (Fig 1). Additionally, tender, retiform purpuric and necrotic indurated plaques with surrounding erythema were noted on her buttocks and proximal inner thighs (Fig 2).

Punch biopsies of an indurated geometric plaque on the central chest and of a retiform necrotic plaque were performed. Both biopsies found extensive calcification of connective tissue fibers (Fig 3) and, to a lesser extent, of dermal and subcutaneous blood vessels (Fig 4), which were highlighted by von Kossa stain. Elastic tissue fiber Verhoeff Van Gieson stain demonstrated fragmentation of dermal elastic fibers. Additionally, the blood vessels in the superficial dermis showed occasional thrombi, hemorrhage, and nuclear dust.

Laboratory values revealed low vitamin D 25-OH (12.6 ng/mL), elevated erythrocyte sedimentation rate (87 mm/h), and normal levels of serum calcium, phosphorus, parathyroid hormone, and creatinine. The patient had a low hemoglobin (Hgb = 8.4 g/dL) and depressed partial thromboplastin time (19.3 seconds; normal, 26.1-33.8 seconds). Her liver function tests, calcium-phosphate product, prothrombin time, white blood cell count, and platelet count were all within normal limits.

Workup for acquired and congenital hypercoagulable states was negative including protein C, protein S, factor V Leiden, prothrombin gene mutation,

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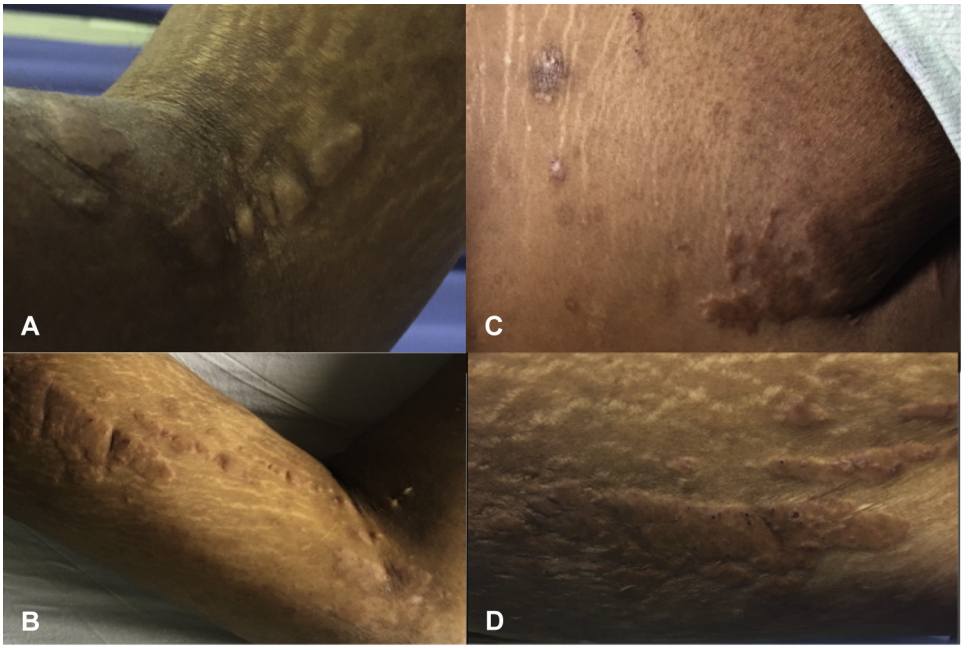

Fig 1. Linear, round, oval, and geometric, skin-colored and yellow-to-brown indurated papules and thin plaques on the upper extremity (**A** and **B**) and trunk (**C** and **D**).

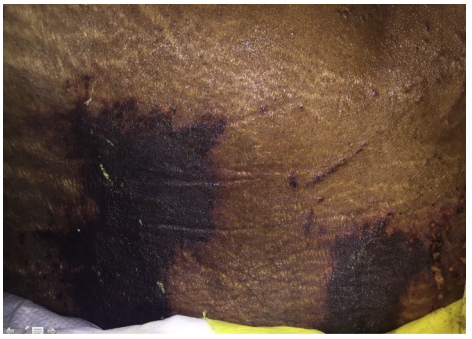

Fig 2. Extensive retiform purpura on the buttocks, characteristic of typical lesions of calciphylaxis.

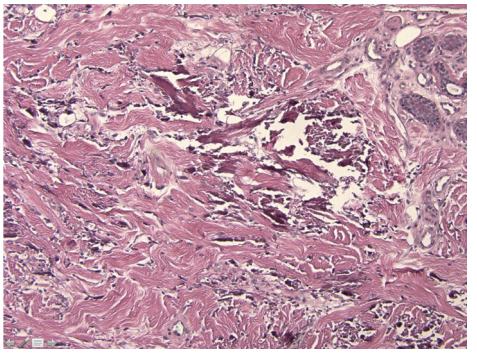

Fig 3. Degeneration and calcifications along the collagen and elastin fibers, adipose tissue, and blood vessels. Diffuse calcification is present throughout the superifical dermis. (Hematoxylin-eosin stain; original magnification: ×40.)

antithrombin 3, cardiolipin IgM/IgG, antiphospholipid panel, and lupus anticoagulant. Additionally, c-ANCA, p-ANCA, cryoglobulins, cryofibrinogens, comprehensive heparin-PF4 IgG antibody, and urine toxicology screen were negative. Tissue cultures were negative. Computed tomography scan of the chest, abdomen, and pelvis found no evidence of malignancy but was notable for splenic infarct due to thrombosis, splenomegaly, and diffuse calcification in the breasts. Cardiac echocardiogram displayed a thickened left atrium with some evidence of calcifications.

Despite treatment with intravenous sodium thiosulfate, plasmapharesis, and intravenous bisphosphonates, as well as discontinuation of systemic steroids, there was significant and rapid progression of new and extensive retiform purpura and necrotic ulcerations. The patient died of the disease only 5 weeks after initial presentation.

DISCUSSION

Calciphylaxis is a rare, life-threatening microvascular occlusion syndrome that is characterized by small and medium blood vessel calcification, intimal proliferation, fibrosis, and thrombosis.[2] The constellation of findings eventually leads to ischemia and target organ hypoperfusion.[2] Cutaneous involvement may present as tender erythema, subcutaneous firm plaques, livedo reticularis, and retiform purpura

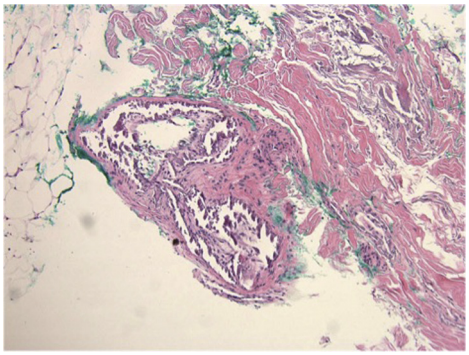

Fig 4. Calcification of medium-sized blood vessels and adipose tissue. (Hematoxylin-eosin stain; original magnification: ×20.)

with overlying vesicles and bullae[7]; skin necrosis and retiform ulceration can also occur.[7] However, the simultaneous occurrence of raised, geometric, plateau-like, firm brown papules and plaques (Fig 1) in addition to the typical retiform necrotic plaques of calciphylaxis is a distinct presentation. In our patient, both lesion morphologies were characterized histologically by fragmentation of dermal elastic fibers and calcification of connective tissue fibers and dermal and subcutaneous blood vessels.

Interestingly, we identified one report of a man with focal segmental glomerulosclerosis who presented with extensive skin and soft tissue calcifications in the setting of elevated phosphate and parathyroid hormone levels[8]; these deposits clinically closely resembled our patient's firm brown papules and plaques. However, biopsies were not performed, and histologic comparison cannot be drawn. Moreover, in our patient, these firm brown papules and plaques rapidly progressed into the typical retiform and deep necrotic ulcerations that involved greater than 80% body surface area. Clinical progression with such primary lesion morphology has not been described in patients with calciphylaxis and thus may represent a unique presentation that precedes the development of typical calciphylaxis lesions.

There is a relative paucity of literature providing a thorough review of all the possible histologic findings of calciphylaxis described to date. In addition to the well-recognized vascular calcifications and microthrombi, there are reports of septal and lobular panniculitis, interstitial deposition of calcium, and epidermal, hair follicle, sweat gland, panniculus, and perineural calcifications.[9] Interestingly, similar to our histopathologic findings, pseudoxanthoma elasticum–like changes have been described in the dermis and subcutaneous tissue of patients with calciphylaxis, albeit corresponding to characteristic necrotic ulcerations clinically.[10] In our case, although elastic tissue fiber Verhoeff Van Gieson stain showed fragmentation of elastic fibers, the morphology was not similar to that seen in pseudoxanthoma elasticum. Our patient's histologic findings were similar in both lesion morphologies, which, to our knowledge, have not been described together in the same patient.

When initially considering our patient's presentation, dystrophic calcification, which is a subtype of calcinosis cutis, was a main consideration.[1] However, calcinosis cutis in patients with SLE is typically a rare and late complication of a long-standing severe disease.[11] It is usually focal and localized with limited deposits of calcium,[1] which is in stark contrast to our patient's extensive firm brown papules and plaques. Other diagnoses considered included dystrophic versus metastatic calcium deposits and cutaneous mucinosis in association with SLE versus other deposition diseases. Despite an unusual presentation, we believe our patient's presentation was caused by a combination of calciphylaxis and catastrophic calcification of connective tissue. Well-recognized risk factors for calciphylaxis were present in our patient, including systemic corticosteroid use,[12] female sex,[13] increased erythrocyte sedimentation rate,[12] and vitamin D deficiency.[10] Of note, the lack of an identifiable cause of a hypercoagulable state in this patient despite such a rapid progression of cutaneous necrosis raises concerns that there are other unrecognized mechanisms driving thrombosis in these types of cases. This may suggest that other causes such as bland occlusion by intravascular calcium with or without additional mechanisms should be considered. We hope that our increased knowledge of calciphylaxis and description of similar cases will help to shed more light on the underlying pathophysiology.

Overall, the unique features of our case posed a diagnostic and therapeutic challenge. The simultaneous development of extensive geometric papules and plaques with retiform necrotic ulcerations, extensive calcification of connective tissue fibers, and an accelerated fatal disease course, is atypical and rare compared with classic uremic calciphylaxis. Determining whether this case constitutes a peculiar clinical presentation of calciphylaxis versus a clinical variant of calciphylaxis, description of similar cases will be required. We report this case to expand the clinical and histologic spectrum of calciphylaxis; more importantly, we hope to raise awareness about this highly aggressive and rapidly progressive case of fatal nonuremic calciphylaxis in a patient with well-controlled SLE. Because of significant morbidity and mortality associated with calciphylaxis, rapid

diagnosis and a multidisciplinary approach are of paramount importance.

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