Leg ulcers in systemic lupus erythematosus associated with underlying dystrophic calcinosis and bone infarcts in the absence of antiphospholipid antibodies

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INTRODUCTION

Leg ulcers occur in systemic lupus erythematosus (SLE) owing to vasculitis, antiphospholipid antibodies, and, rarely, pyoderma gangrenosum or calcinosis cutis. We report the unusual case of a 34-year-old woman with chronic SLE without antiphospholipid antibodies, who had a leg ulceration and bone infarction with dystrophic soft tissue calcification throughout the lower extremities.

CASE REPORT

A 34-year-old African-American woman with an 11-year history of SLE, on prednisone (20–50 mg daily with occasional pulse doses) and cyclophosphamide, presented with painful, enlarging bilateral lower extremity ulcerations. Her SLE was complicated by proven chronic osteomyelitis of the right distal tibia and infarction of the left distal tibia.

On examination, she had two, 2-cm ulcerations with punched-out borders on her right foot, a tender 10- × 6-cm irregularly shaped, foul-smelling, deep ulceration with a granulating base and spicules of calcium on her left medial calf partially overlying her shin, and a 4- × 4-cm round ulcer with a fibrinous base above the left medial malleolus (Fig 1, *A*). She had no ulcerations or lesions on her digits. Multiple hard subcutaneous nodules were on both calves. Femoral and pedal pulses were present bilaterally, and skin overlying her feet was warm. Neurologic examination was unremarkable.

Abbreviations used:

aCL:	anticardiolipin antibody
APLAs:	antiphospholipid antibodies
AVN:	avascular necrosis
LA:	lupus antibody
MRI:	magnetic resonance imaging
SLE:	systemic lupus erythematosus

Laboratory analysis was notable for pancytopenia (white blood cells, 600 per mm^3; hemoglobin, 6.3 g/dL; platelet count, 39,000 per mm^3) and an elevated erythrocyte sedimentation rate (142 mm/h). Basic metabolic profile, serum calcium, phosphorus, parathyroid hormone levels, alkaline phosphatase, and liver function test results were normal. Extensive workup findings were negative for comorbidities, including hyperparathyroidism, sickle cell disease or hemoglobin-SC disease, cryoglobulinemia, antiphospholipid antibodies (APLAs), dermatomyositis, scleroderma, overlap syndrome, or an active flare of lupus.

Lower extremity plain radiographs showed bilateral vascular calcifications and diffuse soft tissue calcifications (Fig 2). Magnetic resonance imaging (MRI) 2 years before presentation found a left distal tibia bone infarction (Fig 3). An MRI was repeated at this time, because of concern for recurrent osteomyelitis, however, demonstrated curvilinear low signal in the bone marrow of the distal tibia bilaterally, consistent with bone infarction, and soft tissue calcification overlying the left tibial bone infarction,

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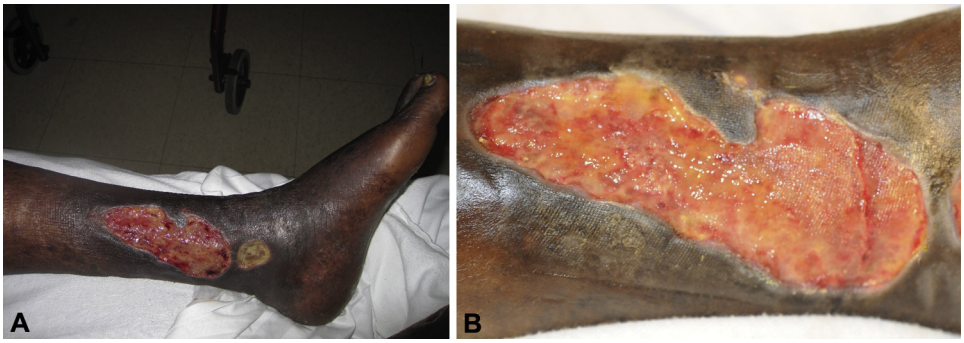

Fig 1. Clinical presentation of ulcer. **A**, 10- × 6-cm irregularly shaped deep ulceration with a granulating base and spicules of calcium on the left medial calf partially overlying the shin and a 4- × 4-cm round ulcer with a fibrinous base above the left medial malleolus. **B**, Spicules of yellow-white chalky material—calcium—extruding from ulceration.

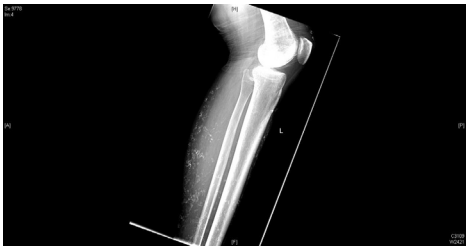

Fig 2. Radiograph of left leg shows multiple discrete, irregular areas of calcification in the soft tissue.

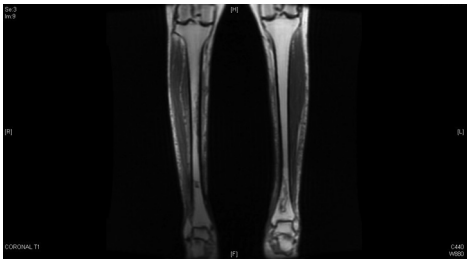

Fig 3. Coronal T1 MRI of lower extremities shows a curvilinear margin of low signal in the left distal tibia, consistent with bone infarction.

underneath the location of the large ulceration. Noninvasive flow studies were negative for arterial disease. The patient was followed up with as an outpatient by dermatology and plastic surgery departments, with debridement of her ulcerations. Two years later, she again presented with ulceration of unknown duration. Punch biopsy of the ulceration found calcium deposits (Fig 4), and the diagnosis of calcinosis cutis was confirmed. The patient's ulcers healed with local wound care and serial debridements over the course of a year.

DISCUSSION

Dystrophic calcification, a common finding in connective tissue diseases (diffuse cutaneous systemic sclerosis, limited cutaneous sclerosis [which may be classified as CREST syndrome of calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia], dermatomyositis, and overlap syndromes), occurs in areas of underlying tissue injury or hypoperfusion with normal levels of serum calcium and phosphorous (in the absence of chronic renal failure and hyperparathyroidism) and is thought to involve a dysregulation in mitochondrial calcium homeostasis secondary to cell death.[1,2] The deposition of calcium phosphate in the damaged tissue is an example of locus minoris resistance, which is a rare finding in SLE, often seen only incidentally on imaging late in the disease.[1] In uncommon instances, as in this case, the crystalline material of calcinosis causes chronic or recurrent skin ulcerations.[1] In the evaluation of skin ulcers in SLE, we recommend careful examination for the white opaque spicules of calcium as the cause of the nonhealing skin ulceration (Fig 1, *B*).

More unusual is the presence of peripheral vascular calcification in SLE in the absence of chronic renal failure, hemodialysis, diabetes, and secondary hyperparathyroidism. The chronic inflammatory state of SLE with active acute lupus in other organ systems may be the cause of the vascular and soft tissue calcification.[3] Why this patient developed calcinosis and other patients with SLE do not is not known.

Osteonecrosis, or bone death caused by ischemia, in SLE is not uncommon. Osteonecrosis occurs with prominent symptoms at a rate of 3% to 30%, and is likely higher when asymptomatic osteonecrosis is accounted for.[4] Osteonecrosis in SLE is largely secondary to avascular necrosis (AVN), which, by definition, occurs in the epiphysis or subarticular bone that forms part of a joint.[4,5] Osteonecrosis of the metaphysis or diaphysis of the bone is referred to

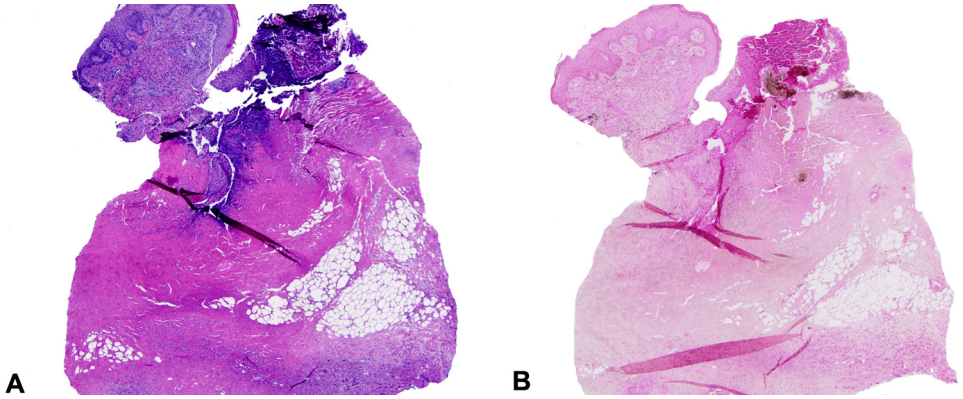

Fig 4. Ulcer with calcium deposits in hematoxylin-eosin stain (**A**) and von Kossa stain (**B**) highlighting calcium. (Original magnification: ×4.)

Table I. Clinical characterization of patients with SLE and multiple bone infarction

Case	Age/ Sex	Duration SLE (y)	Location of osteonecrosis	Ulceration	Calcinosis	Presence of APLAs	Systemic steroid therapy
Salesi et al[7]	21/F	3	Infarct in metaphysis of femur, AVN of femoral head bilaterally	No	No	Yes (aCL)	Yes
Fajardo-Hermosillo et al[8]	26/F	2	Osteonecrosis of distal tibia, proximal tibia, distal fibula, and talus bilaterally	Yes (pretibial)	No	Yes (aCL)	Yes
Perez-Pampin et al[9]	51/F	21	Osteonecrosis of distal femur and proximal tibia bilaterally	No	No	Yes (aCL)	Yes
Chatterjee[10]	48/F	>20	Infarct in distal femur bilaterally, proximal tibia bilaterally, distal tibia, tali, calcanei, navicular, distal radius, lateral femoral condyles; AVN right lunate	No	No	Yes (LA)	Yes
Current case	34/F	11	Infarct in distal tibia bilaterally	Yes (pretibial)	Yes	No	Yes

aCL, Anticardiolipin antibody; *LA*, lupus antibody.

as *bone infarction* and is rarely seen in SLE.[5] Nontraumatic causes of osteonecrosis in SLE include steroid usage and the presence of APLAs and other hypercoagulable states.[4] Zizic et al[6] proposed that steroids, outside of the known associations with poor wound healing, cause increased pressure within the bone marrow secondary to intramedullary adipocyte hypertrophy and hyperplasia. This results in compression of blood vessels and decreased perfusion of surrounding bone.[6]

There are approximately 40 cases reported in the literature of dystrophic calcinosis occurring in SLE. Many of these patients were on systemic steroids or had some type of tissue injury, such as myopathy, skin ulcerations, or, rarely, osteonecrosis as a cofactor for dystrophic calcification. There are only 4 reported cases of multiple bone infarctions in SLE, all with simultaneous antiphospholipid antibodies and a known history of systemic steroid therapy (Table I). However, bone infarctions in SLE associated with dystrophic calcification and leg ulcers in the absence of antiphospholipid antibodies suggests a different mechanism. To our knowledge, this is the first reported case in which both calcinosis cutis and bone infarction in SLE occurred concurrently, although there are several reports of AVN of the femur occurring with dystrophic calcinosis in SLE.

A plausible explanation for the unique concurrence of findings is dystrophic calcification in the vasculature of the bone, skin, and peripheral vessels from the acute and chronic autoinflammatory state of SLE. Once initiated, the deposition of calcification continues with cellular necrosis and tissue damage, acid milieu, and hypercoagulability propagating the process locally with further calcium precipitation.[2,3,11] Therapeutic options for dystrophic calcification with ulceration are anecdotal, but the use of sodium thiosulfate solution is reported to be successful.[12]

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