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

Margo Lederhandler, MD, Whitney Valins, MD, Zena Zoghbi, MD, and Marc E. Grossman, MD, FACP
New York, New York

Key words: antiphospholipid antibodies; calcinosis; dystrophic calcification; lupus; osteonecrosis; ulcers.

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.

Laboratory analysis was notable for pancytopenia (white blood cells, 600 per mm³; hemoglobin, 6.3 g/dL; platelet count, 39,000 per mm³) 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.
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.\(^5,6\) Osteonecrosis of the metaphysis or diaphysis of the bone is referred to

---

**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.
Bone infarction and is rarely seen in SLE. Nontraumatic causes of osteonecrosis in SLE include steroid usage and the presence of APLAs and other hypercoagulable states. Zizic et al 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.

There are approximately 40 cases reported in the literature of dystrophic calcification 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 autoimmune inflammatory 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.

Therapeutic options for dystrophic calcification with ulceration are anecdotal, but the use of sodium thiosulfate solution is reported to be successful.

**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          | 21/F    | 3               | Infarct in metaphysis of femur, AVN of femoral head bilaterally                          | No         | No         | Yes (aCL)         | Yes                     |
| Fajardo-Hermosillo et al | 26/F   | 2               | Osteonecrosis of distal tibia, proximal tibia, distal fibula, and talus bilaterally     | Yes (pretibial) | No         | Yes (aCL)         | Yes                     |
| Perez-Pampin et al    | 51/F    | 21              | Osteonecrosis of distal femur and proximal tibia bilaterally                           | No         | No         | Yes (aCL)         | Yes                     |
| Chatterjee           | 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.
REFERENCES
1. Reiter N, El-Shabrawi L, Leinweber B, Berghold A, Aberer E. Calcinosi cutis: part I. Diagnostic pathway. J Am Acad Dermatol. 2011;65(1):1-12; quiz 3-4.
2. Enoch S, Kupitz S, Miller DR, Harding KG. Dystrophic calcification as a cause for non healing leg ulcers. Int Wound J. 2005;2(2):142-147.
3. Mandelbrot DA, Santos PW, Burt RK, et al. Resolution of SLE-related soft-tissue calcification following haematopoietic stem cell transplantation. Nephrol Dial Transplant. 2008;23(8):2679-2684.
4. Abu-Shakra M, Buskila D, Shoenfeld Y. Osteonecrosis in patients with SLE. Clin Rev Allergy Immunol. 2003;25(1):13-24.
5. Saini A, Saifuddin A. MRI of osteonecrosis. Clin Radiol. 2004;59(12):1079-1093.
6. Zizic TM, Marcoux C, Hungerford DS, Dansereau JV, Stevens MB. Corticosteroid therapy associated with ischemic necrosis of bone in systemic lupus erythematosus. Am J Med. 1985;79(5):596-604.
7. Salesi M, Karimifar M, Mottaghi P, Sayedbonakdar Z, Karimzadeh H. A case of SLE with bilateral osteonecrosis of femoral heads and bone infarct in distal of femur. Rheumatol Int. 2010;30(4):527-529.
8. Fajardo-Hermosillo LD, Lopez-Lopez L, Nadal A, Vila LM. Multifocal osteonecrosis in systemic lupus erythematosus: case report and review of the literature. BMU Case Rep. 2013;2013:1-6.
9. Perez-Pampin E, Mera A, Campos J. Bone infarctions in a patient with systemic lupus erythematosus and anti-cardiolipin antibodies. J Clin Rheumatol. 2010;16(1):54.
10. Chatterjee S. Bone infarcts in a woman with systemic lupus erythematosus and antiphospholipid antibody syndrome. CMAJ. 2006;174(4):455-456.
11. Walsh JS, Fairley JA. Calcifying disorders of the skin. J Am Acad Dermatol. 1995;33(5 Pt 1):693-706; quiz 7-10.
12. Wolf EK, Smidt AC, Laumann AE. Topical sodium thiosulfate therapy for leg ulcers with dystrophic calcification. Arch Dermatol. 2008;144(12):1560-1562.