TEACHING CASE REPORT

Bone infarcts in a woman with systemic lupus erythematosus and antiphospholipid antibody syndrome

The Case: A 48-year-old woman with systemic lupus erythematosus (SLE) diagnosed more than 20 years ago presented to our clinic with a history of generalized pain, profound fatigue, oral ulcers, dry eyes and mouth, and hair loss. She complained of severe pain in her fingers, wrists, knees, hips and ankles. She also reported significant morning stiffness and muscle soreness. In the past, she had had immune thrombocytopenic purpura, several deep venous thromboses and an episode of pulmonary embolism. She was taking warfarin (2.5 mg daily), hydroxychloroquine (200 mg twice daily), acetaminophen–propoxyphene combination therapy as required for pain, and prednisone (5 mg/d).

The patient was afebrile. There was no overt synovitis, but in addition to several fibromyalgia tender points, there was tenderness over her wrists, elbows, knees and ankles. Radiographs of her long bones showed evidence of multiple bone infarcts and avascular necroses (Fig. 1 A–D). A technetium-99m radionuclide bone scan showed evidence of a healed infarct of the right lunate and lateral femoral condyles (Fig. 1 E–G).

The antinuclear antibody titre, determined by means of indirect immunofluorescence assay (IFA), was greater than 1:640 (homogeneous pattern), and serologic tests for anti–SS-A and anti–SS-B antibodies yielded positive results. The patient had active SLE, as evidenced by an elevated erythrocyte sedimentation rate (32 mm/h), a positive enzyme immunoassay (EIA) result for anti-dsDNA antibody, confirmed by *Crithidia lucillae* assay by IFA (titre 279

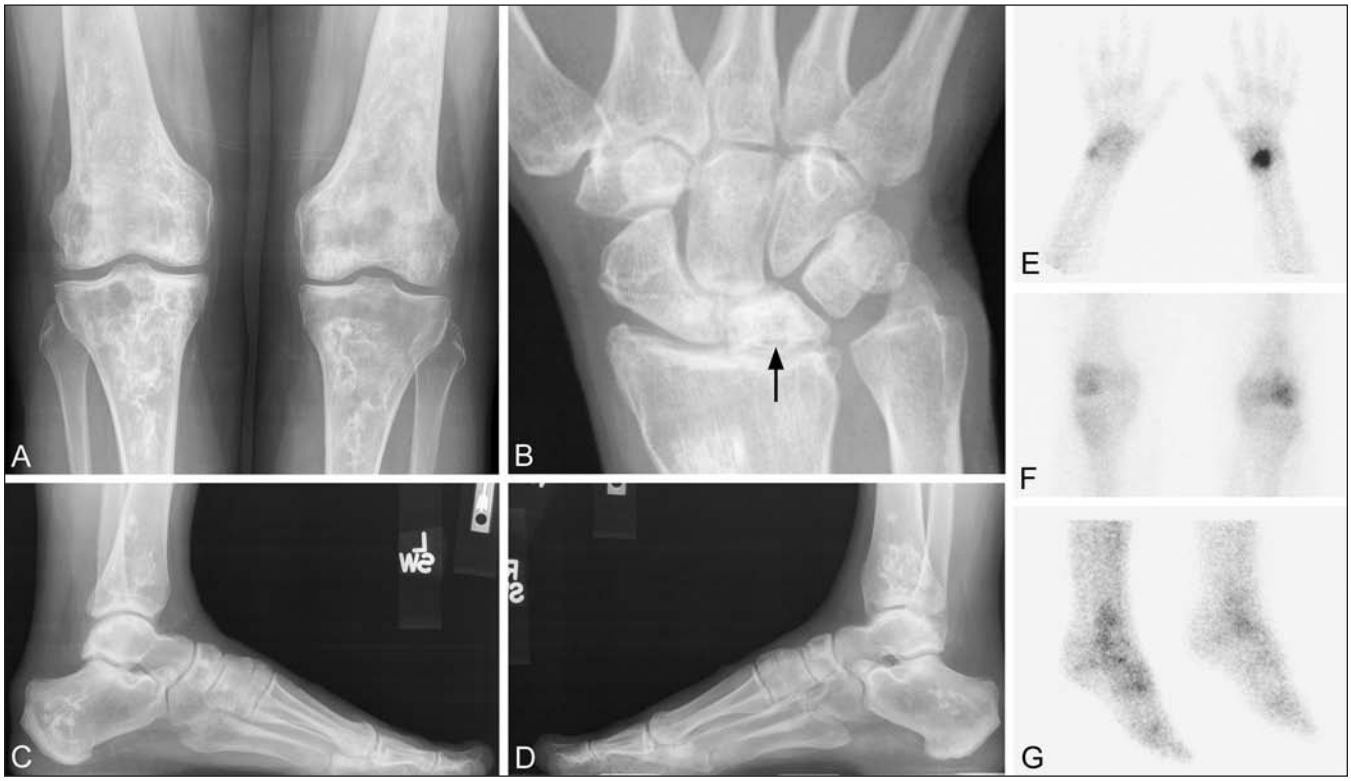

Fig. 1: (A) Sclerotic areas, showing serpentine pattern, in distal femurs extending into articular surfaces and in proximal tibias extending into articular surface on right side. Findings are consistent with bony infarcts. Mild narrowing of medial joint spaces bilaterally, but no articular collapse. (B) Avascular necrosis (arrow) in right lunate (Kienböck's disease), with degenerative changes of radiocarpal joint. Vague opacity in distal aspect of radius likely represents bone infarct. Multiple areas of increased density in several bones of left (C) and right (D) foot (tali, calcanei and navicular bones) and in distal aspect of tibia, consistent with presence of multiple bone infarcts. Technetium-99m radionuclide bone scan showed increased uptake in distal right radius consistent with a healing bone infarct (E). Healed infarct of right lunate (E) and in proximal aspect of right navicular bone (G) were noted. Uptake in lateral femoral condyles (F) was probably due to bone infarcts as well.

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[normal < 30] IU/mL), and low levels of complement (C3 0.6 [normal 0.7–2.6] g/L; C4 0.1 [normal 0.2–0.6] g/L). The patient had a prolonged prothrombin time of 18.6 (normal 9.9–13) seconds, an international normalized ratio (INR) of 1.7 (normal 0.9–1.2) and an activated partial thromboplastin time (aPTT) of 56.1 (normal 24.6–34) seconds. The prolonged prothrombin time was consistent with her history of warfarin therapy. The prolonged aPTT was not due to heparin, since a screening assay for heparin yielded negative results. The patient was positive for IgM anticardiolipin antibodies (16 [normal < 12] MPL units) but negative for IgG cardiolipin antibodies. The circulating anticoagulant assay (incubated aPTT mixing study) yielded a positive result for an immediate-acting inhibitor. Results of the dilute Russell viper venom test and platelet neutralization procedures were both positive. The laboratory findings were consistent with a lupus anticoagulant.

Our patient had 3 major potential causes of avascular necrosis and bone infarcts: SLE, antiphospholipid antibody syndrome and chronic steroid use.

Avascular necrosis results from death of bone marrow and trabecular bone because of an impaired blood supply. Two main forms have been described: post-traumatic and nontraumatic. The post-traumatic form develops from traumatic displacement of the bone fragments, which leads to disrupted blood supply and ischemia to the affected bone. The nontraumatic form occurs because of interrupted blood flow due to intravascular thrombi and can result from various conditions (Box 1).

Box 1: Nontraumatic causes of avascular necrosis

- Systemic lupus erythematosus
- Antiphospholipid antibody syndrome and other hypercoagulable states
- Alcoholism
- Pregnancy
- Corticosteroid therapy
- Sickle cell disease
- Pancreatitis
- Inflammatory bowel disease
- Cytotoxic drugs
- Hematologic malignant diseases
- Gaucher's disease
- Idiopathic

Antiphospholipid antibody syndrome is referred to as "primary" when it occurs alone; however, it can also be associated with SLE, other rheumatic diseases, and certain infections and drug therapies. It is a common cause of avascular necrosis. Patients with antiphospholipid antibody syndrome may display a constellation of clinical features (Box 2).[1] The syndrome is associated with the presence of anticardiolipin antibodies or lupus anticoagulant, or both. Lupus anticoagulant activity can be assessed even in the presence of warfarin therapy.[2]

Polyarthralgia and musculoskeletal pain in SLE is usually a result of lupus arthropathy or secondary fibromyalgia. SLE patients with bone pain should be tested for the lupus anticoagulant, and if it is present, avascular necrosis should be suspected. Avascular necrosis in SLE patients can occur even in the absence of corticosteroid use.[3]

Our patient had been receiving steroids intermittently for her lupus and immune thrombocytopenic purpura. The maximum (peak) dose ever received was 30 mg of prednisone daily; the maximum duration of high-dose therapy (20 mg/d) was 9 months, and it occurred 20 years before the current presentation. The patient had begun low-dose prednisone therapy (2.5–10 mg daily) a year before presentation.

The syndrome of multiple avascular necroses and bone infarcts is a rare cause of musculoskeletal pain in patients with SLE. Prevention of further progression may require reduction of the steroid dose and intensification of therapeutic anticoagulation in patients with antiphospholipid antibody syndrome, although the latter hypothesis has not been formally evaluated.

Our patient's warfarin dose was increased to achieve a therapeutic INR (2–3), mycophenolate mofetil therapy was started to treat the active SLE symptoms, and the prednisone dose was maintained at 5 mg/d. Hydroxychloroquine therapy was continued because, in addition to treating the musculoskeletal manifestations of SLE, it is known to have a prophylactic role in antiphospholipid antibody syndrome. With this regimen the patient has responded well, with a decline in her pain and no further occurrence of bone lesions.

Box 2: Features of antiphospholipid antibody syndrome

- Venous thrombosis (deep vein thrombosis, pulmonary embolism)
- Arterial thrombosis
- Recurrent fetal loss
- Thrombocytopenia
- Livedo reticularis
- Transient ischemic attack and stroke
- Hemolytic anemia
- Migraine
- Raynaud's phenomenon
- Renal disease (thrombotic microangiopathy)
- Pulmonary hypertension
- Cutaneous ulcers
- Valvular heart disease
- Adrenal insufficiency
- Occlusion in multiple vascular beds leading to multiple-organ failure (catastrophic antiphospholipid syndrome); rare

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