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The Clinical Picture

A 48-year-old woman with an ecchymotic rash

Livedo reticularis is the most commonly described skin lesion

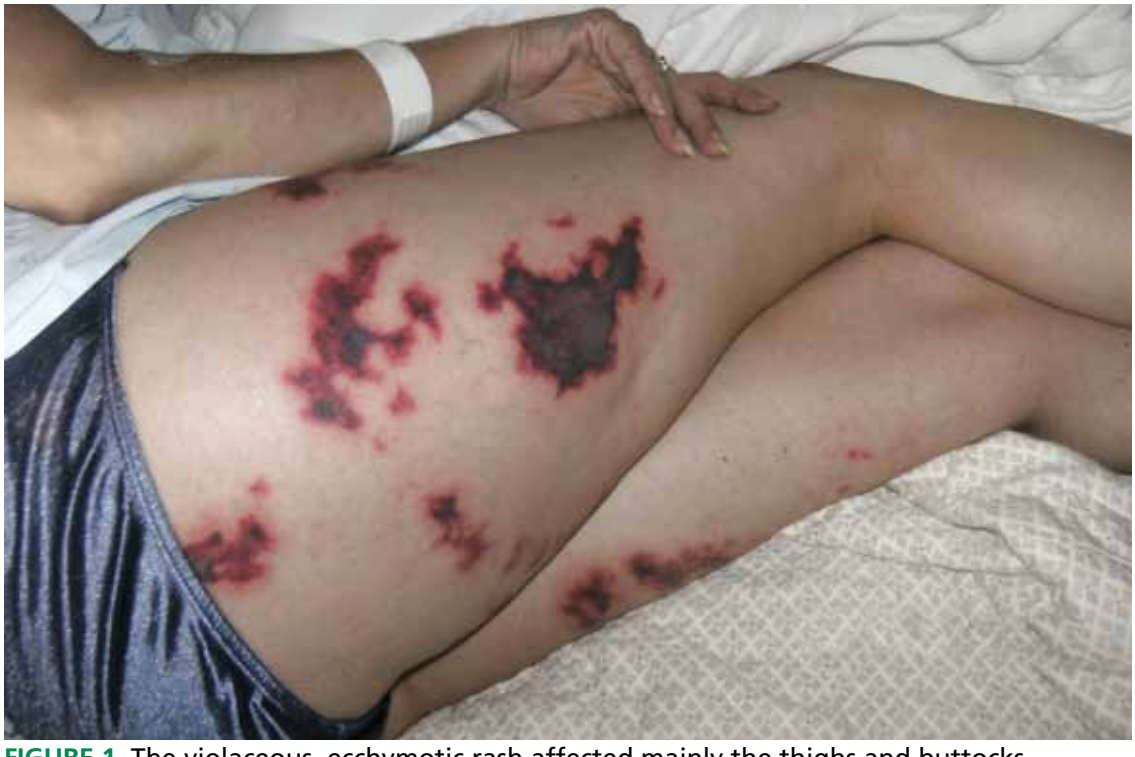

FIGURE 1. The violaceous, ecchymotic rash affected mainly the thighs and buttocks.

A 48-year-old woman was admitted to the hospital with a painful ecchymotic rash on the thighs, buttocks, and arms (**FIGURE 1**). She also complained of pain, swelling, and stiffness in her elbows, knees, and feet, with morning stiffness lasting several hours. The lesions began about 2 months previously on the thighs and then gradually spread to other areas.

She had no constitutional symptoms and no history of venous thromboembolism, stroke, pregnancy loss, recent anticoagulation, or endovascular procedures.

A complete blood cell count, comprehensive metabolic panel, and urinalysis were normal. Serologic tests for hepatitis B and C were negative. Antinuclear antibody was positive by enzyme immunoassay (optical density ratio of 4.6 [< 1.5 is considered negative]). Double-stranded DNA antibody was detected by enzyme immunoassay at 92 IU/mL (< 30 is considered negative), confirmed by indirect immunofluorescence with *Crithidia luciliae* as the substrate. The immunoglobulin M (IgM) cardiolipin antibody titer was minimally elevated at 20 IgM phospholipid units (reference range 0–11), and beta-2-glycoprotein 1 antibodies were not detected. However, test results for

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TABLE 1

How our patient fulfilled the diagnostic criteria for having a lupus anticoagulant

CRITERIA	OUR PATIENT'S TEST RESULTS	COMMENTS
Prolongation of phospholipid-dependent clotting tests	Activated partial thromboplastin time (APTT) prolonged Dilute Russell viper venom time (DRVVT) ratio 1.24 (reference range 0.95–1.17)	The prolonged APTT was not due to heparin, as a screening assay for heparin was negative; the thrombin time was normal at 14.9 seconds (< 18.6 is considered normal), which makes an effect of heparin or a direct thrombin inhibitor unlikely
Evidence of inhibitory activity shown by the effect of the patient's plasma on pooled normal plasma (mixing test)	Immediate-acting inhibitor present DRVVT 1:1 mix 45.9 seconds (reference range 31.8–44.6)	A clotting time of the mixed plasma that corrects toward normal indicates deficient clotting factor replenished by the normal plasma; however, in the presence of a lupus anticoagulant, the clotting time does not correct
Evidence that the inhibitory activity depends on phospholipid	Platelet neutralization test positive Hexagonal phase phospholipid neutralization assay (screening) 101.8 seconds (reference range 45.7–62.9); confirmatory test 62.7 seconds (reference range 46.8–60.8)	Diagnosis of a lupus anticoagulant is confirmed with phospholipid-sensitive functional clotting testing; normalization of the prolonged clotting time by adding phospholipid to the plasma demonstrates phospholipid dependence
Specific factor deficiencies have been excluded	These assays were not performed	There was no suspicion of a specific factor deficiency, as the clotting time did not correct in the incubated mixing studies

this patient satisfied the diagnostic criteria for the presence of a lupus anticoagulant (TABLE 1).[1]

Q: What is the most likely diagnosis?

- ☐ Chronic meningococcemia
- ☐ Cholesterol embolism
- ☐ Antiphospholipid syndrome
- ☐ Cryoglobulinemic vasculitis
- ☐ Heterozygous protein C deficiency

A: The most likely diagnosis is skin necrosis due to intravascular thrombosis, consistent with antiphospholipid syndrome. By clinical and laboratory criteria, the patient has systemic lupus erythematosus. Pain and swelling in multiple joints is indicative of polyarthritis associated with lupus. Retesting 12 weeks later again detected lupus anticoagulant, confirming the diagnosis of antiphospholipid syndrome.[2]

Skin biopsy specimens demonstrated intraluminal fibrin deposition in small capillaries and venules in the superficial and mid-reticular dermis (FIGURE 2), consistent with the clinical history of antiphospholipid syndrome. A very mild perivascular infiltrate of small lymphocytes was also noted. However, changes of an inflammatory destructive vasculitis were not seen.

In the hospital, the patient was started on unfractionated heparin, later switched to warfarin. Her skin lesions gradually cleared, her pain diminished significantly, and no new lesions appeared after the start of anticoagulation therapy. For her lupus, she was started on hydroxychloroquine (Plaquenil),

She was started on unfractionated heparin, later switched to warfarin; her lesions gradually cleared, and her pain diminished significantly

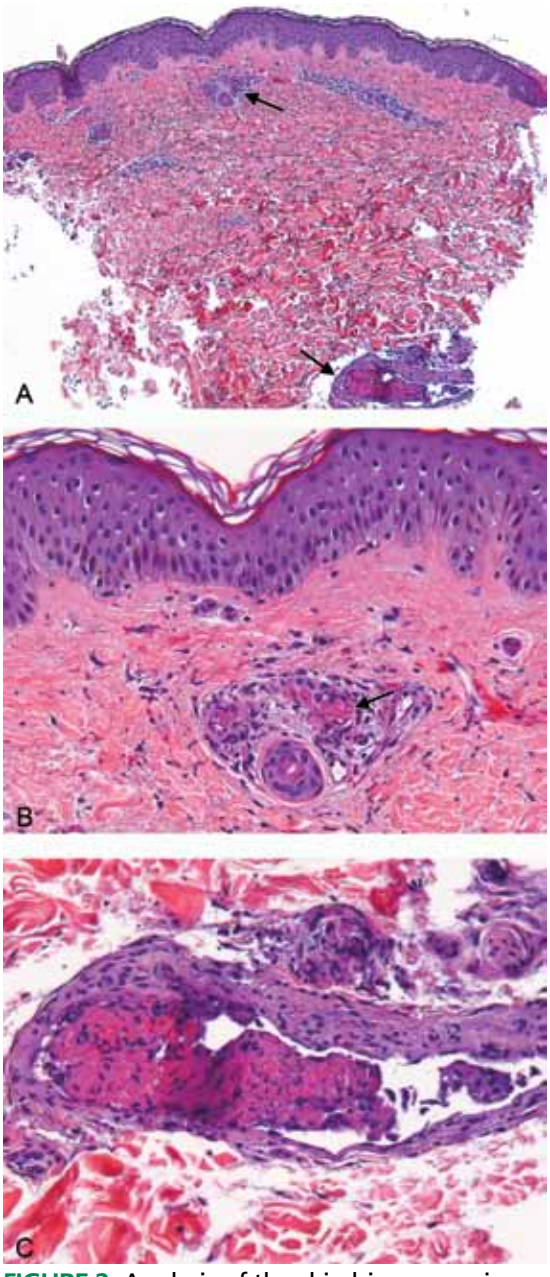

FIGURE 2. Analysis of the skin biopsy specimens revealed (A) superficial and deep dermal small-vessel thrombosis (arrows) (hematoxylin and eosin, × 5); (B) intravascular thrombosis involving a small superficial dermal arteriole (arrow) (hematoxylin and eosin, × 20); and (C) intravascular thrombosis involving a small deep dermal venule (hematoxylin and eosin, × 20).

which has been suggested to also have an adjuvant antithrombotic role in antiphospholipid syndrome.[2] On a follow-up visit 3 months later, she was doing well.

MORE ABOUT ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome is termed primary when no underlying disease is identified, and secondary when it occurs in conjunction with an autoimmune rheumatologic disease, an infection, malignancy, or certain drugs.[3] It is the most common cause of acquired thrombophilia.[4] Arterial or venous thromboses and recurrent miscarriages are salient clinical features.

Laboratory abnormalities include the presence of a lupus anticoagulant and anticardiolipin and beta-2-glycoprotein 1 antibodies.

Skin manifestations include livedo reticularis, purpuric macular lesions, atrophie blanche, cutaneous infarcts, ulceration, and painful nodules.[5] Livedo reticularis, a violaceous, lace-like cutaneous discoloration, is the most commonly described skin lesion, present in 20% to 50% of cases.[5,6] Cutaneous necrosis may involve the legs, face, and ears, or it may be generalized.[6]

The prothrombotic state is believed to be immune-mediated, with complement activation.[2] Endothelial cells and monocytes are activated by antiphospholipid antibodies with activity against beta-2-glycoprotein 1, resulting in up-regulation of tissue factor and in platelet activation.[2] Histopathologic examination reveals noninflammatory vascular thromboses with endothelial damage.[5]

Although antiphospholipid syndrome seems to be immune-mediated, immunosuppressive therapy has not proved very effective,[3] and anticoagulation is the recommended treatment.[3,7]

THE OTHER DIAGNOSTIC POSSIBILITIES

Chronic meningococcemia, sometimes associated with terminal complement deficiency, is associated with a petechial rash in 50% to 80% of cases. The rash can become confluent, resulting in hemorrhagic patches with central necrosis, resembling the lesions in our patient.

However, these skin lesions are due to thrombi in the dermal vessels, associated with leukocytoclastic vasculitis. These dermatopathologic changes were not seen in our patient. Moreover, meningococci were not identified in blood cultures or in the luminal thrombi and vessel walls.

Cholesterol embolism occurs when cholesterol crystals break off from severely atherosclerotic plaques, either spontaneously or after local trauma induced by angiography or aortic injury. The crystals shower downstream through the arterial system, often immediately occluding arterioles 100 to 200 µm in diameter.

Our patient had no such history, and the skin biopsy did not show the characteristic "cholesterol clefts"—biconvex, needle-shaped clefts left by the dissolved crystals of cholesterol within the occluded vessels.

Cryoglobulinemic vasculitis is an immune-complex-mediated condition involving small- to medium-size vessels, often associated with hepatitis C virus infection. Skin lesions appear in dependent areas and include erythematous macules and purpuric papules.

Cryoglobulins were not detected in our patient's sera, nor did the skin biopsy indicate the typical leukocytoclastic vasculitis seen in this condition.

Heterozygous protein C deficiency causes venous thromboembolism and warfarin-induced skin necrosis. Spontaneous thrombosis of cutaneous arterioles (as in our patient) is not a usual manifestation. Also, our patient had normal protein C levels and no history of warfarin use before the skin lesions developed.

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