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A Tale of Two Rashes

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PRESENTATION

A rash is often an important clue as to the etiology of a systemic illness. In this case, 1 patient developed 2 distinct rashes that led to two diagnoses both associated with C4 complement deficiency.

A 72-year-old woman with endstage renal disease presented to our emergency department with an 8-day history of pain and swelling in her left arm. She recalled that she had experienced similar symptoms 4 months previously; at that time, she had been treated with angioplasty of an occluded vascular graft in the same extremity.

Her medical history was otherwise significant for a hospital admission 10 years previously for management of malignant hypertension, dyspnea, and seizures. At that time, she had marked hypertension, peripheral edema, and bilateral pleural effusions. Her serum creatinine level was 2.4 mg/dL, and she had proteinuria (4.16 g protein per 24 hours). Antinuclear antibody testing was positive, with an atypical speckled pattern. Anti-Ro and anti-La antibodies also were positive (titer not reported), but her anti-double stranded DNA antibody titer was negative. Her rheumatoid factor level was mildly elevated (17 IU/mL; normal range, 0–15 IU/mL). Monoclonal IgM kappa and polyclonal IgG cryoglobulins were present at 3% total concentration. Complement testing yielded a normal C3 level (102 mg/dL) but no detectable C4. Hepatitis B surface and core antibodies, but not surface antigen, were detected. Hepatitis C testing was negative. Histologic analysis of a kidney biopsy performed at the time was consistent with cryoglobulinemia (Figure 1).

The patient was diagnosed with essential mixed (type II) cryoglobulinemia of nonviral etiology resulting from C4 deficiency and treated with plasmaphoresis and azathioprine. By the time of discharge, her cryoglobulinemia had resolved and her serum creatinine had improved to 1.9 mg/dL. After this discharge, she continued to have refractory hypertension, and numerous agents were used to control her blood pressure, including hydralazine. Azathioprine was discontinued for unknown reasons.

Six months before the current admission, she had been admitted to an outside hospital for malignant hypertension and found to have acute renal failure. Hemodialysis was initiated through a tunneled percutaneous vascular catheter, and a left upper-extremity vascular graft was placed. Shortly thereafter, she had developed pale, pruritic, non-tender, discoid plaques on the dorsum of her right hand. Over several months, the plaques extended proximally to involve her right arm, upper chest, back, face, and ears. Trials of topical steroids, topical antibiotics, and systemic antibiotics had failed to improve or prevent spreading of the plaques. On questioning, she recalled that hydralazine had been restarted before their appearance.

Approximately 1 week before the current presentation, she had developed a new rash on her bilateral lower extremities. This rash was different from the previous rash, being composed of small violaceous papules that were pruritic and nontender. She denied recent exposure to insects or new creams, lotions, or laundry detergents.

The patient was visiting relatives in Tennessee, but lived alone in California. She denied current or former tobacco, alcohol, or illicit drug use. She was disabled, but had formerly worked in the retail industry. A niece had died from complications related to systemic lupus erythematosus. Her medications at the present admission included metoprolol, lisinopril, clonidine, aspirin, furosemide, and hydralazine.

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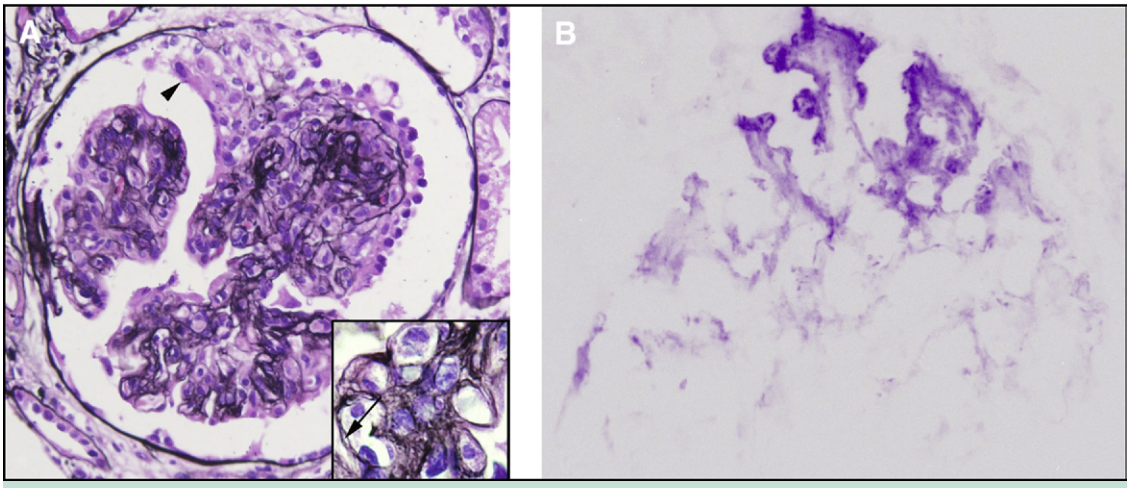

Figure 1 Histologic glomerular analysis performed 10 years prior to the current admission. **(A)** Jones silver staining showing global endocapillary proliferation and small cellular crescent (*arrowhead*) and widespread basement membrane splitting (*arrow in insert*). Original magnification: ×400 (inset, ×2000). **(B)** Immunofluorescence staining for C3 complement showing 2+ diffuse, global irregular, granular mesangial, and capillary loop staining. Original magnification: ×800.

ASSESSMENT

The patient was a pleasant, thin, age-appropriate African-American woman in no apparent distress. On admission, her vital signs were: blood pressure, 135/73 mm Hg; pulse rate, 86/minute; respiratory rate, 16/minute; temperature, 36.8°C; and oxygen saturation, 97% on room air. Skin examination revealed multiple, well-defined pink-to-violaceous plaques with peripheral scale and central atrophy involving the right arm, upper chest, and back, with atrophic, scarred plaques over the face and ears. Alopecia was seen in the areas of the discoid rash. The patient's left arm was swollen, erythematous, and warm, but free of discoid plaques. She had a palpable thrill at the site of her arteriovenous fistula. Examination of both lower extremities revealed multiple violaceous, palpable, nonblanching papules of 2 to 3-mm in diameter (Figure 2).

Laboratory evaluations were notable for elevation of blood urea nitrogen to 45 mg/dL and a white blood cell count of 1.5×10^3 cells/μL (53% neutrophils, 24% lymphocytes, 17% monocytes, and 2% basophils). Red blood cell and platelet counts were within normal limits. The antinuclear antibody titer was positive (>1:160) with a speckled pattern. Lupus anticoagulant was negative. Cryoglobulins were present at 4% total concentration.

Venous Doppler ultrasonography revealed a deep venous thrombosis within the left axillary vein without graft thrombus. Unfractionated heparin and warfarin were initiated to manage the thrombosis.

DIAGNOSIS

The clinical appearance of the patient's rash and known C4 deficiency suggested a diagnosis of lupus. To help distinguish between idiopathic and hydralazine-induced lupus, the patient was tested for antibodies against histones and double-stranded DNA, but neither was detected. Histologic analysis of a right upper-arm skin biopsy revealed acanthosis and parakeratosis with scale crust formation. Scattered dyskeratotic cells were noted, as well as focal vacuolar changes along the basal layer. The dermis exhibited a mild-to-moderate perivascular infiltrate with visible mucin deposition (Figure 3).

The lack of double-stranded DNA autoantibodies or lupus manifestations other than rash argued against idiopathic lupus, but the lack of antihistone antibodies argued against hydralazine-induced lupus. The patient's lack of systemic manifestations, together with her serologic profile and skin biopsy results, led to a diagnosis of subacute cutaneous lupus erythematosus, a condition characterized clinically by annular or papulosquamous plaques that preferentially affect the shoulders, arms, neck, and upper torso. It is important to distinguish subacute cutaneous lupus erythematosus from idiopathic lupus because the former is rarely complicated by life-threatening systemic complications and may thus be treated more conservatively. As in our patient, antinuclear and anti-Ro auto-antibodies are usually present in subacute cutaneous lupus erythematosus,[1] although it is important to note that in our patient, anti-Ro antibodies appeared 10 years before the onset of the rash, probably associated with her cryoglobulinemia.

A variety of medications, including calcium channel blockers, beta-blockers, angiotensin-converting enzyme inhibitors, and thiazide diuretics have been associated with onset of subacute cutaneous lupus erythematosus.[2,3] The time between drug initiation and onset of symptoms has been reported to range from 2 weeks to 3.2 years.[3] Although our patient's rash was temporally related to her use of hydralazine, which is a common known cause of drug-induced lupus,[4] to our knowledge, hydralazine has never been reported in association with subacute cutaneous lupus