DIAGNOSTIC DILEMMA
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It Started with a Rash

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PRESENTATION

A single 1-2 mm reddish spot on the sole of the right foot proved to be more ominous than it appeared—despite its spontaneous improvement after 1-2 days. Soon after, the patient, an 18-year-old male, developed multiple similar spots on the soles of both feet, and over a period of 4-5 days, the lesions gradually spread until his lower legs, arms, and palms also were involved. These were non-pruritic, painless, 1-5 mm petechiae that spared the trunk, head, neck, and groin.

The patient stated that he had experienced fatigue, malaise, and severe myalgias and arthralgias for 1 week. The myalgias had been especially severe in the lower extremities and were limiting his ability to walk or even get out of bed. His appetite was poor, and he was mildly light-headed. Recently, a severe sore throat resolved without antibiotics. About 2 weeks before his present illness, the patient had an insect bite on the calf. The resulting non-pruritic red rash cleared in 2 days. He denied fever, chills, nausea, vomiting, headache, photophobia, neck stiffness, or confusion.

Otherwise, the young man's medical history included no chronic health problems and no medications. He had not changed soaps or toiletries and had not traveled lately. A high school senior, he lived at home; his girlfriend lived in the local college dormitory. He said he was not sexually active and had never used tobacco, alcohol, or illegal drugs.

ASSESSMENT

The patient was alert, oriented, and afebrile with a pulse of 107 beats per minute, a respiratory rate of 26 breaths per minute, and blood pressure of 112/56 mm Hg. His lips and tongue were pale. Small petechial lesions were visible on his soft palate, and palpable purpuric lesions were evident on the dorsal, palmar, and plantar surfaces of his hands and feet (Figure 1). Movement of the neck caused some pain on the left side. A few nontender lymph nodes in the left anterior and posterior cervical areas were palpable. Reproducible tenderness was noted in the thigh muscles. The patient had no neck stiffness, photophobia or organomegaly. Range of motion was not limited in any joints.

Hematologic studies showed a white blood cell count of 8.84×10^3 cells/mm^3 with 78% neutrophils, normocytic anemia with hemoglobin of 6.7 g/dL, and a normal platelet count. The corrected reticulocyte count was inappropriately low (1.94%), with a reticulocyte production index of 0.97%. Serum chemistries and a liver panel were unremarkable except for an albumin of 2.8 g/dL and total bilirubin of 2.3 mg/dL. The international normalized ratio was mildly elevated (1.2), as was the fibrinogen level (570 mg/dL), but the partial thromboplastin time was normal (34.1 seconds). D-dimer was significantly elevated (> 10,000 ng/mL). Urine was cloudy and dipstick-positive for protein and blood, and urine microscopy was notable for both red and white blood cells (571 and 42 per high power field, respectively).

The patient was admitted to the intensive care unit due to concerns that he might have Rocky Mountain spotted fever or less likely, meningococcemia. After obtaining blood and cerebrospinal fluid for diagnostic testing, the patient was started on intravenous ceftriaxone and doxycycline. Examination of the cerebrospinal fluid revealed no white blood cells, normal glucose and protein levels, and an unremarkable Gram stain. In addition, studies for direct bacterial antigens, including group B *Streptococcus*, *Neisseria meningitidis* serogroups A, B, C, Y, and W-135, *Escherichia coli* K1, *Streptococcus pneumonia,* and *Haemophilus influenza*e serotype B were negative. Blood cultures, serum *Rickettsia rickettsii* DNA-polymerase chain reaction (PCR), and indirect immunofluorescence for rickettsial antibody were performed, but results were not immediately available. Results from a chest x-ray and computed tomography of the head were unremarkable. A biopsy sample of the rash was

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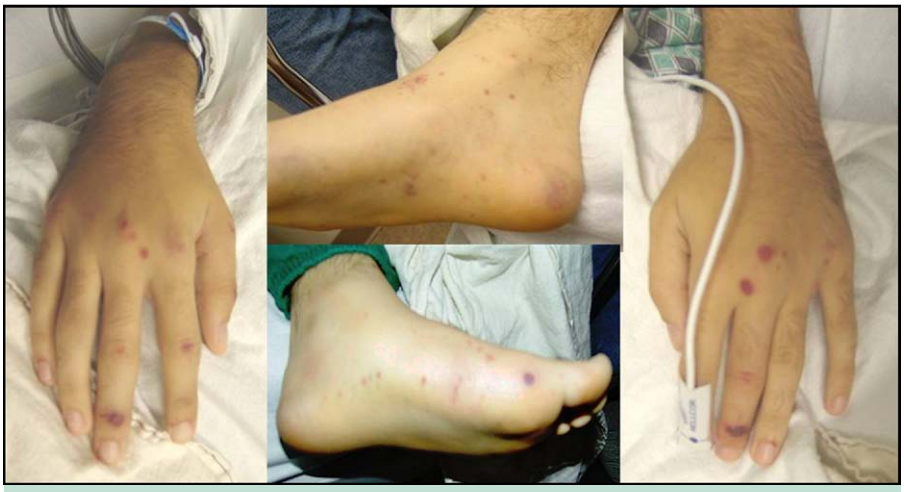

Figure 1 Palpable purpuric lesions were seen on the patient's hands and feet.

tested for *Rickettsia* species. Two units of packed red blood cells were administered.

DIAGNOSIS

Even with antimicrobial therapy, only minimal improvement of the patient's rash was noted. Cultures of blood, urine, and cerebrospinal fluid remained negative after 2 days. The serum rickettsial antibody panel and serum DNA-PCR also were negative. On day 3, the patient became hypoxemic and required supplemental oxygen, 3-4 L/min. The next day, he developed a cough with rusty sputum and occasional hemoptysis. Chest films now showed bilateral diffuse alveolar infiltrates (Figure 2).

Despite administration of 6 units of peripheral red blood cells, the patient remained anemic. He never developed fever or leukocytosis. The skin biopsy, negative for rickettsial organisms, revealed leukocytoclastic vasculitis. A repeat urinalysis confirmed persistent hematuria and proteinuria. Antibiotics were discontinued after 1 week of therapy because all evaluations for potential infectious etiologies were negative.

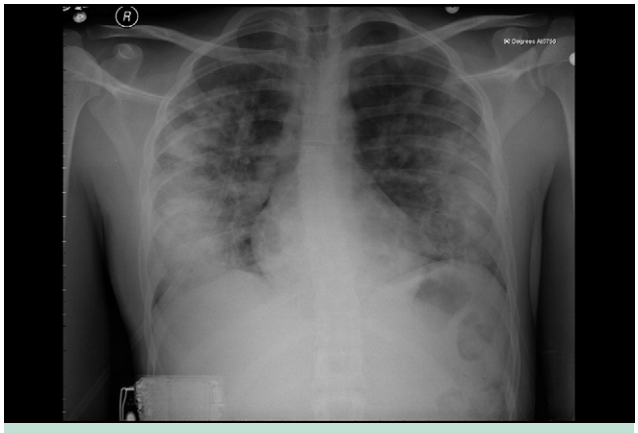

Figure 2 Chest films showed bilateral diffuse alveolar infiltrates.

Persisting rash and involvement of multiple systems—pulmonary (hemoptysis with respiratory distress), renal (hematuria, proteinuria), and hematologic (persistent anemia, elevated d-dimer)—suggested an ongoing autoimmune vasculitic syndrome. The following studies were ordered: erythrocyte sedimentation rate, C-reactive protein level, antinuclear antibody test, lupus panel, antineutrophil cytoplasmic antibody (c-ANCA) test, complement levels (C3, C4, and CH50), serum rapid plasma reagin test, fluorescent treponemal antibody (FTA-ABS) test, and hepatitis B and C serologies. A strongly positive titer of c-ANCA/ anti-proteinase 3-antibody suggested Wegener's granulomatosis. Renal biopsy revealed segmental necrotizing glomerulonephritis consistent with Wegener's granulomatosis.

Typically, Wegener's granulomatosis initially involves the ear, nose, sinuses, or throat, and the symptoms become progressively worse (Table). It is difficult to establish whether the sore throat experienced by our patient was the initial symptom of Wegener's granulomatosis. However, in about 10% of patients, disease first manifests with cutaneous involvement, and up to 45% of patients develop skin

Table American College of Rheumatology Criteria for Diagnosis of Wegener's Granulomatosis*

Oral or nasal inflammation (painful or painless oral ulcers or purulent or bloody nasal discharge)
Abnormal chest radiograph showing nodules, fixed infiltrates, or cavities
Abnormal urinary sediment (red blood cell casts or more than 5 red blood cells per high power field)
Granulomatous inflammation on biopsy of an artery or perivascular area

Fulfillment of 2 out of 4 criteria has a sensitivity of 88% and specificity of 92%.

*Table was adapted from Leavitt et al.[3]

lesions during the disease course.[1,2] Mucocutaneous involvement is relatively more frequent in Wegener's granulomatosis when compared to Churg Strauss syndrome or microscopic polyangiitis.[2] The presence of antineutrophil cytoplasmic antibodies combined with the clinical criteria help make the diagnosis.

MANAGEMENT

Treatment depends on the severity of Wegener's granulomatosis as defined by the European League Against Rheumatism classification scheme.[4] Localized disease is confined to the upper and/or lower respiratory tree; early systemic disease is identified by any systemic involvement that is not life- or organ-threatening; generalized disease threatens the function of the kidneys (serum creatinine < 5.6 mg/dL) or other vital organs; severe disease is marked by failure of the kidneys (serum creatinine > 5.6 mg/dL) or other vital organs; and refractory disease progresses despite immunosuppressive therapy.

Our patient had severe disease and was started on methylprednisolone, 10 mg/kg, and intravenous cyclophosphamide, 2 mg/kg daily. Three days later, methylprednisolone was changed to oral prednisone, 60 mg daily for 4 weeks. The dosage was gradually tapered to a low dose of 10 mg daily, which was maintained for 6 months to obtain complete remission. At the same time, oral cyclophosphamide, 2 mg/kg daily, was started and was continued until stable remission was obtained.

In addition, trimethoprim-sulfamethoxazole was given for *Pneumocystis carinii* pneumonia prophylaxis during this period.[5,6] Glucocorticoid-cyclophosphamide therapy induces remission in about 90% patients, of which 75% show no recurrence. Methotrexate may be preferred over cyclophosphamide in patients with mild disease and good renal function. Plasmapheresis might be beneficial for patients with severe disease, pulmonary hemorrhage, or disease that fails to respond to immunosuppressive therapy.[7]

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