

clinicopathological conference

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An 18-Year-Old Male Presenting with Rash

Introduction

We discuss a presentation of rash in a young male as the third published case in the monthly Clinicopathological Conference conducted by the University of Illinois at Urbana-Champaign. A clinical faculty member is presented with a case of which he/she has no prior knowledge and then proceeds to describe the clinical reasoning involved in reaching a final diagnosis. This case was discussed in November 2008.

Discussants

Chief Discussant: Karen White, MD

Infectious Disease: Niveditha Reddy, MD

Pathology: Ike Uzoaru, MD

Initial Case Presentation

An 18-year-old Caucasian male presented with a nonpruritic rash on his arms and legs of one week's duration. It initially started with a single 1–2 mm reddish spot on the sole of the right foot that healed spontaneously in one to two days. It was soon followed by the appearance of multiple similar spots bilaterally on the soles of both feet that gradually spread to involve the lower legs, arms and palms over the next four to five days. The rash was painless, with lesions from 1–5 mm in size that seemingly spared the trunk, head, neck and groin. In the week prior to presentation, the patient felt fatigued and developed severe generalized myalgias and arthralgias of multiple joints. Myalgias had been especially severe in the lower extremities and limited the patient's ability to walk or even get out of bed in the days immediately prior to admission. He had a poor appetite and mild light-headedness. Other pertinent history included a recent severe sore throat,

which resolved without antibiotics, and an insect bite on the calf while playing soccer about two weeks prior to admission. A nonpruritic red rash followed the insect bite but resolved in about two days. The patient denied experiencing fever, chills, nausea, vomiting, headache, photophobia, neck stiffness or confusion.

The patient had been treated with antibiotic eye drops for conjunctivitis about 10 days prior to admission but denied a history of chronic health problems. He was not on any medications. There had been no change in soaps or cosmetics and no recent travel. The patient's sister had an apparent viral illness 10 days before admission. Otherwise family history was not contributory. The patient lived at home, but his girlfriend lived in the local college dormitory. He denied being sexually active and stated he had never used tobacco, alcohol or illegal drugs.

Discussion

The key feature in this patient is the petechial-purpuric rash affecting the extremities bilaterally. Petechiae and purpura are nonblanching reddish spots in the dermis of the skin caused by the leakage of small amounts of blood from the capillaries and differ mainly in size, with purpura being ≥ 3 mm and petechiae being ≤ 2 mm. In general, the significance of purpura depends highly on the overall clinical picture and ranges from serious illness like meningococcemia, thrombocytopenia, or endocarditis to an entirely benign etiology such as petechiae appearing after a hard bout of cough. Although the clinical presentation is not classical for meningococcemia, the patient is a young adult with higher than average risk due to contact with his girlfriend who lives in a dormitory. The fact that the disease is transmitted by respiratory droplet infection and is fatal if not treated early makes it important to consider this diagnosis

first. Another fatal condition associated with a similar distribution of rash and tick bite is Rocky Mountain spotted fever, although, in a classic case, the rash starts at the wrist and ankles and progresses both centrally and to palms and soles.

Other important infectious etiologies include viral syndromes secondary to coxsackievirus A9, echovirus 9, Epstein-Barr virus and cytomegalovirus infections. Additional potential diagnoses include gonococcemia, disseminated intravascular coagulation (DIC), and autoimmune conditions like systemic lupus erythematosus (SLE). Cutaneous small vessel vasculitis or leukocytoclastic vasculitis can be secondary to drugs or environmental exposures, infections like hepatitis C and autoimmune connective tissue disease. Another vasculitis that often follows upper respiratory infections is Henoch Schonlein purpura.

Case Presentation Continued

The patient's vitals revealed mild tachycardia (heart rate of 107), tachypnea (respiratory rate 26), normal temperature (98.8 F) and normal blood pressure (113/57). On examination, the patient was alert and oriented, did not have a toxic appearance and was lying comfortably in his bed. His lips and tongue appeared pale. He had small petechial lesions on the soft palate and palpable purpuric lesions on the distal extremities. The rash included dorsal, palmar and plantar surfaces of the hands and feet. (Figure 1) There was some pain on the left side of the neck with movement that seemed muscular in nature. There were a few palpable nontender lymph nodes in the left anterior and posterior cervical areas. There was reproducible tenderness in the thigh muscles. The remainder of examination was unremarkable including no neck stiffness, photophobia or organomegaly. Range of motion was not limited in any joints.

Discussion

The fact that his vitals are stable and the patient does not look very sick lowers the suspicion for bacterial infections associated with rashes such as staphylococcus and streptococcus. The examination reveals a palpable rash that also helps to narrow the differential.

The presence of arthralgias, myalgias, fatigue and distribution of the rash suggests a systemic inflammatory process. The subacute onset of arthralgia and association with rash helps limit the differential for inflammatory arthritis. Systemic lupus erythematosus frequently causes arthritis and

Figure 1. Petechial and purpuric lesions observed on left hand and right foot.



a wide variety of other clinical features including rash. The rash for lupus is usually malar or discoid and typically photosensitive but still an important part of the differential, especially if laboratory investigations corroborate the diagnosis. Sarcoidosis can cause both acute and chronic arthritis. Juvenile rheumatoid arthritis (JRA) is common among this age group and can be associated with a rash; the number of joints involved varies based on whether it is oligoarticular, polyarticular or systemic JRA. Systemic JRA is usually accompanied with high fevers, and fever is not present in this patient. Many times, these patients will have an associated iritis or iridocyclitis and involved joints are usually

tender, stiff and swollen. Several types of vasculitis are associated with arthralgias, rash and multisystem involvement. Solid organ cancers, leukemia, and lymphoma may be associated with paraneoplastic syndromes that can present with fatigue, rash, arthralgia, weight loss and lymphadenopathy, though it is unlikely in this case.

The isolated left anterior cervical lymphadenopathy is most likely benign. It could be a remnant from the recent pharyngitis or a subclinical viral infection from the patient's sister, with other possibilities lower in the differential including other viral infections (adeno virus, herpes virus, coxsackie virus, and CMV), cat scratch disease, atypical mycobacteria or mycobacterium tuberculosis. If lymphadenopathy were generalized, there would be concern for infectious mononucleosis or myeloproliferative diseases.

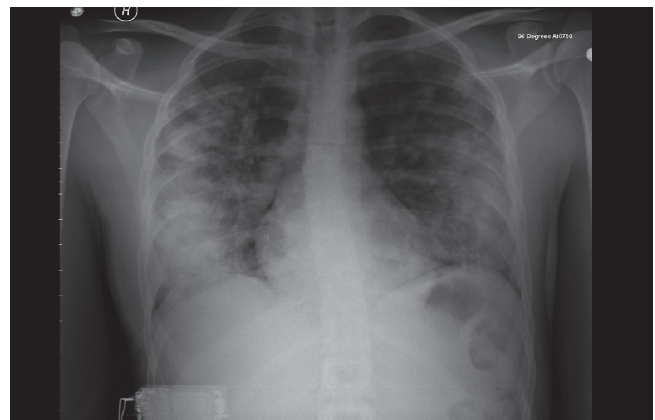
Clinical Investigations and Hospital Course

The patient was admitted to the Intensive Care Unit (ICU) due to concerns about meningococemia and Rocky Mountain spotted fever, although the suspicion was not very strong. After obtaining blood and cerebrospinal fluid (CSF) for diagnostic testing, the patient was started on intravenous ceftriaxone and doxycycline. Hematological studies revealed WBC count of $8.84 \times 10^3/\mu\text{L}$ with 78% neutrophils, no bands, severe normocytic anemia with hemoglobin of 6.7 g/dL, and a normal platelet count. Corrected reticulocyte count was inappropriately low (1.94%), with a reticulocyte production index of 0.97%. Serum chemistries and liver panel were unremarkable except for albumin of 2.8 g/dL and total bilirubin of 2.3 mg/dL. There was mild elevation of INR (1.2) and fibrinogen (570 mg/dL) but normal PTT (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/hpf and 42/hfp, respectively). Lumbar puncture revealed no white blood cells, normal glucose (66 mg/dL), normal protein (14 mg/dL) and an unremarkable Gram's stain. Cerebrospinal fluid studies for direct bacterial antigens including group B streptococci, *Neisseria* A, B, C, Y, W-135, *E. coli* K1, *Streptococcus pneumoniae* and *H. influenzae* type B were negative. Blood cultures, serum *Rickettsia rickettsii* DNA-PCR and rickettsial antibody were obtained, but results were not immediately available. No significant findings were observed on the patient's chest films. Computed tomography (CT) of the head

was unremarkable. The rash was biopsied and sent for general pathology and testing for rickettsia.

Packed red blood cells (PRBC, 2 units) were administered shortly after admission. The patient's rash was felt to improve after initiation of antimicrobial therapy. Blood, urine and CSF cultures were negative after two days. Serum rickettsial antibody panel and serum DNA-PCR were also negative. On day three, the patient became hypoxic and required 3–4 L/min supplemental oxygen to keep oxygen saturation above 90%. By hospital day five, he had developed cough with rust colored sputum and occasional hemoptysis. Repeat chest films showed diffuse alveolar infiltrates involving all lobes of both lungs. (Figure 2)

Figure 2. Chest radiograph on hospital day five showing diffuse, bilateral alveolar infiltrates.



The patient continued to be anemic despite receiving six units of PRBC. He never developed fever or leukocytosis, but his INR and D-dimer remained elevated (1.2 and $>10,000$ ng/mL respectively). Skin biopsy revealed leukocytoclastic vasculitis and was negative for rickettsial organisms. Repeat urinalysis confirmed persistent hematuria and proteinuria. Antibiotics were discontinued after a week of therapy in view of negative evaluation for potential infectious etiologies. The persistence of rash and the involvement of multiple systems including pulmonary (hemoptysis with respiratory distress), renal (hematuria, proteinuria) and hematological (persistent anemia, elevated D-dimer) suggested an ongoing autoimmune, vasculitic syndrome. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibodies (ANA), lupus panel, antineutrophil cytoplasmic antibodies

(ANCA), complement levels (C3, C4 and CH50), serum rapid plasma reagin (RPR) test, fluorescent treponemal antibodies (FTA-ABS), and hepatitis B and C serologies were done for further evaluation. A strongly positive c-ANCA/antiproteinase 3-antibody titer was measured suggesting Wegener's granulomatosis. Renal biopsy revealed segmental necrotizing glomerulonephritis consistent with Wegener's granulomatosis.

The patient was initiated on high-dose corticosteroids and then transferred to a more specialized regional referral center for concomitant cyclophosphamide therapy.

Final diagnosis:

Generalized Wegener's granulomatosis.

Discussion

Wegener's granulomatosis (WG) is a rare systemic vasculitis first described in 1936 by Friedrich Wegener. It is characterized by necrotizing granulomatous inflammation of the upper and lower respiratory tracts, focal glomerulonephritis, systemic vasculitis of small arteries and veins, and the presence of antineutrophil cytoplasmic antibodies.^{1,2} Wegener's granulomatosis may involve any organ system including mouth, eyes, ears, nose, throat, lungs, skin, central or peripheral nervous systems, and kidneys.³ A recent review article reports prevalence ranging from 24–157 per million, annual incidence rates from 3–14 per million, and a declining disease risk from north to south in the Northern Hemisphere.⁴ Multiple genetic and environmental factors that have not been fully identified appear to be involved in the development of WG.⁴ The course of the disease varies from indolent to a rapidly progressive form associated with high morbidity and mortality.

Although, WG can affect any age group, the vast majority of patients are in their fourth or fifth decade with a median age of 41 years at the time of diagnosis. Less than 15% of cases occur in children.

American College of Rheumatology (ACR) criteria are helpful in identifying patients with WG. Meeting two of the following four criteria classifies a patient with the diagnosis of WG:

1. Oral or nasal inflammation (painful or painless oral ulcers or purulent or bloody nasal discharge)
2. Abnormal chest radiograph showing nodules, fixed infiltrates, or cavities

3. Abnormal urinary sediment (red blood cell casts or more than five red blood cells per high power field)
4. Granulomatous inflammation on biopsy of an artery or perivascular area⁵

In validation studies, ACR criteria have 88% sensitivity and 92% specificity for diagnosing WG. The ACR criteria do not include the results of c-ANCA. While pulmonary and renal involvement is common in WG, they may not be present on initial presentation. The first symptoms of WG (index symptoms) are typically those of ear, nose, or throat involvement as documented by Lane (37% of patients) and Hoffman (73% of patients). Common presenting symptoms include bloody or purulent nasal discharge, rhinorrhea, ulcers of the oral and/or nasal cavities, polyarthralgias, and myalgias. Only about 10% of WG cases present with mucocutaneous or only cutaneous involvement as initial manifestations.^{6,7} Skin findings often are attributed to allergies, contact dermatitis, etc. resulting in delayed diagnosis. Cutaneous manifestations are important in WG as these are noted in approximately 45% of patients at some point in the course of illness and can be an important clue to the diagnosis. The cutaneous involvement may occur as palpable purpura, ulcers, vesicles, papules or subcutaneous nodules.⁷ Mucocutaneous involvement is more frequent in WG compared to Churg Strauss Syndrome (CSS) or Microscopic Polyangiitis (MPA).⁷ In this case, rash preceded the onset of upper and lower respiratory tract and renal involvement by one to two weeks. Skin biopsy findings in conjunction with the clinical course, c-ANCA serology and chest radiographs helped to confirm the diagnosis of WG.

The management of WG requires potent immunosuppressive therapy, making it essential that the diagnosis be firmly established prior to treatment. The diagnosis of WG should be confirmed by tissue biopsy at a site of active disease. When possible, nasopharyngeal (NP) biopsies are preferred, though NP biopsies have all the features to confirm the diagnosis of WG in only about one-third of specimens.⁸ Skin biopsies demonstrate leukocytoclastic vasculitis with little or no complement or immunoglobulin, and renal biopsies show focal and pauci-immune glomerulonephritis. These findings are consistent with but not confirmatory of WG. Open or thoracoscopic biopsies of pulmonary parenchymal lesions demonstrating granulomatous vasculitis and palisading granulomatous inflammation of lung

parenchyma have a diagnostic yield of over 90% but are much more invasive than other biopsy procedures.⁸ Unfortunately, transbronchial biopsies are diagnostic in fewer than 10% of cases.⁸

If not treated, WG has a one-year mortality of approximately 80%.⁹ The choice of treatment protocol depends on disease severity. The European League Against Rheumatism (EULAR) recommends the following classification scheme:¹⁰

1. Localized – confined to the upper and/or lower respiratory tree
2. Early systemic – any systemic involvement that is not life or organ threatening
3. Generalized – threatens renal or other organ function, Cr < 5.6 mg/dL
4. Severe – failure of kidneys or other vital organs, Cr > 5.6 mg/dL
5. Refractory – progressive despite immunosuppressive therapy

Severe disease is treated initially with oral prednisone 1 mg/kg daily (with or without methylprednisone 7 to 15 mg/kg for three days) along with oral cyclophosphamide 2 mg/kg daily or intravenous cyclophosphamide. Glucocorticoid-cyclophosphamide combinations are able to induce remission in about 90% patients of which 75% obtain complete remission.^{7,11-14} Steroids are usually continued at 60–80 mg for about two to four weeks, tapered slowly to about 20 mg by the end of two months and then continued at low dose for six to nine months until complete remission is obtained. Cyclophosphamide is also continued until stable remission is obtained. Patients receiving cyclophosphamide need prophylaxis with trimethoprim-sulfamethoxazole to prevent *Pneumocystis carinii* infection.^{15,16} Methotrexate may be preferred over cyclophosphamide in patients with mild disease and good renal function. Methotrexate is especially useful if patients have poor bone marrow reserve. Patients treated with methotrexate and glucocorticoids need close follow up due to a higher relapse rate than glucocorticoid-cyclophosphamide regimens.¹⁷ Plasmapheresis may be beneficial for patients with severe disease, pulmonary hemorrhage, or disease that fails to respond to immunosuppressive therapy.^{18, 19}

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