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Wegener's granulomatosis with cardiac involvement masquerading as Lyme disease

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ABSTRACT

Cardiac conduction disease is an infrequent complication of Wegener's granulomatosis (WG). We describe a case demonstrating an association between WG and complete atrioventricular dissociation. This manifestation was initially interpreted as Lyme disease based on these cardiac findings, arthritis, myalgias and positive Lyme serology. The clinical overlap between these disorders and the appropriate use of respective serologies is discussed.

Case report

A 23-year-old woman initially presented with erythematous skin lesions on extensor surfaces, night sweats, worsening of longstanding, generalized myalgias and arthralgias. One week prior, she was placed on doxycycline based on a positive IgM and IgG ELISA for Lyme disease. Although she was a Maryland resident from a wooded area, she denied a history of rash or tick bites. She had complained for six months of progressive myalgias with synovitis of large joints and an unexplained 5 kg weight loss. Her medical history was significant for chronic relapsing otitis media. She was not taking medications and denied overseas travel.

Physical examination revealed erythematous macules with a dusky center on the elbows. Her heart rate was 50 beats/min. The remaining cardiovascular, pulmonary and abdominal exams were normal. Slight thickening and hydrarthrosis of the knees and ankles were observed. No mucosal lesions, periungual telangiectasias, or lymphadenopathy were observed.

Laboratory studies in the emergency room revealed a hematocrit of 31%, and white cell count of 9,900 cells/microliter with a normal differential. Complement levels were normal and creatinine was 1.0 mg/dl. Chest radiograph was unremarkable. Westergren sedimentation rate was 80 mm/hr, urinalysis was positive for 1-5 red blood cells without casts. An electrocardiogram was obtained revealing complete heart block. A transthoracic echocardiogram showed an ejection fraction of 75% without valvular vegetations. She was admitted and empirically started on intravenous doxycycline and azithromycin. After admission, further serologies showed rheumatoid factor (RF) positive at a dilution of 1:160. Antinuclear antibodies (ANA) and human immunodeficiency virus (HIV) serologies were negative.

By day three, her rash had evolved to papulonecrotic lesions on both elbows (Fig. 1) as well as on the right first distal interphalangeal joint. Purpuric macules and papules were present on both lower extremities, most pronounced distally and extending to the buttocks. Repeated blood cultures were consistently negative. There was no clinical improvement. On day 4, serum creatinine rose to 2.8 mg/dl, hematocrit fell to 19.3% and she developed dyspnea with hemoptysis, requiring increasing oxygen. Repeated chest radiography demonstrated new bilateral alveolar infiltrates.

Histopathologic examination of the right thumb lesion showed polymorphonuclear-predominant vasculitis in the superficial and deep dermal vessels with associated palisading granulomas, giant cells and degenerated collagen (Fig. 2). Direct immunofluorescence evaluation of the specimen demonstrated dense IgG deposition in the same vessels. Renal biopsy showed segmental fibrinoid necrosis with crescentic changes (Fig. 3). C-ANCA was positive at 1:512 with anti-proteinase 3 antibodies greater than 100 (normal less than 3.5). Repeat Lyme ELISA was negative.

Based on the clinical and immunopathologic findings, the diagnosis of Wegener's granulomatosis was established and intravenous methylprednisolone at 1 gm/square meter and oral cyclophosphamide at 2.5 mg/kg/day was initiated. Her clinical course rapidly deteriorated, progressing to hypoxic respiratory failure, requiring mechanical ventilation. Intravenous cyclophosphamide was administered at 750 mg/square meter supplemented with daily plasmapheresis, with a total of 8 sessions at 2-3 liters each. Her renal and pulmonary functions rapidly deteriorated requiring hemodialysis and she eventually succumbed to hypoxic res-

piratory failure. Autopsy was unavailable.

Discussion

Wegener's granulomatosis (WG) is a systemic vasculitis affecting small and medium vessels, and one of the most common pulmonary-renal-cutaneous syndromes in rheumatology (1). This patient had two types of skin lesions: 1) purpuric macules and papules on the lower extremities; 2) papulonecrotic lesions on the elbows and dorsum of the hands. The former, being more common and sensitive, represents small vessel vasculitis (SVV) and the latter, being less common and more specific, represents palisading neutrophilic and granulomatous dermatitis, or cutaneous extravascular necrotizing granulomas. These lesions are not pathognomonic, but highly suggestive of the ANCA-mediated cutaneous vasculitides, namely Churg-Strauss syndrome (CSS) and WG.

This patient's constitutional symptoms, synovitis, and chronic otitis media prior to admission likely represented smoldering WG. Later, the discovery of positive RF at 1: 160 without clinical evidence of rheumatoid arthritis (RA) may have prompted investigation for vasculitides that commonly demonstrate positive RF, including WG, CSS, and type II cryoglobulinemia. The lack of peripheral eosinophilia, normal C4, and negative HIV and viral hepatitis serologies, are not exclusionary, but make the diagnosis of cryoglobulinemia or CSS unlikely.

Any organ can be affected by WG. Cardiac involvement, encompassing valvular abnormalities (2), myocarditis, pericarditis, coronary arteritis, and conduction defects has an incidence between 8% to 40% (3). Both early and limited disease show less cardiac involvement and complete heart block is an extremely rare complication, with only six previously reported cases in the literature (3-8). Because of this patient's ventricular rate, she most likely had involvement of or near the atrioventricular node, accounting for an escape rhythm of 50 bpm.

The use of ANCA serologies in the evaluation of pulmonary-renal vasculitic syndromes has been recognized by the Chapel Hill Consensus Conference as an important diagnosic tool (9). The sensitivity of C-ANCA for active Wegener's is 91% and the specificity is 99% (10). If the pretest probability is less than 5%, a positive C-ANCA likely represents a false-positive (10) as in some cases of endocarditis (11). It is unclear if this patient's initial presentation of recurrent otitis media, arthralgias, myalgias and hematuria would have met this 5% threshold. Once the disease progressed to pulmonary and renal insufficiency, with characteristic cutaneous findings, the increased pretest probability obviated the diagnostic utility of C-ANCA. A negative

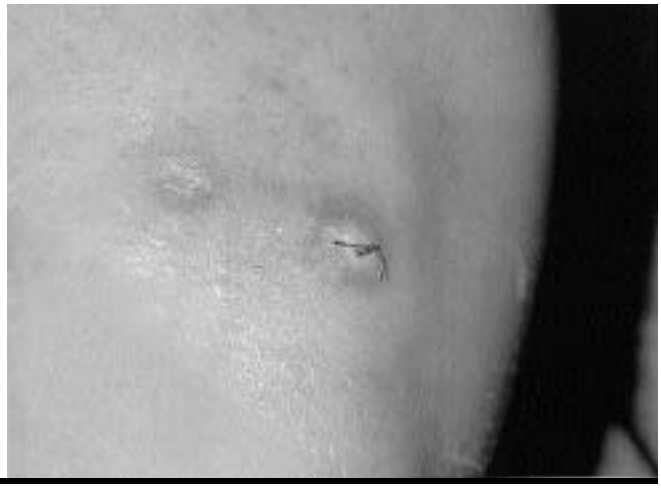

Fig. 1. Necrotic ulcer with halo of erythema on the patient's elbow.

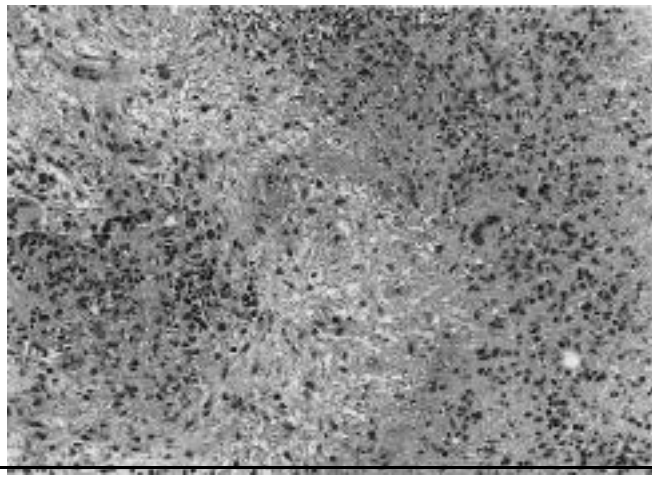

Fig. 2. Hematoxylin and eosin staining of skin biopsy demonstrating characteristic cutaneous extravascular necrotizing granulomas.

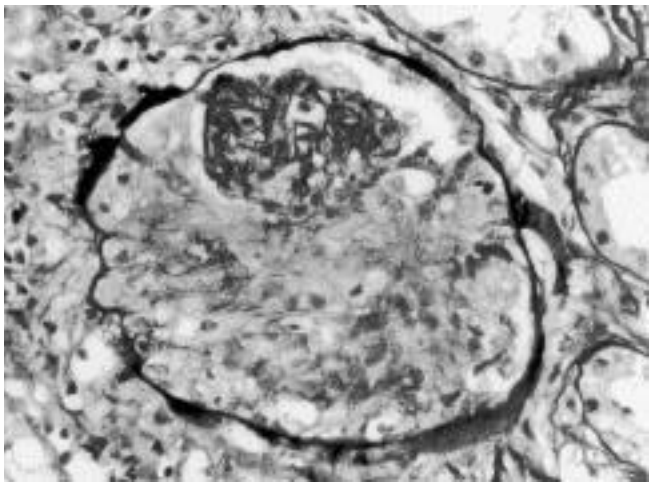

Fig. 3. Hematoxylin and eosin staining of renal biopsy specimen demonstrating crescentic glomerulonephritis.

result would not have excluded WG, as C-ANCA-negative cases are well documented (12).

There is no standard, specific test for the diagnosis of Lyme disease; however Lyme testing is recommended when the pretest probability falls between 20-80% (13). The presence of erythema migrans in a patient from an endemic area yields a pretest probability greater than 80%, necessitating treatment without prior testing (14). When non-specific symptoms dominate, the pretest probability is less than 20% and positive serology will more likely represent a false-positive result (13). Positive ELISAs should be interpreted cautiously as there is little inter- or even intra-laboratory reliability, and false-positive results can occur in other systemic diseases (14). Therefore, a positive ELISA requires a supportive Western blot. However, a positive Western blot does not necessarily diagnose Lyme disease and may only reflect prior *Borrelia* exposure (14). Disseminated Lyme follows days to weeks after infection affecting cardiovascular, central nervous (15) or musculoskeletal systems. Joint involvement occurs intermittently with swelling and pain in primarily large joints, which may become persistent after several attacks. Cardiac disease occurs in approximately 5% of untreated cases with atrioventricular block of varying degrees (14).

This case emphasizes several key points: 1) the importance of ANCA serologies and cutaneous findings in aiding the diagnosis of WG as well as the necessity of prompt immunohistopathologic evaluation in WG; 2) WG may mimic Lyme, both in its preponderance of non-specific constitutional symptoms, as well as in cases when either disease presents with cardiac conduction defects; 3) the pitfalls of over diagnosis of Lyme disease based on non-specific constitutional symptoms and highly unreliable serologic markers.

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