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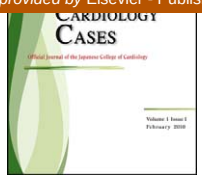

Case Report

Cardiac manifestations of Wegener's granulomatosis: Case report and review of the literature

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Summary Wegener's granulomatosis, first characterized as a clinical syndrome in 1936, is a rare form of vasculitis of the small- and medium-sized blood vessels affecting mainly the upper and lower respiratory tracts as well as the kidneys. This review article describes the case of a 45-year-old man who developed aortic regurgitation and third degree heart block secondary to Wegener's granulomatosis. He subsequently presented to our institution 3 years later with pulmonary hemorrhage. The ensuing literature review reveals that historically clinical cardiac involvement in Wegener's has been rare, particularly with valvular lesions. However, recent literature has shown an increase in reported cases of cardiac valvular lesions in Wegener's. The presented case report along with recently reported case reports highlight the morbidity and mortality associated with such cardiac lesions. We believe routine cardiovascular supervision including echocardiography and electrocardiograms are important for the screening and monitoring of patients with Wegener's granulomatosis.

Background

Wegener's granulomatosis (WG), first characterized as a clinical syndrome in 1936, is a rare form of vasculitis of the small- and medium-sized blood vessels affecting mainly the upper and lower respiratory tracts as well as the kidneys [1]. The clinical signs and symptoms can be of various forms including upper airway, eye, and ear disease such as epistaxis, chronic sinusitis, sensory hearing loss, scleritis, episcleritis, and uveitis. In the lower respiratory tract, nodules, infiltrates, cavitary lesions, and pulmonary hemorrhage presenting as hemoptysis are the hallmark signs of this vasculitis. Wegener's can also involve the renal microvasculature in up to 75% of cases in the form of rapidly progressive glomerulonephritis and renal failure. However, cardiac involvement has traditionally been a rare manifestation of WG, approximately 6–12% [2,3].

Case presentation

We present a case of a 45-year-old man who was found to have severe cardiac manifestations of WG. He initially presented to our institution with the chief complaint of

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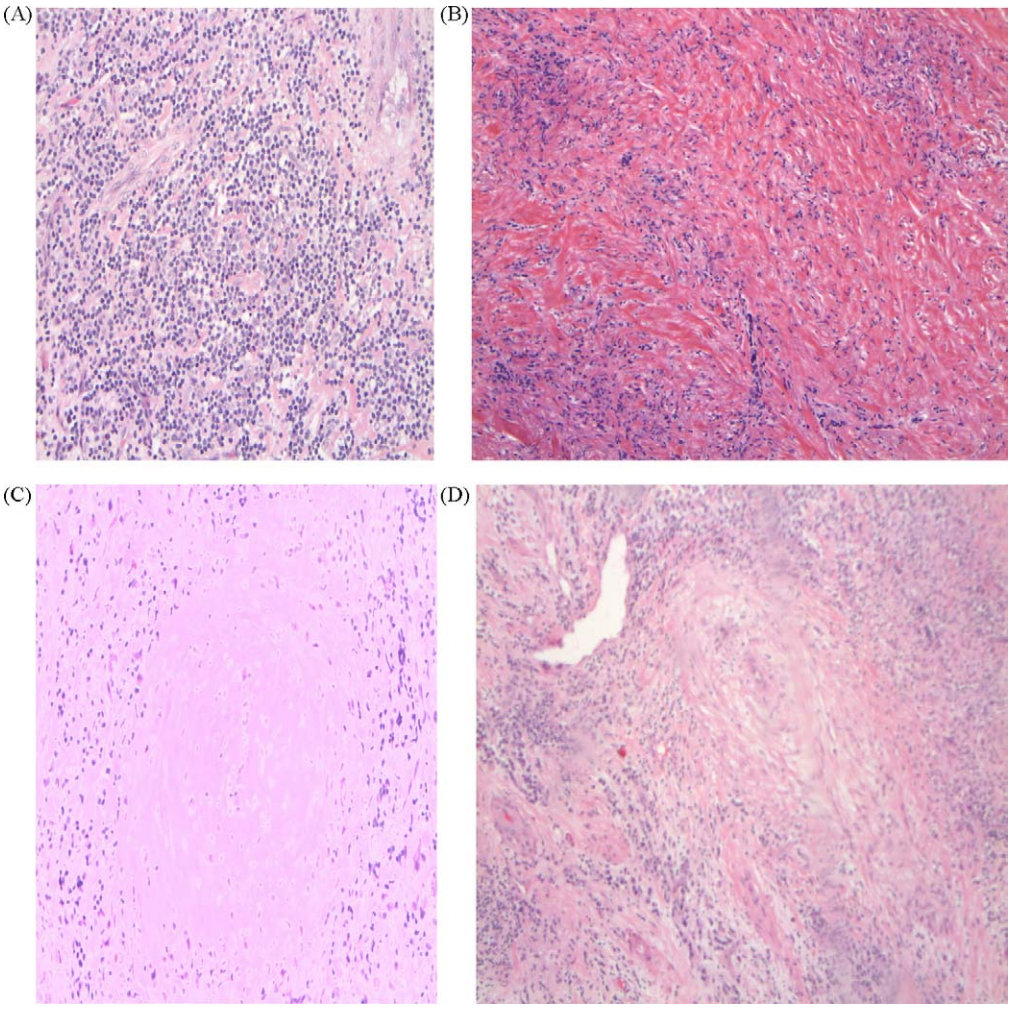

Figure 1 (A) Aortic leaflet frozen section demonstrating mixed inflammatory infiltrate with two small granulomas. (B) Aortic wall frozen section demonstrating aortitis and collagen necrosis with poorly formed granulomas. (C) Left coronary leaflet demonstrating large granuloma at center of picture. (D) Left coronary leaflet demonstrating mixed vasculitis, poorly formed granulomas.

left-sided chest pain and shortness of breath. On physical examination he was in respiratory distress using accessory muscles and was noted to have 3/6 diastolic murmur over the 2nd intercostal space along the right parasternal border. The initial diagnostic workup involved a complete blood count and metabolic panel, electrocardiogram (ECG), serial cardiac enzymes, and continuous telemetry monitoring. The ECG was significant for bradycardia secondary to 3rd degree atrioventricular block. While in the emergency room, the patient developed a 5-s pause on telemetry with subsequent transient loss of consciousness. The patient was immediately transferred to the coronary care unit for placement of a temporary transvenous pacing wire. A transthoracic echocardiogram performed the following day revealed a dilated left ventricle with preserved ejection fraction in the setting of severe aortic regurgitation with associated mild aortic stenosis. The following week, the patient underwent a porcine aortic valve replacement and permanent pacemaker implantation. The aortic wall, aortic valve leaflet, and left coronary leaflet of the aortic valve were biopsied and sent for frozen section analysis. The histopathology revealed aortitis and valvulitis with a mixed inflammatory infiltrate with granulomatous inflammation, surrounding microabscesses, and collagen necrosis consistent with WG (Fig. 1). Poorly formed granulomas were noted along with scattered giant cells and vasculitis. Although the septal myocardium was not biopsied, it was presumed the disease process had infiltrated into the conduction system of the heart leading to complete heart block. Additionally, a biopsy of the right ventricular epicardium revealed dense collagenous fibrosis. Immunohistochemical staining analysis was not performed, and specific stains for bacteria, acid fast bacilli, fungi, and spirochetes were negative. Post-operative transthoracic echocardiogram showed normal ventricular size and function with trace aortic regurgitation and dilated aortic root. The patient was discharged on low-dose steroids with a rheumatology follow-up appointment. Prior to this admission, the patient had been diagnosed 5 years prior with WG and was following up with his own private rheumatologist infrequently as an outpatient. He was noted to have been diagnosed with the disease with a positive c-ANCA titer (antineutrophil cytoplasmic antibodies) as well as relatively high antinuclear antibodies titer in the setting of associated symptoms. He initially presented to his primary care

doctor with complaints of chronic epistaxis and ocular pain later diagnosed as scleritis on ophthalmological examination. During this time he was treated intermittently with oral steroids, and underwent a brief course of treatment with cyclophosphamide, curtailed by noncompliance. During this 5-year interval he suffered minor bouts of epistaxis and scleritis sporadically. He was seeing an ophthalmologist who was prescribing him ocular steroid drops during his flares, described as a ''raging scleritis''. He also noted during this time episodes of dyspnea that were progressively getting worse, culminating in his admission to our institution. There were no episodes of hemoptysis reported.

Three years after these cardiac findings and surgical intervention, this patient returned to the emergency room at our institution with the chief complaint of hemoptysis for 3 days. Based on initial physical examination, vitals and laboratory, there was a low suspicion for infection. A chest computed tomography was obtained and interpreted as unilateral right sided pulmonary edema with possible multifocal pneumonia. A bronchoscopy performed the following day revealed diffuse bilateral alveolar hemorrhage. Tissue biopsies were not obtained during this procedure secondary to risk of further hemorrhage. Bronchial alveolar lavage revealed hemosiderin laden macrophages consistent with pulmonary hemorrhage. Pulse dosed steroids were initiated at 150 mg IV twice daily spanning a 72-h course for presumed WG of the lower respiratory tract. The patient tolerated this effective steroid regiment well, and was discharged on the fifth day. During this admission, there were no signs of renal involvement secondary to WG. Urinary analysis and microscopy were negative for protein, red blood cells, or red cell casts. A full vasculitis workup was initiated at this time, but likely completed on an outpatient basis of which the results are not known. This patient was lost to follow-up. During the period between his first admission for shortness of breath and the second for hemoptysis, he reported similar symptoms of intermittent epistaxis with concomitant sinusitis as well as episodes of scleritis.

Although a lung biopsy was not obtained, this patient's overall symptoms in these two admissions in conjunction with a positive c-ANCA and cardiac biopsy findings are consistent with the diagnosis of WG. The differential diagnoses of Churg Strauss syndrome and giant cell arteritis can be entertained but are less likely given the absence of eosinophilia as well as eosinophilic granulomas on biopsy. Giant cell arteritis does not typically involve microvasculature, but rather medium and large arteries of the head. Furthermore, the patient denied any symptoms of asthma, the hallmark pulmonary findings of Churg Strauss syndrome. In accordance with American College of Rheumatology acceptance criteria for randomized control trials, this patient has a high sensitivity and specificity for having WG.

Review of the literature

Wegener's involvement of the heart has been reported at autopsy in 30% of patients with known WG [1]. However, the percentage of clinical cardiac involvement in WG is low with sources citing 6—12% prevalence [2,3]. The majority of these cases involved the myocardium and pericardium. In a study by the National Institute of Health in the 1980s, out of 85 patients being observed for WG, only 12% had clinical cardiac involvement predominantly of the pericardium and myocardium. Clinical manifestations of cardiac valvular lesions have historically been even rarer [2]. A careful review of the literature reveals about 20 case reports that have been published depicting clinical presentations of either aortic or mitral valve lesions pathologically or clinically diagnosed as WG. In one case reported from the University of California, San Francisco in 1989, a 77-year-old woman was admitted for signs and symptoms of severe heart failure. A transthoracic echocardiogram revealed severe aortic insufficiency accompanied by mild left ventricular dilation. Pathology of the aortic valve demonstrated myxomatous changes and degeneration of collagen consistent with collagen vascular disease. Prior pathological analysis from a pulmonary lesion in this patient had shown necrotizing granulomatous inflammation and arteritis consistent with WG [4]. That same year a case was reported from Russia, of a 29-year-old man with significant lung and renal vasculitis, who later developed ''heart enlargement and systolic—diastolic noise in Botkin point''. The patient died 6 months later. At autopsy, vasculitis with granulomatosis, as well as destructive changes in the intima, were found in both the supravalvular part of aorta and at the base of the valve with severe fibrinous valvulitis. These findings were consistent with WG [5]. Ten years later, a case was reported of a 17-year-old male presenting with low-grade fever, arthralgia, sore throat, and fatigue of 3 weeks' duration. A transthoracic echocardiogram was performed in the workup revealing grade 2 aortic insufficiency. Blood cultures were negative, but with strong clinical suspicion, the diagnosis of WG was made with an ANCA titer of 1:512 [6].

Discussion

The traditional view of WG as portrayed in the preceding paragraph, has been that of rare cardiac involvement, particularly valvular. However, more recent studies have shown otherwise. In a study performed by Morelli et al. [7], two-dimensional, Doppler and color-Doppler transthoracic echocardiograms were performed on nine patients affected by WG. In all of these patients, cardiac abnormalities were found including valvular damage, left ventricular systolic dysfunction, and pericardial effusions. More specifically, valvular disease was found in eight of the patients, three of which involved aortic valve insufficiency requiring replacement. In 2003, Herbst et al. reported the case of a 56-year-old woman with a sessile mass on the anterior leaflet of her mitral valve with significant regurgitation. The initial impression was that of an atrial myxoma. During surgery, they discovered an intense inflammatory process also affecting the aortic valve and contiguous myocardium which was diagnosed as WG [8]. Identical to our case, Strizhakov et al. [9] reported the case of a female patient with WG who developed aortic regurgitation and third degree heart block requiring pacemaker implantation.

The case presented above at Beth Israel Medical Center contributes to the growing body of literature in support of cardiac manifestations in WG. Although documented, cardiac manifestations have not been incorporated into the standard care and treatment of such patients. As previously

discussed, cardiac lesions typically affect the pericardium and myocardium. However, valvular involvement and conduction defects have been increasingly reported in the setting of WG. The presented case report and review of the literature highlights the incidence along with the morbidity and mortality associated with valvular cardiac lesions in WG. We believe routine cardiovascular supervision including echocardiography and electrocardiograms are important for the screening and monitoring of patients with WG. The effects of treatment with steroids and/or cyclophosphamide on these cardiac manifestations are currently unknown, but nevertheless serve as an avenue for future research endeavors.

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