Rapidly Progressive Cardiac Failure Due to Giant Cell Myocarditis

A Clinical Pathology Conference Held by the Division of Rheumatology at Hospital for Special Surgery

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Received: 31 December 2014/Accepted: 23 April 2015/Published online: 3 June 2015
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Keywords giant cell myocarditis · autoimmune disorder

Clinical Presentation

A 56-year-old Hispanic female from the Dominican Republic with no history of cardiac disease presented to an outside hospital in November 2012 with fever, abdominal pain, nausea, and vomiting.

One year prior to admission, the patient developed frequent flu-like symptoms with subjective fever, chills, diaphoresis, and myalgias. These symptoms would last about 1 week and resolve spontaneously. The patient's daughter described at least six such episodes in the past year. She denied any exertional dyspnea, palpitations, chest pain, exercise intolerance, orthopnea, paroxysmal nocturnal dyspnea, or lower extremity edema.

In October 2012, the patient visited the Dominican Republic. There she was admitted to a local hospital for

swelling of the face and neck and generalized body rash that, per the patient's daughter, "resembled hives." She denied any breathing, speech, or swallowing difficulties. The patient was treated with prednisone and hydroxyzine (doses unknown). By the time of discharge, the swelling had resolved and the rash was improving except for desquamation and light brown macular lesions on the palms.

Two weeks following that admission and 2 days prior to her flight back to the United States of America (USA), the patient started to complain of nausea, vomiting, abdominal pain, subjective fever, chills, and myalgias. She also complained of chest discomfort. Upon arrival in the USA, she presented to an outside hospital for evaluation on November 19th 2012. On physical examination, she was tachycardic with a heart rate of 120 bpm and hypotensive with a blood pressure of 95/40 mmHg. Laboratory analysis revealed an elevated troponin of 4.6 ng/mL. An electrocardiogram (EKG) showed sinus tachycardia at 126 bpm and a normal axis. The QTc was prolonged at 427 ms. There were sub-millimeter P-R depressions but no S-T elevations or depressions. There was a Q wave in V1 and V2 with low voltage. Given the elevated troponin, there was concern for a non-ST elevation myocardial infarction and the patient was transferred to our institution for cardiac catheterization.

The patient's past medical history was notable for hypertension, hyperlipidemia, diabetes mellitus type 2, and chronic renal insufficiency with a baseline creatinine of 1.3 mg/dL. Patient had an allergy to shellfish. She denied the use of tobacco, alcohol, or illicit drugs. Family history was notable for hypertension and diabetes in many relatives, but there was no family history of sudden death, autoimmune, or connective tissue disease.

The patient's physical examination was significant for an elevated jugular venous pressure, distant heart sounds, and crackles in the lung bases. On examination of the skin, hyperpigmented macules and scaly plaques on hands with mild desquamation were found.

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Electronic supplementary material The online version of this article (doi:10.1007/s11420-015-9449-5) contains supplementary material, which is available to authorized users.

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Laboratory values were notable for white blood cell count of 16.7/uL, hemoglobin of 10.9 g/dL, creatinine of 1.17 mg/dL, troponin I of 14.15 ng/mL, lactate of 17.5 mmol/L, lactate dehydrogenase of 296 IU/L, erythrocyte sedimentation rate (ESR) of 98 mm/h and C reactive protein (CRP) of 25.32 mg/dL (Table 1). There was no peripheral eosinophilia. Cytomegalovirus (CMV) IgM and IgG antibodies were positive, but CMV polymerase chain reaction testing was negative. Serologies for Hepatitis B and C, Epstein Barr Virus (EBV), varicella, enteric cytopathic human orphan (ECHO) virus, and Human Immunodeficiency Virus (HIV) as well as blood and urine cultures were negative. Coxsackie Types B1-B6 were negative but type B4 serologies were positive with a titer of 1:320. Autoimmune serology panel including antinuclear antibody (ANA), double-stranded DNA (dsDNA), extractable nuclear antigens (ENA), anti Jo1, anti SCL 70, and anti-neutrophil cytoplasmic antibodies were negative. Although chronic Chagas disease should be considered in the differential diagnosis in a patient with cardiac symptoms and recent travel, serologies were not tested given the patient's fulminant course and the pathologic findings discussed below.

Repeat EKG at our institution revealed sinus tachycardia with right bundle branch block, possible anterior wall myocardial infarction, and nonspecific repolarization abnormality (Fig. 1). Left heart catheterization showed non-obstructive coronary disease with an ejection fraction of 30%, cardiac output of 1.9 L/min, and equalization of diastolic pressures. A bedside transthoracic echocardiogram

was performed in the catheterization lab that showed no pericardial effusion, no valvular disease, and normal right ventricular function with reduced ejection fraction. A biopsy of the right ventricle was performed.

Pathological Discussion

On light microscopy, the ventricular biopsy showed extensive myocardial necrosis with diffuse inflammatory infiltrate consisting predominantly of lymphocytes and multinucleated giant cells, macrophages, eosinophils, plasma cells, and few neutrophils (Fig. 2). A diagnosis of giant cell myocarditis (GCM) was made based on the presence of myocyte necrosis associated with multinucleated giant cells and a mixed inflammatory infiltrate.

Other diagnostic considerations in the case included sarcoidosis and hypersensitivity myocarditis. However, sarcoidosis has well-defined granulomas and does not have a diffuse mixed inflammatory infiltrate with myocyte damage. Hypersensitivity myocarditis is associated with eosinophilic infiltrates, but the presence of multinucleated giant cells with extensive necrosis on biopsy excluded that diagnosis.

Endomyocardial biopsy is the gold standard for confirming the diagnosis with a sensitivity of 80–85% and positive predictive value of 71% in patients with GCM [17]. Biopsy reveals serpiginous areas of myocardial necrosis [7] and diffuse intramyocardial inflammatory infiltrate consisting of abundant lymphocytes, with eosinophils and plasma cells, and prominent multinucleated giant cells [7]. The hallmark is the presence of giant cells, fused epithelioid histiocytes usually 40 to 50 μ m in size with multiple nuclei. In later stages, mural thrombus can be present. Despite extensive myocardial damage, it is unusual to see pericarditis or endocarditis [7].

Clinical Discussion

GCM is a rapidly fatal inflammatory cardiac disease, first described in 1905 by Saltykow [1]. It typically affects young to middle-aged adults, with a mean age of 43 years [16]. There is no gender predominance. Patients (often previously healthy) present with a flu-like syndrome and can develop congestive heart failure (in 75%), palpitations, chest pain, heart block, sustained refractory ventricular tachycardia, rapidly progressive hemodynamic deterioration, intractable arrhythmias, and sudden death [16]. GCM can progress to death within days to months. Median survival in untreated patients is 5.5 months from symptom onset until the time of death or transplantation [4, 16]. There is a better prognosis in patients diagnosed early and treated with immunosuppressive medications. In a study comparing ventricular biopsies of patients with GCM with biopsies from donor heart specimens, most differentially expressed genes were involved in Th1 pathway, highlighting the immunological basis for this disease [1].

GCM is associated with systemic autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis,

Table 1 Significant laboratory values at admission

Laboratory test	Value	Reference range
Creatinine serum	1.17	[0.44–1.03 mg/dL]
Glucose random	199	[74–118 mg/dL]
Calcium, serum	7.6	[8.9–10.3 mg/dL]
Total protein	5.9	[6.1–7.9 g/dL]
Albumin level	2.5	[3.5–4.8 g/dL]
Aspartate aminotransferase	53	[15–41 IU/L]
Alanine aminotransferase	41	[14–54 IU/L]
Alkaline phosphatase	68	[32–91 IU/L]
Bilirubin, total	0.8	[0.3–1.2 mg/dL]
Lactate dehydrogenase	296	[98–192 IU/L]
Bilirubin, direct	0.3	[0.1–0.5 mg/dL]
WBC count	16.7	[3.4–11.2 $\times$ 10(3)/uL]
Neutrophil (%)	80.8	[45.0–75.0%]
Hemoglobin	10.9	[11.7–15.3 g/dL]
Hematocrit	33.6	[35.0–45.0%]
Platelet count	308	[150–450 $\times$ 10(3)/uL]
Thyroid-stimulating hormone (TSH)	0.23	[0.34–5.60 uIU/mL]
Erythrocyte sedimentation rate (ESR)	98	[0–30 mm/h]
C reactive protein (CRP)	25.32	[0.00–0.99 mg/dL]
Aldolase	13.5	[1.5–8.1 U/L]
Myoglobin	236	[25–58 ng/mL]
Creatine kinase	212	[38–234 IU/L]
CK-MB	36.9	[0.6–6.3 ng/mL]
Ferritin	276.2	[11.0–306.8 ng/mL]
Interleukin 6 (IL 6)	23	pg/mL
Troponin I	14.15	[0.01–0.04 ng/mL]
Lactate	17.5	mmol/L
Hemoglobin A1C	7.2	[$\leq$ 5.6%]

Fig. 1. EKG at admission shows sinus tachycardia with right bundle branch block, possible anterior wall myocardial infarction, and nonspecific repolarization abnormality.

inflammatory bowel disease, myasthenia gravis, Sjogren's syndrome, polymyositis, and autoimmune thyroid disease in about 20% of cases [4, 16]. However, the disease may also be triggered by viral infections such as human herpes and coxsackie virus [1]. Whatever the initial inciting event, the final common pathway involves a sustained autoimmune response directed against the myocardium.

Conduction abnormalities may be identified on electrocardiogram in patients with GCM; however, these findings are nonspecific. Echocardiography may initially show ventricular thickening and worsening systolic function which can progress to ventricular dilatation over the next few days [1]. Cardiac magnetic resonance imaging (MRI) is thought to be a useful imaging modality in these patients, but very few patients are stable enough to undergo this procedure. Subtle distinguishing features were reported on cardiac MRI in patients with atrial GCM in a small case series [13]. The utility of other cardiac imaging modalities such as computed

tomography (CT) or positron emission tomography (PET) has not yet been established in GCM. In patients with cardiac sarcoidosis, Fluorodeoxyglucose - PET (FDG-PET) studies can be useful to identify areas of focal myocyte damage and/or inflammation and help direct biopsy [10] and by analogy could be used in patients with suspected GCM. Cardiac imaging alone, however, is generally not helpful in determining the specific etiology of myocarditis.

Initial therapy for patients with GCM should be directed towards maintaining hemodynamic stability and providing symptomatic relief. Control of heart failure and left ventricular dysfunction is essential; patients may require mechanical support such as an intra-aortic balloon pump. In addition, expeditious treatment with immunosuppressive agents is recommended.

Data for use of immunosuppressive therapy in GCM comes largely from retrospective studies and is based on the assumption that GCM is a T-cell mediated process. In the early 1990s, GCM patients were treated with prednisone and azathioprine in addition to heart failure treatment [4]. In 1997, Leslie Cooper et al. described a series of 63 patients with GCM. Thirty patients did not receive immunosuppressive agents and had a median survival of 3 months; 11 patients received corticosteroids alone and survived 3.8 months. Greater survival benefit was seen in the 22 patients who received steroids plus azathioprine or cyclosporine with a survival of 11.5 and 12.6 months, respectively [4]. Based on this, triple therapy with cyclosporine, prednisone, and azathioprine was often used [6].

A randomized open label trial by Cooper et al. compared responses to muromonab (OKT3) plus cyclosporine and prednisone to cyclosporine and prednisone alone [5]. The primary end point of this study was transplant-free survival at 12 months. The study reported marked improvement in the inflammatory infiltrates as well as an increase in fibrosis seen on myocardial biopsy in the OKT3 group after 4 weeks of treatment [5]. A recent study by Kandolin et al. in 2013 showed a transplant-free survival of 77% ($n=63$) at 1 year and 63% at 2 years on combined immunosuppression

Fig. 2. Giant cell myocarditis. The image shows a dense chronic inflammatory infiltrate with myocyte damage. The infiltrate consists of multinucleated giant cells (*long arrows*), eosinophils (*short arrows*), and other inflammatory cells consisting of lymphocytes, plasma cells, and macrophages.

Fig. 3. EKG on hospital day 10 representing ventricular asystole.

including steroids, azathioprine, and cyclosporine [2, 3, 11]. Rituximab was used successfully in one case in the literature [18]. There is data in the literature to guide approaches to maintenance of remission. However, abrupt withdrawal of immunosuppression can result in recurrent, fatal GCM [11]. Ventricular assist devices (VAD) in GCM are not used as destination therapy but can serve as a bridge to heart transplantation in patients who fail to respond to medical therapy. Murray et al. published a small case series of six patients with confirmed GCM and rapidly declining cardiac function who underwent placement of VAD and also received treatment with azathioprine and daclizumab [14]. Four of these 6 patients went on to receive orthotopic cardiac transplantation. In posttransplant follow-up, 2/4 patients had recurrence of disease. Despite these results, the most consistently effective therapy is cardiac allograft transplantation. In the 1997 landmark study by Cooper et al., 34/63 patients underwent cardiac transplantation approximately 6 months after symptom onset. GCM recurred in 9 of those patients an average of 3 years after transplant [4].

Immunologic Discussion

The pathophysiology of GCM is not completely understood but is thought to be a T-cell driven process. The proof for this concept comes from animal models. Shibata et al. reproduced fulminant myocarditis in a Lewis rat model by injection with cardiac myosin and Freund's adjuvant [12]. The rats exhibited acute and severe myocarditis at 3 weeks that was histopathologically similar to human GCM. The inflammatory lesions were dominated by CD4+ T-cells and macrophages, suggesting that CD4+ T-cells were responsible for the pathogenesis [12]. Furthermore, Hanawa et al. investigated the effects of anti-alpha beta T-cell receptor antibodies in rat experimental autoimmune myocarditis characterized by multinucleated giant cells. Short-term therapy delayed the onset of myocarditis [8]. The authors theorized that impairment of T-cell function by occupancy of the receptor was responsible for suppressing the development of myocarditis in the animals [8].

GCM-associated autoantibodies include those that bind cardiac myosin and cross react with the beta-adrenergic receptor [1]. Although anti-skeletal muscle and anti-myocardial antibodies have also been identified in many patients, they have poor specificity since they are also identified in healthy controls [12]. Neumann et al. examined circulating heart-reactive antibodies in patients with myocarditis and cardiomyopathy; 60% of myocarditis patients and 20% of idiopathic cardiomyopathy patients had high titers of antibodies to heart tissue [15]. Such antibodies may also be present in rheumatic heart disease, myocardial infarction, post-cardiac surgery, and in viral myocarditis [9]. Thus, it is unclear whether these antibodies are active players in the pathology of the disease or just reflect the presence of myocyte damage.

Hospital Course

The patient was transferred to the Cardiac Care Unit for management of cardiogenic shock. An intra-aortic balloon pump was placed for persistent hypotension despite fluids and vasopressors. Given the biopsy confirming GCM, hydrocortisone 100 mg was started intravenously every 8 h with no significant improvement. There was extensive damage to the myocardium with very little hope for recovery. The patient's EKG showed worsening S-T elevations. She was treated with extracorporeal membrane oxygenation (ECMO). Patients on ECMO are prone to infection by being severely ill; therefore, additional immunosuppressive therapy would only further increase the risk of infection. Although the patient was positive for CMV IgM and IgG, it was ultimately thought unlikely to be contributing to her cardiomyopathy since CMV polymerase chain reaction testing was negative, and false positive CMV IgM positivity is common. Furthermore, viral myocarditis usually presents with lymphocytic infiltrates on biopsy, not giant cell infiltrates. However, antiviral and antibacterial therapies were used throughout the patient's hospital stay.

She also required repeat catheterization (to rule out an embolized thrombus or newly developed thrombus of the coronary vessels). The patient was intubated for airway protection prior to this procedure given her poor mental status.

Three days later, the patient's urine output decreased, her acidosis worsened, and she had elevated lactate with a decline in mean arterial pressure prompting the initiation of continuous veno-venous hemofiltration and titration of vasopressors. Nonetheless, her EKG progressed to ventricular asystole (Fig. 3). Transthoracic echocardiogram at bedside showed translational motion of the heart but no evidence of ventricular contraction. 'Smoke' was seen in the left ventricle indicative of stagnant blood, but no distinct thrombus was identified. A transesophageal echocardiogram showed total cardiac standstill and a left atrial thrombus extending into the pulmonary veins as well as thrombus in the pulmonary artery and into the ascending aorta. Given that she had no residual cardiac function and given that the presence of extensive intracardiac thrombi precluded her from receiving a cardiac transplant, the decision was made with the family to withdraw care and the patient deceased soon after.

GCM is a rare yet fatal disease that affects young individuals. It can be seen in association with other systemic autoimmune diseases or viral illnesses. It is important to consider this entity in the differential diagnosis of patients presenting with myocarditis or cardiomyopathy. One of the highlights of this case was the rapid recognition of profound cardiac failure and the ability to provide adequate hemodynamic support. In cases of fulminant cardiac failure, one should maintain high clinical suspicion for giant cell myocarditis. Finally, timely referral for cardiac biopsy with expert pathologic opinion could provide definitive diagnosis for this disease and, in some cases, alter outcomes.

Disclosures

Conflict of Interest: Ersilia M. DeFilippis, BA, Sonali Narain, MD, MPH, Irina Sobol, MD, Navneet Narula, MD, Anne Bass, MD, and Doruk Erkan, MD have declared that they have no conflict of interest.

Human/Animal Rights: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5).

Informed Consent: Informed consent was waived from all patients for being included in the study.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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