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Conduction Dysfunction and Near Expunction: Giant Cell Myocarditis

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PRESENTATION

A patient who had been in relatively good health was suddenly on a cataclysmic course. The 70-year-old man presented to his primary care physician with shortness of breath. Five days prior, he experienced increasing pulmonary congestion and required additional help from his nocturnal continuous positive airway pressure device for improved sleep quality. Twenty-four hours after the onset of symptoms, he had increasing orthopnea. By the following day, he needed to stay upright in a chair to breathe comfortably. At that point, he decided to be evaluated.

A 12-lead electrocardiogram showed new trifascicular block without signs of acute ischemia (Figure 1). The patient was then transferred to a rural emergency department, where he was given intravenous (IV) diuresis for signs of heart failure. His subacute symptoms, combined with the new electrocardiogram findings, prompted coronary angiography. The procedure revealed mild nonobstructive coronary disease that was unchanged from prior studies. However, transthoracic echocardiography disclosed new globally impaired left ventricular systolic function (ejection fraction, 35%), and he was transferred to our hospital.

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The patient had known nonobstructive coronary artery disease with preserved left ventricular ejection fraction, as well as obstructive sleep apnea. He had not had a viral prodrome and had no personal or family history of rheumatologic disease or cardiomyopathy.

ASSESSMENT

On admission, the patient had a blood pressure of 117/71 mm Hg, a pulse rate of 84 beats per minute, a respiratory rate of 16 breaths per minute, and an oxygen saturation of 99% on room air. His cardiopulmonary examination was unremarkable, although he did have 1+ pitting edema of the lower extremities. His laboratory data was notable for a plasma cardiac troponin I level of 21.9 ng/mL (normal, <0.01 ng/mL) and an N-terminal pro b-type natriuretic peptide (NT-proBNP) level of 183 pg/mL (normal, 0–900 pg/mL). A consultant in advanced heart failure evaluated the patient, and immediately after, he developed complete heart block, which degenerated to sinus arrest with hypotension. The patient then became unresponsive and was intubated.

DIAGNOSIS

Just 36 hours after the patient first presented to his primary care physician's office, he was in cardiogenic shock. Norepinephrine was administered intravenously via a central venous catheter to reverse the patient's hemodynamic and electrical disarray, and transcutaneous pacing was begun, followed by transvenous cardiac pacing. In addition, IV methylprednisolone was administered because we suspected the patient had an autoimmune infiltrative cardiomyopathy.

To evaluate this possibility, we performed an endomyocardial biopsy, which showed a mixed inflammatory infiltrate with mononuclear cells, eosinophils, and multinucleated giant cells and multifocal coagulative myocyte necrosis. These histologic observations were consistent with a diagnosis of giant cell myocarditis (Figure 2).

It is extremely difficult to diagnose giant cell myocarditis based on clinical presentation alone. The preponderance of presenting signs and symptoms, combined with the sometimes swift progression of disease, can catch the treating clinician unaware and make it difficult to recognize the disease early in its course. Our patient's clinical presentation was quite subtle. His symptoms, beginning with shortness of breath, evolved rapidly over a period of 1 week, illustrating the often subacute nature of this disorder. However, a constellation of signs and symptoms can greatly increase the index of suspicion for inflammatory cardiomyopathy.

In general, the disease is more prevalent among women than men, and it tends to manifest in the fifth or sixth decade of life, usually with little overlap in presenting signs and symptoms (Table 1).^{1,2} One clue to an infiltrative myocardial process, such as giant cell myocarditis, is a combination of new-onset ventricular and atrial arrhythmias, as well as new intraventricular conduction abnormalities. These suggest electrical discontinuity in both the intrinsic conduction system and at regions of myocyte apposition where intercellular electrical continuity through the gap junction is an absolute requirement.³

When these findings are associated with acute-onset symptomatic systolic dysfunction and a plasma cardiac troponin concentration that is disproportionate to the observed patient symptoms, the treating clinician should be immediately alerted to the possibility of giant cell myocarditis. This is especially true in the proven absence of acute coronary occlusion or unchanged nonobstructive coronary artery disease. Our patient underwent angiography at another facility followed by endomyocardial biopsy at ours.

Ultimately, an endomyocardial biopsy is essential to histologically confirm the diagnosis of giant cell myocarditis. Historically, endomyocardial biopsy was rarely completed in an evaluation of acute-onset heart failure of unknown etiology.⁴ In our patient's case, the biopsy revealed active myocarditis soon after empiric treatment had been initiated.

A commonly used noninvasive alternative to biopsy is to look for areas of myocardial inflammation and scarring with gadolinium-enhanced cardiac magnetic resonance imaging (MRI) or with a combination of ¹⁸F-fluorodeoxyglucose positron emission tomography and resting myocardial perfusion imaging with technetium (99m Tc) tetrofosmin single-photo emission computed tomography.⁵ Our patient's disease advanced too quickly for us to use noninvasive imaging in our decision making. MRI can also be helpful in targeting an endomyocardial biopsy to regions of myocardial inflammation.⁵ Although early use of MRI might prevent endomyocardial biopsies in some patients, most patients undergo biopsy.¹

MANAGEMENT

Immunosuppression is the cornerstone of treatment for giant cell myocarditis.⁶ High-dosage corticosteroids are often combined with cyclosporine and azathioprine or with antithymocyte immunoglobulin, a formulation of antibodies against human T cells that can slow the progression of autoimmune myocarditis.⁶ Our patient was being maintained on IV methylprednisolone when IV antithymocyte immunoglobulin was initiated. Cyclosporine and azathioprine were added several days later. The 4-drug regimen reversed the patient's clinical condition from cardiogenic shock to mild systolic heart failure in just 3 days.

Over the next few days after the reversal, the patient developed both atrial fibrillation with rapid ventricular response, as well as sustained ventricular tachycardia, and so IV amiodarone was administered. In the following weeks, the cyclosporine, azathioprine, and steroid dosages were titrated with the goal of suppressing inflammation, allowing remission, and preventing the need for cardiac transplant. Transplant-free survival rates are considerably higher with combined immunosuppression.^{1,6} His hemodynamic and electrical abnormalities gradually dissipated, and he was weaned from IV norepinephrine. He was then extubated and underwent implantable cardioverter defibrillator placement for secondary prevention before discharge from the coronary care unit.

A surveillance endomyocardial biopsy, performed on an outpatient basis 6 weeks after discharge, verified resolution of infiltrative mononuclear cells (Figure 3). The patient now continues immunosuppression with cyclosporine, mycophenolate, and prednisone. A repeat biopsy, obtained several months later, demonstrated a largely healed myocardium without evidence of myocarditis. His last transthoracic echocardiography showed normalization of

his previously impaired left ventricular function. Recognition of, and at the very least a high index of suspicion for, giant cell myocarditis is key to early initiation of immunosuppression and supportive therapies. Timely treatment can prevent cardiac inflammation from precipitating aberrancies in cardiac conduction and irreversible cardiogenic shock.

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Figure 1.

Electrocardiogram obtained on admission showed sinus rhythm with first-degree atrioventricular block, left anterior fascicular block, and a right bundle branch block.

Figure 2.

(A) Examination of a biopsy specimen revealed coagulative myocyte necrosis with mixed inflammatory cells, including mononuclear cells (white arrowheads), eosinophils (black arrowhead), and multinucleated macrophages or ‘giant cells’ (yellow arrowhead). (B) Immunofluorescence of cardiac myocytes for complement C4d demonstrated strong cytoplasmic myocyte positivity for complement C4d, indicative of coagulative necrosis. (C) CD68 immunostaining for monocytes and macrophages identified multinucleate CD68-positive giant cells (encircled).

Figure 3. Myocardial biopsy was performed after several months of treatment. **(A)** Myocardium devoid of active inflammation (hematoxylin and eosin, 100 $\times$ original magnification). **(B)** This normal myocardium, displayed under 20 $\times$ magnification, has small areas of interspersed early fibrosis (white arrowheads).

Table 1

Published Characteristics of Patients with Giant Cell Myocarditis

Demographic	Statistic
Age of onset	52.5±12.5 years
Gender	69% female
Signs and Symptoms	Percentage of Patients (%)
Congestive heart failure	31
AV block	31
VT	22
Chest pain + S-T changes	13

AV = atrioventricular; VT = ventricular tachycardia.