Fulminant Myocarditis: Brief Review

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Abstract
Fulminant myocarditis (FM) is a rare disease characterized by acute hemodynamic impairment and ventricular arrhythmias due to severe myocardial inflammation. It is typically preceded by a viral infection but any of multiple other toxic and infective agents may also be the inciting agent. Diagnosis is based on biomarkers and/or cardiac imaging, but endomyocardial biopsy is the standard test for confirming the diagnosis. FM usually requires therapeutic support of cardiac function and treatment of malignant arrhythmias. Contrary to prior concepts, recent evidence has revealed that patients with FM are more likely to die or need heart transplantation than those with the nonfulminant form of the disease. Early recognition and aggressive management are essential for favorable outcomes.

Key Words: acute myocarditis; fulminant myocarditis; giant cell; lake louise criteria; endomyocardial biopsy; Coxsackie virus; adenovirus; echocardiography; magnetic resonance imaging

Introduction
Myocarditis is an inflammatory disease of the myocardium that can result from myriad infectious, toxic, or autoimmune processes. However, presentation after a viral disease is the most common onset. Although the course of myocarditis is commonly self-limiting, the acute, nonfulminant form can progress to fulminant myocarditis (FM) (Figure). FM is an acute process with hemodynamic derangement and malignant ventricular arrhythmias [1-3]. Treatment includes support of ventricular function and management of arrhythmias. It has recently been reported that mortality from FM is considerably greater and cardiac transplantation more likely than are associated with the nonfulminant form [1]. These findings refute earlier reports of a lower mortality from FM than from the non-fulminant form [1-3]

Epidemiology
Because of variable presentation, the incidence of FM is unclear but acute myocarditis is estimated to occur in <25 cases per 100,000 population [4] and it may develop in 1-5% of patients with acute viral infections [5]. During the first year of the disease, mortality may be as high as 20% and it then decreases and plateaus after ~3 years [6]. The Marburg Myocarditis Registry reported that FM developed in 2.5% of 1,000 patients presenting with myocarditis [7] but in those hospitalized with myocarditis, ~30% were diagnosed with FM. Despite these reports, there are no systematic data on the true prevalence and incidence of FM.

Etiology
Both FM and nonfulminant myocarditis have similar initial pathogenesis. The typical initiating factors are infections, toxins or adverse reactions to medications [3, 6-9]. However, viral infections (Coxsackie A and B and adenovirus), are the most common initiating factors [9, 10]. FM presents as three histologic types: lymphocytic, eosinophilic, or giant cell [3, 6, 8, 11-15]. Lymphocytic myocarditis is the dominant form of FM and the eosinophilic and giant cell subtypes are considered alternative forms. Pathogenesis of all 3 forms of FM most frequently involves direct, virally mediated myocyte damage and/or immune-mediated cellular damage [8] Lymphocytic myocarditis is usually caused by viruses, but other microorganisms and infection by parasites have also been recognized as causative [12]. Giant cell myocarditis is mediated by T cell-induced inflammation resulting from autoimmune disease [13] and is associated with multinucleated giant cells on endomyocardial biopsy [13]. Most cases of eosinophilic myocarditis are associated with hypersensitivity reactions [14].
Presentation

Although the presentation of FM is variable, there are certain features that distinguish it from acute nonfulminant myocarditis. FM has an acute onset after a viral prodrome, progresses to severe cardiovascular impairment, and biopsy evidence most commonly reveals dense lymphocytic myocarditis. The course may culminate in complete resolution or death within a month [15].

In contrast to the severe heart failure of patients with FM, acute nonfulminant myocarditis presents with mild-moderate symptoms of cardiac dysfunction. In milder presentations of FM, findings include hypotension, fatigue, chest pain, palpitations, and dyspnea [3]. More severe presentations comprise aborted sudden death, malignant arrhythmias, and systemic dysfunction from inadequate perfusion, respiratory impairment and aborted sudden death [16]. Myocarditis should be considered in patients with acute onset heart failure, arrhythmias, and chest pain not attributable to other disease processes including noninflammatory cardiomyopathies or coronary heart disease [17].

Diagnosis

Diagnosis of suspected FM comprises three approaches [18-24]: (1) biomarkers, (2) imaging, and (3) histology. Major increases of cardiac troponins, creatine kinase MB, and white blood cells and evidence of end-organ damage (e.g., increases in blood urea nitrogen, creatinine, and transaminases), indicate myocardial injury, dysfunction, and circulatory impairment. FM produces higher plasma concentrations of C-reactive protein and creatinine kinase MB than acute non-fulminant myocarditis [18].

Both cardiac magnetic resonance imaging (CMR) and echocardiography are useful for identifying FM. CMR provides optimal imaging quality for detecting FM. Diagnosis of myocarditis by CMR is based on 2 of 3 findings of the CMR-specific diagnostic results known as the Lake Louise criteria: (1) myocardial edema, (2) myocardial hyperemia or global relative enhancement, and (3) myocardial fibrosis or late gadolinium enhancement [3, 19, 20, 21, 22]. Echocardiography evaluates cardiac anatomy and function and is helpful in distinguishing acute myocarditis from inflammatory cardiomyopathies and other overlapping cardiac conditions. The usual findings in FM are near-normal left ventricular diastolic dimensions, increased septal thickness, and reduced left ventricular ejection fraction (LVEF) [16]. The latter finding predicts a fulminant course [23].

The primary test for diagnosis of FM is histologic confirmation of myocarditis by endomyocardial biopsy (EMB) [24] which should be performed early in cases of suspected FM. Immunohistochemistry supports the diagnostic capacity of EMB, which is essential for differentiating lymphocytic from nonlymphocytic myocarditis [23]. Evidence of infiltrating lymphocytes and myocyte lysis confirms the lymphocytic form of myocarditis [24].

Management

Management is based on each patient’s presentation and therapeutic requirements [3, 24-26]. Those with a clinically unstable presentation should undergo EMB early. Heart failure is managed according to the guidelines of the major cardiology societies [25]. Initial treatment focuses on stabilization of hemodynamic function to avert organ damage. Positive inotropic agents may be required to maintain systemic perfusion and vasodilator therapy may be utilized if blood pressure is adequate [3]. If medical therapy is inadequate, mechanical circulatory support (MCS) is employed [24, 26]. It may include intra-aortic balloon pump or, in chronic severe cardiac dysfunction, extracorporeal oxygenation may be utilized [26, 27, 28]. Ventricular assist devices can be implanted to support circulatory adequacy for prevention of end-organ damage and afford time for recovery or for bridging to cardiac transplantation.

The role of immunosuppressive therapy for FM has not been clarified [3]. For giant cell and eosinophilic myocarditis, steroids (e.g., methylprednisolone followed by a gradual oral prednisone taper) are basic management, with antithymocyte globulins and cyclosporine utilized as adjunctive therapy. Muromonab-CD3 and sirolimus have also improved transplant-free survival in patients with giant cell myocarditis [8, 29]. In FM secondary to systemic diseases (i.e., sarcoidosis), steroids alone or in combination with azathioprine or methotrexate are first line therapy [3]. Intravenous immunoglobulin (IVIG) has improved LV function and decreased arrhythmias in some adult patients with acute FM but recent evidence has shown no decrease in in-hospital mortality with IVIG for treatment of FM [30]. There are currently no randomized, prospective trials of IVIG in this patient population, but several case reports have suggested short- and long-term benefit with IVIG [31, 32].

Prognosis

Figure: Development and Major Categories of Fulminant Myocarditis
Estimation of prognosis in FM patients has been based on correlation of clinical data with long-term outcome. Factors associated with increased mortality or need for cardiac transplantation are presence of intramyocardial viral genomes, biventricular dysfunction, pulmonary capillary wedge pressure ≥15 mm Hg, echocardiographic evidence of myocardial fibrosis, and histopathology reflecting lymphocytic, giant cell, or granulomatous etiologies of myocarditis [33]. Treatment requiring biopsy-proven myocarditis is an important limitation in considering the accuracy of a FM diagnosis.

Until recently, it was believed that mortality in patients with FM was paradoxically lower than that in acute nonfulminant myocarditis [2, 16, 34]. Previous studies suggested that patients with FM had more rapid recovery of LVEF with less likelihood of long-term dysfunction and mortality than those with the nonfulminant type [2, 16, 28]. However, more recent and larger studies indicate that FM is associated with overall worse outcomes: lower post-hospital LVEF, higher in-hospital mortality, and more frequent cardiac transplantation [1, 3, 35]. In addition, a recent registry of over 400 patients that included both acute FM and nonfulminant myocarditis revealed a trend of worse outcomes in those with FM [1, 35].

Summary

FM is a rare, severe form of myocarditis. The presentation is a characteristic, acute onset of severe heart failure and malignant ventricular arrhythmias commonly preceded by a viral prodrome. Diagnosis is based on biomarkers and cardiac imaging, but endomyocardial biopsy remains the primary method for documentation. Acute hemodynamic impairment and malignant arrhythmias are managed by current pharmacologic and interventional methods and the role of immunosuppressive agents remains unclear.

Disclosures

The authors have no conflicts of interest to disclose.

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