Acute Heart Failure due to Fulminant and Giant Cell Myocarditis

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Abstract
Acute or fulminant nonischemic, dilated cardiomyopathy (DCM) is an uncommon cause for heart failure with a highly variable prognosis that is in part dependent on histopathology and in part on clinical presentation. Once common causes of acute DCM are excluded using standard clinical tests, the specific inflammatory and infectious causes of DCM should be systematically evaluated and treated. Specific histopathologic forms include fulminant lymphocytic myocarditis, which has an excellent prognosis with standard heart failure care. By contrast, giant cell myocarditis, which may be fulminant or acute, has a poor prognosis and frequently requires heart transplantation or immunosuppression for long-term survival. Noninvasive tests that may support the diagnosis of fulminant or acute myocarditis include cardiac magnetic resonance imaging and biomarkers of cardiac injury. Certain clinical, hemodynamic, and echocardiographic variables predict risk of death or transplant in acute myocarditis. This article will compare the presentation, prognosis, and treatment options for several uncommon causes for acute heart failure and suggest certain clinical scenarios in which the likelihood of specific histopathologic disorders is high enough to warrant endomyocardial biopsy if noninvasive tests are inconclusive.

Key Words:
Myocarditis · Dilated cardiomyopathy · Acute heart failure syndrome

Introduction
The syndrome of acute heart failure is frequently associated with a newly diagnosed dilated, hypokinetic left ventricle (DCM) with or without right ventricular dysfunction. Common causes of acute DCM that should be excluded by medical history, physical examination, electrocardiography, echocardiography, and sometimes coronary angiography include acute ischemia, heart rhythm-related, pericardial, valvular, peripheral vascular, congenital, and familial disorders [1]. A careful medical history often reveals that acute heart failure turns out to actually be an acute manifestation of a chronic cardiomyopathy. Once the common disorders are excluded, specific inflammatory and infectious causes for DCM should be considered. These disorders include acute viral myocarditis and a number of idiopathic myocarditis such as the eosinophilic disorders, giant cell myocarditis (GCM), cardiac sarcoidosis (or idiopathic granulomatous myocarditis), and acute lymphocytic myocarditis [2]. Although relatively little is known about the pathogenesis of myocarditis, descriptive clinical studies have revealed a strong correlation between histopathologic forms of myocarditis and prognosis [3].

Fulminant Lymphocytic Myocarditis
Fulminant lymphocytic myocarditis (FLM, Figure 1a) is a clinicopathologic entity defined by the sudden onset of heart failure within 2–3 weeks of a distinct episode of a viral illness [4]. The degree of left ventricular dysfunction is usually severe, and the
patients may be febrile and have an elevated leukocyte count. If supportive care that may include intravenous inotropes, intraaortic balloon counterpulsation, or even a ventricular assist device, can sustain the patient through the acute illness, prognosis is excellent [5].

McCarthy et al. examined 147 patients with myocarditis, 15 of whom had fulminant disease. Transplant-free survival was 93% at 11 years, which was significantly better than the survival for acute lymphocytic myocarditis [5]. The same group performed echocardiography on eleven fulminant and 43 acute myocarditis patients at presentation and determined that the left ventricle is often thick, but not dilated and the ejection fraction is markedly depressed in fulminant myocarditis. Patients with FLM had smaller left ventricular diastolic dimensions (5.3 ± 0.9 cm) with increased septal thickness (1.2 ± 0.2 cm) at presentation, compared to those with acute myocarditis who had increased diastolic diameter (6.1 ± 0.8 cm; p < 0.01 vs. fulminant) and normal septal thickness (1.0 ± 0.1 cm; p = 0.01 vs. fulminant) [6]. Thus, echocardiography, and by extrapolation magnetic resonance imaging, can help distinguish FLM from acute lymphocytic myocarditis.

Amabile et al. recently reported a case series of eleven children with FLM [7]. The median age was 1 year (range 0–9 years), and the mean left ventricular ejection fraction (LVEF) was 22%. A virus was identified in five patients: parvovirus B19 (n = 2), Epstein-Barr (n = 1), varicella zoster (n = 1), and coxsackie (n = 1). All patients received corticosteroids, and seven received intravenous immunoglobulin. Although intravenous inotropic support was required by nine patients, eight were mechanically ventilated, and five experienced cardiocirculatory arrest, the ten survivors were asymptomatic with normalized LVEF. Therefore, FLM in infants seems to have the same excellent prognosis as in adults.

The etiology of FLM and the reasons for the excellent prognosis are not known. The acute inflammation is often presumed to be a response to an acute viral infection because of the association of FLM with viral genomes in children, and high frequency of an antecedent viral illness [5]. Indeed, an extensive body of literature supports the causal relationship between enteroviruses and acute lymphocytic myocarditis [8].

In the clinical setting of FLM, the inflammation that contributes to heart failure may be beneficial by eliminating the virus from the heart. This may be one explanation for the largely negative results of treatment trials (in adults) aimed at altering this acute immune response. Although the concept of successful viral clearance is an attractive paradigm, data to document viral clearance in humans following fulminant, versus acute, myocarditis is lacking. Since the risks of performing serial endomyocardial biopsies (EMB) in patients who have fully recovered after fulminant myocarditis for the sole purpose of determining viral clearance seems not justified, we will likely never know why patients with fulminant myocarditis have such a good prognosis.

However, EMB at the time of presentation in suspected FLM is indicated for two reasons. If lymphocytic myocarditis is present, most adult patients seem to improve with standard care and no immunosuppression. The role for immune therapy with steroids and/or intravenous immunoglobulin in children has not been assessed in controlled trials, but uncontrolled case series suggest an association with good long-term prognosis. EMB may exclude the uncommon and sometimes clinically similar disorders of necrotizing eosinophilic myocarditis (NEM) and GCM which usually respond to the specific therapies discussed below. One important limitation of EMB for lymphocytic myocarditis is the low sensitivity that is likely due to patchy involvement of the myocardium and variability in interpretation [9–11]. Therefore, a normal or nondiagnostic biopsy does not exclude lymphocytic myocarditis.

In the setting of nondiagnostic findings on EMB, cardiac magnetic resonance imaging (CMR) can be useful to guide EMB to areas of active inflammation [12] and to distinguish ischemic from nonischemic acute cardiomyopathy. Laissy et al. prospectively examined 55 patients with a clinical presentation suggestive but not typical of acute myocardial infarction (AMI) with early- and delayed-perfusion CMR to differentiate acute myocarditis from AMI [13]. 31 patients had AMI confirmed by coronary angiography. In AMI patients delayed enhancement demonstrated a smaller number of segmental vascular distributions, while myocarditis patients usually had diffuse or nodular (83%) patchy distribution in a nonsegmental vascular distribution. All of the patients with AMI had segmental distribution of subendocardial defects (p < 0.001) by first-pass perfusion imaging and significantly different distributions (p < 0.001) on delayed enhancement compared to the myocarditis patients. A limitation of this technology is that CMR cannot differentiate histopathologic types of myocarditis that may require specific therapy such as GCM, cardiac sarcoidosis, or NEM.

Most patients with acute (as compared to fulminant) myocarditis have a mild illness with partial or complete recovery of ventricular function. In 109 patients at Massachusetts General Hospital with lymphocytic myocarditis, predictors of death or transplantation included syncope, bundle branch block, and an ejection fraction < 40% [14]. Higher pulmonary artery pressures were associated with a lower transplant-free survival (hazard ratio 1.5 [1.1–2.1];