Fulminant and acute lymphocytic myocarditis: the prognostic value of clinicopathological classification

Myocarditis, characterized by myocardial inflammation, may lead to left ventricular dysfunction, heart failure, arrhythmias, conduction system disorders, and sudden death\(^1\). While lymphocytic infiltration is most common, both eosinophilic\(^2\) and giant cell myocarditis\(^3\) are recognized entities. Lymphocytic myocarditis may result from systemic endocrinological, rheumatological, or toxic disorders\(^4–6\); but is more commonly a manifestation of viral infection, either primarily or secondary to an immune response\(^7\). In the past 15 years, while substantial effort has been expended developing and applying a precise histological classification scheme\(^8\), only a few investigators have addressed the variable clinicopathological syndromes with which patients may present\(^9,10\).

In 1991, our group proposed a clinicopathological scheme of lymphocytic myocarditis based on the similarities between myocarditis and the four syndromes with which viral hepatitis manifests: fulminant, acute, chronic–active, and chronic–persistent\(^9\). Patients with fulminant myocarditis had a very distinct and more favourable natural history than those with acute myocarditis (this group comprising the majority of patients with myocarditis). Patients with fulminant myocarditis (approximately 10% of the total) had a distinct onset of symptoms of short duration prior to presentation with severe congestive heart failure. These patients could date their symptoms to within a 2-day period and often had fever. By contrast, the presentation of acute myocarditis resembled that of adult patients with congestive heart failure, with gradual yet progressive development of fatigue, exercise limitation, and dyspnoea. The only way patients with acute myocarditis could be separated from other forms of cardiomyopathy and heart failure was by endomyocardial biopsy demonstrating lymphocytes with or without myocyte necrosis. The most clinically relevant observation was that fulminant myocarditis patients, although much more ill at presentation had an improved chance of full recovery and long-term survival. At the initial presentation, however, these patients required aggressive haemodynamic support with positive inotropic drugs, intra-aortic balloon pump support, or mechanical left ventricular assistance. In a recent publication comparing the long-term survival of 15 patients with fulminant and 132 with acute myocarditis, we show that 93% of fulminant patients survived with 12 year follow-up compared to 45% of acute patients\(^6\). In a multivariate analysis of predictors of mortality, the adjusted hazard ratio associated with fulminant myocarditis was 0.10 (95% confidence intervals 0.01–0.88, \(P=0.04\)), suggesting that the diagnosis of fulminant myocarditis portended an excellent prognosis. In addition, while seven patients with acute myocarditis underwent heart transplantation, none with fulminant required this procedure\(^6\).

These findings have obvious clinical implications for the small number of patients (estimated by us to be ~200 per year in the United States) with fulminant myocarditis. At our institution, we recognized approximately two cases of this syndrome each year between 1984 and 1998. Community physicians and cardiologists should consider this syndrome in patients with a distinct flu-like illness and the rapid development of signs or symptoms of congestive heart failure. These patients should undergo echocardiography, which shows that patients with fulminant myocarditis have non-dilated left-ventricular chambers, thickened myocardium suggestive of oedema, and decreased fractional shortening\(^11\). Patients with such findings should be referred for urgent endomyocardial biopsy. The detection of fulminant myocarditis compared with other causes of new-onset and severe congestive heart failure may allow separation of patients who are likely to recover dramatically and not require heart transplantation.

In marked contrast to the steady number of patients presenting annually with fulminant myocarditis, the number of patients with acute myocarditis has fallen dramatically at our institution over the past decade. This reduction mirrors the fall in reports of enterovirus infection to the Centers for Disease Control, an epidemiological observation that is consistent with epidemic–pandemic viral infection patterns\(^12\).

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Although the number of patients with acute myocarditis is presently very low at our location, we must consider recurrences and geographic variation. The different patterns of patient presentation suggests that the aetiology of fulminant and acute myocarditis may vary. Possibilities include variable host–immune responses or different viruses\[^{13,14}\]. Alternatively, fulminant myocarditis may represent an autoimmune reaction not related to virus infection at all\[^{15}\].

Where should future research be focused? Given the availability of techniques such as polymerase chain reaction\[^{16}\] and immunological detection of cytokines and cellular epitopes\[^{14}\], it should now be possible to more accurately detect myocardial viral infection and characterize specific immunological reactions. Although the myocarditis treatment trial did not provide evidence that immunosuppression would improve patient outcome\[^{17}\] natural history and research considerations suggest that heart biopsy is valuable for patients with suspected myocarditis. Presently, endomyocardial biopsy is the most definitive procedure given the limitations of sampling error\[^{18}\]. Other techniques may have the potential to aid in the diagnosis but have not been established as equivalent or superior to biopsy\[^{19}\].

A correct diagnosis of myocarditis has important therapeutic implications for individual patients. The pathophysiological understanding of lymphocytic myocarditis in humans will be advanced only by efforts to obtain myocardial specimens that enable the testing of novel pathophysiological or therapeutic hypotheses.

**References**


**J. M. HARE**

**K. L. BAUGHMAN**

*Johns Hopkins School of Medicine*

*Baltimore, Maryland, U.S.A.*