Determining the etiology of cardiac dysfunction in patients with heart failure influences management and prognosis. Myocarditis, diagnosed by the current histopathological Dallas criteria, accounts for 10% of patients with new-onset cardiac dysfunction submitted to endomyocardial biopsy. Despite complete evaluation including history, physical examination, blood work, echocardiography, coronary angiography, and endomyocardial biopsy, 50% of patients with dilated cardiomyopathy have no etiology identified. Recent data suggest that patients in the "idiopathic" category may be suffering from myocardial inflammation due to persistent viral replication or autoimmune activation after a viral infection. These studies raise the question of whether the current histopathological criteria for myocardial inflammation (the Dallas criteria) are sensitive enough to identify the population with viral or autoimmune-related heart compromise.

The Dallas criteria were proposed in 1986 and provided a histopathological categorization by which the diagnosis of myocarditis could be established. Dallas criteria myocarditis requires an inflammatory infiltrate and associated myocyte necrosis or damage not characteristic of an ischemic event. Borderline myocarditis requires a less intense inflammatory infiltrate and no light microscopic evidence of myocyte destruction. These criteria have been used exclusively by American investigators over the last 2 decades. Sampling error, variation in expert interpretation, variance with other markers of viral infection and immune activation in the heart, and variance with treatment outcomes all suggest that the Dallas criteria are no longer adequate.

Chow et al and Hauck et al demonstrated by biopsying postmortem hearts of patients who had died with myocarditis that, from a single endomyocardial biopsy, histological myocarditis could be demonstrated in only 25% of samples. With >5 biopsies, Dallas criteria myocarditis could be diagnosed in approximately 10% of samples. A recent MRI study used focal imaging abnormalities to guide heart biopsy investigation of possible myocarditis. The authors showed that the earliest myocardial inflammatory abnormalities were evident in the lateral wall of the left ventricle, and only these sites revealed myocarditis by histological examination. Therefore, there is considerable sampling error associated with establishing the diagnosis of myocarditis.

In addition, there are variations in the interpretation of histological samples. Of the 111 patients included in the Myocarditis Treatment Trial diagnosed with myocarditis by heart biopsy, only 64% had that diagnosis confirmed by the expert pathology panel who reviewed the histopathological material. In a separate analysis, 7 expert pathologists’ interpretations of histopathological findings from endomyocardial biopsies of 16 patients with dilated cardiomyopathy varied remarkably in the assessment of significant fibrosis (25% to 69%), hypertrophy (19% to 88%), nuclear changes (31% to 94%), lymphocyte count per high-power field (0% to 38%), and the diagnosis of myocarditis. Definite or probable myocarditis was diagnosed in 11 of 16 patients by at least 1 pathologist. However, of the 11 patients, 3 of 7 pathologists agreed on the diagnosis of myocarditis in 3 patients, and 2 of 7 pathologists agreed on the diagnosis of myocarditis in 5 patients. Therefore, even expert observers do not agree on the interpretation of histopathological material that has undergone routine staining.

Myocarditis may be associated with a number of conditions including HIV/AIDS, ischemia, and inflammatory states such as sarcoidosis and immune disease such as lupus erythematosus. Excluding causes of myocardial inflammation of known etiology allows investigators to address the larger and more important category of patients with "primary" (or postviral) myocarditis. Primary viral myocarditis includes several forms of myocarditis that are defined by their clinical pathological manifestations. These include fulminant, chronic active, eosinophilic, and giant cell myocarditis. Fulminant myocarditis has a distinct onset usually within 2 weeks of presentation. Patients present with profound left ventricular dysfunction but usually not left ventricular dilatation. The endomyocardial biopsy shows multiple foci of active inflammation and necrosis. Patients recover or die within 2 weeks with complete histological and functional recovery of the myocardium in survivors. Chronic active myocarditis has an indistinct onset with moderate ventricular dysfunction on presentation and active or borderline myocarditis by biopsy. These patients display ongoing inflammation and fibrosis resulting in the development of a restrictive cardiomyopathy usually 2 to 4 years after presentation. Eosinophilic myocarditis may be attributed to eosinophilic syndromes or allergic reactions resulting in left ventricular compromise.
with eosinophil and myocyte damage demonstrated by endomyocardial biopsy. These patients respond to treatment of the eosinophilic disorder and/or withdrawal of the offending agent. Patients with giant cell myocarditis present with congestive heart failure, ventricular arrhythmias, or heart block. Despite institution of medical therapy, patients with giant cell myocarditis continue to have poorly controlled congestive heart failure or ventricular arrhythmias. Untreated, patients will die in <6 months. Patients have a characteristic endomyocardial biopsy with giant cells and active inflammation that may respond to aggressive immunosuppressive therapy. Therefore, several forms of myocarditis are characterized by their clinical pathological manifestations. The largest population of patients presenting with subacute myocardial deterioration is indistinct from patients presenting with idiopathic cardiomyopathy.

A number of investigators have shown that virus may be present in the myocardium without Dallas criteria myocarditis. Martin et al demonstrated in 34 children with clinical presentations compatible with myocarditis that 26 heart biopsy samples were positive for viral pathogens, and 13 of the 26 positive samples had no evidence of myocarditis by histopathological examination. Other investigators have confirmed the presence of viral pathogens in samples of cardiac tissue from patients with cardiomyopathy and myocarditis. Pauschinger et al found 24 of 94 patients with idiopathic dilated cardiomyopathy to have either adenoviral or enteroviral polymerase chain reaction positivity. A meta-analysis of polymerase chain reaction studies in patients who had heart biopsies with presumed myocarditis or cardiomyopathy demonstrated an odds ratio of 3.8 for viral presence in both categories compared with control patients. In a selected sample of 45 patients with left ventricular dysfunction and suspected myocarditis and 26 controls, nonreplicative enterovirus was demonstrated in 18 of 45 patients (40%) compared with none of the controls. Of the 18 patients with nonreplicative virus, 10 (56%) were found to have active viral replication as well (strand negative). Why et al discovered in 120 patients with idiopathic dilated cardiomyopathy that the 34% who were enteroviral positive had a significantly worse outcome over 2 years (P=0.02) compared with those who were enteroviral negative. Therefore, virus can exist in the myocardium (even in a replicative form) in the absence of myocardial inflammation adequate to meet Dallas criteria and may adversely affect outcome.

There is also dissociation between Dallas criteria myocarditis and response to immune modulation therapy. In the Myocarditis Treatment Trial, there was no difference in the 1- or 5-year survival or 28-week ejection fraction in patients with Dallas criteria myocarditis treated with immunosuppressive therapy or placebo. Other authors have used alternative criteria to diagnose immune-related heart disease. Wojnicz et al found 84 of 202 patients with new-onset cardiomyopathy to be HLA positive, while only 27% were positive by Dallas criteria for myocarditis. HLA has previously been shown to be upregulated in patients with myocarditis and is less “focal” than lymphocytic infiltration. HLA-identified patients were treated with immunosuppressive therapy or placebo. Although there was no difference in primary outcome (death, transplant, or hospitalization), the ejection fraction in the immunosuppressive group increased from 24% to 36%, whereas it remained stagnant in the placebo group (25% to 27%). Even in patients demonstrating Dallas criteria myocarditis, response to treatment may be influenced by the presence of virus or immunological response to infection. Frustaci et al identified Dallas criteria myocarditis in 112 of 652 patients with new-onset heart failure. Forty-one of the 112 had progressive congestive heart failure despite standard medical therapy. These patients were treated with prednisone and azathioprine for 6 months. Twenty responded, and 21 failed to respond. Those responding increased their ejection fraction from 23% to 47%, whereas the ejection fraction of the nonresponders remained stable. Those who responded had evidence of antihuman antibodies (90%) versus nonresponders (0%). Those who failed to respond displayed viral persistence in heart tissue (84% of patients), whereas only 13% of responders had viral persistence. Therefore, the presence of Dallas criteria myocarditis does not identify patients who respond to immune modulation therapy. Evidence of viral persistence may imply a worse prognosis and identify patients who fail to respond to immunosuppressive therapy. Alternatively, patients with immune activation, demonstrated by HLA upregulation or antihuman antibodies, may respond to immunosuppressive therapy despite absence of Dallas criteria myocarditis.

Defining the etiology of the 50% of patients currently labeled as idiopathic with new-onset heart failure is critical to determining their outcome and treatment options. We must now redefine the diagnosis of viral and postviral immune-related heart dysfunction. This classification should include clinicopathological entities such as fulminant, chronic persistent, eosinophilic, and giant cell myocarditis that are easily recognized by their clinical course and/or histology on heart biopsy. Those without distinct clinical pathological manifestations encompass a much broader category and will include patients with viral persistence and immune upregulation. With this approach, we may identify clinical pathological correlates and natural history of disease specific for a given virus.

McNamara et al and Mason et al demonstrated that some patients with new-onset left ventricular compromise display significant recovery of ventricular function with or without histological evidence of myocardial inflammation by the Dallas criteria. The ability to modify the outcome of those who fail to improve spontaneously or to enhance the recovery of those who increase their ejection fraction may significantly alter the prognosis of this population and lessen the burden of chronic disabling heart failure that they otherwise will face.

The time has come to redefine viral and autoimmune heart disease with the use of methodologies available in the 21st century. Clinicians, pathologists, immunologists, and molecular cardiologists must contribute to the new criteria, which should include clinical presentation, histopathology, immunohistochemistry, viral polymerase chain reaction, cardiac antibody assessment, and imaging results.

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