Distinct Forms of Myocarditis

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The study by Davidoff and colleagues in this issue of Circulation is helpful because it establishes clinically useful distinctions between two forms of myocarditis. In thinking about etiologies of myocarditis, I find it helpful to consider six categories. The first, viral myocarditis, is caused by ongoing myocardial infection, such as by coxsackievirus B3 or mumps virus. All other infectious causes form the second category. Chagas’ disease (Trypanosoma cruzi), toxoplasmosis, and diphtheria are examples. Among these, only Chagas’ myocarditis is common, and it might be the most common etiology of myocarditis throughout the world. The third category is hypersensitivity to drugs and other exogenous agents. This is rare. The fourth category is autoimmune, which is more common and includes myocarditis associated with systemic lupus erythematosus, Kawasaki syndrome, and probably at least some if not most instances of peripartum myocarditis. The fifth category is lymphocytic myocarditis. This might also be called post–viral myocarditis because a history of a recent viral syndrome can be elicited in a fairly large minority of cases, but it should be distinguished from the category of active viral myocarditis. Many experts believe that it usually results from a pathological immune response to recent viral infection (which might often be subclinical). It might be more accurate to name this category “idiopathic myocarditis” because the precise etiology is not known for certain. However, the term “lymphocytic myocarditis” has the advantage of providing a description of the histological findings in this type of myocarditis, which is by far the most common form detected by endomyocardial biopsy in North America. When cardiologists use the term “myocarditis,” they are generally referring to this category of the disease. The sixth category is giant cell myocarditis. Though its cause is also unknown, its histological appearance is distinct, and Davidoff and colleagues1 have confirmed that its clinical course is distinct from that of lymphocytic myocarditis.

The course of giant cell myocarditis observed by Davidoff et al1 was strikingly worse than that of lymphocytic myocarditis. Only 20% of patients with giant cell myocarditis, compared with 70% with lymphocytic myocarditis, were known to be alive and to have not required cardiac transplantation at the time of follow-up, despite a 30% longer period of follow-up in the latter group. Subjects with giant cell myocarditis were more likely to have ventricular tachycardia and to require a permanent pacemaker. They experienced a decline in left ventricular function over time, while the group with lymphocytic myocarditis did not.

The latter observation is important. It is common for patients with lymphocytic myocarditis to spontaneously improve.2 A wait-and-see approach is prudent, except, perhaps, in those cases presenting with cardiogenic shock or advanced congestive failure and cardiac dilatation. This same approach might not be appropriate in patients with giant cell myocarditis. Davidoff et al1 did observe a better outcome in this condition than previously reported, but the outcome was not good. Although scientifically satisfactory evidence cannot be cited, I recommend a trial of immunosuppressive therapy in patients with giant cell myocarditis because the condition might have an immunological basis and without intervention the outcome is usually unsatisfactory.

What are giant cells? There is considerable controversy.3–7 Morphologically, they are large, multinucleated cells. They are usually found next to (and possibly attached to) myocytes. Investigators using a variety of intracellular probes have found these giant cells to have characteristics of macrophages. Others have failed to identify those characteristics, even with the use of the same probes. However, to date no probes used on tissue from patients with giant cell myocarditis are perfectly sensitive in detecting macrophages. Some investigators have found myocardial components such as myoglobin in giant cells, suggesting a myocardial origin of the cells, while other researchers have not. One way to reconcile these conflicting observations is to accept the histiocytic or monocytic origin of giant cells in myocarditis and view the occasional presence of myocardial constituents to be a result of phagocytosis of myocytes by the macrophages. Even with these assumptions, however, the pathogenic mechanisms responsible for giant cell myocarditis remain to be elucidated. Because the disease has been seen in association with numerous

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conditions known to be due to disordered immunity (such as ulcerative colitis, myasthenia gravis, systemic lupus erythematosus, myositis, Sjögren’s syndrome, giant cell arteritis, thymoma, dermatomyositis, pernicious anemia, and chronic active hepatitis), it seems almost certain that giant cell myocarditis has an autoimmune etiology. Perhaps it is an unusually aggressive form of lymphocytic myocarditis, the aggressiveness accounting for appearance of giant cells. Even if this speculation were correct, the finding of giant cells on biopsy should trigger a much more assertive clinical response than the finding of lymphocytes alone.

A few more points regarding the study by Davidoff and colleagues should be made. Although they provided a rationale for combining cases with and without systemic sarcoidosis, it would be incorrect to assume that the two groups are really clinically equivalent, or that they have the same etiology. Most previous authors have separated the two disorders. The increased statistical power Davidoff et al gained by grouping the two diseases might serve to misinform more than clarify. In this regard, it might be especially important to remember that the response of cardiac sarcoidosis to immunosuppressive therapy has been shown to be impressive, while responses of giant cell myocarditis are less so. Uncertainty about the use of immunosuppression in the latter condition should not discourage clinicians from its application in the former.

Though they suggest it, Davidoff et al are not providing a natural history study of giant cell myocarditis. Nine of the 10 subjects received immunosuppressive therapy, and many received additional therapies such as pacemaker implantation, pharmacological treatment of congestive heart failure, and cardiac transplantation. Thus, a 50% actuarial survival at 4 years probably does not accurately depict the natural course of this disease.

There are several points that deserve emphasis in the article by Davidoff and associates. Both lymphocytic and giant cell myocarditis can be detected by endomyocardial biopsy. They are among the most common of six distinct types of myocarditis. The former is relatively benign, so that potentially risky therapy need not be applied urgently, while the latter is an aggressive condition and should be treated promptly. Research is needed to further define pathogenesis and treatment of both disorders.

References
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