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Myocarditis and Idiopathic Dilated Cardiomyopathy

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Idiopathic dilated cardiomyopathy (IDC) accounts for 25% of cases of heart failure in the United States. Understanding the relationship between an inciting event or agent and the development of IDC has progressed only recently. Once IDC has developed, treatment is palliative and little can be done to alter the natural course of the disease. Active myocarditis, a suspected precursor of IDC, is myocardial inflammation and injury without ischemia. The disease ranges from a self-limited flulike illness to one of serious consequence with arrhythmias, heart failure, or death. Many agents have been associated with myocarditis, and the clinical manifestations depend on an interplay between the inciting agent and the host response. The development of a murine model and the expanded use of endomyocardial biopsy using the Dallas criteria have increased our understanding of myocarditis and its sequelae. Therapy consists of managing symptoms using conventional medical regimens for heart failure. Immunosuppressive therapy should be reserved for patients with biopsy-proven disease who have failed conventional therapy. Continued deterioration warrants ventricular assistance and consideration of cardiac transplantation.

More than 3 million people in the United States are affected by heart failure, with more than 750,000 new cases diagnosed and 250,000 deaths each year.[1] The economic effect is great: The expenditure of approximately $38 billion dollars in 1991 represented 5.4% of federal health care dollars spent that year. The true impact of the additional disability and loss of productivity has not yet been calculated. Idiopathic dilated cardiomyopathy (IDC)—namely, left ventricular dilation and systolic dysfunction in the absence of coronary, valvular, or congenital heart diseases—accounts for 25% of these cases.[2] Progress has only recently been made, however, in our understanding of the relationship between the inciting event or agent and the development of IDC. Regrettably, once it has developed, the treatment is palliative and little can be done to alter the natural history if the precipitating factors are persistent.

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Active myocarditis, a suspected common precursor of IDC, is defined as inflammation and injury of the myocardium in the absence of ischemia.[3] The spectrum of disease varies from a benign, self-limited flulike illness to one of serious consequence manifested by arrhythmias, heart failure, or death. Many agents (**Table I**) have been associated with active myocarditis, and the clinical manifestations depend on an interplay between the inciting event or agent and host response. Progress has been made in understanding the mechanisms that result in clinical disease, and they have been the focus of intense investigation. Myocardial injury may result from one or more of the following: myocyte infection with replication of the offending agent resulting in cellular destruction; destruction due to activated cellular or humoral defense mechanisms, or both, triggered by the infectious agent; exogenous toxins produced by the pathogen; and coronary endothelial invasion resulting in microvascular spasm.[2,4]

PATHOGENESIS

Woodruff[5] reported that myocardial infection occurred when coxsackievirus B3 (CVB3), the most commonly identified cause of human myocarditis in the immunocompetent host, was injected into weanling mice. Replicating virus was obtainable for 7 to 9 days after inoculation, but evidence of heart failure was absent during this phase, as was histologic evidence for inflammation. Histologic examination of Swiss ICR mice infected with CVB3 6 months earlier showed persistent inflammation and early signs of heart failure. By 15 months, there was no histologic evidence for inflammation, although heart failure had developed with mural thrombosis and left ventricular dilatation.[6]

Data obtained from murine models imply that myocardial damage occurs in two phases. The first, or acute phase, involves myocardial cell infection with replication and cell lysis, with the virus being cleared by macrophages, natural killer cells, and neutralizing antibodies. The second, or chronic phase, involves myocardial infiltration by inflammatory cells and production of cardiotropic antibodies. Myocardial damage may be minimal or severe (**Figure 1**).

Viral clearance is unaffected during the acute phase if antithymocyte serum is administered to BALB/c mice, but the progressive inflammatory response is attenuated.[7] Cell-mediated immune responses, rather than humoral, are more important during the chronic

TABLE I

Myocarditis-Inducing Agents

- Infectious agents
  - Viral agents
    - Coxsackievirus (A, B)
    - ECHO
    - Influenza (A, B)
    - Polio
    - Herpes simplex
    - Varicella-zoster virus
    - Epstein-Barr virus
    - Cytomegalovirus
    - Mumps
    - Rubella
    - Rubeola
    - Vaccinia
    - Coronavirus
    - Rabies
    - Hepatitis B
    - Arbovirus
    - Junin virus
    - Human immunodeficiency virus
  - Bacterial, rickettsial, spirochetal agents
    - *Corynebacterium diphtheriae*
    - *Salmonella typhi*
    - ß-Hemolytic streptococci
    - *Neisseria meningitides*
    - *Legionella pneumophila*
    - *Listeria monocytogenes*
    - *Campylobacter jejuni*
    - *Coxiella burnetii* (Q fever)
    - *Chlamydia trachomatis*
    - *Mycoplasma pneumoniae*
    - *Chlamydia psittaci* (psittacosis)
    - *Rickettsia rickettsii* (Rocky Mountain spotted fever)
    - *Borrelia burgdorferi* (Lyme disease)
    - *Mycobacterium tuberculosis*
  - Protozoal agents
    - *Trypanosoma cruzi* (Chagas' disease)
    - *Toxoplasma gondii*
  - Metazoal agents
    - Trichinosis
    - Echinococcosis
  - Fungal agents
    - Aspergillosis
    - Blastomycosis
    - Candidiasis
    - Coccidioidomycosis
    - Cryptococcosis
    - Histoplasmosis
    - Mucormycosis
- Toxic agents
  - Anthracyclines
  - Catecholamines
  - Interleukin-2
  - Interferon alpha-2
- Hypersensitivity

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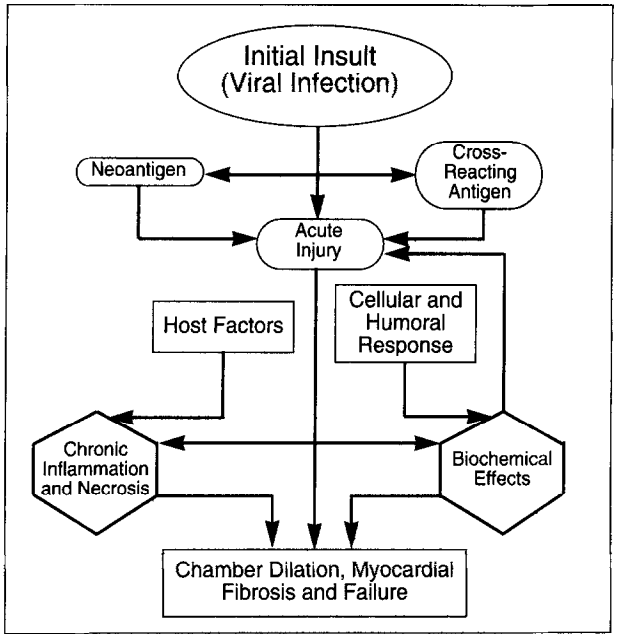

Figure 1. Paradigm of myocardial injury resulting from viral infection.

phase of the disease in this model. Recent studies have suggested that the stimulus for this cell-mediated response is either a neoantigen located on myocardial fibroblasts or an autoimmune cytotoxic T-cell response.[2,8] Humoral immune responses may play a role in myocyte injury and dysfunction by development of autoantibodies to the ß-receptor, myosin, and the adenosine diphosphate-adenosine triphosphate (ADP-ATP) carrier protein.[9-11] Thus a viral infection, although clinically quiescent, triggers an autoimmune cellular, and possibly humoral, response leading to myocardial inflammation and necrosis, which eventually culminate in a pathophysiologic state similar to IDC. Myocarditis leads to IDC in this murine model.

Observations of increased enteroviral antibody titers in patients with myocarditis or IDC have traditionally been offered as evidence that enteroviruses are the causative agents.[12] Unfortunately, enteroviral infections are common in the general population, and it has been difficult to ascertain if acute and convalescent titers coincide with the onset of heart dysfunction. Fletcher and colleagues[13] found 34% of their patients with IDC had coxsackievirus B viral titers 1:40, but unfortunately this was the same incidence found in controls. Cambridge and colleagues[14] found that if the level of viral titers used as a cutoff point is increased to 1:1,024, 30% of patients had abnormal levels as opposed to 2% of controls. Similar results were obtained by Kitaura[15] in Japan, who found a significantly greater proportion of patients with IDC had coxsackievirus B1 titers greater than 1:16 when compared with controls. These two studies suggest that patients with IDC have a greater prevalence of coxsackievirus B infection than the general population. On the other hand, infection with cardiotropic viruses is extremely common, and most adults have been exposed to them and may even have experienced subclinical myocarditis, yet did not develop IDC.

Despite these compelling data, the association between enteroviral infection and myocarditis was

TABLE II
Clinical Features of Active Myocarditis

Symptoms
Chest discomfort, frequently nonspecific
Shortness of breath
Palpitations
Flulike syndrome
Signs
Tachycardia
Irregular pulse
Transient gallop
Elevated jugular venous pressure
Laboratory findings
Electrocardiographic changes, including ST segments, heart block
Increased creatine kinase-MB
Increased erythrocyte sedimentation rate
Increased white blood cell count
Dilated myocardial chambers per echocardiogram
Cardiomegaly per chest roentgenogram

largely inferential. Successful viral culture from myocardium of patients with IDC is so uncommon that a positive culture in an immunocompetent host is reportable. Identification of enteroviral acid in myocardial tissue provides more direct evidence that these viruses initiate myocarditis. Advances in molecular biology have introduced new techniques to detect viral genomes. The most commonly used techniques are slotblot or in situ hybridization and polymerase chain reaction.

Bowles and associates[16] and Archard and coworkers[17] reported that coxsackie-genomic sequences were detected using a CVB2-specific probe and slotblot hybridization in more than 50% of human hearts with biopsy-proven active or healing myocarditis or IDC. Although questions about the specificity of the probe arose, making the data difficult to interpret, this was the first study implicating the persistence of the enterovirus. Several investigators using in situ hybridization to detect enteroviral genomes in myocardial tissue suggested 18% to 53% of patients with myocarditis may have myocardial enteroviral infection.[12] Intriguing questions are left unanswered. To date, the capability of these genomes to replicate as intact viruses has not been demonstrated. It has been suggested that these genomes are nonreplicating defective viral fragments and may be immunogenic or mere markers of previous infection. The answers await further study.

Some investigators have suggested that microvascular spasm may play a role in the development of myocardial damage. In this hypothesis, endothelial cell infection or damage from the resultant immune response leads to the microvascular abnormality. Sole and Liu[2] suggest that repetitive cycles of microvascular spasm lead to dissolution of myocardial matrix and that a multifocal loss of cardiac muscle ultimately leads to myocardial failure. The precise role of microvascular spasm and its impact on the development of myocarditis is as yet unresolved.

CLINICAL MANIFESTATIONS

The clinical expression of myocarditis is a spectrum of disease ranging from an asymptomatic state to progressive deterioration of cardiac function and ultimately death. Occasionally a patient may present with acute unexplained heart failure, and the diagnosis is suspected only after other more common etiologies are excluded. The natural history of the disease is poorly described and unpredictable. Some patients have complete resolution of symptoms and suffer no sequelae. Others progress to fulminant heart failure. The development of heart failure, which may be the first clinical manifestation, typically occurs late in the disease and is clinically indistinguishable from IDC. Sudden death may also be an early manifestation of myocarditis, but can occur at any stage of the disease. The exact timing from infection to cardiac dysfunction is variable.

Complaints at presentation may include fatigue, shortness of breath, dyspnea on exertion, palpitations, and precordial discomfort.[18] A flulike syndrome often antedates cardiac symptoms, but is usually forgotten by the patient. Physical examination is nonspecific and frequently unrevealing. Tachycardia, out of proportion to heart failure, is common. Distant heart sounds and a transient gallop or a systolic murmur, or both, may be present. Fulminant cases reveal findings consistent with heart failure.

Fever, leukocytosis, and an elevated erythrocyte sedimentation rate (>60) are frequent but nonspecific laboratory findings (**Table II**).[19] Variable and transient electrocardiographic changes may be noted, with ST-segment and T-wave abnormalities being the most frequent. Rhythm disturbances, including atrial and ventricular arrhythmias, are common. Conduction defects are common, and more than 20% of patients have left bundle branch block.[20] Although usually transient without sequelae, atrioventricular block can be a cause of sudden death in patients with acute myocarditis.

In patients with clinical heart failure and myocarditis, nonspecific findings such as left ventricular systolic dysfunction, enlarged left ventricular cavity size, and increased wall thickness and wall motion abnormalities may be seen on echocardiography. Left ventricular thrombi are detected in 15% of patients. Radiographic findings range from normal heart size to cardiomegaly, with pulmonary congestion seen in more severe cases. Radionuclide scanning using gallium-67 or indium-111 antimyosin antibody may reveal inflammation or necrosis suggestive of myocarditis, but these tests lack the necessary sensitivity and specificity to be applied as screening tools.[20]

Some patients experience a clinical syndrome consistent with myocardial infarction with typical chest pain, ST-T segment changes, wall motion abnormalities, enzyme alterations, and even Q-wave development, but have normal coronary arteries angiographically.[21] In these patients, endomyocardial biopsy may be appropriate to confirm myocarditis-associated necrosis.

DIAGNOSIS

The diagnosis of myocarditis may be suggested by the clinical manifestations, but frequently follows only after other etiologies are ruled out. It is more readily considered in young, previously healthy patients, but is more problematic in older patients with multiple comorbid illnesses that may predispose them to or result in cardiac dysfunction. Frequently these patients undergo an exhaustive workup culminating in angiography and myocardial biopsy before the diagnosis is made.

Serologic evidence, such as a fourfold rise in viral neutralizing, complement fixation, or hemagglutination-inhibition titer is supportive but not confirmatory of the diagnosis of viral myocarditis.[18] The virus may occasionally be cultured from stool, blood, urine, or throat washings, but again only suggests a causative agent.

Confirmatory evidence of active myocarditis is only established by endomyocardial biopsy. Right ventricular biopsy from the right internal jugular or femovenous approach is preferred by most cardiologists. Left ventricular biopsy may be warranted, however, if suspicion of myocarditis is high and right ventricular biopsy did not confirm active myocarditis because of suspected sampling error. Although endomyocardial biopsy was used for IDC or suspected cases of myocarditis prior to 1986, a lack of histologic standards frequently led to differences in interpretation by individual pathologists. In preparing for the multicenter Myocarditis Treatment Trial, a group of expert pathologists convened at a consensus conference and established the Dallas criteria. These criteria define inflammatory heart disease as active myocarditis, borderline myocarditis, or no myocarditis. Active myocarditis is defined by myocardial leukocyte infiltration with necrosis in the absence of ischemia. Borderline myocarditis involves infiltration without necrosis; this specific diagnosis cannot be made when inflammatory cells are not seen. The adoption of the Dallas criteria has led to 90% concordance among experienced pathologists,[22] and although myocarditis cannot be ruled out by biopsy because of sampling error in patients with focal disease, the diagnosis now can be made with a high degree of confidence.

TABLE III

Management of Myocarditis-Induced Congestive Heart Failure

Rest
Salt and fluid restriction
Digitalis glycosides
Angiotensin-converting enzyme inhibitors
Diuretics
Anticoagulants
Antiarrhythmics
Immunosuppression (controversial)

TREATMENT

The primary focus of the initial management of IDC is relief of symptoms of heart failure (**Table III**). Patients with volume overload should be treated with diuretics and sodium and water restriction. Angiotensin-converting enzyme (ACE) inhibitors should be initiated in all patients with systolic dysfunction who tolerate these agents. The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) showed that patients with New York Heart Association classes III and IV symptoms had improved survival when treated with enalapril.[23] The Studies of Left Ventricular Dysfunction (SOLVD) study showed that patients with less severe disease also benefited.[24] For those patients intolerant of ACE inhibition, the Veterans Heart Failure Trial (VeHFT I and II), which concluded that hydralazine and isosorbide dinitrate in combination improve outcome but to a lesser degree than ACE inhibition, may be important.[25,26]

Digitalis glycosides are commonly administered, although close monitoring is necessary to avoid digitalis toxicity. In refractory patients, the short-term use of dobutamine may be beneficial. In the murine models, forced physical activity enhanced the myocyte necrosis and inflammatory response resulting in increased mortality. Even though confirmatory studies have not been performed in man, it is wise to restrict physical activity.

The decision to treat ventricular arrhythmias, a life-threatening complication that may occur even with minimal left ventricular dysfunction, is difficult. Myocarditis may resolve spontaneously or respond to immunosuppression with a reduction in the risk of further arrhythmias.[27] Antiarrhythmic agents and immunosuppressive therapy both have substantial side effects. If myocarditis persists, the rationale for antiarrhythmic agents is clearer. Treatment with an automatic implantable cardioverter defibrillator or amiodarone should be reserved for life-threatening situations because of a high likelihood of spontaneous improvement.

Corticosteroids have frequently been used in the treatment of myocarditis, but the benefit is unproven.

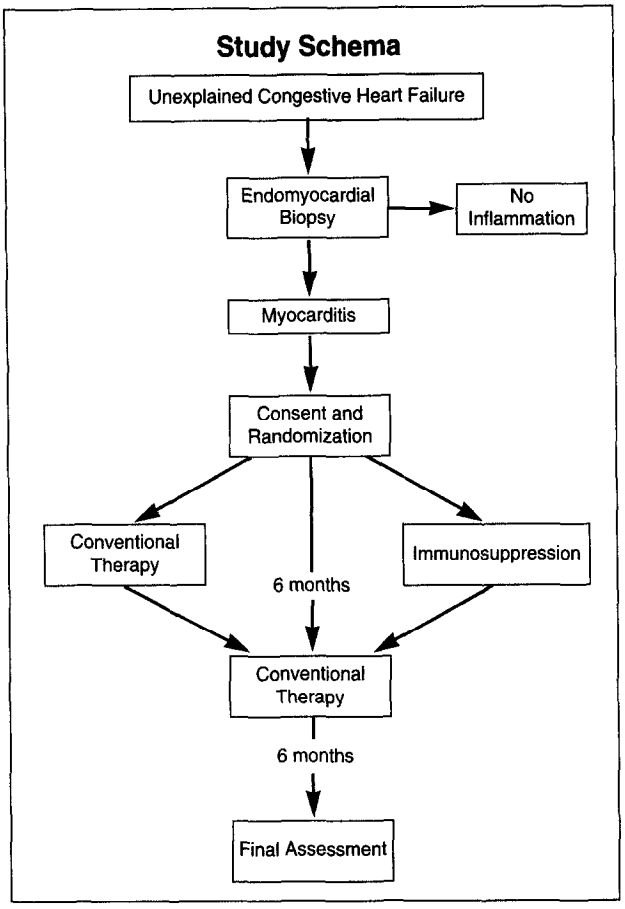

Figure 2. Myocarditis Treatment Trial study design. (From O'Connell JB, Mason JW,[31] with permission.)

Preliminary studies that followed the expanded application of endomyocardial biopsy for detection of cardiac allograft rejection to include patients with unexplained heart failure resulted in a therapeutic dilemma for clinicians. Interest increased in therapeutic modalities that modify the immune mechanisms felt to be responsible for the inflammation identified by biopsy. Corticosteroids and other immunosuppressive drugs were reported as beneficial for patients with biopsies positive for myocarditis. Although the studies were uncontrolled and therapy was not standardized, the optimistic results enhanced the broad use of immunosuppressive drugs in active myocarditis.

The NIH-sponsored multicentered Myocarditis Treatment Trial was established to evaluate the efficacy of immunosuppression in the treatment of active myocarditis.[19] Patients with ejection fractions below 45%, unexplained heart failure, and biopsy-proven myocarditis (Dallas criteria) were randomized to conventional treatment for heart failure alone or to conventional treatment with prednisone combined with cyclosporine or azathioprine. Patients were observed for 6 months on randomized drug treatment and for another 6 months on conventional treatment alone before the final evaluation at 1 year (**Figure 2**). Enrollment began in 1986 and was completed in 1990.[28]

Ejection fraction, exercise treadmill testing, endomyocardial biopsy, right heart hemodynamics, electrocardiogram, 24-hour ambulatory monitoring, and echocardiography were performed at baseline and at 12, 28, and 52 weeks. Peripheral blood was collected for lymphocyte subsets, natural killer cell activity, antibody-dependent cellular cytotoxicity, and for humoral antibodies. Endomyocardial biopsies were studied for lymphocyte subsets, antibodies, and enteroviral genomes.[28] The results of the trial are currently being analyzed and will shed light on the efficacy of immunosuppression (see addendum). At this time, immunosuppression cannot be recommended unless the patient is deteriorating rapidly despite conventional medical management.

Some patients experience continued hemodynamic deterioration despite maximal pharmacologic maneuvers. A substantial percentage of these patients have a potential for reversibility of their condition if kept alive with mechanical ventricular assistance.[29] Regrettably, there are no clinical indicators such as biopsy findings, immunologic testing, other laboratory findings, or severity of hemodynamic dysfunction to assist in predicting eventual outcome and the likelihood of spontaneous recovery.

Cardiac transplantation should be considered in patients who progress to refractory heart failure and show no benefit from a trial of immunosuppression. Nevertheless, the high spontaneous recovery rate even with extreme degrees of left ventricular decompensation has prompted a recommendation for prolonged mechanical support if necessary, with adequate time for recovery before considering transplantation. Unfortunately, patients undergoing transplantation for active myocarditis have a 1-year survival, which is poorer than patients transplanted for other reasons (58% versus 82%, respectively),[30] and have a rejection rate twice that of control recipients. The poor outcome following transplantation may be due to the intense immunologic activity targeting cardiac antigens prior to transplantation, predisposing to early rejection. Beyond the early posttransplantation period, the survival rate is indistinguishable from that of other recipients.

SUMMARY

The development of a murine model and the expanded use of endomyocardial biopsy using the Dallas criteria have broadened our understanding of myocarditis and its sequelae. A high index of suspicion by the clinician is essential for the correct diagnosis. Numerous tests are available to support the diagnosis, but endomyocardial biopsy remains the gold standard. Therapy is directed toward the manage-

ment of symptoms using conventional medical regimens for heart failure. Although controversial, immunosuppressive therapy should be reserved for patients with biopsy-proven disease who have failed conventional therapy. Continued deterioration warrants ventricular assistance and consideration for cardiac transplantation. Further elucidation of the use of endomyocardial biopsy and immunosuppressive therapy awaits the final results of the Myocarditis Treatment Trial. Undoubtedly, further advances in our understanding of the pathophysiology will have the greatest impact on altering the disease process.

ADDENDUM

Since acceptance of the manuscript, the Myocarditis Treatment Trial Results were reported.[32] The investigators could not demonstrate a difference in outcome in patients receiving immunosuppression. Publication of these results does not alter the conclusion of this manuscript.

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