IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 16, Issue 4 Ver. II (April. 2017), PP 13-18
www.iosrjournals.org

Myocarditis-A Quick Review

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Myocarditis(Inflammation Of The Heart)

It can result from multiple causes but most commonly attributed to infective agents that can injure the myocardium through direct invasion, production of cardiotoxic substances, or chronic inflammation with or without persistent infection. Myocarditis may present with a wide range of symptoms, ranging from mild dyspnea or chest pain that resolves without specific therapy to cardiogenic shock and death. Dilated cardiomyopathy with chronic heart failure is the major long-term sequela of myocarditis. Most often, myocarditis results from common viral infections; less commonly, specific forms of myocarditis may result from other pathogens, toxic or hypersensitivity drug reactions, giant-cell myocarditis, or sarcoidosis. The prognosis and treatment of myocarditis vary according to the cause, and clinical and hemodynamic data usually provide guidance to decide when to refer a patient to a specialist for endomyocardial biopsy. The aim of this review is to provide a practical and current approach to the evaluation and treatment of suspected myocarditis.

Definition

The standard Dallas pathological criteria for the definition of myocarditis require that an inflammatory cellular infiltrate with or without associated myocyte necrosis be present on conventionally stained heart-tissue sections[1]. These criteria are limited by variability in interpretation, lack of prognostic value, and low sensitivity, in part due to sampling error[2,3]. These limitations have led to alternative pathological classifications with criteria that rely on cell-specific immunoperoxidase stains for surface antigens, such as anti-CD3, anti-CD4, anti-CD20, anti-CD68, and anti–human leukocyte antigen[4,5]. Criteria that are based on immunoperoxidase staining have greater sensitivity and may have prognostic value.[6] Preliminary studies suggest that noninvasive cardiac magnetic resonance imaging (MRI) may provide an alternative method for diagnosis without the risks of biopsy. For example, regions of myocarditis are reported to correlate closely with regions of abnormal signal on cardiac MRI.[7,8] The lack of consensus regarding the value of invasive studies such as endomyocardial biopsy and the overall good prognosis for patients with mild, acute dilated cardiomyopathy who have suspected myocarditis have led to recent recommendations that endomyocardial biopsy should be considered on the basis of the likelihood of finding specific treatable disorders.[9]

Clinical Features And Incidence

Acute myocarditis is frequently first diagnosed as nonischemic dilated cardiomyopathy in a patient with symptoms that have been present for a few weeks to several months. However, manifestations range from subclinical disease to sudden death, with new-onset atrial or ventricular arrhythmias, complete heart block, or an acute myocardial infarction–like syndrome. Cardiac symptoms are variable and may include fatigue, decreased exercise tolerance, palpitations, precordial chest pain, and syncope. Chest pain in acute myocarditis can result from an associated pericarditis or, occasionally, from coronary-artery spasm.[10]

The true incidence of myocarditis in the community is unknown. Endomyocardial biopsy is used infrequently because of perceived risks and the lack of a widely accepted and sensitive histologic standard. Seroepidemiologic data are difficult to interpret because of the heterotopic effect of enteroviruses, which may cause an amnestic antibody response to other coxsackievirus B strains.However, the observation that viral genomes are more common in cardiac tissue from patients with chronic dilated cardiomyopathy than in tissue from patients with valvular or ischemic cardiomyopathy supports the concept that viral myocarditis leads to a substantial disease burden in the community. Furthermore, myocarditis is an important cause of sudden death, as well as childhood cardiomyopathy.

Table 1. **Clinical Scenarios for the Diagnosis of Myocarditis.***

Clinical Scenario	Duration of Illness	Pathological Correlates	Prognosis	Treatment
Acute myocardial infarction–like syndrome with normal coronary arteries	Several hours or days	Active lymphocytic myocarditis or, rarely, necrotizing eosinophilic myocarditis or giant-cell myocarditis	Good if lymphocytic myocarditis is present on biopsy	Supportive
Heart failure with normal-sized or dilated left ventricle and hemodynamic compromise	Less than 2 wk	Active lymphocytic myocarditis or, less commonly, necrotizing eosinophilic myocarditis or giant-cell myocarditis	Good in fulminant lymphocytic myocarditis, but acute care often requires inotropic or mechanical circulatory support	Supportive; possible use of corticosteroids or IVIG in children
Heart failure with dilated left ventricle and new ventricular arrhythmias, high-degree heart block, or lack of response to usual care within 1 to 2 wk	A few weeks or months	Giant-cell myocarditis, eosinophilic myocarditis, or lymphocytic myocarditis	Poor; high likelihood of death or need for cardiac transplantation if giant-cell myocarditis is found on biopsy	Variable therapy according to histopathological results
Heart failure with dilated left ventricle without new ventricular arrhythmias or high-degree heart block	A few weeks or months	Nonspecific changes most likely, with the presence of viral genomes in 25 to 35% of patients and of lymphocytic myocarditis (Dallas criteria) in about 10%	Good in the first several years, but a risk of late disease progression with heart failure and cardiomyopathy	Supportive; definition of genomic predictors of risk under investigation
Heart failure with eosinophilia	Any duration	Eosinophilic or hypersensitivity myocarditis, eosinophilic endomyocarditis	Poor	Supportive, including identification and treatment of underlying cause; possible use of corticosteroids for hypersensitivity myocarditis
Heart failure with dilated left ventricle and new ventricular arrhythmias, high-degree heart block, or lack of response to usual care in 1 to 2 wk	More than several months	Cardiac sarcoidosis (idiopathic granulomatous myocarditis) or specific infection (e.g., *Trypanosoma cruzi* and *Borrelia burgdorferi*); nonspecific changes most likely	Increased risk of need for pacemaker or implantable cardioverter–defibrillator if sarcoidosis is confirmed on biopsy	Supportive; corticosteroids for biopsy-proven cardiac sarcoidosis
Heart failure with dilated left ventricle without new ventricular arrhythmias or high-degree heart block	More than several months	Nonspecific changes most likely; increased number of inflammatory cells shown by sensitive immunostaining in up to 40% of patients and the presence of viral genomes in 25 to 35%	Depends on functional class ejection fraction and the presence or absence of inflammation and viral genomes on biopsy	Supportive; antiviral treatment and immunosuppression under investigation

* IVIG denotes intravenous immune globulin.

Etiology

Viral and postviral myocarditis remain major causes of acute and chronic dilated cardiomyopathy. Seroepidemiologic and molecular studies linked coxsackievirus B to outbreaks of myocarditis from the 1950s through the 1990s. The spectrum of viruses that were detected in endomyocardial biopsy samples shifted from coxsackievirus B to adenovirus in the late 1990s and, in the past 5 years, to parvovirus B19 and other viruses, according to reports from the United States and Germany[11]. Many other viruses have also been associated less frequently with myocarditis; these viruses include Epstein–Barr virus, cytomegalovirus, and human herpesvirus 6. Myocarditis can result from infection with Borrelia burgdorferi (Lyme disease).

Myocarditis is the most common cardiac pathological finding at autopsy of patients infected with the human immunodeficiency virus (HIV), with a prevalence of 50% or more[12]. Drug-induced hypersensitivity reactions and systemic hypereosinophilic syndromes can cause a specific myocarditis . Numerous medications, including some anticonvulsants, antibiotics, and antipsychotics, have been implicated in hypersensitivity myocarditis. Eosinophilic myocarditis is characterized by a predominantly eosinophilic infiltrate in the myocardium and may occur in association with systemic diseases, such as the hypereosinophilic syndrome, the Churg–Strauss syndrome, Löffler's endomyocardial fibrosis, cancer, and parasitic, helminthic, or protozoal infections[13, 14, 15]. Two idiopathic and histologically similar disorders, giant-cell myocarditis and cardiac sarcoidosis, are rare but important causes of cardiomyopathy.

Diagnosis

Biomarkers of cardiac injury are elevated in a minority of patients with acute myocarditis but may help confirm the diagnosis. Troponin I has high specificity (89%) but limited sensitivity (34%) in the diagnosis of myocarditis[16]. Clinical and experimental data suggest that increased levels of cardiac troponin I are more common than increased levels of creatine kinase MB in acute myocarditis.[17] A few serologic and imaging biomarkers have been associated with poor clinical outcome. For example, relatively high serum levels of Fas ligand and interleukin-10 may predict an increased risk of death[18, 19] although these assays are not widely available.

In acute myocarditis, the electrocardiogram may show sinus tachycardia with nonspecific ST-segment and T-wave abnormalities. Occasionally, the changes on electrocardiography are suggestive of an acute myocardial infarction and may include ST-segment elevation, ST-segment depression, and pathologic Q waves. Pericarditis not infrequently accompanies myocarditis clinically and is often manifested in pericarditis-like changes seen on electrocardiography. The sensitivity of the electrocardiogram for myocarditis is low (47%).[20] The presence of Q waves or left bundle-branch block is associated with higher rates of death or cardiac transplantation.[21]

Echocardiography is useful primarily to rule out other causes of heart failure, since there are no specific features of acute myocarditis. Echocardiographic patterns of dilated, hypertrophic, restrictive, and ischemic cardiomyopathies have been described in histologically proven myocarditis. Segmental or global wall-motion abnormalities in myocarditis can simulate myocardial infarction.[22] In the Myocarditis Treatment Trial, increased sphericity and left ventricular volume occurred in acute, active myocarditis.[23] Fulminant myocarditis may be distinguished from acute myocarditis by a smaller left ventricular cavity size and increased wall thickness.[24] The loss of right ventricular function was the most powerful predictor of death or the need for cardiac transplantation in a series of 25 patients with biopsy-confirmed myocarditis.[25]

Cardiac MRI is being used with increasing frequency as a diagnostic test in suspected acute myocarditis[26, 27] and may be used to localize sites for endomyocardial biopsy Endomyocardial biopsy should be performed in patients with unexplained, new-onset heart failure of less than 2 weeks' duration in association with a normal-size or dilated left ventricle and hemodynamic compromise, for suspected fulminant myocarditis. Endomyocardial biopsy should also be performed in patients with unexplained, new-onset heart failure of 2 weeks' to 3 months' duration in association with a dilated left ventricle and new ventricular arrhythmias or Mobitz type II or second-degree or third-degree heart block and in patients who do not have a response to usual care within 1 to 2 weeks, for suspected giant-cell myocarditis.

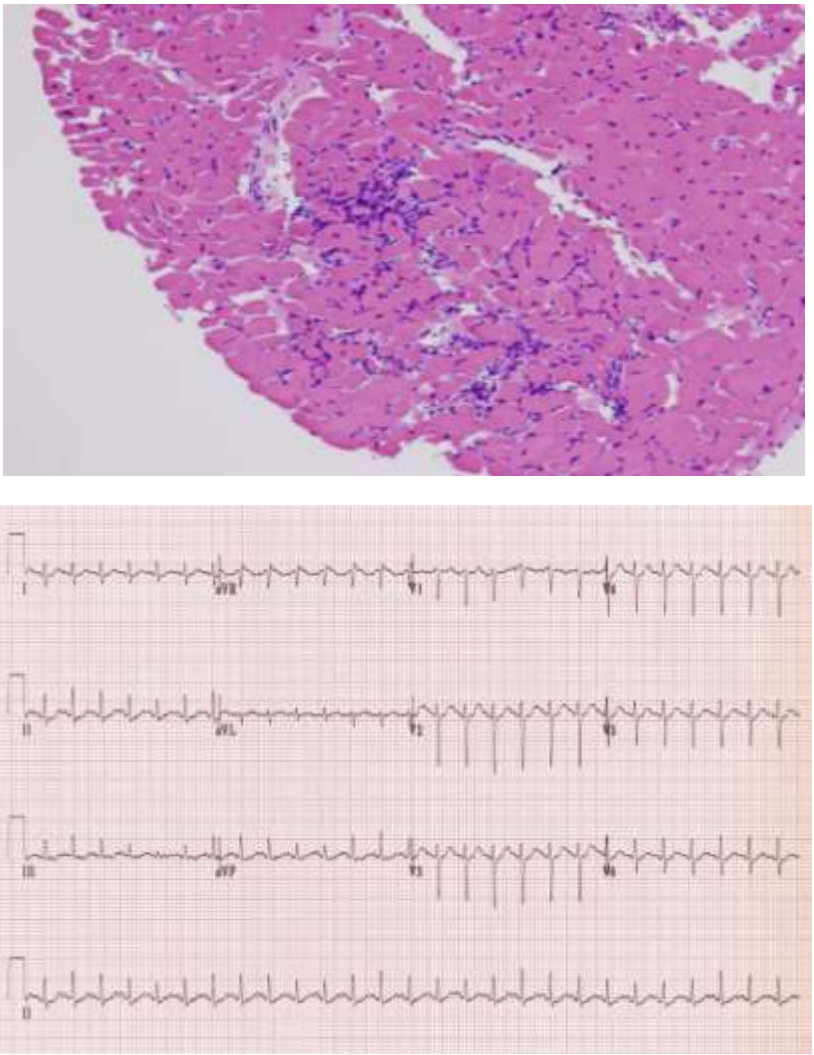

Fig 1:H and E, low power, showing numerous lymphocytes with associated myocyte damage in myocarditis

Fig 2: Sinus tachycardia with non-specific ST segment changes seen in acute myocarditis.

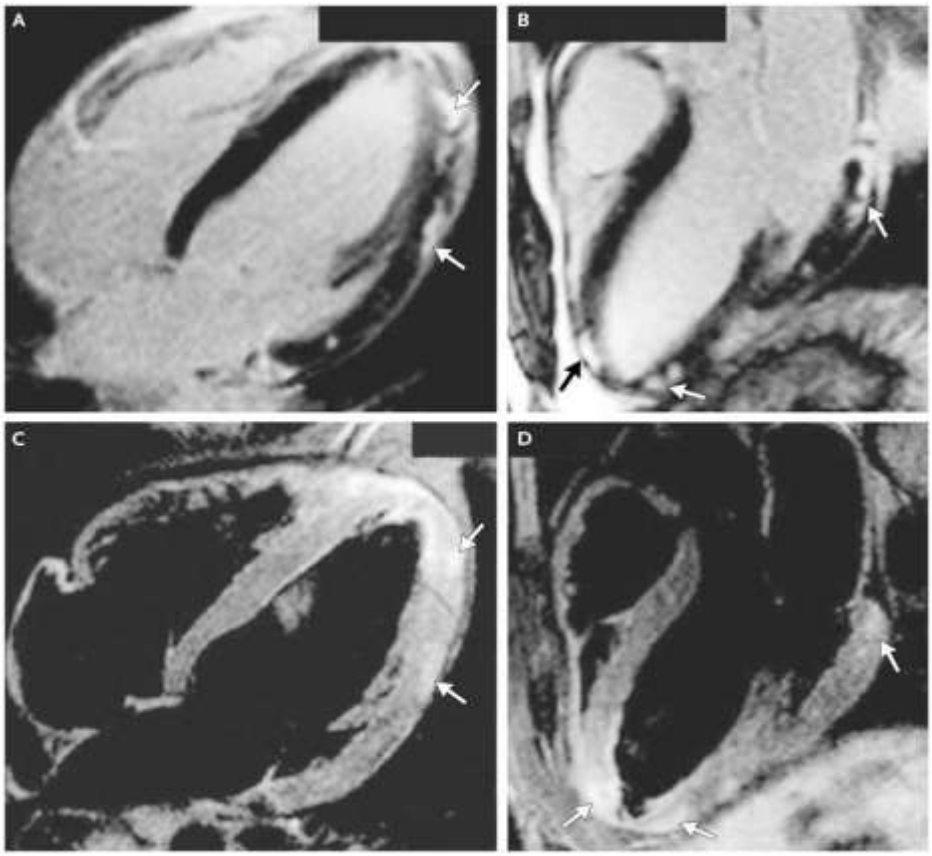

Fig 3: Contrast-Enhanced Magnetic Resonance Imaging (MRI) of the Heart of a 24-Year-Old Man with Acute Myocarditis.Cardiac MRI is being increasingly used to evaluate suspected acute myocarditis and to localize sites for endomyocardial biopsy, with additional detail shown with delayed gadolinium enhancement (Panel A, arrows), in a four-chamber view (Panel B, arrows), and in T2-weighted three-chamber views (Panels C and D, arrows).

Treatment

The mainstay of therapy for acute myocarditis is supportive therapy for left ventricular dysfunction. Most patients will improve with a standard heart-failure regimen that includes the administration of angiotensin-converting–enzyme inhibitors or angiotensin-receptor blockers, beta-blockers such as metoprolol and carvedilol, and diuretics, if needed. In patients whose condition deteriorates despite optimal medical management, case series suggest a role for mechanical circulatory support, such as ventricular assist devices or extracorporeal membrane oxygenation, as a bridge to transplantation or recovery.

Since no clinical trials of therapy for heart failure have been conducted specifically in patients with myocarditis, the only relevant studies describe animal models. Patients recovering from acute myocarditis should refrain from aerobic activity for a period of months after the clinical onset of the disease, based on studies in rodents with myocarditis in which increased death rates were associated with sustained exercise.[28] The reintroduction of aerobic activities somewhat depends on the severity of left ventricular dysfunction and the extent of recovery.[29] The use of candesartan improved survival in a murine model of viral myocarditis (60%, vs. 18% with no candesartan treatment).[30] The use of carteolol, a nonselective beta-blocker, improved histopathological results and reduced wall thickness in coxsackievirus B myocarditis.[31] The use of nonsteroidalantiinflammatory drugs was associated with increased mortality.[32, 33, 34] Taken together, these data support the application of the current heart-failure guidelines to patients with heart failure from myocarditis.

In patients with acute myocarditis, therapy for arrhythmias is also supportive, since such arrhythmias usually resolve after the acute phase of the disease, which can last several weeks. However, in acute myocarditis, temporary pacemakers may be required for patients with symptomatic bradycardia or complete heart block. Patients with symptomatic or sustained ventricular arrhythmias may need amiodarone and possibly an implantable cardioverter–defibrillator, even if active inflammation is still present. The prognostic importance and treatment of nonsustained ventricular arrhythmias in acute myocarditis have not been systematically evaluated.

Antiviral and immunomodulatory effects that have been shown in experimental models and uncontrolled case series suggest that intravenous immune globulin (IVIG) might have a therapeutic use in myocarditis. However, in the Intervention in Myocarditis and Acute Cardiomyopathy trial, patients with acute dilated cardiomyopathy who were treated with IVIG did no better than those given placebo.[35] Therefore, the routine use of IVIG for acute myocarditis in adults is not recommended. IVIG has not been evaluated rigorously for the treatment of chronic dilated cardiomyopathy with inflammation or viral persistence. IVIG may have a role in the treatment of acute pediatric myocarditis.[36]

Results from several randomized, controlled trials of immunosuppression for acute myocarditis were negative or only marginally positive.[37] These studies suggest that immunosuppression is not beneficial in the routine treatment of acute lymphocytic myocarditis. Future trials involving patients with acute myocarditis are probably not feasible since the disease affects so few patients, has a highly variable clinical prognosis, and is associated with substantial improvement in left ventricular function with usual care.[38] Unlike lymphocytic myocarditis, transplant-free survival in patients with giant-cell myocarditis may be prolonged with a combination of cyclosporine and corticosteroids.[39]There may be a broader role for immunosuppression in patients with chronic, moderate-to-severe cardiomyopathy, whose condition is unlikely to improve further after optimal care has been given for 6 to 12 months. In one trial involving 84 patients with chronic dilated cardiomyopathy and human leukocyte antigen expression on cardiomyocytes, the use of azathioprine and prednisone was associated with improvement in cardiac function and in New York Heart Association functional class.[40] Other approaches to modify immune activation that are under investigation in this population include immunoadsorption and immunomodulation.

Summary And Future Directions

This review discusses an approach to suspected myocarditis according to the likelihood of finding a treatable disorder. A major issue for the future is whether the diagnosis of myocarditis will continue to require histologic confirmation. Cardiac MRI is a promising tool but requires additional validation for noninvasive diagnosis and prognosis in acute and chronic myocarditis. On the horizon, analysis of messenger RNA and protein markers from peripheral-blood components may be able to detect a clinically meaningful inflammatory signal in high-risk populations without the risk of endomyocardial biopsy. [41] Treatment of subpopulations of chronic viral-associated and nonviral myocarditis with biopsy-guided therapy is an area of active investigation. Our understanding of the immunologic regulation of viral cardiac infection is derived primarily from research in animal models. The insights from these models may be explored in human studies in the next decade to develop new diagnostic tests and possibly pathway-specific treatments.

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