Myocarditis

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Myocarditis is an underdiagnosed cause of acute heart failure, sudden death, and chronic dilated cardiomyopathy. In developed countries, viral infections commonly cause myocarditis; however, in the developing world, rheumatic carditis, *Trypanosoma cruzi*, and bacterial infections such as diphtheria still contribute to the global burden of the disease. The short-term prognosis of acute myocarditis is usually good, but varies widely by cause. Those patients who initially recover might develop recurrent dilated cardiomyopathy and heart failure, sometimes years later. Because myocarditis presents with non-specific symptoms including chest pain, dyspnoea, and palpitations, it often mimics more common disorders such as coronary artery disease. In some patients, cardiac MRI and endomyocardial biopsy can help identify myocarditis, predict risk of cardiovascular events, and guide treatment. Finding effective therapies has been challenging because the pathogenesis of chronic dilated cardiomyopathy after viral myocarditis is complex and determined by host and viral genetics as well as environmental factors. Findings from recent clinical trials suggest that some patients with chronic inflammatory cardiomyopathy have a progressive clinical course despite standard medical care and might improve with a short course of immunosuppression.

Introduction

Myocarditis refers to the clinical and histological manifestations of a broad range of pathological immune processes in the heart. Alterations in the number and function of lymphocyte subsets and macrophages and antibody-mediated injury are typically found in patients with acute and chronic myocarditis. The immune reaction in the heart causes structural and functional abnormalities in cardiomyocytes, which in turn leads to regional or global contractile impairment, chamber stiffening, or conduction system disease. Patients with acute myocarditis often present with non-specific symptoms of chest pain, dyspnoea, or palpitations; however, sometimes acute viral myocarditis can cause cardiac damage without symptoms, and the risk of chronic dilated cardiomyopathy (DCM) in this setting is uncertain. Immune-mediated cardiac injury and dysfunction can also occur in chronic myocarditis.

Classification

Myocarditis can be classified by cause, histology, immunohistology, and clinicopathological and clinical criteria (panel, figure 1). From each categorisation, the treating clinician should consider what information will provide unique prognostic and therapeutic information in a given clinical scenario. For example, assessment of left ventricular function in acute myocarditis is useful because more severe ventricular dysfunction is associated with greater risk of death or need for heart transplantation. An eosinophil-rich infiltrate with giant cells on heart biopsy can result from the uncommon but serious diagnosis of giant-cell myocarditis. Molecular studies on heart tissue, including viral genome amplification and transcriptome microarrays, can help identify specific pathogens or prognostically important inflammatory pathways.[1,2]

Although classifications on the basis of endomyocardial biopsy (EMB) results clearly have value, we have organised this Seminar around clinical classification for two reasons: (1) most clinical facilities have limited abilty to perform EMB and (2) the clinical value of EMB to provide prognosis and guide treatment is unproven for many clinical scenarios.[3] We propose a three-tiered classification for acute myocarditis, which is primarily distinguished by increasing diagnostic certainty (table 1). An asymptomatic patient can be classified as having possible subclinical acute myocarditis if other causes of acute cardiac disease are excluded, and if they have a recent trigger for myocarditis, such as a recent viral illness, and one of the following findings: (1) an otherwise unexplained rise in troponin concentrations; (2) electrocardiographic changes suggestive of acute myocardial injury; or (3) abnormal cardiac function on echocardiogram or cardiac MRI. If a patient meets the criteria for possible subclinical myocarditis but also has one of four clinical syndromes consistent with acute myocarditis (acute heart failure, chest pain, presyncope or syncope, or myopericarditis), then they can be categorised as having probable acute myocarditis. If myocarditis is confirmed by histological studies, then the diagnosis is definite myocarditis, irrespective of the clinical syndrome.

In the course of chronic DCM, myocarditis can present as clinical deterioration without a clear cause. No clinically available serological or imaging tests can reliably identify inflammation or active cardiac viral infection in chronic DCM. Therefore, in patients with chronic DCM who deteriorate despite usual heart failure management, EMB might be considered to guide cause-specific treatment.

Common clinical scenarios associated with myocarditis

Possible subclinical acute myocarditis

Possible subclinical acute myocarditis has been inferred from transient increases in troponin or electrocardiogram (ECG) abnormalities after an acute viral illness or vaccination. During the influenza A epidemic (H3N2) in Japan from 1998 to 1999, myosin light chain was raised in 11·4% of patients who did not have cardiac symptoms.[4] 1 in 200 people had increased troponin 1 concentrations without symptoms of heart failure or chest pain after smallpox vaccination,[5] yet the incidence of clinical myocarditis is lower at 5·5 per 10 000.[6] The long-term risk of developing heart failure in patients with isolated

laboratory evidence of cardiac injury is not known. Nonetheless, experimental and epidemiological data suggest that chronic DCM can result from acute myocarditis.[7] Therefore, further research is needed to define the long-term clinical significance of possible subclinical acute myocarditis.

Acute heart failure with DCM

A clinical syndrome of dyspnoea, fatigue, and exercise intolerance, often with paroxysmal nocturnal dyspnoea and orthopnoea after an upper respiratory or gastrointestinal infection suggests post-viral myocarditis. Patients typically have a dilated ventricle, but occasionally the ventricular structure and function might suggest restrictive or even hypertrophic cardiomyopathy. Increased left ventricular wall thickness in fulminant myocarditis is a result of active inflammation and might regress over several weeks.[8] In this scenario, the risk of death or need for heart transplantation is closely linked to the amount of haemodynamic compromise, which is identified by assessment of left and right ventricular function and pressure. For most adult patients who have acute DCM in the setting of suspected myocarditis, both ventricular function and clinical status improve with standard heart failure treatment.[9] The disease is often more fulminant in children than adults, but, in children, recovery of cardiac function is better than in non-inflammatory DCM, although supportive therapy can include mechanical circulatory support.[10]

A small subset of adults who present with a sudden onset of severe heart failure within 2 weeks of a viral illness might need inotropic or mechanical circulatory support, but usually recover if they survive the initial illness.[8] If patients with fulminant or acute DCM develop sustained or symptomatic ventricular tachycardia, high-degree heart block, or fail to respond to standard heart failure treatment, then prognosis is worse and a more serious form of myocarditis, such as giant-cell myocarditis, should be considered.[11] EMB is indicated in patients with fulminant or acute heart failure who do not respond to usual care or who have sustained or symptomatic ventricular tachycardia or high-degree heart block because EMB can identify a specific histological cause and guide cause-specific treatment.[3] Prognosis is poor if the biopsy reveals extensive fibrosis without inflammation.[12]

Myopericarditis resembling an acute coronary syndrome

Myocarditis can mimic an acute coronary syndrome, often with globally preserved left ventricular function.[13] When inflammation occurs in the pericardium, the presentation can mimic an acute myocardial infarction but without significant coronary artery disease on angiography. Yilmaz and colleagues[14] noted coronary vasospasm with intracoronary acetylcholine testing in the absence of epicardial coronary disease in 70% of patients with clinical evidence of acute myocardial infarction and myocarditis proven on biopsy. In a series of patients with acute myocardial infarction-like syndrome and normal coronary arteries, 78% had evidence of myocarditis on scintigraphy.[15] In a study by Kuhl and colleagues,[16] 17 (71%) of 24 consecutive patients examined within 24 h after onset of chest pain without coronary artery disease had viral genomes detected in their myocardium (12 had parvovirus B19, three had enterovirus, and two had adenovirus). In most studies, such patients had good short-term prognosis, but the amount of ventricular compromise is still a borderline predictor of death risk.[17] A minority of patients develop persistent or recurrent myopericarditis with normal ventricular function that might respond to colchicine or non-steroidal anti-inflammatory drugs.[18]

Panel: Selected classifications for myocarditis

Cause
- Viral, such as enteroviruses (eg, Coxsackie B), erythroviruses (eg, Parvovirus B19), adenoviruses, and herpes viruses
- Bacterial, such as *Corynebacterium diphtheriae*, *Staphylococcus aureus*, *Borrelia burgdorferi*, and *Ehrlichia* species
- Protozoal, such as *Babesia*
- Trypanosomal, such as *Trypanosoma cruzi*
- Toxic: alcohol, radiation, chemicals (hydrocarbons and arsenic), and drugs, including doxorubicin
- Hypersensitivity: sulphonamides and penicillins

Histology
- Eosinophilic
- Giant cell
- Granulomatous
- Lymphocytic

Immunohistology (not mutually exclusive)
- World Heart Federation: 14 or more CD3+ or CD68+ cells per high power field
- Increased expression of human leucocyte antigens (eg, HLA-DR)
- Increased expression of adhesion molecules (eg, intracellular adhesion molecule 1)

Clinicopathological
- Fulminant
- Acute
- Chronic active
- Chronic persistent

Clinical (not mutually exclusive)
- Acute heart failure
- Syncope
- Chest pain resembling an acute myocardial infarction
- Myopericarditis

This panel is a partial list of categories and criteria within common classification schemes.

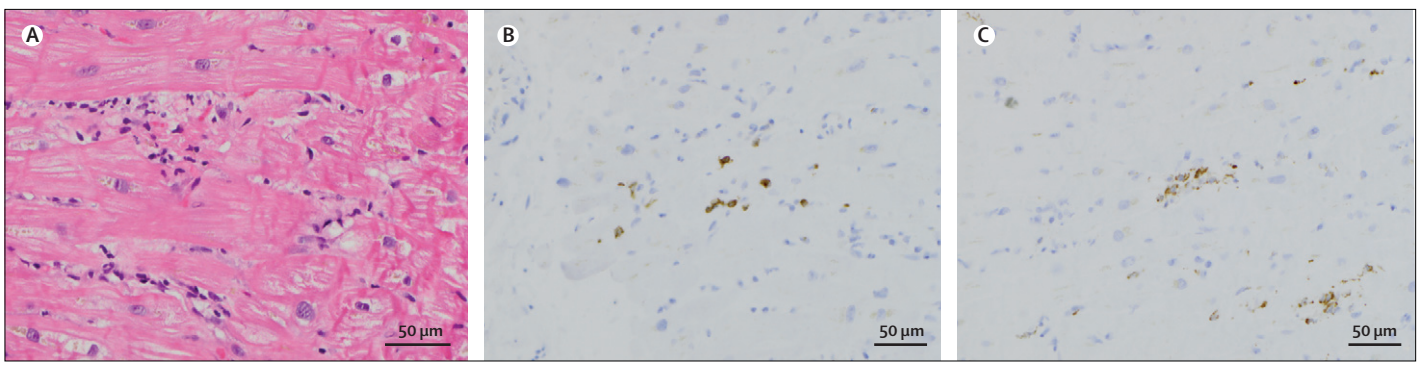

Figure 1: **Histological samples from patients with myocarditis**
(A) Endomyocardial biopsy showing an extensive interstitial lymphoplasmacytic infiltrate associated with myocardial necrosis in a patient with myocarditis. Presence of T lymphocytes (B) and macrophages (C) shown by antibody stains against CD3 and CD68. Image courtesy of Joesph J Maleszewski.

	Criteria	Histological confirmation	Biomarker, ECG, or imaging abnormalities consistent with myocarditis	Treatment
Possible subclinical acute myocarditis	In the clinical context of possible myocardial injury without cardiovascular symptoms but with at least one of the following: 1 Biomarkers of cardiac injury raised 2 ECG findings suggestive of cardiac injury 3 Abnormal cardiac function on echocardiogram or cardiac MRI	Absent	Needed	Not known
Probable acute myocarditis	In the clinical context of possible myocardial injury with cardiovascular symptoms and at least one of the following: 1 Biomarkers of cardiac injury raised 2 ECG findings suggestive of cardiac injury 3 Abnormal cardiac function on echocardiogram or cardiac MRI	Absent	Needed	Per clinical syndrome
Definite myocarditis	Histological or immunohistological evidence of myocarditis	Needed	Not needed	Tailored to specific cause

ECG=electrocardiogram.

Table 1: **A three-tiered clinical classification for the diagnosis of myocarditis on the basis of level of diagnostic certainty**

Syncope from ventricular arrhythmias or heart block
Uemura and colleagues[19] reported that three (6%) of 50 patients with unexplained atrioventricular heart block had myocarditis. Heart block or sustained or symptomatic ventricular arrhythmias in the setting of a cardiomyopathy should also raise suspicion for specific causes of myocarditis. For example, Lyme disease and Chagas diseases are associated with heart block, ventricular arrhythmias, and chronic myocarditis (figure 2).[20,21] Diphtheria is associated with bradyarrhythmias and heart block. Patients who present with chronic DCM and have new ventricular arrhythmias or second-degree or third-degree heart block are at risk for cardiac sarcoidosis (idiopathic granulomatous myocarditis).[22,23] Myocarditis associated with ventricular tachycardia can also mimic arrhythmogenic right ventricular dysplasia or cardiomyopathy.[24]

Heart failure associated with progressive or chronic DCM
Myocarditis defined by immunohistological criteria is present in up to 40% of patients with chronic DCM who have symptoms of heart failure despite standard medical care.[25] In patients with chronic DCM, imunohistological evidence of myocarditis is much more common than inflammation on routine histology. Kindermann and colleagues[26] showed that the risk of death or need for cardiac transplantation in patients with myocarditis is worse in those with inflammation than in those without, as assessed by immunohistology. Findings from a case-control study suggested that patients with heart failure caused by chronic myocarditis and anti-cardiac antibodies but no viral genomes on EMB had a good response to immunosuppressive treatment.[27] In a randomised, placebo-controlled trial, a course of prednisone and azathioprine improved left ventricular function in patients with chronic inflammatory cardiomyopathy and no active viral infection.[28]

Cause

Myocarditis can result from a wide spectrum of infectious pathogens, including viruses, bacteria, chlamydia, rickettsia, fungi, and protozoans, as well as toxic and hypersensitivity reactions. Viruses are the infectious pathogens most frequently implicated in reports of acute myocarditis. In the 1950s and 1960s, experimental and later seroepidemiological studies

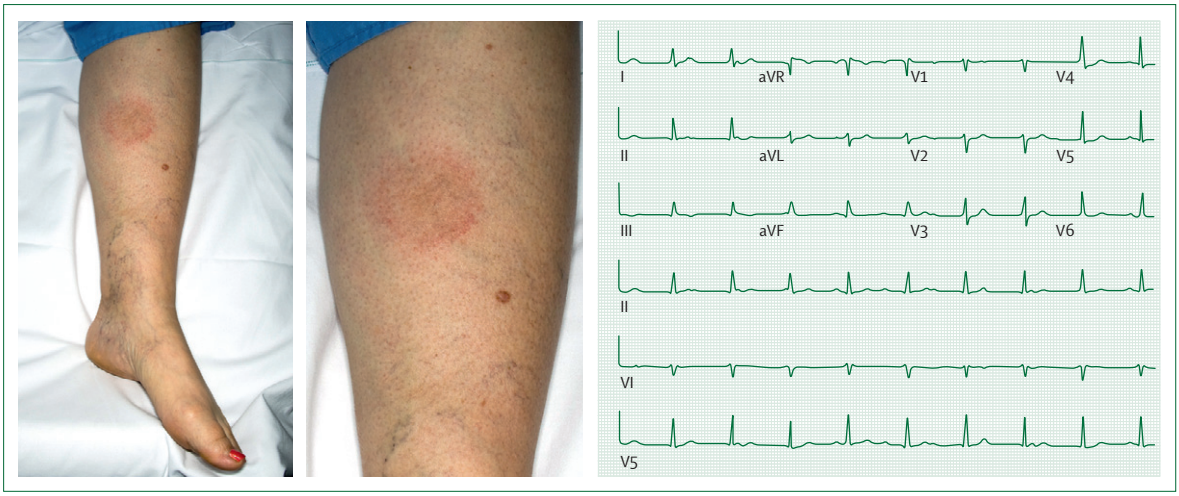

Figure 2: **Lyme disease in a patient with myocarditis**
(A) Erythema migrans (bull's eye rash) in a patient with Lyme myocarditis. (B) Electrocardiogram from the patient revealed complete heart block.

linked enteroviruses, particularly group B Coxsackie viruses, to myocarditis.[29,30] In the 1980s, molecular techniques, including PCR, identified other viral genomes in the heart tissue of patients with acute myocarditis, broadening the spectrum of viruses associated with myocarditis.[31,32] At present, the most frequently identified genomes are parvovirus B19 and human herpes virus 6, although enteroviruses are still an important cause is some regions.[33,34] Because heart biopsy and viral genome analysis are rarely done in many regions of the world, the prevalence of viral myocarditis in much of Africa, Asia, the Middle East, and South America is unknown.

Corynebacterium diphtheriae can cause myocarditis associated with bradycardia in nonimmunized children. *Trypanosoma cruzi*, the cause of Chagas disease, has been a leading cause of myocarditis in parts of rural South and Central America.[35] The age-standardised incidence of myocarditis due to *C diphtheriae* has been estimated at nearly 50 cases per 100 million worldwide, with a much higher incidence in the former Soviet Union.[36] *T cruzi* infection can occur in childhood after transcutaneous inoculation with excreta contaminated with the parasite from the haematophagous Reduviids. After an acute phase of mild febrile illness, a prolonged (10–30 year) asymptomatic latent phase follows. During this asymptomatic phase, subclinical cardiac involvement can be identified by Holter monitoring and echocardiography.[37,38] Systolic and diastolic left ventricular dysfunction and ventricular arrhythmias have been documented in a high percentage of patients with chronic asymptomatic Chagas disease.[39] Anti-heart antibodies directed against myosin heavy chain, mitochondrial antigens, the β_1 adrenergic receptor, and muscarinic acetylcholine 2 receptors are increased in patients with *T cruzi* infection who develop myocarditis.[40] Ventricular aneurysms, biventricular systolic or diastolic heart failure, and cardiac autonomic dysfunction characterise chronic Chagas cardiomyopathy.[35]

Myocarditis in patients with advanced HIV infections can result in chronic DCM and is associated with poor prognosis.[41,42] DCM in HIV can occur from cardiotoxicity induced by viral glycoprotein 120, opportunistic infections, autoimmune response, drug-related cardiac toxicity, and possibly nutritional deficiencies.[43] HIV-1 and viral glycoprotein 120 both induce myocyte and endothelial apoptosis, whereas antiviral drugs can cause gap junction and mitochondrial dysfunction. Highly active antiviral therapy (HAART) significantly reduces the incidence of HIV-associated myocarditis and DCM. Before HAART was available, the prevalence of cardiomyopathy was as high as 30% and symptomatic heart failure was 5% in patients with HIV.[44] HAART regimens have reduced the incidence of HIV-associated cardiomyopathy by seven times, which has resulted in increased longevity and improved quality of life in HIV-infected patients.[44] However, HAART is only available to a small percentage of the global HIV-infected population. Therefore, programmes to increase the availability of HAART in regions of the world where HIV and other infectious diseases are endemic should reduce the rates of myocarditis and DCM.

Non-infectious causes of myocarditis are uncommon but important because of the substantial morbidity associated with these conditions and the potential for specific treatments. For example, patients with systemic inflammatory diseases such as rheumatoid arthritis have an increased cardiovascular mortality rate compared with the general population.[45–47] In patients with extra-articular manifestations of rheumatoid arthritis, the incidence of non-ischaemic cardiomyopathy, such as myocarditis, was estimated to be as high as 39% in the 1980s.[48] This rate has decreased with the advent of disease-modifying anti-rheumatic drugs.[46,48] The refinement of non-invasive

diagnostic methods, such as cardiac MRI, to differentiate between ischaemic and non-ischaemic cardiac manifestation of rheumatoid arthritis are needed to further reduce the cardiac morbidity and mortality associated with rheumatoid arthritis and other systemic inflammatory disorders.

Eosinophilic myocarditis can be grouped by cause, including types associated with systemic disease (eg, hypereosinophilic syndrome, Churg-Strauss syndrome, and malignancies); those associated with drugs or vaccines (hypersensitivity eosinophilic myocarditis); and those associated with parasitic infections such as *Toxocara canis*[49] and idiopathic acute necrotising eosinophilic myocarditis.[50] Hypersensitivity myocarditis is particularly difficult to recognise because the clinical features characteristic of a drug hypersensitivity reaction—including non-specific skin rash, malaise, fever, and eosinophilia—are absent in most cases.[51,52] Drugs associated with hypersensitivity myocarditis include clozapine, sulfonamide antibiotics, methyldopa, and some anti-seizure drugs. The rate of possible myocarditis after smallpox vaccination was 5·5 per 10 000 in the US civilian vaccination programme.[6] Fortunately, myocarditis after other vaccines is rare.[53]

Acute necrotising eosinophilic myocarditis and giant-cell myocarditis are two rare idiopathic disorders that present with fulminant or acute heart failure, which is frequently associated with ventricular arrhythmias or heart block. These disorders share histological features of extensive myocyte necrosis, little fibrosis in the acute setting, and an eosinophil-rich infiltrate, suggesting that they might share a common pathogenesis. Both disorders might respond to multi-drug immunosuppression.[54] In the case of giant-cell myocarditis, treatment with cyclosporine, high-dose steroids, and muromonab-CD3 was associated with a 91% 1-year survival.[55]

Pathogenesis

Myocarditis results from the interaction of an external environmental trigger with the host's immune system. The availability of murine enteroviral models of myocarditis has facilitated much of our understanding of the disorder.[56,57] From the pathophysiological point of view, the disease can be conceptually divided into three phases: (1) acute viral, (2) subacute immune, and (3) chronic myopathic.

Viral phase

Myocarditis is most commonly initiated by the introduction of a virus from a potentially pathogenic strain (eg, enteroviruses such as coxsackievirus), or reactivation of a dormant pathogen (eg, parvovirus B 19). The virus can proliferate in the permissive tissues of the susceptible host and ultimately reaches the myocardium or blood vessels through haematogenous or lymphangitic spread, or both. Clinically, the viral phase is typically short and often missed by clinicians. Once the virus reaches the target cells, it uses its specific receptor or receptor complex for targeted cell entry. Coxsackievirus uses the coxsackie-adenoviral receptor, which is a junctional protein that links one cell to another.[58–60] The nature of the receptors might partially explain why coxsackieviruses and adenoviruses are common causative viruses for myocarditis.

Viral proliferation in myocytes can cause direct tissue injury. However, most tissue damage in myocarditis results from the interaction of the viral trigger with the immune system. Entry of the virus through its receptor also activates immune signalling systems, including tyrosine kinases p56^{lck}, Fyn, and Abl.[58,60] Activation of these signals modifies the host cell cytoskeleton to permit more viral entry. At the same time, these signals mediate the activation of immune cells, which are critically dependent on p56^{lck} and Fyn.

Immune activation after viral entry

The balance of immune response by the host is a major determinant of patient outcome. On the one hand, the immune response is activated to eliminate as many virus-infected cells as possible to control the infection. On the other hand, it needs to be modulated and turned off when appropriate; otherwise there will be excessive tissue damage from the inflammatory response, which could lead to direct organ dysfunction.

Viral persistence can expose the host to prolonged antigenic trigger, chronic immune activation, and the potential for chronic myocarditis. Persistence of the viral genome, such as coxsackievirus, in the myocyte has been directly linked to the development of DCM through cytoskeleton remodelling.[61]

Innate immunity

The earliest host responses to the viral presence are members of the innate immune system. Innate immunity is an evolutionarily conserved host protective system that activates inflammatory responses through moieties such as toll-like receptors (TLRs). TLRs are present on all cell types, and TLR-3 and TLR-4 are particularly abundant in the cardiovascular system. These receptors recognise common antigenic patters from viruses, bacteria, foreign nucleic acid sequences, or oxidised proteins. Once engaged, they transmit a cascade of signals to activate nuclear transcription factors, such as nuclear factor κB, and lead to inflammatory cytokine production and immune activation.[62,63]

Acquired immunity

Signals from the innate immune system also sets in motion the activation and expansion of T cells and B cells that recognise specific peptide sequences as part of acquired immunity. This system is triggered by the recognition of a precise non-self molecular pattern by the variable region of the T-cell receptor, after a danger or stress signal by the host. The stimulated T cell will clonally expand to attack the source of the antigen, which could be

the original viral coat protein or sometimes parts of the myocardium (such as myosin) that might resemble the molecular sequence of the virus (molecular mimicry), triggering autoimmunity.

Activation of acquired immunity can lead to the production of T-killer cells that can directly attack the virus and virally infected cells. The activation of T cells also leads to the activation of B cells and the production of specific antibodies to neutralise the antigen. This response results in subacute and chronic inflammation in myocarditis and contributes to the subsequent myocyte necrosis, fibrosis, and remodelling. The T-cell receptor activation sequence ultimately leads to the detrimental phenotype of the disease and supports the idea that decreasing inflammation from acquired immunity while finding ways to control the virus through innate immunity will lead to the most beneficial outcomes in myocarditis.

Myopathy phase

If the inflammatory response persists, the heart can undergo remodelling, with modification of the cardiac structure and function, which leads to the development of DCM. The inflammatory process from both innate and acquired immunity (described earlier) can also lead to release of cytokines, which are potent activators of matrix metalloproteinases that can digest the interstitial collagen and elastin framework of the heart and, in turn, participate in inflammation.[64] A family of matrix metalloproteinases, including urokinase-type plasminogen activator, contribute to cardiac dilatation and inflammation.[33] Additionally, the activation of cytokines such as transforming growth factor can lead to activation of the SMAD signalling cascade, which causes production of profibrotic factors, leading to pathological fibrosis. The final result can be DCM, with its attendant systolic and diastolic dysfunction, and progressive heart failure. Studies in patients receiving interferon beta suggest that type 1 interferons might be able to modulate not only the viral load but also the remodelling of the affected hearts.[33] Therapeutic drugs such as angiotensin modulators and β blockers modify the remodelling process and are equally effective for treatment of a dilated heart after myocarditis.

Diagnosis

When myocarditis is suspected, more common causes of cardiovascular disease, such as atherosclerotic and valvular heart disease, should be excluded according to present American Heart Association (AHA), American College of Cardiology Foundation (ACCF), European Society of Cardiology (ESC), and Heart Failure Society of America (HFSA) guidelines.[65–67]

In patients with clinically suspected acute myocarditis, confirmatory testing usually begins with serum biomarkers. Troponin 1 was raised in 34% of patients with acute myocarditis who had up to 2 years of symptoms at the time of enrolment into the US Myocarditis Treatment Trial cohort.[68] However, in sicker patients who were treated in hospital and who had acute or fulminant myocarditis, creatine kinase-MB concentrations of greater than 29·5 ng/mL predicted in-hospital mortality with a sensitivity of 83% and a specificity of 73%.[69] In acute or fulminant myocarditis, higher interleukin-10 and soluble Fas concentrations are associated with an increased risk of death; however, tests for these markers are not commonly used clinically.[70,71] In acute myocarditis, presence of anti-heart antibodies might predict risk of death or need for transplantation.[72] Non-specific serum markers of inflammation, such as C-reactive protein, erythrocyte sedimentation rate, and leucocyte count, are frequently increased in patients with suspected myocarditis, but low specificity limits their diagnostic value.

There are non-specific changes on ECG in most patients with myocarditis. These changes include sinus tachycardia, ST-wave and T-wave abnormalities, and occasionally atrioventricular or bundle branch block.[73] Electrocardiographic changes that are associated with poor prognosis in acute myocarditis include widened QRS and Q waves.[74] Pericarditis with PR depression and diffuse ST segment elevation often accompanies epicardial inflammation.

New regional or global wall motion abnormalities that are not associated with a coronary distribution are a useful confirmatory and prognostic finding in acute myocarditis.[75] In fulminant cases, there might be wall thickening due to oedema, and increased ventricular sphericity. Impaired right ventricular function is a strong predictor of death or need for transplantation. In one study, 14 of 23 patients, of those with right ventricular dysfunction died or needed a transplant compared with none of those with normal right ventricular function (p=0·03).[76] Perhaps the greatest value of standard echocardiography in the assessment of acute myocarditis is for exclusion of primary valvular and congenital disease or pericardial constriction.

Cardiac MRI is becoming routine and is a sensitive non-invasive test for confirmation of acute myocarditis.[77] In 82 patients with non-ischaemic DCM and myocarditis, all of whom had EMB, the correct diagnosis was obtained with cardiac MRI alone in 66 patients (80%).[78] The sensitivity and specificity of cardiac MRI for the diagnosis of acute myocarditis varies with the sequences used (table 2). A combination of T2-weighted MRI and post-gadolinium early and late T1-weighted MRI provides the best sensitivity (67%) and specificity (91%) for diagnosis.[79] However, T1 weighted imaging after gadolinium contrast might not distinguish acute myocarditis from chronic scarring.[80]

Histological or immunohistological evidence of an inflammatory cell infiltrate with or without myocyte damage is the gold standard for the diagnosis of myocarditis. In clinical practice, EMB should be used when the incremental prognostic and therapeutic information gained from biopsy outweighs the risk and cost. An AHA/ACCF/ESC joint scientific statement[3] recommended that EMB should be done (class 1

	Validation	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)
T2 and LGE	Clinical histology	25	95	56	86
T2, LGE, or both	Clinical histology	60	66	62	79
Any 1 of 3	Clinical histology	88	48	70	68
Any 2 of 3	Clinical histology	67	91	78	91

PPV=positive predictive value. T2=T2-weighted MRI. LGE=late gadolinium enhancement. Adapted with permission from Friedrich and colleagues.[79]

Table 2: **Accuracy of several combinations of cardiac MRI tissue criteria for the diagnosis of myocarditis**

indication) in patients with heart failure and (1) a normal sized or dilated left ventricle, less than 2 weeks of symptoms, and haemodynamic compromise; or (2) a dilated ventricle, 2 weeks to 3 months of symptoms, new ventricular arrhythmias or Mobitz type 2 second-degree or third-degree heart block, or who fail to respond to usual care within 1–2 weeks. The scientific statement recommends that EMB be considered in several other clinical scenarios for which there is less robust evidence of incremental diagnostic, prognostic, or therapeutic value.

Since the publication of the joint scientific statement, the major complication rate of EMB has been shown to be less than one in 1000 when done by experienced operators.[81] A strategy of early EMB in children with suspected acute myocarditis can be used to identify those who will respond to medical treatment and to decrease the need for heart transplantation.[82] Left ventricular biopsy is as safe as right ventricular biopsy.[83] Finally, EMB-based criteria (inflammation present on immunohistology and viral genomes absent on PCR) can identify patients with chronic DCM who respond to immunosuppression. The decrease in procedural risk and increase in diagnostic and therapeutic value is extending the role of EMB at medical referral centres that have the necessary technical expertise.

Treatment according to clinical scenario

Possible subclinical acute myocarditis

The optimum management strategy for patients who have a rise in troponin concentrations or ECG changes suggestive of myocarditis or myopericarditis without cardiovascular symptoms is not known. These patients are often encountered during a medical assessment for non-cardiovascular disorders such as a flu-like illness. The short-term prognosis of possible subclinical acute myocarditis is good, but the long-term consequences are unknown. If ventricular function is normal, a reasonable therapeutic approach is to clinically reassess the patient after 1–2 weeks to ensure that troponin concentrations normalise and that symptoms of heart failure or arrhythmia do not develop. If the left ventricular ejection fraction is less than 40%, we recommend that an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and possibly a β adrenergic blocker be given, as suggested in the present AHA/ACCF, HFSA, and ESC guidelines for the management of stage B heart failure.[65–67]

Probable acute myocarditis

Treatment for probable acute myocarditis varies according to the presenting clinical scenario. In patients who present with an acute DCM and a syndrome of heart failure, supportive measures and pharmaceutical treatment with neurohormonal blockade is indicated, as is standard for chronic heart failure. Although clinical studies in myocarditis have not been done, captopril and candesartan improve myocarditis in murine myocarditis models.[84,85] Most patients with acute myocarditis respond well to standard heart failure treatment. In addition to medical management, we recommend that patients with acute myocarditis refrain from competitive athletics for a period of up to 6 months after the acute infection or until ventricular recovery has been documented by non-invasive imaging.[86]

Routine treatment of probable or definite acute viral or lymphocytic myocarditis with immunosuppressive drugs is not recommended for adults. In the US Myocarditis Treatment Trial,[87] the placebo and immunosuppression (prednisone with either azathioprine or cyclosporin) arms had similar changes in left ventricular ejection fraction and transplant-free survival. In acute myocarditis, inflammation often has the beneficial effect of complete viral clearance. Exceptions include patients with uncommon, non-infectious, histological forms, including giant-cell myocarditis, cardiac sarcoidosis, and eosinophilic myocarditis; and those with myocarditis associated with inflammatory disorders such as systemic lupus erythematosus.

In small case series of acute paediatric myocarditis due to probable or definite lymphocytic myocarditis or Kawasaki disease, intravenous immunoglobulin has been effective.[88–90] However, in the Intervention for Myocarditis and Acute Cardiomyopathy trial,[91] there were no significant differences in transplant free survival between the intravenous immunoglobulin treatment group and placebo in adult patients who had DCM of less than 6 months duration. Therefore, in adults with probable acute myocarditis, there is insufficient evidence to recommend use of intravenous immunoglobulin.[92]

Chronic DCM

Up to 40% of patients with chronic DCM who fail to respond to usual care have immunohistochemical evidence of myocardial inflammation.[25] In two randomised trials of patients with chronic inflammatory cardiomyopathy, immunosuppression with azathioprine and prednisone resulted in an improvement in quality of life and left ventricular ejection fraction as compared to placebo.[25,28] In the Tailored Immunosuppression in Inflammatory Cardiomyopathy trial by Frustaci and colleagues,[28] 85 patients with chronic inflammatory cardiomyopathy without persistent viral infection were enrolled and randomised to either prednisone and azathioprine or placebo. Prednisone and azathioprine

treatment was associated with a mean left ventricular ejection fraction increase from 26% to 46%. Larger trials are needed to assess whether immunosuppression will affect the risk of death or admission to hospital in this population.

Although there are abundant data supporting the role of viral infection in the pathogenesis of myocarditis and DCM, there are no published randomised clinical trials of antiviral therapy in this population. In patients with chronic DCM and persistent viral genomes, one case series[33] suggested that 6 mIU interferon beta three times per week for enteroviral or adenoviral infection can eliminate viral genomes and improve left ventricular function as compared with placebo. The applicability of these data to other common viruses, including parvovirus B19, is not known.

Mechanical circulatory support or extracorporeal membrane oxygenation can allow a bridge to transplantation or recovery in patients with cardiogenic shock despite optimum medical care.[93,94] Time to recovery in acute myocarditis varies from a few days to a few months.[95,96] Survival after transplantation for myocarditis in adults is similar to survival after cardiac transplantation for other reasons,[97] however, survival after transplantation in children with myocarditis seems to be reduced.[98] Patients with giant-cell myocarditis have a 20–25% risk of recurrence in the allograft heart.[11]

Myopericarditis resembling an acute coronary syndrome

Patients who present with an acute myocardial infarction pattern usually recover with normal left ventricular ejection fraction; however, the likelihood of recovery is still dependent on left ventricular function.[13,15] Colchicine at an initial dose of 1–2 mg followed by reduced daily doses for up to 3 months can improve chest pain from associated pericarditis.[18] Non-steroidal anti-inflammatory drugs such as indometacin should be used with caution and generally be reserved for patients with normal ventricular function because they worsen myocarditis in murine models.[99]

Syncope from ventricular arrhythmias or heart block

Patients with ventricular arrhythmias or heart block due to acute myocarditis should be admitted to hospital for electrocardiographic monitoring. The 2006 ACC/AHA/ESC guidelines for the management of ventricular arrhythmias recommended that acute arrhythmia emergencies be managed conventionally in the setting of myocarditis.[100] Generally, the indications for an implantable cardiac defibrillator are the same as for non-ischaemic DCM. However, because of the relatively high risk of death or need for transplantation, the presence of symptomatic ventricular arrhythmias or heart block in giant-cell myocarditis or cardiac sarcoidosis might warrant early consideration for an implantable cardiac defibrillator.

Summary

The aim of this Seminar was to provide a clinical classification and guidelines for the assessment and treatment of suspected myocarditis in medical environments and epidemiological research where biopsy is unfeasible at present. We have emphasised the strengths and limitations of non-invasive methods such as echocardiography and cardiac MRI. Recently, several clinical scenarios in which EMB results added unique prognostic data or guide therapy have been defined. Therefore, we recommend that patients with a class 1 indication for EMB, who present to a medical centre without EMB capability, should be transferred to a centre where EMB can be done when feasible. Finally, ongoing translation of mechanistic insights from animal models to clinical care are permitting cause-specific treatment of viral and non-viral myocarditis and improving clinical outcomes in many forms of myocarditis.

Contributors

SS, PPL, and LTC did the literature search and wrote the manuscript, LTC reviewed and revised the manuscript.

Conflicts of interest

PPL ans SS declare that they have no conflicts of interest. LTC has received consultancy fees from Sanofi Pasteur.

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