REVIEW

Viral Myocarditis: Clinical and Paraclinical Diagnosis

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Abstract

Myocarditis is an inflammatory disease of the myocardium, that can be produced by a multitude of infectious or noninfectious agents. The incidence rate of the disease is between 10 to 22 per 100,000 individuals. Among the infectious causes, viruses are considered to be the most frequent pathogens. Regarding the clinical presentation, viral myocarditis may have a wide variety of manifestations, ranging from asymptomatic disease to chest pain, myalgia, fatigue, heart failure, arrhythmias and, in some cases, sudden death. A definitive diagnosis of viral myocarditis involves histological evidence for myocarditis associated with positive viral polymerase chain reaction (PCR). Endomyocardial biopsy represents the gold standard for diagnosis; in the absence of histological, immunologic and immunohistochemical criteria, a definitive diagnosis cannot be established.

Keywords: viral myocarditis, endomyocardial biopsy, histology.

Rezumat

Miocardita este o boală inflamatorie a miocardului, care poate fi produsă de o multitudine de agenți infecțioși sau neinfectioși. Rata de incidență a bolii este cuprinsă între 10 și 22 la 100.000 de persoane. Printre cauzele infecțioase, virusurile sunt considerate cei mai frecvenți agenți patogeni. În ceea ce privește prezentarea clinică, miocardita virală poate avea o mare varietate de manifestări, de la boală asimptomatică la dureri toracice, mialgii, astenie fizică, insuficiență cardiacă, aritmii și, în unele cazuri, moarte subită. Un diagnostic definitiv al miocarditei virale implică dovezi histologice pentru miocardită asociate cu reacția de polimerizare în lanț (PCR) pozitivă pentru virus. Biopsia endomiocardică reprezintă standardul de aur pentru diagnostic; în absența criteriilor histologice, imunologice și imunohistochimice, nu se poate stabili un diagnostic definitiv.

Cuvinte cheie: miocardita virală, biopsie endomiocardică, histologie.

INTRODUCTION

Myocarditis has been defined by the *World Health Organization* as an inflammatory disease of the myocardium that is nonischemic in origin[1]. It can affect both genders, all age groups and all ethnicities; however, it is mainly a disease of young and middle-aged adults, the median age at diagnosis being 42 years[2]. Myocarditis can be an acute, subacute or chronic disorder and patients with myocarditis may present with focal or global

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myocardial involvement[3]. It is a frequent cause of dilated cardiomyopathy and sudden cardiac death.

ETIOLOGY AND PATHOGENESIS

Despite the scientific progress made in the last decades, the etiology of myocarditis often remains uncertain. Acute myocarditis can be caused by toxic agents, such as drugs or heavy metals, it can be immune-mediated (triggered by allergens, organ transplant rejection or autoimmune disorders) or it may have an infectious etiology. Many infectious agents, like bacteria, protozoa, helminths and fungi, are implicated in the development of the disease; however, research studies suggest that viral infections are the most common cause of myocarditis[3] (Table 1).

The pathophysiological progress of viral myocarditis consists of 3 different phases[4]. During the first phase, virus-mediated lysis causes direct destruction of cardiomyocytes; impaired cellular structures facilitate the entry of the virus into the cells, leading to myocite injury and cardiac dilatation. However, due to the innate immune response, this initial phase may manifest as subclinical myocarditis. The second phase is characterised by a specific immune response; viral antigens, presented at the cell surface by the MHC class I, are detected by primed T-cells which destroy the infected cardiac cells. Another way the inflammatory response is sustained is through molecular mimicry, as some myocardial cellular antigens may share epitopic similairites with viral antigens[5]. The third phase is characterised by the development of dilated cardiomyopathy, as a consequence of extensive myocardial injury.

It remains unclear why some patients develop myocarditis, while others do not[6]. The cardiotropic viruses that cause myocarditis are common viral agents in human infectious diseases and more than 90% of subjects will be infected by one or more of them in their lifetime. However, less than 10% of these patients develop histologically-proven myocarditis, suggesting that genetic factors may also play an important role in the development of clinical myocarditis and/or progression to dilated cardiomyopathy[7].

Table 1. Viral causes of myocarditis

RNA viruses	DNA viruses
Coxsackieviruses A and B	Adenoviruses
Echoviruses	Parvovirus B19
Poliomyelitis virus	Cytomegalovirus
Influenza A and B viruses	Human herpes virus-6
Respiratory syncytial virus	Epstein-Barr virus
Hepatitis C virus	Varicella-zoster virus
Rubella virus	Herpes simplex virus
Yellow fever virus	Variola virus
Rabies virus	Vaccinia virus
Human immunodeficiency virus-1	

CLINICAL MANIFESTATIONS

Clinical manifestations of acute myocarditis range from non-specific systemic symptoms to fulminant hemodynamic collapse. This diversity of possible clinical scenarios implies that a high level of suspicion early in the course of the disease is required in order for the diagnosis of myocarditis to be made[8] (Table 2).

Acute viral myocarditis may manifest in the begining with flu-like symptoms of the upper respiratory tract (fever, arthralgias, myalgia, pharyngitis etc) or gastrointestinal tract (nausea, abdominal pain), before the onset of cardiac symptoms[6]. Manifestations that suggest cardiac involvement, like palpitations, chest pain, dyspnea, fatigue, may follow days or even weeks after initial non-specific systemic symptoms[9-11]. Some patients may present with more severe cardiac manifestations, such as life-threatening arrhythmias or cardiogenic shock.

DIAGNOSIS OF MYOCARDITIS

Establishing the diagnosis of myocarditis can be challenging and it is often a diagnosis of exclusion. Myocarditis should be suspected in patients who present with or without cardiac signs and symptoms, who have high levels of cardiac biomarkers (troponin), with changes on the ECG that suggest acute myocardial injury, arrhythmia, or global or regional abnormalities of LV systolic function, especially if the clinical findings are new and cannot be explained[3].

The diagnostic evaluation of patients with suspected myocarditis should include history and physical examination, ECG and laboratory testing, cardiac imaging, cardiac catheterization in selected patients and, if clinically indicated, an endomyocardic biopsy.

The physical examination may show signs of heart failure, such as elevated jugular venous pressure, edema, a third heart sound. In patients with severe left ventricle or right ventricle dilation, murmurs of functional mitral or tricuspid regurgitation may be heard on auscultation of the heart.

Blood tests (inflammatory and cardiac biomarkers) performed in patients with myocarditis are nonspecific.

Table 2. Clinical profiles of acute myocarditis[8]

Acute coronary syndrome-like	New onset or worsening heart failure in the absence of CAD and known causes of HF	Life-threatening condition in the absence of CAD and known causes of HF
Acute chest pain	New onset or progressive HF over 2 weeks to 3 months: dyspnea, peripheral edema, chest discomfort, fatigue	Life-threatening arrhythmias and aborted sudden death
ST/T wave changes	Impaired systolic LV and/or RV function; +/- increase in wall thickness; +/- dilated LV and/or RV on echocardiography or CMR	Cardiogenic shock
With/without normal LV and/or RV dysfunction on echocardiography or CMR	Symptoms possibly started after a respiratory or gastrointestinal infection	Severely impaired LV function
With or without increased TnT/TnI	Non-specific ECG signs	

Abbreviation: LV=left ventricle; RV=right ventricle; CMR=cardiac magnetic resonance; TnT=troponin T; TnI=troponin I; HF=heart failure; CAD=coronary artery disease.

Elevated troponin I or T, elevated acute phase reactants (elevated C-reative protein and erythrocyte sedimentation rate), high levels of BNP and NT-proBNP may be seen in these patients, but also in patients with pericarditis or acute coronary syndrome, thus showing their limited utility in diagnosing myocarditis and in distinguishing it from other pathologies.

Viral antibody titer testing is rarely indicated in the diagnosis of viral myocarditis, due to its low specificity and the delayed rising of viral titers, which would have no impact on therapeutic decisions.

In patients with myocarditis, the ECG may be normal or it may show nonspecific abnormalities like ST-segment changes, atrial tachycardia, atrial fibrillation, single atrial or ventricular ectopic beats. ECG is mainly obtained to exclude alternate causes of cardiac symptoms.

Cardiac imaging is an important tool in the diagnosis of myocarditis. Echocardiography may show nonspecific findings, such as ventricular dilation, thickened ventricular wall, ventricular thrombus, left and/or right ventricular dysfunction, pericardial effusion, or, in patients with less severe forms of myocarditis, it may be completely normal[12,13]. Echocardiography may be useful to rule out non-inflammatory causes of heart failure such as valvular heart disease, and also to distinguish fulminant from acute myocarditis: in fulminant myocarditis, the size of the left ventricle is within normal range, with a thickened left ventricular wall, whereas in acute myocarditis, the left ventricular diastolic dimension is increased. Regional wall motion abnormalities may be present in both myocarditis and acute coronary syndrome (ACS); in these cases, coronary angiography is needed to distinguish between myocarditis and ACS due to obstructive coronary artery disease.

Cardiac magnetic resonance imaging (MRI) provides supportive evidence of myocarditis. T2-weighted edema ratio, global relative enhancement and late gadolinium enhancement can be used to differentiate between ischemic and non-ischemic cardiomiopathy. Cardiac MRI assesses ventricular dysfunction and filling patterns and characterizes myocardial tissue, localizing areas of edema, hyperemia and fibrosis.

Endomyocardial biopsy (EMB) confirms the diagnosis of myocarditis. According to the *American College of Cardiology/American Heart Association* guidelines, the implementation of a right or left ventricular EMB is indicated when there is a strong reason to believe that the results will have a meaningful effect on subsequent therapeutic decisions (Table 3)[14,15]. EMB remains the

Table 3. Indications for endomyocardial biopsy[12]

EMB is recommended in the following settings	EMB is suggested in the following settings
Patients with unexplained fulminant HF (new onset HF of less than two weeks duration associated with hemodynamic compromise)	HF of >3 months duration associated with dilated LV and new ventricular arrhythmias, second or third degree AV block, or failure to respond to usual care within one or two weeks
Unexplained new onset HF of two weeks to three months duration associated with a dilated LV and new ventricular arrhythmias, Mobitz type II second-degree AV block, third-degree AV block, or failure to respond to usual care within one to two weeks.	HF associated with dilated cardiomyopathy associated with suspected allergic reaction and/or eosinophilia.
	Other specific clinical settings when other evaluation is inconclusive and diagnosis may impact treatment or prognosis

Abbreviations: EMB=endomyocardial biopsy; HF=heart failure; LV=left ventricle; AV=atrio-ventricular

gold standard for establishing the definite diagnosis of myocarditis. However, in patients with focal distribution of histological lesions, EMB's specificity and sensitivity are limited; therefore, in order to optimize diagnostic accuracy, multiple specimens should be taken: at least three samples, each 1–2 mm in size (from the right or from the left ventricle or from both). In patients who present with exclusive left or right heart failure and myocarditis, decision for left or right heart biopsy should be made based on the additional clinical information. However, biventricular sampling has been shown to increase diagnostic yield to 73% in patients with suspected myocarditis, right ventricular sampling alone having a fairly low sensitivity[16].

Tissue obtained from EMB should be analysed using histology, immunohistochemistry, and viral PCR, allowing identification and quantification of viral infection markers. The presence of viral genome in endomyocardial biopsy samples is considered the standard criteria for viral persistence.

CONCLUSIONS

Viral myocarditis is an inflammatory disease that presents diagnostic challenges. A broad spectrum of viral genomes have been found to be responsible for acute myocarditis, with coxsackie virus and parvovirus B19 being the leading causes of myocarditis.

The variable clinical presentation, ranging from seemingly benign symptoms, such as shortness of breath or fatigue, to life-threatening cardiogenic shock, requires a high level of suspicion and the use of appropriate investigations for the diagnosis of acute myocarditis. The exclusion of coronary artery disease and other cardiovascular or extra-cardiac non-inflammatory diseases is mandatory in all cases of suspected myocarditis.

Compliance with ethics requirements: The authors declare no conflict of interest regarding this article.

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