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Review

Diagnosis of myocarditis: Current state and future perspectives

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ABSTRACT

Myocarditis, i.e. inflammation of the myocardium, is one of the leading causes of sudden cardiac death (SCD) and dilated cardiomyopathy (DCM) in young adults, and is an important cause of symptoms such as chest pain, dyspnea and palpitations. The pathophysiological process of disease progression leading to DCM involves an ongoing inflammation as a result of a viral-induced auto-immune response or a persisting viral infection. It is therefore crucial to detect the disease early in its course and prevent persisting inflammation that may lead to DCM and end-stage heart failure. Because of the highly variable clinical presentation, ranging from mild symptoms to severe heart failure, and the limited available diagnostic tools, the evaluation of patients with suspected myocarditis represents an important clinical dilemma in cardiology. New approaches for the diagnosis of myocarditis are needed in order to improve recognition, to help unravel its pathophysiology, and to develop new therapeutic strategies to treat the disease. In this review, we give a comprehensive overview of the current diagnostic strategies for patients with suspected myocarditis, and demonstrate several new techniques that may help to improve the diagnostic work-up.

1. Introduction

Myocarditis is an inflammation of the myocardium as a result of an infection, autoimmune disease or cardiotoxic agent [1]. This inflammation can lead to acute heart failure, chest pain and life threatening arrhythmias [2–4]. Cardiac function may rapidly deteriorate and patients may become hemodynamically unstable and require supportive therapy or even cardiac transplantation [5]. Furthermore, patients with myocarditis have an increased risk of sudden cardiac death (SCD) [6–8] and the development of a dilated cardiomyopathy (DCM) [9]. Therefore it is important to detect the disease early in its course. However, myocarditis is one of the most challenging diagnosis in cardiology and is often under-recognized due to the heterogeneity of its clinical presentation that overlaps with other cardiac diseases, such as an acute coronary syndrome [10]. Endomyocardial biopsy (EMB) is the gold standard for diagnosing myocarditis and its underlying cause, and it may contribute to the selection of patients who might benefit from specific therapeutic measures. Although EMB is safe in experienced hands, there is a small risk of potentially serious complications [11]. Sensitivity of EMB is negatively influenced by sampling error, and the (immuno)histochemical assessment of the biopsy material is challenging [12–15]. Also, EMB cannot be used for risk stratification or to predict the progression to DCM. In addition, prognosis is good in the majority of patients and effective therapy is not available for most causes. EMB is therefore not part of routine clinical practice in patients with suspected myocarditis. Cardiac magnetic resonance (CMR) is a good non-invasive alternative but with current techniques the diagnosis can still be missed [16]. Also, CMR cannot determine the underlying cause of myocarditis, and, so far, cannot be used for risk stratification or prediction of outcome, both crucial for patient management [17]. In this review, we will discuss the current diagnostic approach in patients with suspected myocarditis and demonstrate new techniques that may help to improve the diagnostic work-up and risk stratification.

2. Classification and etiology

Symptom onset, histological features and underlying etiologic agents may each contribute to the classification of myocarditis into distinct subtypes [1] (Table 1). Based on the onset of symptoms, myocarditis is divided into fulminant, acute or chronic myocarditis [18]. The chronic state can be further subdivided according to the stage of inflammation into persistent inflammation, chronic viral infection (with or without inflammation) or healed inflammation (with or without irreversible damage to the heart) [18,19]. The types of infiltrates found in EMB samples can also classify myocarditis, and provide important clues to an underlying etiology [20]. Lymphocytic

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Table 1
Classification of myocarditis

Clinicopathology
Fulminant
Acute
Chronic
Persistent inflammation
Viral infection with or without inflammation
Healed inflammation with or without irreversible damage to the heart
Histology
Lymphocytic
Giant cell
Granulomatous
Eosinophilic
Neutrophilic
Etiology
Infectious: viral, bacterial, spirochaetal, fungal, protozoal, parasitic, and rickettsial
Autoimmune: allergens, alloantigens, and autoantigens
Toxic agents: drugs, alcohol, radiation, and chemicals

myocarditis is by far the most common form. Histological findings may include the presence of multinucleated giant cells, granulomas, neutrophilic or eosinophilic granulocytes [21,22]. Finally, myocarditis can be categorized by its underlying etiology. There are numerous causes of myocarditis, yet the etiology remains undetermined in most cases. Viral infection of the myocardium is the most common identified cause of myocarditis [17]. There are up to 20 known cardiotropic viruses that may elicit myocarditis. In Europe and North America, viral genomes of parvovirus B19 (PBV19), human herpes virus 6 (HHV6) and enterovirus (EV) are detected in the majority of cases [23–25]. An immune response against cardiac myocytes is another important cause of myocarditis, which may be triggered by the viral infection, a specific allergenic agent such as medication, or cardiac transplantation, but is also found in systemic autoimmune disorders, such as systemic lupus erythematosus, rheumatoid arthritis and scleroderma. In addition, toxic agents including cocaine, amphetamines and certain cytostatic drugs can lead to myocardial inflammatory disease also. Other less frequent causes of (toxic) myocarditis include animal bites, insect stings and heavy metals [17].

3. Clinical presentations, differential diagnosis and initial evaluation

Myocarditis has a heterogeneous clinical manifestation which can be divided into the following presentation types: acute coronary syndrome like (ACS-like) symptoms, new-onset heart failure, life threatening arrhythmias and chronic heart failure. Symptoms or signs are not unique to myocarditis and initial evaluation using ECG, blood studies and echocardiography are not specific. Clinical clues to the disease include elevated inflammatory markers and gastrointestinal or respiratory infection preceding the onset of symptoms, however these may all be absent [2,26]. Also, viral serology cannot be used for the diagnosis of myocardial infection [27,28].

3.1. ACS-like presentation

A large proportion of patients with myocarditis presents with ACS-like symptoms. Differentiating between myocarditis and acute myocardial infarction (AMI) presents a clinical dilemma because both can present with ST-segment elevation, regional myocardial dysfunction and cardiac enzyme release [29]. The clinical challenge is further illustrated by the fact that even if coronary angiography (CAG) reveals unobstructed coronary arteries, AMI secondary to vasospasm or embolism is often assumed to be the case in clinical practice. However, several studies using CMR demonstrated that myocarditis was the correct diagnosis in the majority of these patients, and not AMI [30,31]. Pericarditis often coincides with myocarditis. In this spectrum, perimyocarditis refers to acute pericarditis with signs of myocarditis demonstrated by troponin release or myocardial dysfunction [32–34].

3.2. New onset heart failure

Patients with myocarditis may also present with symptoms and signs of heart failure. The suspicion of myocarditis is generally raised when more common causes of heart failure like ischemic, valvular and hypertensive heart disease are excluded [35]. Echocardiography typically shows global impairment of cardiac systolic function and in some cases a thickened ventricular wall as a result of edema can be seen [36,37]. In patients with fulminant myocarditis, cardiac function may rapidly deteriorate leading to hemodynamic instability that requires supportive therapy, whereas patients with nonfulminant myocarditis usually have a more gradual course [5].

3.3. Life threatening arrhythmias

Myocarditis can also result in arrhythmias and conduction disturbances, that may be severe and life threatening, such as atrioventricular (AV) blocks, ventricular fibrillation/flutters and sustained ventricular tachycardia [38,39]. Myocarditis is one of the most common findings at autopsy in young adults who died of sudden cardiac death [6,8]. Although a viral syndrome is sometimes reported, these individuals are usually asymptomatic until death [40]. In general, the diagnostic evaluation of life-threatening arrhythmias includes 12 lead ECG, echocardiography and in some cases CAG. Myocarditis may be suspected when there is no evidence of coronary artery disease or distinct electrophysiological abnormalities [41].

3.4. Chronic heart failure

DCM, i.e. LV systolic dysfunction with an associated LV dilatation, may be the first manifestation of late-stage myocarditis. DCM is considered to be the chronic component of myocarditis which develops when the disease progresses to a persistent state of inflammation [42]. These patients typically present to the outpatient clinic with gradual progression of heart failure. The acute phase of myocarditis may have passed unnoticed or with mild symptoms only. Next to myocarditis, DCM can be the result of various other causes, and the differential diagnosis is therefore extensive [43]. Although clinical features can provide clues to the underlying cause, without EMB and/or genetic testing the cause of DCM remains unknown in up to half of the cases [44].

4. Diagnosis

4.1. Endomyocardial biopsy

EMB may provide information about the presence of viral genome, fibrosis, cell death, the type of inflammatory infiltration and the deposition of iron, proteins or lipids [45]. The underlying cause of myocarditis can only be determined by an EMB because non-invasive tests are limited in their ability to assess these features. EMB is required before targeted therapy can be initiated [17]. Immunosuppression proved to be beneficial in autoimmune mediated myocarditis but detrimental in viral myocarditis [27,46]. EMB is considered to be a relative safe procedure when performed by an experienced physician [11,47,48]. Risks of major complications are comparable between right sided EMB (RV-EMB) and left sided EMB (LV-EMB), although the types of complication are different [11,48]. RV-EMB is associated with a higher risk of cardiac perforation while LV-EMB has a higher risk of stroke. There is still controversy in many medical centers about the role of EMB in the diagnosis and treatment of myocarditis, mostly because the procedural risks do not always outweigh the incremental value of EMB, as the majority of myocarditis patients have a good prognosis. The highest