Viral Myocarditis

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32.1 Overview

Myocarditis is a localized or diffuse acute or chronic inflammatory lesion of myocardium. The etiology of myocarditis is not clear, and the etiology of myocarditis can be divided into infective myocarditis, immune-mediated myocarditis, and toxic myocarditis. The most common pathogen of infectious myocarditis is virus. Immune-mediated myocarditis can be secondary to some autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis. In addition, some exogenous physical and chemical factors can also lead to myocarditis, such as injuries caused by drugs, heavy metals and radioactive factors, snake bites, and electric injuries. Among myocarditis, viral myocarditis is the most common.

Viral myocarditis refers to a localized or diffuse inflammatory disease of myocardium caused by viral infection, which belongs to infectious myocardial disease. At present, about 20 kinds of viruses have been found to be related to myocarditis, the most common virus is enterovirus, especially Coxsackie B virus, and other common viruses include adenovirus, influenza virus, Epstein–Barr virus, cytomegalovirus, and parvovirus B19. Viral myocarditis may have acute, subacute, or chronic course of disease. Some patients have a history of respiratory tract or intestinal infection a few days to several weeks before onset. Its clinical manifestations depend on the extent and location of the lesion, and mild patients can be asymptomatic. Common symptoms include chest tightness, chest pain, palpitation, dyspnea, fatigue, and general malaise. Severe cases may have heart failure, cardiogenic shock, and sudden death. Most patients can be cured after proper treatment, and very few patients may die of severe arrhythmia, acute heart failure, and cardiogenic shock in the acute stage [1].

Diagnosis of myocarditis: Endomyocardial biopsy (EMB) is the gold standard for the diagnosis of myocarditis, including routine microscopic examination, immunohistochemical staining, and virus PCR detection. However, EMB is an invasive examination and its sensitivity is low due to sampling error, so it is not regarded as a first-line examination clinically. EMB is more often used to evaluate the condition of patients to guide treatment or when patients are suspected to have special types of myocarditis (such as cytomegalovirus myocarditis).

Clinical diagnosis of myocarditis: Histological examination is still the gold standard for the diagnosis of myocarditis, but the diagnosis of clinically suspected myocarditis can be made according to the clinical manifestations of patients combined with noninvasive diagnostic examination (including typical cardiac magnetic resonance abnormalities). In 2013, the European Society of Cardiology (ESC) proposed the diagnostic criteria for clinically suspected myocarditis [2] (Table 32.1).

Etiological diagnosis index: Diagnosis can be confirmed by one of the following results of endocardium, myocardium, pericardium (biopsy and pathology), or pericardial puncture fluid examination. ① The virus has been isolated and ② viral nucleic acid has been detected by virus nucleic acid probe.

Etiological reference index: One of the following can be considered to be caused by virus in combination with clinical manifestations. ① The virus has been isolated from feces, throat swabs, or blood, and the titer of isotype antibody in convalescent serum has increased or decreased by more than 4 times compared with that in the first sample of serum; ② specific IgM antibody is positive in serum at the early stage of disease course; and ③ viral nucleic acid has been detected from blood by virus nucleic acid probe. On the basis of meeting the diagnosis of myocarditis, ① if it meets one of the etiological diagnosis indexes, it can be diagnosed as viral myocarditis and ② if it meets one of the etiological reference indexes, it can be clinically diagnosed as viral myocarditis.

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Table 32.1 Diagnostic criteria for clinically suspected myocarditis

Clinical manifestations
– Acute chest pain
– New (several days to 3 months) or aggravated dyspnea and/or fatigue during rest/exercise, which may be accompanied by signs of left heart failure and/or right heart failure
– Subacute/chronic (more than 3 months) or aggravated dyspnea and/or fatigue during rest/exercise, which may be accompanied by signs of left heart failure and/or right heart failure
– Palpitations and/or unexplained arrhythmic symptoms and/or syncope, and/or abortive sudden cardiac death
– Unexplained cardiogenic shock
Diagnostic criteria
I. Characteristics of ECG/Holter test: Any of the following new abnormalities in the 12-lead ECG/Holter test: First-degree to third-degree atrioventricular block or bundle branch block, ST/T changes (ST segment elevation or T wave inversion), sinus arrest, ventricular tachycardia or ventricular fibrillation, cardiac arrest, atrial fibrillation, significantly reduced amplitude of R wave, intraventricular conduction delay (QRS wave widening), abnormal Q wave, low voltage, frequent premature ventricular contraction, or supraventricular tachycardia
II. Elevated serum troponin T or I (TnT/TnI)
III. Cardiac imaging (echocardiography, angiography, or cardiac magnetic resonance) shows functional and structural abnormalities: New unexplained left ventricular and/or right ventricular dysfunction (segmental wall motion abnormality, global systolic or diastolic dysfunction). The disease may also be accompanied by ventricular dilatation, wall thickening, pericardial effusion, and/or intracavitary thrombosis
IV. Histological features of cardiac magnetic resonance (CMR): myocardial edema and/or late gadolinium enhancement (LGE)
Myocarditis should be suspected if the following manifestations occur
1 or more clinical manifestations and 1 or more diagnostic criteria for different categories (I–IV) or the patient are asymptomatic;
2 or more different diagnostic criteria (I–IV)

32.2 Pathological Manifestations

Viral infection can directly damage myocardium or cause degeneration and necrosis of myocardial fibers and infiltration of interstitial lymphocytes and monocytes through an autoimmune reaction. At present, it is considered that the pathogenesis of viral myocarditis mainly includes two stages: direct damage of virus to myocardium in the first week after infection, and immune response-mediated damage to myocardial cells caused by viral infection in the second week.

The pathological changes of myocarditis mainly include inflammatory cell infiltration and myocardial injury. According to pathological characteristics, myocarditis can be divided into active myocarditis and nascent myocarditis. The pathological manifestation of active myocarditis is inflammatory infiltration of myocardium with necrosis and/or degeneration of adjacent myocardial cells, and there is no typical manifestation of ischemic injury related to coronary artery disease. The infiltrating cells are usually monocytes, but they may also be neutrophils and occasionally eosinophils. Nascent myocarditis refers to the infiltration of only a small number of inflammatory cells, without myocardial cell necrosis.

In subacute and chronic myocarditis, interstitial fibrosis may replace myocardial cells and myocardial fiber hypertrophy may also occur.

32.3 Imaging Manifestations

1. Echocardiography: It is an important method to detect impaired ventricular dysfunction in patients with suspected myocarditis (even subclinical myocarditis). Patients with myocarditis may show left ventricular dilatation, left ventricular structural changes, and abnormal wall motion. Fulminant myocarditis often leads to myocardial interstitial edema and loss of systolic function due to significant inflammatory reaction, showing thickened wall and decreased systolic function, but without left ventricular dilatation. On the contrary, acute myocarditis causes significant left ventricular dilatation, normal or slightly thickened wall, and decreased left ventricular systolic function. Echocardiography can also find other symptoms, including pericardial involvement, asymptomatic intracardiac thrombosis, and functional mitral or tricuspid regurgitation.
2. X-ray and CT: The cardiac shadow of most patients with viral myocarditis is not enlarged or only slightly enlarged. Left ventricular insufficiency leads to signs of pulmonary congestion or pulmonary edema, such as enhanced hilar vascular shadow, increased upper pulmonary vascular shadow, blurred lung field, etc. Acute alveolar pulmonary edema is characterized by butterfly-shaped hilum and large patchy fusion shadow in the lung field. If complicated with viral pneumonia, severe diffuse lesions or inflammatory infiltration of the whole lung may occur in addition to severe heart failure and pulmonary congestion consolidation, the lung is manifested as the so-called “white lung”, in which process respiratory distress and ARDS occur in patients. Pleural effusion and interlobar pleural thickening may also occur in some patients.
3. MRI: Cardiac MRI (CMR) imaging is radiation-free and noninvasive, which is the most important noninvasive examination method for diagnosing myocarditis. Besides evaluating cardiac morphological and functional abnormalities, CMR can locate and quantitatively and qualitatively analyze some histopathological features of

myocarditis, such as myocardial edema, congestion, necrosis, or fibrosis. Currently, three main CMR techniques are available for myocarditis imaging: ① T_2WI is used to evaluate myocardial edema; ② gadolinium contrast-enhanced T_1WI can evaluate myocardial congestion in the early stage; and ③ late gadolinium enhancement (LGE) is used to evaluate myocardial necrosis and fibrosis. In 2009, "Lake Louise Criteria" was put forward in JACC White Paper on cardiovascular magnetic resonance in myocarditis [3]: ① Segmental or diffuse increase of myocardial signal on T_2WI (myocardial T_2WI signal/skeletal muscle T_2WI signal ≥2.0). ② Gadolinium contrast-enhanced T_1WI shows the increased enhancement rate of myocardium/skeletal muscle in the early stage [myocardial signal enhancement rate/skeletal muscle signal enhancement rate ≥ 4.0 or myocardial signal enhancement rate ≥ 45%, signal enhancement rate (%) = (SI after enhancement – SI before enhancement) / SI before enhancement]. ③ Late gadolinium enhancement (LGE) T_1WI shows at least one delayed enhancement focus, and the distribution of lesions is inconsistent with typical ischemic changes, usually involving subepicardial layer or myocardial middle layer, and rarely involving subendocardium. According to such criteria, myocarditis can be diagnosed when at least the above two items are met clinically (Fig. 32.1). If no more than one item of the above criteria is met, but myocarditis is highly suspected clinically and the initial CMR examination is performed shortly after symptoms occur; then 1–2 weeks later, reexamination should be performed with CMR.

Morphological abnormalities: Acute or subacute myocarditis may show transient ventricular wall thickening, left ventricular dilatation, and left ventricular mass increase.

32.4 Diagnostic Key Points

1. Endocardial myocardial biopsy is the gold standard for the diagnosis of myocarditis.
2. On the basis of meeting the diagnosis of myocarditis: ① if it meets one of the etiological diagnosis indexes, it can be diagnosed as viral myocarditis and ② if it meets one of the etiological reference indexes, it can be clinically diagnosed as viral myocarditis.
3. Cardiac MRI is the most important noninvasive examination method for the diagnosis of myocarditis in clinical practice, and the typical manifestation is segmental or diffuse hyperintensities of myocardium on T_2WI. Gadolinium contrast-enhanced T_1WI shows myocardial enhancement in the early stage. Gadolinium contrast agent T_1WI shows delayed enhancement foci, and the lesions usually involve subepicardial layer or myocardial middle layer. Other signs include transient ventricular wall thickening, left ventricular dilatation, left ventricular mass increase, pericardial effusion, and so on.

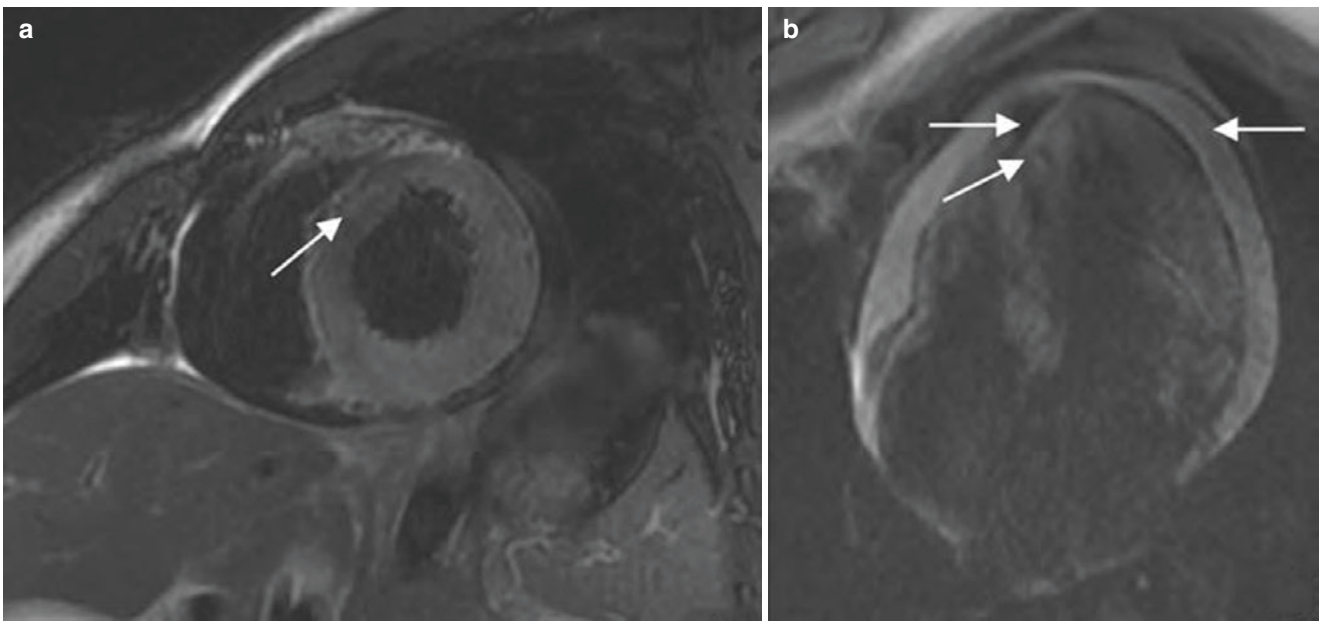

Fig. 32.1 Viral myocarditis. (**a**) In enhanced MRI scan of heart, T_2WI black-blood technique shows diffuse hyperintensities of left ventricular myocardium (arrow) and (**b**) late gadolinium enhancement (LGE) T_1WI showed patchy delayed enhancement of left ventricular myocardium (arrow)

32.5 Differential Diagnosis

1. Myocardial infarction: Different from myocarditis, myocardial injury caused by myocardial infarction mainly invades subendocardial myocardium and develops to middle myocardium and epicardium to varying extent.
2. Other types of myocarditis: For example, the imaging manifestations of immune-mediated myocarditis are similar to those of infective myocarditis, so it is difficult to distinguish them by imaging examination alone, comprehensive analysis of clinical characteristics and serological examination is required. If necessary, endocardial myocardial biopsy must be performed to find etiological evidence.

32.6 Research Status and Progress

The clinical manifestations of myocarditis are complex and diverse with different severity. The mild cases are influenza-like, and the severe cases show acute myocardial infarction, severe arrhythmia, and heart failure. Many studies have shown that myocarditis is an important inducement of dilated cardiomyopathy (DCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC).

MRI technology has been developing rapidly. With the development of hardware, coil technique, and post-processing software, the image quality has been enhanced and the accuracy and sensitivity of CMR diagnosis of myocarditis are further improved. However, T_2WI is often interfered by arrhythmia and motion artifacts in clinical practice. Some new imaging methods reflecting tissue characteristics, such as T_1-mapping and T_2-mapping, can overcome these limitations to a certain extent and improve the diagnostic accuracy and are gradually applied to the study of MR imaging of myocarditis. Comprehensive application of these imaging methods is beneficial for CMR to play the potential great role [4, 5].

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