Acute Myocarditis: From Clinical Presentation to Cardiac Imaging

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Abstract: Myocarditis is an inflammatory disease of the myocardium. Despite the progress of laboratory data and cardiac imaging, the diagnosis of myocarditis remains a problem in clinical practice.

We report the role of non invasive cardiac imaging techniques as echocardiography and cardiac magnetic resonance in the diagnosis of acute myocarditis.

Keywords: Myocarditis, cardiac imaging, cardiac magnetic resonance.

INTRODUCTION

The recent definition and classification of cardiomyopathies identifies myocarditis as an inflammatory disease of the myocardium (inflammatory cardiomyopathy) classified among the acquired primary cardiomyopathies [1].

Despite the simplicity of this definition, the diagnosis and treatment of myocarditis remain a problem in clinical practice.

Magnetic resonance imaging as well as computed tomography have showed high accuracy in the diagnosis of many diseases. Particularly, cardiac magnetic resonance (CMR) is considered as the referral method for the identification of pathological substrate of many myocardial diseases [2].

The new imaging techniques and the recent patents address this topic proposing different approaches to be used for the diagnosis of myocarditis.

CLINICAL PRESENTATION, PATHOPHYSIOLOGY AND PATHOLOGY

There are many causes of myocardial inflammation [3, 4]. However, viral infections through direct or immune-mediated myocardial damage represent the most common cause of myocarditis in the Western countries.

The pathogenesis of viral myocarditis can be divided into three phases. In the first phase, there is viral proliferation. In the second phase, there is myocardial tissue damage, either directly or through an immune-mediated mechanism. In the third phase, there is fibrosis and ventricular remodelling [5]. Therefore, myocardial damage due to myocarditis is characterized by the inflammation and subsequent development of myocardial fibrosis. This may be located in any area of the heart muscle, although myocardial damage due to myocarditis prefers a multifocal distribution ("patch distribution"), with predominant involvement of the epicardium of the left ventricular lateral wall [6]. Histologically, viral myocarditis is characterized by the simultaneous presence of abundant inflammatory infiltrate (predominantly lymphocytes and macrophages) and fibrotic tissue with a non-ischemic pattern [6].

THE KEY ROLE OF CARDIAC IMAGING

Although the diagnosis of myocarditis can be reached through a combination of clinical diagnostic criteria, laboratory data, and electrocardiographic findings, often in clinical practice, the differential diagnosis from other forms of cardiomyopathy, such as ischemic and dilated cardiomyopathy, is controversial [7-9].

The variability of clinical presentation (fever, dyspnea, chest pain, diarrhea, heart failure, and sudden cardiac death), the absence of specific laboratory data, and the absence of specific electrocardiographic or echocardiographic patterns of inflammatory cardiac involvement, give primary relevance to the development of new cardiac imaging techniques for the diagnosis of myocarditis.

The difficult diagnosis contributes to an underestimation of the real incidence of this disease, even though approximately 9-12% of sudden cardiac deaths and about 9% of dilatative cardiomyopathies are attributable to myocarditis [10-12]. Therefore, in clinical practice, imaging techniques may become essential during the diagnostic process for a correct prognostic stratification and for testing treatment effectiveness in patients affected by myocarditis.

Nevertheless, in recent years, there has been a downsizing of invasive methods, such as myocardial biopsy, previously considered the gold standard in making the diagnosis of myocarditis [12, 13]. With the Dallas criteria, to obtain an 80% diagnostic sensitivity requires at least 17 biopsies. This criteria also shows a low specificity for the clinical diagnosis of myocarditis due to the abundance of inflammatory cells associated with fibrosis that are found in many other non-inflammatory cardiac conditions [13, 14].

The diagnostic accuracy of myocardial biopsy can be improved with the molecular analysis of the viral DNA extracted from the myocardium by using the polymerase chain reaction (PCR) (immunohistochemical analysis) [13, 14].

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NON-IONIZING CARDIAC IMAGING

Echocardiography

Echocardiography is the imaging technique, first performed in patients with suspected myocarditis [15, 16] because it can detect ventricular size and wall motion abnormalities. The most accurate echocardiographic sign of acute myocarditis is an increased wall thickness due to edema, which is reversible and subsides a few months after the acute phase [15, 16].

Furthermore, echocardiography can detect complications, such as pericardial effusion, thrombus formation and involvement of the right ventricle. Its results are extremely useful in assessing the response to therapy: contractile recovery and wall thickness reduction. The limits of this method are the low specificity in differentiating myocarditis from ischemic and dilated cardiomyopathy (disorders of contraction and dilation are not specific findings of myocarditis) and the low sensitivity in the cases of focal myocarditis with normal ventricular wall motion representing almost one third of myocarditis cases [16].

In order to increase the diagnostic accuracy of echocardiography, in recent years, various applications of echocardiographic methods have been proposed, particularly the backscatter and Doppler tissue derived techniques [17, 18]. Despite encouraging results (presence of greater parietal echogenicity in patients with histologically proven myocarditis), assessment by backscatter tissue is not routinely applied due to the inability to completely differentiate myocarditis from other causes of ventricular systolic dysfunction [18]. The application of tissue Doppler has been suggested as an aid in patients with acute myocarditis [19].

Recently, two dimensional strain echocardiography has shown impairment of longitudinal segmental deformation in patients with epicardial damage due to myocarditis and preserved wall motion [20]. Although, the above applications may increase diagnostic sensitivity, there is still low specificity for differentiating myocarditis from other cardiomyopathies, particularly from ischemic heart disease.

Finally, echocardiography is able to identify left ventricular dimensions and function, the presence of complications and the effect of therapy, but does not allow a differential diagnosis with ischemic heart disease.

CARDIAC MAGNETIC RESONANCE IMAGING

CMR is established in clinical practice for the diagnosis and management of many cardiac diseases. It provides anatomic and functional information and is the most precise technique for quantification of ventricular volumes, function and mass. Among CMR techniques used in clinical practice, delayed contrast enhancement (DCE) is an accurate and reliable method used in the diagnosis of ischemic and nonischemic cardiomyopathies. The most important clinical applications of CMR are: assessment of myocardial viability, evaluation of congenital heart disease with shunt calculation, of valvular disease, evaluation of pericardial disease, evaluation of aortic disease, evaluation of cardiac masses and evaluation of cardiomyopathies [2].

Particularly, the use of CMR has greatly changed diagnostic and therapeutic processes with acute myocarditis. CMR permits recognition of macroscopic tissue characteristics. Particularly, the CMR protocol in myocarditis includes: 1) A cine study by SSFP sequence to quantify volumes and function; 2) The use of T2-weighted images, which allows detection of edema during the acute phase (Fig. **1A**), 3) T1-weighted images (inversion recovery), which with the delayed contrast enhancement (DCE) technique after administration of contrast medium (gadolinium) allows the highlighting of acute myocardial

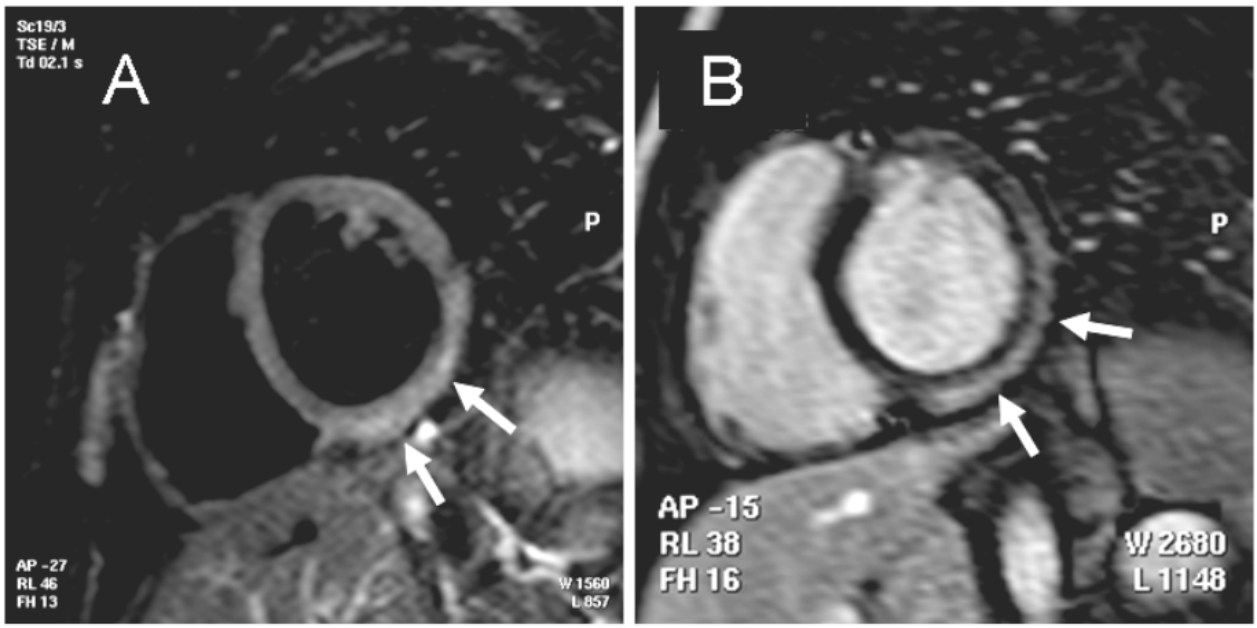

Fig. (1). In basal short-axis view, fat suppressed T2-weighted image shows high signal spots (focal edema) in subepicardial layer of the infero-lateral and inferior wall (**A**). Delayed enhancement showed hyperenhanced area (fibrotic tissue) in subepicardial layer of the inferior, infero-lateral and antero-lateral wall (**B**).

damage (edema, inflammatory infiltrate, fibrosis) and possible chronic scarring (Fig. **1B**) [15, 20].

A recent meta-analysis published by Liu *et al.* [21], demonstrated a mean sensitivity of 86% and a specificity of 95% for CMR during diagnosis of myocarditis. Those positive results could even be improved, when we perform a protocol, including T2-weighted sequences and gradient echo inversion recovery T1-weighted sequences after administration of gadolinium (DCE method) [22].

The main advantage of CMR as compared with other imaging techniques, particularly echocardiography, is the high spatial resolution, which allows tracing of the myocardial damage, often located at the level of the epicardial ventricular wall.

It is sometimes difficult to distinguish between acute myocardial infarction (MI) and acute myocarditis, since both conditions are characterized by chest pain, myocardial-specific enzyme elevation and electrocardiographic, findings characterized by ST segment and T wave changes.

The precise localization of myocardial damage obtained by CMR may help in the differential diagnosis between myocarditis and infarction: in particular, the CMR excludes MI when the endocardial layer is not affected by the disease. The endocardium is always involved in case of MI (ischemic wavefront) (Figs. **2**, **3**), whereas in myocarditis, even if the damage can be located in any area of the heart, it tends to be localized mainly in the epicardium of the lateral wall (Fig. **3**).

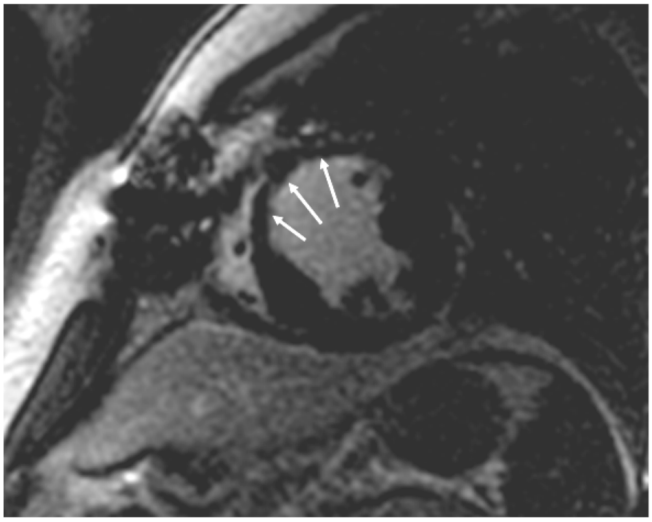

Fig. (2). In distal short-axis view, delayed enhancement shows hyperenhanced area in subendocardial layer of the antero-septal and anterior wall.

However, a transmural localization of damage doesn't permit to exclude an ischemic pattern and therefore, other invasive and non-invasive imaging techniques are needed to exclude or confirm a coronary artery disease.

Furthermore, CMR is able to evaluate the effectiveness of the treatment undertaken and the selection of patients for invasive methods, such as biopsy [21].

Mahrholt *et al.* [22] have recently used the DCE technique to guide ventricular biopsy. Immunohistochemical biopsy performed in areas with DCE-CMR has shown a positive predictive value of 71% and a negative predictive value of 100% for myocarditis [18]. Therefore, once we have selected patients for biopsy, the CMR with DCE will guide the seat cytological collection.

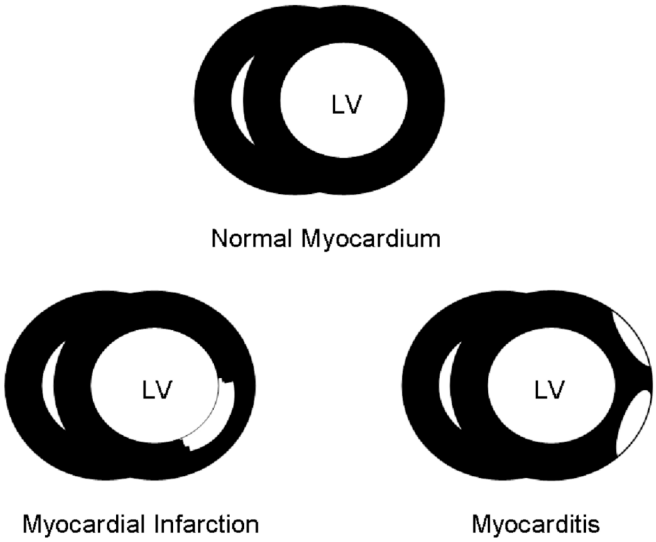

Fig. (3). Different DE patterns among normal subjects, myocardial infarction and myocarditis. If hyperenhancement is present, the endocardium should be involved in patients with ischaemic disease. Epicardial hyperenhancement strongly indicates a 'non-ischaemic' aetiology suggesting myocarditis.

A recent article of Zagrosek *et al.* [23], demonstrated that CMR, including an assessment with both T2-weighted sequences and T1-weighted early acquired (early contrast enhancement) and late (DCE) after injection of gadolinium, enabled a differentiation of reversible from irreversible myocardial damage, as well as the acute phase of myocarditis.

The same authors showed that at 18 months follow-up, the difference in the amount of edema, evidenced in T2-weighted sequences, was the major independent predictor of changes in end-diastolic volume.

For those reasons, CMR is currently considered as the technique giving the most accurate non-invasive diagnosis of myocarditis [24].

TREATMENT OF VIRAL MYOCARDITIS

The clinical presentation and cardiac function play an important role in the therapeutic management of myocarditis. Immunosuppressive agents can be inappropriate, if myocarditis was caused by the direct effect of persisting virus but potentially useful to suppress an ongoing autoimmune inflammatory response. Therefore, the use of steroids remains a discretionary clinical option in acute myocarditis. Diuretics, angiotensin converting enzyme (ACE) inhibitors, beta blocking agents, and spironolactone can be used in patients with heart failure.

RECENT PATENTS IN MYOCARDITIS

Only few patents are specific for the diagnosis of myocarditis:

1. A method for T-wave electrocardiographic monitoring in ambulatory patients with unexplainable

fatigue and suspected to have subacute myocarditis [25].

2. A new assay method consisting in a kit of antibodies capable to detect polypeptide fragments of dystrophin protein cleavage by enteroviral protease 2A. This protein is a result of an enteroviral infection in the heart [26].

3. Another recent patent provides a kit based on assaying for cardiac troponin autoantibodies as an independent indicator of cardiac pathology (myocarditis, cardiomyopathy, and/or ischemic heart disease). In particular, this assay method can be employed in subjects which have an autoimmune disease [27].

CONCLUSION

The diagnosis of myocarditis arises from the integration of clinical information, immunohistochemical analysis, laboratory data and imaging findings.

Today, CMR is the main technique for identifying tissue damage secondary to myocarditis, and concomitantly may allow the exclusion of myocardial damage secondary to MI.

Further studies are needed in order to correlate the histological and imaging information with the various treatment options.

ABBREVIATIONS

PCR = Polymerase chain reaction

CMR = Cardiac magnetic resonance

DCE = Delayed contrast enhancement

MI = Myocardial infarction

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