Myocarditis in Systemic Diseases and the Role of Cardiovascular Magnetic Resonance

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Myocarditis is the inflammatory reaction of the heart due to infectious, toxic, or autoimmune causes. This process can be induced either by exogenous (bacteria, viruses or parasites), or endogenous (autoimmune processes, toxins, etc.) pathogenic factors.1 Although there has been a great deal of discussion in the international community about the role of viral myocarditis,2-6 limited data are available about myocarditis in systemic diseases7-9 and most of them refer to systemic lupus erythematosus (SLE).10,11 The exact mechanism of myocardial inflammation in these diseases varies according to the pathophysiology of the underlying disease.

Evidence of myocarditis in systemic diseases

Systemic vasculitis, an inflammatory necrotizing disease of the blood vessel wall, occurs as a secondary complication in autoimmune, connective tissue diseases.12 The presence of myocarditis has already been reported in many rheumatology papers on necrotizing vasculitis, SLE, and rheumatoid arthritis.13 In Kawasaki disease, myocardial inflammation is universal during the acute phase (100% of cases in both postmortem analysis and myocardial biopsy) and continues to be present during the convalescence phase of the disease.14 In Churg-Strauss syndrome, a form of systemic, necrotizing vasculitis, heart involvement is characterized not only by fibrosis, but also by an active inflammation and may influence therapeutic decisions, even if the Churg-Strauss syndrome is considered to be under clinical remission.15 The differential diagnosis in Churg-Strauss syndrome includes other types of eosinophilic myocarditis that are characterized by eosinophilic infiltration of the myocardium and may occur during the course of the hypereosinophilic syndromes. Usually it responds to withdrawal of the provocative agent or to treatment of the underlying disorder, although corticosteroids maybe needed.16 The clinical manifestations of eosinophilic myocarditis include heart failure and endocardial or valvular fibrosis.

Two idiopathic and histologically similar disorders, giant-cell myocarditis and cardiac sarcoidosis, although rare, should be mentioned. Giant-cell myocarditis is usually fatal. In addition to the idiopathic or primary form, giant-cell myocarditis has been associated with other conditions, including autoimmune diseases such as thymoma, drug hypersensitivity, and celiac disease. It presents as an acute inflammation with ventricular tachycardia and/or heart block with rapid clinical deterioration, despite optimal therapy.17 Giant-cell myocarditis associated with celiac disease can be worsened, if the celiac disease is left untreated. If celiac disease is associ-
ated with autoimmune myocarditis, a gluten-free diet, alone or in combination with immunosuppressives, can improve the one-year survival in giant-cell myocarditis.16,17

Sarcoidosis is a granulomatous disease of unknown etiology that can affect any organ including the heart. Cardiac involvement is uncommon, but is potentially fatal, and sudden death accounts for over half of the fatalities from cardiac sarcoidosis. It produces symptoms in only 5% of patients, although it has been found in 20-50% at autopsy. Granulomata of heart tissue can serve as foci for abnormal automaticity and explain the reentry mechanism leading to ventricular tachycardia. Sarcoidosis involving the heart warrants prompt therapy with steroids, immunosuppressives, or both. The use of an automatic implantable cardioverter defibrillator in combination with aggressive corticosteroid therapy (with or without immunosuppressive therapy) is recommended in sarcoidosis with ventricular tachycardia.18

In SLE, immune-complex mediated vascular disease results in interstitial inflammation and secondary myocyte injury.10 Circulating antibodies such as antimyocardial or anticardiolipin antibodies may also contribute to lupus myocarditis.10 The clinical detection of SLE myocarditis ranges from 3 to 15%, although it is more common in autopsy studies, suggesting the subclinical presentation of the disease.11 A recent postmortem study, in the era of corticosteroids, found lower frequencies, around 0-8%. The clinical presentation is similar to myocarditis due to other causes and can progress to dilated cardiomyopathy. Myocarditis, even when mild, should be treated immediately with high-dose steroids.

The presence of myocarditis has been also documented in scleroderma. In a retrospective review of scleroderma patients, a highly significant association between myositis and myocarditis was documented. Despite an excellent clinical response to steroids, and while they were in therapy, life-threatening conduction system defects appeared in some of these patients.19,20 The coexistence of cardiomegaly, increased cardiac enzymes, tachycardia, reduced ejection fraction, ECG abnormalities and resolution after intense immunosuppression, in the absence of other causes, is consistent with scleroderma myocarditis.21

In rheumatoid arthritis, the presence of myocarditis, due to vasculitis, has been documented in acute congestive heart failure.22 Endomyocardial biopsy revealed heavy endothelial deposits of IgM in small vessels of the myocardium. Prednisone therapy resulted in resolution of heart failure.22,23 Cardiomyopathy associated with rheumatoid arthritis may be the result of focal, non-specific, diffuse necrotizing or granulomatous myocarditis. These entities may be found in 3-30% of rheumatoid arthritis patients in postmortem studies.22,23

In Takayasu disease, the coexistence of myocarditis with subclavian stenosis has already been reported.24-27 Traditionally, the cardiac lesions of Takayasu disease are considered to be the result of aortic regurgitation, hypertension, coronary artery disease and pulmonary vascular involvement. However, in some cases, left ventricular dysfunction was documented without other concurrent diseases. According to previous studies, the natural killer cells and T-lymphocyte-mediated autoimmunity play major roles in the vascular cell injury of Takayasu disease, by releasing the cytotoxic factor perforin. The infiltrating lymphocytes are mainly perforin-secreting T-lymphocytes, and the immunosuppressive therapy in conjunction with conventional heart failure treatment dramatically improves left ventricular dysfunction.24,28

The frequency of heart involvement in patients with myositis varies from 6-75%, depending on whether clinically manifested or subclinical cardiac involvement is considered and the methods used.29,30 Even though cardiovascular events are common causes of death in myositis, clinically overt involvement is rarely evident. However, the increasing number of subclinical cardiac cases suggests that the heart is frequently involved, but is overlooked during the clinical evaluation. Overt cardiac manifestations may appear at the time of diagnosis, or may be manifested after the treatment has been initiated. Heart failure usually occurs simultaneously with the skeletal muscle inflammation, but it may also develop despite low inflammatory activity of skeletal muscles during immunosuppressive treatment or even in remissions of the disease.31

Myasthenia gravis is also included in the group of autoimmune neuromuscular diseases and is characterized by muscle weakness and fatigue, due to skeletal muscle involvement. The prevalence of the disease is approximately 1:7500 (maximal prevalence between the second and third decade in women and the fifth and sixth decade in men), although it may appear at any age. Cardiac involvement may present several forms, ranging from asymptomatic ECG changes to ventricular tachycardia, myocarditis, conduction disorders, heart failure and sudden death.32

In muscular dystrophinopathies (Duchenne and...
Becker disease) the absence or decrease of dystrophin leads to progressive skeletal muscle atrophy and heart failure. Additionally, it has been documented that the abnormal dystrophin can act as a potential susceptibility gene for viral infection of the myocardium. In a recently published study by our group, we documented the rapid left ventricular deterioration over the next 2 years in Duchenne muscular dystrophy patients who had evidence of myocarditis on cardiac magnetic resonance imaging. The findings of myocardial inflammation and viral genomes in the myocardium further supported the hypothesis that myocarditis can act as a precipitating factor for the development of heart failure in Duchenne muscular dystrophy.

In autoimmune thyroid diseases, the classic high-output thyrotoxic heart disease is generally considered as a direct effect of thyroid hormone on the myocardium. In contrast, the cause of the less common low-output heart failure is generally unknown. In a study group consisting of 11 patients, of mean age 47 years at the diagnosis of hyperthyroidism and of 52 years at the diagnosis of cardiac dysfunction, the endomyocardial biopsy revealed severe lymphocytic myocarditis in a patient with severe ophthalmopathy and showed borderline myocarditis in a patient without ophthalmopathy.

Thalassemia, an iron-overload disease, can be occasionally complicated by myocarditis. Iron overload patients are at high risk of acquiring transfusion-transmitted infections that contribute to inflammation of various organs, including the liver and heart. Although the liver inflammation is well documented, there are only a few reports about the possible role of myocarditis as a factor involved in the pathogenesis of left ventricular systolic dysfunction in these patients.

Role of cardiovascular magnetic resonance imaging (CMR) in the diagnosis of myocarditis during the course of systemic diseases

Recently, CMR has emerged as an important technique in the evaluation of cardiovascular disease. CMR contributes to the diagnosis of myocarditis using three types of images: T2-weighted (T2-W), early T1-weighted images taken 1 min and delayed enhanced images taken 15 minutes after the injection of contrast agent. T2-W is an indicator of tissue free-water content, which is increased in inflammation or necrosis, such as myocardial infarction or myocarditis. However, it is not possible to differentiate between necrosis and inflammation only by the use of T2-W images. When a short TI inversion recovery (STIR) sequence was used, the increase in T2 signal intensity demonstrated good accuracy in discriminating between myocarditis and controls.

To further enhance the detection of pathology on CMR, images after early (EGE) and late gadolinium (LGE) injection should be obtained. There are some methodical concerns about EGE, because it is difficult to establish stable conditions after the application of gadolinium, due to the continuous change in the zero run-through after the application of contrast media. Therefore, the time at which the images were taken is crucial. Furthermore, the EGE depends on the assumption that the skeletal muscles exhibit a “normal” pattern of gadolinium enhancement. This assumption is invalid if the inflammation also involves the skeletal muscles.

The third parameter that should be also evaluated is the presence of late gadolinium enhancement contrast (LGE). Fibrosis is distinguished by bright late enhanced areas dispersed in a “cougar-like pattern” and can be focal, intramural or subepicardial (Figure 1).

Currently, more sophisticated techniques, which are able to provide detailed information about both diffuse edema and fibrosis, have become available and are of great interest for systemic diseases. For this purpose, quantitative T2 mapping was proved reliable for the identification of myocardial edema, without the limitations encountered by T2-W images, and could offer the potential for increased accuracy in the detection of myocardial edema. Ad-
ditionally, the application of T1 mapping, which has recently been used to identify diffuse fibrosis in heart failure, looks promising for the detection of diffuse fibrosis in myocarditis.45

Until now, CMR has been successfully used for the evaluation of myocardial inflammation in different type of vasculitis,7-13 Kawasaki disease,14 myositis,46,47 SLE,10,11,48,49 and Takayasu arthritis.24-25 It is important to note that LGE in Churg-Strauss syndrome or other kinds of vasculitis can present an epicardial, intramyocardial and/or diffuse subendocardial pattern15 that is completely different from that of infectious myocarditis. CMR can also reveal myocardial inflammation in SLE and Churg-Strauss with subtle clinical symptoms and normal inflammatory indexes7-9. Additionally, it can offer multiple advantages in the evaluation of heart involvement in vasculitis, combining coronary artery anatomy and viability,7,8,50-52 because in these diseases different pathologic processes, involving different parts of the heart and/or vessels, can coexist in the same patient. In Takayasu arthritis, CMR gives information about both myocardial inflammation and the subclavian arteries or aorta, which are frequently involved during the course of the disease.26

LGE has shown a higher sensitivity than conventional laboratory tests in the detection of myocarditis in inflammatory myopathies.46,47 LGE was also sensitive to the changes that occurred when myositis patients with myocarditis were treated for 6 months with corticosteroids and other immunosuppressants.46 However, its sensitivity and specificity need further evaluation. Another important point is the unreliability of EGE in acute inflammatory myopathies due to muscular inflammation. In these cases only an absolute increase of more than 50% can be used as an inflammatory sign.53 Additionally, in dystrophinopathies like Duchenne and Becker disease, LGE findings due to myocardial degeneration may already exist and under these circumstances a serial CMR evaluation could be of great value.54

In cardiac sarcoidosis, during the acute myocardial inflammation, sarcoid infiltrates are visible on CMR as intramyocardial, epicardial or endocardial hyperenhancement in a non-ischemic pattern with increased signal intensity on both T2-W and LGE images. The early initiation of corticosteroid therapy can prevent malignant arrhythmias and improves left ventricular function. According to some studies, LGE was positive in 26% of patients without clinical evidence of cardiac involvement, and extended to the adjacent endocardium, epicardium, or both.55 Additionally, LGE was more than twice as sensitive for cardiac involvement as current consensus criteria. Myocardial damage detected by LGE was associated with future adverse events, including cardiac death.55

In myocarditis in b-thalassemia, T2 images may be inaccurate. The T2 is already decreased due to iron overload, so conclusions cannot be drawn unless a recent CMR examination, from before the clinical presentation of myocarditis, is available.

In conclusion, CMR, due to its sensitivity in detecting slight tissue composition changes, is the only imaging technique that can provide early, detailed, non-invasive information and has the potential to change the therapeutic approach in myocarditis during the course of systemic diseases. However, further studies are needed to assess its diagnostic significance during the acute and chronic phase of systemic diseases, and its possible contribution as a treatment guide.

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