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Cardiac magnetic resonance imaging in myocardial inflammation in autoimmune rheumatic diseases: An appraisal of the diagnostic strengths and limitations of the Lake Louise criteria

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ABSTRACT

Myocardial inflammation in autoimmune rheumatic diseases (ARDs) is the endpoint of various pathophysiologic processes. The Lake Louise-criteria is the most popular approach for the diagnosis of myocarditis. However, due to the diversity of myocardial inflammation in ARDs, some issues should be acknowledged.

Of the three Lake Louise indices, early and late gadolinium enhancement (EGE and LGE respectively) measurements may be affected by co-existing disease processes or be present due to a fibrotic ARD like systemic sclerosis, leaving T2-ratio as the only uniformly robust measurement across ARDs. It thus becomes apparent that the Lake Louise criteria suffer from a number of limitations when ARD patients are assessed based on them. The introduction of T1/T2 mapping allowed the quantification of intramyocardial fibrosis missed by LGE and the detection of myocardial oedema respectively, both commonly found in ARDs.

The Lake Louise criteria play an important role in the evaluation of AIMI in ARDs. However, the pathophysiologic background of cardiac involvement in ARDs should always be acknowledged in their evaluation. Even though the inclusion of T1/T2 mapping and ECV may better describe diffuse oedema and fibrosis, further investigation pertaining to their implementation in ARD assessment algorithms through multicenter studies is needed.

1. Introduction

Myocardial inflammation in autoimmune rheumatic diseases (ARDs) is the endpoint of various causes, including autoimmune myocardial inflammation (AIMI), vasculitis and effects of disease modifying medications. Until now, little is known about the role of viral or other opportunistic factors that may promote myocardial inflammation in ARDs [1].

AIMI may coexist with hypertension, coronary artery disease and/or diffuse fibrosis, leading to increased cardiovascular morbidity and mortality. Specifically, AIMI in systemic lupus erythematosus (SLE) is immune-complex-mediated and documented by immunofluorescence studies demonstrating granular immune complex and complement deposition in myocardial perivascular tissues. In combined SLE-antiphospholipid syndrome, small vessel vasculitis mimicking myocardial inflammation has been also described [1].

Small vessel vasculitis, such as Churg–Strauss syndrome (CSS), affects mainly small-sized arteries, evolving into fibrinoid necrosis of the vascular media with non-infectious granulomata. Heart involvement was identified in ~85% of cases, presenting as heart failure with reduced ejection fraction (HFrEF). In a CSS patient series by Guillevin et al., 8% of patients died from cardiac disease in the acute CSS phase [2]. In medium vessel vasculitis, such as Kawasaki disease, a coexistence of coronary ectasia/aneurysm with myocarditis and/or myocardial infarction is observed and early diagnosis conveys important clinical implications for both cardiovascular and rheumatic treatment [3]. Finally, in large vessel vasculitis, such as Takayasu disease, a coexistence of great vessel stenosis with AIMI may occur and necessitates prompt treatment [4].

In rheumatoid arthritis (RA) two patterns of AIMI have been described: a granulomatous and a non-specific form and may be observed in quiescent RA, as the first sign of relapse. Furthermore, small vessels vasculitis is not unusual during the course of RA [4]. AIMI in systemic sclerosis (SSc) is a distinct entity occurring in a "millieu" of diffuse myocardial fibrosis. It may present either as silent, chronic inflammation, or as a cardiac emergency demanding prompt

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immunologic treatment [5,6]. Inflammatory myopathies (IMs) are rare autoimmune diseases and include dermatomyositis, polymyositis, necrotizing myopathy and inclusion body myositis. They are characterized by inflammation of skeletal muscle and other internal organs and may lead to irreversible damage and death. Only a small percentage presents with clinically overt cardiac disease; however, heart involvement is a leading cause of death, while early detection remains a challenge [7].

Finally, antimalarial drugs, such as hydroxychloroquine, used for the treatment of SLE, RA and sarcoidosis, represent another rare cause of myocardial inflammation leading finally to cardiomyopathy [8]. In light microscopy the presence of myocardial fibrosis with myocyte vacuolisation is typical for the diagnosis and lamellar bodies on electron microscopy are pathognomonic of this condition [8].

Cardiovascular Magnetic Resonance (CMR) imaging has been successfully used for the evaluation of cardiac lesions in CTDs. Excellent reproducibility, operator independency and capability of performing tissue characterization make CMR a valuable tool for early detection of AIMI [4]. This manuscript discusses the strengths and limitations of currently used Lake Louise criteria for myocarditis diagnosis in ARDs.

2. Lake Louise criteria for the evaluation of myocardial inflammation in ARDs: strengths and limitations

According to Lake Louise criteria, myocardial to skeletal muscle T2 ratio, early (EGE) and late gadolinium enhancement (LGE) imaging should be evaluated. The examination is considered as positive for myocarditis, if 2/3 of the examined indices are positive [9]. These criteria have been successfully used in acute myocarditis detection, with sensitivities and specificities ranging from 53–92% and 57–95%, respectively. However, lower values were seen when endomyocardial biopsies (EMBs) were used as reference standard instead of clinical/angiographic findings [10]. In an EMB-based study, Lurz et al. differentiated the diagnostic performance of the criteria for acute and chronic myocarditis [11]. In acute myocarditis, sensitivity and specificity were 76% and 54%, respectively. However, they were considerably less powerful in chronic myocarditis, yielding low sensitivity and specificity for the diagnosis of EMB-documented chronic myocarditis at 63% and 40%, respectively [12]. In a study on EMB-documented acute and chronic myocarditis, T2-mapping alone yielded an area under an ROC curve (AUC) of 0.81 and 0.77 for the detection of acute and chronic myocarditis, respectively, while the criteria yielded an AUC of 0.56 and 0.53, respectively [12]. These raise concerns about the diagnostic value of the Lake Louise criteria, particularly in patients with chronic myocarditis, a key feature in ARDs [9].

The ARDs with evidence of AIMI, documented in autopsy, are presented in Table 1. Due to the "multifaceted" pathophysiology of AIMI in ARDs, a number of facts should be acknowledged, when we evaluate the Lake Louise criteria in ARDs.

1. Initially, an increase of T2 ratio and/or T2 mapping maybe the only abnormal CMR index in AIMI and can remain abnormal for months without other abnormalities, probably because immunosuppressive treatment prevents full expression of myocardial inflammation, as expected by the Lake Louise criteria [12]. Accordingly, Zhang et al. reported elevated T2-mapping values in low-activity SLEs, with negative LGE [13].
2. EGE measurements maybe not feasible, if there is concurrent skeletal muscle inflammation commonly occurring in SSc [5,6] and IMs [7].
3. LGE can be positive in both myocarditis and vasculitis presenting as patchy, subepicardial or intramyocardial lesions, with Lake Louise criteria unable to distinguish between them. However, in some types of vasculitis, such as CSS and small vessel vasculitis of RA-SLE, LGE may have a pattern of diffuse subendocardial lesions easily differentiated from those due to myocarditis [4].
4. Specifically in SSc, several difficulties may be encountered using the Lake Louise criteria, including the following:
   a) Diffuse myocardial fibrosis constitutes the "trademark" of SSc and thus cannot be considered as an acute myocarditis index. Even the application of T1 mapping is unable to distinguish between oedema and fibrosis, due to SSc [5,6]. In addition, there is great variation in LGE signal intensity, while the significance of this variation remains unknown. A signal intensity above 5 standard deviations (SD) of the normal myocardium should be considered as full intensity LGE and a grayscale analysis of intermediate-signal intensity LGE should be performed for cases with ≥2SD but <5SD of the normal myocardium [13].
   b) In parallel with replacement fibrosis, identified by LGE in SSc, diffuse interstitial fibrosis can also develop. The latter remains unidentified by LGE with only new CMR indices including T1 mapping and extracellular volume index (ECV) able to assess it [5,6] (Figs. 1, 2).
   c) Detection of AIMI in SSc is highly significant, as such patients should be promptly treated with immunosuppressive medication [5,6]. To conclude, we suggest a modification of the criteria to incorporate increases of all CMR inflammatory indices and in particular of T2 values (quantified by T2 mapping) for diagnosing AIMI, especially in SSc with silent presentation.
5. Lake Louise criteria may remain abnormal even if the underlying disease is quiescent, with patients being asymptomatic and optimally treated with immunosuppressive and cardiac medication [14]. This should remain an important consideration, when handling such patients.

3. New CMR indices in myocardial inflammation due to ARDs

Currently proposed T1-based indices reflect myocardial disease involving both myocytes and interstitium, without gadolinium administration (native T1), while ECV is a direct gadolinium-based measurement

Table 1
ARDs with evidence of myocardial inflammation, documented in autopsy.

Systemic lupus erythematosus
Rheumatoid arthritis and other seronegative arthritis
Systemic sclerosis
Vasculitis of large, medium and small vessels
Inflammatory myopathies
Sarcoidosis

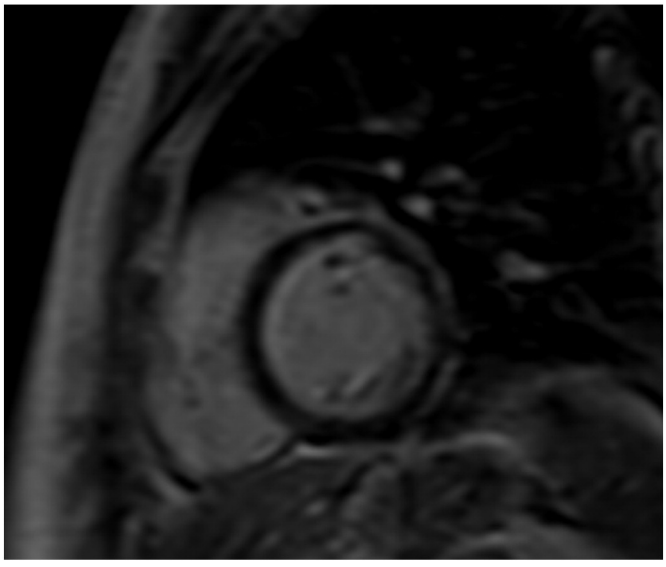

Fig. 1. Inversion recovery image from a SSc patient showing no evidence of LGE.

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