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CLINICAL RESEARCH

Cardiac magnetic resonance imaging with late gadolinium enhancement in acute myocarditis: Towards differentiation between immune-mediated and viral-related aetiologies

Imagerie par résonance magnétique cardiaque avec rehaussement tardif dans la myocardite aiguë : vers la différenciation des étiologies dysimmunitaires et virales

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Abbreviations: CMR, cardiac magnetic resonance imaging; LGE, late gadolinium enhancement.

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KEYWORDS
Acute myocarditis;
Immune-mediated;
Viral-related;
Cardiac magnetic resonance imaging

Summary

Background. — Diagnosing immune-mediated myocarditis is challenging because of non-specific clinical signs and symptoms. Cardiac magnetic resonance imaging (CMR) provides subepicardial late gadolinium enhancement (LGE) in the setting of acute myocarditis, but the diagnostic value of LGE pattern for differentiating between immune-mediated and viral-related aetiologies remains unknown.

Aims. — To determine the value of LGE pattern for differentiating between immune-mediated and viral-related aetiologies in patients with acute myocarditis.

Methods. — One hundred and five patients with acute myocarditis who underwent CMR, including LGE variables, were included retrospectively. Viral-related aetiology was retained with a negative autoimmune and autoinflammatory assessment at diagnosis and 6-month follow-up.

Results. — Aetiology was immune-mediated in 31 patients and viral-related in 74 patients. Patients with immune-mediated myocarditis were older (55 ± 16 vs. 31 ± 12 years; $P < 0.001$) and more likely to be female (52% vs. 14%; $P < 0.001$) than those with viral-related myocarditis. There was no difference in left ventricular ejection fraction between the immune-mediated and viral-related myocarditis groups (53 ± 15% vs. 57 ± 8%; $P = 0.61$). Regarding LGE, patients with viral-related myocarditis were more likely to have basal anteroseptal, mid anteroseptal, mid anterior and basal anterolateral location. Patients with immune-mediated myocarditis were more likely to have apical septal, apical inferior, apical lateral, mid anterolateral and basal inferior location. Segments with difference in prevalence of LGE between aetiologies were summed to build a score where positive significant association with immune-mediated myocarditis was quoted 1 and positive significant association with viral-related myocarditis was quoted −1. A score ≥ 0 differentiated immune-mediated from viral-related myocarditis with 94% sensitivity and 77% specificity (area under the receiver operating characteristic curve 0.88; $P < 0.001$).

Conclusion. — CMR provides arguments for differentiating immune-mediated from viral-related acute myocarditis by showing preferential LGE localization in apical septal, apical inferior, apical lateral and basal inferior segments.

MOTS CLÉS
Myocardite aiguë ;
Dysimmunitaire ;
Viral ;
Imagerie par résonance magnétique cardiaque

Résumé

Contexte. — Le diagnostic de la myocardite dysimmunitaire (MD) est difficile en raison de symptômes et signes cliniques aspécifiques. L'imagerie par résonance magnétique (IRM) cardiaque fourni un rehaussement tardif (RT) sous-épicardique du gadolinium dans le diagnostic de myocardite aiguë, mais la valeur diagnostique RT pour la différenciation des MD et virales (MV) demeure inconnue.

Objectifs. — Cette étude vise à déterminer la valeur du RT dans la différenciation les MD et MV chez les patients atteints de myocardite aiguë.

Méthodes. — Cent cinq patients atteints d'une myocardite aiguë ayant eu une IRM cardiaque avec RT ont été inclus rétrospectivement. Le diagnostic de MV a été retenu au décours d'une évaluation auto-immune et auto-inflammatoire négative au diagnostic et au suivi à 6 mois.

Résultats. — Le diagnostic de MD et de MV a été retenu chez 31 et 74 patients, respectivement. Les patients atteints de MD étaient plus âgés (55 ± 16 contre 31 ± 12 ans ; $p < 0{,}001$) et plus susceptibles d'être des femmes (52 % contre 14 % ; $p < 0{,}001$) que ceux atteints de MV. Il n'y avait pas de différence entre les MD et les MV en termes de fraction d'éjection du ventricule gauche (53 ± 15 % contre 57 ± 8 % ; $p = 0{,}61$). En ce qui concerne le RT, les patients atteints de MV étaient plus susceptibles d'avoir une localisation antéro-septale basale, antéro-septale médiane, antérieure médiane et antéro-latérale basale que ceux atteints de MD. Les patients atteints de MD étaient plus susceptibles d'avoir une localisation septale apicale, inférieure apicale, latérale apicale, antéro-latérale médiane et inférieure basale que ceux atteints de MV. Les segments présentant une différence de prévalence de RT entre les étiologies ont été additionnés pour obtenir un score où une association positive avec la MD a été cotée 1 et une association positive avec la MV, −1. Un score ≥ 0 différencie la MD de la MV avec une sensibilité de 94 % et une spécificité de 77 % (aire sous la courbe ROC 0,88 ; $p < 0{,}001$).

Conclusion. — L'IRM cardiaque fournit des arguments pour différencier les MD des MV en montrant une localisation préférentielle du RT en regard des segments septo-apical, inféro-apical, latéro-apical et inféro-basal.

Background

Systemic immune-mediated diseases, including autoimmune and autoinflammatory diseases, may directly affect the myocardium, leading to myocardial inflammation, cardiomyocyte dysfunction or loss and heart failure [1]. Cardiac involvement in systemic immune-mediated diseases is associated with adverse outcomes [2]. The clinical presentation of myocarditis is unspecific, and cardiac involvement in systemic immune-mediated diseases can be heterogeneous. The differentiation between myocarditis as part of a systemic immune-mediated disease and isolated myocarditis can be difficult, leading to late recognition or underdiagnosis and undertreatment of cardiac involvement [3]. Because diagnosis of immune-mediated myocarditis is essential for therapeutic choices, the European Society of Cardiology recently published a position paper on the diagnosis and management of myocardial involvement in systemic immune-mediated diseases [4]. However, in the absence of previously known systemic immune-mediated disease, diagnosis of immune-mediated myocarditis can be challenging. In patients with newly diagnosed myocarditis, the presence of underlying systemic immune-mediated disease is associated with distinct baseline clinical features [2]. However, to date, there is no imaging technique allowing differentiation between immune-mediated myocarditis and isolated (typically viral-related) myocarditis. Subepicardial late gadolinium enhancement (LGE) pattern by cardiac magnetic resonance imaging (CMR) allows differentiation between myocarditis and coronary artery disease [5], and correlates with disease activity in rheumatoid arthritis [6] and systemic sclerosis [7]. However, the value of LGE pattern in differentiating between immune-mediated and viral-related myocarditis has not been shown.

The aim of this study was to determine the value of CMR in differentiating between immune-mediated and viral-related aetiologies in a cohort with acute myocarditis, with regard to the myocardial pattern of LGE.

Methods

Study population

Patients admitted to the Department of Cardiology at Rangueil Hospital (Toulouse, France) with a final diagnosis of acute myocarditis and referred for CMR between 2015 and 2017 were included retrospectively. Only patients with onset of cardiovascular symptoms within 1 week before admission were considered. Patients with history or current diagnosis of ischaemic heart disease or alternative diagnosis at discharge were excluded. Thus, the study cohort included 105 patients with acute myocarditis.

Patients were divided into two groups according to the supposed inflammatory mechanism: viral-related myocarditis (acute myocarditis presenting with viral prodromal symptoms; $n = 74$) and immune-mediated myocarditis (acute myocarditis presenting with a clinical history or systemic findings suggestive of autoimmune or autoinflammatory disease; $n = 31$). Viral-related aetiology was definitely retained after excluding circulating hypereosinophilia, and with a negative autoimmune and autoinflammatory assessment at diagnosis and at 6-month follow-up. Immune-mediated aetiology was finally retained according to anamnestic, clinical or laboratory features indicating possible autoimmune or systemic disorder, and after excluding circulating hypereosinophilia at diagnosis and at 6-month follow-up. Systemic immune-mediated disease was retained when fulfilling at least two of the major criteria proposed by Witebsky and Rose (i.e. direct evidence from transfer of pathogenic antibody or pathogenic T cells; indirect evidence based on reproduction of the autoimmune disease in experimental animals; or circumstantial evidence from clinical clues) [8].

The study conformed with the principles outlined in the Declaration of Helsinki. All patients were informed at the admission that their clinical data could be used for research purpose, and gave their consent. The study was approved by our institutional review board.

Diagnosis of myocarditis

Clinically, myocarditis was suspected based on medical history, presenting symptoms (chest discomfort, dyspnoea) and signs, altered electrocardiogram, echocardiography and biomarkers of myocardial necrosis and inflammation, and after exclusion of coronary artery disease (either by coronary angiography or after ruling out LGE suggestive of coronary artery disease by CMR). Based on risk-benefit considerations, CMR was the non-invasive technique of choice for confirming the diagnosis, while endomyocardial biopsy was pursued in patients with haemodynamic compromise and/or severe myocardial dysfunction (i.e. left ventricular ejection fraction < 35% by transthoracic echocardiography at admission). Patients were excluded if they had concomitant coronary artery disease, based on medical history or on the results of coronary angiography or CMR.

CMR protocol

CMR was performed in breath-hold mode with the use of a 1.5T MR commercial scanner — either Avanto (Siemens Medical Solutions, Erlangen, Germany) or Intera (Philips Medical Systems, Best, The Netherlands) — using a 12-element phased-array cardiac coil with vector-cardiac gating in all patients. Following scout imaging, balanced steady-state free precession breath-hold images were acquired: slice thickness 6 mm (long-axis and four-chamber views) or 8—10 mm (contiguous short-axis views) with no gap between slices, from the atrioventricular ring to the apex. Subsequently, standard sequences for T2-weighted and LGE-CMR images were obtained in the same long-axis, four-chamber and short-axis orientations, 10 minutes after injection of 0.2 mmol/kg of gadolinium dimeglumine (Magnevist; Berlex Imaging, Wayne, NJ, USA), using a phase-sensitive inversion recovery spoiled gradient echo sequence. Diagnosis of acute myocarditis was retained when patients expressed regional subepicardial or midwall oedema visible on T2-weighted sequences associated with LGE [9].

CMR analysis

Image analysis was performed independently by a single observer (F. S.). In brief, the endocardial border was outlined on the short-axis cine images on the right and left ventricles, in systole and diastole, from the base to the apex. Volumes and ejection fractions were calculated using clinically available software: Argus (Siemens Medical Solutions) and ViewForum (Philips Medical Systems). The extent of LGE was planimetered on the short-axis contrast images, and confirmed on an orthogonal view (either long-axis or four-chamber) with the use of an image intensity level ≥ 2 standard deviations above the mean of remote myocardium to define LGE. The 17-segment model, as defined by the American Society of Echocardiography, was used to localize LGE within the left ventricle. For each segment, the extension of subepicardial or midwall LGE through the myocardium was then assessed and classified as null, < 25%, between 25% and 50% or > 50% of the myocardial thickness.

Statistical analysis

Continuous variables are expressed as means ± standard deviations. Nominal values are expressed as numbers and percentages. Because laboratory findings were not normally distributed, results are presented as median values (interquartile ranges). Association between the mean values of continuous variables was compared using the Mann—Whitney rank sum test. Nominal variables were investigated by Fisher's exact test. The accuracy of LGE location for predicting myocarditis aetiology was assessed by computing the areas under the receiver operating characteristic curves, and the best cut-off value was defined as the point with the highest sum of sensitivity and specificity. Differences were considered statistically significant for *P*-values < 0.05. All analyses were performed using standard statistical software (SPSS, version 20; SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

A total of 105 consecutive patients with acute myocarditis confirmed by CMR were enrolled in the study. Demographics, medical history and results of laboratory testing are listed in Table 1. Patients with immune-mediated myocarditis were older (55 ± 16 vs. 31 ± 12 years) and more likely to be female (52% vs. 14%), with more history of arterial hypertension and diabetes, but were less likely to be smokers compared with patients with viral-related acute myocarditis. At presentation, patients with immune-mediated myocarditis were more likely to have heart failure symptoms, with more dyspnoea, an increased heart rate and a higher concentration of N-terminal prohormone of B-type natriuretic peptide compared to patients with viral-related myocarditis. There was no difference in left ventricular ejection fraction assessed by transthoracic echocardiography. Extracardiac symptoms were more frequent in patients with immune-mediated myocarditis, whereas chest pain was present in almost all patients with viral-related myocarditis. High-sensitivity C-reactive protein and leucocyte cell count were higher in patients with immune-mediated myocarditis, whereas troponin concentrations were lower. Patients with viral-related myocarditis had a higher prevalence of ST-segment elevation at presentation, whereas patients with immune-mediated myocarditis were more likely to have arrhythmia (3—10%, patients with atrial fibrillation; and 1—3%, patients with non-sustained ventricular tachycardia). Endomyocardial biopsy was performed in 16% of patients with immune-mediated myocarditis compared with no patients with viral-related myocarditis. There were no procedural complications. The final diagnoses of the autoimmune diseases associated with immune-mediated myocarditis are presented in Table 2. Dedicated investigations and a disease specialist confirmed all diagnoses.

CMR pattern

T2-positive hypersignal was present in 2.3 ± 1.7 segments among patients with viral-related myocarditis, and in 2.7 ± 2.2 segments among patients with immune-mediated myocarditis ($P = 0.42$). T2-positive hypersignal was more frequent in segment 6 in patients with viral-related myocarditis (54% vs. 23%; $P = 0.001$), whereas it was more frequent in segment 16 in patients with immune-mediated myocarditis (32% vs. 4%; $P = 0.003$).

Subepicardial or midwall LGE was present in 3.5 ± 2.5 segments among patients with viral-related myocarditis, and in 3.5 ± 2.8 segments among patients with immune-mediated myocarditis ($P = 0.86$). Among segments with LGE, the extension of LGE through the myocardium was < 25% and between 25% and 50% of the myocardial thickness in 85% and 15% of the segments, respectively, for patients with viral-related myocarditis, and in 80% and 20% of the segments, respectively, for patients with immune-mediated myocarditis ($P = 0.35$). Left ventricular volumes and ejection fraction by CMR according to the aetiology are presented in Table 3. Prevalence of LGE by segment according to the aetiology, and difference in prevalence by segment between viral-related and immune-mediated myocarditis are presented

Table 1 Baseline characteristics.

	Viral-related myocarditis ($n = 74$)	Immune-mediated myocarditis ($n = 31$)	P
Age (years)	31 ± 12	55 ± 16	< 0.0001
Men	64 (86)	15 (48)	< 0.0001
Body mass index (kg/m^2)	26 ± 4	24 ± 4	0.09
Cardiovascular risk factors			
Diabetes mellitus	0 (0)	5 (16)	0.002
Hypertension	2 (3)	5 (16)	0.023
Hypercholesterolaemia	5 (7)	4 (13)	0.25
Active smoking	28 (38)	4 (13)	0.009
History of smoking	11 (15)	6 (19)	0.38
Clinical presentation			
Orthopnoea/paroxysmal dyspnoea	0 (0)	7 (22)	< 0.0001
Palpitations	2 (3)	1 (3)	0.65
Chest pain	73 (99)	11 (35)	< 0.0001
Cardiogenic shock	0 (0)	2 (6)	0.09
Extracardiac symptoms	15 (20)	25 (80)	< 0.0001
Fever	7 (9)	5 (16)	0.25
NYHA stage			
I	70 (95)	19 (61)	< 0.0001
II	4 (5)	5 (16)	0.08
III	0 (0)	5 (16)	0.002
IV	0 (0)	2 (6)	0.09
Respiratory tract infection	18 (24)	10 (32)	0.27
Gastrointestinal disorders	8 (11)	4 (13)	0.50
Flu syndrome	19 (26)	5 (16)	0.21
Systolic blood pressure (mmHg)	112 ± 13	121 ± 23	0.19
Diastolic blood pressure (mmHg)	75 ± 11	74 ± 9	0.76
Heart rate (beats/min)	77 ± 13	86 ± 14	0.002
ECG at admission			
Normal	21 (28)	11 (35)	0.24
ST-segment elevation	43 (58)	5 (16)	< 0.001
Other abnormal ST-T segment	12 (16)	9 (29)	0.11
Bundle branch block	1 (1)	2 (6)	0.19
Arrhythmia	0 (0)	4 (13)	0.007
Laboratory findings			
hs-CRP at admission (mg/L)	27 (11–63)	58 (10–220)	0.09
Troponin T at admission (ng/mL)	479 (308–1057)	296 (50–844)	0.015
Peak troponin T (ng/mL)	949 (396–1540)	423 (114–965)	0.026
Leucocyte cell count (10^9/L)	9 (7–11)	11 (8–17)	0.004
NT-proBNP (ng/mL)	382 (103–1076)	3562 (487–9202)	< 0.0001
Creatinine (μmol/L)	85 (74–95)	65 (55–94)	0.013
Echocardiography at admission			
LVEF (%)	57 ± 8	53 ± 15	0.61
Indexed LVEDV (mL)	60 ± 11	60 ± 20	0.71
Coronary angiography performed	30 (41)	13 (42)	0.53
Endomyocardial biopsy performed	0 (0)	5 (16)	0.002

Data are expressed as mean ± standard deviation, number (%) or median (interquartile range). ECG: electrocardiogram; hs-CRP: high-sensitivity C-reactive protein; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal prohormone of B-type natriuretic peptide; NYHA: New York Heart Association.

in Figs. 1 and 2, respectively. Segments with difference in prevalence of LGE between aetiologies were summed to build a score where positive significant association with immune-mediated myocarditis was quoted 1 and positive significant association with viral-related myocarditis were quoted −1. The final score ranged from −5 to 5. The area under the receiver operating characteristic curve for the diagnosis of immune-mediated myocarditis using the score was 0.88 (95% confidence interval 0.82—0.94; $P < 0.001$) (Fig. 3). The sensitivity and specificity of the score to diagnose immune-mediated myocarditis were 94% and 77%, respectively, when the score was zero or positive.

Table 2 Autoimmune diseases associated with immune-mediated myocarditis (31 cases).

Autoimmune disease	Number of patients (%)
ANCA-associated vasculitis	9 (29)
Systemic lupus erythematosus	4 (13)
Systemic sclerosis	4 (13)
Adult-onset Still's disease	3 (10)
Antisynthetase syndrome	2 (6)
Behcet's disease	2 (6)
Hashimoto thyroiditis	2 (6)
Neutrophilic dermatosis	1 (3)
Sjogren's syndrome	1 (3)
Ankylosing spondylitis	1 (3)
Crystalglobulin-induced disease	1 (3)
Undifferentiated connective tissue disease	1 (3)

ANCA: antineutrophil cytoplasmic antibody.

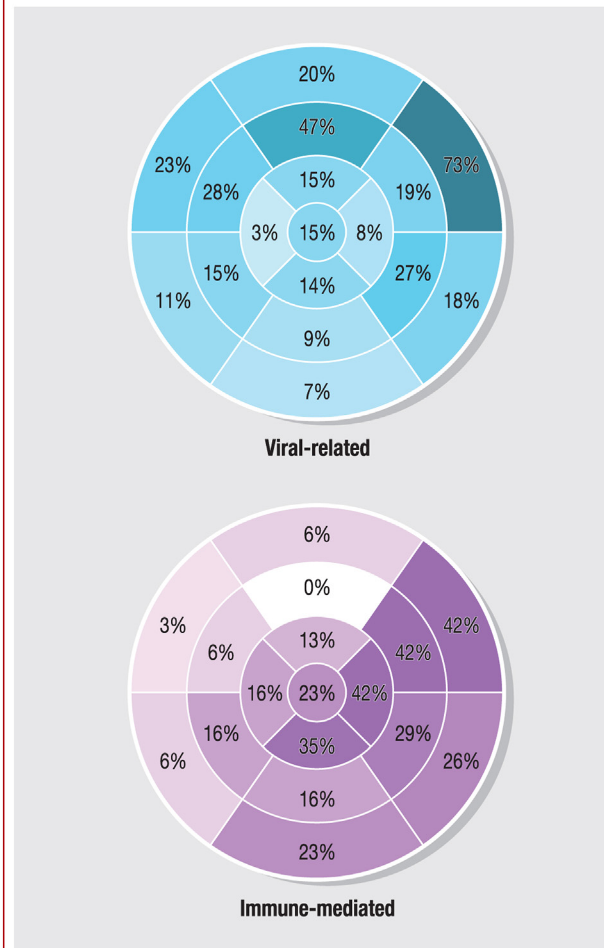

Figure 1. Spatial distribution of the prevalence of subepicardial late gadolinium enhancement by segment, according to aetiology, represented as bull's eye maps.

Discussion

Our study shows that there is a difference in subepicardial or midwall LGE location between immune-mediated and viral-related acute myocarditis: viral-related myocarditis is more likely to have basal anteroseptal, mid anteroseptal, mid anterior and basal anterolateral LGE location, whereas immune-mediated myocarditis is more likely to have apical septal, apical inferior, apical lateral, mid anterolateral and basal inferior location than viral-related myocarditis.

By summing segments associated with aetiology where association with immune-mediated myocarditis is quoted 1 and association with viral-related myocarditis is quoted −1, a score ≥ 0 differentiates both aetiologies with 94% sensitivity and 77% specificity. A score ≥ 2 raises the specificity and should lead to the suspicion of immune-mediated myocarditis. To our knowledge, this is the first study showing to potential ability of CMR to differentiate between immune-mediated and viral-related acute myocarditis.

LGE in acute myocarditis can have multiple patterns, each with a different prognostic impact [10]. In patients with viral-related acute myocarditis, a previous study showed that LGE pattern depends on the virus involved: patients with parvovirus B19 have typical subepicardial LGE in the lateral wall, whereas patients with human herpesvirus 6 and with human herpesvirus 6/parvovirus B19 myocarditis have septal LGE [11]. It is interesting to note that, in this study, LGE mainly affected the basal and medial segments, with an anterior predominance, and affected the apical segments only very slightly, which corresponds typically to a viral aetiology, according to our results.

Although there are statistical differences in the location of the LGE between viral-related and immune-mediated acute myocarditis, the pattern of each aetiology is not so clear, and there is a likely overlap between the different aetiologies. Systemic immune-mediated diseases include a heterogeneous set of pathologies, and their expression has

Table 3 Cardiac magnetic resonance findings according to myocarditis aetiology.

	Viral-related myocarditis($n = 74$)	Immune-mediated myocarditis($n = 31$)	P
Indexed LVESV (mL/m^2)	36 ± 9	40 ± 22	0.95
Indexed LVEDV (mL/m^2)	79 ± 12	82 ± 27	0.95
LVEF (%)	55 ± 7	51 ± 15	0.70

Data are expressed as mean ± standard deviation. LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVEF: left ventricular ejection fraction.

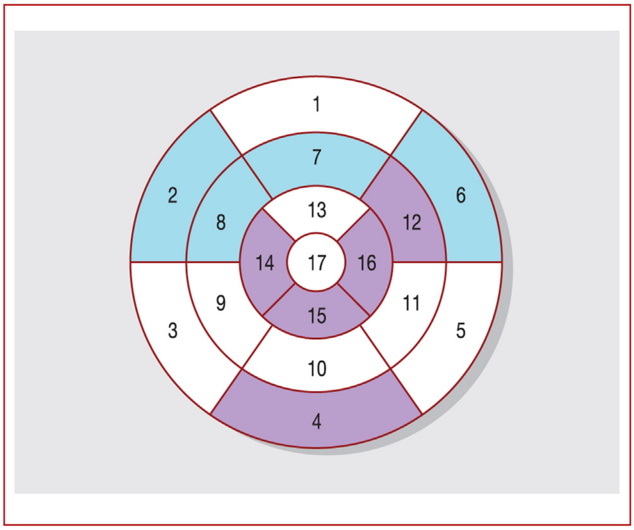

Figure 2. Left ventricular segments with difference in prevalence of subepicardial late gadolinium enhancement between aetiologies, represented as a bull's eye map: blue segments are statistically associated with viral-related myocarditis and purple segments with immune-mediated myocarditis.

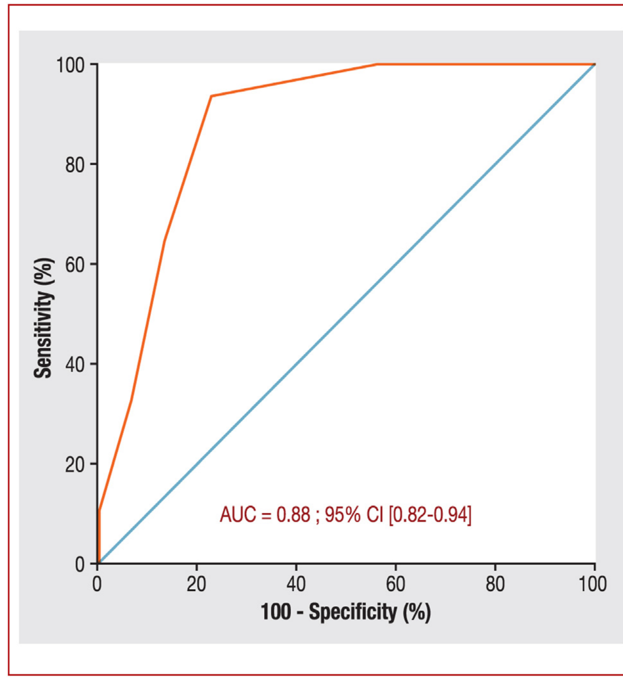

Figure 3. Receiver operating characteristic curve for the diagnosis of immune-mediated myocarditis, using the diagnostic score based on late gadolinium enhancement location. AUC: area under the curve; CI: confidence interval.

long been known to be influenced by environmental factors [12]. Cardiac inflammatory disease has been described in association with many systemic immune-mediated diseases. As the expression of systemic immune-mediated diseases is influenced by many external factors, it is legitimate to believe that associated immune-mediated myocarditis and its expression depends on many factors, and does not represent a homogeneous spectrum. This is also true for viral-related myocarditis, for which the pattern of the LGE depends on the virus involved [11].

Finally, myocarditis consists of a set of heart-specific immune processes, and the distinction between isolated viral-related and immune-mediated aetiologies is unclear. In some cases, viral ribonucleic acid and inflammation persist in the heart, triggering myocardial autoimmune reactions [1], leading to an overlap between isolated viral-related aetiology and immune-mediated response. It is also likely that immune inflammatory cardiomyopathy may be particularly prone to viral infections, making aetiological assessment complex.

Study limitations

Our study has all the limitations associated with retrospective, single-site, limited-sample studies. Furthermore, and as mentioned previously, immune-mediated acute myocarditis has been classified as a single entity, whereas it includes a heterogeneous set of pathologies. Our results are limited to 31 patients with immune-mediated myocarditis and have not been validated in an external cohort. However, while not providing any definitive conclusions, this pilot study suggests that an LGE pattern of acute myocarditis could lead to the suspicion of an associated systemic immune-mediated disease.

Diagnosis of acute myocarditis theoretically requires endomyocardial biopsy, using established histological, immunological and immunohistochemical criteria [13]. Detection of inflammation and the viral genome by polymerase chain reaction remain the gold standard strategies for the diagnosis of viral myocarditis. We cannot certify the viral aetiology of the myocarditis we have explored. However, the viral genome is detected in the myocardium in fewer than half of the cases, and virus serology has no relevance for the diagnosis of myocardial infection [14]. Furthermore, because LGE is not systemically present in acute myocarditis [15], we cannot exclude having missed some myocarditis without a positive LGE. However, because we did not perform systematic endomyocardial biopsy, we have chosen to focus on specificity, to avoid overdiagnosis of myocarditis.

Finally, our study does not use the latest CMR parametric mapping sequences, which have shown incremental value for the diagnosis of acute myocarditis [16]. Patients were included between 2015 and 2017, and mapping sequences were not yet implemented at that time. However, while it seems undeniable that such sequences can bring a benefit, most centres still use — and will continue to use — LGE, and the objective of our study was to describe a pattern of immune-mediated myocarditis, regardless of the technical aspect. This work opens the prospect of new studies using the latest existing techniques. Our results will have to be confirmed and refined using mapping sequences.

Conclusions

CMR provides arguments for differentiating between immune-mediated and viral-related acute myocarditis by showing a different subepicardial LGE pattern.

Immune-mediated myocarditis appears to have preferential LGE localization in apical septal, apical inferior, apical lateral and basal inferior segments. LGE pattern by CMR could lead to suspicion of systemic immune-mediated disease associated with acute myocarditis.

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None.

Disclosure of interest

The authors declare that they have no competing interest.

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