CASE SERIES

Accordion sign in COVID 19 related acute myocarditis, an old sign for a novel context? A cardiac magnetic resonance case series report study

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ABSTRACT

INTRODUCTION: The COVID-19 pandemic is related to a higher incidence of myocarditis; we present a case series of seven patients, admitted with COVID-19 related acute myocarditis, evaluated with cardiac magnetic resonance imaging, showing an altered profile of the free wall of the right ventricle, no longer present after six months follow-up. MATERIALS AND METHODS: Seven patients have been evaluated for COVID-19 related acute myocarditis, all patients have been evaluated with cardiac magnetic resonance imaging both in the acute setting and after six months follow-up. RESULTS: In the acute phase, myocarditis was confirmed in keeping with the current diagnostic criteria. In five out of seven cases, the presence of a crinkling profile of the free wall of the right ventricle was observed; at six months follow up, remission in four out of the five cases and a significant reduction in the remaining case, of the previously described findings, was observed. CONCLUSIONS: Crinkling appearance in the profile of the free wall of the right ventricle, detectable with cardiac magnetic resonance imaging, might represent a morphological feature present in the acute setting of COVID-19 related myocarditis; several underlying physiopathological mechanisms are conceivable. Further studies are needed to confirm this correlation, define the underlying mechanisms and the prognostic implication related to it. This is the first report in the literature that has considered such findings to the best of our knowledge.

KEYWORDS: cardiac magnetic resonance imaging; right ventricle; myocarditis; COVID-19 disease

BACKGROUND

The COVID-19 pandemic is related to a higher incidence of myocarditis [1], cardiac magnetic resonance imaging (CMRi) represents the gold standard in imaging for the diagnosis of the disease [2], allowing the detection and quantization of non-ischemic myocardial edema and injury; however, CMRi also allows a more accurate definition of the morphology and function of the cardiac chambers. In this regard, we present a case series of seven patients evaluated with CMRi in the acute phase of myocarditis related to a COVID-19 infection, five of which showing an altered profile of the free wall of the right ventricle, no longer present or significantly less evident after six months follow-up.

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MATERIALS AND METHODS

From the beginning of the pandemic to now, in the Magnetic Resonance Laboratory of 'Di Summa-Perrino' Hospital di Brindisi, seven patients have been evaluated for myocarditis COVID-19 related. All patients have been scanned on Philips Achieva 1.5 Tesla system. SSFp, DIR/T1w, TIR/T2w, LGE sequences were performed. Post-processing has been performed on Philips MR Cardiac Explorer software; all the exams have been attended, evaluated, post-processed and reported both by two Radiologists and a Cardiologist with level III CMR accreditation. All patients were admitted to the Cardiology unit for Covid-19 infection, demonstrated by positive Reverse Transcription-Polymerase Chain Reaction (RT-PCR) swab, complicated by myocarditis, defined according to the current diagnostic criteria [3]. All the patients have been evaluated with the dosage of C-Reactive Protein (CRP) expressed in mg/dL with reference values of 0 to 1 mg/dL and high sensitivity troponin (HsTn),

expressed in ng/L with reference values of 0 to 32 ng/L, electrocardiogram (ECG), transthoracic echocardiography (TTE) and CMRi both in the acute setting and after six months follow-up. Coronary angiography was performed in all patients only in the acute setting; the comparison of the morphological aspects concerning the right ventricle was carried out side by side, with the same sections at the same phase of the cardiac cycle.

RESULTS

Five of the seven patients reported chest pain as the main onset symptom, one reported dyspnea, and the remaining did not report specific symptoms. All patients exhibited nonspecific ECG changes in the repolarization phase, elevated HsTn and CRP values, normal volume and preserved global systolic function of both right and left ventricles both on TTE and CMRi. In all cases, coronary angiography showed the evidence of coronary arteries free from significant stenosis; all patients showed the presence of myocardial edema with subepicardial distribution in the sequences of TIR/T2w with corresponding striae of enhanced signal with subepicardial distribution on late Gadolinium enhancement (LGE) sequences. In five out of seven cases, the presence of a crinkling profile of the free wall of the right ventricle was observed; this phenomenon appeared to involve mainly the mid-apical segments of the wall and was more evident in the systolic phase of the cardiac cycle. DIR/T1w and TIR/T2w sequences showed no signal alterations at the RV free wall; at six months follow-up, for all seven patients, there was recovery from COVID-19 infection documented by a negative RT-PCR swab and all patients were free from symptoms presenting normal HsTn and CRP values. Remission of electrocardiographic abnormalities was observed in six out of seven patients and regression of edema detectable by CMRi with residual LGE striae with subepicardial distribution was observed in six out of seven patients, findings compatible with residual scar in healed myocarditis, while persisting edema with residual LGE striae with subepicardial distribution was observed in the remaining patient, as per persistence of active inflammation; this latter case showed normal HsTn and upper limit CRP value. Normal volume and preserved global systolic function on both right and left ventricle were confirmed on TTE and CMRi. Also, no signal alterations were detected at the RV free wall on and DIR/T1w and TIR/Tw sequences on CMRi; remission in four out of the five cases and a significant reduction in the remaining case of the previously described changes in the profile of the free wall of the right ventricle was observed; demographic, clinical, CRP, HsTn and ECG data are reported in Table 1 for acute setting and Table 2 for six months control; TTE and CMRi data are reported in Table 3 for acute setting and Table 4. for six months control. CMRi images of two cases are shown in Figure 1 and Figure 2.

DISCUSSION

The COVID-19 pandemic is related to a higher incidence of myocarditis and general CMRi diagnostic criteria for the diagnosis of myocarditis has been well defined recently and include detection and quantization of non-ischemic myocardial edema on T2 mapping and TIR/T2 weighted, native T1, as well as extracellular volume and LGE sequences for inflammatory injury [3,4]; more specifically, the central role of CMRi and its use in the Covid 19 disease management pathway has been defined as well [5]. The evaluation of the right ventricle in the context of cardiac imaging has always been a challenging area; the introduction of CMRi allowed a clearly more accurate definition of the morphology and function of the right ventricle in comparison to the tests available up until its advent [6-8]. However, even through CMRi, if it is true that the evaluation of the volumes and function of the right ventricle is relatively simple and above

Table 1 - Acute setting. Demographic, symptoms, C-reactive protein, high sensitivity troponin and ECG data in the acute phase.

Patient	Gender	Age	Onset symptoms	C-PR mg/dL	HsTn peak ng/L	ECG Repolarization changes
1	F	57	chest pain	12	5673	infero-lateral
2	M	24	chest pain	7.8	11567	septal, anterior
3	F	36	general discomfort	6.8	2378	anterior, inferior
4	M	19	chest pain	11	4536	antero-lateral
5	M	34	dyspnea	5.3	3456	inferior
6	F	41	chest pain	12.7	8970	inferior
7	M	43	chest pain	3.7	7908	infero-lateral

Table 2 - Six months follow-up. Demographic, symptoms, C-reactive protein, high sensitivity troponin and ECG data at six months follow-up.

Patient	Gender	Age	Symptoms	C-PR mg/dL	HsTn ng/L	ECG Repolarization changes
1	F	57	no	0.5	12	no
2	M	24	no	0.4	4	no
3	F	36	no	0.3	2	no
4	M	19	no	0.8	7	antero-lateral
5	M	34	no	1	11	no
6	F	41	no	0.5	6	no
7	M	43	no	0.7	7	no

Table 3 - Acute setting. Transthoracic echocardiography (TTE) and cardiac magnetic resonance imaging (CMRi) findings in the acute phase; EDVi: end diastolic volume indexed; E.F.: ejection fraction; LGE: late gadolinium enhancement; RV: right ventricle.

Patient	Gender	Age	TTE EDVi (ml/m2)	TTE E.F. (%)	CMRi EDVi (ml/m2)	CMRi E.F. (%)	Edema	LGE	RV wall profile
1	F	57	66	58	80	57	infero-lateral	infero-lateral	crinkling
2	M	24	53	56	66	61	infero-septal, antero-septal, anterior	infero-septal, antero-septal, anterior	normal
3	F	36	40	64	60	65	antero-lateral, infero-lateral	antero-lateral, infero-lateral	crinkling
4	M	19	71	67	88	65	antero-lateral	antero-lateral	crinkling
5	M	34	66	59	85	63	inferior	inferior	normal
6	F	41	58	60	77	65	inferior	inferior	crinkling
7	M	43	57	71	73	68	infero-lateral	infero-lateral	crinkling

Table 4 - Six months follow-up. Transthoracic echocardiography (TTE) and cardiac magnetic resonance imaging (CMRi) findings at; EDVi: end diastolic volume indexed; E.F.: ejection fraction; LGE: late gadolinium enhancement; RV: right ventricle.

Patient	Gender	Age	TTE EDVi (ml/m2)	TTE E.F. (%)	CMRi EDVi (ml/m2)	CMRi E.F. (%)	Edema	LGE	RV wall profile
1	F	58	68	59	79	59	no	infero-lateral	normal
2	M	24	54	60	67	64	no	infero-septal, antero-septal, anterior	normal
3	F	37	43	66	61	67	no	antero-lateral	mildly crinkling
4	M	19	67	65	87	69	no	antero-lateral	normal
5	M	35	71	60	84	67	inferior	inferior	normal
6	F	41	60	63	76	67	no	inferior	normal
7	M	43	68	59	79	59	no	infero-lateral	normal

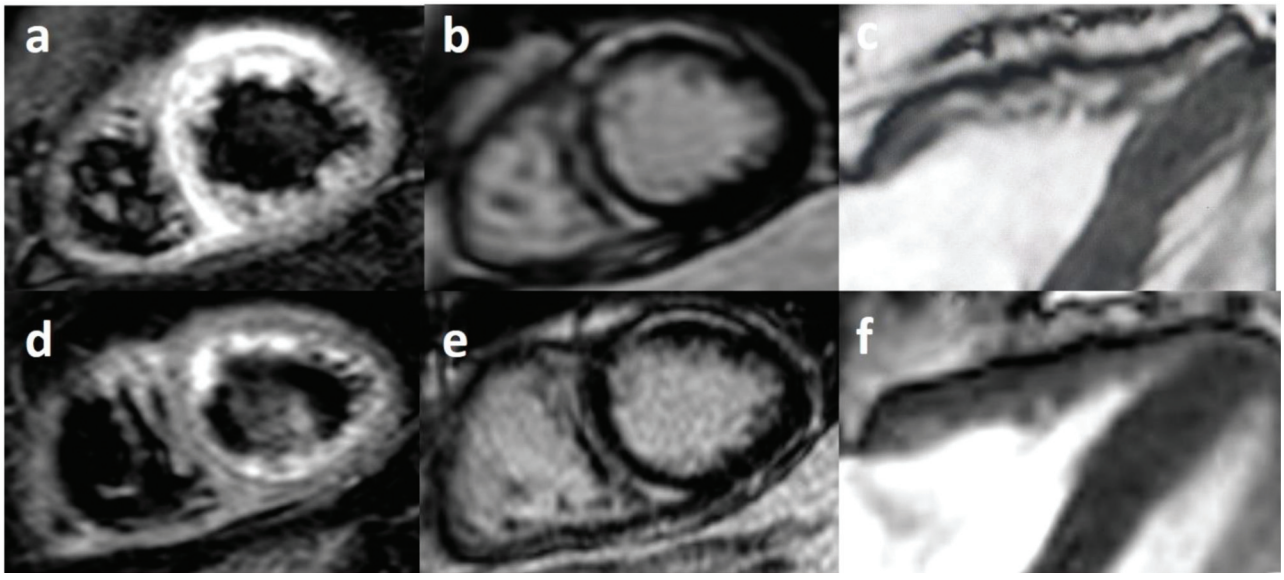

Fig. 1. Case 2. A 24-years-old Caucasian man, admitted to Hospital for myocarditis COVID-19 related; in the acute phase, CMRi showed infero-septal, antero-septal, anterior edema (a) with corresponding LGE (b) with a distribution typical of inflammation; furthermore, in the acute setting there was evidence of crinkling aspect of the profile of all of the segments of the free wall of the right ventricle (c); on six month follow-up, remission of edema (d) with persistence of LGE (e) as per residual scar in healed myocarditis; furthermore the remission of the morphological findings of the profile of the right ventricle free wall was observed (f).

all by now standardized, the morphological evaluation of the free wall of the right ventricle still represents a very challenging and still somewhat operator-dependent evaluation. Also, similar limitations affect the evaluation of signal changes indicating fat substitution, edema, increased ECV and/or fibrosis on DIR/T1w, TIR/T2w and LGE sequences [9]. The altered profile of the free wall of the right ventricle, consisting of a crinkling appearance, often described as '*Accordion Sign*', detected with different imaging techniques, for many years has been an essential criterion for the definition of arrhythmogenic right ventricular cardiomyopathy (ARVC/D) [10], later, this description was relatively less considered as such, probably also based on the heterogeneity of its definition, in favor of more defined criteria such as the

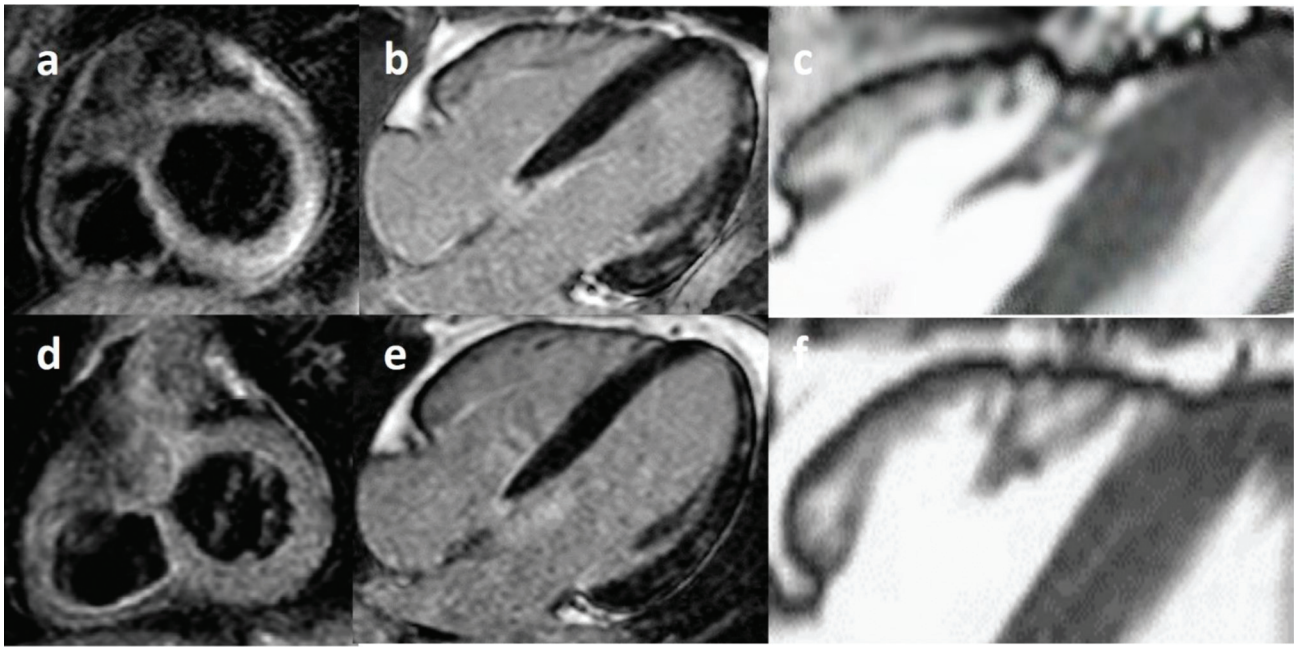

Fig. 2. Case 3. A 36-years-old Caucasian woman, admitted to Hospital for myocarditis COVID-19 related; in the acute phase, CMRi showed antero-lateral and infero-lateral edema (a) with corresponding LGE (b) with a distribution typical of inflammation; furthermore, in the acute setting there was evidence of crinkling aspect of the profile of the mid-apical segments of the free wall of the right ventricle (c); on six month follow-up, remission of edema (d) with persistence of LGE (e) as per residual scar in healed myocarditis; furthermore a significant reduction of the morphological findings of the profile of the right ventricle free wall was observed (f).

presence of bulging areas, aneurysms, dyssynergia areas, the increase in cavity volumes and the reduced global systolic function [11,12]; however, while in ARVC/D it is now well established that there is myocyte transformation with fibroadipose replacement (dysontogenic theory) [13], such is obviously, not likely operative in Covid-19 related myocarditis. On the other hand, there is growing evidence suggesting possible inflammatory pathways taking part of the pathogenesis of ARVC/D as well, and myocarditis has been described as one of the possible clinical onset of ARVC/D [14,15]; for these reasons, when in presence of morphological alterations in the profile of the free wall of the right ventricle, it is challenging in the acute setting, to differentiate between infectious or immune-mediated myocarditis and myocarditis as an onset manifestation of ARVC/D; In our study, on CMRi, we observed a reversible presence of an altered profile, consisting in a crinkling profile, of the free wall of the right ventricle, present in the acute phase, no longer present or in any case significantly attenuated at six months follow-up in five out of seven cases; this feature was not detectable on TTE, both in the acute setting and at six months control; the reversibility of the findings described at the right ventricle, observed in our study, would make the hypothesis of primary disease (ARVC/D) less likely and would rather suggest a possible association between the findings and the acute phase of myocarditis of viral or immune-mediated origin, like that related to COVID-19 infection appears to be in relation to what might be the underlying pathophysiological mechanisms. Suppose the correlation between the findings described and myocarditis was confirmed, in that case, we hypothesize that the possible mechanisms underlying the finding could include the diffuse increase in ECV and the development of diffuse edema, not detectable with the TIR / T2 sequences, which it could hesitate, given the characteristics of the RV wall, in an alteration of the profile of the wall rather than in the thickening of the wall. Another possible mechanism hypothesized by us might lie, similarly to ARVC/D, in the development of multiple small focal areas of altered kinetics which together give this irregular aspect of the wall; this latter assumption would find support in the fact that the finding appears more evident in the systolic phase of the cardiac cycle; furthermore, the absence of an altered signal at the level of the free wall of the right ventricle in the TIR/T2w and DIR/T1w sequences, despite the presence of morphological wall alterations, might not be surprising in light of what similarly occurs in ARVC/D, in which the presence of aneurysms or wall bulging does not necessarily correspond to signal alterations in the aforementioned sequences, especially in the early stages of the disease [16]. Differently from the 'classical' accordion sign, which can be diffuse or focal and, in any case, involve all districts of the right ventricular wall [17], in our case, the phenomenon appeared to involve mainly the mid-apical segments of the wall with relative sparing of the basal ones. Regarding the prevalent location of the findings and the association with COVID-19 disease, we hypothesize that COVID-19 must preferentially affect the right ventricular longitudinal fibers, which are the predominant force generate units for the right ventricular free wall. More specifically, we further conjecture the mid and apical RV fibers may be more preferentially injured, permitting the otherwise less impaired basal fibers to coalesce and consequently collapse upon the more apical myocardium with the resultant localization of the accordion sign observed.

LIMITATIONS

The sample is limited, including only seven patients, allowing just observational considerations rather than a statistical analysis.

The definition of alterations in the right ventricle free wall profile is not well established yet.

CONCLUSIONS

Crinkling appearance in the profile of the free wall of the right ventricle, also described as '*Accordion Sign*', detected with cardiac magnetic resonance imaging, might represent a morphological feature associated with myocarditis related to COVID-19 infection in the acute setting; besides, these findings were not detectable on TTE, both in the acute setting and at six months control, confirming the unique role of CMRi in the morphologic evaluation of the cardiac chambers; due to the main limitations of the study, represented by the small population and the still not well-established definition of the alterations in the profile of the right ventricle free wall, further studies are needed to confirm this hypothesis; if the correlation between the described findings and acute myocarditis were confirmed, further studies would be needed to define both the possible underlying physiopathological mechanisms and the prognostic implication related to it. This is the first report in the literature that has considered such findings to the best of our knowledge.

Consent

Written informed consent was obtained from every patient for publication of this case series report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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NA.

Declarations of interest

None for each of the Authors.

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