toxic shock syndrome and Kawasaki disease-like symptoms together with cardiac inflammation (4, 8). This new entity, called MIS-C for multisystem inflammatory syndrome in children, shares similarities with Kawasaki disease with different clinical signs and outcome. Kawasaki disease is an autoimmune systemic disease characterized by systemic inflammation in all medium-sized arteries during the acute febrile phase (9) that affects predominantly children < 5 years of age. In our series, patients were older, from 8 to 12 years old (9). In Kawasaki disease, a prominent feature is the appearance of coronary artery dilatation or aneurysm(9), which was not evidenced in our series.

In our institution, children with myocarditis admitted to the ICU undergo cardiac MRI as a clinical routine protocol to document the diagnosis and to assess the severity of myocarditis (10). We found MRI signs of diffuse myocardial edema and hyperemia without evidence of focal myocardial necrosis/fibrosis, contrary to recent published data for adults with myocarditis related to COVID-19 (11, 12). Our findings are consistent with histopathological analysis of hearts with Kawasaki disease, which demonstrated little evidence of myocardial cell degeneration or necrosis but mainly cell infiltration of macrophages and neutrophils in myocardial interstitium (13). Our findings might be explained by the difference between viral myocarditis and post-infectious myocarditis related to MIS-C in COVID-19. Viral myocarditis results from injury by virus infiltration and immune response to this injury. As in Kawasaki disease, the MIS-C myocarditis corresponds to an inflammatory infiltration of the interstitial myocardium. A potential mechanism for myocardial manifestations of Kawasaki disease is the occurrence of a cytokine storm syndrome. Rowley et al. suggested that the immunologic cascade of Kawasaki disease is due to infection with an RNA virus that enters through the upper respiratory tract (14). SARS-CoV-2 could be a candidate for such an inflammatory response in MIS-C.

Regarding the outcome, myocarditis resolved rapidly in our series as demonstrated by normal echocardiographic follow-up and cardiac MRI findings in patient 1, as in Kawasaki disease, in which myocardial inflammation peaks 10 days after disease onset and disappears gradually after

20 days (15). We did not find complications such as circulatory failure in the acute phase, development of artery aneurysm as in Kawasaki disease or resistance to intravenous immunoglobulin (16).

Our case series had limitations. First, we did not examine the coronary artery with MR angiography sequences. Instead, we used echocardiography in accordance with international recommendations of evaluation of the coronary artery. In the initial phase of Kawasaki disease, coronary artery abnormalities are usually screened by transthoracic echocardiography (17) with quantitative assessment of luminal dimensions several times during the acute and the recovery phases (9). Second, our patients might not reflect the entire spectrum of patients with myocarditis related to COVID-19 because of referral bias related to ICU admission. Finally, there are known issues with native-T1 such as variation in sequences, different sensitivities to T2 effects, lack of standardization and normal values, and partial dependence on heart rate.

In conclusion, this case series illustrates cardiac MRI findings in children and adolescents admitted to the ICU with myocarditis and MIS-C related to COVID-19. In our series, the most common findings were age > 5 years, increased levels of brain natriuretic peptide and troponin I, echocardiography changes with transient systolic dysfunction associated with cardiac MRI signs of diffuse myocardial edema and hyperemia without evidence of focal myocardial necrosis or replacement fibrosis. All patients recovered rapidly, with no evidence of coronary artery dilatation or aneurysm. The pathophysiology of MIS-C is still unexplained, but our cardiac MRI findings support the hypothesis of an immune response to an antigen rather than a direct complication secondary to SARS-CoV-2 infection.

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REFERENCES

1. Nathan N, Prevost B, Corvol H. Atypical presentation of covid-19 in young infants. Lancet 2020;395:1481.doi: 10.1016/S0140-6736(20)30980-6
2. Jones VG, Mills M, Suarez D, Hogan CA, Yeh D, Bradley Segal J, et al. Covid-19 and kawasaki disease: Novel virus and novel case. Hosp Pediatr 2020.doi: 10.1542/hpeds.2020-0123
3. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during covid-19 pandemic. Lancet 2020.doi: 10.1016/S0140-6736(20)31094-1
4. Belhadjer Z, Meot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Acute heart failure in multisystem inflammatory syndrome in children (mis-c) in the context of global sars-cov-2 pandemic. Circulation 2020.doi: 10.1161/CIRCULATIONAHA.120.048360
5. Burkhardt BEU, Menghini C, Rucker B, Kellenberger CJ, Valsangiacomo Buechel ER. Normal myocardial native t1 values in children using single-point saturation recovery and modified look-locker inversion recovery (molli). J Magn Reson Imaging 2020;51:897-903.doi: 10.1002/jmri.26910
6. Ferreira VM, Schulz-Menger J, Holmvang G, Kramer CM, Carbone I, Sechtem U, et al. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: Expert recommendations. J Am Coll Cardiol 2018;72:3158-76.doi: 10.1016/j.jacc.2018.09.072
7. Caruso D, Zerunian M, Polici M, Pucciarelli F, Polidori T, Rucci C, et al. Chest ct features of covid-19 in rome, italy. Radiology 2020:201237.doi: 10.1148/radiol.2020201237
8. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe kawasaki-like disease at the italian epicentre of the sars-cov-2 epidemic: An observational cohort study. Lancet 2020.doi: 10.1016/S0140-6736(20)31103-X
9. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. Diagnosis, treatment, and long-term management of kawasaki disease: A scientific statement for health professionals from the american heart association. Circulation 2017;135:e927-e99.doi: 10.1161/CIR.0000000000000484
10. Howard A, Hasan A, Brownlee J, Mehmood N, Ali M, Mehta S, et al. Pediatric myocarditis protocol: An algorithm for early identification and management with retrospective analysis for validation. Pediatr Cardiol 2020;41:316-26.doi: 10.1007/s00246-019-02258-1
11. Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, et al. Cardiac involvement in a patient with coronavirus disease 2019 (covid-19). JAMA Cardiol 2020.doi: 10.1001/jamacardio.2020.1096
12. Kim IC, Kim JY, Kim HA, Han S. Covid-19-related myocarditis in a 21-year-old female patient. Eur Heart J 2020;41:1859.doi: 10.1093/eurheartj/ehaa288
13. Harada M, Yokouchi Y, Oharaseki T, Matsui K, Tobayama H, Tanaka N, et al. Histopathological characteristics of myocarditis in acute-phase kawasaki disease. Histopathology 2012;61:1156-67.doi: 10.1111/j.1365-2559.2012.04332.x
14. Rowley AH, Baker SC, Shulman ST, Rand KH, Tretiakova MS, Perlman EJ, et al. Ultrastructural, immunofluorescence, and rna evidence support the hypothesis of a "new" virus associated with kawasaki disease. J Infect Dis 2011;203:1021-30.doi: 10.1093/infdis/jiq136
15. Mavrogeni S, Bratis K, Karanasios E, Georgakopoulos D, Kaklis S, Varlamis G, et al. Cmr evaluation of cardiac involvement during the convalescence of kawasaki disease. JACC Cardiovasc Imaging 2011;4:1140-1.doi: 10.1016/j.jcmg.2011.04.021
16. Gatterre P, Oualha M, Dupic L, Iserin F, Bodemer C, Lesage F, et al. Kawasaki disease: An unexpected etiology of shock and multiple organ dysfunction syndrome. Intensive Care Med 2012;38:872-8.doi: 10.1007/s00134-012-2473-8
17. Ou P, Kutty S, Khraiche D, Sidi D, Bonnet D. Acquired coronary disease in children: The role of multimodality imaging. Pediatr Radiol 2013;43:444-53.doi: 10.1007/s00247-012-2478-z

Table 1. Clinical and biological findings and treatment of patients with myocarditis related to COVID-19 infection

		Patient 1	Patient 2	Patient 3	Patient 4
Clinical findings	Age (years)	8	12	11	6
	Body mass index (kg/m²)	14.5	27.9	22.9	16.5
	Initial symptoms	fever for 4 days, abdominal pain	fever for 5 days, abdominal pain, vomiting and diarrhea	fever for 2 days, vomiting, abdominal pain, fatigue	fever for 7 days, abdominal pain, vomiting, diarrhea
	Physical examination at the ER	conjunctivitis, cheilitis and rash	conjunctivitis and pharyngeal enema, trunk and thighs rash	palm rash	cheilitis, cervical adenopathy, trunk and palm rash
	Body temperature (°C)	40.2	40	40.5	40
	Blood pressure	81/49 (60)	104/53 (68)	103/60 (74)	86/47 (61)
	Heart rate (bpm)	138	132	134	159
	Oxygen saturation % (ambient air)	92	99	91	94
	ECG	normal	ST segment depression	decreased T-wave amplitude	normal
Biological findings	Troponin I (ng/L)	125	4607	545	340
	BNP (ng/L)	2305	918	3214	3140
	CRP (mg/L)	131	340	456	310
	Sodium (mmol/L)	128	129	134	130
	Potassium (mmol/L)	4.6	3	5.1/3.2	5.7/3
	Lymphocytes (/mm3)	780	510	400	710
	Blood cultures	negative	negative	negative	negative
	Nasopharyngeal SARS-CoV-2 RT-PCR	negative	negative	negative	negative
	Blood SARS-CoV-2 serology	positive (IgG+, IgM-)	positive (IgG+, IgM-)	positive (IgG+, IgM-)	positive (IgG+, IgM+)
	Stool SARS-CoV-2 RT-PCR	not performed	negative	negative	negative
	Respiratory sample SARS-CoV-2 RT-PCR	not performed	not performed	negative	not performed
Treatment	Intravenous Ig	yes	yes	yes	yes
	Vaso-active agents	yes	no	yes	yes
	Volume expanders	yes	no	yes	yes
	Prednisolone	yes	yes	no	yes
	Aspirin	yes	yes	no	yes
	High-flow oxygen therapy	yes	no	yes	yes
	Invasive ventilation	no	no	yes	no
	Out-of-hospital treatment	steroid, aspirin	steroid	no	steroid, aspirin

ER: emergency room, ECG: electrocardiography, BNP: brain natriuretic peptide, CRP: C-reactive protein, RT-PCR: reverse transcription polymerase chain reaction, Ig: immunoglobulin

Table 2. Cardiac MRI findings in patients with myocarditis related to COVID-19 infection

	Reference values	Patient 1	Patient 2	Patient 3	Patient 4
LV diameter (mm)		39	53	54	43
LV thickness (mm)		7.5	6.8	8.8	5.0
Dyskinesis/hypokinesis		no	no	no	no
LVEF (%)		68	51	56	52
LVEDV index (ml/m²)		51	93	74	83
LVESV index (ml/m²)		16	45	32	40
Mass index (g/m²)		44	58	54	50
RVEF (%)		63	53	57	55
RVEDV index (ml/m²)		60	87	70	57
RVESV index (ml/m²)		22	41	30	26
RatioT2 myocardium/muscle	<2	1.1	2.2	2.4	2.4
Myocardial T2 (ms)	[46-50]	47	NA	NA	62
Myocardial native T1 (ms)	[950-1058]	1050	1112	1124	1169
LGE present		NA	no	no	no
Pericardial effusion		no	yes	yes	yes

LV: left ventricle, RV: right ventricle, EF: ejection fraction, EDV: end-diastolic volume, ESV: end-systolic volume, LGE: late gadolinium enhancement

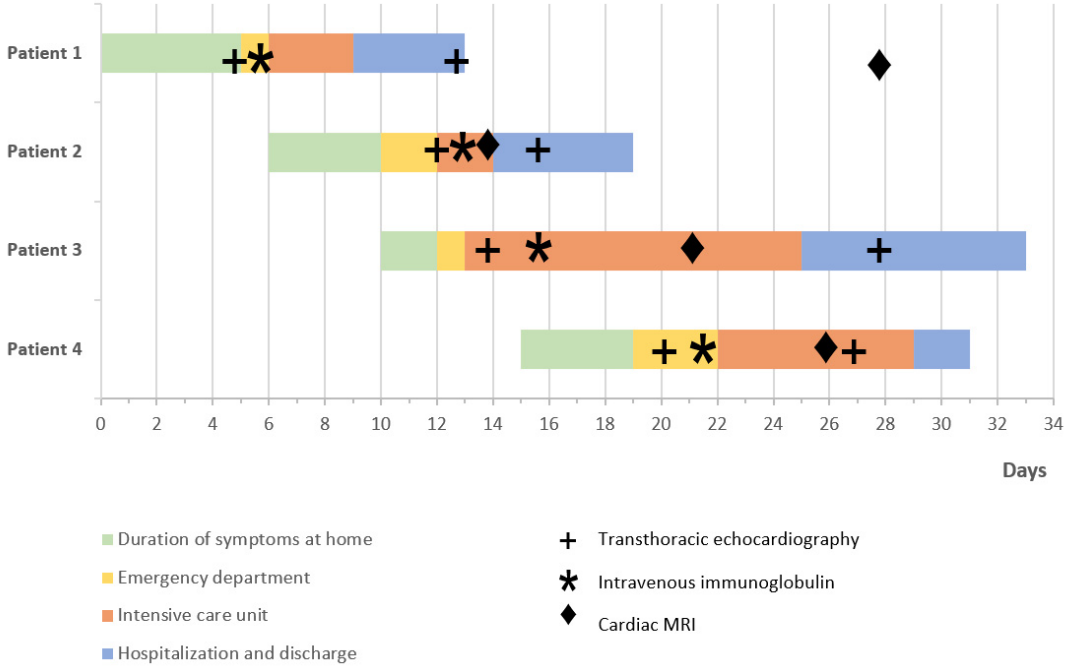

Figure 1. Timeline of illness onset, hospitalization, time of echocardiography and cardiac MRI and symptom resolution for the four children with COVID-19–related Kawasaki-like symptoms.

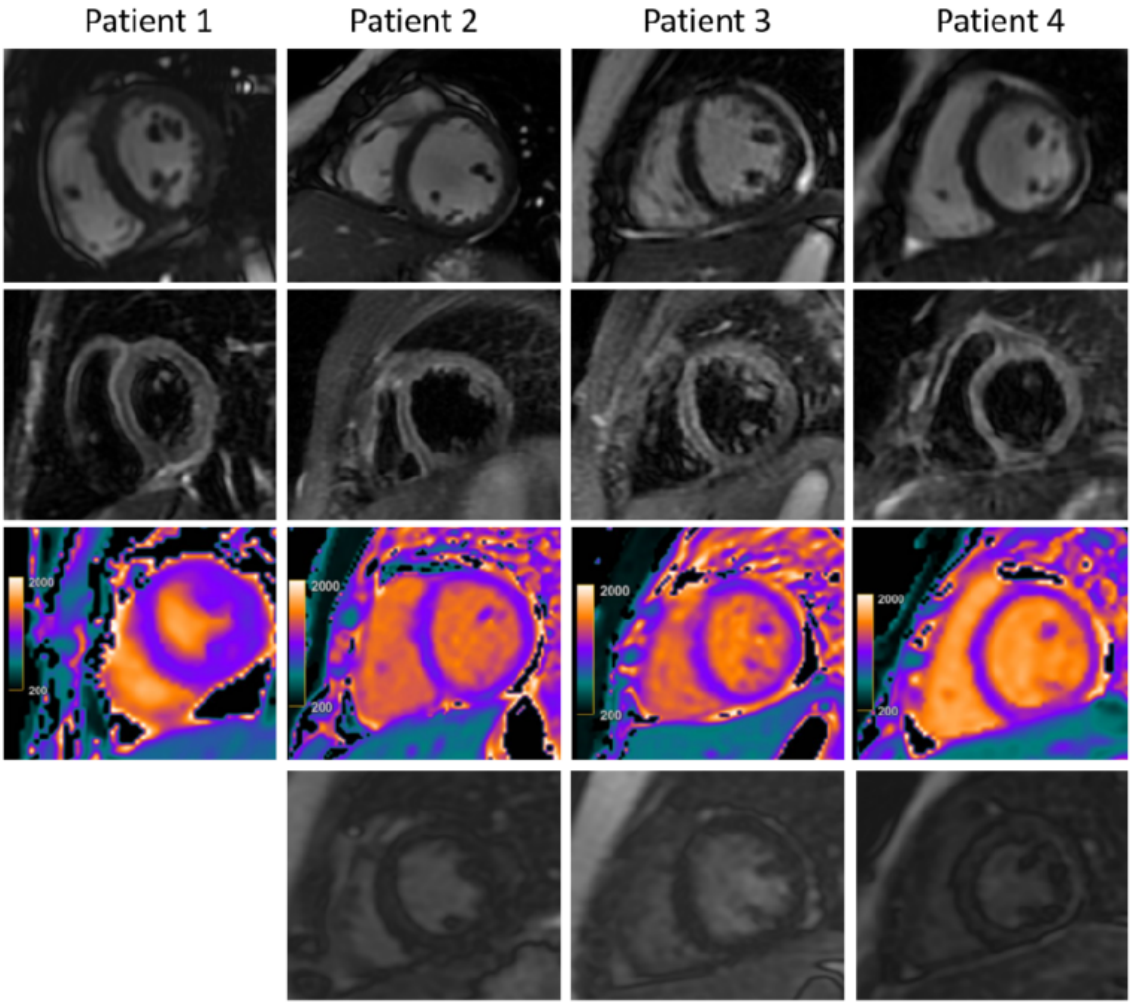

Figure 2. Cardiac MRI for four children with clinical diagnosis of acute myocarditis in the setting of COVID-19–related Kawasaki-like symptoms. The top panel demonstrates minimal pericardial effusion on cine images. The second panel demonstrates increased T2-STIR signal intensity with average ratios between myocardium and muscle > 2 in patient 2 (12-year-old male), patient 3 (11-year-old female) and patient 4 (6-year-old female). The third panel demonstrates abnormal native-T1 mapping, which was > 1100 ms in patients 2, 3 and 4 and normal in patient 1 (8-year-old female). The bottom panel demonstrates absence of late gadolinium enhancement (LGE) in patients 2 and 3. Myocardial null times were recognized as too short in patient 4 but could not be repeated due to lack of further patient cooperation; however review of Look Locker images and additional sequences revealed no LGE.

Supplemental data

Table E1. Transthoracic echocardiography findings at admission and at clinical follow-up in patients with myocarditis related to COVID-19 infection

	Patient 1	Patient 2	Patient 3	Patient 4
Transthoracic echocardiography at admission				
Appearance of myocardium	normal	diffuse echo-bright appearance	normal	normal
Dyskinesis/hypokinesis	hypokinesis	septal dyskinesis	hypokinesis	no
LVEF (%)	24	61	54	59
FS (%)	10	33	30	31
VTI (cm)	10.9	/	15	16.5
HR (bpm)	147	/	162	124
Valvular disease	mitral regurgitation	no	mitral regurgitation	no
Pericardial effusion	no	no	yes	yes
Coronary artery dilatation/aneurysm	no	no	no	no
Transthoracic echocardiography follow-up				
Appearance of myocardium	normal	normal	normal	normal
Dyskinesis/hypokinesis	no	no	no	no
LVEF (%)	70	74	68	67
FS (%)	39	43	37	36
VTI (cm)	/	29.8	25	23.1
HR (bpm)	/	51	75	98
Valvular disease	no	no	no	no
Pericardial effusion	no	yes	no	no
Coronary artery dilatation/aneurysm	no	no	no	no

LVEF: left ventricular ejection fraction, FS: fractional shortening, VTI: velocity time integral, HR: heart rate