COVID-19 Acute Myocarditis and Multisystem Inflammatory Syndrome in Adult Intensive and Cardiac Care Units

Guillaume Hékimian, Mathieu Kerneis, Michel Zeitouni, Fleur Cohen-Aubart, Juliette Chommeloux, Nicolas Bréchot, Alexis Mathian, Guillaume Lebreton, Matthieu Schmidt, Miguel Hié, et al.

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Guillaume Hékimian[1], MD; Mathieu Kerneis[2], MD; Michel Zeitouni[2], MD; Fleur Cohen-Aubart[3], MD, PhD; Juliette Chommeloux[1], MD; Nicolas Bréchot[1], MD, PhD; Alexis Mathian[3], MD, PhD; Guillaume Lebreton[4], MD, PhD; Matthieu Schmidt[1], MD, PhD; Miguel Hié[3], MD; Johanne Silvain[2], Marc Pineton de Chambrun[1], MD; MD, PhD; Julien Haroche[3], MD, PhD; Sonia Burrel[5], PharmD, PhD; Stéphane Marot[5] ; Charles-Edouard Luyt[1], MD, PhD ; Pascal Leprince[4], MD, PhD; Zahir Amoura[3], MD, MSc; Gilles Montalescot[2], MD, PhD; Alban Redheuil[6], MD, PhD; Alain Combes[1], MD, PhD

[1] Sorbonne Université, Institut de Cardiométabolisme et Nutrition (ICAN), Service de Médecine Intensive Réanimation, Hôpital La Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France

[2] Sorbonne Université, ACTION Study Group, INSERM UMRS1166, ICAN - Institute of CardioMetabolism and Nutrition, Institut de Cardiologie, Hôpital Pitié-Salpêtrière (AP-HP), Paris, France.

[3] Sorbonne Université, Inserm UMR-S 1135, Centre d'Immunologie et des Maladies Infectieuses (CIMI-Paris), Groupe Hospitalier Universitaire APHP, site Pitié-Salpêtrière, service de médecine interne 2, Institut E3M, Hôpital Pitié-Salpêtrière, Paris, France

[4] Sorbonne Université, Service de chirurgie cardiaque et thoracique, Hôpital La Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France

[5] Sorbonne Université, INSERM UMRS_1136, Institut Pierre Louis d'Epidémiologie et de Santé Publique (iPLESP), Service de virologie, Hôpital La Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France

[6] Sorbonne Université, LIB-Laboratoire d'imagerie biomédicale, INSERM, CNRS, ICAN Institute of CardioMetabolism and Nutrition, ACTION Study Group, Cardiothoracic Imaging Unit, Hôpital Pitié-Salpêtrière (AP-HP), Paris, France

Correspondence : Guillaume Hékimian, e-mail: guillaume.hekimian@aphp.fr, Service de Médecine Intensive Réanimation, Hôpital La Pitié-Salpêtrière, 47-83 boulevard de l'hôpital, 75013, Paris, France

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To the editor:

Hyperinflammatory shock was recently described in children during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. The clinical presentation of these patients involved fever, cutaneous rash, abdominal symptoms, distributive shock and acute cardiac injury. This multisystem inflammatory syndrome had similarities with classical, incomplete or most severe forms of the Kawasaki disease[1–5]. The frequent troponin elevation and left ventricular dysfunction suggested the presence of acute myocarditis, although description of cardiac magnetic resonance imaging (MRI) is lacking.

This case series describes the clinical presentation, characteristics, and management of the patients aged over 16 with coronavirus disease 2019 (COVID-19) admitted for suspected acute or fulminant myocarditis (according to the European Society of Cardiology and the American Heart Association definitions [6,7]), including multisystem inflammatory syndrome, in the adult intensive and acute cardiac care units of a tertiary French center.

Methods

From February 25th to June 25th 2020, 20 patients were admitted in our institution for clinically suspected acute or fulminant myocarditis (viral, n= 16, autoimmune, n=3 and toxic, n=1). Eleven patients had a confirmed SARS-CoV-2 infection based on positive reverse transcriptase- polymerase chain reaction (RT-PCR) or serology. Our study reports these eleven cases. In accordance with the ethical standards of our hospital's institutional review board and French law, all patients or close relatives were informed that their personal data were collected in this case series and that they could decline inclusion. The National Commission for Informatics and Liberties approved this study (no.1950673).

Results

Clinical presentation

The clinical, biological and imaging characteristics of the 11 patients are described in the **Table**. Patients were aged between 16 and 40 years, five were women, and none had severe comorbidities. All the patients presented with an acute non-ischemic left ventricular dysfunction and a troponin elevation at admission (on average 153 fold the ULN). Nine patients had a positive SARS-CoV-2 serology with negative (n=6) or slightly positive SARS-CoV-2 RT-PCR (n=3). Two patients had a positive blood and respiratory SARS-CoV-2 RT-PCR and negative serology. The most frequent symptoms were severe asthenia (n=9), dyspnea (n=7), abdominal pain or diarrhea (n=6), headache (n=5), and chest pain (n=3). Nine patients had fever and 10 had hypotension and tachycardia. An erythematous rash was observed in only 3 patients and 3 had conjonctivitis. The electrocardiogram showed sinus tachycardia in 9 patients. One patient had an acute atrio-ventricular block with a left bundle branch block and 5 patients had ST or T wave abnormalities mimicking acute coronary syndrome. Noteworthy, half of these patients had no signs of COVID- 19 pneumonia on chest computed tomography (CT). Left ventricular ejection fraction (LVEF) was moderately to severely impaired in all patients. Biological findings showed important elevation of C-reactive protein, fibrinogen, D-dimers, lymphopenia and hypoalbuminemia. Acute kidney injury occurred in 4 patients. Among the 6 patients who could undergo cardiac MRI, the diagnosis of myocarditis was established according to the Lake Louise criteria. Six patients had coronary angiography, coronary CT or coronary MRI and none of them had coronary aneurysm. Finally, 8 patients met the diagnosis criteria for classic (n=1) or incomplete (n=7) Kawasaki disease [8].

Treatment and outcomes

Supportive care included dobutamine and norepinephrine infusion in 6 patients. Two patients required veno-arterial Extra Corporeal Membrane Oxygenation (ECMO). Six patients required mechanical ventilation. Three of them received veno-venous ECMO for severe ARDS. Five patients received intravenous immunoglobulins, followed by corticosteroids in 3 of them. LVEF normalized in 6 patients and recovered over 40% in 4 in a mean time of 8 days but one patient on veno-arterial ECMO did not recover and died.

Discussion

This report describes acute or fulminant myocarditis among COVID-19 patients, including post-infectious Multisystem Inflammatory Syndrome also called Kawasaki's disease like syndrome. This severe syndrome, described in children, involved 8 of the 11 patients admitted in our adult cardiac and intensive care units. Not only pediatricians should be aware of this COVID- 19 complication. Indeed, some adults were affected in this series, and adolescents aged over 16 may be hospitalized in adult units and treated by physicians usually taking care of adults. During this period, 1190 adults were admitted in our hospital for COVID- 19. Despite being rare, this clinical presentation requires immediate recognition, hemodynamic support and specific management.

Typically, these patients had high grade fever, severe asthenia, abdominal pain and diarrhea, hypotension related to capillary leak syndrome and vasoplegia, and pronounced biological inflammatory syndrome. In contrast with children, only few of these patients had rash or conjonctivitis.

Interestingly, among the 8 patients with Multisystem Inflammatory Syndrome, 2 had a symptomatic COVID- 19 infection one month ago and none of these 8 patients had clinical or radiological signs of COVID- 19 pneumonia at the time of myocarditis diagnosis. This suggests that symptomatic or asymptomatic SARS-CoV-2 infection would be followed a few

weeks later by a hyper-inflammatory response and immune-mediated systemic and cardiac damage. The combination of positive serology at the time of admission with negative or slightly positive RT-PCR is another argument for the post-infectious immunologic nature of this complication of SARS-CoV-2.

Cardiac MRI demonstrated diffuse signs of edematous myocarditis. This pattern suggests myocardial inflammation and rules out ischemic injury, stress induced cardiomyopathy or type 2 myocardial infarction. Since all patients recovered within a few days or had severe coagulation disorders while on veno-arterial-ECMO, endomyocardial biopsies were not performed but would be of interest.

Finally, all of these patients should receive early supportive care and appropriate diagnostic exams. The role of specific therapies with proven benefits in Kawasaki disease, including immunoglobulins, corticosteroids, tocilizumab or anakinra remains unknown and requires further investigations in this setting.

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	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11
Age, gender, body mass index (kg/m²)	40, male, 26	19, female, 24	22, male, 38	19, male, 22	16, male, 18	16, female, 24	17, male, 32	25, female, 23	17, female, 18	37, male, 35	29, female, 22
Smoker	0	0	0	0	0	0	0	0	0	0	0
Comorbidities	Diabetes mellitus	none	Diabetes mellitus, asthma	none	none	none	Moderate aortic regurgitation, LVEF 60%	none	none	hypertension	none
Previously symptomatic COVID- 19 episode	none	none	none	none	none	Anosmia and cough one month ago	none	none	none	none	Anosmia and positive COVID-19 RT-PCR one month ago
Clinical presentation	apyretic, dyspnea, severe asthenia	38.3°C fever, dyspnea, cough	39.4°C fever, dyspnea, cough, severe asthenia	40°C fever, headache, diarrhea, dyspnea, severe asthenia	41°C fever, anosmia, abdominal pain, rash[1], hands and feet erythema, conjonctivitis, strawberry tongue, chest pain, severe asthenia, adenopathy	40°C fever, headache, abdominal pain, hands and feet erythema, dyspnea, severe asthenia	40.4°C fever, headache, abdominal pain, diarrhea, dyspnea, severe asthenia, conjonctivitis	39.5°C fever, headache, abdominal pain, diarrhea, chest pain, dyspnea, severe asthenia, myalgia, arthralgia, adenopathy	apyretic, chest pain, dyspnea	39.7°C fever, headache, diarrhea, severe asthenia	40°C fever, abdominal pain, diarrhea, rash, conjonctivitis, severe asthenia
Delay between symptoms and hospital admission, days	2	9	1	4	7	8	4	8	1	7	3
SBP (mmHg), DBP (mmHg), Heart rate (bpm)	66/37/127	70/42/140	96/57/128	85/46/130	68/45/120	108/55/120	147/36/140	96/50/120	87/46/130	98/52/81	80/50/115
Electrocardiogram	Sinus tachycardia	sinus tachycardia	sinus tachycardia	sinus tachycardia	diffuse ST elevation sinus tachycardia	diffuse ST depression sinus tachycardia	Sinus tachycardia	negative T waves in D2-D3-aVF sinus tachycardia	ST elevation in aVR, diffuse ST depresssion, sustained ventricular tachycardia with cardiac arrest	New first degree atrio-ventricular block with left bundle branch block	negative T waves in V4-V6 sinus tachycardia
Echo: LVEF, %/ LVOT VTI, cm	45%, 16 cm	30%, 14 cm	30%, 15 cm	15%, 8 cm	20%, 13 cm	45%, 15 cm	20%, 11 cm	50%, 15 cm	20%, 8 cm	45%, 15 cm	50%, 16 cm
Chest CT scan specific COVID- 19 infiltrate	severe	mild	severe	none	mild	none	none, pulmonary edema	none	none, Pulmonary edema	none	none
Cardiac MRI	no	no	no	Yes, at day 7 Diffuse edema LVEF 44%	Yes, at day 4 Diffuse Edema Lateral epicardial	yes Diffuse Edema	no	yes Diffuse Edema	no	yes Inferior and Lateral LV Edema	yes Diffuse edema LVEF 57%

					necrosis LVEF 33%	LVEF 47%		Intramural Necrosis LVEF 43%		LVEF 55%	
SARS-CoV-2 RT PCR (CT)[1]	positive in BAL and blood (CT 13)	negative at all sites	positive in nasopharyngeal swab and blood (CT 29)	negative at all sites	slightly positive in nasopharyngeal swab (CT 35)	negative at all sites	slightlty positive in nasopharyngeal swab (CT 37)	negative at all sites	slightly positive in nasopharyngeal swab (CT 36)	negative at all sites	negative at all sites
SARS-CoV-2 serology (IgG+) at admission, index[2]	negative	positive (2.1)	negative	positive (3.2)	positive (4.6)	positive (6.7)	positive (6.2)	positive (1.9)	positive (1.6)	positive (5.9)	positive (0.8)
Peak of Troponin, ng/l / NT pro BNP, pg/ml	439/ 6025	10652/ 2585	166/ -	806/26956	2545/ -	64/1689	138/ 35000	2542/ 24540	4905/ 3362	1164/ 35000	200/ 21298
Fibrinogen, g/l / D-dimer, ng/ml	3.2/ 7530	7.9/ 4235	7.5/ 3930	7.7/ -	5.6/ 6920	8.0/2130	8.0/5320	10.0/3110	2.1/ 240	8.5/ 4340	7.4/ 1200
PCT, mg/l /CRP, mg/l /Ferritin, mg/l / Triglycerids, g/l	170/ 321/ 3280/ 5	68/ 438/ 645/ -	3.5/ 202/ 16576/ 2	15/ 280/2124/2.5	104/ 349/ 4490/-	7.4/ 313/ 1807/ 2	400/ - / 13928/ 2.3	12/ 389/ 712/ 1.5	33/ 13/ 268/ 0.48	8.7/ - / 4485/ 2.5	0.5/ 206/ 456/ -
Sodium, mmol/l / Urea, mmol/l / Creatinin, µmol/l/ Albumin, g/l	154/ 12/ 267/ 29	123/ 13.6/ 272/ 33	131/ 2.1/ 93/ 25	139/ 4.5/ 72/ 27	120/ 32/ 377/ 29	134/ 5.8/ 56/ 29	129/ 20/ 402/ 18	135/ 5/ 72/ 24	133/ 2.4/ 52/ -	129/ 35/ 534/ 23	145/ 4.3/ 56/ 21
ASAT, IU/l/ ALAT, IU/l/ total bilirubin, µmol/l / PT, %	147/140/22/56	32/ 62/ 75/ 49	123/ 91/ 6/ 53	211/ 222/ 8/ 83	117/ 56/ 15/ 69	25/ 20/ 11/ 74	118/ 52/ 41/ 50	65/ 103/ 19/ 74	86/ 13/ 5/ 51	121/ 211/12/ 58	22/ 17/ 8/ 76
Hemoglobin, g/dl/ white cells, G/l/ lymphocytes, G/l/ Platelets, G/l	9.1/0.7/0.48/72	11.7/ 10.3/ 0.31/ 191	10/ 9.3/ 1.86/ 227	11.6/ 7.4/ 2.3/ 416	12.2/ 18.5/ 0.4/ 191	11.7/ 9/ 0.6/ 227	10.3/ 44.1/ 1.1/ 161	11.6/ 18.5/ 0.87/ 301	9.7/ 3.1/ 0.45/ 283	10.5/ 25.5/ 1.5/ 264	12.7/ 8.4/ 1.4/ 272
pH/pO2, mmHg/pCO2, mmHg/ lactate, mmol/l	7.12/ 73/ 61/7	7.39/ 95/ 34/ 2.9	7.43/ 79/ 38/ 1	7.4/ 97/ 34/ 2.5	7.35/ 124/ 34/ 3.6	-	7.22/ 103/ 40/ 5.2		7.41/ 112/ 33/ 1.7	7.43/ 110/ 27/ 1.1	-
LDH, IU/l / CK, IU/l	576/ 4500	388/ 331	1299/ 703	387/ 380	364/ 229	258/ 46	599/ 616	208/ 49	311/ 518	363/ 209	208/ 63
Criteria for classic Kawasaki disease diagnosis*	no	no	no	no	yes	no	no	no	no	no	no
Criteria for incomplete Kawasaki disease diagnosis*	no	yes	no	yes	-	yes	yes	yes	no	yes	yes
Hemodynamic support	Dobutamine 15 γ/kg/min, Norepinephrine 40 mg/h, VA	Dobutamine 2.5 γ/kg/min, Norepinephrine 3 mg/h	None	Dobutamine 5γ/kg/min, Norepinephrine 1 mg/h	Dobutamine 8 γ/kg/min, Norepinephrin 2.6 mg/h	none	Dobutamine 15 γ/kg/min, Norepinephrin 37 mg/h	none	Dobutamine 5γ/kg/min, Norepinephrin 18 mg/h, VA	none	none

	ECMO for 8 days								ECMO for 50 days		
Respiratory support	Mechanical ventilation for 48 days and VV ECMO for 21 days	None	Mechanical ventilation for 38 days	None	Mechanical ventilation for 5 days	none	Mechanical ventilation for 16 days	Nasal Oxygenation, 4l/min	Mechanical ventilation for 50 days	none	none
Secondary complications	Multiorgan failure	At day 7, ARDS requiring mechanical ventilation for 25 days and VV- ECMO for 15 days	Worsening of the ARDS requiring VV-ECMO for 5 days	none	none	none	Multiorgan failure	none	Multiorgan failure	ischemic stroke	none
Specific anti-inflammatory or immunosuppressive treatment	none	none	none	none	Immunoglobulins 2g/kg	none	Immunoglobulins 2g/kg, corticosteroids 2mg/kg/day	none	Immunoglobulins 2g/kg, corticosteroids 2mg/kg/day	Immunoglobulins 2g/kg, corticosteroids 2mg/kg/day	Immunoglobulins 2g/kg
LVEF evolution	60% at day 8	50% at day 4	45% at day 11, 60% at day 27	50% at day 7, 60% at day 14	45% at day 6	60% at day 5	45% at day 10, 50% at day 15	50% at day 6	No recovery, on VA-ECMO until death	60% at day 4	60% at day 3
ICU length of stay, days	50	40	41	7	7	6	26	7	51	19	3
Outcome	alive	alive	alive	alive	alive	alive	alive	alive	Dead	alive	alive

Table. Characteristics of the 11 COVID- 19 patients with myocarditis or Multisystem Inflammatory Syndrome.

[1] assessed using Cobas® SARS-CoV-2 Test - Roche Diagnostics

[2] assessed using IgG Anti-SARS-CoV-2 Abbot Diagnostics

*according to reference 8

Abbreviations: RT-PCR: reverse transcriptase polymerase chain reaction; SBP: systolic blood pressure; DBP: diastolic blood pressure; bpm: beats per minute; LVEF: left ventricular ejection fraction; LVOT VTI: left ventricular outflow tract velocity time integral; MRI: magnetic resonance imaging; CT: cycle threshold value; BAL: bronchoalveolar lavage; PCT: procalcitonin; CRP: C-reactive protein; PT: prothrombin time; LDH: lactate deshydrogenase; CK: creatine phosphokinase; ICU: intensive care unit.