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Coronavirus Disease 2019 Acute Myocarditis and Multisystem Inflammatory Syndrome in Adult Intensive and Cardiac Care Units

To the Editor:

Hyperinflammatory shock was described recently 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 classic, 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 MRI is lacking.

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

Methods

From February 25 to June 25, 2020, 20 patients were admitted in our institution for clinically suspected acute or fulminant myocarditis (viral, 16 patients; autoimmune, three patients; and toxic, one patient). 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 11 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, biologic, and imaging characteristics of the 11 patients are described in Table 1. Patients were aged between 16 and 40 years; five were women, and none had severe comorbidities. All the patients presented with an acute nonischemic left ventricular dysfunction and a troponin elevation at admission (on average 153-fold the upper limits of normal). 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 ten patients had hypotension and tachycardia. An erythematous rash was observed in only three patients; three patients had conjunctivitis. The ECG showed sinus tachycardia in nine patients. One patient had an acute atrioventricular block with a left bundle branch block, and five patients had ST or T wave abnormalities mimicking acute coronary syndrome. Noteworthy, one-half of these patients had no signs of COVID- 19 pneumonia on chest CT scan. Left ventricular ejection fraction was moderately-to-severely impaired in all patients. Biologic findings showed important elevation of C-reactive protein, fibrinogen, D-dimers, lymphopenia, and hypoalbuminemia. Acute kidney injury occurred in four patients. Among the six 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 scanning, or coronary MRI; none of them had coronary aneurysm. Finally, eight 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 six patients. Two patients

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TABLE 1] Characteristics of the 11 Patients With COVID-19 With Myocarditis or Multisystem Inflammatory Syndrome

Characteristic	Patient										
	1	2	3	4	5	6	7	8	9	10	11
Age, y; sex; BMI, kg/m^2	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 1 mo earlier	None	None	None	None	Anosmia and positive COVID-19 RT-PCR 1 mo earlier
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,[a] hands and feet erythema, conjunctivitis, 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, conjunctivitis	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, conjunctivitis, severe asthenia
Delay between symptoms and hospital admission, d	2	9	1	4	7	8	4	8	1	7	3
SBP (mm Hg)/DBP (mm Hg)/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
ECG	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 atrioventricular block with left bundle branch block	Negative T waves in V4-V6 sinus tachycardia
Echo: LVEF, %/LVOT VTI, cm	45/16	30/14	30/15	15/8	20/13	45/15	20/11	50/15	20/8	45/15	50/16
Chest CT scan specific COVID-19 infiltrate	Severe	Mild	Severe	None	Mild	None	None, pulmonary edema	None	None, Pulmonary edema	None	None

(Continued)

TABLE 1] *(Continued)*

Characteristic	Patient										
	1	2	3	4	5	6	7	8	9	10	11
Cardiac MRI	No	No	No	Yes, at day 7; diffuse edema; LVEF 44%	Yes, at day 4; diffuse edema; lateral epicardial necrosis; LVEF 33%	Yes; diffuse edema; LVEF 47%	No	Yes, diffuse edema; intramural necrosis; LVEF 43%	No	Yes, inferior and lateral LV edema; LVEF 55%	Yes, diffuse edema ; LVEF 57%
SARS-CoV-2 RT PCR (CT)[a]	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	Slightly 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[b]	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	439/6,025	10,652/2,585	166/—	806/26,956	2,545/—	64/1,689	138/35,000	2,542/24,540	4,905/3,362	1,164/35,000	200/21,298
Fibrinogen, g/L/D-dimer, ng/mL	3.2/7,530	7.9/4,235	7.5/3,930	7.7/—	5.6/6,920	8.0/2,130	8.0/5,320	10.0/3,110	2.1/240	8.5/4,340	7.4/1,200
PCT, mg/L /CRP, mg/L /ferritin, mg/L /triglycerides, g/L	170/321/3,280/5	68/438/645/—	3.5/202/16,576/2	15/280/2,124/2.5	104/349/4,490/—	7.4/313/1,807/2	400/—/13,928/ 2.3	12/389/712/1.5	33/13/268/0.48	8.7/—/4,485/2.5	0.5/206/456/—
Sodium, mM/urea, mM /creatinine, 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, International Units/L/ALAT, International Units/ 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/ WBC count, 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/Po_2, mm Hg/Pco_2, mm Hg/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, International Units/L/CK, International Units/ 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[c]	No	No	No	No	Yes	No	No	No	No	No	No
Criteria for incomplete Kawasaki disease diagnosis[c]	No	Yes	No	Yes	…	Yes	Yes	Yes	No	Yes	Yes

(Continued)

TABLE 1] *(Continued)*

Characteristic	Patient										
	1	2	3	4	5	6	7	8	9	10	11
Hemodynamic support	Dobutamine 15 γ/kg/min; norepinephrine 40 mg/h; VA ECMO for 8 d	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; norepinephrine 18 mg/h; VA ECMO for 50 d	None	None
Respiratory support	Mechanical ventilation for 48 d; VV ECMO for 21 d	None	Mechanical ventilation for 38 d	None	Mechanical ventilation for 5 d	None	Mechanical ventilation for 16 d	Nasal oxygenation, 4l/min	Mechanical ventilation for 50 d	None	None
Secondary complications	Multiorgan failure	At day 7, ARDS requiring mechanical ventilation for 25 d and VV-ECMO for 15 d	Worsening of the ARDS requiring VV-ECMO for 5 d	None	None	None	Multiorgan failure	None	Multiorgan failure	Ischemic stroke	None
Specific antiinflammatory or immunosuppressive treatment	None	None	None	None	Immunoglobulins 2 g/kg	None	Immunoglobulins 2 g/kg; corticosteroids 2 mg/kg/d	None	Immunoglobulins 2 g/kg; corticosteroids 2 mg/kg/d	Immunoglobulins 2 g/kg; corticosteroids 2 mg/kg/d	Immunoglobulins 2 g/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, d	50	40	41	7	7	6	26	7	51	19	3
Outcome	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Dead	Alive	Alive

ALAT = alanin aminotransferase; ASAT = aspartate aminotransferase; bpm = beats per minute; CK = creatine phosphokinase; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; DBP = diastolic BP; ECMO = extracorporeal membrane oxygenation; LDH = lactate dehydrogenase; LV = left ventricle; LVEF = left ventricular ejection fraction; LVOT VTI = left ventricular outflow tract velocity time integral; NT pro BNP = N terminal brain natriuretic peptide; PCT = procalcitonin; PT = prothrombin time; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SBP = systolic BP; VA = venoarterial; VV = venovenous.

[a]Assessed using Cobas SARS-CoV-2 Test (Roche Diagnostics).

[b]Assessed using IgG Anti-SARS-CoV-2 (Abbot Diagnostics).

[c]According to Reference 8.

required venoarterial extra corporeal membrane oxygenation (ECMO). Six patients required mechanical ventilation. Three of them received venovenous ECMO for severe ARDS. Five patients received IV immunoglobulins, followed by corticosteroids in three of them. Left ventricular ejection fraction normalized in six patients and recovered >40% in four patients in a mean time of 8 days, but one patient on venoarterial ECMO did not recover and died.

Discussion

This report describes acute or fulminant myocarditis among patients with COVID-19, including postinfectious multisystem inflammatory syndrome, also called Kawasaki's disease-like syndrome. This severe syndrome, described in children, involved eight of the 11 patients admitted in our adult cardiac and ICUs. Not only pediatricians should be aware of this COVID- 19 complication. Indeed, some adults were affected in this series, and adolescents >16 years old may be hospitalized in adult units and treated by physicians who usually care of adults. During this period, 1,190 adults were admitted in our hospital for COVID-9. 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 biologic inflammatory syndrome. In contrast with children, few of these patients had rash or conjunctivitis.

Interestingly, among the eight patients with multisystem inflammatory syndrome, two had a symptomatic COVID-19 infection 1 month earlier, and none of these eight patients had clinical or radiologic 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 hyperinflammatory response and immune-mediated systemic and cardiac damage. The combination of positive serologic results at the time of admission with negative or slightly positive RT-PCR is another argument for the postinfectious 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. Because all patients recovered within a few days or had severe coagulation disorders while receiving venoarterial ECMO, endomyocardial biopsies were not performed, but would be of interest.

Finally, all of these patients should receive early supportive care and appropriate diagnostic examinations. 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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