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LETTER TO THE EDITOR

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A child with a severe multisystem inflammatory syndrome following an asymptomatic COVID-19 infection: A novel management for a new disease?

To the Editor,

Clinical presentation of coronavirus disease-2019 (COVID-19) is only in part due to viral infection itself, with the host response playing an important role.[1-3] Despite the mild clinical course during the acute phase of infection in children, latest ongoing research works are pointing the attention towards a hyperinflammatory shock or a Kawasaki-like disease as a possible consequence to COVID-19 exposure.[4,5]

A 9-year-old male was admitted to our Pediatric Emergency Unit due to fever and abdominal pain starting 7 days before admission. Family history revealed a recent exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The father has had a bilateral interstitial pneumonia until 7 days before the onset of symptoms in the child. His mother had a history of cough and fever before husband admission, with negative nasopharyngeal swabs performed at that time. On examination, the child was alert, with no respiratory symptoms, nor conjunctivitis, rash, or peripheral edema. He underwent blood and microbiological exams including blood specimens for cultures and nasopharyngeal swabs for SARS-CoV2 nucleic acid. Relevant laboratory investigations are reported in Table 1. At baseline, leukocytosis with neutrophilia and relative lymphopenia were found. Inflammatory markers were strongly elevated. Several significantly altered parameters suggested liver function abnormality, with hypertransaminasemia, acute renal injury, with elevated blood urea nitrogen and serum creatinine, and myocardial injury, with elevated high sensitivity cardiac troponin, and brain natriuretic peptide (BNP). Thrombophilic screening was unremarkable.

Empiric antibiotic therapy (intravenous ceftriaxone 2 g/d) after sampling for cultures were started. Respiratory syncytial virus and influenza viruses A and B were negative. Blood, urine, and stool cultures were sterile. He was tested for COVID-19 antibodies which showed positivity of both IgG and IgM (qualitative test), confirmed by a quantitative analysis which showed a high level of IgG (1:85 292) and a weak positivity of IgM (1:2098). Maternal COVID-19 serology revealed IgG positivity and IgM negativity.

Chest X-ray upon admission was negative. Baseline electrocardiogram was normal. Echocardiography (at baseline and repeated after 2 days) showed no ventricular dysfunction, no dilated coronaries or pericoronal hyperechogenicity. Chest computed tomography (CT) on the 2nd day showed two small bilateral areas of atelectasis associated to minimal pleural effusion. Abdominal CT was unremarkable. Azythromycin and methylprednisolone (2 mg/kg/d) were started. Because of the high levels of BNP and troponin, subcutaneous heparin was added and methylprednisolone dosage was then increased to 5 mg/kg/d. Due to an increase of the QT interval on electrocardiogram, azythromycin was replaced with doxycycline. The patient gradually recovered and fever disappeared after 48 hours. Laboratory exams dramatically improved. He was discharged with oral steroid and heparin therapy and a close follow-up was planned.

This picture represents a new pediatric condition following an asymptomatic COVID-19 infection. A rise in the number of critically ill children presenting with an unusual clinical picture overlapping a Kawasaki disease (KD) has been reported.[4,5] Unlike these reported cases admitted to pediatric intensive care units for the severity of the clinical picture, our patient was clinically well. However, laboratory parameters strongly suggested a multiorgan involvement due to infection or inflammation. No pathological organism was identified in all cultured samples. The hypothesized link between COVID-19 infection and the hyperinflammatory syndrome was strongly supported by serological pattern (both qualitative and quantitative analysis), and by confirmed family exposure. However, the infection at the time of clinical presentation was resolved as confirmed by repeated negativity of SARS-CoV2 on nasopharyngeal swabs. It is hypothesizable that virus persistence is not the cause of poor outcome in pediatric cases, but it is likely the subsequent inflammatory cascade plays a pivotal role in the development of the condition. The hypothesis of a cytokine storm was confirmed by high levels of interleukin (IL)-6 and IL-2 on admission, which decreased in association to all laboratory parameters after steroid therapy. Nevertheless, the inflammatory response observed in pediatric patients differs from what described in adults with COVID-19. In adults, acute respiratory distress syndrome may directly lead to respiratory failure, which is the cause of death in a proportion of fatal COVID-19 cases.[6] In these patients, the viral infection induces a massive release of cytokines that is responsible for death.[6] The milder clinical spectrum of COVID-19 infection in children compared with adults has been explained, at least in part, with an expanded pool

TABLE 1 Relevant laboratory parameters at admission and during the hospital stay

Test		Admission	12 h	20 h	29 h	33 h	46 h	70 h	120 h	144 h	216 h
CBC											
	Hb/Hct (g/dL)/(%)	11.3/30.8	–	10.9/30	–	–	11.4/31.7	11.5/33.1	12.2/35.3	11.9/34.4	11/32
	WBC ($\times 10^3$/μL)	23.11	–	18.45	–	–	16.8	16.97	17.28	22.37	17.11
	Neutrophils ($\times 10^3$/μL)	21.61	–	16.21	–	–	14.67	14.64	12.19	19.97	14.01
	Lymphocyte ($\times 10^3$/μL)	1.03	–	1.6	–	–	1.45	1.7	3.7	1.5	2.23
	Monocytes ($\times 10^3$/μL)	0.31	–	0.31	–	–	0.66	0.59	1.28	0.84	0.86
	PLT ($\times 10^3$/μL)	260	–	292	–	–	389	413	461	458	372
CMP											
	BUN/Cr (mg/dL)	118/1.63	98/1.0	78/0.89	52/0.61	–	–	–	–		-/0.32
	AST/ALT (units/L)	214/115	–	239/176	227/19	–	194/208	166/264	62/170	43/138	25/88
	LDH (units/L)	969	685	–	–	–	605	583	506	409	415
	Troponin (ng/L)	434	282	–	–	75	61	49	33	9	6
	BNP (pg/mL)	825	–	–	–	–	733	430	94	–	–
Tryglycerides (mg/dL)	225	–	–	–	–	–	–	270	–	264	
Inflammatory markers											
	PCT (ng/mL)	25.79	–	8.95	5.02	–	3.13	1.43	0.54	0.26	0.13
	CRP (mg/L)	420.8	–	275.3	228	–	146.2	65.4	24.72	11.12	3.81
	Ferritin (ng/mL)	3997	–	4488	–	–	–	1071	655	572	487
	Fibrinogen (mg/dL)	1109	–	–	–	–	968	561	394	255	
	D-dimero (ng/mL)	1806	–	–	–	–	3494	5106	6385	4913	2099
	IL-2	3157	–	–	–	1527	–	–	–		
	IL-6	33	–	–	–	4.9	–	–	–		

Abbreviations: Albumin (normal value [nv] 3.4-4.8 g/dL); ALT, alanine aminotransferase (nv 8-40 units/L); AST, aspartate aminotransferase (nv 5-58 units/L); BNP, brain natriuretic peptide (nv <100); BUN, blood urea nitrogen test (nv 10-38 mg/dL); CBC, complete blood cell count; CMP, comprehensive metabolic panel; Cr, creatinine (nv 0.10-0.40 mg/dL); CRP, C-reactive protein (nv 0.0-5.0mg/L); D-dimer (nv 0.00-270.00 ng/mL); Ferritin (nv 10.00-320.00 ng/mL); Hb, hemoglobin; Hct, hematocrit; IL-2, interleukin-2 (nv <710); IL-6, interleukin-6 (nv <5); LDH, lactate dehydrogenase (nv 300-550 units/L); PCT, procalcitonin (nv 0.0-0.5 ng/mL); PLT, platelets; WBC, white blood cells.

of naïve T cells compared with T cell repertoire of older patients.[7] The appearance of systemic inflammatory syndrome coincides in our case with antiviral IgG appearance and decrease of IgM. This serological pattern has been reported in 80% of patients with coronavirus-associated SARS pneumonia.[8] In our patient uncontrolled inflammation has induced a multiorgan damage with a severe involvement of the cardiac system. However, no coronaritis was detected nor the patient met the diagnostic criteria of KD, with the exception of the history of prolonged fever.

As for therapy, immunoglobulins and steroids have been proposed as therapeutic options for hyperinflammatory shock in children during this pandemic. In our case, immunoglobulins were not started considering the absence of coronary vessels involvement and other clinical elements of KD. Steroids dosage was modulated on the basis of clinical and laboratory responses.

Unlike other recent pandemics, why are we observing an immune-related medium-term toxicity during the COVID-19 pandemic? A possible explanation may be that the clinical presentation of COVID-19 infection is more consistent with a subacute rather than an acute viral illness. Indeed, median incubation period and time to intensive care admission and/or mechanical ventilation are generally longer than previous pandemics.[1] However, the mechanism underlying the development of severe inflammatory response, particularly following an asymptomatic acute COVID-19 infection, is still poorly defined. Our data suggests a close medium-term monitoring of children with COVID-19 infection, even though with mild or no signs of acute viral infection.

CONFLICT OF INTERESTS

All the authors declare that there are no conflict of interests.

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