

Immunological assessment of pediatric multisystem inflammatory syndrome related to COVID-19

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Key points

The pathophysiology of MIS-C related to COVID-19 is unclear. We show that there is a post-infectious inflammatory syndrome with elevation in all cytokines despite confirmation of a strong and specific humoral response to SARS-CoV2. The expressions of perforin and NK cell degranulations were normal despite overlapping phenotype with haemophagocytic lymphohistiocytosis.

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Abstract

Background. Recently, cases of multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 have been reported worldwide. Negative RT-PCR testing associated with positive serology in most cases suggests a post-infectious syndrome. Because the pathophysiology of this syndrome is still poorly understood, extensive virological and immunological investigations are needed.

Methods. We report a series of four pediatric patients admitted to Geneva University Hospitals with persistent fever and laboratory evidence of inflammation meeting published definition of MIS-C related to COVID-19, to whom an extensive virological and immunological workup was performed.

Results. RT-PCRs on multiple anatomical compartments were negative whereas anti-SARS-CoV-2 IgA and IgG were strongly positive by ELISA and immunofluorescence. Both pseudo- and full virus neutralization assays showed the presence of neutralizing antibodies in all children, confirming a recent infection with SARS-CoV-2. Analyses of cytokine profiles revealed an elevation in all cytokines, as reported in adults with severe COVID-19. Although differing in clinical presentation, some features of MIS-C show phenotypic overlap with haemophagocytic lymphohistiocytosis (HLH). In contrast to patients with primary HLH, our patients showed normal perforin expression and NK cell degranulation. The levels of soluble IL-2 receptor (sIL-2R) correlated with the severity of disease, reflecting recent T-cell activation.

Conclusion. Our findings suggest that MIS-C related to COVID-19 is caused by a post-infectious inflammatory syndrome associated with elevation in all cytokines, and markers of recent T-cell activation (sIL-2R) occurring despite a strong and specific humoral response to SARS-CoV2. Further functional and genetic analyses are essential to better understand the mechanisms of host-pathogen interactions.

Keywords: multisystem inflammatory syndrome in children; SARS-CoV-2; immunological and virological workup

Introduction:

Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, children have been relatively unaffected by the disease, accounting for less than 2% of diagnosed cases [1-4]. While severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused more than 920 000 deaths around the world, the mortality among children is extremely low [5].

However, since March 2020, clusters of children with severe hyperinflammatory syndromes suggestive of atypical Kawasaki disease (KD) or toxic shock syndrome have been reported in Europe and the U.S [6-9].

In recently published case series, abdominal complaints and cardiac involvement were common and inflammatory markers were systematically elevated. Most of these cases had a positive COVID-19 serology, indicating recent infection [7, 10-15].

These clinical pictures have been named Multisystem Inflammatory Syndrome in children (MIS-C) or pediatric MIS (PMIS) by The World Health Organization (WHO) [16].

The severity of the inflammatory syndrome, the response to IVIG and immunomodulators and the inconsistent detection of the virus point to an immunological phenomenon instead of a phenomenon directly mediated by the virus. However, the aetiology, mechanism and possible risk factors of this post-infectious inflammatory syndrome related to COVID-19 have not yet been elucidated.

To better understand this phenomenon, we evaluated the SARS-CoV-2-specific antibody response and its neutralizing capabilities among children with MIS-C, as well as a detailed cytokine profile at various time of hospitalisation and searched for any defect of the immune system in these children. We also correlated the clinical presentation, immunological findings and response to treatment.

Methods:

In this case series, children with MIS-C according to the WHO case definition [16], admitted between April 11th and April 26th 2020 in the PICU or the general pediatric ward of Geneva University Hospitals were enrolled.

Patients were defined as “severe” if they required PICU management for hemodynamic instability and/or organ failure, and “moderately severe” if they needed hospitalization in the general pediatric unit due to a poor clinical status incompatible with ambulatory management.

For any suspected MIS-C, an inflammatory workup (including C-reactive protein (CRP), procalcitonin (PCT), fibrinogen, ferritin), full liver function tests, renal function, cardiac assessment function tests (including Troponin, pro-BNP and D-Dimers), and coagulation function (Quick, international normalized ratio, prothrombin time) were performed at admission and then repeatedly, according to clinical evolution. For severe cases, markers of macrophagic activation syndrome were also measured (ferritin, haptoglobin, D-dimers, triglycerides, lactate dehydrogenase).

Microbiology work-up included blood, urine and stool bacterial cultures, viral serologies (HIV, viral hepatitis) and viral PCR (Epstein-Barr virus, Cytomegalovirus, Adenovirus, +/- Herpes simplex virus 1&2, parvovirus B19), RT-PCR for Enterovirus and SARS-CoV-2 as previously described [17]. A detailed virological workup was performed at admission in all patients. All virological investigations were performed at the Geneva Centre for Emerging Viral Diseases. SARS-CoV-2 IgA and IgG serologies were done using the Euroimmune enzyme-linked immunosorbent assay (ELISA). Results were confirmed using recombinant immunofluorescence (rIFA) [18]. Then, the quantification of the neutralizing antibodies were performed using both full virus and VSV-based pseudo-neutralization as both methods were available in our Centre. While work with SARS-CoV-2 for the plaque-reduction neutralization assay (PRNT) requires a biosafety laboratory (BSL) class 3 and is resource-intensive and time-consuming until results are available, a VSV-based pseudoneutralization assay can be performed under BSL-2 conditions, allowing higher sample throughput and shorter time to read-out. Recently the VSV-based pseudoneutralization system used in our laboratory was shown to correlate

well with SARS-CoV-2 PRNT titers. Thus it can be a reliable method to assess SARS-CoV-2 neutralizing antibodies as proof of previous infection [19].

A detailed immunological workup was performed to exclude an immune defect or hypergammaglobulinemia. It included dosage of immunoglobulins IgG, IgA and IgM and vaccine antibodies measured between days 6 and 12 of illness as previously described [20]. Investigations of possible reductions or increase in some subpopulations of lymphocytes and in particular activated T cells expressing HLA-DR+ were assessed through simple lymphocyte immunophenotyping according to [21, 22] after the first week of illness, as the patient were too lymphopenic at admission. An extended lymphocyte immunophenotyping with CYTOF [23] was also performed at day 16 for patient 1 and at day 12 for patient 4 (including the expression of CD25 on CD4 cells).

Patients' cytokine profiles were analyzed at presentation and during disease course until recovery in order to better understand the pathophysiology of MIS-C and also to guide the choice of immunomodulator treatments. The proinflammatory cytokines IL-1 β , TNF- α , IL-6, and IL-17; the chemokines IL-8 and monocyte chemoattractant protein-1 (MCP-1/CCL2); and the regulatory cytokines IL-10 and IL-1 receptor antagonist (IL-1 ra) were measured using a commercially available multiplex beads immunoassay, based on the Luminex platform, as previously described [24]. Serum levels of soluble IL-2 receptor (sIL-2R) were measured using an enzyme immunoassay kit (R&D system, Minneapolis, Minn., USA).

Finally, a NK-cell function test was done using a degranulation assay as described previously [25] in the three most severe patients between days 8-16 of illness, to exclude cytotoxicity defects of NK cells, given some similarities of MIS-C with haemophagocytic lymphohistiocytosis (HLH) [26].

The radiology exams were performed according to their clinical point of call (chest X-rays and chest CT scans for patients with chest pain and/or breathing difficulties and abdominal ultrasounds and abdominal CT scans for patients with digestive symptoms).

The study was approved by the local Ethics committee of Geneva. Written informed consent for the publication of this manuscript was provided by the parents of each child.

Results:

Clinical presentation, evolution and management

Between April 11 and April 26, 2020, four pediatric patients presented to the emergency department at the University Hospitals of Geneva with the newly described MIS-C associated with COVID-19 [16]. All of them required hospitalization and two of them were admitted to the pediatric intensive care unit (PICU). All children were previously healthy and two of them were obese with a BMI-for-age above the 95th -percentile. Median age was 10 years (range: 10-13) and all were male. All patients developed their first symptoms at home during the confinement period that started in Switzerland on March 16th and three of them had known household exposure to SARS-CoV-2. Demographics, clinical findings, imaging findings, treatment, and outcome for those four children are shown in Table 1. Clinical presentations were similar to previous reports [7, 8, 15, 27] and the most commonly reported initial symptoms were persistent fever with abdominal pain and vomiting. One patient reported also severe sore throat and a rash, and one patient had conjunctivitis. Two of the patients progressed to warm, vasoplegic shock, refractory to volume resuscitation and required noradrenaline infusion for hemodynamic support. A chest CT scan was performed in three patients and showed the presence of uni- or bilateral lung consolidations and signs of fluid overload, but an absence of the typical ground glasses opacities described in adult patients with COVID-19. In the context of the persistent abdominal pain and elevated fever, all four patients had an abdominal CT scan which showed acute mesenteric lymphadenitis in all four children and ileocolitis with thickening of bowel wall in two of them. The two patients admitted to the PICU required respiratory support, with non-invasive mechanical (NIV) ventilation for 5 days for patient 1, and endotracheal intubation with mechanical ventilation (MV) for 4 days for patient 2. Cardiac function remained normal in patient 1 and the vasopressor support could be weaned off after 4 days. Patient 2 required longer vasopressor support, for a total of 9 days, and developed bilateral coronary artery dilatation. Shortly

after his admission to the PICU, continuous renal replacement therapy (CRRT) was initiated in patient 2 both to support renal function in context of acute kidney injury, and also to help with the clearance of pro-inflammatory cytokines. Three patients (1, 2 and 4) had a 5-day course of hydroxychloroquine treatment with the addition of azithromycin in two of them, which was well tolerated. Patient 2, who presented with the most severe form of MIS-C received also a 7-day course of hydrocortisone (50mg² i.v. loading dose, followed by 25 mg² i.v. every 6 hours), a 5-day course of the interleukin1 receptor antagonist anakinra (100mg once daily subcutaneous), and one dose of intravenous immunoglobulin (IVIG) (2g/kg) after the echocardiographic diagnosis of coronary artery dilatation. In context of persistent fever despite hydroxychloroquine treatment, patient 4 also received a single dose of intravenous tocilizumab (8mg/kg), an anti-IL-6 receptor antibody. Blood cultures were negative in all four patients and molecular testing for other viruses than SARS-CoV-2 came back negative with the exception of a positive PCR for adenovirus in the stools from patient 4 (blood PCR negative).

The laboratory workup of our four patients showed that they all presented with lymphopenia at admission and elevated markers of inflammation including CRP >100mg/l in all four patients. The levels of PCT, D-dimers and the neutrophil to lymphocyte ratio (NLR, a known marker of physiological stress) were all higher in the “severe” patients 1 and 2 compared to the “moderately severe” patients 3 and 4. We observed a progressive decrease in all the measured proinflammatory markers for all the patients when recovering. As of May 13th, all four patients recovered completely except patient 2 who has a persisting coronary dilatation. They were all discharged home with good general conditions and close follow-ups at the cardiology and immunology clinic.

Virological investigations

All children tested negative by RT-PCR for SARS-CoV-2 on nasopharyngeal specimens (NPS). Furthermore, RT-PCR was also negative in the serum (n=3 patients) and stools (n=3 patients). However, serological testing for SARS-CoV-2 showed positive IgA and IgG antibodies in all patients, confirmed by rIFA. Neutralizing antibody titers using both VSV-based pseudo- neutralization assays and SARS-CoV-2 PRNT showed high titers of neutralizing antibodies, ranging from 1:80 to 1:320 for

the pseudo-virus PRNT assay with 90% neutralization (PRNT90) and > 1:320 in all four children for wild-type virus PRNT90 assays.

Immunological investigations

First, all measured cytokines, not just the proinflammatory ones, were increased in patients during the disease course in the acute phase with progressive normalization with time, and higher levels in the more severely affected children (Figure 1). Notably, we also analyzed the cytokine profile of a male patient of the same age infected with SARS-CoV-2 but without MIS-C at various time-points from infection and we did not observe any increase in the listed cytokines. The levels of sIL-2R, which is a marker of T-cell activation, was also measured at admission in all four children and the levels correlated with disease severity as previously reported in adults with severe COVID-19 [29].

Immunophenotyping of lymphocytes performed after the first week of onset of symptoms, because of profound lymphopenia at admission, showed normal numbers and percentages of all T, B and NK cells (Supplemental Table 1 and 2). The expression of HLA DR and CD25 on T cells were normal, with the exception of a slight increase in patient 4 (HLA DR on T cells: 16% at day 7 of illness and 1.3% at day 11). The levels of sIL-2R were increased at admission in all four patients.

Perforin expression and CD107a upregulation tests performed in the three most severely affected patients in the second week of onset of symptoms showed normal results (Supplemental Figure 1). The levels of IgG, IgA and IgM was also normal and there was no increase in auto-reactive antibodies (Supplemental Table 1 and 2). Vaccine induced antibodies were protective for all antigens, except pneumococcal serotypes contained in the Prevenar13 (PCV13) vaccine.

Discussion

In this case series we report the clinical, inflammatory and immunologic responses related to the newly described MIS-C related to COVID-19.

As previously described, the four children presented clinically with gastro-intestinal symptoms and persisting fever, with imaging confirming the presence of ileo-colitis [7, 9, 14]. Two patients who had consulted previously in the emergency room, came back a few days later with a rapidly decompensated vasoplegic shock, requiring rapid treatment in the PICU with aminergic and ventilation support. The fact that the levels of PCT, D-dimers and NLR were higher in the patients with the most severe presentation that these three parameters could represent potential useful severity markers for children presenting with MIS-C associated with COVID-19 as previously reported for D-dimers [28].

As previously reported, all of our patients tested negative for SARS-CoV2 by RT-PCR but had detectable antibodies specific for the virus. To our knowledge, we are the first group to report results on extensive antibody testing in children presenting with MIS-C. We confirmed SARS-CoV-2-specific antibodies with multiple serological assays including ELISA (IgA, IgG), rIFA (IgG) and two neutralization assays, described above. The latter two showed high titers of neutralizing antibodies in all four children. Even though the presence of neutralizing antibodies against SARS-CoV-2 does not allow inference of causality between MIS-C and SARS-CoV-2, it confirms that all four patients had a recent exposure to SARS-CoV-2 and that they developed a MIS-C despite an appropriate adaptive immune response. This is consistent with the fact that most patients had a household-history of SARS-CoV-2 exposure round 2-3 weeks earlier, which is in line with high antibody titers observed at the time of hospitalization [9, 30, 31].

Concerning the immunology workup, an increase in all the cytokines was observed in the acute phase of the disease, in particular IL-6 and IL-1, with normalization correlating with clinical recovery, and following the immunomodulatory treatment in two patients. In comparison, the cytokines were not increased in a male of similar age infected with SARS-CoV-2 but without MIS-C

at various time-points from infection. The peak concentrations of all cytokines were usually higher in the children with the most severe presentation.

The normal lymphocyte immunophenotyping assessed in the second week of illness after the lymphopenia phase suggests an absence of a numeric defect in the T, B and NK cells as being the cause of MIS-C post COVID-19. It is possible that the markers of T-cell activation (expression of HLA DR and CD25) were not identified in three of the four children, because they were taken at later phase of the illness (after day 11). Indeed, the levels of sIL-2R at admission were increased in all the patients, suggestive of a recent T-cell activation. This, together with documented viral clearance, argues against a severe T cell defect with lack of viral clearance. Although differing in the clinical presentation and NLR, some features of MIS-C (such as hyperferritinaemia and hypercytokinaemia) show phenotypic overlap with HLH. In addition, reduced cytotoxic cell/perforin functionality by various factors (including high BMI, male gender, and age >70 years) have been suggested as possible factors for severe COVID-19 in adults [32]. Perforin expression and CD107a upregulation tests have been shown to be highly accurate in identifying patients with primary HLH due to cytotoxicity defects [26]. However, both tests, performed in the three most severely affected patients, showed normal results, excluding a defect in cytotoxicity.

In our patients, we did not observe any increased expression of HLA DR or CD25 on T cells in the second week of disease onset, except in patient 4, who had 16% HLA DR+ T cells at day 7 of illness. Similarly, the concentration of sIL-2R was increased in all four children with levels correlating with the severity of disease. As previously described in Kawasaki disease, it may be possible that superantigenic activity of SARS-CoV-2 could trigger massive activation of T-cells with extensive release of cytokines. A recent report has demonstrated that the SARS-CoV-2 spike exhibited superantigenic character strengthened by a recent mutation in the European strain, which could explain the development of MIS-C as well as increased cytokine release in severe adult-COVID-19 [33].

We found normal subpopulations of all lymphocytes, and normal levels of total antibodies and vaccine antibody except for pneumococcal antibodies specific for serotypes contained in the PCV13. This lack of protection is regularly observed in children of this age, due to a lack of exposure since administration of PCV13 during infancy and the subsequently decreasing circulation of PCV13-serotypes. Most children had normal non-PCV13-antibodies. All these results indicate that these children have a normal cellular immune capacity

It is therefore possible that these children could have a dysregulation of the inflammasome, and that the SARS-CoV-2 may induce an extensive innate immune response and T cell activation in susceptible children, responsible for the clinical MIS-C. Further genetic studies would be necessary to verify this hypothesis. It is possible that the presence of immune complexes could be parts of the components of the inflammatory process in MIS-C, as described in KD [34]. However, we did not have any circulating-ICs detection assays available to test this hypothesis.

Regarding treatment, children responded to IVIG and corticosteroids, and less often interleukin-6 inhibitors, and interleukin-1Ra inhibitor in the paediatric series published so far [7, 9-11, 35]. In adults, the COVID19-related cytokine release syndrome appears to show a response to immunomodulators [36]. Chloroquine and hydroxychloroquine have been reported to inhibit viral replication [37], and also decrease the release of pro-inflammatory cytokines [38]. Tocilizumab could decrease the hyper-inflammation in severe cases of COVID19 [39, 40]. However, a previous report of four children treated with Tocilizumab for KD suggested that this treatment could accelerate the formation of coronary artery aneurysms [41]. Little is known about the best treatment to treat this new syndrome. Further research is needed.

Overall, our data provide evidence of recent SARS-CoV-2 infection in a group of children admitted with MIS-C, as demonstrated by the presence of anti-SARS-CoV-2 IgA and IgG antibodies by ELISA, and rIFA. The presence of neutralizing anti-SARS-CoV-2 antibodies shows that these children were able to mount a humoral immune response against SARS-CoV-2. The longitudinal profile of cytokines confirms that there is a post-infectious inflammatory syndrome associated with

elevation in all cytokines, which normalize over time and possibly following the immunomodulators. This COVID-19 associated MIS-C has some similarities with KD and HLH, but without defect of the cellular immune responses, as seen in adults [42, 43]. The physiopathology is not clear. From our results we can say that there was no degranulation defect of NK cells, which could have altered the clearance of the infected cells and elimination of the macrophages and led to important pro-inflammatory responses [44]. There was no decrease in adaptive immunity, with production of low-quality antibodies, which could have increased the amount of infected cells leading to an extensive activation of innate immune responses. We believe that there might be other factors which might lead to a dysregulation of the inflammasome. More studies about host-pathogen interactions are needed to evaluate why only a small subset of children infected with SARS-CoV-2 develop this MIS-C.

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Author contributions:

SG, FT, NW, MR, AL, CL, AP, MB, AB participated in patient's enrolment, analysis and interpretation of data, and writing the manuscript. JP and SV conducted the degranulation test of NK cells, analyzed the data and review the manuscript. IE, GT, LK conducted all the virological experiments, analyzed and interpreted the virological data and reviewed the manuscript. MP did the extended lymphocyte typing by CYTOF and analyzed the data and review the manuscript. CE, AD helped in analyzing the immunological data and revised the manuscript. PRL guided all the cytokine profiles experiments, analyzed the data and reviewed the manuscript. GBR participated in the patient's enrolment, coordination of all the immunological experiments, interpretation of data, and writing the manuscript.

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Conflicts of Interest: The authors declare that they have no relevant conflicts of interest in relation to this manuscript.

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Figure legends

Figure 1. Cytokine response in subjects presenting with multisystem inflammatory syndrome related to COVID-19. (a) Time course of serum cytokine levels taken before, during and after any immunomodulatory treatment. Serum samples were obtained at different time points according to the first day of symptoms. Dashed lines represent mean values from two age-matched healthy control subjects. Patient n°1 was treated with hydroxychloroquine and azithromycin from day of illness 7 to 12; patient n°2 was treated with hydroxychloroquine and azithromycin from day of illness 8 to 13, hydrocortisone from day of illness 8 to 14, anakinra (anti-IL-1) from day of illness 9 to 14 and a single dose of intravenous immunoglobulin at day 16 of illness; patient n°4 was treated with hydroxychloroquine from day of illness 5 to 9 and a single dose of tocilizumab at day of illness 7. **(b)** Serum cytokine concentration at hospital admission in four subjects presenting with multisystem inflammatory syndrome related to COVID-19 and two healthy controls. Dashed line on sIL-2R graph represents normal range value (< 5ng/mL). Data are presented as single value and mean concentration in the healthy controls group. Intensive care unit (ICU).

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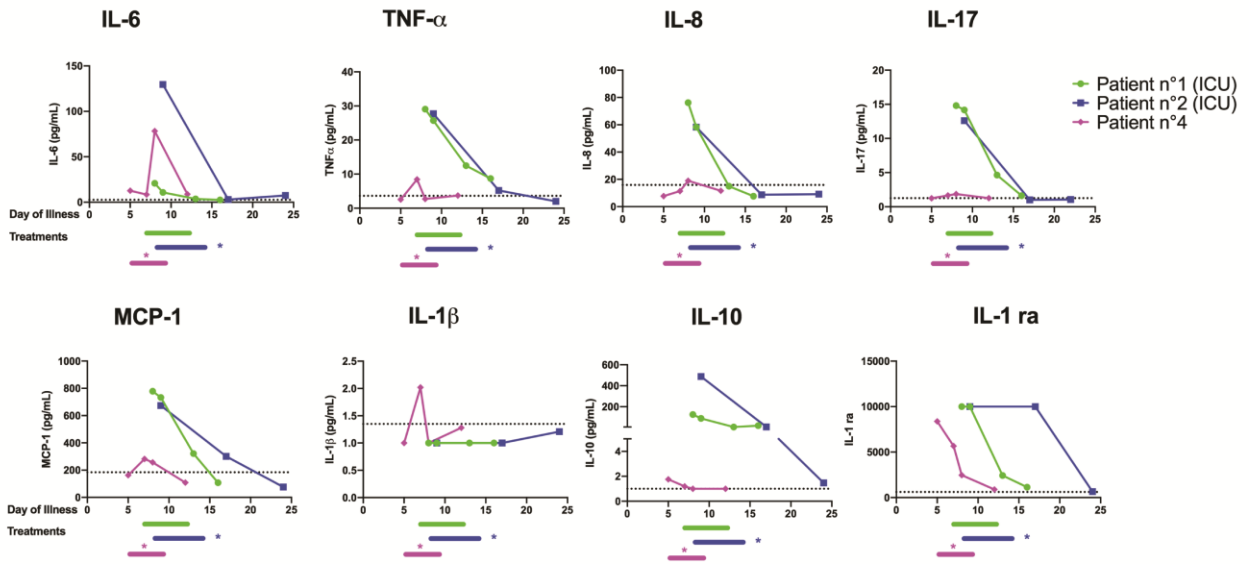
Table 1 Demographics, clinical findings, imaging findings, treatments, and outcome

	Age; weight; BMI; comorbidities	Clinical presentation			Organ support	Pharmacological treatment	Imaging results	Laboratory results	Microbiology results	PICU and hospital length of stay; outcome
		Initial	At admission	PICU referral						
Patient 1 (male, Asian)	10 years; 52 kg; BMI 25.9 kg/m ² ; no comorbidities	6 days fever > 39°C; headache; dry cough; abdominal pain; vomiting; conjunctivitis	Day 6 of illness; BP 86/44 mmHg; HR131 beats/min; RR 36 breaths/min; work of breathing; SatO ₂ 96% RA	Yes	NIV	Noradrenaline, hydroxychloroquine, azithromycin, heparin, piperacillin/tazobactam	Right lobar consolidation with fluid overload; ileocolitis and acute mesenteric lymphadenitis	NLR 16; ferritin 751 µg/L; CRP 190 mg/L; procalcitonin 14.8 µg/L; albumin 25g/L; D-dimers 9161 ng/mL; troponin 166 ng/L; platelets 78 x10 ⁹ /L	SARS-CoV-2 positive (negative PCR but positive serological testing with IgG and IgA antibodies); likely COVID-19 exposure from two brothers	7 days in PICU; 12 days total at the hospital; alive
Patient 2 (male, African)	10 years; 55 kg; BMI 29 kg/m ² ; no comorbidities	7 days fever > 39°C; abdominal pain; vomiting	Day 7 of illness; BP 85/51 mmHg; HR115 beats/min; RR 39 breaths/min; SatO ₂ 98% RA	Yes	MV, RRT	Noradrenaline, vasopressin, hydroxychloroquine, azithromycin, hydrocortisone, anakinra (IL-1 receptor antagonist), IVIG, heparin, ASA, meropenem, vancomycin, caspofungin	Bilateral basal lung consolidations; acute mesenteric lymphadenitis; Mild LV systolic impairment; dilatation of the right and left anterior descending coronary arteries	NLR 30; ferritin 2753 µg/L; CRP 328 mg/L; procalcitonin >100 µg/L; albumin 21 g/L; D-dimers 6499 ng/mL; troponin 299 ng/L; platelets 118 x10 ⁹ /L	SARS-CoV-2 positive (negative PCR but positive serological testing with IgG and IgA antibodies)	14 days in PICU; 19 days total at the hospital; alive
Patient 3 (male, Caucasian)	13 years; 65 kg; BMI 18.6 kg/m ² ; no comorbidities	8 days fever > 39°C; abdominal pain; odynophagia; rash	Day 8 of illness; BP 101/68 mmHg; HR116 beats/min; RR 17 breaths/min; SatO ₂ 98% RA	No	None	Azithromycin, ceftriaxone, heparin	Bilateral basal lung consolidations with pleural effusion; acute mesenteric lymphadenitis	NLR 8.8; ferritin 492 µg/L; CRP 265 mg/L; procalcitonin 2.7 µg/L; albumin 32 g/L; D-dimers NP ng/mL; troponin 199 ng/L; platelets 104 x10 ⁹ /L	SARS-CoV-2 positive (negative PCR but positive serological testing with IgG and IgA antibodies); likely COVID-19 exposure from mother	8 days total at the hospital; alive
Patient 4 (male, Hispanic)	10 years; 32 kg; BMI 14.8 kg/m ² ; no comorbidities	3 days fever > 39°C; abdominal pain	Day 3 of illness; BP 121/76 mmHg; HR 145 beats/min; RR 20 breaths/min; SatO ₂ 100% RA	No	None	Hydroxychloroquine; tocilizumab (anti-IL-6 receptor antibody), heparin, ceftriaxone, metronidazole	Ileo-colitis and acute mesenteric lymphadenitis and a splenic hemangioma	NLR 8.9; ferritin NP µg/L; CRP 120 mg/L; procalcitonin 1.1 µg/L; albumin 23 g/L; D-dimers 3755 ng/mL; troponin 7 ng/L; platelets 208 x10 ⁹ /L	SARS-CoV-2 positive (negative PCR but positive serological testing with IgG and IgA antibodies); likely COVID-19 exposure from father; adenovirus positive in stools	9 days total at the hospital; alive

^A ASA = acetylsalicylic acid; BMI= body mass index; BP= blood pressure; COVID-19= coronavirus disease 2019; CRP = C-reactive protein; FiO₂ = fraction of inspired oxygen; HR = heart rate; IVIG = human intravenous immunoglobulin; LV = left ventricle; MV = mechanical ventilation via endotracheal tube; NIV = non-invasive ventilation; NLR = neutrophil to lymphocyte ratio; NP = not performed; PCR = polymerase chain reaction; PICU = paediatric intensive care unit; RA = room air; RR = respiratory rate; RRT = renal replacement therapy; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SatO₂ = oxygen saturation;

Figure 1

(a)



(b)

