We describe 2 children with persistent fever and profuse diarrhea who developed signs of mucocutaneous involvement (conjunctivitis, fissured lips, skin rash, erythema, and edema of the hands and feet). Blood tests revealed elevated markers of inflammation, lymphopenia, thrombocytopenia, and complement consumption. Afterward, diffuse edema with hypoalbuminemia appeared in the context of a capillary leak syndrome. In both patients, repeated nasal swabs were negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), but each patient had high titers of immunoglobulin G and immunoglobulin M against the SARS-CoV-2 virus. The negative PCR results in the presence of immunoglobulin M and immunoglobulin G suggested that the inflammatory response developed in the late phase of viral infection, when SARS-CoV-2 was not detectable in the upper airway. In this report, we describe patients with what we propose to name as SARS-CoV-2–induced Kawasaki-like hyperinflammatory syndrome. SARS-CoV-2–induced Kawasaki-like hyperinflammatory syndrome seems to be caused by a delayed response to SARS-CoV-2. It resembles Kawasaki disease complicated by macrophage activation syndrome, although it has peculiar features, such as prodromal diarrhea, capillary leak syndrome, and myocardial dysfunction. Intravenous corticosteroid treatment appears to be helpful.
with conjunctivitis, polymorphous rash, swollen extremities, and persistent fever. This patient was treated as if she had Kawasaki disease (KD) with intravenous immunoglobulin and acetylsalicylic acid and improved.4

In this report we describe two cases of severe hyperinflammation with similar clinical and laboratory findings. Neither patient had a positive nasal swab result, but both had high immunoglobulin G (IgG) and immunoglobulin M (IgM) titers against SARS-CoV-2.

CASE REPORTS

Patient 1

On April 14, 2020, a 12-year-old boy presented to our emergency department with a 2-day history of high fever and abdominal pain. His previous medical history was unremarkable. On admission, blood tests revealed significant lymphocytopenia (lymphocyte level of 560 cells per mm³) and elevated levels of inflammatory markers (Fig 1). A nasopharyngeal swab was negative for SARS-CoV-2. A chest radiograph and echocardiogram were normal, whereas an abdominal ultrasound revealed mesenteric lymphadenitis. Empirical antibiotics were started, without clinical improvement. During the following days, he developed mild conjunctivitis, erythema and cracked lips, skin rash, erythema and edema of the hands and feet, petechial elements (Fig 2), persistent high fever, diarrhea (10–20 times daily), and vomiting. He also developed mild thrombocytopenia, complement consumption, pleural effusion, weight gain, hypoalbuminemia with mild proteinuria, and an increased ferritin level (580 ng/mL). Treatment with methylprednisolone at 2 mg/kg was initiated, with immediate defervescence, prompt general improvement, and normalization of blood tests. Meanwhile, he developed cardiac involvement (reduced systolic function and pericardial effusion on an echocardiogram, elevated troponin T levels with normal creatine kinase myocardial band levels, and electrocardiographic signs of myocardial injury). He continued intravenous corticosteroid for 2 weeks, with subsequent normalization of cardiac function.

Patient 2

On April 18, 2020, a 7-year-old boy arrived in our emergency department with a 5-day history of fever, nausea and vomiting, diarrhea, and abdominal pain. He had a previous diagnosis of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis. Both parents were healthcare workers. The mother had anosmia and taste dysfunction for 1 month. A physical examination revealed bilateral conjunctivitis; modest eyelid and scrotal erythema; skin rash on palms and soles, limbs, and back; petechial elements in the lower limbs; dry lips; and de-
epithelialized tongue (Fig 2). Blood tests revealed lymphocytopenia, thrombocytopenia, low C3 and C4 levels, hypoalbuminemia, and significantly increased levels of ferritin (897 ng/mL) and other inflammatory markers (Fig 1). A chest radiograph and electrocardiogram were normal, whereas an ultrasound of the abdomen revealed the presence of enlarged mesenteric lymph nodes. A nasopharyngeal swab specimen was negative for SARS-CoV-2. Broad-spectrum empirical antibiotics were started. Subsequently, the patient developed hypotension, tachycardia, and tachypnea with oxygen desaturation. Noninvasive respiratory support was initiated, and he received a crystalloid solution, followed by vasopressors. After fluid resuscitation he developed right pleural effusion and cardiomegaly. Laboratory and instrumental tests on hospital day 3 (illness day 7) confirmed the cardiac injury (eg, abnormal troponin T levels, elevated pro-brain natriuretic peptide levels, and high levels of D-dimer, with reduced systolic function on echocardiography). Treatment was switched to intravenous immunoglobulin at 2 g/kg and methylprednisolone at 2 mg/kg, and we continued antibiotic therapy. The patient had progressive improvement in clinical condition, laboratory, and imaging results.

Because of the uncertainty about the cause of both of these cases, we measured anti-S-specific IgG antibodies to SARS-CoV-2 (LIAISON SARS-CoV-2 S1/S2 IgG [reported specificity 98.5%]; DiaSorin, Saluggia, Italy) and found that both patients had moderate to high positive titers of IgG antibodies versus SARS-CoV-2. A second confirmatory test (Eradikit COVID19 [reported specificity 98.1%]; In3Diagnostic, Turin, Italy) found IgG and IgM antibodies directed toward SARS-CoV-2 in both patients.

**DISCUSSION**

These two cases reveal a novel severe inflammatory syndrome that may develop in children during the late phase of SARS-CoV-2 infection. SARS-CoV-2 acute infection may mimic KD because it may present with persistent fever, rash, and conjunctivitis; our cases highlight that SARS-CoV-2 infection may trigger a severe inflammatory syndrome even after seroconversion, when the virus might not be detected in upper airways.5

These two patients presented with diarrhea, abdominal pain, high fever, elevated C-reactive protein (CRP) and
procalcitonin levels, and a low lymphocyte count (phase 1). Despite appropriate broad-spectrum antibiotic therapy, fever persisted, and mucocutaneous involvement appeared: conjunctivitis, fissured lips, and acral rash. Both then developed, in phase 2 of their illness, progressive thrombocytopenia, C3 and C4 consumption, hepatomegaly, capillary leak syndrome with severely decreased albuminemia, diffuse edema, and, in one case, severe hypotension requiring fluid resuscitation therapy. Both patients improved after intravenous corticosteroid therapy, but they developed what appeared to be myocarditis in a third phase.

On initial presentation, we believed they had a gastrointestinal bacterial infection. In the second phase, both patients fulfilled KD diagnostic criteria. However, they had unusual features, such as the age at disease onset and a low platelet count. This last finding is not frequent among patients with KD, except when macrophage activation syndrome (MAS) simultaneously develops. MAS is a rare life-threatening complication of autoinflammatory and autoimmune diseases\(^6\) that develops in 1.1% to 1.9% of patients with KD. In 2015 Wang et al\(^7\) published a report of 8 patients with macrophage activation syndrome in Kawasaki disease (MAS-KD). All patients had serum ferritin levels >684 ng/mL and aspartate aminotransferase levels >100 U/L, 87.5% had a platelet count of <100 000/mm\(^3\). Coronary involvement occurred in 25% of patients.

MAS-KD has many similarities with the clinical picture of our patients, although these two patients had unique features (Supplemental Table 1), such as the absence of coronary involvement, the development of myocardial dysfunction, and rapidly progressive capillary leak syndrome.

Our patients did not have a PCR positive for SARS-CoV-2, but they had serological evidence of an infection by using two different and highly specific tests. Although little is known regarding the antibody kinetics, presence of IgM versus SARS-CoV-2 may be considered as a marker of a recent infection.\(^8\) IgM cross-reactivity is improbable because nasal swabs were negative for other coronaviruses (229E, NL63, OC43, and HKU1).

The association between coronaviruses and KD was hypothesized in the past; in particular, Esper et al\(^9\) in 2005 found a PCR positive for New Haven coronavirus in 8 of 11 infants with classic KD. Regarding SARS-CoV-2, recent reports suggest that it causes capillary inflammation in the lungs and skin, with complement activation through both alternative and lectin pathways.\(^10\) A direct viral infection of the endothelial cells and diffuse endothelial inflammation can be found in the kidneys, heart, and liver of patients affected by SARS-CoV-2.\(^11\) SARS-CoV-2 shares this capillary tropism with other coronaviruses; in particular, severe acute respiratory syndrome coronavirus 1 causes complement activation in mouse lungs, and C3\(^{−/−}\) mice have considerably less respiratory dysfunction than wild-type mice.\(^12\) These data suggest that the mucocutaneous involvement, as well as the decrease of C3, C4, and platelet counts, may be a consequence of a microvasculopathy that leads to capillary leakage. The clinical picture described in our report has many analogies with a well-known hyperinflammatory syndrome caused in cats by feline coronavirus: feline infectious peritonitis.

Feline infectious peritonitis is a fatal immune-mediated disease; its effusive form is characterized by fluid accumulation in body cavities as a consequence of immune complex deposition and macrophage activation.\(^13\)

Tavazzi et al\(^14\) demonstrated the presence of viral SARS-CoV-2 particles in a myocardial biopsy of a patient with severe myocarditis. SARS-CoV-2 infection can be a trigger for cardiac injury, secondary to a combination of direct vascular and myocardial infection plus proinflammatory stimulation, which can occur at the same time or even post infection.\(^15\)

We emphasize that heart function improved slowly; further follow-up will be needed to determine if heart function will fully recover.

These two patients had mild respiratory symptoms. In fact, the most significant manifestation was diarrhea. We are now evaluating whether SARS-CoV-2 is present in the stools, but the validity of such testing is unknown.

**CONCLUSIONS**

SARS-CoV-2 infection appears to have led to a late-phase serious inflammatory syndrome in these two children. Although the clinical presentation bears some similarities to KD-MAS, unusual features, such as capillary leak, were present. We propose that this clinical phenotype be named SCiKH syndrome (or SARS-CoV-2-induced Kawasaki-like hyperinflammatory syndrome).

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doctors who helped us in treating these patients.

ABBREVIATIONS
CRP: C-reactive protein
IgG: immunoglobulin G
IgM: immunoglobulin M
KD: Kawasaki disease
MAS: macrophage activation syndrome
MAS-KD: macrophage activation syndrome in Kawasaki disease
PCR: polymerase chain reaction
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

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