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Abbreviations:
SCiKH Syndrome= SARS-CoV-2 induced Kawasaki-like Hyperinflammatory Syndrome
WHO= World Health Organization
IVIG= intravenous immunoglobulin
ASA= Acetylsalicylic acid
KD= Kawasaki Disease
MP= Methylprednisolone
PFAPA=periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis
proBNP= pro-brain natriuretic peptides
PCT= Procalcitonin
MAS= Macrophage Activation Syndrome
FIP= Feline Infectious Peritonitis

Table of Contents Summary: In our paper we describe the first two cases of Kawasaki-like Hyperinflammatory Syndrome in two children with high titer of IgG against the SARS-CoV-2 virus.

Contributors' Statement Page
Dr Licciardi gave substantial contribution to conception and design, drafted the article, reviewed and revised the manuscript.
Dr Pruccoli and Dr Denina contributed to conception and design, collected data, described the case reports, and reviewed and revised the manuscript.
Dr Parodi and Dr Taglietto collected data, provided iconography and revised the manuscript.
Prof Rosati performed the serologic test and interpretation of data, and reviewed the manuscript.
Dr Montin supervised data collection and critically reviewed and revised the manuscript.
All authors approved the final version of the manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract

We describe two 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 for SARS-CoV-2 were negative but each had high titers of IgG and IgM against the SARS-CoV-2 virus. The negative PCR in the presence of IgM and IgG suggest that the inflammatory response developed in the late phase of viral infection when SARS-CoV-2 was not detectable in the upper airway.

This report describes patients with what we propose to name as SARS-CoV-2-induced Kawasaki-like Hyperinflammatory Syndrome (SCiKH Syndrome). SCiKH 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.

Introduction

On January 7th, 2020, the Chinese Center for Disease Control and Prevention isolated a novel coronavirus, SARS-CoV-2, from the throat swab sample of a patient affected by interstitial pneumonia. Since then, SARS-CoV-2 cases have spread rapidly through China and worldwide, leading the WHO to declare a pandemic state on March 11th, 2020. SARS-CoV-2 initial symptoms are flu-like, such as rhinorrhea, fever, cough, fatigue, myalgia, and less frequent diarrhea. In some

patients, the infection can lead to severe interstitial pneumonia followed by multi-organ failure. Since the first reports, the development of systemic inflammation has been proposed as a key factor related to poor outcomes.[1]

Preliminary data suggest that SARS-CoV-2 infection in children is usually milder. In Italy, as of 5/8/2020, 215,665 people were infected by SARS-CoV-2, with less than 2% being under 18 years. Only three pediatric deaths have been reported[2]. Systemic hyperinflammation due to SARS-CoV-2 infection is currently considered rare in children[3]. The initial case appears to have been a 6-month-old girl with SARS-CoV-2 who presented with conjunctivitis, polymorphous rash, swollen extremities, and persistent fever. This patient was treated as if she had Kawasaki Disease (KD) with IV immunoglobulin (IVIG) 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 but both had high IgG and 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 showed significant lymphocytopenia (lymphocyte 560/mm3) and elevated inflammatory markers [Figure 1]. Nasopharyngeal swab for SARS-CoV-2 was negative. Chest X-ray and echocardiogram were normal, while abdominal ultrasound revealed mesenteric lymphadenitis. Empiric 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 [Figure 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 increased ferritin (580 ng/ml). Treatment with methylprednisolone (MP) 2 mg/kg was initiated with immediate defervescence, prompt general improvement, and normalization of blood tests. In the meanwhile, he developed cardiac involvement (reduced systolic function, and pericardial effusion on echocardiogram, elevated Troponin T with normal CK-MB, 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 (PFAPA syndrome). Both parents are healthcare workers. The mother had anosmia and taste dysfunction for one month. 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 [Figure 2]. Blood tests showed lymphocytopenia, thrombocytopenia, low C3 and C4, hypoalbuminemia, and significantly increased ferritin (897 ng/ml) and other inflammatory markers [Figure 1]. Chest X-Ray and ECG were normal, while ultrasound of the abdomen revealed the presence of enlarged mesenteric lymph nodes. A nasopharyngeal swab specimen was negative for SARS-CoV-2. Broad-spectrum empiric antibiotics were started. Subsequently, the patient developed hypotension, tachycardia and tachypnea with oxygen desaturation. Non-invasive

respiratory support was initiated and he received a crystalloid solution followed by vasopressors. After fluid resuscitation he developed a right pleural effusion and cardiomegaly. Laboratory and instrumental tests on hospital day 3 (illness day 7) confirmed the cardiac injury (e.g., abnormal Troponin T, elevated pro-brain natriuretic peptides (proBNP), and high levels of D-dimer with reduced systolic function on echocardiography). Treatment was switched to IVIG 2 g/kg and MP 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, Diasorin; reported specificity 98.5%), and found that both patients had moderate to high positive titers of IgG antibodies versus SARS-CoV-2. A second confirmatory test (In3diagnostic Eradikit COVID19, reported specificity 98.1%) found IgG and IgM antibodies directed towards SARS-CoV-2 in both patients.

Discussion

These two cases illustrate 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 Kawasaki Disease (KD) as 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 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 (PCT), and low lymphocyte count (phase1). 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 and capillary leak syndrome with severely decreased albuminemia, diffuse edema, and in one case severe hypotension requiring fluid resuscitation therapy. Both patients improved after IV 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 low platelet count. This last finding is not frequent among KD patients, except when MAS simultaneously develops. MAS is a rare, life-threatening complication of auto-inflammatory/autoimmune diseases[6] that develops in 1.1-1.9% of patients with KD. In 2015 Wang et al. published a report of 8 patients with MAS in KD (MAS-KD)[7]. All patients had serum ferritin >684 ng/ml and AST>100 U/l, 87.5% had platelet count <100000/mm3. 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 (Table 1, supplementary material) such as the absence of coronary involvement, the development of myocardial dysfunction, and rapidly progressive capillary leak syndrome.

Our patients did not have a positive PCR test for SARS-CoV-2 but they had serologic evidence of an infection 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 as nasal swabs were negative for other coronaviruses (229E, NL63, OC43, HKU1).

The association between coronaviruses and KD was hypothesized in the past, in particular Esper et al. in 2005 found a positive PCR for New Haven coronavirus in 8 out of 11 infants with classic KD[9]. Regarding SARS-CoV-2 recent reports suggest that it causes capillary inflammation in lung 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 kidney, heart, and liver of patients affected by SARS-CoV-2[11]. SARS-CoV-2 shares this capillary tropism with other coronaviruses; in particular, SARS-CoV-1 causes complement activation in mouse lungs, and that 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, 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 hyper inflammatory syndrome caused in cats by feline coronavirus: Feline Infectious Peritonitis (FIP). FIP 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. demonstrated the presence of viral SARS-CoV-2 particles in a myocardial biopsy of a patient with severe myocarditis[14]. 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 in order to determine if heart function will fully recover.

These two patients had very 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.

In conclusion, 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: SARS-CoV-2 induced Kawasaki-like Hyperinflammatory Syndrome.

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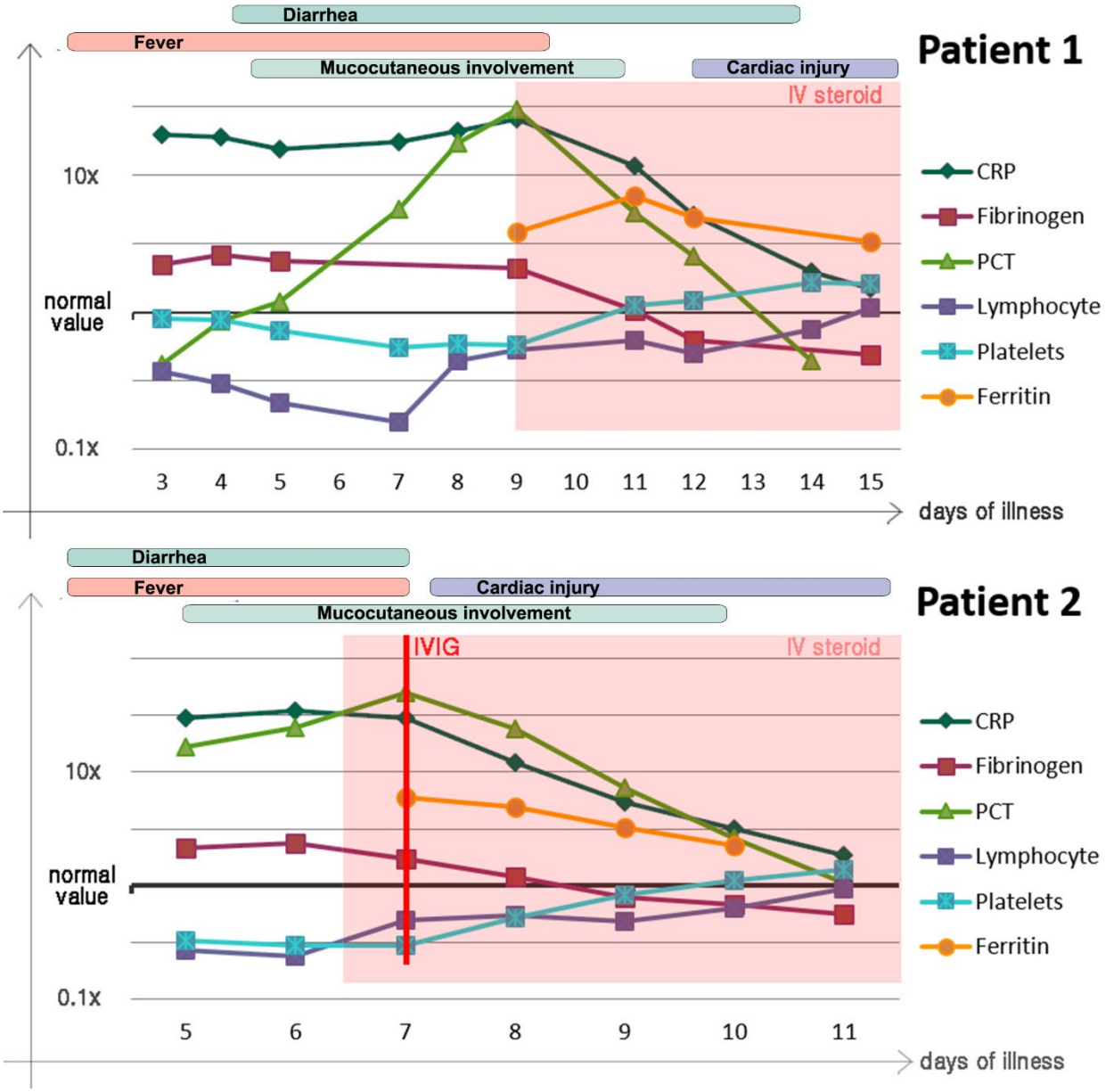

Figure 1: Timeline of patients' symptoms, laboratory findings and therapy. Laboratory findings are expressed as ratio of normal value. Normal values were considered as follows: CRP 10mg/L, Fibrinogen 300 mg/dL, PCT 2 ng/mL, Lymphocyte 1500/mm3, Platelet 250000/mm3, Ferritin 150 ng/mL. Y scale is expressed as Log 10 scale.

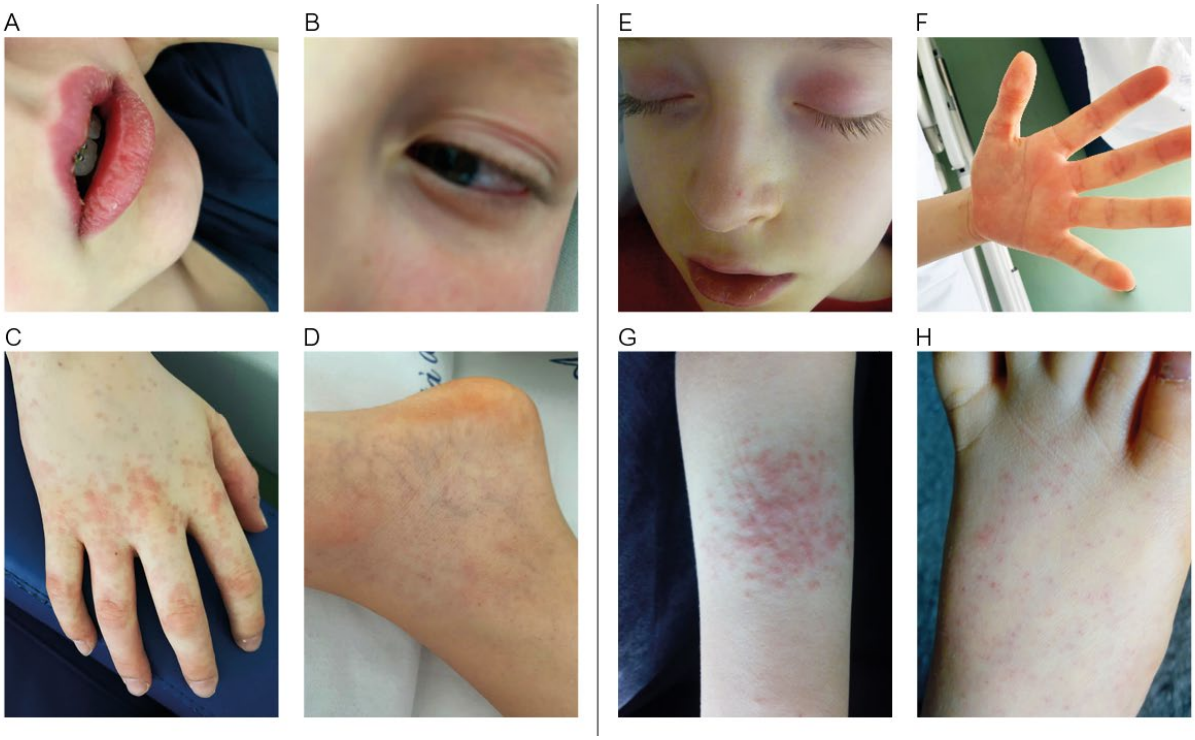

Figure 2: Cutaneous manifestations on day 5 of illness. Patient 1: erythema and cracking of lips (A), mild conjunctivitis (B), erythema and edema of the hands (C), petechial elements on feet (D). Patient 2: modest eyelid erythema (E), skin rash on palms (F), cutaneous erythema (G), petechial elements on feet (H).

Table 1, supplementary material: Comparison between SCikH syndrome and other common pediatric rheumatological diseases. SCiKH= SARS-COV2 induced Kawasaki-like hyperinflammatory syndrome.

	This report (SciKH Syndrome)	Kawasaki Disease	KD+MAS	SARS-Cov infection in adult
Lymphopenia	Yes	Possible	Possible	Frequent*
Low Platelets	Yes	No (usually high platelets)	Yes	Frequent*
C-Reactive protein >150mg/L	Yes	Yes	Yes	Possible
ProCalcitonin >10 ng/ml	Yes	Unusual	Unusual	Possible*
C3 and C4 consumption	Yes	No	Possible (Reported in sJIA MAS)	Unknown
Ferritin >500 ng/ml	Yes	Possible	Yes	Possible*
Diarrhea	Yes	Possible	Possible	Possible*
Rash	Acral vasculitis	Polymorphous	Polymorphous	Acral vasculitis reported
Non-exudative Conjunctivitis	Yes	Yes	Yes	Yes
Fissured Lips	Yes	Yes	Yes	Unknown
Hepatomegaly	Yes	Possible	Yes	Possible
Capillary Leak	Yes	Rare	Possible (Reported in sJIA MAS)	Unknown
Coronary dilatation	No	Pathognomonic but not always present	Pathognomonic but not always present	No dilatation but coronary acute syndrome reported
Myocardial hypokinesia or increased troponin	Yes	Rare	Rare	Elevated troponin have been reported*

KD= Kawasaki Disease, KD+MAS= Macrophage Activation Syndrome in Kawasaki Disease, sJIA = sistemic Juvenile Idiopathic Arthritis *= marker of poor prognosis in adults according to Zhou et al. *(Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, Lancet. 2020;395(10229):1054–1062)*