COVID-19 AND HYPER INFLAMMATION SYNDROME: DIFFERENT PRESENTATION AND MANAGEMENT

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COVID-19 AND HYPER INFLAMMATION SYNDROME: DIFFERENT PRESENTATION AND MANAGEMENT

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Editorial: COVID-19 and hyper inflammation syndrome: Different presentation and management

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COVID-19, SARS-CoV-2, children, MIS-C, Kawasaki disease (KD)

Editorial on the Research Topic
COVID-19 and hyper inflammation syndrome: Different presentation and management

More than 2 years after the declaration of a pandemic for SARS-CoV-2 infection, COVID-19 is still a major public health, social and economic issue worldwide (1). Although children are less severely affected by SARS-CoV-2 infection than adults, during these years the impact of COVID-19 on the pediatric population has clearly emerged in all its facets, which were not entirely evident at the beginning of the pandemic (2, 3).

Most clinical studies were carried out in developed countries, but pediatric COVID-19 represents a relevant problem even in developing countries, where performing well-designed clinical studies may be more difficult (4–6). The articles included in this Research Topic are from different continents (Europe, Asia, and America) and investigated several aspects of the clinical presentation, pathophysiological mechanisms, and medical management of SARS-CoV-2 infection in children.

Through their case reports, Generalić et al., Emeršič et al., Artamonova et al., and Matsubara et al. emphasized how COVID-19 can also present with protean and unusual clinical manifestations in children.

However, the most challenging clinical aspect of pediatric SARS-CoV-2 infection is represented by the multisystem inflammatory syndrome in children (MIS-C). In their article submitted in the first part of 2021, Matucci-Cerinic et al. analyzed MIS-C by comparing it with Kawasaki Disease (KD). They listed the main similarities and differences between these hyper-inflammatory disorders and hypothesized that MIS-C could be viewed as a disorder included in the KD spectrum, instead of representing a

completely new inflammatory disorder of childhood. In detail, they suggested that the development of KD or MIS-C phenotypes during or after SARS-CoV-2 infection might depend on several factors, including (but not limited to) viral load, virulence of SARS-CoV-2 strain(s), child's age, intensity/kinetics of the immune response, ethnic/genetic background, and comorbidities. Additional research seemed to support this view that some common pathophysiological patterns are shared by KD and MIS-C. For instance, Ghosh et al. (7) evidenced some similar cytokine patterns and, in general, host immune responses in MIS-C and KD. From the clinical side, Yilmaz Ciftdogan et al. (8) analyzed the characteristics of MIS-C in 614 children with and without overlap with KD: they reported that almost half patients with MIS-C had clinical features overlapping with KD and, in particular, incomplete forms.

However, even though MIS-C and KD may be part of the same clinical and pathological spectrum and share some immunological mechanisms, these two entities differ by age of presentation and other clinical/immuno-genetic aspects, of course, as emphasized by Dhaliwal et al. These authors also stressed the concerns regarding the specific long-term cardiovascular sequalae of MIS-C, since these children present with acute myocardial injury/myocarditis. In this regard, Mamishi et al. also discussed the importance of the myocardial systolic evaluation in children affected with COVID-19, even in patients without MIS-C.

Therefore, although MIS-C and KD may be included in the same immuno-pathological spectrum, there are clinical and prognostic differences, which require these two entities to be timely and clearly diagnosed and differentiated, in order to grant patients with the most appropriate clinical management (9). The study by Kostic et al. aimed to create a Kawasaki/MIS-C differentiation score (KMDscore) for the discrimination between these two diseases. Indeed, compared with COVID-19 in general and KD, patients with MIS-C may have significantly higher prevalence of cardiac complications and more elevated markers of inflammation and cardiac damage: therefore, diagnostic scores could be a useful tool for distinguishing MIS-C from KD and, thus, should be a priority for clinical research (10).

In addition to a prompt and precise diagnosis of MIS-C, the appropriate medical care and treatment is the other fundamental point for a successful outcome in these sick children (11). In this special collection, several groups reported their clinical experiences. Menchaca-Aguayo et al. described 90 Mexican patients diagnosed with pediatric inflammatory multisystem syndrome, temporally associated with "SARS-CoV-2 (PIMS-TS)/multisystem inflammatory syndrome in children (MIS-C)." They reported a good clinical outcome with null mortality by treating their patients with corticosteroids, alone or combined with intra-venous immunoglobulin (IVIG). They also described those factors resulting more significantly associated with pediatric intensive care unit admission in their center, which were older age, shock at admission, and hypoalbuminemia. According to their initial experience with MIS-C patients in Italy, Brisca et al. proposed a multistep anti-inflammatory treatment protocol for MIS-C based on the "Gaslini severity assessment tool" for MIS-C, which differentiates these patients in 4 classes eligible to progressively more intense treatments (class I: IVIG 2 g/kg; class II: IVIG 2 g/kg + methylprednisolone 2–3 mg/kg/day; class III: IVIG 2 g/kg + pulsed methylprednisolone 10–30 mg/kg/day; class IV: IVIG 2 g/kg + pulsed methylprednisolone 10–30 mg/kg/day + anakinra 5–10 mg/kg/day–max. 100 mg.). Licciardi et al. also supported the importance of a tailored step-up treatment (including IVIG, methylprednisolone and anakinra) of MIS-C for a more successful outcome. Recent (systematic) reviews and meta-analyses further supported the aforementioned therapeutic approach, in general (12–14).

In conclusion, all these research efforts from many countries have significantly contributed to increase the knowledge on pathophysiological, diagnostic, and therapeutic aspects of MIS-C and, in general, pediatric COVID-19 in the last 2 years.

Author contributions

DP drafted and wrote the manuscript. OK and VZ reviewed the manuscript. All authors approved published version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Multisystem Inflammatory Syndrome in Children: Unique Disease or Part of the Kawasaki Disease Spectrum?

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One of the most intriguing and mysterious phenomena observed during the COVID-19 pandemic has been represented by the occurrence of the multisystem inflammatory syndrome in children and adolescents (MIS-C). Patients with this condition have some overlapping signs and symptoms with those of Kawasaki disease (KD), but also display clinical features that are uncommon or less frequent in this illness, such as diarrhea, abdominal pain and myocardial involvement. The sickest patients may develop multiorgan failure and shock, usually due to myocarditis. Management is based on the administration of intravenous immunoglobulin, glucocorticoids and, in the most severe instances, anakinra. It is still debated whether MIS-C and KD represent different illnesses or are part of the same disease spectrum. The aim of the present review is to analyze critically the evidence in favor of the latter hypothesis and to provide the authors' personal interpretation of the relationship between the two conditions.

Keywords: Kawasaki disease, multisystem inflammatory syndrome in children, COVID-19, MIS-C, SARS-CoV-2, toxic shock syndrome, macrophage activation syndrome

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INTRODUCTION

One of the most challenging and enigmatic phenomena observed during the COVID 19 pandemic has been the emergence of the multisystem inflammatory syndrome in children (MIS-C) (1–7). The presenting signs and symptoms were a mix of those of Kawasaki disease (KD) and toxic shock syndrome (TSS), and were characterized, among others, by fever, gastrointestinal complaints, and cardiac involvement. A number of these children required urgent intensive care treatment due to the development of multiorgan failure and circulatory shock, usually of myocardial origin. Some had evidence of macrophage activation syndrome (MAS). Laboratory abnormalities included markedly elevated acute phase reactants, increased ferritin and D-dimer, hypoalbuminemia as well as lymphopenia and relative thrombocytopenia. Patients with myocarditis had elevated levels of pro-B-type natriuretic peptide (proBNP) and troponin. Management was based on the administration of intravenous immunoglobulin (IV Ig) and glucocorticoids. In some instances, IL-1, IL-6 or tumor necrosis factor inhibitors were given. A temporal association with SARS-CoV-2 infection has been hypothesized because some children tested positive for the virus, either by reverse transcriptase-polymerase chain reaction (RT-PCR) or serology, or were exposed to potential contact with a household member affected with COVID-19.

The severity of this condition contrasted with the initial reports from China and Western countries, which had shown that relatively few children and adolescents were affected by COVID-19, and that most of those infected had experienced milder disease compared to adults (8–10). However, epidemiologic data indicated that the onset of MIS-C occurred 3–8 weeks after prior infection or known exposure, suggesting that SARS-CoV-2 acted as a trigger of a post-infectious inflammatory process (likely driven by some aspect of the adaptive immune system) (2, 11). Indeed, the vast majority (>80–90%) of children are positive for antibodies to SARS-CoV-2, whereas a smaller subset may be positive on RT-PCR for the virus. However, based on high cycle thresholds to detect the virus by RT-PCR in MIS-C patients, it is likely the virus is no longer infectious. In parallel with the rise in the number of articles describing the features of this condition in various parts of the world, an intense debate began regarding whether MIS-C and KD represent different illnesses with overlapping clinical features or are on the same disease spectrum. Although most experts favor the assumption that MIS-C is a novel entity with respect to KD (4, 11–17), some, including us, have argued that the two disorders may be a continuum, with some of the differences in phenotypic severity being due to the magnitude or kinetics of the immune response (18).

In the present viewpoint, we examine critically the evidence that supports the latter hypothesis and provide our interpretation of the relationship between the two conditions.

RELATIONSHIP BETWEEN KD AND SARS-COV-2

During COVID-19 pandemic a large number of children with classic or incomplete KD by the American Heart Association (AHA) criteria (19) were seen in affected countries. Many of these cases appeared to be related to SARS-CoV-2 infection, as they tested positive on either RT-PCR or serology. In Italy, most instances of KD occurred during the lockdown period imposed by public health authorities to contain the spread of the epidemic. Because in these months (March–May 2020) children stayed at home and neither attended school nor had social interactions with peers, they were likely not exposed to infectious agents other than the SARS-CoV-2. It is, thus, conceivable that at least a fraction of the cases of "genuine" KD seen during the pandemic were linked to SARS-CoV-2, as it has been ascertained for MIS-C. Furthermore, considering that KD has long been thought to be related to an infectious and/or environmental trigger, albeit still elusive (20), if one admits that SARS-CoV-2 did not play a causative role, a profound drop in the prevalence of KD should have been expected during the lockdown, owing to the lesser overall infectious morbidity in the pediatric population.

CLINICAL SIMILARITIES BETWEEN KD AND MIS-C

Although most children with MIS-C in the reported series did not fulfill the AHA criteria for KD, all had persistent fever and a variable proportion displayed one or more of the typical clinical manifestations of KD, namely rash, conjunctivitis, lips or oral changes, erythema/edema of the extremities, or cervical lymphadenopathy. Notably, the majority of children meeting the case definition for MIS-C seen at authors' hospital had conjunctival injection that spared the limbus, a sign characteristic of KD (19). These observations underscore the presence of many similarities in the clinical phenotype of the two conditions.

One of the arguments that are put forward to support the diversity between the two illnesses is that children with MIS-C have a high frequency of signs and symptoms that are unusual or occur rarely in KD, especially abdominal pain, vomiting, diarrhea, myocardial injury, and signs of meningeal irritation. However, all these features can be seen in classic KD. Vomiting, diarrhea and abdominal pain are part of the gastrointestinal symptoms of KD, together with hepatitis and hydrops of the gallbladder (16). Myocardial dysfunction occurs frequently in acute KD, and myocardial inflammation has been documented by scintigraphy in 50–70% of cases (19, 21). In addition, during the acute stage of KD, electrocardiography may show sinus and atrioventricular node functional abnormalities, with prolonged PR interval and non-specific ST and T-wave changes or low voltage (19). Note that pro-BNP and serum troponin, used in MIS-C to assess the severity of myocarditis, have been proposed as useful markers of cardiac involvement in KD (22, 23). Extreme irritability, exceeding that observed in other febrile illnesses, and aseptic meningitis are common neurologic findings of KD (19, 24). The development of coronary artery dilatation or aneurysms in some patients with MIS-C is difficult to reconcile with the hypothesis of the diversity of the two illnesses, as this complication has previously been attributed only to KD in pediatric patients.

As compared with KD, MIS-C is marked by more intense inflammation and by the frank tendency toward the development of shock and, to a lesser extent, MAS. However, TSS, which is seen in around 5% of children with KD (25), has many aspects in common with the shock syndrome of MIS-C. The development of MAS has been reported in 1–2% of cases of KD, but it is thought to be underrecognized (26). Thrombocytopenia is another feature of MIS-C that is not typical of KD, which is characterized by thrombocytosis. However, a drop in platelet count is frequently encountered in both KD-associated TSS and MAS. A further distinctive hematologic abnormality of MIS-C is lymphopenia, which is usually not observed in KD, and is a hallmark of severe COVID-19, although its pathophysiology is unclear (27). Hyponatremia, rhabdomyolysis, and image findings of corpus callosum inflammation can also occur in MIS-C.

There are several similarities in the therapeutic approach to MIS-C and KD. A high proportion (70–80%) of children with MIS-C have been treated initially with IVIG. Because this therapeutic intervention is part of the standard protocol for KD, its choice implies that many physicians who first saw these patients had the clinical impression of KD, although the choice of this intervention could be due to the aim to control a potentially infectious process or to possibly prevent acquired coronary artery changes. In case of non-response to IVIG, shock or organ-threatening disease, adjunctive therapy with glucocorticoids was

TABLE 1 | Main similarities and differences between MIS-C and KD.

Clinical manifestations common to both KD and MIS-C
Fever, skin rash, conjunctival injection, cervical adenopathy, lip and oral changes, swollen hands and feet, irritability
Clinical manifestations frequent in MIS-C, but less common in KD
Abdominal pain, diarrhea, meningeal signs, myocarditis, MAS (1–2% in KD, but 20–30% in MIS-C), toxic shock syndrome (5–7% in KD, but 30–40% in MIS-C)
Laboratory abnormalities seen in MIS-C, but not in KD
Lymphopenia, relative thrombocytopenia (with the exception of MAS and TSS, in which thrombocytopenia is frequent)
Other similarities between MIS-C and KD
The vast majority of children with MIS-C were given initial treatment with IVIG
Glucocorticoids were effective in patients with IVIG resistance, myocarditis or major complications (TSS or MAS)
The IL-1 inhibitor anakinra is used in severe instances of both MIS-C and KD
Both MIS-C and KD pursue a self-limited course, with recovery within 2–3 weeks
Some children with MIS-C developed coronary aneurysms
Both MIS-C and KD occurred during the lockdown, in the spring of 2020, when children were likely not exposed to infectious agents other than SARS-CoV-2*
After the end of May 2020, after the abate of COVID-19 epidemic, MIS-C and KD disappeared simultaneously*
The second wave of COVID-19, in the fall of 2020, was accompanied by a resurgence of both MIS-C and KD*
Main difference between MIS-C and KD
Children with MIS-C are older than those with KD(median age in MIS-C > 5 years vs. <5 years in KD)

MIS-C, multisystem inflammatory syndrome in children; KD, Kawasaki disease; TSS, toxic shock syndrome; MAS, macrophage activation syndrome; IVIG, intravenous immunoglobulin.
**Observation made in Italy.*

usually given (28), which is analogous to the regimens proposed for IVIG-refractory KD (19, 29). The IL-1 inhibitor anakinra has been occasionally employed for treatment of MIS-C resistant to IVIG and glucocorticoids or impending MAS. This biologic medication is becoming increasingly more popular also for the management of KD after failure of IVIG and its efficacy in KD is being scrutinized in a phase IIa trial (30).

A further similarity between the two condition is the self-limited clinical course, which usually lasts 2–3 weeks. Recently, with improved recognition and treatment of MIS-C, the average hospital stay, even for patients presenting with shock, has decreased to nearly 5 days (31). Finally, the parallelism between MIS-C and KD has been underscored in the experience in Italy by their simultaneous disappearance after the regress of the pandemic, at the end of May 2020, and by their concurrent reemergence around 1 month after the resurgence of COVID-19, in the fall of 2020.

The main similarities and differences between KD and MIS-C are summarized in **Table 1**.

WHY THE AGE OF CHILDREN WITH MIS-C IS HIGHER THAN THAT OF CHILDREN WITH KD?

A feature that is pointed to as distinguishing MIS-C as a unique disease process vs. KD is that the median age of MIS-C cases was 9–10 years in the largest reported series (1–6, 32), whereas KD occurs predominantly in children 5 years of age or younger and has a peak incidence at around 10 months of age (33). There are, however, several reasons that may explain why younger children are more spared than older children and adolescents by COVID-19, in general, and, as a consequence, also by MIS-C.

In the first years of life, the immune system may be more "trained" to fight against viral infections owing to repeated vaccination procedures (34, 35). Notably, an amino acid sequence homology between glycoprotein components of SARS-CoV-2 and measles and rubella viruses has been identified. Using an antibody epitope prediction online tool, the homologous sequence appeared to have an epitope property and to be involved in antibody production. These findings have led to suggest that humoral immunity created through the measles, mumps and rubella (MMR) vaccine could provide a defense against COVID-19 (36). Younger children can also be protected against SARS-CoV-2 in virtue of a cross-reactive immunity induced after the encounter with other coronaviruses, which are a frequent cause of respiratory tract infections in preschool age.

Another potential explanation for the lower rates of SARS-CoV-2 infection in children is the lower expression of the cell surface enzyme angiotensin-converting enzyme 2 (ACE2), a receptor that has been proven to bind to SARS-CoV-2 spike protein and to promote internalization of the virus into human cells (37). In a recent study, children aged 4–9 years were found to have lower gene expression of ACE2 in nasal epithelial samples compared with older children, young adults, and adults (38). It should be recognized, however, that the vast majority of children infected with SARS-CoV-2 do not develop MIS-C irrespective of previous vaccination with MMR and that the lower expression of ACE2 may explain the lesser severity of COVID-19, but does not explain why some children develop MIS-C and some do not.

Notably, a recent study has suggested that ACE2 expression decreases with aging (39). It could be postulated that if an individual has higher ACE2 expression, even if the virus blocks ACE2 via binding, the amount of remaining ACE2 might still be significant. Given the antinflammatory role of ACE2, its higher expression may thus, provide protection against MIS-C.

The distinctive lesser susceptibility to develop MIS-C in the early ages might also be secondary to the immaturity of the immune system, which may be less able to mount a hyperinflammatory response or a cytokine storm syndrome (40).

Epidemiologic studies of MIS-C suggest that younger children are more likely to present with KD-like features, while older children are more likely to develop gastrointestinal symptoms (severe abdominal pain, vomiting, diarrhea), myocarditis and shock, and may be more likely to present with the features of MAS (17, 41). Notably, children presenting on the severe spectrum of classic KD with TSS or MAS are usually older and are boys, consistent with the demographic described in MIS-C (18). The coronary changes, when seen, seem also more likely to develop in the younger KD-like group.

A UNIQUE DISEASE SPECTRUM?

Of the 149 cases of inflammatory illness in children and adolescents registered in Italy between February and May 2020

(32), 96 met the AHA criteria for classic or incomplete KD, 10 met the same criteria plus the case definition for MIS-C, and another 43 only met only the case definition for MIS-C. The clinical diversities between patients with MIS-C and KD paralleled those observed in other series, and children with MIS-C tested positive for SARS-CoV-2 more frequently that those with KD. However, the occurrence of the two illnesses in the same population, during the same period of time, and when children were exposed to virtually no infectious agent other than the SARS-CoV-2 due to the lockdown confinement suggests, on epidemiological grounds, that they represent a disease continuum, with KD being at the more benign end of the spectrum and MIS-C at the most severe end.

PROPOSED COMMON PATHOPHYSIOLOGY OF KD AND MIS-C

The etiology of KD is unknown, but it is generally considered the consequence of an abnormal immune response, in genetically predisposed children, to infectious triggers entering through the upper respiratory tract. Multiple infectious agents have been suspected over the years, including respiratory RNA virus. In 2005, a group from New Haven (CT, USA) detected a novel human coronavirus, named New Haven coronavirus (HCoV-NH), in the respiratory secretions of 8 of 11 children with KD vs. 1 of 22 controls tested by RT-PCR. A serological test was not performed (42). Another study made in Japan evaluated the association between two different coronaviruses (HCoV-NL63 and HCoV-229E) and KD through serological tests. No difference in HCoV-NL63 antibody positivity was found between patients and controls on immunofluorescence assay, whereas antibody level for HCoV-229E was higher in patients with KD (43). Although the association between KD and the coronavirus family has not been confirmed in subsequent studies (19), these observations appear intriguing in the light of the possible relationship between KD and SARS-CoV-2.

As highlighted elsewhere (44), autoinflammatory diseases have taught us that many rheumatic conditions may represent syndromes rather than diseases. A variety of monogenic illness have, indeed, been found to mimic the clinical features of polyarteritis nodosa (45, 46), Behçet disease (47), rheumatoid factor positive polyarthritis (48), systemic juvenile idiopathic arthritis (49) and systemic lupus erythematosus (50). These observations indicate that many conditions that have been traditionally called "diseases" are actually "syndromes," whose pathophysiology may be exemplified as a sort of funnel, that is, as a stereotyped way of reacting to multiple different etiologic factors in individuals possessing a particular genetic predisposition. The recognition of the etiology may be of paramount relevance for the treatment, as demonstrated by the dramatic effectiveness of anti-tumor necrosis factor agents in polyarteritis nodosa associated with ADA2 mutation (51).

In our view, the funnel model may be well-suited to illustrate the common pathophysiology of KD and MIS-C (**Figure 1**). In the case of MIS-C, an extremely aggressive and invasive virus like SARS-CoV-2, which has shown the capacity to cause a cytokine storm syndrome in adults with COVID-19 pneumonia, could induce, when presents with a massive viral load, a clinical phenotype much more inflammatory and acute than that of KD, and marked, in addition to the typical manifestations of KD, by a higher frequency of less common or atypical disease manifestations and of serious complications, such as myocarditis, TSS and MAS.

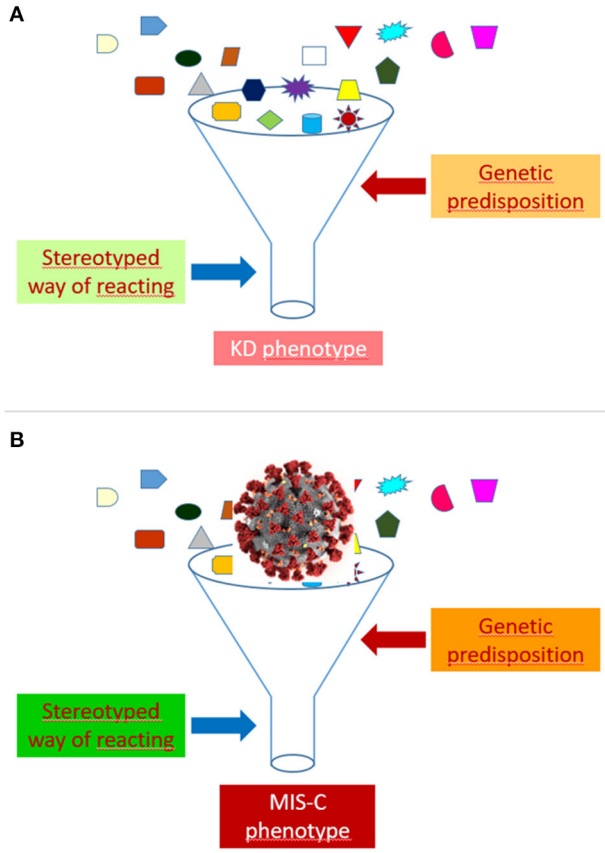

FIGURE 1 | Funnel model of the pathophysiology of Kawasaki disease (KD) **(A)** and multisystem inflammatory syndrome in children (MIS-C) **(B)**.

The development of a KD or a MIS-C phenotype after the contact with SARS-CoV-2 might depend on several factors, including, but not limited to, viral load, virulence of viral strains, child age, intensity or kinetics of the immune response, ethnic or socio-economic factors, comorbidities (especially obesity), and genetic background. Differences between patients in the viral burden could account for the more frequent positivity of SARS-CoV-2 tests in more severe cases.

Henoch-Schönlein purpura (HSP), the most common vasculitis in children, is also a syndrome. It is often preceded by a respiratory tract infection and multiple case studies have suggested a correlation with virtually all respiratory pathogens (52). Although usually benign, it can occasionally cause severe involvement of the kidney, gastrointestinal tract and central nervous system. Like KD, the pathophysiology of HSP appears consistent with an abnormal and stereotyped immune reaction to an infectious agent in genetically predisposed individuals.

Although rather different, HSP has a self-remitting course, like KD.

Although the genetic determinants of KD are still elusive, that susceptibility is shaped by genetic influences is suggested by the preferential involvement of males, the predilection for particular racial/ethnic groups, with an incidence in Japan, Chorea and Taiwan 10- to 20-fold higher than in the United States, and the observation of an increased risk in family members and twins (19). The hypothesis of a common predisposing background between KD and MIS-C is corroborated by the report that 2 of 28 patients with MIS-C had KD in the past (53).

The role of genetic determinants in the induction of MIS-C vs. KD is highlighted by the marked epidemiologic differences among ethnic groups. In the United States, MIS-C had a greater impact on children of Afro-American and Hispanic ethnicity (5, 6) as in France and UK, were children of Afro-Caribbean descent were particularly hit (1, 3, 54). Conversely, MIS-C was apparently not observed in Japan and Chorea, countries characterized by a markedly elevated prevalence of KD. Despite a very high impact of COVID-19, MIS-C was not reported in China. These issues may lead to speculate that subjects belonging to ethnic groups less affected by classic KD may be distinctly susceptible to develop a more aggressive phenotype of KD, including MIS-C.

That a shared genetic background may underlie a continuum of inflammatory disorders of varied severity has been suggested by the detection of genetic similarities among recurrent aphthous stomatitis, periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome, and Behçet disease. The genotypic overlap places these disorders on a common spectrum, with recurrent aphthous stomatitis on the mild end, Behçet disease on the severe end, and PFAPA intermediate (55).

Recent studies suggest that a defective antiviral response may be contributory in some patients with COVID-19. Inborn errors of type I interferon immunity and auto antibodies against type I interferons have been discovered in the most severe cases of COVID-19 (56, 57). It is, thus, conceivable that host immune dysregulation, as well as a molecular mimicry between SARS-CoV-2 and self-antigens, may be involved in the induction of the severe inflammatory manifestations of MIS-C.

The inflammatory response in MIS-C was found to share several features with KD, but also to differ from this condition in the proportion of particular subsets of T-lymphocytes, the characteristics of IL-17A-mediated immunopathology, the concentration of biomarkers of arterial inflammation and damage, and the profile of autoantibodies to proteins involved in immune response or to structural components of heart and blood vessels (58). However, the meaning of this study is affected by the choice of contrasting children with MIS-C with a historical cohort of KD seen before COVID-19 pandemic. In our view, the comparison of patients with the features of MIS-C and KD seen during the course of the pandemic could provide better insights into the relationship between the two conditions, particularly in the light of their common relationship with SARS-CoV-2.

CONCLUSIONS AND FUTURE DIRECTIONS

Based on the above considerations, we favor the hypothesis that MIS-C is on the KD spectrum, instead of representing a new childhood inflammatory disorder separate from KD. The occurrence of a KD-like condition in association with SARS Cov-2 infection underscores the notion that KD is not a disease, but rather a syndrome, whose main features and phenotypic severity depend on the magnitude and type of the immune response as well as on the characteristics of the host and of the triggering infectious agent (44). Notably, the interpretation of KD as a syndrome is in keeping with the first description by Tomisaku Kawasaki, who called it "acute febrile mucocutaneous lymph node syndrome" (59, 60). It should be recognized, however, that there are still limited data on MIS-C, particularly regarding well-established diagnostic criteria, pathophysiology, and outcome information. Thus, further studies of the genetic and immunopathologic background are required to establish more precisely the relationship between MIS-C and KD. More in general, the spectrum of pathology that has emerged during the pandemic offers a unique opportunity for investigations aimed to elucidate the pathophysiology not only of KD, but also of other inflammatory disorders whose causative factors and mechanisms are still unknown.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Little Hearts Are Affected by COVID19: Importance of the Myocardial Systolic Evaluation

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Background: Identifying the cardiac changes could help design measures to recover the cardiovascular system and lessen the mortality and morbidity rate. Accordingly, this cross-sectional study was performed to evaluate the echocardiography indices which are indicators of the cardiac alterations of the children with COVID19 infection.

Methods: This study was performed as a cross-sectional study evaluating echocardiography indices in children infected with COVID19. Fifteen children, known cases of the COVID19, and 14 healthy children were enrolled. Evaluated parameters include left ventricle ejection fraction (LVEF), left ventricle end-diastolic diameter (LVED), mitral valve Sa (MV Sa), Tricuspid annular plane systolic excursion (TAPSE), and laboratory parameters.

Results: The participants' mean age and weight were 62.8 (±48.0) months and 19.95 (±15.67) kg, respectively. None of the laboratory and echocardiography parameters differed between males and females, between patients with and without positive past medical history, between the patients with and without respiratory tract symptoms, and between patients with and without GI tract symptoms (P.0.05). Patients had significantly higher TAPSE ($p = 0.027$), although MV Sa ($p = 0.01$) was significantly higher among healthy children. LV EF ($p = 0.425$) and LVED diameter ($p = 0.603$) were not different significantly. None of the patients had pericardial effusion, pleural effusion, and cardiac tamponade.

Conclusion: The heart can be involved during the disease course in children, even at the level of echocardiography indices. This could contribute to a worse prognosis, higher morbidity, and mortality rate, especially in patients with overt myocardial involvement. Non-classic indicators, including LVEF, may not be conclusive for cardiac involvement in non-symptomatic patients.

Keywords: COVID19, myocarditis, heart, echocardiography, pediatrics, children

INTRODUCTION

The novel coronavirus pandemic, SARS-COV-2 (COVID19), has become a significant concern due to its high mortality rate and unknown nature. Although this virus typically involves the respiratory tract, other organs are also involved with extra-pulmonary manifestations (1, 2). The clinical manifestations range from being asymptomatic or having mild respiratory symptoms to having severe life-threatening respiratory and heart failure (3). Better recognition of the extra-pulmonary manifestations leads to take appropriate and in-time measures to reduce the mortality and morbidity rates (1). On the other hand, The virus behavior in pediatric patients has been poorly defined (4). Previous studies have shown that Less than 1% of the pediatric population with <10 years of age and 2.4% with <18 years of age are infected by COVID19 (5). Similar to the adult population, the respiratory tract is affected most commonly (6). As the respiratory and cardiovascular systems are interconnected, respiratory system involvement directly affects the cardiovascular system. It causes increased right heart afterload, cardiac tamponade, virus-caused myocardial damage, altered ejection fraction, and Kawasaki disease among children (7).

Cardiovascular involvement has been widely described in the literature, though most studies focused on adult populations. One of the most notorious cardiac manifestations is myocardial damage (8); patients with myocardial injury are often considered to have a poor prognosis (9). Previous reports showed a milder clinical course for infants; few of them needed the intensive-care unit administration. Currently, there is insufficient data on cardiovascular and myocardial involvement in COVID19 pediatric patients (2, 10). Identifying the cardiac changes could help design measures to recover the cardiovascular system and lessen the mortality and morbidity rate. Accordingly, this study was performed to evaluate the echocardiography indices to evaluate children's myocardial systolic alterations in COVID19 infection.

MATERIALS AND METHODS

Study Design

This study was performed as a cross-sectional study evaluating echocardiography indices in children infected with COVID19. Fifteen children, known cases of the COVID19, and 14 healthy children were enrolled. The patients were admitted to COVID19 specific ward regarding their symptoms and undergone echocardiography based on their symptoms, including tachycardia. The healthy controls were selected from the patients referred to our clinic for non-specific non-cardiac chief complaints such as chest pain or palpitation. The COVID19 infection was considered positive if positive clinical evaluations of the COVID19 by infectious consultation existed, plus the positive chest CT results and positive reverse transcriptase-polymerase chain reaction (RT-PCR) of the nasopharyngeal swab. The COVID19 pneumonia was considered positive in the case following features that were found in the CT scan: the presence of ground-glass opacity (GGO) mainly in the peripheral and posterior lungs that did not spare the subpleural regions, consolidation, GGO with consolidation, or interlobular septal thickening (11). Echocardiography was performed by a single pediatric cardiologist on the 7th day following the initiation of the symptoms, and electrocardiography (ECG) was also obtained on the same day. Evaluated parameters include left ventricle ejection fraction (LVEF), left ventricle end-diastolic diameter (LVED), mitral valve Sa (MV Sa), and Tricuspid annular plane systolic excursion (TAPSE). Sa was not assessed on the right side because of the imaging limitations in the patients. The laboratory findings of the COVID19 patients, including complete blood count (CBC), CD4, CD8, erythrocyte sedimentation rate (ESR), procalcitonin, LDH, C-reactive protein (CRP), d-dimer, Aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were also recorded. Patients with a previous history of cardiac disease were excluded from the study.

Statistical Analysis

All data were analyzed using the SPSS version 22. Results are presented as the number (percent), mean (+ standard deviation), and mean (interquartile range). Student's *t*-test, Mann Whitney test, and Chi-square test were applied. A *P*-value below 0.05 was considered statistically significant.

Ethical Considerations

This study has been approved by the Research Deputy and the Ethics Committee of Tehran University of Medical Sciences (Reference number: IR.TUMS.VCR.REC.1399.218) and conducted by the ethical standards laid down in the 1964 Declaration of Helsinki and all subsequent revisions. The informed consent form was obtained from all parents following the explanation of the goal of the study.

RESULTS

The participants' mean age and weight were 62.8 (±48.0) months and 19.95 (±15.67) kg, respectively. Thirteen (44.8%) patients were female. The age ($p = 0.290$), weight ($p = 0.851$) and gender ($p = 0.139$) were not different significantly between cases and controls. All patients experienced low-grade fever (<38°C); only six patients had a significant fever (over 38°C), and four of them experienced high-grade fever for more than five consecutive days, other detailed information regarding the clinical manifestations of the patients with COVID19 is shown in **Table 1**. Of note, there were non-specific cardiac initial symptoms such as tachycardia, which could be explained in COVID19 organ involvement. Three patients had a positive past medical history (PMH) (2 had acute lymphoblastic leukemia, and one had aplastic anemia). The laboratory findings are summarized in **Table 2**. None of the laboratory and echocardiography parameters differed between males and females, between patients with and without positive PMH, between the patients with and without respiratory tract symptoms, and between patients with and without GI tract symptoms ($P = 0.05$).

Patients had significantly higher TAPSE ($p = 0.027$), although MV Sa ($p = 0.01$) was significantly higher among healthy children. LV EF ($p = 0.425$) and LVED diameter ($p = 0.603$)

TABLE 1 | Clinical presentations of the 15 evaluated patients with COVID19.

Clinical presentations	Number (percent)
Fever	
Low grade fever (<38°C)	15 (100%)
High grade fever (>38°C)	6 (40%)
High grade fever for more than 5 consecutive days	4 (26.67%)
Myalgia	6 (40%)
GI symptoms	6 (40%)
Abdominal pain	4 (26.67%)
Vomiting	1 (6.67%)
Diarrhea	1 (6.67%)
Respiratory tract symptoms	6 (40%)
Dyspnea	5 (33.3%)
Dry cough	5 (33.3%)
Respiratory distress	1 (6.67%)
Seizure	1 (6.67%)
Disseminated cutaneous eruptions	1 (6.67%)

TABLE 2 | Laboratory results of the 15 patients with COVID19.

Test	Mean (± SD)	Median (IQR)
Complete blood count		
WBC (/mcL)	–	16,390 (4,180–11,720)
Neutrophils (%)	62.6 (±22.6) %	–
Lymphocytes (%)	29.55 (±22.88) %	–
RBC (*10^{12}/L)	–	6.7 (3.23–4.9)
Hb (gr/dL)	11 (±2.27)	–
Plt (*10^3/mcL)	198.36 (±119.42)	–
ESR (mm/h)	51.6 (±41)	–
CRP (mg/L)	–	66.09 (13–78)
Procalcitonin (ng/mL)	–	0.45 (0.01–0.37)
CD4 (*10/mm^3)	35.6 (±19.16)	–
CD8 (*10/mm^3)	18.8 (±9)	–
LDH (U/L)	–	569.36 (379–593)
D-dimer (mcg/mL)	–	0.9 (0.2–1.5)
ALT (U/L)	–	186.9 (13.5–157.5)
AST (U/L)	–	124.1 (18.25–124.25)

were not different significantly (**Table 3**). None of the patients had pericardial effusion, pleural effusion, and cardiac tamponade. Eight patients had a heart rate of more than 100 bpm, the rhythm, PR, and QT intervals were normal in all patients.

DISCUSSION

The present study was conducted to evaluate the echocardiography cardiac alterations of the pediatrics with the COVID19 infection. Despite normal ECG in all individuals, TAPSE and MV SA significantly differed between those with COVID19 and healthy controls. It is noteworthy that LVEF and LVED diameter did not change in these patients.

TABLE 3 | Echocardiography parameters among COVID19 patients and healthy children.

Echocardiography parameters		Mean	SD	*p*-value
LVEF	Patients	72.14	5.972	0.425
	Healthy children	69.14	12.403	
LVED	Patients	30.1643	3.61378	0.603
	Healthy children	31.3923	7.59687	
MV Sa	Patients	10.1000	1.46603	0.01
	Healthy children	12.2231	2.43658	
TAPSE	Patients	20.7429	2.58121	0.027
	Healthy children	17.6607	5.37774	

Hypoxia contributes to remarkable inflammation, which causes cell damage, especially the myocytes (12). Cardiac complications, including heart failure, arrhythmia, and myocardial infarction, are not rare among adult patients infected with COVID19 (13). A study of 138 known COVID19 adult patients revealed that myocarditis occurred for 7.2% of all 138 patients and 22% of patients admitted in ICU (13). In another study of 419 patients found interventricular septum thickening, increased LVED diameter, decreased LVEF in 11 patients (14); unlike the previous study, we did not find any significant difference in terms of LVEF and LVED diameter among infected pediatrics and healthy ones. The number of pediatrics infected with COVID19 is lower than in adults; few cases of severe infection and myocarditis have been reported (15, 16). Trogen et al. (16) reported a 17-year-old boy admitted due to fluid-responsive septic shock with increased troponin I and brain natriuretic peptide consistent with myocarditis. Lara et al. described a 12-year-old girl with COVID19 infection, complete heart block, increased troponin I, and severely depressed systolic function, consistent with fulminant myocarditis due to COVID19 (15). It is estimated that 40–70% of the world's population will be infected with COVID19 (17), which shows that more infected children will be diagnosed and admitted. Two cases of acute myocarditis in previously healthy children have been reported; by the increasing number of infected children, especially more susceptible ones with comorbidities, it is not surprising to see a raised number of this complication in pediatric populations. Given the high infectibility and prevalence, it is essential to know the disease course and complications properly, especially those complications that cause increased mortality and morbidity rates such as myocarditis. Our study confirmed the cardiac changes in infected children; however, the evaluated indices were not different between genders, between patients with and without positive PMH, and between patients with different clinical symptoms. It is noteworthy that only three infected children had positive PMH, which is not enough for accurate judgment. However, the results show that COVID19 pediatric patients' hearts are affected by these conditions. The alarm goes for us those cardiac alterations could result in a worse clinical course and raised mortality and morbidity in pediatrics.

Right ventricular function is a significant component of overall cardiac function with prognostic importance in predicting

symptomatic limitation and multiple cardiovascular diseases (18). COVID19-related myocarditis may present with signs of right-sided heart failure (19) due to impaired pulmonary functions, increased right heart afterload and preload caused by sustained volume overload. In this regard, Zeng et al. indicated increased pulmonary artery systolic pressure (PASP) and TAPSE in a 63-year-old COVID19 patient, suggesting progressive aggravation of the pulmonary lesion and unexpected decrement of these markers several days before death. This was considered to be related to the right heart's functional decline caused by sustained overload (20). Similarly, the TAPSE was increased in our patients; however, only LVEF was measured as a screening method for evaluating the systolic function. In line with the previous study and ours, Ramcharan et al. demonstrated increased inflammatory markers and TAPSE in all individuals, decreased LVEF in 80% and presence of pericardial effusion in 53% (21). Li et al. demonstrated that the right longitudinal ventricular strain and TAPSE are essential predictors of higher mortality in COVID19 patients and are an independent determinant of outcomes in COVID19 patients (22).

Multisystem inflammatory syndrome in children (MISC) is characterized by high-grade fever, evidence in favor of increased inflammation in lab tests, multiorgan (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological) involvement; in addition to positive COVID19 PCR or antigen or exposure to a suspected or confirmed COVID19 patient (23). It is an immunologically mediated condition, as it occurs during the post-infection period and includes a spectrum from Kawasaki-like disease to toxic shock syndrome (24, 25). MISC could be associated with altered cardiac parameters (26); however, in the series of patients evaluated in the current study, none of them fulfilled the MISC, typical or atypical Kawasaki disease criteria. All the patients were evaluated for coronary artery involvement, which was negative for all of them.

Unfortunately, because of the critical medical situation imposed by the COVID19 crisis and the limitations of the facilities, it was not possible for all patients to undergone assessments of the additional laboratory findings associated with myocardial infarction (e.g., CK, pro-BNP and/or troponin). We learned from these findings that the heart is also involved during the disease course in children, even at echocardiography indices. This could contribute to a worse prognosis, higher morbidity, and mortality rate, especially in patients with overt myocardial involvement; furthermore, non-classic indicators, including LVEF, may not be conclusive for cardiac involvement in non-symptomatic patients. Putting all together, evaluating potential cardiac changes before and during the therapy is crucial; since it leads to taking appropriate measures to prevent further damage to the heart.

Study Limitations

There are some limitations to be acknowledged; first, the sample size was small. Furthermore, all echocardiogrphies were performed by a single cardiologist, which reduced interpersonal bias, but it has bias regarding the generalizability of the evaluated echocardiography indices. Besides, the cardiologist was not blinded, which could introduce bias.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research Deputy and the Ethics Committee of Tehran University of Medical Sciences. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

EA and SM equally contributed to the conception and design of the research. AZ deigned the total structure of the manuscript and determined the patients should be involved. EH and AG drafted the manuscript. MK analyzed the data. MM interpreted it and reviewed and finalized the manuscript. HE and MG contributed to the acquisition. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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frontiers in Pediatrics

CASE REPORT
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Hematuria as an Early Sign of Multisystem Inflammatory Syndrome in Children: A Case Report of a Boy With Multiple Comorbidities and Review of Literature

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Introduction: While the clinical course of SARS-CoV-2 infection seems to be milder or asymptomatic within the pediatric population, growing attention has been laid to the rare complication elicited by virus, multisystem inflammatory syndrome in children temporarily associated with COVID-19 (MIS-C). Published definition and criteria of MIS-C include persistent fever, multisystem involvement, and elevated markers of inflammation, without obvious microbial inflammation or other plausible diagnosis. However, the aim of this case report is to emphasize the diversity of symptoms of MIS-C, beyond the defined criteria.

Case Presentation: We present a 10-year-old boy with 8p23.1 microdeletion syndrome and multiple comorbidities who initially came to our attention due to hematuria, persistent fever, rash, and elevated markers of inflammation. Within the next 2 days, his condition worsened despite the broad-spectrum antibiotic therapy. Assuming his past history of SARS-CoV-2 exposure, MIS-C was suspected. A high level of clinical suspicion was further supported by significant clinical features (vomiting, abdominal pain, conjunctivitis, arrhythmia, and mild left ventricular systolic dysfunction with pleural effusion) along with laboratory findings (elevated ESR, CRP, proBNP, D-dimers and fibrinogen, positive IgG SARS-CoV-2 antibodies, and negative microbiological cultures). The patient was given intravenous immunoglobulin (IVIG) and began to show instantaneous clinical and laboratory improvement.

Conclusion: Despite numerous reports of MIS-C cases in children, there are still many uncertainties regarding the clinical presentation and laboratory findings, as well as mechanisms beyond this intriguing disorder. In our case, for the first time hematuria is reported as an early symptom of MIS-C. We strongly believe that reporting various manifestations and outcomes in MIS-C patients will lead to improved diagnosis, treatment, and overall understanding of this novel inflammatory condition.

Keywords: hematuria, multisystem inflammatory syndrome in children (MIS-C), SARS-CoV-2, kidney, Kawasaki disease

INTRODUCTION

The first experience from the beginning of the COVID-19 pandemic showed that children rarely developed severe or critical illness (1) or die from the infection as compared with adults (2, 3). Nevertheless, since the beginning of the pandemic, multisystem inflammatory syndrome in children (MIS-C), a new phenomenon with temporal association with COVID-19, has become a great concern of parents and pediatricians worldwide (4–6).

The pathogenesis of this syndrome remains largely unknown, but immunological mechanisms and vasculopathy have been implied (7). Literature data are growing on this subject, and although a unique definition and criteria have still not been established, prospective studies and case series have described multiorgan involvement, most commonly including the gastrointestinal, mucocutaneous, cardiac, and respiratory systems (8, 9). Renal involvement is a rather rarely reported manifestation of MIS-C, most commonly presented as acute kidney injury (AKI) in children with a complicated disease course, and seldom as hematuria, proteinuria, and pyuria (**Table 1**) (10–31). With continued pandemic and increasing awareness of this syndrome among clinicians, it is expected that more cases of MIS-C will be diagnosed and unusual presentations are likely to be seen, while, on the other hand, extensive medical and public attention might result in overdiagnosis of MIS-C, which highlights the need for reporting informative cases (32). Therefore, we describe an unusual case of a boy who initially presented with hematuria, persistent fever, rash, and elevated markers of inflammation, while, within the next 2 days he developed multisystem involvement and met the criteria for MIS-C. Moreover, we performed a literature review of MIS-C patients presenting with renal symptoms. The aim of this case report is to emphasize the diversity of symptoms of MIS-C, beyond the defined criteria.

METHODS

A systematic literature search was conducted to identify MIS-C patients with renal involvement. The Scopus and MEDLINE/PubMed databases were searched (from November 1, 2019, to August 30, 2021) by entering the following keywords "MIS-C" and "kidney" according to the published guidance on narrative reviews. The following parameters were noted from the studies including MIS-C patients: renal impairment, treatment, and outcome. Twenty-two articles describing 277 patients with renal manifestation of MIS-C were found during the literature search (**Supplementary Figure 1**).

Abbreviations: ACE2, angiotensin-converting enzyme 2; AKI, acute kidney injury; ANCA, anti-neutrophil cytoplasmic autoantibody; COVID-19, coronavirus disease-2019; CRP, C-reactive protein; EFLV, left ventricular ejection fraction; ESC, erythrocyte sedimentation rate; ICU, intensive care unit; IVIG, intravenous immune globulin; IgA, immunoglobulin A; IgG, immunoglobulin G; MIS-C, multisystem inflammatory syndrome in children; proBNP, pro-B-type natriuretic peptide; PCR, polymerase chain reaction; RBC, red blood cell; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMA, thrombotic microangiopathy.

CASE PRESENTATION

We present a 10-year-old boy with 8p23.1 microdeletion syndrome who presented to our pediatric emergency department at the end of February 2021, with dry cough and fever lasting for 2 days. Additional medical problems of the patient, associated with microdeletion syndrome, included psychomotor delay, behavioral complications, and complex congenital heart disease that underwent complete surgical correction in infancy. Despite the variety of comorbidities, his underlying medical conditions have been well controlled. His recent medical history included exposure to SARS-CoV-2 infection. The patient's mother, a nurse in a COVID-19 intensive care unit, tested positive for SARS-CoV-2 after onset of symptoms in January 2021. At that time, our patient remained asymptomatic. In the middle of February, he developed dry cough with subfebrile temperature that resolved over several days, but no test for SARS-CoV-2 was performed.

At physical examination, he was febrile and well appearing. He had erythematous maculopapular rash on the right lower leg, while auscultation revealed decreased breathing sound on the right side. Laboratory tests showed neutrophilic leukocytosis, an elevated C-reactive protein (CRP 149.75 mg/l), and hematuria (135 RBC/μl). Initial chest X-ray showed no obvious consolidation or pleural effusion. He was discharged with a diagnosis of acute respiratory infection and recommended to take amoxicillin/clavulanate orally.

The patient returned to our emergency department the following day due to persistent fever, vomiting, prostration, loss of appetite, and abdominal pain, but without significant guarding or peritoneal signs. Due to further elevation of CRP (222.59 mg/l) and progression of hematuria (4,200 RBC/μl) with proteinuria (2+ by dipstick analysis), the patient was admitted to inpatient care. The preadmission screening polymerase chain reaction (PCR) test of SARS-CoV-2 was negative. An abdominal x-ray showed stool burden, while abdominal ultrasound revealed a small amount of free fluid, with no other specific findings. Acute surgical emergency was ruled out by a pediatric surgeon consultant, and constipation was successfully managed with glycerin suppositories and lactulose solution. Further management included intravenous administration of crystalloid solutions and ceftriaxone, but his condition continued to worsen within the next 2 days. He developed bilateral conjunctivitis and irregular heart rhythm. Electrocardiography detected nodal rhythm with ventricular extrasystoles, while echocardiography revealed pleural effusion and mild left ventricular systolic dysfunction (EFLV 46–59%) without coronary artery abnormalities. Moreover, pro-B-type natriuretic peptide (proBNP) was elevated (12,270 ng/l).

The differential diagnosis at this point included sepsis, myocarditis, and Kawasaki disease. Nevertheless, all three were ruled out by negative blood and urine cultures and normal values of troponin I, creatinine kinase, and platelets, while repeated echocardiography showed no increase of coronary arteries. Assuming his past history of SARS-CoV-2 exposure, MIS-C was finally suspected after 5 days of fever. A high level of clinical suspicion was supported by positive SARS-CoV-2 immunoglobulin G (IgG) and rising erythrocyte sedimentation

TABLE 1 | Clinical characteristics, treatment modalities, and outcome of MIS-C patients with renal impairment.

First author (ref. no.)	MIS-C Pts	Kidney manifestation	Treatment	Outcome
Cassim (10)	1	Myoglobinuria, AKI	IVIG, corticosteroids, renal replacement therapy, ICU	Complete recovery
Rodriguez-Smith (11)	19	AKI 6/19	IVIG 17/19, corticosteroids 16/19, anakinra 5/19, antibiotics 14/19, antiviral 1/19, ICU 12/19	NA
Sica (12)	1	AKI	IVIG, corticosteroids	Recovered with new onset hepatic steatosis
Basalely (13)	55	AKI 10/55	Anakinra 49/55, corticosteroid 35/55, IVIG 6/55, remdesivir 1/55, ICU 34/55	AKI resolved in 90%
Duarte-Neto (14)	3	AKI 3/3	IVIG 2/3, corticosteroids 1/3, antibiotics 2/3, antiviral 2/3, ICU 3/3	Death 3/3
Eckard (15)	2	AKI 2/2	remestemcel-L 2/2	Residual hypertension 1/2
Abdel-Haq (16)	33	AKI (common among ICU pts)	IVIG 29/33, infliximab 14/33, corticosteroids 1/33, antibiotics 27/33, remdesivir 2/33, ICU 22/33	Recovered 33/33 (100%), thrombotic complication 1/33 (3%)
Onyeaghala (17)	1	AKI	Corticosteroids, antibiotics, hydroxychloroquine	Complete recovery
Fernandes (18)	69	AKI 17/69	Corticosteroids 32/69, IVIG 41/33, remdesivir 5/69, ICU 44/69	Discharged home 66/69 Death 0/69
Biko (19)	10	Non-obstructing renal calculi 1/10	IVIG 7/10, corticosteroids 6/10, donated plasma antibodies 2/10, ICU 9/10	Discharged home 9/10 Death 0/10
Ozsurekci (20)	7	AKI 7/7	Plasma exchange 7/7, continuous renal replacement therapy 2/7, favipiravir 2/7	Discharged home 6/7 Death 0/7
Diorio (21)	18	AKI 5/18 Proteinuria 12/18	NI	Discharged home 18/18
Nino (22)	1	AKI	Antibiotics, tocilizumab, corticosteroids, ICU	Complete recovery
Greene (23)	1	AKI	Antibiotics, tocilizumab, IVIG, corticosteroids, ICU	Complete recovery
Mahajan (24)	1	Hematuria and pyuria AKI	IVIG, corticosteroids, anakinra, remdesivir, ICU	Discharged with diffuse ectasia in the LAD demonstrated
Lee (25)	1	AKI	IVIG, corticosteroids	Discharged with EFLV shortening (28–32%)
Grewal (26)	28	Variable degrees of hematuria, proteinuria and pyuria, AKI 15/28	ICU 28/28, kidney replacement therapy 8/28	Deaths 0/28
Stefanachi (27)	1	End-stage renal disease	Antibiotics, corticosteroids, hyperimmune plasma, kidney replacement therapy, ICU	Discharged with antihypertensive therapy
Plouffe (28)	1	Transient microhematuria, idiopathic acute renal infarction	Aspirin	Recovered
Garcia-Dominguez (29)	4	Transient AKI 2/4	IVIG 3/4, corticosteroids 3/4, antibiotics 4/4	Recovered 4/4
Blumfield (30)	16	AKI 5/16	Corticosteroids 10/16, IVIG 5/16, anakinra 2/16	Discharged 15/16 Deaths 0/16
Del Greco (31)	4	AKI 4/4	Antibiotics 3/4, IVIG 2/4, enoxaparin 1/4, corticosteroids 4/4	Discharged 4/4

rate (ESR 40 mm/h), CRP (269.5 mg/l), proBNP (12.270 ng/l), D-dimers (2.13 mg/l), fibrinogen (7.0 g/l), and hypoalbuminemia (34.0 g/l), as shown in **Tables 2**, **3** and **Figure 1**.

During this period, hematuria started to resolve, but low-grade proteinuria persisted (24-h urine protein 0.41 g/dU). Global kidney function tests (urea and creatinine), urine output, liver function test, ferritin levels, complement components (C3, C4), and total complement activity (CH50) were within the normal range during the whole course of the disease. There was no cytopenia or decrease in hematological parameters and no casts in urine sediment. Moreover, there were no episodes of hypotension, a decrease in blood oxygen saturation, and no need for inotrope support (**Table 2**). Finally, on the morning of the seventh day of illness, IVIG was administered in a single dose of 2 g/kg. Therapeutic effects included prompt downtrend of fever, inflammatory markers, and proteinuria, as shown in **Figure 1**, along with gradual improvement of left ventricular systolic function (EFLV 65–68%) and complete resolution of pleural effusion within the next few days. After 10 days of ceftriaxone therapy, the patient was discharged from the hospital. Outpatient

TABLE 2 | Clinical, laboratory and imaging findings.

CLINICAL FINDINGS	
Significant clinical findings	**Other**
Persistent fever ≥ 48 h	Unchanged neurological status
Abdominal pain and vomiting	No signs of acute abdomen
Maculopapular rash and non-exudative conjunctivitis	Normal urine output
Arrhythmia	Normal blood pressure and oxygen saturation
COVID-19 exposure prior to the onset of symptoms	
IMAGING FINDINGS	
Pathological	**Normal**
Small amount of free abdominal and perihepatic fluid	No signs of an abdominal inflammation
New-onset pleural effusion	Normal initial chest X ray
Left ventricular systolic dysfunction (EFLV 46%–59%)	No coronary artery abnormalities
Nodal heart rhythm and premature ventricular beats	
LABORATORY FINDINGS	
Pathological	**Normal**
CRP (up to 269.5 mg/l)	RBC, Hb, Hct
WBC (up to 20.41 × 10^{12}/l)	Platelets
Neutrophilia (up to 84%)	PV, APTV
ESR (up to 40 mm/s)	Procalcitonin
Fibrinogen (up to 7.0 g/l)	Urea, creatinine
D-dimers (up to 2.13 mg/l)	C3, C4, CH50
proBNP (up to 12,270 ng/l)	Ferritin
Albumin (up to 34.0 g/l)	Troponin I
SARS-CoV-2 IgG positive, IgM negative	Total protein
	IgG, IgA, IgM
	AST, ALT, GGT, LDH
	SARS-CoV-2 PCR nasal swab negative
	Negative microbial samples (urine culture, hemoculture, stool, pharyngeal and nasal swab)
URINE EXAMINATION (SPOT)	
Dipstick	**Microscopy**
Leukocyte esterase up to 2+	RBC up to 4,200/mm^3
Protein up to 2+	WBC up to 25/mm^3
Ketones up to 1+	No urinary casts
Urobilinogen up to 1+	
Blood up to 3+	
Nitrites and glucose negative	
URINE EXAMINATION (24 H)	
Proteinuria 0.41 g	

follow-up after 4 weeks revealed complete normalization of clinical and laboratory findings, with no new symptoms and/or signs after 6 months.

DISCUSSION

Children with clinical and laboratory findings associated with inflammation have always presented a diagnostic challenge in everyday clinical practice. On top of many established immune-mediated disorders, in the era of the COVID-19 pandemic MIS-C needs to be considered as well, especially in children unresponsive to antimicrobial therapy (**Table 3**). Nevertheless, despite the growing number of reports in the literature, the full extent of the MIS-C manifestations remains unknown. Conversely, a wide range of reported symptoms and signs makes the diagnostic process of this novel syndrome confusing or delayed. Therefore, early recognition and valid interpretation of characteristic features lead to accurate diagnosis and proper treatment, and eventually to elucidation of the underlying mechanisms.

TABLE 3 | Stepwise pathway to diagnosis.

	(A) IDENTIFICATION OF CARDINAL SYMPTOMS AND SIGNS	(B) CONSIDERATION OF LIKELY DIAGNOSIS	(C) SELECTION OF APPROPRIATE WORK-UP	(D) INITIATION OF TREATMENT
1	Increased fever and inflammatory markers (CRP, ESR, WBC)	Bacterial infection	Search for source of infection (e.g., urinalysis, chest X-ray, microbiology); SARS-CoV-2 PCR	Antibiotics
NO IMPROVEMENT WITH ANTIBIOTIC TREATMENT				
2	Persistent fever Abdominal pain Vomiting Rash Conjunctivitis Pleural effusion Arrhythmia Hematuria Proteinuria (dipstick test)	Resistant bacterial infection (e.g., intra-abdominal infection, pyelonephritis) Immune-mediated diseases (e.g., sJIA, MAS, Kawasaki disease, MIS-C) Glomerulonephritis (primary and secondary)	Electrolytes and acid-base status Liver function tests Lipid blood test Ferritin Coagulation Troponin I and proBNP Urea, creatinine, cystatin C 24-h urine protein test SARS-CoV-2 serology ECG Echocardiography Kidney ultrasound	None
MIS-C DIAGNOSIS ESTABLISHED				
3	SARS-CoV-2 IgG Elevated d-dimers, fibrinogen and proBNB Persistent hematuria Persistent proteinuria (24-h urine test) Left diastolic dysfunction	Vasculitis SLE PIGN	Complement	IVIG
COMPLETE RESOLUTION OF SYMPTOMS AND SIGNS				
4	No relevant symptoms or signs	None	Follow up urine analysis, CBC, CRP, ESR, urea, and creatinine; ANA, ANCA, kidney biopsy (in case of hematuria and/or proteinuria relapse)	None
NO RELAPS OF SYMPTOMS AND SIGNS				

Although an enhanced understanding of the processes beyond the MIS-C is essential for effective treatment, despite many recent efforts they remain inconclusive. Different pathogenesis traits have been proposed, but the predominant theory is the postinfection antibody-mediated disease (7, 33, 34). However, evidence is mounting that vasculopathy has an important role in MIS-C (33, 34). Evidence supporting this theory incorporates the resemblance of MIS-C and Kawasaki disease, a known vasculitis (35–37). Similar features of these two inflammatory disorders include prolonged fever, increased inflammatory markers, rash, non-exudative conjunctivitis, and mucous involvement (cracked lips, strawberry tongue) (33, 35–37). Despite these resemblances, there are also marked differences in clinical manifestations, such as older age of onset, more frequently observed gastrointestinal involvement, and a more severe disease course in MIS-C, as well as dissimilarities in laboratory findings, such as lymphopenia, thrombocytopenia, and elevated D-dimer levels in MIS-C (33, 35, 37). Comparison of inflammatory cells and 180 plasma proteins in patients with MIS-C and Kawasaki disease revealed that both conditions have elements of hyperinflammation and vasculitis but a different cytokine pattern, suggesting different pathogenesis (33). Other noteworthy characteristics of MIS-C implying vasculopathy is the common presence of coagulation disorders (34, 38, 39). Elevated levels of D-dimer and von Willebrand factor are seen in almost all patients with MIS-C, while fibrinogen levels and prothrombin time are also frequently increased (34, 38, 39). In addition, an intriguing case report has been published, describing intestinal ischemia in a patient with MIS-C presenting with severe abdominal pain and pseudoappendicular syndrome, suggesting intestinal vasculitis (40).

Moreover, it has been suggested that MIS-C could be a severe form of acute COVID-19 infection (7, 34). This theory is supported by the fact that children mostly lack respiratory symptoms and therefore a nasal swab positive for COVID should not be expected. Instead, Rowley et al. proposed PCR analysis

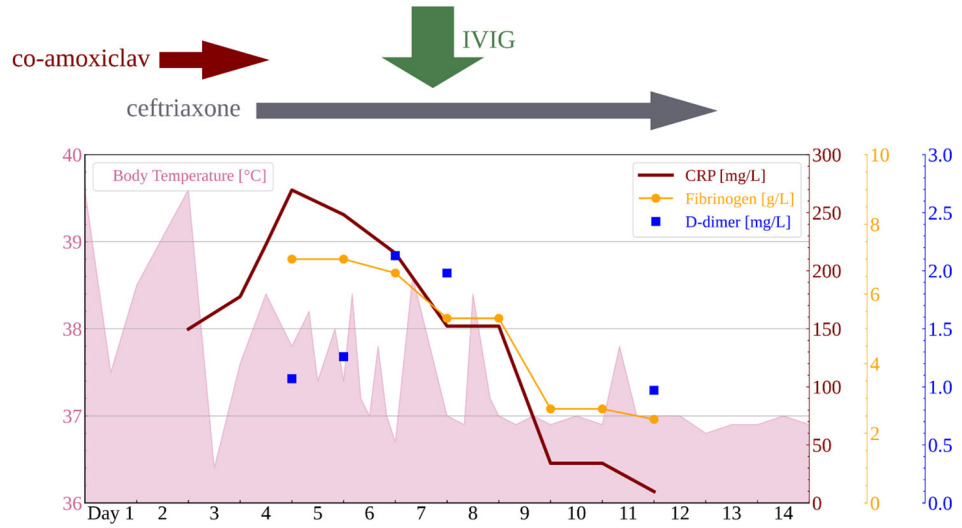

FIGURE 1 | Body temperature and laboratory findings.

on stool samples since children mainly have gastrointestinal symptoms (7). On the other hand, the respiratory mucosal epithelium is most commonly the entry point of virus in adults (41), and therefore, it is fair to mark the lung as a "primary battle zone." Accordingly, the highest levels of SARS-CoV-2 virus per cell were detected within the respiratory tract. Nevertheless, viral particles were also isolated from many other organs, including the kidney, liver, brain, heart muscle, blood, small intestine, and even sweat glands and skin (41). Many studies reported that SARS-CoV-2 was isolated from the kidney in COVID-19 patients with kidney involvement or coexisting chronic kidney disease (42). Multiorgan tropism and its affinity and affection of the kidney especially indicate that AKI might be a consequence of direct viral toxicity (42). However, it remains unclear if the cell invasion is the sole mechanism responsible for kidney manifestations of COVID-19. Angiotensin-converting enzyme 2 (ACE 2) has been identified as the cell entry receptor for SARS-CoV-2, making the tubular cells that harbor ACE2 especially vulnerable and resulting in tubular damage (43). On the contrary, new cases of collapsing glomerulopathy emerged in patients of African ancestry who are homozygous for *APOL* risk alleles, potentially suggesting other specific molecular mechanisms (44).

The European Renal Association revealed that advanced chronic kidney disease is an independent risk factor for poorer outcome of COVID-19 (45), while *de novo* kidney disease is commonly seen in hospitalized patients with COVID-19 as well, especially in those critically ill (46). The available literature most commonly describes renal involvement in children with MIS-C as acute renal failure or AKI (4, 39, 47–50). The prevalence of renal involvement varies greatly depending on the studied population (4, 39, 47–49). Two French studies, in which complicated MIS-C cases needing intensive care were enrolled, described a prevalence of 59 and 70%, respectively (4, 48), while a large US cohort of 570 MIS-C patients reported AKI in 18% of patients (42, 47); an Iranian study reported renal failure in 29% of patients (49). In most studies, the course of renal failure was not elaborated in detail (38, 47, 49). In the US study, kidney injury was sought a complication of severe MIS-C (47); in the Iranian study a consequence of high levels of ACE2 in the kidney (49). Since renal failure is present more frequently in COVID and MIS-C patients needing intensive care, circulatory shock may be an important contributor to renal failure development (4, 48, 51).

Additionally, among 277 MIS-C patients with renal involvement identified during our literature search, the most commonly reported manifestation was AKI (**Table 1**). Compared to patients without AKI, it was more frequent among patients who had cardiac dysfunction, required inotropic support, and ICU admission (26). Accordingly, pathogenesis of AKI appears to be predominantly pre-renal (26). On the other hand, severity of kidney dysfunction in patients with AKI did not correlate with degree of cardiac dysfunction (26). Beside AKI, other renal manifestations or urinalysis results in MIS-C patients were described only in few articles, reporting variable degrees of hematuria, proteinuria, and pyuria (21, 24, 28). Interestingly, abnormal urinalysis as indicator of renal parenchymal injury was present in a significant proportion of AKI patients (21, 24). Furthermore, proteinuria was a predominant symptom in MIS-C patients who also met the clinical criteria for thrombotic microangiopathy (TMA) (21). TMA is a clinical syndrome defined by the presence of hemolytic anemia, thrombocytopenia, and organ dysfunction due to endothelial cell damage and formation of microscopic blood clots in capillaries and small arteries. Soluble C5b9 (Sc5b9), a biomarker of complement activation and TMA, was elevated in patients with SARS-CoV-2

disease, as well as in MIS-C patients (21). Consequently, increased plasma levels of the terminal complement complex (sC5b9) suggest that complement activation and thrombotic microangiopathy are prevalent in COVID-19 and MIS-C patients (21). Although many of the described patients beside IVIG required an additional treatment with glucocorticoids, antibiotics, biological agents, and even plasmapheresis and renal replacement therapy, in many complete recovery was reported (10, 17, 22, 23, 28, 29).

It remains unknown whether hematuria and proteinuria were really absent in the published cohorts or they were underreported. Although hematuria and proteinuria might have been neglected in MIS-C patients, they are rather common manifestations of adult COVID-19 infection (51–53), ranging from 7 to 63% of patients for proteinuria (51) and 26.7% (52) and 40.9% (53) for hematuria. Histopathological analysis of renal tissue of COVID patients revealed viral fragments in the cytoplasm of proximal tubules as well as podocytes, which could potentially explain proteinuria (51). Another common finding in adults is obstruction of glomerular lumen and peritubular capillaries by erythrocyte aggregates (51). In children, hematuria and SARS-CoV-2 infection were described in a 9-year-old girl who presented with increased temperature, cough, and gross hematuria, which resolved spontaneously (54). SARS-CoV-2 was isolated not only from her nasal swab but also from her urine sample (54). Another case describes a 13-year-old boy who presented with purpuric rashes, mild hematuria, elevation of serum IgA, and biopsy-confirmed leukocytoclastic vasculitis secondary to asymptomatic SARS-CoV-2 infection (55). This is in line with the notion that hematuria is most commonly associated with vasculitis syndromes such as immunoglobulin A (IgA) nephropathy or anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (56). Furthermore, recent findings suggest that gross hematuria can damage the glomeruli and lead to AKI (56).

In our patient, there were no signs of kidney function deterioration, hypotension, or need for inotropic support, although a moderate cardiac dysfunction was noted. Moreover, he had no signs of TMA or complement dysfunction. Besides, he had a complete and persistent resolution of all symptoms and signs following only IVIG therapy, without further need for glucocorticoid treatment. Therefore, no additional laboratory tests or invasive procedures were performed. Consequently, limitations of this case presentation are lack of ANA and ANCA screening and lack of kidney biopsy results, which restricts the conclusion about the possible underlying mechanisms in our patient. Nevertheless, of note is that ANCA-associated vasculitis after COVID-19 was described in a few patients presenting with hematuria, proteinuria, and AKI (57, 58). Hence, SARS-CoV-2 infection is suspected to be the trigger of subsequent development of immune-mediated disorders, which prompts a long follow-up in susceptible patients.

In summary, the pathogenesis of renal involvement in COVID-19 is probably multifactorial, and proposed mechanisms include direct infection of renal parenchyma *via* ACE2 receptors which are highly present in kidney tissue (43, 52, 59), microvascular injury caused by cytokine storm and/or hypercoagulability (25, 43, 51, 59), and circulatory shock (4, 48, 49).

To the best of our knowledge, this is the first detailed case of hematuria and concomitant proteinuria in an MIS-C patient. Since additional investigations and follow-up revealed no other pathological finding, we are confident that hematuria in the presented patient was a part of MIS-C. This is further supported by the fact that our patient had no sign of hypovolemia, which could have potentially caused kidney damage, and prompt response to IVIG therapy. Since proteinuria and hematuria have resolved, we did not proceed with further investigations.

We report this unusual MIS-C case because the COVID-19 pandemic is still ongoing, and the number of MIS-C cases will probably continue to grow. Moreover, it is not false to predict that other possible pandemics in the future might also cause similar symptoms. We strongly believe that unusual and yet undescribed clinical presentations are useful for the practicing clinicians, especially with diseases like MIS-C, where early recognition is essential for treatment and good outcomes. Moreover, detailed clinical reports can also inform further research on pathogenesis and possible treatment options. Finally, we consider our case to be another piece of evidence tipping the scale toward the underlying process in MIS-C.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from the individuals for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

LL conceptualized the work. AG and MD drafted this manuscript. IK, KV, and LL revised this manuscript. All authors were involved in the clinical management of the patient and read and approved the manuscript for submission.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2021.760070/full#supplementary-material

Supplementary Figure 1 | The schematic overview of the articles on MIS-C patients with renal impairment included in the literature research.

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BRIEF RESEARCH REPORT
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MIS-C Treatment: Is IVIG Always Necessary?

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Background: MIS-C is a potentially severe inflammatory syndrome associated with SARS-CoV-2 exposure. Intravenous immunoglobulin (IVIG) is considered the first-tier therapy, but it implies infusion of large fluid volumes that may worsen cardiac function.

Patients and Methods: Since April 2020, we have developed a treatment protocol that avoids the infusion of IVIG as first-line therapy in the early phase of MIS-C. In this study, we retrospectively analyzed a cohort of consecutive patients treated according to this protocol between 01/04/2020 and 01/04/2021.

Results: In the last year, 31 patients have been treated according to the protocol: 25 with high-dose pulse MP (10 mg/kg) and 6 with 2 mg/kg. 67.7% of the patients responded to the initial treatment, while the others needed a step-up, either with Anakinra (25.8%) or with MP dose increase (6.5%). IVIG was administered in four patients. Overall, only one patient (3.2%) needed ICU admission and inotropic support; one patient developed a small coronary artery aneurysm.

Conclusions: Timely start of MP therapy and careful fluid management might improve the outcomes of MIS-C patients.

Keywords: MIS-C, SARS-CoV-2, therapy, IVIG (intravenous immunoglobulin) administration, steroid

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INTRODUCTION

Multisystem inflammatory syndrome in children (MIS-C) is a newly described disease, characterized by fever, abdominal pain, lymphopenia, myocardial dysfunction, and some additional clinical features—such as conjunctival injection, oral erythema, and cutaneous rash—which are also typical of Kawasaki Disease (KD) (1).

Since the very first reports, MIS-C has been temporally linked to SARS-CoV-2 exposure. At present, even if the pathogenesis remains unknown, an increasing body of epidemiological and biochemical evidence supports the hypothesis that it is a post-infectious process developing 4–6 weeks after SARS-CoV-2 infection (2).

MIS-C can be a severe disease, requiring ICU admission in up to 73.3% of the patients and causing the development of coronary artery anomalies (CAA) in up to 21.9% of the patients (3). The partial clinical overlapping has led most physicians to treating MIS-C like KD; hence, intravenous immunoglobulin (IVIG) is the most frequently prescribed first-tier therapy in MIS-C (1). Nevertheless, IVIG administration implies infusion of large fluid volumes (40 ml/kg) that may worsen the myocardial dysfunction in the early phase of disease (4).

Since April 2020, at OIRM (Ospedale Infantile Regina Margherita, Turin, Italy), we have been treating MIS-C patients with intravenous methylprednisolone (MP) alone, adding subcutaneous Anakinra as a step-up therapy, in order to decrease the need of IVIG during the first days after disease onset. The aim of the study is to analyze the outcomes of the patients treated according to our treatment protocol, between April 2020 and April 2021.

METHODS

Setting and Treatment Protocol

OIRM is the main pediatric hospital in Piedmont, a region in Northwest of Italy (4,341,375 inhabitants, 723,208 <20 years of age) (5). At OIRM, all the patients suspected to have MIS-C undergo a comprehensive diagnostic work-up, including cell blood count, C-reactive protein (CRP), serum IgG, and RT-PCR on nasal swab for SARS-CoV-2, NT-pro-B-type natriuretic peptide (NT-pro-BNP), and echocardiogram. Patients satisfying the preliminary case definition of MIS-C (6) and having positive SARS-CoV-2 IgG are treated according to an internal step-up treatment protocol that does not include IVIG as first-tier therapy.

The initial treatment in all the patients is MP: if myocardial involvement is present [hypotension according to age-, gender-, and height-adjusted chart (7); or Ejection Fraction (EF) <50%; or NT-pro-BNP ≥1,500 pg/ml], the patient receives high-dose pulse IV MP 10 mg/kg/day (single dose) for 3–5 days; otherwise, low-dose IV MP 2 mg/kg/day (single dose) is administered. After 48 h, if CRP increases and/or fever persists, the treatment is intensified either with a MP dose increase or by adding subcutaneous Anakinra 5 mg/kg/day (**Figure 1**). After achieving clinical response, MP therapy is switched to oral prednisone before discharge and tapered over 4 weeks; Anakinra is tapered over 2 weeks. IVIG is reserved for patients with suspected CAA at any ultrasound evaluation [defined according to American Heart Association 2017 Guidelines for KD (8)], or presenting persistent symptoms despite defervescence and CRP reduction, or as a third-line therapy in patients unresponsive to MP and Anakinra. IVIG is infused over 18 h; in case of urine output decrease or worsening of cardiac function, the infusion speed is lowered. In case of concomitant severe heart failure, a 2-day IVIG infusion regimen is preferred (4).

For coronary monitoring, echocardiography is carried out by an experienced pediatric cardiologist every other day in the first week after admission, before discharge, and 6 weeks later.

Considering the high prevalence of myocardial dysfunction, all the patients with MIS-C undergo careful monitoring of fluid balance. We use the Holliday and Segar formula for calculating the minimal maintenance water needs, and oral hydration is preferred over intravenous liquid infusion, whenever possible. During the hospitalization, we tailor liquid intake considering multiple variables, such as daily weight variation, intake/output balance, and blood creatinine.

Regarding prophylactic anticoagulation, every patient diagnosed with MIS-C is evaluated according to an institutional risk assessment model: the patients with high risk receive enoxaparin 100 U/kg/day until discharge or thrombotic risk

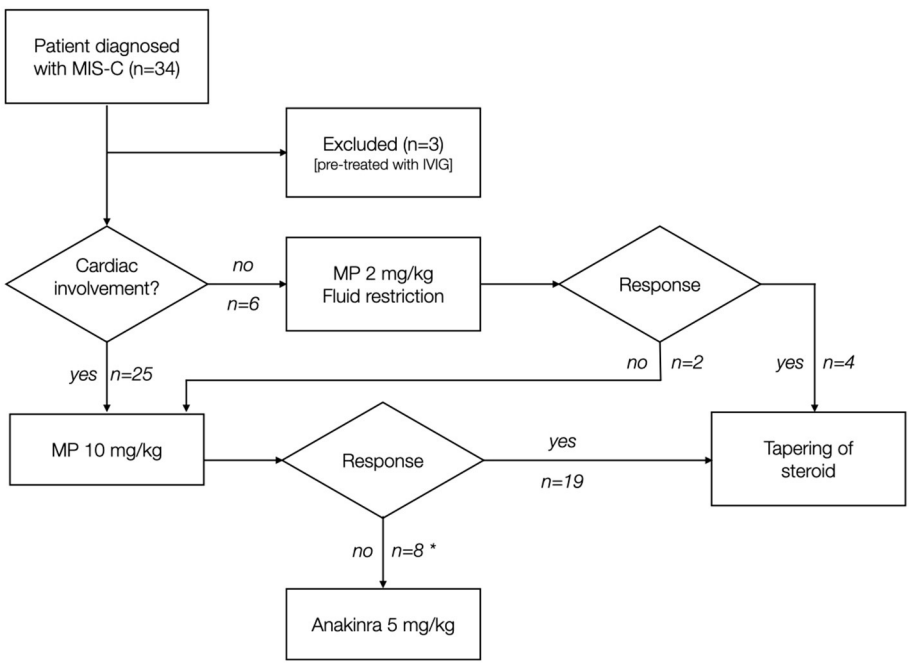

FIGURE 1 | Treatment strategy of patients included in the study. MP was used in patients as first-tier monotherapy. Clinical response was defined as defervescence and CRP reduction after 48 h from the first MP dose. *4 patients received IVIG.

reduction, whichever comes first (9). Finally, anti-aggregation with acetylsalicylic acid (3–5 mg/kg/day) is prescribed when a CAA is documented or suspected during any US examination. The patients with persistent CAA receive anti-aggregation therapy according to American Heart Association 2017 Guidelines for KD (8).

Study Design, Data Collection, and Statistical Analysis

We performed a retrospective analysis of the patients with MIS-C, treated according to the abovementioned protocol, between 01/04/2020 and 01/04/2021, at OIRM. The patients who had received IVIG prior to the admission to our hospital and those with negative SARS-CoV-2 serology were excluded from further analysis.

We divided the patients into two groups, according to the MP starting dose: high-dose pulse (Group A) or low dose (Group B). As primary outcomes, we considered the following: the rate of ICU admission after starting treatment, the rate of inotropic support needs after starting treatment, and the incidence of CAA. As secondary outcomes, we evaluated the following: the number of days between MP first dose and CRP halving, the number of days between MP first dose and NT-pro-BNP halving, and the days between first pathological echocardiogram and EF normalization.

The local ethical committee approved the data collection on March 24, 2020; an informed consent was obtained, in accordance with the Declaration of Helsinki.

Statistical analysis was performed by using GraphPad Prism 6.0. The differences between groups were analyzed using Mann–Whitney *U*-test for continuous variables and Fisher's exact test for categorical variables. All the tests were two tailed and the significance was set at $p \leq 0.05$.

RESULTS

Patients and Baseline Features

In the period considered, 34 patients diagnosed with MIS-C were treated at OIRM. Among these, three patients received IVIG as first-line therapy, so they were excluded from further analysis. Overall, 31 patients (91.2%) were treated according to the protocol; epidemiological, clinical, laboratory, and echocardiographic features at first evaluation are summarized in **Tables 1**, **2**. The median time between disease onset and the first dose of MP was 5 (4–6) days. Twenty-five patients (80.7%) were treated with high-dose pulse MP (Group A): 32% had EF <50%, 100% had NT-pro-BNP >1,500 ng/ml, and 64% had hypotension.

Patients of Group A and Group B had similar features at disease onset (**Tables 1**, **2**), except for the baseline pro-BNP level (8,231 vs. 698 pg/ml, $p < 0.001$) and the prevalence of hypotension (64 vs. 0%, $p = 0.007$). Fifty-two percent of Group A patients received high-dose pulse IV MP 10 mg/kg/day for 5 days, while the others were treated for 3 days.

Post-treatment Course and Outcomes

Eight patients of Group A (32%) needed a step-up by Anakinra 5 mg/kg/day due to persistent fever (87.5%) or CRP increase (12.5%); four patients (12.9%) received IVIG: one due to persistent irritability despite satisfactory CRP decrease and fever resolution, two due to a suspicion of CA dilatation, not confirmed by the follow-up ultrasound (*z*-score always <1.5), and one due to the development of a small right CA aneurysm (5 mm, *z*-score 4). The mean time between the first MP dose and IVIG administration was 5 days.

Six patients (19.3%) were treated with low-dose MP (Group B), and two (33.3%) of them needed MP dose increase due to persistence of fever (**Figure 1**).

After clinical response was achieved, MP therapy was switched to oral prednisone, and tapered over 4 weeks in all the patients. The median follow-up after disease onset was 133 days (IQR 95–163).

All the patients recovered: detailed outcomes are described in **Table 3**. Overall, one patient (3.2%) needed ICU admission and inotropic support, and one developed a CAA 6 days after the start of MP. Median CRP halving time was 2 days (2 days in Group A and 5 days in Group B), NT-pro-BNP halved in 3 days in Group A, while EF normalized in 5 days. Acute kidney injury was observed in one patient of Group A.

TABLE 1 | Demographic and clinical features of Group A and Group B.

	Group A	Group B	*p*-value
Patients	25	6	–
Age (years)	8 (7–11)	9 (6–10.5)	0.90
Female	44.0%	50.0%	0.79
Ethnic group	84.0% White European 12.0% West African 4.0% South American	83.3% White European 16.7% South American	1.0
Previous positivity of SARS-CoV-2 swab	36.0%	33.3%	0.90
Close relative positive for SARS-CoV-2	76.0%	83.3%	0.70
Fever >38°C	100%	100%	1.00
Days of fever	5 (4–6)	4 (3–6)	0.42
Conjunctivitis	96.0%	66.7%	0.09
Mucositis	44.0%	66.7%	0.39
Lymphadenitis	48.0%	33.3%	0.66
Hand or feet lesions	36.0%	66.7%	0.21
Rash	72.0%	50.0%	0.36
Abdominal pain	76.0%	66.7%	0.63
Diarrhea	24.0%	33.3%	0.63
Vomit	60.0%	16.7%	0.08
Hypotension[§]	64.0%	0%	**0.007**

[§]*According to age-, gender-, and height-adjusted chart (7).*
Continuous variables are described as median and interquartile range.
Bold font indicates statistical significance.

DISCUSSION

MIS-C is an emerging inflammatory syndrome affecting children a few weeks after SARS-CoV-2 exposure, which shares some

TABLE 2 | Laboratory features of Group A and Group B.

	Group A	Group B	*p*-value
WBC count (/mm^3)	9,590 (6,490–12,160)	6,590 (6,338–7,195)	0.19
Lymphocyte (/mm^3)	780 (450–1,080)	695 (618–773)	0.83
Neutrophil (/mm^3)	8,410 (5,080–10,370)	5,815 (5,190–8,460)	0.44
Platelet (*1,000/mm^3)	131.0 (106.0–180.0)	132.5 (99.3–165.0)	0.78
CRP (mg/L)	224 (125–316)	179 (150–209)	0.89
PCT (ng/ml)	10.3 (3.7–33.1)	12.7 (4.6–20.5)	0.37
Ferritin (ng/ml)	634 (493–1078)	342 (278–461)	0.08
ESR (mm/h)	49 (32–54)	58 (51–61)	0.10
Albumin (g/dl)	3.2 (2.8–3.4)	3.4 (3.1–3.9)	0.61
ALT (UI/L)	44 (19–58)	24 (18–32)	0.14
AST (UI/L)	36 (27–57)	29 (27–41)	0.38
Na (mmol/L)	131 (129–132)	133 (132–136)	0.08
Creatinine (mg/dl)	0.47 (0.41–0.62)	0.53 (0.33–0.65)	0.99
INR	1.22 (1.07–1.35)	1.34 (1.22–1.45)	0.60
aPTT ratio	0.96 (0.91–1.1)	1.01 (0.93–1.03)	0.80
Fibrinogen (mg/dl)	631 (573–700)	628 (493–650)	0.56
D-dimer (ng/ml)	4,284 (2,548–4,906)	2,058 (1,548–3,210)	0.13
Positive swab for SARS-CoV-2	12.0%	16.7%	1.00
IgG against SARS-CoV-2	100%	100%	1.00
Ejection fraction <50%	32.0%	0%	0.29
NT-proBNP pg/ml	8,231 (4,586–12,571)	698 (147–1,197)	**<0.001**
NT-proBNP >1,500 pg/ml	100.0%	0%	**<0.001**
Troponine (ng/L)	48 (27–120)	9 (8–29)	0.09

Continuous variables are described as median and interquartile range.
Bold font indicates statistical significance.

TABLE 3 | Outcomes and concomitant hematological treatment of Group A, Group B, and overall cohort.

	Group A	Group B	Total
Patients	25	6	31
MP response*	68.0%	100%**	74.2%
ICU admission	4.0%	0%	3.2%
Inotrope support	4.0%	0%	3.2%
Acute kidney injury[#]	4.0%	0%	3.2%
Coronary artery anomalies	4.0%	0%	3.2%
CRP halving time	2 (2–3) days	5 (3–5) days	2 (2–3) days
NT-proBNP halving time	3 (2–5) days	–	3 (2–5) days
EF normalization time	5 (4–5) days	–	5 (4–5) days
Concomitant hematological treatment			
LMWH[§]	52.0%	0%	41.9%
Acetylsalicylic acid[◦]	12.0%	0%	9.7%

Continuous variables are described as median and interquartile range.
**Defined as defervescence and CRP reduction after 48 h from the first MP dose.*
***Two patients needed dose adjustment.*
[#]According to Kidney Disease Improving Global Outcomes definition for AKI (10).
[◦]Acetylsalicylic acid was prescribed when a suspicion of coronary abnormality was suspected during US examination.
[§]Low-molecular-weight heparin was prescribed according to an institutional risk assessment model (9).

features with KD. No treatment trial in MIS-C has been published so far, but IVIG is the most widely adopted treatment (1). IVIG therapy was borrowed from KD; nevertheless, its use in the early phase of MIS-C raises some concerns. Firstly, IVIG administration implies infusion of large volumes (40 ml/kg) that may cause heart overload especially in patients with myocardial dysfunction (4). Moreover, IVIG increases oncotic pressure and consequently causes liquid shift, which may further worsen fluid overload in these patients, who often present hypoalbuminemia and third-spacing. As far as we know, this is the first report of MIS-C patients treated according to an IVIG-sparing protocol, developed to avoid IVIG infusion in the early phase of the disease, when the risk of heart failure is high.

The outcomes of the patients treated according to the above-described protocol (see Method) are rather encouraging. Notably, only one patient among 31 needed ICU admission and inotropic support. Regarding CAA, only one patient (3.2%) developed a small aneurysm (z-score = 4), which is stable 4 months after discharge. Interestingly, the only patient who developed CAA was treated later than the others (8 vs. 5 days), suggesting that a timely start of MP may be protective. The positive outcomes of our cohort could not be attributed to a selection bias. Indeed, the baseline features of our cohort are comparable to other MIS-C cohorts; notably, the rate of patients with myocardial involvement is high (81%), with a mean pro-BNP level at disease of 6,540 pg/ml (11). Several factors might explain our results. First, the vast majority of our patients received MP in the earliest phase of the disease. A recent multi-omics study in MIS-C suggests that IV glucocorticoids have a rapid effect on decreasing the level of many soluble biomarkers associated with type II IFN response (IFN-γ, CXCL9), T-cell activation (sCD25), cell adhesion (sE-Selectin/sCD62E), and monocyte/macrophage activation (sTNFRII, M-CSF, and ferritin, IL-6); this evidence may support the utility of steroids in MIS-C treatment (12).

So far, three real-life retrospective studies have been conducted regarding the use of steroids to treat MIS-C (2, 11, 13). In two of them, the authors compared the outcomes of the patients treated with steroids and IVIG vs. IVIG alone. Ouldali et al. found that adding MP to IVIG led to a significant decrease of hemodynamic support needs and a reduction in length of ICU stay; Son et al. found that the patients treated with steroids and IVIG had a lower risk of new or persistent cardiovascular dysfunction compared to the ones treated with IVIG alone (2, 11).

The effect of steroid treatment without IVIG has been less studied. As far as we know, only a recent paper by the BATS consortium describes the outcomes of a cohort treated with steroids as a first-line monotherapy. The authors report that the inotropic or ventilator support rate of the cohort was 17.2%. Unfortunately, the data collected by the BATS consortium were obtained in patients treated with non-homogeneous protocols; therefore, a direct comparison with our results is not possible (13). Of note, in the BATS study, 47.5% of the patients treated

with steroids also received IVIG in the days following disease onset, and none received Anakinra. The explanation for the differences of the BATS outcomes and ours may lay in the second-line therapies: Anakinra in our protocol, IVIG in BATS (13). Furthermore, our fluid management (see Materials), aimed at decreasing the risk of overload, may have further reduced the ICU admission rate.

Our study has some limitations, including the sample size and the absence of a control group, which hampers firm conclusions regarding the comparison with IVIG-based protocols. Moreover, the comparison with previously published cohorts may be affected by different inclusion criteria, as we only enrolled patients with SARS-CoV-2-positive serology. Nevertheless, the very first published MIS-C cohorts showed much higher rates of ICU admission (73.3%), inotropic support (55.3%), and aneurysm incidence (10.3%) (3). These early reports might have been affected by the poor knowledge of MIS-C in 2020, and current outcomes might have improved worldwide.

Despite its limitations, our study highlights the importance of a tailored step-up treatment of MIS-C. As a first-line therapy, MP alone seems a good option, especially in countries where IVIG is not available. The response rate to MP in our cohort was satisfactory, but 25.8% of the patients needed further step up. To treat patients with persistence of fever and/or CRP increase, we preferred Anakinra to IVIG, due to its low effect on fluid overload. All the patients treated with IL-1 receptor antagonist had a clinical and laboratory response within 48 h. Even if IVIG protective role against CAA formation has never been proven in MIS-C, infusing IVIG 2 g/kg seems a reasonable option in patients showing CAA at any time point (1). In case of IVIG infusion, great attention should be paid to fluid overload, especially in the earliest days of the disease (1, 4).

In conclusion, our results suggest that favorable outcomes in MIS-C could be achieved by sparing IVIG infusion in the earliest phase of the disease; compared to previously published studies, the incidence of CAA does not increase. A prospective randomized controlled trial should be designed, to define the effective role of IVIG and steroids in MIS-C treatment.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico Interaziendale A.O.U. Città della Salute e della Scienza di Torino—A.O. Ordine Mauriziano—A.S.L. Città di Torino. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

FL conceived the study, wrote the statistical analysis plan, analyzed the data, and drafted and revised the paper. LB monitored data collection, designed graphic figures, and drafted and reviewed the paper. MD, CC, RM, GP, FM, EP, and IR collected data and revised the manuscript. CO reviewed the literature and revised the article. DM conceived the study and drafted and critically reviewed the paper. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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CORRECTION
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Corrigendum: MIS-C Treatment: Is IVIG Always Necessary?

Francesco Licciardi[1,2], Letizia Baldini[3], Marta Dellepiane[1], Carlotta Covizzi[3], Roberta Mogni[3], Giulia Pruccoli[1], Cecilia Orsi[4], Ivana Rabbone[4], Emilia Parodi[1,2], Federica Mignone[1,2] and Davide Montin[1,2]*

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Keywords: MIS-C, SARS-CoV-2, therapy, IVIG (intravenous immunoglobulin) administration, steroid

A Corrigendum on

MIS-C Treatment: Is IVIG Always Necessary?
by Licciardi, F., Baldini, L., Dellepiane, M., Covizzi, C., Mogni, R., Pruccoli, G., Orsi, C., Rabbone, I., Parodi, E., Mignone, F., and Montin, D. (2021). Front. Pediatr. 9:753123. doi: 10.3389/fped.2021.753123

In the original article, there was an error. Incorrect reference numbers and authors names were cited in the text. "2, 9, 12" has been updated to "2, 11, 13," "…ICU stay (11); Del Borrello et al. and Sacco et al. found…" has been updated to "…ICU stay; Son et al. found…," and "9, 12" has been updated to "2, 11."

A correction has been made to **Discussion**, Paragraph Number 3:

"So far, three real-life retrospective studies have been conducted regarding the use of steroids to treat MIS-C (2, 11, 13). In two of them, the authors compared the outcomes of the patients treated with steroids and IVIG vs. IVIG alone. Ouldali et al. found that adding MP to IVIG led to a significant decrease of hemodynamic support needs and a reduction in length of ICU stay; Son et al. found that the patients treated with steroids and IVIG had a lower risk of new or persistent cardiovascular dysfunction compared to the ones treated with IVIG alone (2, 11)."

The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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BRIEF RESEARCH REPORT
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Distinguishing Between Multisystem Inflammatory Syndrome, Associated With COVID-19 in Children and the Kawasaki Disease: Development of Preliminary Criteria Based on the Data of the Retrospective Multicenter Cohort Study

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Objectives: Diagnostic between multisystem inflammatory syndrome associated with COVID-19 in children (MIS-C) and Kawasaki disease (KD) can make difficulties due to many similarities. Our study aimed to create a Kawasaki/MIS-C differentiation score (KMDscore) allowing discrimination of MIS-C and KD.

Study design: The retrospective multicenter cohort study included clinical, laboratory, and instrumental information about MIS-C ($n = 72$) and KD ($n = 147$). The variables allowed to discriminate both conditions used to construct and validate the diagnostic score called the KMDscore.

Results: Patients with MIS-C were older, had earlier admission to the hospital, had a shorter time before fever resolution, two times frequently had signs of GI and CNS involvement observed, and had more impressive thrombocytopenia, higher level of CRP, ferritin, ALT, AST, LDH, creatinine, triglycerides, troponin, and D-dimer compared to KD patients. Respiratory signs in MIS-C were presented with pleuritis, acute respiratory distress syndrome, oxygen dependency, lung infiltration, and ground-glass opacities in CT. The heart involvement with fast progression of myocarditis provided the severity of MIS-C and ICU admission due to 12 times higher arterial hypotension or shock and required cardiotonic. No differences in the frequency of CA lesions were seen in the majority of cases. Five criteria, CRP >11 mg/dl (18 points), D-dimer >607 ng/ml (27 points), age >5 years (30 points), thrombocytopenia (25 points), and GI involvement (28 points), were included in the KMDscore. The summa >55 points allowed to discriminate MIS-C from KD with a sensitivity of 87.5% and specificity of 89.1%.

Conclusion: The KMDscore can be used to differentiate the diagnostic of MIS-C from KD.

Keywords: multisystem inflammatory syndrome, Kawasaki disease, children, hypercytokine syndrome, cytokine storm syndrome, COVID-19, SARS-CoV-2

INTRODUCTION

In December 2019, the first case of a new coronavirus infection with the severe acute respiratory syndrome (SARS-CoV-2) was registered in China for the first time. Since then, the COronaVIrus Disease 2019 (COVID-19) pandemic has rapidly developed into a global health emergency around the world.

This disease is observed relatively less often in children than in adults (1–5% of diagnosed diseases among the population at the beginning of the pandemic) (1). At the moment, it is up to 16% of all COVID-19 cases (2). The clinical course of COVID-19 in children, as in adults, mainly manifests with fever and respiratory symptoms; however, more frequently it proceeds in an asymptomatic or mild form, without development of severe pneumonia (3, 4). At the same time, since April 2020, there have been many reports that a new coronavirus infection may be associated with a childhood hyperinflammatory condition that fully or partially meets the criteria of Kawasaki disease (KD) (5).

KD is an acute systemic vasculitis of unknown etiology, affecting predominantly children under 5 years, characterized by fever, bilateral conjunctival hyperemia, oropharyngeal mucosa changes, erythematous rash, erythema and indurative palms and feet edema, and cervical lymphadenopathy. Approximately 20–25% of untreated patients develop changes in coronary arteries of varying severity from asymptomatic dilatation to giant aneurysms, thrombosis, myocardial infarction, and sudden death (6).

For the first time, the suspicion of the possible connection between COVID-19 and KD was put forward by Jones et al., who reported a case of classic KD in a 6-month-old girl with a positive PCR result for SARS-CoV-2 (7). Also among the first who described this problem were groups of researchers from Italy (8) and France (9). However, this disorder occurs in older children than KD. It is also often manifested with gastrointestinal symptoms (diarrhea, abdominal pain, vomiting) and heart damage (myocarditis, pericarditis), often leading to myocardial damage and shock, while these clinical manifestations are less common in KD (10). The severity and pronounced similarity of the symptoms of this new syndrome and KD caused terminological dilemmas—in addition to the name Kawasaki-like syndrome, others appeared—hyperinflammatory shock, Kawa-COVID, a multisystem inflammatory syndrome in children (MIS-C), or pediatric inflammatory, multisystem syndrome temporarily associated with SARS-CoV-2 (PIMS-TS), and since July–August 2020, two of the latter names have mainly been fixed in the literature. MIS-C is quite rare, and the incidence at the beginning of the pandemic in children was about 2 per 100,000 people or <1% of children with confirmed SARS-CoV-2 infection (11). However, in a more recent study, the frequency of MIS-C cases is 1:4,000 children who have suffered COVID-19 infection (12). Despite the similarities in the clinical picture, the diseases might have different outcomes and treatment approaches. Thus, KD required IVIG 2 g/kg as the first treatment line, followed by repeated IVIG, corticosteroids, and TNF-a inhibitors. MIS-C required systemic corticosteroids, IVIG, IL-1, and IL-6 inhibitors. Interestingly, anti-IL1 and IL-6 treatment did not show its efficacy in KD as anti-TNFa (13).

Our study is aimed to compare clinical and laboratory features of MIS-C and KD and to create the discrimination criteria between two diseases.

METHODS

Patients

In the retrospective multicenter cohort study, we took the information from all medical records of patients who satisfied the criteria of MIS-C and KD at two university-affiliated tertiary hospitals in Russia and the biggest hospital for COVID-19-infected children (St. Petersburg, Irkutsk). We included all available cases of MIS-C ($n = 72$) from May 2020 to April 2021 and KD ($n = 147$) from September 2010 to February 2021. The diagnosis of MIS-C and KD was made according to the existing criteria (5, 14). We extracted the following medical information: demographics (age, sex), clinical features (highest recorded temperature, duration of fever, signs of involvement GI, CNS, respiratory and cardiovascular systems, presence of sore throat, rash, conjunctivitis, red dry, cracked lips, bright mucosa, cervical lymphadenopathy, distal extremity changes, peeling of the fingers, face swelling, hepatomegaly, splenomegaly and presence of arthritis), laboratory findings (complete blood count, ESR, ALT, AST, total protein, albumin, ferritin, LDH, CRP, triglycerides, creatinine, troponin I, fibrinogen, and D-dimer), treatment options, and transferring to ICU. Heart involvement meant the presence of any of the following: myocarditis (tachycardia, accompanied with at least one of the following signs: ECG and EchoCG changes, positive troponin I and/or BNP test), arterial hypotension/shock, pericarditis, or coronary artery (CA) lesions defined on EchoCG (5, 15). The laboratory parameters in the medical records were obtained on the peak of the disease (highest or lowest meanings). In MIS-C, we took epidemiological data about the presence of COVID-19 disease, type of identification (PCR throat or nasal swab, IgM, IgG), family or close contact, and time since the COVID-19 and MIS-C. For diagnostics of cytokine storm, we calculated HScore (16). For treatment of MIS-C and KD, we used the national and international treatment guidelines (5, 17–19).

Ethics

Approval of the local ethical committee was not required since the study used data from clinical charts. All patients

TABLE 1 | Comparison of clinical and laboratory data between MIS-C and KD.

Parameter	MIS-C (n = 72)	KD (n = 147)	*p*
Demographics			
Age, years	8.9 (5.3, 11.8)	2.8 (1.0, 4.8)	0.0000001
Gender, male, n (%)	45 (62.5)	79 (53.7)	0.180
Days before hospital admission	5.0 (3.0, 9.0)	9.0 (5.0, 19.0)	0.000002
Clinical signs			
Duration of fever, days	11 (8, 13)	14 (9, 23)	0.001
Gastrointestinal symptoms, n (%)	58/71 (81.7)	58 (39.5)	0.0000001
Neurological symptoms, n (%)	31/69 (44.9)	34 (23.1)	0.001
Sore throat, n (%)	52/69 (75.4)	79 (53.7)	0.002
Rash, n (%)	59 (81.9)	108 (73.5)	0.166
Conjunctivitis, n (%)	64/69 (92.8)	108 (73.5)	0.001
Dry cracked lips, n (%)	42/66 (63.6)	42/95 (44.2)	0.015
Bright mucous, n (%)	52/69 (75.4)	93 (63.3)	0.078
Respiratory signs, n (%)	40 (55.6)	58 (39.5)	0.024
Cervical lymphadenopathy, n (%)	50/66 (75.8)	104 (70.8)	0.450
Hand/foot erythema/edema, n (%)	51/65 (78.5)	91 (61.9)	0.018
Peeling of fingers, n (%)	35/62 (56.5)	81 (55.1)	0.858
Face swelling, %	40/65 (61.5)	41/146 (28.1)	0.000004
Hepatomegaly, n (%)	50/70 (71.4)	100/133 (75.0)	0.327
Splenomegaly, n (%)	31/69 (44.9)	75/138 (54.3)	0.094
Arthritis/arthralgia, n (%)	17/69 (24.6)	39 (26.5)	0.767
CNS involvement, n (%)	31 (43.0)	34 (23.1)	0.001
Heart involvement, n (%)	51 (70.8)	73 (49.7)	0.003
Myocarditis, n (%)	34 (47.2)	34 (23.1)	0.0003
Pericarditis, n (%)	31 (43.1)	44 (29.9)	0.055
Coronary artery dilatation/aneurysm, n (%)	13 (18.1)	36 (24.5)	0.283
Hypotension/shock, n (%)	34 (47.2)	6 (4.1)	0.0000001
ICU admission, n (%)	37 (51.4)	12 (8.2)	0.0000001
Laboratorial			
Hemoglobin, g/l	103.5 (91.0, 113.0)	104.0 (94.0, 114.0)	0.558
White blood cells, 10^9/l	15.8 (11.1, 20.9)	14.0 (8.7, 21.2)	0.360
Platelets, 10^9/l	185 (95, 445)	520 (383, 666)	0.0000001
Thrombocytosis, n (%)	20/70 (28.6)	103/145 (71.0)	0.0000001
Thrombocytopenia, n (%)	36/70 (51.4)	7/144 (4.9)	0.0000001
ESR, mm/h	43 (28, 53)	48 (28, 62)	0.142
C-Reactive protein, mg/dl	16.3 (10.2, 24.2)	3.53 (1.0, 10.4)	0.0000001
Ferritin, μg/l	366 (209, 643)	120 (71, 239)	0.000004
Increased ferritin, n (%)	43/54 (79.6)	21/44 (47.7)	0.001
ALT, IU/l	46.0 (25.0, 78.0)	26.0 (14.9, 68.5)	0.003
Increased ALT, n (%)	38/70 (54.3)	47/140 (33.6)	0.004
AST, IU/l	53.0 (33.9, 87.0)	38.0 (30.0, 63.0)	0.0183
Increased AST, n (%)	46/55 (83.6)	52/112 (46.4)	0.000004
Serum protein, g/l	56.0 (49.0, 62.0)	68.9 (63.0, 75.8)	0.0000001
Albumin, g/l	30.6 (25.8, 34.0)	38.0 (33.0, 43.0)	0.0000001
Triglycerides, mmol/l	2.3 (1.8, 3.3)	1.0 (0.0, 2.1)	0.0001
Creatinine, mmol/l	57.2 (43.6, 71.4)	39.0 (34.3, 44.9)	0.0000001
LDH, IU/l	339 (248, 637)	291 (237, 357)	0.021
Increased LDH, n (%)	43/63 (68.3)	17/83 (20.5)	0.0000001
Troponin, pg/ml	10.0 (3.5, 4.2)	7.0 (2.0, 10.0)	0.016
Fibrinogen, g/l	4.6 (2.3, 6.5)	3.2 (2.5, 4.5)	0.097
D-Dimer, ng/ml	1,855 (938, 3,266)	584 (243,1,893)	0.001
HScore	112 (90, 142)	75 (68, 91)	0.0000001
Treatment and outcomes			
IVIG treatment, n (%)	37/67 (55.2)	127 (86.4)	0.000001
IVIG repeated course, n (%)	2/50 (4.0)	11/85 (12.9)	0.089
Acetyl salicylic acid, n (%)	42/67 (62.7)	128 (87.1)	0.00004
Corticosteroid treatment, n (%)	61/69 (88.4)	30 (20.4)	0.0000001
Biologics, n (%)	2/43 (4.7)	2/88 (2.3)	0.456
Stay in hospital, days	25 (18, 35)	18 (13, 24)	0.00001

(Continued)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; LDH, lactate dehydrogenase; MIS-C, multisystem inflammatory syndrome in children.

were appropriately anonymized. All patients' representatives and patients 15 years and older gave the consent in their case reports form allowing to use the medical information anonymously.

Statistics

Sample size was not calculated initially. Statistical analysis was performed with the software STATISTICA, version 10.0 (StatSoft Inc., Tulsa, OK, USA). All continuous variables were checked by the Kolmogorov–Smirnov test, with no normal distribution identified. Continuous variables are presented as median and interquartile ranges (IQRs). Categorical variables are presented as proportions. Missing data were not imputed or included in the analyses. Pearson's χ^2 test or the Fisher's exact test in the expected frequencies <5 was used to compare the categorical variables. A comparison of two quantitative variables was carried out using the Mann–Whitney test. The ability of each variable to discriminate MIS-C from KD was evaluated with sensitivity and specificity analysis, AUC-ROC (area under the receiver operating characteristic curve) with 95% confidence interval (CI), and calculation of the odds ratio (OR) for the detection of the best cutoffs of continuous variables. The higher values of OR of variables interfere with the better discriminatory ability. We used the "best" threshold for our data's ROC curve analysis because

it provides the most appropriate mean between sensitivity and specificity. $p < 0.05$ was considered statistically significant. By univariate analysis, each of the variables of interest was associated with the positive diagnosis of MIS-C, with a p of <0.05. They were therefore included in a multivariate logistic model to assess their independent contribution to the outcome. Binary variables included in the model (e.g., thrombocytopenia) were coded as present or absent. The threshold value was based on a ROC curve analysis, retaining the value at which sensitivity plus specificity was maximized. No interaction terms were included in the model. The pseudo R^2 statistic was used for assessing the goodness of fit of the model. The coefficients resulting from this multiple logistic regression analysis were used to assign score points for the construction of the KMDscore. For each variable that was significantly associated with the outcome in the logistic regression, the rule was to multiply the beta value for each range by 100 and round off to the nearest integer.

RESULTS

Epidemiology of COVID-19 in the Patients With MIS-C

COVID-19 infection was confirmed by throat/nasal swab SARS-CoV-2 PCR in 12/68 (17.7) at the moment of hospital admission due to MIS-C; both IgM and IgG antibodies against SARS-CoV-2 virus were positive in 25/62 (40.3%), while IgG only in 59/62 (95.2%). Close family contacts were identified in 33/72 (45.8). Twenty-two patients (30.6%) had symptomatic COVID-19 infection after family contacts, which were confirmed only clinically and epidemiologically. Patients had mild to moderate fever, anosmia, sneezing, and coughing. No cases of pneumonia or hospital admission were identified. Between COVID-19 infection or close family contact and MIS-C onset, the median time was 30.0 (21.0, 40.0) days.

Clinical Differences Between MIS-C and KD

Patients with MIS-C had higher age and similarity in gender distribution with slight male predominance. Patients with MIS-C had earlier admission to the hospital and a shorter time before fever resolution.

Regarding clinical signs, patients with MIS-C had signs of GI (abdominal pain, vomiting, diarrhea, peritoneal signs) and CNS (irritability, headaches, seizures, aseptic meningitis) involvement two times more frequently. Approximately 65% of MIS-C patients admitted to ICU had CNS involvement. Kawasaki-associated signs were also frequent in MIS-C: sore throat, rash, conjunctivitis (hemorrhagic in MIS-C and non-purulent in KD), mucous involvement (bright lips and dry, cracked lips), distal edema, and face swelling. Respiratory disorders in MIS-C were presented with pleuritis, acute respiratory distress syndrome, oxygen dependency, lung infiltration, and ground-glass opacities in CT. The heart involvement was linked to the severity of MIS-C and ICU admission in the majority of cases. We have not seen differences in the frequency of CA lesions, but in MIS-C, the CA lesions were presented with mild or moderate CA dilatation and were reversible, compared to KD, where aneurysms (including giant ones) were. The frequency of pericarditis was of borderline significance. Myocarditis in MIS-C was characterized by fast progression (heart dilatation, decreasing LV ejection fraction, transient ECG changes—AV-blocks and repolarization disturbances) and was associated with arterial hypotension or shock, which required inotropic support with cardiotonic. Patients with heart involvement had increased troponin I, proBNP, CK, CK-MB, and LDH. Hypotension/shock with multiorgan failure accompanied with myocarditis and ARDS were the main reasons for ICU admission in both diseases, 12 times higher in MIS-C and only in a few patients with KD. Arterial hypotension/shock did not correlate with the degree of LV ejection fraction lowering. Data are shown in **Table 1**.

Laboratory Differences

Patients with MIS-C had more impressive thrombocytopenia and higher levels of CRP, ferritin, ALT, AST, LDH, creatinine, triglycerides, troponin, and D-dimer. Data are shown in **Table 1**.

Creation of the Differentiation Model

In the next step, we selected continuous and categorical variables with statistical significance, and analysis of sensitivity and specificity with OR calculation was done. Data are shown in **Table 2**. Then, we extracted parameters with highest sensitivity, specificity, OR, and clinical meaningfulness. We excluded duplicated parameters, and multivariate analysis was allowed to extract five criteria: CRP >11 mg/dl, D-dimer >607 ng/ml, age >5 years, thrombocytopenia, and GI involvement. In the multivariate analysis, only five variables from the initial 29 included in the model remained significantly associated with the probability of being classified as having MIS-C. The optimal cutoff was selected as the threshold giving the highest value for the sum of sensitivity and specificity. The area under the curve (AUC) = 0.927 (0.884–0.958), DS for MIS-C >55 points, allowed to discriminate MIS-C from KD with sensitivity of 87.5% and specificity of 89.1% (**Table 3**; **Figure 1**). The pseudo R^2 statistic for the model was 0.73 ($p < 0.0001$). The maximum possible score assigned to each variable varied from 18 for CRP > 11 mg/dl to 30 for age >5 years (**Table 3**). Missing data were scored as 0.

DISCUSSION

We are presenting the experience in diagnostics of MIS-C associated with COVID-19 at several pediatric clinics in Russia (St. Petersburg, Irkutsk) comparing them with a historical cohort of patients with KD. In general, the data obtained about both diseases are comparable with previously published studies. Special attention is focused on this new pathology due to the rapid development and high frequency of life-threatening complications—shock and multiorgan failure, as well as heart damage and coagulopathy (9, 11, 20). There are two sets of criteria for MIS-C diagnostics: the WHO criteria and CDC-criteria. We used WHO criteria, which might be to some extent focused on cardiac involvement, as CDC-criteria are more relevant to hyperinflammation, but all of our patients satisfied both sets of criteria (14, 21). Fortunately, MIS-C is

TABLE 2 | Sensitivity, specificity, and odds ratios of clinical and laboratorial predictors, allowing to discriminate MIS-C and KD.

Clinical predictors	*Se*	*Sp*	OR (95% CI)	*p*
Age >5 years	76.1	83.5	16.0 (7.9, 32.4)	0.000001
Duration of fever <14 days	74.4	58.9	4.2 (1.9, 9.0)	0.0002
Respiratory signs	55.6	60.5	1.9 (1.1, 3.4)	0.024
Gastrointestinal signs	81.7	60.5	6.9 (3.5, 13.6)	0.0000001
CNS involvement	44.9	76.9	2.7 (1.5, 5.0)	0.001
Sore throat	75.4	46.3	2.6 (1.4, 5.0)	0.0024
Conjunctivitis	92.8	26.5	4.6 (1.7, 12.3)	0.001
Dry cracked lips	63.6	55.8	0.45 (0.24, 0.86)	0.015
Hands/feet erythema/edema	78.5	38.1	2.2 (1.1, 4.4)	0.018
Face swelling	61.5	71.9	4.1 (2.2, 7.6)	0.000004
Hypotension/shock, n (%)	47.2	95.9	21.0 (8.2, 53.8)	0.0000001
Any heart involvement, n (%)	55.2	13.6	2.5 (1.4, 4.5)	0.003
Myocarditis, n (%)	47.2	76.9	3.0 (1.6, 5.4)	0.0003
Pericarditis, n (%)	43.1	70.1	1.8 (0.99, 3.2)	0.055
ICU admission, n (%)	51.4	91.8	11.9 (5.6, 25.2)	0.0000001
Laboratorial predictors				
Platelets $\leq 264 \times 10^3$ μl	62.9	88.7	13.2 (6.5, 26.9)	0.0000001
Thrombocytosis	28.6	29.0	0.16 (0.09, 0.31)	0.000000
Thrombocytopenia	51.4	95.1	20.7 (8.5, 50.6)	0.0000001
C-reactive protein > 11 mg/dl	74.6	79.1	11.1 (5.6, 22.3)	0.0000001
Ferritin > 260 ng/ml	70.4	79.2	9.0 (3.6, 22.4)	0.000001
Hyperferritinemia	79.6	52.3	4.3 (1.8, 10.4)	0.001
ALT > 22 U/l	82.9	46.8	4.3 (2.1, 8.6)	0.00003
Increased ALT	54.3	66.4	2.4 (1.3, 4.2)	0.004
AST > 50 U/l	55.1	66.9	2.5 (1.4, 4.5)	0.003
Increased AST	83.6	53.6	5.9 (2.6, 13.2)	0.000004
Serum protein ≤ 65 g/l	84.3	68.3	11.6 (5.5, 24.4)	0.0000001
Albumin ≤ 35 g/l	83.9	67.5	10.8 (4.7, 24.6)	0.0000001
Triglycerides > 1.38 mmol/l	32.0	12.5	14.9 (4.2, 52.4)	0.000004
Creatinine > 49.5 mmol/l	68.2	86.6	13.8 (6.1, 31.4)	0.0000001
Troponin > 25 pg/ml	5.1	58.8	13.0 (2.7, 62.8)	0.0002
D-Dimer > 607 ng/ml, n (%)	48.0	3.8	27.1 (5.9, 123.6)	0.0000001
Increased LDH, n (%)	68.3	79.5	3.3 (1.5, 7.4)	0.000000
HScore > 105, n (%)	56.5	76.2	4.2 (2.3, 7.7)	0.000002

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ICU, intensive care unit; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; LDH, lactate dehydrogenase; MIS-C, multisystem inflammatory syndrome in children; OR, odds ratio; Se, sensitivity; Sp, specificity.

a rare condition, which involves one of each 4,000 children, infected with COVID-19 (12). The obtained data demonstrate similarities and differences between MIS-C and KD. Both of these conditions are considered as hyperinflammatory syndrome with multisystem involvement, on an immunopathological basis under the influence of a trigger factor which is a new coronavirus infection for MIS-C; for KD, a specific trigger has not been found yet.

In general, there is much in common between these two diseases, including many similarities in clinical phenotypes, and some patients with MIS-C fulfill the AHA criteria for KD (5). In both diseases, fever, mucocutaneous manifestations, conjunctivitis, hand and foot erythema/edema, and cervical lymphadenopathy are observed, but we noted that rash in MIS-C was more diffuse and extensive compared to KD (8, 9, 20, 22). In our research, these symptoms were also quite similar in both studied conditions. Patients with MIS-C were admitted to the hospital earlier than KD patients were, possibly due to raising concerns for the families the coronavirus presents. The main unifying sign of both diseases, except fever, mucocutaneous and lymph-node involvement, and systemic inflammation biomarkers, is the involvement of the heart and coronary arteries (9, 20, 22). Cardiac involvement in KD manifested with development of CA aneurisms, their subsequent thrombosis, and heart attack (5, 23). MIS-C is predominantly characterized by the acute myocardial injury with increased troponin I level and reversible dilatation of CA with rear CA thrombosis and heart attack (9, 11, 20, 22).

The main discriminative factors between two diseases are onset age, high CRP, thrombocytopenia, increased D-dimer, and GI involvement. MIS-C occurs in all age groups, but still the majority of patients are high school students, those with KD usually are younger, and 76% of them are children under 5 years old (24). The median onset age of the affected children of MIS-C in our study is 8.9 (5.3, 11.8) years, which is comparable to the previously published results where the median age ranges from 6 to 12 years (11, 22, 25, 26). However, it is important to emphasize that MIS-C can also occur in children under 1 year of age (27). Also, a hyperinflammatory condition similar to MIS-C in young adults after COVID-19 has been reported (28).

Diversity between the two illnesses is also obvious as there are signs and symptoms with high frequency in MIS-C which are less commonly or rarely presented in KD patients. For example, gastrointestinal symptoms are more common for MIS-C according to many studies including our observation (11, 22, 29). It should also be noted that among the studied patients with gastrointestinal disorders in our MIS-C group, one had acute appendicitis, which required laparoscopic appendectomy, and the "white" appendix was removed. Similar cases are also described in previously published works (30, 31). In addition, among significant differences between MIS-C and KD there are myocardial injury, hypotension/shock, and neurological disorders in MIS-C patients that are less frequent in KD (8, 20, 22, 32). Sixty-five percent of MIS-C patients admitted to ICU had CNS involvement and had serous meningitis and cerebral venous thrombosis as the most serious complications. Unless cardiac involvement can be presented in both diseases, there are some differences in the nature of cardiac findings. Thus, myocarditis is more common in MIS-C patients, while CA aneurisms are more typical for KD (9, 32–34).

Speaking of laboratory values, elevated inflammatory biomarkers were seen in both conditions in our study as well as in previously published articles (8, 20, 29). However, for example, CRP levels were significantly higher in MIS-C patients in our study, as well as in previously published articles (29). For assessment of cytokine storm syndrome, we applied HScore, which was created earlier for hemophagocytic lymphohistiocytosis. HScore >105 was associated with the severest signs of MIS-C: myocarditis [OR = 4.2 (95% CI: 1.5,

TABLE 3 | Variables included in the development of the diagnostic set and KMDscore calculation.

	β	SE	*p*		No. of points (criteria for scoring)**
CRP >11 mg/dl	0.18	0.73	0.016	CRP	0 (<11.0 mg/dl) or 18 (≥11.0 mg/dl)
D-Dimer >607 ng/ml	0.27	0.64	0.00006	D-dimer	0 (≤607 ng/ml) or 27 (>607 ng/ml)
Age >5 years	0.30	0.62	0.000004	Age	0 (≤5 years) or 30 (>5 years)
Thrombocytopenia*	0.2	0.62	0.0001	Platelets*	0 (no) or 25 (yes)
GI involvement	0.28	0.61	0.00001	GI involvement	0 (no) or 28 (yes)

**Thrombocytopenia defined as platelets < 150 × 10^3 μl.*
***DS cutoff > 55 points.*

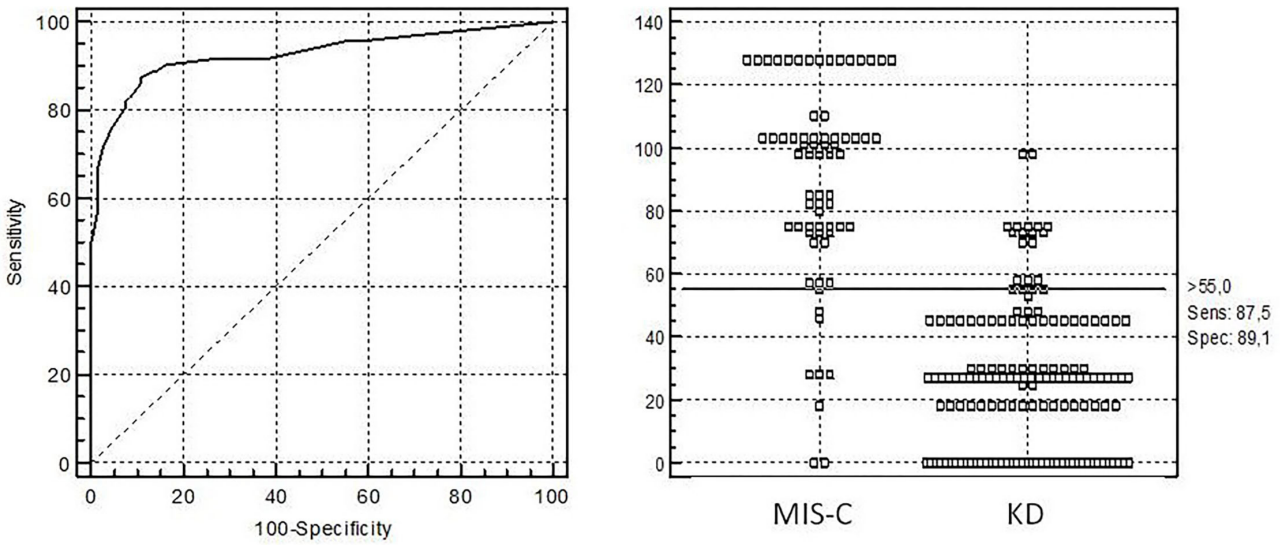

FIGURE 1 | Receiver operating characteristic (ROC) curve analysis for diagnosis of multisystem inflammatory syndrome in children with diagnostic score (KMDscore) computed with the developmental data set. The optimal cutoff was selected as the threshold giving the highest value for the sum of sensitivity and specificity. Area under the curve (AUC) = 0.927 (0.884–0.958), DS for MIS-C >55 points with sensitivity of 87.5% and specificity of 89.1%.

11.5), $p = 0.005$], pericarditis [OR = 7.1 (95% CI: 2.4, 21.6), $p = 0.0003$], shock [OR = 3.7 (95% CI: 1.4, 10.3), $p = 0.009$], and GI involvement [OR=5.4 (95% CI: 1.3, 22.3), $p = 0.013$]. HScore is a simple tool which might be used for assessment of severity of MIS-C. Additionally, there is a difference in platelet levels in MIS-C and KD patients in our study, with median of 185 and 520*10^9/l, respectively. Thrombocytosis is typical for KD, but less common in MIS-C patients, who quite often have a tendency toward thrombocytopenia, especially at onset or during the peak of the disease (8, 20, 22, 29). Additionally, elevated biochemical markers of cardiac injury and highly elevated ferritin and D-dimer are typical for MIS-C patients (20, 22, 29). These findings seem to be less common for KD patients. For example, in our study median ferritin was 366 μg/l in the MIS-C group and 120 in the KD cohort, and D-dimer levels were also significantly different in studied conditions, 1,855 and 584 ng/ml, respectively. However, it is also reported that elevated D-dimer can actually be the risk factor of CA damage in KD patients (35).

MIS-C is close in manifestations to Kawasaki-shock syndrome as they are united by the fulminant development of heart injury, similar gastrointestinal symptoms, hyponatremia, and hypoalbuminemia (34). Factors causing the development of shock in KD are not fully understood, but an important role in its pathogenesis is played by more pronounced inflammation and especially intense and very rapidly developing vasculitis with thrombosis and endothelial damage (36). Probably, endothelial damage in MIS-C differs from KD, due to the unique characteristics of the pathogen SARS-CoV-2 and its affinity to the endothelium. The vascular wall damage due to COVID is primarily caused by the virus penetration into the cells of the vascular endothelium through the ACE2 receptor, and then after a certain period of time immuno-mediated endothelial damage develops (37).

The pathogenetic basis for both MIS-C and KD is the dysregulation of the innate immune response, and as a result in both diseases there is an excessive production of pro-inflammatory cytokines, up to a cytokine storm, which occurs much more frequently in MIS-C than in KD. Gruber et al. (38) detected the presence of autoantibodies in patients with MIS-C against not only endothelial but also gastrointestinal and immunocompetent cells, and obviously this is due to a number of pathophysiological and clinical differences. Neutralizing antibodies against SARS-CoV-2 can activate IL-18 and IL-16, myeloid chemotaxis, and activation

of lymphocytes, monocytes, and natural killers, which lead to neutrophil activation, hypercoagulation, and thrombosis (38). These changes are not typical for children suffering from acute COVID-19, but characteristic for severe forms of COVID-19 in adults (39). NETosis on the basis of MIS-C in children and severe forms of COVID-19 in adults may provoke severe cytokine storm and inflammation leading to microthrombosis and irreversible involvement of the cardiorespiratory system (40). The main unresolved question is if MIS-C is a unique self-limited condition, related to COVID-19 infection, or it is the severest variant of KD triggered by the SARS-CoV-2 virus. The viral etiology of KD was previously described, and different types of coronaviruses (HCoV-NL63 and HCoV-NL229E) were mentioned as a possible cause of KD, but other studies did not confirm it (41–44).

Study Limitations

The KMDscore has some limitations as well. First, it was developed using a retrospective study population, with the possibility of bias in the selection of this population. To minimize this bias and to ensure that no patient fulfilling our inclusion criteria was missed, we selected the study population by reviewing the medical records having non-bias diagnosis of MIS-C and KD. The historical nature of the KD cohort also restricted the efficacy of the results because it does not reflect the modern trends in KD in the time of the COVID-19 pandemic. The main difficulties are related to the absence of validated criteria of MIS-C.

CONCLUSION

The DScore can be used to differentiate the diagnostic of having MIS-C from KD, accompanied with other diagnostic tests and procedures. Further investigations are required.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

MK, LB, VC, VS, and YK contributed to the conception and design of the study. IA, ED, AM, EI, TK, OE, VM, LS, and OK organized the database. MK and IA performed the statistical analysis. MK, LB, and IA wrote the first draft of the manuscript, wrote sections of the manuscript, and had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. MK, LB, IA, ED, AM, OE, EI, TK, VM, LS, VS, YK, OK, and VC have contributed equally to all of the following aspects: conception, acquisition of data, drafting, and revising the article. All authors contributed to the article revision, read, and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CASE REPORT
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Case Report: Necrotizing Stomatitis as a Manifestation of COVID-19-Associated Vasculopathy

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Necrotizing stomatitis is a rare, acute-onset disease that is usually associated with severely malnourished children or diminished systemic resistance. We describe a 1-year-old girl who developed necrotizing stomatitis, vasculitic rash, skin desquamation on the fingers and toes, and persistent hypertension after serologically confirmed SARS-CoV-2 infection. Her laboratory investigations revealed positive IgG anticardiolipin and IgG anti-β2 glycoprotein antibodies, and biopsy of the mucosa of the lower jaw showed necrosis and endothelial damage with mural thrombi. Swollen endothelial cells of small veins in the upper dermis were confirmed also by electron microscopy. As illustrated by our case, necrotizing stomatitis may develop as a rare complication associated with SARS-CoV-2 infection and can be considered as a part of the clinical spectrum of COVID-19 vasculopathy. The pathogenic mechanism could involve a consequence of inflammatory events with vasculopathy, hypercoagulability, and damage of endothelial cells as a response to SARS-CoV-2 infection.

Keywords: necrotizing stomatitis, vasculitis, hypertension, SARS-CoV-2, COVID-19 associated vasculopathy, case report, damage of endothelial cell

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INTRODUCTION

SARS-CoV-2 infection is asymptomatic in 15–42% of infected children (1). In symptomatic children, the main clinical manifestations are fever, cough, headache, nausea/vomiting, diarrhea, shortness of breath, sore throat, myalgia, rhinorrhea, abdominal pain, and loss of smell and taste (2, 3).

Since the outbreak of COVID-19, there is a growing number of reports on various skin and mucosal changes associated with COVID-19 as well. The pathogenesis of COVID-19 vasculopathy is most likely thrombotic lymphocytic vasculitis, and the disease has in most cases a benign course (4).

Necrotizing stomatitis (NS) is a rare, acute-onset disease with painful, destructive necrosis and ulceration in gingival, periodontal, and other oral surfaces beyond mucogingival junction. It rarely occurs in pediatric patients and is usually associated with severely malnourished children or diminished systemic resistance such as with human immunodeficiency virus (HIV) infection (5).

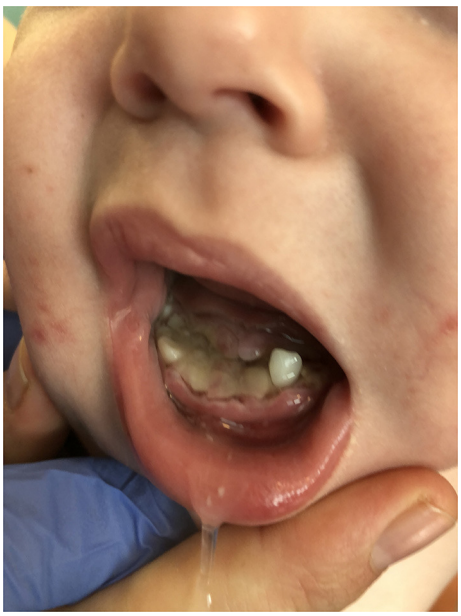

FIGURE 1 | Necrosis of the frontal region of the mandibular alveolar ridge and three missing incisors.

We report a case of a 1-year old girl with NS that developed after SARS-CoV-2 infection. To our knowledge, NS and bone necrosis in a child in association with COVID-19 has not yet been described.

CASE DESCRIPTION

We present a case of a 1-year-old Caucasian girl, whose past medical history was unremarkable. Two and a half months before the initial presentation, the first tooth (lower incisor) erupted and soon after 11 more teeth erupted in the upper and lower jaw.

Two months before admission, the girl traveled abroad with her family. The family negated symptoms of SARS-CoV-2 infection.

The girl initially developed an itchy skin rash. Two weeks later, she developed diarrhea which lasted for 6 days. A pediatrician also noticed acute otitis media and signs of acute stomatitis. Laboratory results showed elevated C-reactive protein (CRP, 60 mg/l) and leukocytosis.

One month after the initial presentation and one week after the resolution of diarrhea, her medical condition worsened, she became irritable, refused to eat solid food, and suddenly lost three deciduous incisors from the lower jaw. The rest of her teeth in the lower jaw were mobile. There was no report of injury or elevated temperature.

Family history was unremarkable.

Clinical Findings

At admission to our hospital, she was hemodynamically stable, afebrile, and irritable. Her heart rate was 176 beats/min. She presented with extensive necrosis of the frontal region of the mandibular alveolar ridge extending to deciduous molars and was missing three incisors (**Figure 1**). The affected area was swollen and exposed, with extensive fibrin coating. Maxillary gingiva showed no signs of gingival or periodontal inflammation. There were some aphthous changes on the tongue and buccally. On the skin, there was a generalized erythematous maculopapular rash with petechiae and scratches on the trunk and buttock. Desquamation of the skin on the fingers and edema of the wrists and ankles was also seen. There was redness of the perigenital region. Peripheral lymph nodes were not enlarged. Neurologic examination was normal.

During hospitalization, the second left incisor in the mandible fell out, the girl had cold limbs, and occasionally a reticular pattern was seen on the skin. Transiently, a wound between the second and third toes on the left foot was present.

The girl had just one peak temperature of 38.2°C; otherwise, she was afebrile and cardiovascularly compensated. On the third day after admission, she developed hypertension with systolic blood pressure between 125 and 140 mmHg and diastolic blood pressure between 60 and 90 mmHg (above the 95th percentile for age and height, which is 105/60 mmHg). She also had a persistent tachycardia with a pulse rate between 150 and 180 beats/min.

Diagnostic Assessment

Laboratory Tests and Serology

In blood laboratory test results, there was a mild elevation of CRP (20 mg/l), negative procalcitonin, leukocytosis, and thrombocytosis. L*actate dehydrogenase* (LDH), liver transaminases, and fibrinogen were elevated as well. Thyroid hormones (T3 and T4) were slightly elevated.

Nasopharyngeal swab was positive for rhinovirus and enterovirus infections but was negative for other viruses including SARS-CoV-2. The swabs of the oral cavity and mandible were negative for pathogenic bacteria and herpesviruses. Skin swabs from several places showed S. aureus and Candida albicans superinfection and a vaginal swab showed the presence of Candida albicans.

The serology for SARS-CoV-2 was found positive for both IgG and IgA antibodies (IgG: 1.88; IgA: 2.17). Blood culture was negative. Her immune status was unremarkable, and primary immunodeficiencies were ruled out with laboratory tests. The girl had normal lymphocyte subpopulations, at presentation minimally elevated IgG levels, and normal IgM and IgA, normal test of phagocytosis, and normal values of complement. Immunoserology testing revealed positive IgG anticardiolipin antibodies (aCL) (12 AUG) and IgG anti-beta2-glycoprotein I antibodies (anti-ß2GPI) [16 AUG]). Vitamin A deficiency, herpes simplex virus 1 and 2, varicella zoster virus, HIV, rubella, and measles infections were ruled out. The urine sample was unremarkable. The plasma renin level was normal for the girl's age [7.3 μg/l/h (ref.: 0–3 years: <16.6 μg/l/h)]. The heart breakdown enzymes were normal.

Imaging

CT and MR imaging of the lower jaw showed diffusely altered bone with edema and necrosis of the mandibular corpus and the above alveolar ridge in the region extending from tooth 84

to tooth 74 (**Figure 2**). It showed severe inflammation of the surrounding soft tissues and muscles as well. There was loss of teeth 71, 81, and 82.

Ultrasound of the abdomen showed slightly enlarged liver. Doppler ultrasound of renal arteries was normal, and thyroid ultrasound was normal as well. Chest X-ray was normal. Electrocardiogram and echocardiogram showed no abnormalities.

Histopathological Evaluation

Biopsy of the mucosa of the lower jaw, tooth, mandible (twice), and skin was performed. During biopsy, teeth 83 and 73 were removed due to total loss of supporting alveolar bone. Histopathologically (**Figure 3a**), biopsy of the mucosa of the lower jaw showed necrosis, granulation tissue, and changes compatible with epulis, corresponding partly to pyogenic granuloma and partly to peripheral ossifying fibroma. No diagnostic changes for lymphoma or Langerhans cell histiocytosis were present. Immunohistochemistry for SARS-CoV-2 was negative. Necrosis and endothelial damage with individual mural thrombi and in some cases the appearance of recanalization of thrombotic changes along small vessels were seen (**Figure 3b**).

Biopsy of the mandible showed vital reactive bone with fibrosis without suppurative inflammation indicative of active infection.

Biopsy of the tooth showed normal structures of the tooth with adjacent structures of the alveolar ridge.

The second biopsy of the soft tissue of the mandible showed minimally reactive bone, and reactive spindle-cell proliferation with individual multinucleated giants of the osteoclast type. Compared with the previous biopsy, the changes were more chronic in appearance with reparative inflammation, without granulation tissue or necrosis.

The samples of skin changes in the sacral area were taken and sent for analysis and possible bacterial and fungal infections. Histopathologically, sacral focal necrosis of the epidermis and swelling of endothelial cells of the dermis were seen (**Figure 4a**). There was no thrombosis and no visible changes typical for malignancy, histiocytosis, or active infection. Stevens–Johnson syndrome (SJS) was also excluded based on the skin-biopsy result. Swollen endothelial cells of small veins in the upper dermis that almost or completely close the lumen were confirmed by electronic microscopy (**Figure 4b**). There were no fibrins or platelets in the lumen of the examined vessels and on the endothelium. Endothelial cell organelles were unremarkable. No viral particles were detected. Immunofluorescence examination was unspecific.

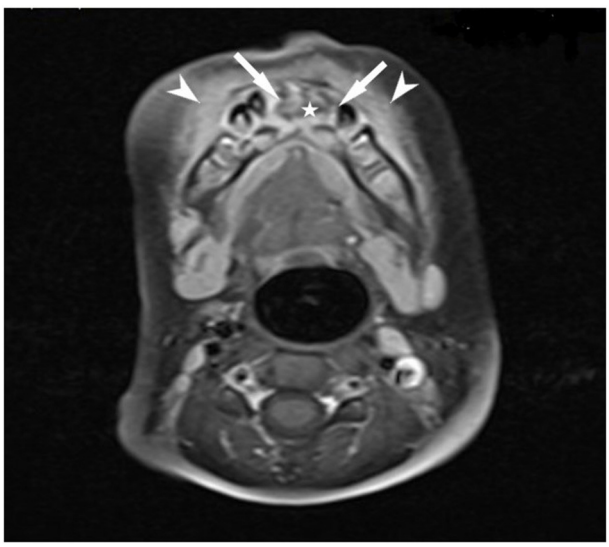

FIGURE 2 | Magnetic resonance imaging of the girl's mandible (T1 TSE fat sat contrast medium sequence) showed areas of bone necrosis (star) with peripheral reactive bone contrast enhancement (arrows) and enhancement of the soft tissue edema (arrowheads).

Genetic Testing

The results of molecular genetic testing by the next-generation sequencing (NGS) method showed no changes in the 4,813 analyzed genes, including 304 genes associated with primary immunodeficiencies, genes associated with COVID-19 vasculitis

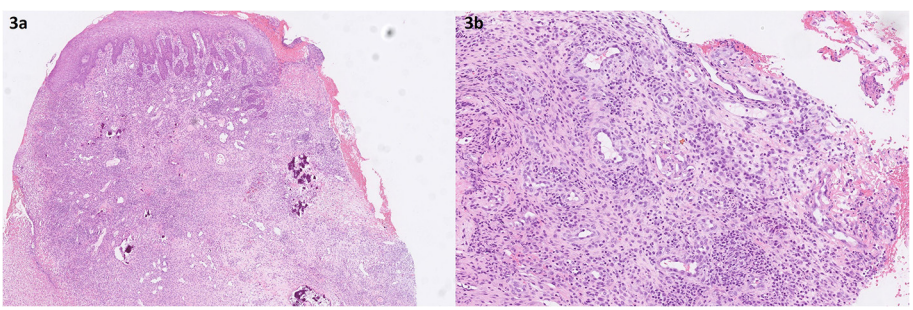

FIGURE 3 | Histopathology of the biopsy specimens taken from the lower jaw (first biopsy). **(a)** Inflamed gingival mucosa with superficial erosions, with granulation tissue and dystrophic calcifications. Retrospectively, calcifications were "reinterpreted" as remains of destructed alveolar bone. HE, original magnification, ×4. **(b)** Recanalization of the small vessels in the inflamed gingival mucosa (mark). Note the intense mixed inflammatory infiltrate in the background and the swollen endothelial cells. HE, original magnification, ×20.

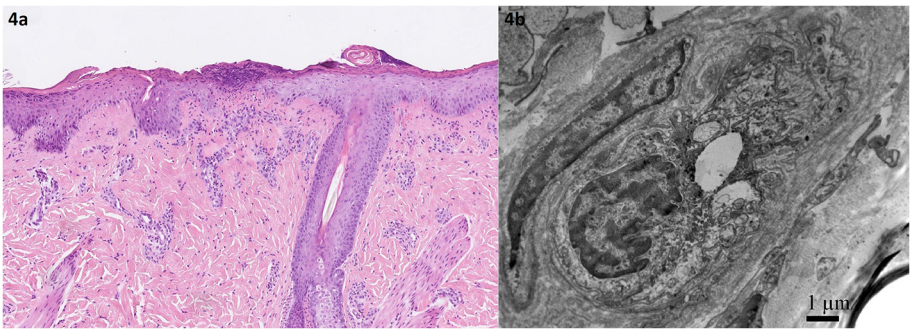

FIGURE 4 | Histopathology of the skin efflorescence in the sacral area. **(a)** Focal epidermal necrosis is present in the center. Note the pronounced underlying small vessels with swollen endothelial cells in the papillary dermis. HE, original magnification, ×6. **(b)** Electron microscopy of swollen endothelial cells obliterating the lumen of the aforementioned small veins.

(*TREX1*), type I interferonopathies (*STING1*, *COPA*), and monogenic vasculitis (*DADA2*) (6, 7).

Treatment

The patient was treated with combined antibiotic therapy with amoxicillin and clavulanic acid intravenously. On the 13th day of hospitalization, we also introduced metronidazole 100 mg q 8 h orally and clindamycin 100 mg q 8 h intravenously and later orally. Because of the suspicion for hypercoagulability, she received antiplatelet therapy with 50 mg of acetylsalicylic acid daily. For the skin, she received ointment with a combination of corticosteroid, antibiotic, and antifungal active substance due to proven superinfection with S. aureus and Candida albicans. Against itching, she received loratadine twice daily. Against oral pain, we applied 1% lidocaine chloride locally three times a day. She needed analgesia (paracetamol 100 mg/6 h) and, due to food refusal, parenteral hydration. Due to tachycardia and arterial hypertension, she received 1 mg of antihypertensive drug amlodipine (0.1 mg/kg) twice daily.

Follow-Up and Outcomes

Two weeks after the beginning of antimicrobial and antiplatelet therapy, the girl showed clinical improvement. The changes in the mandible and skin were no longer so pronounced, and blood pressure gradually decreased. Skin therapy slowly helped to reduce the intensity of the rash. Normalization in inflammatory parameters and decrease of D-dimer value were recorded. Thrombocytosis and slightly elevated LDH and AST persisted. Control thyroid hormones were in the normal range.

A week after discharge, the girl was better, except for her blood pressure, which was still high, so we adjusted the therapy of amlodipine to 2 mg (0.2 mg/kg) twice daily.

Three weeks after the discharge, she stopped antibiotic therapy, and after 1 month she also stopped taking antihypertensive drug amlodipine. Follow-up echocardiography was normal. One month after discharge, the serology for SARS-CoV-2 was negative.

At the last follow-up, almost 1 year after the first admission, the girl was in a better mood, no rash was present, and there was no inflammation in her oral cavity, but six teeth in the lower jaw (73, 72, 71, 81, 82, and 83) were missing, and other teeth showed caries. Her laboratory results were normal, except for persistently positive IgG aCL (11 AUG) and IgG anti-ß2GPI antibodies (16 AUG).

DISCUSSION

Various oral cavity-related manifestations in patients with COVID-19 have been reported, including oral necrotic ulcers and aphthous-like ulcerations. These manifestations usually develop early in the disease course and affect the tongue, lips, palate, and oropharynx (8, 9). Aphthous changes on the tongue and buccally were also observed in our patient. The oral lesions in COVID-19 could be due to the interaction between SARS-CoV-2 and ACE-2 receptors, expressed on epithelial cells of the tongue and salivary glands, which might increase the permeability of the cell walls to foreign pathogens and viral replication in the cells lining the oral mucosa, leading to ulcers and necrosis (8).

Necrotizing periodontal disease was also described in association with COVID-19 (10). SARS-CoV-2 infection may predispose individuals to necrotizing periodontal disease through bacterial coinfection propagated by Prevotella intermedia (11), which was reported in a 35-year-old woman with necrotizing gingivitis due to Prevotella intermedia and COVID-19 (12). Moreover, there was a case report of a 38-year-old man who developed osteonecrosis of maxilla as a possible oral manifestation of COVID-19 (13). To our knowledge, our patient is the first reported case of NS with mandibular bone necrosis after SARS-CoV-2 infection in a child.

Endothelial dysfunction of multiple organs is a well-known feature of severe COVID-19 (14, 15). The SARS-CoV-2 virus binds to the angiotensin-converting enzyme-2 (ACE-2) receptor, which is also present on endothelial cells (16) and thus has a direct effect on them. It can also cause vasculitis and manifests as systemic inflammatory vascular disease (17). Several studies noted viral-like particles in endothelial cells (18, 19). Endothelial dysfunction may cause many of the symptoms by promoting inflammatory and microvascular

thrombotic processes. Disruption of the endothelial barrier and endothelial cell function leads to vasoconstriction, increased vascular permeability, thrombosis, hyperinflammation, and hypertension (20).

In the present case, necrosis and endothelial damage with individual mural thrombi and in some cases the appearance of recanalization of thrombotic changes along small vessels were seen histopathologically. These changes could be linked to the hypercoagulable state and vascular damage in multisystem inflammatory response after SARS-CoV-2 infection. We found no SARS-CoV-2 viral particles in the biopsy samples. In contrast, Colmenero et al. (19) detected SARS-CoV-2 viral particles in endothelial cells in a skin biopsy of seven children with COVID-19 chilblains, and in one case viral particles were visible also on electron microscopy.

Different cutaneous manifestations of vasculitis have also been reported in patients with recent COVID-19 infection (21, 22). In our case, the girl had generalized erythematous maculopapular rash with additional petechiae in some localized areas. She had some clinical features of MIS-C and Kawasaki disease but did not fulfill criteria for either of these two diseases. High fever was present only for 1 day, and she had no conjunctivitis, no lymphadenopathy, and no cardiac involvement. Treatment with intravenous immunoglobulins was considered but was not given since the patient did not meet the criteria for MIS-C or Kawasaki disease. Moreover, application of intravenous immunoglobulin could increase blood viscosity and further reduce arterial and capillary blood flow.

Possible causes for hypertension in our patient were endothelial dysfunction due to swollen endothelial cells and luminal narrowing of the blood vessels or thyroid impairment. Renal artery stenosis was ruled out with a Doppler renal ultrasound. Hypertension persisted even after the normalization of thyroid hormones, so we hypothesize that arterial hypertension could be linked with endothelial dysfunction (21, 22).

Numerous autoimmune manifestations associated with COVID-19 are described in the literature including the presence of several different autoantibodies (23). Anticardiolipin and other antiphospholipid antibodies were frequently reported in patients with COVID-19 (24) and were associated with a more severe disease course (25). It is likely that the presence of aCL in our patient reflects endothelial damage due to SARS-CoV-2 infection and could additionally contribute to the procoagulant state. Our patient also had signs of thyroiditis, which has been reported before in association with SARS-CoV-2 infection (26).

The treatment of NS includes treatment of the acute phase with systemic antibiotics and sometimes with antifungal agents, which are important especially in immunosuppressed patients (27). The treatment of any possible preexisting condition is also important. To lower the possibility for relapses, long-term support should be obtained. In our patient, we obtained a satisfactory response with local and systemic treatment. The girl lost six deciduous teeth along with alveolar bone, and it is unknown at this time whether permanent teeth in this area will be affected. Mucosa healed without any scarring, and it appeared normal in structure and color.

One of the limitations of our case report is the impossibility to determine the causative role of COVID-19 in the disease. The cause of the girl's symptoms and signs could have been some other infection, but it was an unusual combination of clinical and laboratory features that was not previously reported and occurred at the peak of the SARS-CoV-2 epidemic. Moreover, the extensive infectious disease workup was negative except for positive SARS-CoV-2 serology.

Given the disease course, positive SARS-CoV-2 serology, and signs of endothelial cell swelling on the skin biopsy, it appears that NS in this patient was due to COVID-19. The complex pathogenic mechanisms of NS and bone necrosis linked with COVID-19 are still unclear but could be a consequence of inflammatory events with vasculopathy and damage of endothelial cells as a response to the SARS-CoV-2 infection.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

NE, TT, OT, MK and TA contributed in the patient care and treatment. NE and TA wrote the manuscript and reviewed the literature. DK contributed to interpreting and describing the imaging findings. MV contributed to describing histopathological evaluation. All authors contributed to diagnostic procedure, manuscript revision, read, and approved the submitted version.

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The handling Editor declared a past co-authorship with one of the authors TA.

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BRIEF RESEARCH REPORT
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Timely Recognition and Early Multi-Step Antinflammatory Therapy May Prevent ICU Admission of Patients With MIS-C: Proposal for a Severity Score

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In this observational study, we report the clinical, therapeutics and outcome features of 23 patients with multisystem inflammatory syndrome (MIS-C) who have been treated in Gaslini Children Hospital (Genoa, Italy) with a multistep antinflammatory treatment protocol, based on disease severity at admission. Patients were initially assigned to four severity classes on admission and treated accordingly. The therapeutic options ranged from IV immunoglobulin alone to a combination of IVIG plus pulses of methylprednisolone plus anakinra for patients with marked cardiac function impairment or signs of macrophage activation syndrome, with rapid treatment escalation in case of inadequate therapeutic response. With the application of this therapeutic strategy, no patient required admission to Intensive Care Unit (ICU) or invasive mechanical ventilation, and no inotropic drugs administration was required. Early aggressive treatment of MIS-C, with therapeutic interventions modulated based on the severity of clinical manifestations may help to prevent the progression of the inflammatory process and to avoid the need of admission to the ICU. A timely intervention with anti-IL-1 blockers can play a pivotal role in very severe patients that are at risk to have an incomplete response to immunoglobulins and steroids.

Keywords: anakinra, multi-step anti-inflammatory treatment, SARS-CoV-2, pediatric COVID-19, immunoglobulins, kawasaki disease, multisystem inflammatory syndrome in children, intensive care unit

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INTRODUCTION

In the spring of 2020, a multisystem inflammatory syndrome in children (MIS-C) emerged in countries mostly hit by COVID-19 (1–4). Strong viral and epidemiological evidence suggested that SARS-CoV-2 was the trigger of the syndrome. However, the observation of a time lag of 2–6 weeks between the peak of SARS-CoV-2 infection and the onset of MIS-C indicated that the virus acted as a trigger of a post-infectious inflammatory process. (5).

All patients with MIS-C present with fever, and a sizeable proportion of them display some of the typical manifestations of Kawasaki disease (KD), especially rash, cheilitis, and bilateral non-secretive conjunctival injection. However, most cases develop symptoms that are uncommonly seen in KD, such as gastrointestinal complaints (abdominal pain, vomiting and diarrhea), myocarditis associated with cardiogenic-vasoplegic shock, and neurological abnormalities (meningitis-like symptoms or encephalitis) (6). Impaired cardiac function and shock necessitate admission to the Intensive Care Unit (ICU) for 60–80% of patients, and half of them require inotropes and/or fluid resuscitation (5, 7). The fatality rate is approximately 2% (8, 9).

Most patients with MIS-C have been treated with intravenous immunoglobulin (IVIG), alone or in combination with glucocorticoids (10–12). In severe or refractory cases, particularly when myocarditis was present, biologic response modifiers, particularly tumor necrosis factor or interleukin-1 inhibitors, were given (13, 14). However, despite the publication of various therapeutic recommendations (15–17) the treatment of MIS-C remains empirical and little information is available about the effectiveness of proposed strategies.

We describe herein our experience with a therapeutic protocol based on an early aggressive multi-step therapy, which enabled quick control of the inflammatory process and avoided admission to the ICU of all patients with MIS-C seen at our hospital.

METHODS

All consecutive patients seen at the Gaslini Institute of Genoa, Italy from 1st April 2020 to 1st June 2021 who met the case definition of MIS-C (18, 19) were included in the study.

This study was reviewed and approved by the Regione Liguria Ethical Board (IRB# 370/2020). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

All children were treated according to an internal multistep treatment protocol originally devised for KD by expert pediatric rheumatologists (AC, RC, MG, AR) and infectious disease specialists (EC).

Patients were initially assigned to four severity classes developed in our Institute on the basis of their clinical features on admission, the severity of cardiac involvement expressed by echocardiographic findings or cardiac enzymes levels and/or the occurrence of blood tests abnormalities suggestive for macrophage activation syndrome (**Table 1**). The severity classes' descriptors were progressively adapted to the evolving scenario and the growing body of evidence on the new clinical entity.

The steps of the protocol, which is shown in **Figure 1**, were applied as follows. (1) MIS-C patients presenting the American Heart Association (AHA) criteria for complete or incomplete KD (20) with normal left ventricular (LV) ejection fraction (EF>55%) and absence of major abdominal complaints or signs of impending macrophage activation syndrome (MAS) (class I) were given IVIG alone at the standard dosage of 2 gr/kg, as recommended for KD. (2) MIS-C patients with one or more ipokinetic or diskinetic LV segments at the initial echocardiographic evaluation but in the context of a preserved LV global systolic function (EF>50%), and in the absence of major abdominal complaints or signs of impending macrophage activation syndrome (MAS) (class II) were given IVIG plus glucocorticoids upfront by administering intravenous methylprednisolone at 2–3 mg/kg/day in two to four daily doses. (3) MIS-C patients with signs of LV global systolic dysfunction (i.e. EF between 50 and 35%, and/or increased cardiac troponin T level or N-terminal B-type natriuretic peptide level > 1,000/pg/ml) (21), significant abdominal involvement, or impending MAS (class III) were given IVIG plus glucocorticoids as pulses of 10–30 mg/kg/day (maximum 1 gr/day) for 1–5 days (4) MIS-C patients with severe LV global systolic dysfunction (LV EF lower than 35%) and/or arrhythmias (i.e advanced atrioventricular block), hypotension or overt MAS (class IV) were simultaneously started with anakinra at 5–10 mg/kg/day, administered subcutaneously or, in the sickest patients, intravenously.

In patients who did not improve within 24–48 h with the initially selected therapeutic intervention, treatment was escalated throughout the steps outlined above.

For patients with severely depressed cardiac function, we closely monitored for fluid overload, considering adjunctive use of diuretics with IVIG administration possibly given in divided doses (1 g/kg daily over 2 days).

According to our Institute policy, class I patients were managed in the general ward or in the Rheumatology Unit. Patients assigned to class II-IV or patients in class I with worsening of clinical conditions, were admitted to high-dependency unit until stabilization and then transferred to cardiology unit or rheumatology clinics depending on the characteristics of the cardiac involvement (**Figure 2**).

RESULTS

From 1st April 2020 to 1st June 2021 23 patients (11 females, 48, 2%) with MIS-C were treated according to the multistep therapeutic protocol illustrated above. The

Abbreviations: MIS-C, multisystem inflammatory syndrome in children; KD, Kawasaki disease; ICU, intensive care unit; IVIG, intravenous immunoglobulin; LV, left ventricular; EF, ejection fraction; MAS, macrophage activation syndrome.

TABLE 1 | The "Gaslini severity assessment tool" for MIS-C.

Severity classes	MIS-C case definition	Complete-incomplete KD criteria	Severe abdominal involvement*	Signs of cardiac dysfunction at echocardiography	Increased cardiac enzymes	Laboratory features of MAS
Class I	Yes	Yes	No	No	No	No
Class II	Yes	Yes/No	No	Cardiac dyskinesia with normal ejection fraction	No	No
Class III	Yes	Yes/No	Yes	Cardiac dysfunction with ejection fraction < 50% and > 35%	Increased troponin and/or NT-pro BNP > 1,000 pg/ml	Increased ferritin (<1,000 ng/ml)
Class IV	Yes	Yes/No	Yes/No	Cardiac dysfunction with ejection fraction < 35% and/or hypotension/shock		Increased ferritin (> 1,000 ng/ml and/or cytopenia)

*MIS-C, multisystem inflammatory syndrome in children; KD, Kawasaki disease; MAS, macrophage activation syndrome; NT- pro BNP, N-terminal B-type natriuretic peptide level. *Severe abdominal involvement was defined based on the presence of persisting severe abdominal pain, persisting vomiting and/or diarrhea, acute abdomen signs, ascites, pseudo-appendicitis.*

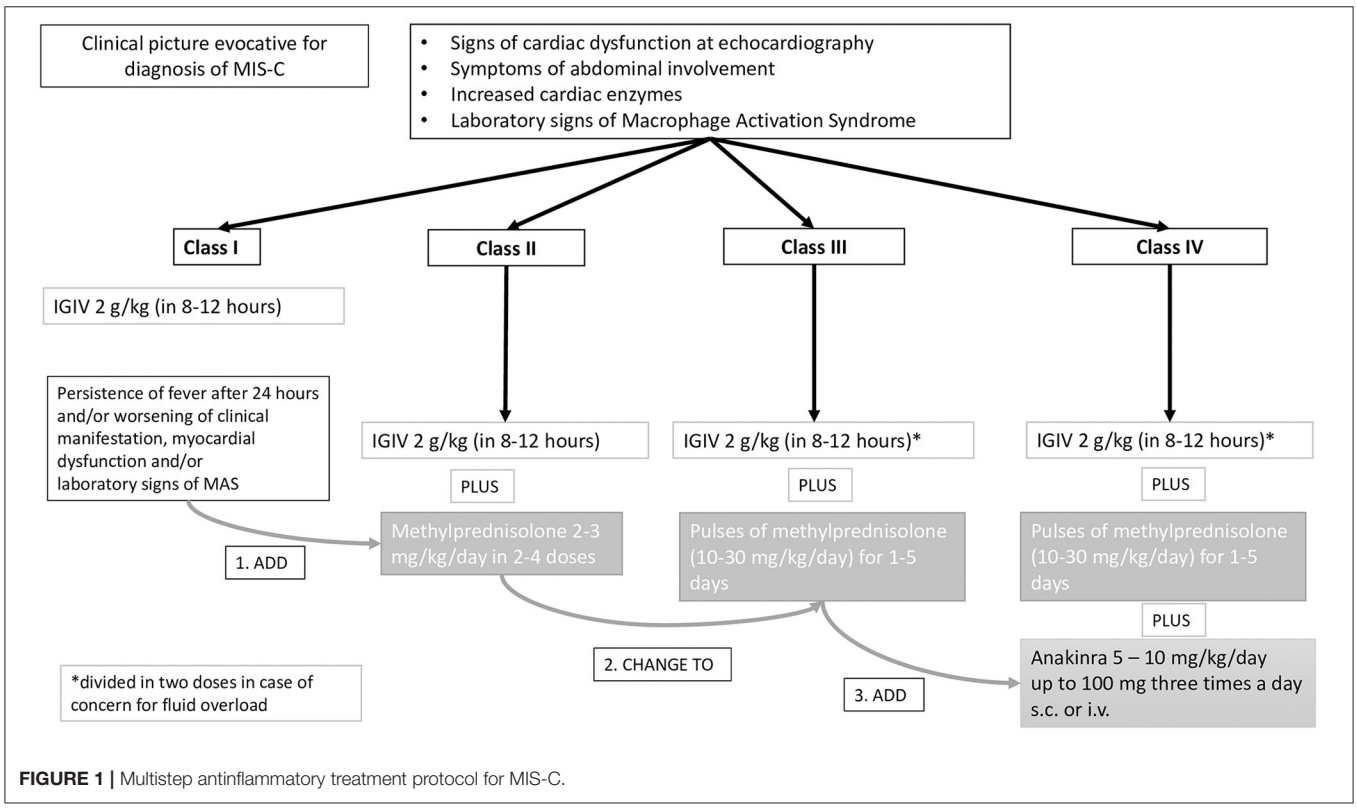

FIGURE 1 | Multistep antinflammatory treatment protocol for MIS-C.

median age at fever onset was 5, 8 (range 2, 4–12, 3) years and the median time between the onset of fever and hospital admission was three (range 2–4) days. No patients had comorbidities.

In patients with confirmed SARS-CoV-2 infection (i.e. patients who had nasopharyngeal swab positive for SARS-CoV-2), the median time between the infection and MIS-C onset was 4 weeks.

The main clinical and laboratory features of the 23 patients at the time of admission are reported in **Table 2**. Five and 7 patients met the AHA criteria for complete or incomplete KD, respectively.

With the application of our severity assessment tool, six patients were assigned to class I, 9 to class II, 5 to class 3, and 3 to class IV.

According to this, in the first 48 h after admission, six patients were given IVIG alone, 14 IVIG plus intravenous methylprednisolone (2–3 mg/kg/day in 9 patients and pulses of 30 mg/kg/day in five patients) and three IVIG, methylprednisolone and anakinra.

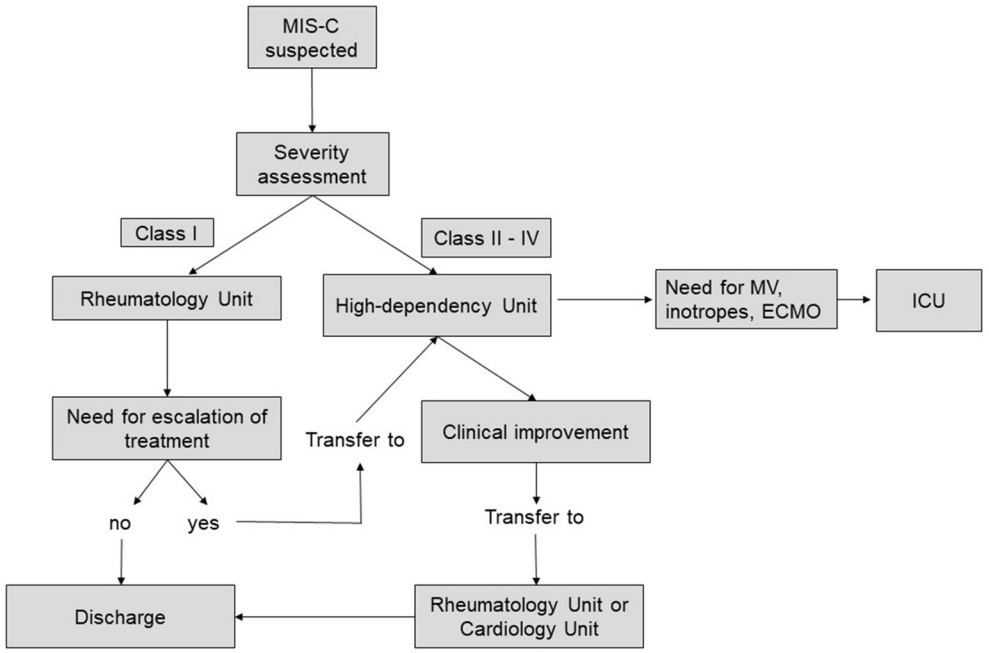

FIGURE 2 | Flow-chart showing location of care for patients with MIS-C.

In 18 (78%) patients, the treatment allocated by the severity score was able to prevent disease progression and to achieve a rapid control of fever, inflammatory markers (**Figure 3**) and cardiac involvement.

In 5 (22%) patients a subsequent therapeutic escalation was required, due to persistence of fever or worsening of cardiac function. Two patients received methylprednisolone (3 mg/kg/day) after IVIG monotherapy and 3 patients required second-line treatment with anakinra (2–3 mg/kg twice a day IV) for lack of improvement after 3 to 6 days.

In these five patients a full normalization of inflammation markers and cardiac function was rapidly obtained.

Altogether, 23 patients were treated with IVIG, 19 with glucocorticoids, and 6 with anakinra. Patients in severity class I received antiplatelet prophylaxis with acetylsalicylic acid; all remaining patients received low molecular weight heparin prophylaxis.

No patient required admission to the ICU or invasive mechanical ventilation, extracorporeal circulatory and respiratory support and no patients needed administration of inotropic drugs.

The median time of normalization of C reactive protein levels was 9.5 (range 6–16) days (**Figure 3**).

Five patients were found to have prolonged QTc interval on EKG during hospitalization. Two of them were temporarily treated with beta blockers therapy. Arrhythmia resolved in all patients.

Eleven patients (48%) had coronary involvement: six patients (26%) were found with coronary artery dilations, four patients (17%) with small coronary artery aneurysm and one patient (4%) with medium coronary artery aneurysm.

All cardiac manifestations normalized prior to hospital discharge without developing any sequelae in all but one patient who showed multiple coronary artery aneurysms at last echocardiogram.

All patients were discharged after a median of 20 (range 14, 5–26, 5) days after admission.

The safety of the treatment was good, with only three patients experiencing transient hypertension related to glucocorticoid treatment. No patient had infections related to the immunosuppressive treatment.

DISCUSSION

We have described our experience with the first 23 patients with MIS-C treated in our Hospital with an early multi-step anti-inflammatory treatment protocol, based on therapeutic interventions tailored based on the severity of the initial clinical manifestations, and rapidly escalated in case of insufficient improvement within the first 24–48 h. Moreover, an integrated multi-specialist organization centered on the presence of a pediatric high-dependency unit closely coordinated with pediatric rheumatologists and cardiologists allowed a similar logistic multi-step approach according to the different disease severity.

With the application of this therapeutic strategy, none of our patients required ICU admission and the outcome was uneventful in all but one patient, a 1-year-old girl assigned to class I on admission, who developed multiple coronary artery aneurysms 2 weeks after receiving treatment with IGIV. The treatment was overall well tolerated, with the exception of the transient occurrence of glucocorticoid-related hypertension in

TABLE 2 | Main clinical features and laboratory studies at presentation of children treated for MIS-C.

Patient characteristics	
Median age (range), yr	5, 8 (2, 4–12, 3)
Male, *n* (%)	12 (52, 2%)
Race/Ethnicity	
Asian	1 (4%)
Black/African American	1 (4%)
White	21 (91%)
Hispanic	6 (26%)
Non-Hispanic	15 (65%)
SARS-CoV-2 status	
Nasopharyngeal PCR positive	3 (13%)
Positive serology	19 (83%)
Confirmed COVID-19 exposure	2 (9%)
Presenting symptoms	*n (%)*
Fever	23 (100%)
Rash	13 (57 %)
Conjunctivitis	18 (78 %)
Cheilitis	14 (61 %)
Cervical lymphadenopathy	13 (57 %)
Gastrointestinal (abdominal pain, vomiting, and/or diarrhea)	19 (83 %)
Respiratory (dyspnea, cough)	8 (35 %)
Neurological	5 (22 %)
Myalgia/myositis	11 (48%)
Heart involvement	20 (87%)
Hypotension	3 (13 %)
Pericarditis	11 (48 %)
Myocarditis	11 (48 %)
Myocardial dysfunction	9 (39 %)
Chest pain	4 (17 %)
Blood tests	*median [IQR]*
WBC count (×103/μL)	9, 89 [8, 56, 12, 16]
Neutrophil (×103/μL)	7, 14 [5, 27–9, 52]
Lymphocyte (×103/μL)	1, 43 [0, 91–2, 74]
Platelets (×103/μL)	183, 5 [152–324, 25]
C-reactive protein (mg/dL)	15, 1 [6–18]
Erythrocyte sedimentation rate (mm/1 h)	60 [52.5–67]
Ferritin (*ng*/mL)	382 [211, 5–522]
D-dimer	2, 9 [2, 4–4.7]
NT- pro–BNP (pg/mL)	1,546 [421, 9–4,217]
Troponin T (*ng*/L)	<0, 1 [<0, 1–<0, 1]
Albumin (g/dL)	2, 91 [2,15]
Aspartate transaminase (U/L)	37 [25–45]
Alanine transaminase (U/L)	25 [12–31]

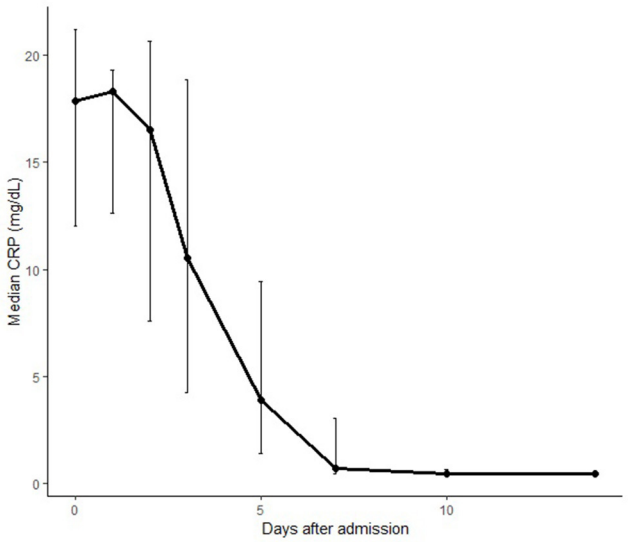

FIGURE 3 | Median C reactive protein levels of patients treated for MIS-C during the disease course.

three patients. Although our findings are limited by the small size of our series, they compare favorably with most literature data, which report a significant frequency of ICU admission, need for vasoactive medications and mechanical ventilation, ranging from 60 to 80%, 12 to 47% and 5 to 49% respectively (5, 6, 8, 9, 21, 22).

Of note, in most of our patients, hospital admission and initiation of anti-inflammatory treatment occurred soon after the beginning of symptoms.

Although the lack of fine details about timing of treatment in published case series does not allow us to make comparisons, this observation supports that early identification and prompt initiation of anti-inflammatory therapy may be key factors to obtain a favorable course of the disease and to prevent use of inotropic drugs, mechanical ventilation or ICU admission.

Most of the largest studies available in the literature are multi-centric. It is therefore likely that, beside the different therapeutic strategies, also the different functional organization of each center could have dramatically influenced the results on disease progression and final outcome. In our hospital patients with signs of cardiac involvement or need for close clinical monitoring, were admitted to high-dependency unit until clinical stability was achieved and then transferred to rheumatology or cardiology unit depending on the characteristics of cardiac involvement (**Figure 2**).

This likely contributed to avoid ICU admissions resulting in significant cost and resource savings and less disruption for patients and their families.

Moreover, since the initial reports of the inflammatory complications related to SARS-COV2 infection, in our hospital, the immuno-rheumatologists raised an internal alert for severe COVID-19 pneumonia (23–25) and, subsequently, for MIS-C (16). Multi-specialist

educational meetings with the aim of raising awareness of the disease among emergency and family pediatricians, likely leading to earlier recognition of our cases, were also organized.

On the basis of our experience, considering the wide variability of clinical signs and symptoms at presentation of MIS-C, and the need to induce rapid immunomodulation, we propose a clinical severity stratification tool that allows the clinician to identify the most appropriate anti-inflammatory therapeutic regimen.

So far, the most common therapeutic approach reported in large cohorts of patients with MIS-C, consists in IVIG and systemic glucocorticoids (15).

However, previous studies in adult patients with severe form of COVID-19 pneumonia and evidence of hyperinflammation, have suggested the potential efficacy and safety of the early use of high doses of intravenous anakinra (24, 25), and subsequently confirmed by an extensive metanalysis data (26) and a recent randomized placebo-control study (27).

Moreover, anakinra is becoming increasingly more popular also for the management of KD after failure of IVIG and its efficacy in KD is being scrutinized in a phase IIa trial (28).

More recently, case reports and case series of patients with MIS-C reported the efficacy of treatment with anakinra, highlighting its role particularly in those children who have insufficient response to IVIG and systemic glucocorticoids (29–31).

At the time of admission, patients who meet the case definition criteria for MIS-C are assigned to four severity classes, on the basis of their clinical features, the severity of cardiac involvement expressed by echocardiographic findings and cardiac enzymes levels and the occurrence of blood tests abnormalities suggestive for macrophage activation syndrome, and treated accordingly.

The therapeutic options ranged from IV immunoglobulin alone for patients in class 1 with no sign of cardiac dysfunction to a combination of IVIG plus pulses of methylprednisolone plus anakinra for those in class four with severe cardiac function impairment or signs of macrophage activation syndrome.

We suggest that the treatment allocated by this severity assessment tool may be able to prevent disease progression and to achieve a rapid control of fever, inflammatory markers and cardiac impairment.

Patients who do not respond to initial treatment within the first 48 h enter in the following therapeutic step and receive a more aggressive anti-inflammatory treatment with the aim of rapidly limiting the course of the illness.

Other authors have proposed similar therapeutic algorithms for the management of MIS-C. Schlapbach et al. (32) suggested a disease stratification based on the presence of shock and supported the use of anakinra in severe patients who do not respond to IVIG and methylprednisolone pulses.

Similarly Handerson et al. (15) recommended IVIG and adjunctive low-to moderate dose of glucocorticoids in patients with shock or presenting with concerning features supporting the use of anakinra only for patients with refractory disease.

Differently, we suggest that early identification of more severe patients (i.e. severity class IV of our assessment tool) and initiation of anakinra as first-line therapy may be decisive in turning off the hyperinflammation which underlies the disease and preventing the need for escalation of care.

In our experience only one patient showed residual cardiac lesion at last ultrasound evaluation before hospital discharge, highlighting the potential for medium and long-term complications. Therefore, it is essential to guarantee an adequate follow-up to these patients scheduling both Echocardiograms and EKG at regular intervals for evaluation of ventricular function and coronary artery dimensions after initial diagnosis. Moreover, in patients with a history of ventricular dysfunction, cardiac magnetic resonance imaging (MRI) may be considered 2–6 months after initial diagnosis for evaluation of ventricular function, edema, diffuse fibrosis, and scar (33).

Our findings should be interpreted in the light of some limitations, which include the retrospective nature of the analysis, the relatively low sample size, the absence of a control group and the short-term outcome.

In conclusion, our experience suggests that early aggressive treatment of MIS-C, with therapeutic interventions modulated based on the severity of clinical manifestations and rapidly escalated in case of inadequate therapeutic response may help to prevent the progression of the inflammatory process and to avoid the need of escalation of care and admission to the ICU. The optimal therapeutic approach to MIS-C should be established through multinational consensus initiatives and, whenever possible, randomized controlled trials.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Regione Liguria Ethical Board. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

GB, RC, and AC conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. DP, GT, and CC collected data, carried out the initial analyses, and reviewed and revised the manuscript. EC, MG, AM, and AR conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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CASE REPORT
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Case Report: COVID-19-Associated ROHHAD-Like Syndrome

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It is known that the SARS-CoV-2 virus may cause neurologic damage. Rapid-onset obesity, hypoventilation, hypothalamus dysfunction, and autonomic dysregulation (ROHHAD) syndrome is a disease of unknown etiology with a progressive course and unclear outcomes. The etiology of ROHHAD syndrome includes genetic, epigenetic, paraneoplastic, and immune-mediated theories, but to our knowledge, viral-associated cases of the disease have not been described yet. Here we present the case of a 4-year-old girl who developed a ROHHAD syndrome-like phenotype after a COVID-19 infection and the results of 5 months of therapy. She had COVID-19 pneumonia, followed by electrolyte disturbances (hypernatremia and hyperchloremia), hypocorticism and hypothyroidism, central hypoventilation—requiring prolonged assisted lung ventilation—bulimia, and progressive obesity with hypertriglyceridemia, dyslipidemia, hyperuricemia, and hyperinsulinemia. The repeated MRI of the brain and hypothalamic–pituitary region with contrast enhancement showed mild post-hypoxic changes. Prader–Willi/Angelman syndrome as well as PHOX2B-associated variants was ruled out. Treatment with non-steroidal anti-inflammatory drugs and monthly courses of intravenous immunoglobulin led to a dramatic improvement. Herein the first description of ROHHAD-like syndrome is timely associated with a previous COVID-19 infection with possible primarily viral or immune-mediated hypothalamic involvement.

Keywords: ROHHAD-syndrome, obesity, central hypoventilation, hypothalamus dysfunction, hypocorticism, autonomic dysregulation, COVID-19, SARS-CoV-2

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INTRODUCTION

COVID-19 viral infection may trigger immune dysregulation affecting different targets. It is known that COVID-19 may cause severe neurologic damage, ranging from anosmia, headache, and memory disturbances to several cases of encephalitis (1–3).

Rapid-onset obesity, hypoventilation, hypothalamus dysfunction, and autonomic dysregulation (ROHHAD) syndrome is a rare and complicated condition presenting in previously healthy children. It was first described in 1965 (4, 5). However, its etiology and pathogenesis remain unknown. Usually, it has a progressive course and unclear outcomes. There are several hypotheses about the etiology of this syndrome, including genetic (6–11), epigenetic (7, 12–14), and paraneoplastic theories (4, 15), but autoimmune etiology is becoming more widely discussed lately (6–9, 11–13, 16–24). Viral-associated cases of the ROHHAD syndrome have not been described yet.

Herein we describe the case of a 4-year-old girl who presented with ROHHAD syndrome-like phenotype timely associated with a previous COVID-19 infection. To our knowledge, this is the first description of ROHHAD-like phenotype timely associated with COVID-19 infection.

CASE DESCRIPTION

A 4-year-old girl was transferred to our hospital with a suspicion of ROHHAD syndrome. She was tall for her age since birth (53 cm, +2.1 SD) and obese since 2 years of age (BMI, 21.0 kg/m^2, +3.4 SD) but otherwise doing well until 3.5 years (**Figures 1A–C**).

At 3.5 years, 3 weeks after her family contracted COVID-19, the girl had pneumonia (day 0). Nasal swab PCR for SARS-CoV-2 was not done at this timepoint. She recovered completely after a course of josamycin at 500 mg twice a day for 7 days. After 3 weeks, another episode of respiratory infection happened (day 18) (at the same time, half of the kindergarten group had respiratory symptoms, and a teacher had confirmed severe COVID-19 pneumonia). The patient had positive IgM against SARS-CoV-2, but the nasal swab PCR for SARS-CoV-2 was negative. 4 days of intravenous dexamethasone, accompanied with antibiotics, was given (**Figures 1D,E**). During the following 6 months (days 42, 64, and 137), she had three more episodes of respiratory distress (CT described the ground-glass opacities as affecting 70% of the lungs), requiring assisted lung ventilation through a tracheostomy tube, with febrile fever of up to 39.2°C and with good response to corticosteroids and antibiotics. After a while, the patient developed strabismus (days 64–80). The girl had constant hyperthermia within 37.6°C without laboratory signs of systemic inflammation.

The patient had features of metabolic syndrome: increased insulin level −207.4 pmol/L (n.v. = 17.8–173), with normal levels of blood glucose and HbA1c, dyslipidemia—triglycerides at 6.3 mmol/L (n.v. = 0.0–1.69), VLDL at 2.89 mmol/L (n.v. = 0.1–1.0), HDL at 0.63 mmol/L (n.v. = 1.04–1.55), and hyperuricemia at 585 mmol/L (n.v. = 150–350) associated with obesity. She had elevated IGF1 at 473–297 mcg/L (n.v. = 49–283). By the provided documents, the girl used to have secondary hypocorticism and hypothyroidism, which resolved over time (days 80–132). Her endocrine function was not evaluated before the COVID-19 infection since she was considered healthy. Proteinuria was intermittent since day 39, and electrolyte disorders persisted since day 46 [hypernatremia 155.8–162 mmol/L (n.v. 130–145 mmol/l), hyperchloremia 116.9–129.6 mmol/L (n.v. 98–107 mmol/l)]. At around the same time, central hypoventilation and bulimia started (days 45–63), explaining the recurrent chest infections.

The antinuclear antibodies, anti-MPO, and anti-PR3 antibodies were negative; immunoglobulins A, M, and G were normal, while the IL6 (10.49 pg/ml, n.v. <7) and C3 complement components (2.74 g/l, n.v. 0.83–1.93) were slightly elevated.

SARS-CoV-2 IgM remained positive over time, decreasing to borderline after 1 year; the erythrocyte sedimentation rate (ESR) and D-dimer remained elevated: ESR, 30→ 70→ 36 mm/h (n.v. = 2–15) and D-dimer, 1.22 → 0.72→ 3.05 mcg/ml (n.v. = 0.09–0.53).

At first admission to our hospital (days 229–268), the girl had hypercapnia ($tcCO_2$, 40–60 mmHg); SpO_2 was 97–100% while she was awake and 92–96% during sleep on assisted lung ventilation, with episodic desaturations to 72–86%. Unfortunately, polysomnography was not available until day 412, when central hypoventilation was proven. On admission, 7.5 months after the disease onset, she continued being obese (BMI, 33.3 kg/m^2) and required assisted lung ventilation through a tracheostomy tube while asleep. She could sit without support, hold hands above her head for more than 10 s, roll prone to supine and supine to prone, and stand for a short time with support. The results of the Denver Development Screening test were as follows: MQ, 0.32 (n.v. >0.75) and DQ = 0.7 (n.v. ≤0.7). Her behavior issues include short periods of "aggression" directed at other people. Cranial innervation was intact despite periodically alternating divergent strabismus (as reported by the mother, the child had transient ptosis at the onset of the disease). The muscle tone was diffusely reduced, without asymmetry, the muscle strength [according to the Medical Research Council (MRC) Scale] was reduced to three points, and the tendon reflexes were alive. There were no meningeal and cerebral symptoms; the coordinating tests were optimal.

A repeat MRI of the brain and hypothalamic–pituitary region with contrast showed mild post-hypoxic changes. In contrast, COVID-associated acute disseminated encephalomyelitis, corpus callosum lesion, brain tumor, post-hemorrhage lesion, and ischemic stroke were ruled out as well as known immune-mediated CNS disorders and primary disease CNS–angiitis. The neurophysiological study did not suggest acute inflammatory demyelinating polyneuropathy and inflammatory or congenital myopathy. The electroencephalography result during wakefulness showed age-appropriate bioelectrical activity.

The chest CT showed interstitial changes and atelectasis in both lungs, which are attributed to hypoventilation.

The echocardiography and electrocardiography (ECG) results were normal, with normal ejection fraction and no signs of pulmonary hypertension, systolic or diastolic dysfunction, or other cardiac issues. During 24-h ECG and arterial pressure monitoring, reduction of heart rate variability and diastolic arterial hypotension were detected. Diastolic arterial hypotension, reduction of heart rate variability, constant hyperthermia within 37.6°C, strabismus, and central hypoventilation were considered autonomic dysregulation.

The karyotyping showed a normal female karyotype (46, XX). The Sanger sequencing and multiplex ligation-dependent probe amplification (MLPA) technology using SALSA MLPA Probemix P318 kit (MRC Holland, The Netherlands) did not find mutations in the *PHOX2B* gene. As a result, polyalanine repeat expansion mutations, non-polyalanine repeat mutations, and whole-gene or exon-specific deletions were excluded. The results of FISH with locus-specific DNA probe Prader-Willi/Angelman SNRPN (15q11)/PML (15q24) was also normal. Whole-exome

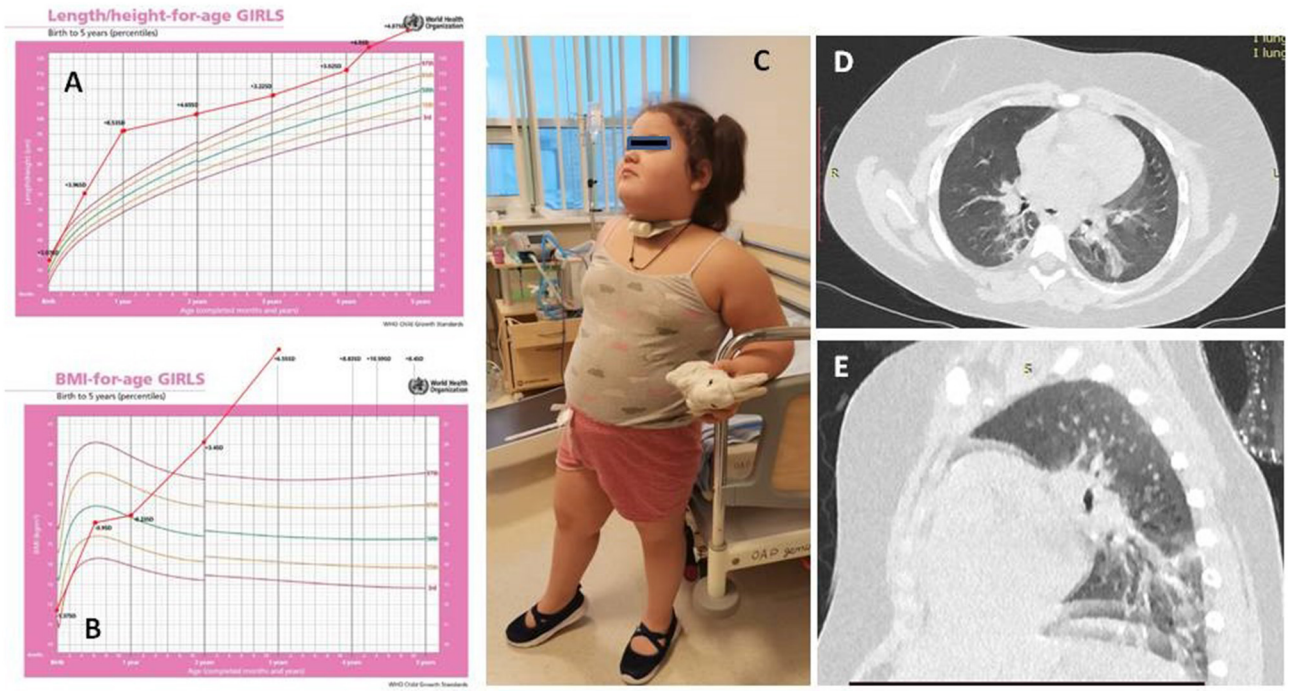

FIGURE 1 | The dynamics of height **(A)** and body mass index **(B)** of the patient. Patient's picture **(C)**. Chest CT **(D,E)**.

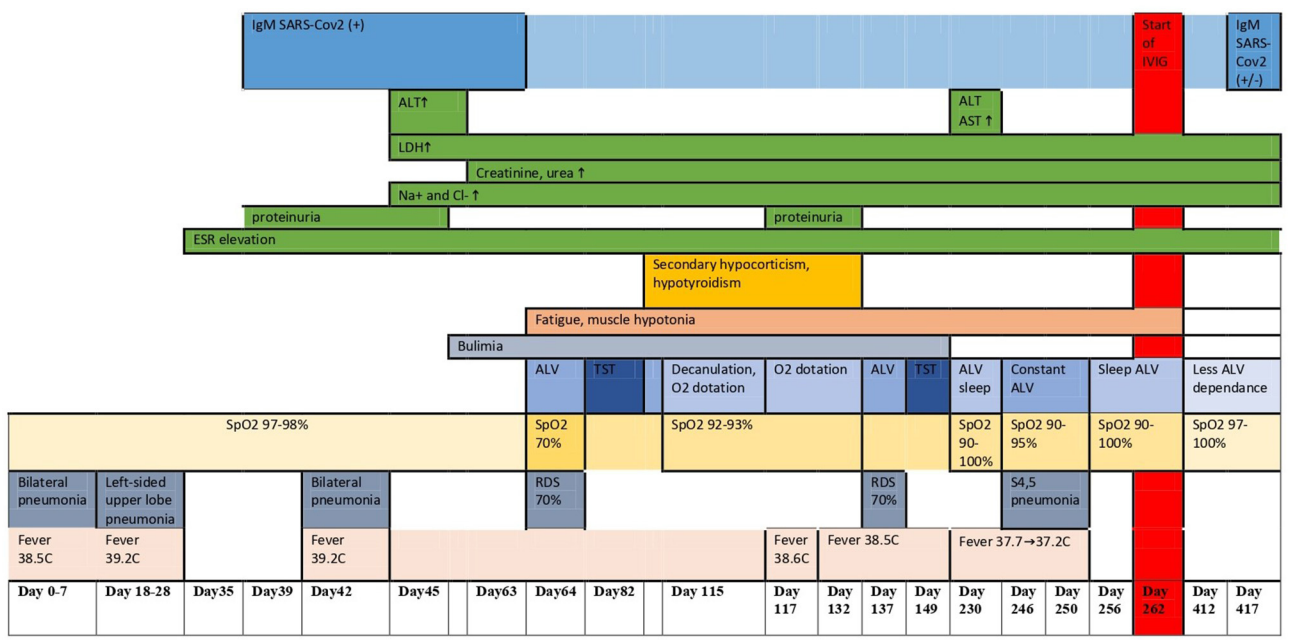

FIGURE 2 | The whole disease course of the patient.

sequencing is in progress. The clinical dynamics, laboratory findings, and imaging allowed us to define the condition as a ROHHAD-like syndrome. The disease course is depicted in **Figure 2** and **Table 1**.

Family History

The Caucasian girl of Russian nationality is from non-consanguineous marriage. Both parents are tall and obese (mother's height, 176 cm; weight, 141 kg; BMI, 45.5 kg/m^2;

TABLE 1 | The laboratory feature dynamics during the disease course.

	Before admission D0-D229	First admission D229-D250	Deterioration D246-D250	Between admissions D313	Second admission D402-D418
Uric acid, umol/L (n.v. 150–350)		393 (↑)			585 (↑)
GGTP, IU/l (n.v. 9–36)		56 (↑)			19
CK, IU/l (n.v. 29–168)		34	37		62
LDH, IU/l (n.v. 125–220)	453 (↑)	360 (↑)	525 (↑)		321 (↑)
AST, IU/l (n.v. 10–31)	33	41	26		27
ALT, IU/l (n.v. 10–31)	57	64–92	42		32.8
Creatinine, umol/l (n.v. 30.93–52.21)	50 (↑)	42.6	47.8		56.0
Urea, mmol/l (n.v. 2.5–6.0)	9.5 (↑)	8.6 (↑)	6.8 (↑)		7.2 (↑)
Glucose, mmol/l (n.v. 3.89–5.83)		4.5	4.6		4.6
Insuline, pmol/l (n.v. 17.8–173)	105.5			200.7 (↑)	207.4 (↑)
Potassium, mmol/l (n.v. 3.5–5.5)	4.6	3.8	4.0	4.1	3.8
Sodium, mmol/l (n.v. 130–145)	161	155.8	154.3	165	156.8
Chloride, mmol/l (n.v. 98–107)	125	122.1	125.3	132	120.2
TSH, mIU/l (n.v. 0.35–4.94)	0.498 (↓)	2.269		4.61	2.627
fT4, pmol/l (n.v. 9–19)	11.1			10.67	11
ACTG, pg/ml (n.v. 7.2–63.3)		21.71		45	35.27
Cortisole, nmol/l (n.v. 101.2–535.7)	234	314		404	172.5
LH, mIU/ml	<0.09	0.1		<0.09	0.1
FSH, mIU/ml	0.17	0.3			0.8
Prolactine, ng/ml (n.v. 4.79–23.3)	20.8	12.18		16.13	11.16
IGF1, ug/l (n.v. 49–283)		473 (↑)			297 (↑)
ESR, mm/h (n.v. 2–15)	24–8	30	77	27	36
C3 complement, g/l (n.v. 0.83–1.93)		2.74 (↑)			2.43 (↑)
CRP, mg/l (n.v. 0.0–10.0)	2.1	4.69	137.83	10	4.65
APTT, s (n.v. 28.6–38.2)		39.7 (↑)	42.1 (↑)		36.7
D-dimer, ug/ml FEU (n.v. 0.09–0.53)			1.22 (↑)		3.05 (↑)

ACTG, Adrenocorticotropic hormone; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST- aspartate aminotransferase; CK, creatine kinase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FSH, follicle-stimulating hormone; fT4, free thyroxine; D, days; GGTP, gamma-glutamyl transferase; IGF1, insulin-like growth factor 1; LDH, lactate dehydrogenase; LH- luteinizing hormone; n.v., normal value TSH, thyroid-stimulating hormone; ↑, upper than normal range; ↓, lower than normal range.

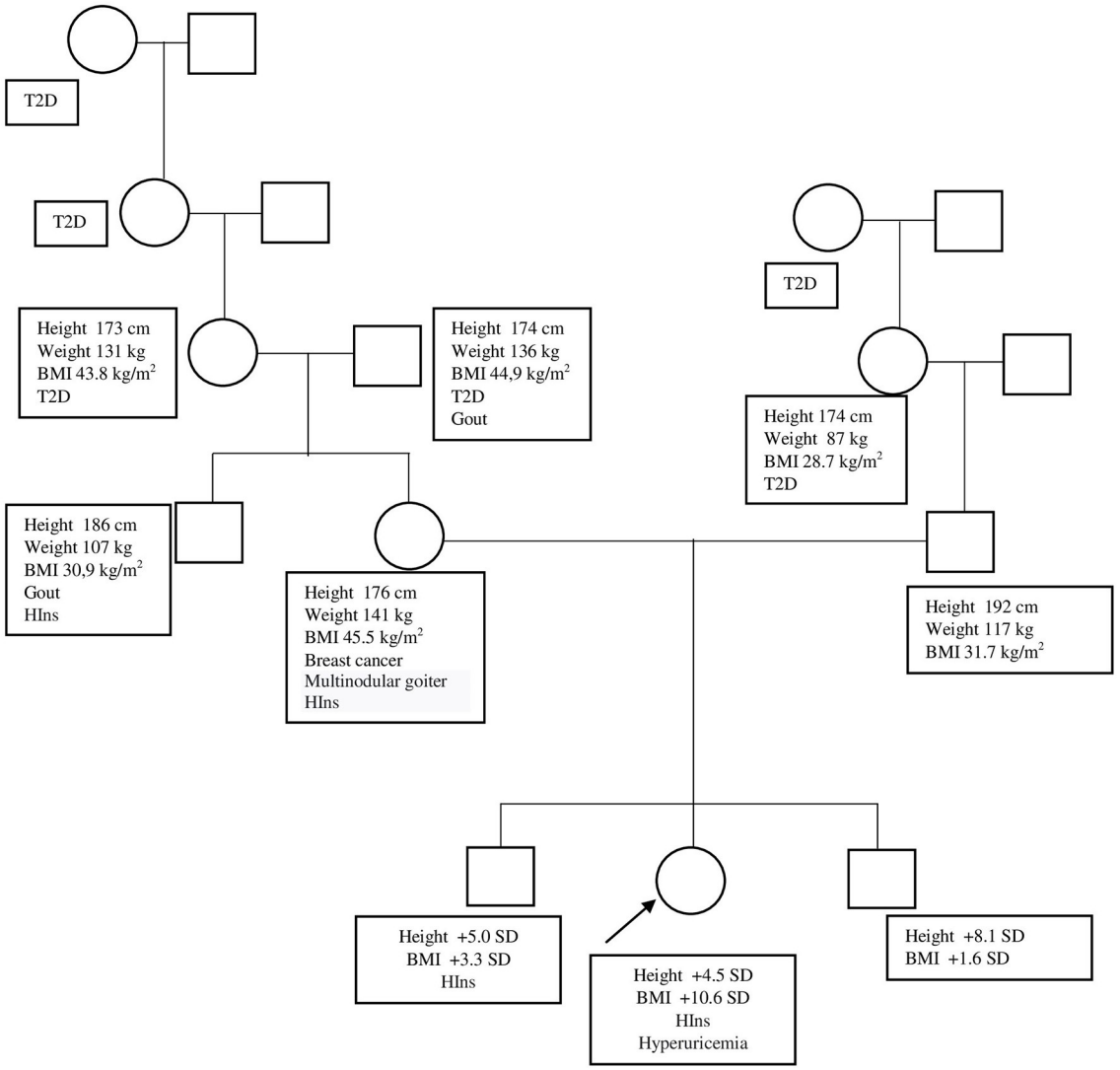

FIGURE 3 | Patient's genealogic tree. BMI, body mass index; HIns, hyperinsulinism; SD, standard deviation; T2D, type 2 diabetes.

father's height, 192 cm; weight, 117 kg; BMI, 31.7 kg/m^2). The girl's grandparents, the girl's uncle from her mother's side, and an elder brother are obese, while her younger brother, who is 1.5 years old, is tall for his age but not obese yet. Most of the relatives developed diabetes mellitus type 2 after 40–45 years of age (**Figure 3**).

Therapy, Progress, and Outcomes

The anti-inflammatory treatment was started from day 262 [ibuprofen at 200 mg three times a day (11 mg/kg/day) for 2 months and monthly intravenous immunoglobulin (IVIG) at 1 g/kg of due weight, divided into two 2-h infusions once a day during 2 days] with dramatic clinical improvement.

After 5 months of therapy, the Denver Development Screening test results were MQ = 0.62 and DQ = 0.72. She had minor muscle hypotonia, and her tendon remained normal. Muscle strength (MRC Scale) was five points in the proximal upper limbs and lower limbs and reduced to four points in the distal upper limbs. She can now walk and run without support, do yoga and pony riding, and climb a small climbing slide. Though the girl remains obese, her BMI decreased (day 229 + 10.59 SD; day 412 + 8.4 SD). The requirement for ventilation decreased (assisted lung ventilation through a tracheostomy tube only during night sleep), and central hypoventilation persists during non-rapid eye movement sleep (**Figure 4**). The inflammation laboratory signs improved as well. Her BMI slightly decreased at 33.0 (+8.4 SD). However, her ESR remained elevated (36 mm/h).

We planned to continue IVIG for another 3 months, following teleconsultation or in-hospital admission for clinical, instrumental, and laboratory evaluation and further treatment decisions (anti-inflammatory therapy discontinuation, prolongation, or escalation and assessment of ventilation needs).

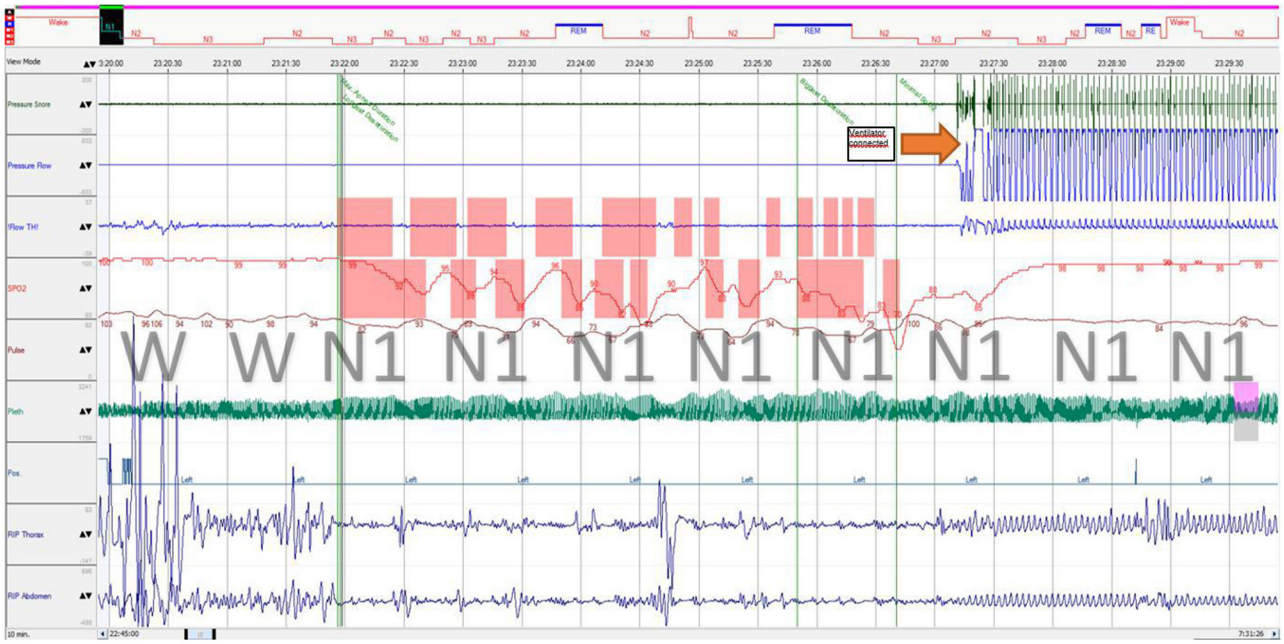

FIGURE 4 | Polysomnography fragment of sleep onset with central breathing impairment followed by assisted ventilation. Immediately after sleep onset, the patient developed breathing movement amplitude decrease (both thoracic and abdominal) with a "periodic breathing"-like pattern associated with progressive desaturation and hypercapnia, which is considered central (airflow was not obtained from the tracheostomy tube during self-breathing). REM, stage rapid eye movement; N1, stage 1 non-rapid eye movement; N2, stage 2 non-rapid eye movement; N3, stage 3 non-rapid eye movement; RIP, respiratory inductance plethysmography; Flow TH, oral thermistor flow sensor; Pleth, photoplethysmography.

DISCUSSION

The girl with a family history of obesity and redundant height, who had the same trajectory of excessive weight and height gain from birth, presented with additional ROHHAD-like symptoms temporarily related to COVID-19 infection. Though other viruses were not searched for, we consider the initial episode as a COVID-19 probable case based on epidemiological, clinical, and serological data. The patient had typical features of the ROHHAD syndrome: central hypoventilation, electrolyte and endocrine disorders, and signs of autonomic dysregulation (febrile temperature without systemic inflammation, arterial hypotension, and strabismus). Considering the girl's physical development prior to the disease family history, we speculate that obesity and tallness might have a genetic nature and do not seem to be wholly associated with respiratory and hypothalamic dysfunctions. On the other hand, a gap between obesity and other symptoms has been reported in some ROHHAD cases (5), and the SARS-CoV-2 virus might have been triggered following ROHHAD symptom presentation. Thus, the diagnosis of classical ROHHAD syndrome seems doubtful. The fluctuating course of the disease with improvement on non-steroidal anti-inflammatory drugs and corticosteroid therapy maintenance of humoral activity (increased ESR and C3) allows assuming the permanent course of the inflammatory process with immune-mediated damage of the hypothalamic–pituitary region.

The amount of data on nervous system involvement in COVID-19 survivors is increasing. Neurologic symptoms can be divided into five major groups: (i) encephalopathies with delirium/psychosis and cognitive impairment; (ii) inflammatory CNS syndromes including encephalitis, acute disseminated encephalomyelitis, and isolated myelitis; (iii) ischemic stroke due to a pro-thrombotic state; (iv) peripheral neurological disorders, including Guillain–Barré syndrome; and (v) other uncategorized syndromes, including autonomic dysfunction with fever, dyspnea, fatigue, and syncope, like in our case (1–3, 25–28). Some of the neurologic symptoms manifested immediately after or even before the lung disease, while in other cases, neurologic symptoms were developed about a month after the disease onset or even later (29). Interestingly, only some of the patients with symptoms of encephalitis had MRI changes and markers of inflammation in the cerebrospinal fluid, which made the diagnosis of COVID-19-associated CNS involvement difficult (1, 29–33). As with other neurotropic viruses, the fundamental question for SARS-CoV-2 infection concerns the relative contribution of viral infection *vs.* host response to the subsequent damage (26).

We could not find data of any single case of detection of SARS-CoV-2 PCR from cerebrospinal fluid (CSF) samples in pediatric patients. Concerns on the presence of SARS-CoV-2 in CSF include the absence of validated tests and appropriate timing of lumbar puncture (33).

In the analysis of CSF of adult patients with SARS-CoV-2 infection and neurological manifestations, SARS-CoV-2 RNA in CSF was detected in 2 of 58 cases (34).

The delayed time of presentation and the presence of autoantibodies let us speculate that, at least, in some cases the virus does not affect CNS itself but promotes a secondary autoinflammatory process, similar to Guillain–Barré syndrome, after COVID-19 infection (30, 35, 36).Since April 2020, a new multisystem inflammatory syndrome in children (MIS-C) was related to SARS-CoV-2 infection (37). More than 186 patients with MIS-C were described so far (38). The majority had cardiovascular system involvement and respiratory failure. Most of them had inflammatory laboratory picture (elevated ESR, C-reactive protein, D-dimer, and ferritin levels, anemia, thrombocytopenia, neutrophilia) (38). Neurological issues were described as well (33, 37). In their systematic review of neurological complications in pediatric patients with SARS-CoV-2 infection, Siracusa et al. (37) showed that most of the cases of CNS involvement in COVID-19 patients, including headache, altered mental status, seizure, muscular weakness, and meningism, happened in the course of the MIS-C. The minority of neurological issues were secondary to cerebrovascular involvement, and only sporadic cases had other reasons. Presuming the inflammatory pathogenesis of the condition, immunosuppressive treatment, including glucocorticosteroids, intravenous immunoglobulin, and anakinra, was tried with good effect (33), just as it happened in our clinical case. Nevertheless, unlike our case, only a short course of immunosuppressive treatment was enough (37).

According to MRI, the temporal lobes, cerebellum, thalami, hippocampus, and pons can be involved (1, 29, 31, 32). However, no reports of hypothalamus or hypophysis involvement have been previously published.

The SARS-CoV-2 virus, causing COVID-19, enters in pneumocytes through binding with angiotensin-converting enzyme 2 (ACE2) receptors. The ACE2 receptors are located in different tissues, including the lungs, pancreas, thyroid, testis, ovary, adrenal glands, pituitary, and hypothalamus. Theoretically, all the abovementioned tissues might be targeted by the SARS-CoV-2 virus with inflammation development and signs of organ involvement (32). SARS-CoV-2 has a lot in common with SARS-CoV, which is tropic to the hippocampus and hypothalamic region. Viral particles were found in endothelial cells and neural tissue in the autopsies of SARS-CoV patients (39). However, in SARS-CoV survivors, only central hypercorticism and central hypothyroidism have already been described (29, 32). Hypothalamic involvement might be presented with central diabetes insipidus, hypopituitarism, hyperprolactinemia, follicle-stimulating, luteinizing, adrenocorticotropic, thyroid-stimulating, and growth hormone deficiencies, and disorders of temperature regulation, sleep rhythm, emotions, and behavior (31). The clinical course of hypothalamitis perfectly corresponds to the classical ROHHAD syndrome. The direct viral involvement of the hypothalamic–pituitary region by SARS-CoV-2 could also be supposed, though it cannot be confirmed in the described case.

Though the etiology and pathogenesis of ROHHAD syndrome remain unknown, an autoimmune theory is widely discussed (6–9, 11–13, 16–24). There are three findings to support this theory: (i) presence of oligoclonal bands (8, 17, 24), B-lymphocytes (13), and specific anti-hypothalamus and anti-pituitary autoantibodies in the CSF (9); (ii) lymphocytic infiltration in the hypothalamus and midbrain (19, 23); and (iii) the association with other autoimmune disorders like celiac disease (13) and autoimmunity-predisposing HLA alleles (DQB1*0201, DQB1*0202, or DQB1*0302) (18).

However, all these findings were discovered in some, but not all, ROHHAD patients, which interfere with the heterogeneity of this syndrome. On the other hand, with COVID-19 encephalitis, MRI and CSF changes were not always present either (1, 29–32). In some COVID-19 encephalitis cases as well, some of the ROHHAD patients were treated with corticosteroids and IVIG with temporary improvement. However, the best results were obtained with high-dose cyclophosphamide treatment (4, 9, 13, 16, 17, 21, 24, 40, 41).

In our case, the timing of the autonomic dysregulation and endocrine disorders, which is approximately 4 weeks after the possible COVID-19 infection, may indicate an immune-mediated mechanism of the disease. The effectiveness of the anti-inflammatory therapy also support this theory.

The limitations of this case report can be considered as the absence of the initial polysomnography data, which does not allow us to indicate the timing of central hypoventilation onset, and the absence of the CSF analysis data (lumbar puncture was not done at the local hospital and was considered to be irrational at 7 months after symptom onset).

CONCLUSION

This case report not only expands available data on the clinical manifestations of COVID-19 in a pediatric population but can also help to understand ROHHAD syndrome's nature and impact on its treatment strategies. Some patients with ROHHAD syndrome might have a viral or immune-mediated nature, so immune-modulating therapy (especially IVIG) might be a promising option. The case may not be conclusively attributed to COVID-19 infection and, at the same time, is rather a ROHHAD-like than ROHHAD syndrome itself. The case presented seems to be a subject for further understanding and follow-up.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

All authors contributed to manuscript revision, read, and approved the submitted version.

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REVIEW
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Mechanisms of Immune Dysregulation in COVID-19 Are Different From SARS and MERS: A Perspective in Context of Kawasaki Disease and MIS-C

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Coronaviruses have led to three major outbreaks to date-Severe Acute Respiratory Syndrome (SARS; 2002), Middle East Respiratory Syndrome (MERS; 2012) and the ongoing pandemic, Coronavirus Disease (COVID-19; 2019). Coronavirus infections are usually mild in children. However, a few children with MERS had presented with a severe phenotype in the acute phase resulting in progressive pneumonic changes with increasing oxygen dependency and acute respiratory distress requiring ventilatory support. A subset of children with a history of SARS-CoV-2 infection develops a multisystem hyper-inflammatory phenotype known as Multisystem Inflammatory Syndrome in Children (MIS-C). This syndrome occurs 4-6 weeks after infection with SARS-CoV-2 and has been reported more often from areas with high community transmission. Children with MIS-C present with high fever and often have involvement of cardiovascular, gastrointestinal and hematologic systems leading to multiorgan failure. This is accompanied by elevation of pro-inflammatory cytokines such as IL-6 and IL-10. MIS-C has several similarities with Kawasaki disease (KD) considering children with both conditions present with fever, rash, conjunctival injection, mucosal symptoms and swelling of hands and feet. For reasons that are still not clear, both KD and MIS-C were not reported during the SARS-CoV and MERS-CoV outbreaks. As SARS-CoV-2 differs from SARS-CoV by 19.5% and MERS by 50% in terms of sequence identity, differences in genomic and proteomic profiles may explain the varied disease immunopathology and host responses. Left untreated, MIS-C may lead to severe abdominal pain, ventricular dysfunction and shock. Immunological investigations reveal reduced numbers of follicular B cells, increased numbers of terminally differentiated $CD4^{+}$T lymphocytes, and decreased IL-17A. There is still ambiguity about the clinical and immunologic risk factors that predispose some children to development of MIS-C while sparing others. Host-pathogen interactions in SARS, MERS and COVID-19 are

likely to play a crucial role in the clinical phenotypes that manifest. This narrative review focuses on the immunological basis for development of MIS-C syndrome in the ongoing SARS-CoV-2 pandemic. To the best of our knowledge, these aspects have not been reviewed before.

Keywords: SARS-CoV, MERS-CoV, SARS-CoV-2, COVID-19, Kawasaki disease, MIS-C, immune dysregulation

INTRODUCTION

Over the last two decades, coronaviruses have become a significant threat to humans. The previous two outbreaks caused by the β-coronaviruses genera, viz. Severe Acute Respiratory Syndrome (SARS) in 2002, and Middle East Respiratory Syndrome (MERS) in 2012, were confined to China and Middle East and East Asia, respectively. The current outbreak, viz. Coronavirus Disease (COVID-19) is caused by SARS-CoV-2, which originated in Wuhan, China and soon turned into a pandemic. It has brought into focus the significant health threat posed by these viruses. As of now, more than 264 million cases of COVID-19 have been reported encompassing virtually every known country. With over 5.2 million deaths, this pandemic has caused severe strain to the existing healthcare system, especially in developing countries (161).

In late April 2020, children in Europe, and later in North America, were reported to develop high grade fever, rash, conjunctival injection, gastrointestinal manifestations, myocarditis, features of hyperinflammation, and in some cases coronary artery aneurysms (CAAs) 4–6 weeks after SARS-CoV-2 infection. There was uncertainty whether these symptoms were related to atypical Kawasaki Disease (KD), Kawasaki disease shock syndrome (KDSS) (1) or toxic shock syndrome (TSS). This unique cluster of symptoms was designated as "Paediatric Multisystem Inflammatory Syndrome temporally associated with SARS-CoV-2 (PIMS-TS)," in the United Kingdom, or "Multisystem Inflammatory Syndrome in Children (MIS-C) associated with COVID-19" by the Centers for Disease Control and Prevention (CDC), Atlanta, United States.

In a large cohort study from the United States, the cumulative incidence of MIS-C was found to be 2.1 per 100,000 individuals younger than 21 (2, 3). The incidence varied from 0.2 to 6.3 per 100,000 across different states. A mortality rate of 1.4 percent was recorded (3). In May 2020, the World Health Organization (WHO) defined MIS-C based on pilot case reports to assist diagnosis of this disease as a post-COVID complication. Though the clinical similarities and differences of MIS-C with KD have been discussed in literature, the molecular basis of immune dysregulation in MIS-C in comparison to previous CoV related pandemics has not been discussed in detail.

Host-pathogen interactions in SARS, MERS and COVID-19 are likely to play a crucial role in the clinical phenotypes that manifests as KD or MIS-C. These characteristics were unique since sequela like MIS-C were not witnessed in earlier CoV outbreaks (SARS and MERS). We aim to review immunological mechanisms governing the display of KD like MIS-C phenotype. This review provides new insights into the complex interplay between these infective and inflammatory disorders.

TAXONOMY OF CORONAVIRUSES

Coronaviruses (CoVs) have historically been implicated in 15–30% of all common colds, but have now also been associated with other severe illnesses such as croup, exacerbations of asthma and bronchiolitis (4–6). Presently, 7 strains of coronaviruses have been found to be pathogenic for humans (7).

The coronaviruses are enveloped viruses that are highly variable in size (80–220 nm). The genetic material consists of single-stranded positive-sense RNA. CoVs belong to the order-Nidovirales, family-Coronaviridae, and subfamily-Orthocoronavirinae. These are enveloped single stranded positive-sense RNA viruses capable of infecting both vertebrates and invertebrates and are divided into four major genera i.e., α, β, γ and δ-coronaviruses (**Figure 1**).

CLINICAL CHARACTERISTICS AND EPIDEMIOLOGY OF COVID-19, KAWASAKI DISEASE AND MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

The α-coronavirus and most β-coronaviruses are implicated in mild respiratory illnesses. However, a group of β-coronaviruses which includes SARS-CoV, MERS-CoV and SARS-CoV-2 have

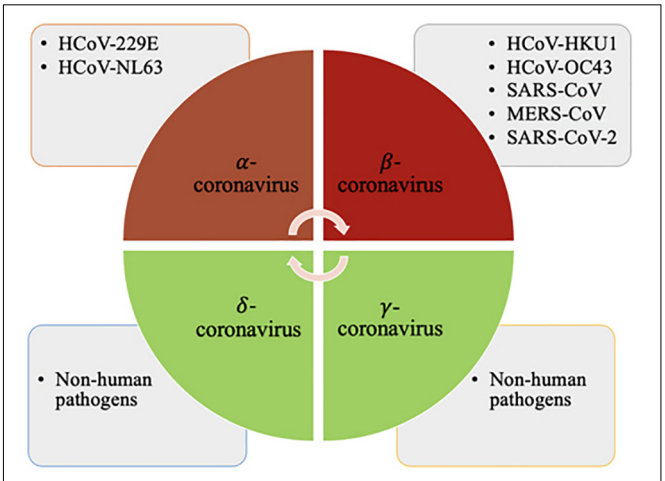

FIGURE 1 | The α-coronaviruses are HCoV-229E, HCoV-NL63; β-coronaviruses are HCoV-HKU1, HCoV-OC43, SARS-CoV, MERS-CoV and SARS-CoV-2; and the γ and δ-coronaviruses comprise species that are non-pathogenic to humans. Created with BioRender.com.

caused major outbreaks and pandemics since the beginning of the 21st century. SARS-CoV-2 has resulted in the ongoing pandemic that has affected all age groups. Comparative details of the three pandemics caused by CoVs have been provided in **Table 1** and **Figure 2**. A new entity, MIS-C was described by various reports at the onset of COVID-19 pandemic post SARS-CoV-2 infection (8, 9).

Kawasaki disease and MIS-C phenotypes overlap in terms of few clinical presentations such as fever, rash, erythema and edema. Previously, a case-control study on Kawasaki disease demonstrated the presence of New Haven coronavirus (HCoV-NH) by a reverse-transcriptase polymerase chain reaction in respiratory secretions of 72.7% KD patients (10). This was taken to be proof of KD being a sequela of viral infection. However, broader epidemiological confirmation, in-depth evaluation of immune response to HCoV-NH, and presence of the virus in biopsy is required to confirm this agent as the causative agent of KD (11). In the current pandemic, KD like symptoms was observed in the pediatric cases of COVID-19, later named as a MIS-C (12). MIS-C diverge to be a distinct pathophysiological mechanism with severe multisystemic hyperinflammation especially myocarditis with cardiac dysfunction. Laboratory parameters suggestive for the diagnosis of MIS-C include serum ferritin, leukopenia, lymphopenia (13). Prognosis in MIS-C is calculated by taking into account cardiovascular complications, such as presence of ventricular dysfunction and coronary artery aneurysms (CAA). CAA occurs in 9–24% of cases with MIS-C (14, 15). These complications have triggered recommendations for immunomodulatory treatments, including intravenous immunoglobulin (IVIG), corticosteroids, biologics, and recommendations for intensive cardiac observation. The choice of IVIG treatment was mainly considered based on similarity to Kawasaki disease (15).

Interestingly, presentation similar to MIS-C was not reported in SARS or MERS. Limited transmission of SARS-CoV and MERS-CoV in previous outbreaks, which were largely endemic, may be a possible explanation to non-emergence of a MIS-C like illness. Another possibility could be that the antigenic and infections determinants of SARS-CoV-2 may be responsible for the MIS-C phenotype. Comparison of demographics, clinical features and laboratory investigations between KD and MIS-C has been summarized in **Table 2**.

SARS-COV/MERS-COV/SARS-COV-2 GENOME AND ANTIGENIC COMPONENTS

The CoVs share similar genetic architecture for encoding the proteins involved in the virion structure and transmissions. However, the number and functions of open reading frames (ORFs) differ amongst the CoVs. The comparative structure of SARS-CoV, MERS-CoV and SARS-CoV-2 genome is shown in **Figure 3**. Order of genes (5′–3′), identified by genomic analysis was as follows: replicase ORF1ab, spike (S), envelope (E), membrane (M) and nucleocapsid (N).

The ORF1ab region spans approximately 67% of the viral genome and contributes to encoding of non-structural proteins (nsps) (16). Nsps have a critical role in CoV RNA synthesis and processing (17). SARS-CoV-2 shares a highly conserved domain of 122–130 amino acid residues with SARS-CoV in nsp1. The spike glycoprotein encoded by the S gene, is recognized as a critical antigenic determinant of host range and pathogenicity as it modulates receptor recognition and cellular entry (18). Cell entry in SARS-CoV-2 is mediated by a carboxypeptidase, angiotensin-converting enzyme 2 (ACE-2), *via* viral spike protein. The S protein is then proteolytically cleaved by a proprotein convertase, furin, into two subunits, S1 and S2, followed by priming of S2 fragment by a host serine peptidase, transmembrane protease serine (TMPRSS2) (19, 20). This novel furin mediated cleavage of the S protein is seen only in SARS-CoV-2 but not in SARS-CoV and MERS-CoV (20). These peptidases serve to unmask a new C-terminal sequence, Arg-Arg-Ala-Arg which facilitates binding of virus to host cells *via* NRP1 receptor (21).

The host secondary receptors in SARS-CoV-2, furin and NRP1 are distinct from SARS-CoV which recruits DC-SIGN and L-SIGN (22). Widespread co-expression of ACE-2 and TMPRSS2 receptors are noted in nasal passages but furin along with ACE-2 and TMPRSS2 are expressed in lung (20). TMPRSS2 belongs to a sub-family of membrane-associated serine protease which along with ACE-2 are expressed by many organ systems. This may explain the enhanced infectivity and exacerbated host response seen in SARS-CoV-2 infection. The spike glycoprotein remains the key target of neutralizing antibodies in the host (23). This protein is also thought to act as a superantigen, causing MIS-C and cytokine storms in adults (24). However, the superantigen property might be related to the configuration of spike protein as SARS-CoV-2 variants evoke variable host immune responses. This phenomenon was observed in the recent omicron variant which was highly infectious but generated a reduced immune response as compared to the delta variant. The SARS-CoV-2 viral proteins and their roles in the host are depicted in **Figure 3**.

Equilibrium dissociation constant of SARS-CoV-2 has been found to be lower than that of SARS-CoV, indicating substantially different affinity for ACE2 between both CoVs (25). Globally, SARS-CoV-2 has evolved at the rate of two mutations per month (26, 27).

Newly discovered variants of the novel SARS-CoV-2 are thought to be potential triggers for MIS-C as there was a dramatic increase in viral infectivity and pathogenicity following the start of the pandemic. The earliest emerging variants include D614G and N439K (B.1.258). The D614G polymorphism has been associated with the MIS-C phenotype (28). Some polymorphic variants (e.g., D839Y/N/E and A831V) have been predicted to enhance the binding affinity with T cell receptor (TCR). These variants were identified in Europe and North America, and have also been associated with the emergence of MIS-C. A causal relationship between these variants and MIS-C has, however, not been established (29).

The newly emerged omicron (B.1.1.529) variant harbors more than 30 mutations in S- protein alone. Modeling studies revealed that molecular interactions in omicron are more stable than

TABLE 1 | Clinical characteristics and epidemiology of SARS, MERS and COVID-19.

Details	SARS	MERS	COVID-19
Year first reported; Country	November, 2002; Foshan, Guangzhou, China	June, 2012; Jeddah, Saudi Arabia	December 2019; Wuhan, China
Total number of cases	8,096 with 774 deaths	2,574 with 886 deaths	Ongoing, ∼ 234 million infected with 4.8 million deaths
Total number of pediatric cases	135	42	∼ 8.5% of cases are children
Total pediatric deaths	None	3	Globally 3,788 deaths till January, 2021 (138); 561 deaths in United States till September, 2021 (CDC, United States)
Mortality rate	9.5%	34.4%	∼ 2.5%
Putative reservoir of infection	Asian civet cat (*Paguma larvata*)	Adult dromedary camels (*Camelus dromedarius*)	?Bat; pangolins; snakes
Mode of Transmission	Human to human—High; direct contact and Indirect contact (droplets or fomites, aerosol transmission and rarely faeco-oral transmission)	Human to human—Low; direct contact with infected camels; close contact with patients	Human to human—High; droplet infection; fomites; aerosols; close contact with patients
Putative Host receptor for viral entry	ACE2	DPP4	ACE2
Treatment	Mainly supportive treatment; ribavirin, steroids were used anecdotally	Mainly supportive treatment	Mainly supportive treatment Following drugs have been tried with variable efficacy: remdesivir, corticosteroids, hydroxychloroquine, lopinavir/ritonavir, ivermectin, tocilizumab, anakinra
Incubation period in days	2–10 (mean: 6.4)	2–13 (mean: 5)	2–14 (mean: 5)
Hematological and biochemical findings	Lymphopenia; thrombocytopenia; hypoalbuminemia; transaminitis; increased lactic dehydrogenase, creatine kinase and C-reactive protein levels	Similar to SARS	Similar to SARS along with elevated D-Dimer, and IL-6

ARDS, acute respiratory syndrome; MODS, multi-organ dysfunction syndrome; ACE-2, angiotensin-converting enzyme-2; DPP4, dipeptidyl-peptidase-4.

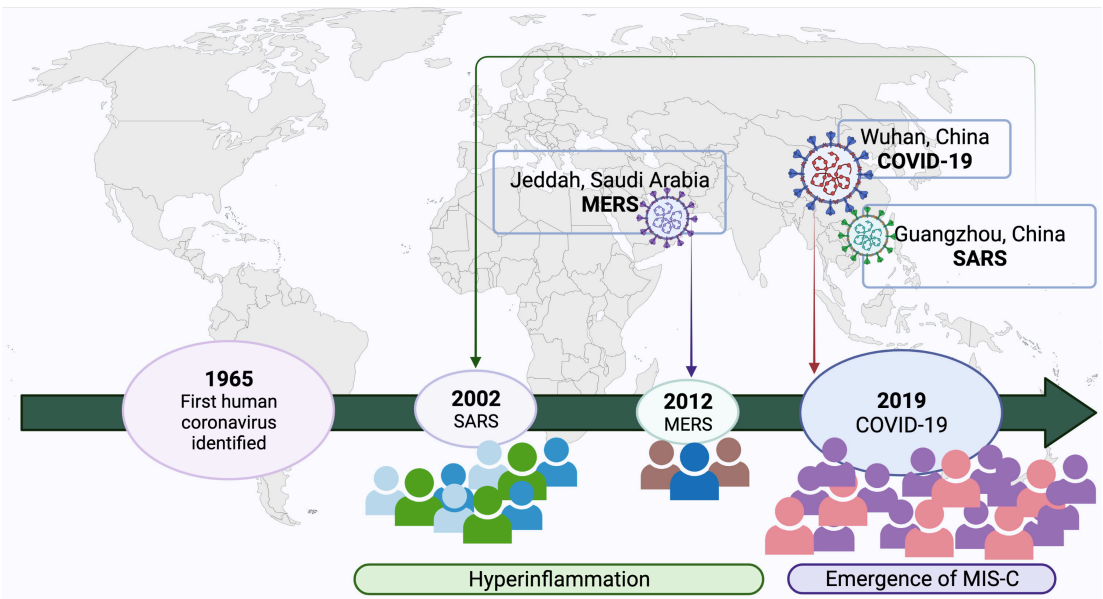

FIGURE 2 | Emergence of coronavirus in humans and relationship with KD-MISC spectrum. Created with BioRender.com.

previous variants resulting in enhanced potency of ACE2-spike protein interactions (30). Moreover, the majority of neutralizing mAbs against the omicron variant loses inhibitory activity (31). This variant has unprecedented infectivity, however, pediatric hospitalizations are reduced by half in the omicron wave, unlike the delta variant. The moderate immune response generated in response to the omicron variant may be due to the unmasking of poorly immunogenic spike peptides.

TABLE 2 | Comparison of demographic and clinical features of Kawasaki disease and SARS-CoV-2 related MIS-C.

Parameters	Kawasaki disease	SARS-CoV-2 related MIS-C
First reported	1967; Tokyo, Japan	April 2020; London, United Kingdom
Trigger	Unknown etiology (Probable infectious trigger in genetically predisposed patients)	SARS-CoV-2
Age group	More common in children < 5 years	4–13 years
Ethnicity	Worldwide; highest incidence in East Asia (Japan, Korea, Taiwan)	Worldwide; paucity of cases in East Asia
Interval between exposure and symptoms	Not known	3–6 weeks
Sex	Male > female	No clear sex bias
Systems involved	Cardiac: Coronary artery aneurysms during convalescent phase (after 3 weeks of fever); myocarditis	Cardiac: Coronary artery aneurysms during acute phase, myocarditis and left ventricular dysfunction CAAs are usually transient
	CNS: Irritability and aseptic meningitis	CNS: Meningitis and encephalitis
	Gastro-intestinal: Gall bladder hydrops	Gastro-intestinal: Abdominal pain (acute pseudo surgical abdomen, peritoneal effusion)
Laboratory parameters	Neutrophilic leukocytosis; thrombocytosis elevated inflammatory parameters (CRP, Procalcitonin, Troponin, Pro-BNP)	Lymphopenia; thrombocytopenia significantly elevated inflammatory parameters (CRP, Procalcitonin, Troponin, Pro-BNP, Ferritin)
Complications	KD shock syndrome (2–7%) MAS (1.3%) (139)	MODS (More than 70%) MAS
Mortality	<0.1% in Japanese cohort	1–2%
Immunological features	High levels of TNF-α, IL-17 Autoantibodies against DEL-1 (anti-inflammatory protein against ICAM-1) Role of IgA in pathogenesis	High levels of plasma—IL-17a Autoantibodies against MAP2K2 and casein kinase family Autoreactive IgG
Treatment	IVIg, steroids, infliximab	IVIg and steroids

CNS, central nervous system; CRP, C-reactive protein; MODS, multiple organ dysfunction; BNP, brain natriuretic peptide; IVIg, intravenous immunoglobulin; MAS, macrophage activation syndrome.

HOST GENETICS IN SEVERE COVID-19, KAWASAKI DISEASE AND MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

Initial SARS-Cov-2 entry is mediated by transmembrane protease serine 2 (TMPRSS2) with one variant (p.Val160Met) reported to be associated with higher viral load and mortality (32). Other components of host immune system, such as, sensing and signaling pathways have also been associated with enhanced infectivity and poor outcomes in SARS-CoV-2 infections. TLR3, Interferon regulatory factor-7 (IRF7), and IRF9 drive type I interferon antiviral responses. These genes are also linked to inborn errors of immunity and individuals with mutations in these genes are predisposed to severe influenza pneumonia (33). Whole exome/genome sequencing based study in 659 cases with severe COVID-19 identified variants in 13 loci, predominantly affecting TLR3 and IRF7 dependent activation of type I IFNs. Zhang et al. proved the association of autosomal recessive *IRF7* deficiency and a failure to mount IFN-I and III responses against SARS-CoV-2 using patient derived plasmacytoid dendritic cells (34). These plasmacytoid dendritic cells mount robust type I interferon response against viral attack. In contrast, amongst the three loci (TLR3, *IRF7* and *IRF9*), Povysil et al. reported association of only one predicted loss of function variant in severe COVID-19 (35). These conflicting reports highlight the need for genome wide association studies (GWAS) with stringent and uniform inclusion/exclusion criteria for better interpretation of genomic data.

Double stranded RNA acts as a ligand for TLR3 which leads to activation of downstream NFκB and IRF3 (36). A population based GWAS reported polymorphism in *TLR3* gene (rs3775291) was associated with increased susceptibility and death in COVID-19 patients (37). Another group of investigators reported that SARS-CoV-2 induces senescence in human cells and amplifies the senescence-associated secretory phenotype (SASP) *via* TLR-3 signaling. These SASP cells produce pro-inflammatory cytokines and damage surrounding tissues (38). Contrary to the observations in human studies, a murine model of lethal influenza infection reported that TLR3-/- mice had longer survival compared to wild type mice. Also, reduced levels of chemokines, fewer infiltrating leukocytes, and less numbers of $CD8^+$ T cells were observed in TLR3-/- mice (39). This study cemented the role of TLR3 in ISG induced restriction of viral replication and lung damage due to TLR3 mediated recruitment of immune cells. Functional studies in human patients with polymorphisms in TLR3 are needed to conclusively define the role of TLR3 in COVID-19.

Similar studies in MIS-C discovered few variants in immune related genes, but these variants differed from those reported previously in severe COVID-19. Lee et al. reported presence of heterozygous variant in two unrelated patients in the suppressor of cytokine signaling 1 (*SOCS1*) gene in children presenting with MIS-C (40). SOCS1 is a critical negative regulator of Type I and II IFN signaling. Chou et al. carried out whole exome sequencing to determine genetic risk factors in 18 patients with MIS-C. Genetic defects in X-linked inhibitor of apoptosis (*XIAP*), cytochrome b beta (*CYBB*), and *SOCS1* were detected. However, in 17% of cases, variants affecting the negative regulation of

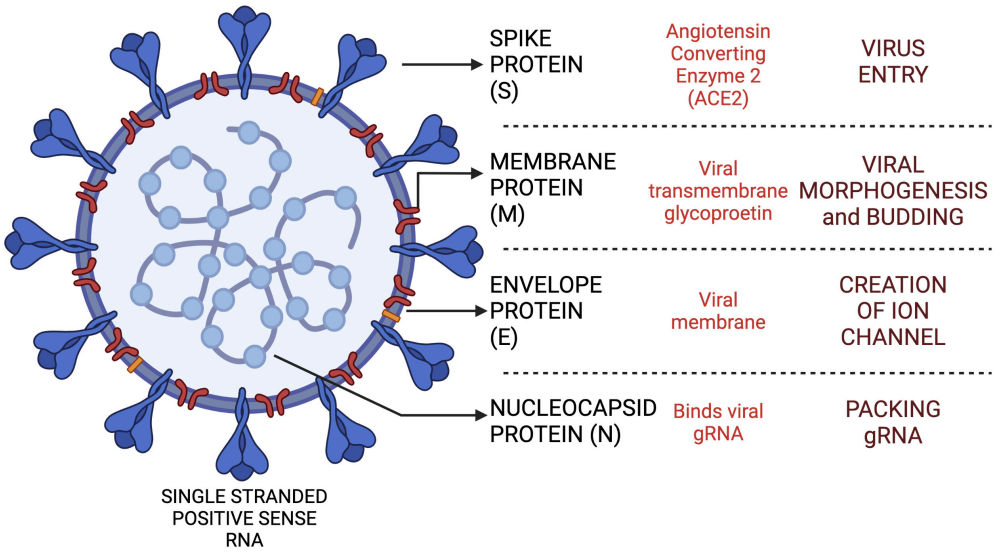

FIGURE 3 | The SARS-CoV-2 viral proteins and functional roles in host cells. Created with BioRender.com.

interferon were detected (41). This suggests that there may be a genetic predisposition to development of MIS-C but large scale GWAS remain to be carried out. Though MIS-C and KD share similar clinical features, the genetic risk factors vary amongst these conditions. GWAS studies have linked a number of genetic loci to the pathogenesis of KD, as described in the **Table 3**.

HOST PATHOGEN INTERACTIONS IN COVID-19, KAWASAKI DISEASE AND MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

Pattern Recognition Receptors and Type I Interferons Response

Innate immune system confers protection against viral infections, including SARS-CoV, MERS-CoV and SARS-CoV-2 by acting as first line of defense (42, 43). Components of the CoVs trigger host innate immunity. Viral pathogen-associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs) are recognized by endosomal as well as cytosolic pattern recognition receptors (PRRs). The viral spike-S protein, single-stranded and double-stranded RNA (ssRNA and dsRNA respectively) act as ligands for PRRs such as Toll Like Receptors (TLRs)-2, 3, 7/8, retinoic acid-inducible gene-I-like receptors (RIG1) and melanoma differentiation associated protein (MDA-5). These PRRs sense viral nucleic acid and activate downstream transcription factors including nuclear factor-kappa B (NF-κB), interferon regulatory factors (IRFs)-IRF3 and IRF7. These downstream transcription factors cause production of proinflammatory cytokines and induction of anti-viral type-I interferons (IFN). IRF3/7 homodimerize and translocate to nucleus and induce synthesis of type I IFNs (IFNα and IFNβ). Subsequently, IFNs bind to IFN α/β receptor (IFNAR) activating Jak/Stat pathway and trigger production of antiviral interferon-stimulated genes (ISGs). This mechanism may protect host cells from exacerbated viral replication and cellular damage (44).

TLR adaptor myeloid differentiation primary response 88 (MyD88) signaling activates nuclear factor kappa light-chain-enhancer of activated B cell (NF-kB) resulting in synthesis of pro-inflammatory cytokines. These cytokines further prime NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome leading to production of pro inflammatory cytokine-IL-1β facilitating pyroptosis (45). These observations are in sync with a recent transcriptome profiling of respiratory epithelial cell lines infected with SARS-CoV-2. The study demonstrated a robust pro-inflammatory cytokine response and low IFN levels (46). ORF6, ORF9b, and ORF3b-encoded proteins in SARS-CoV-2, have been demonstrated to decrease antiviral type I IFN (IFN-I) production and signaling (21, 47, 48). Also, SARS-CoV-2 non-structural proteins (nsp) -3 and -6 were shown to suppress IFN activation through the IRF3 pathway (49). This initial postponement of IFN-I response is followed by unrestricted viral reproduction and dissemination in the infected host thereby resulting in a subsequent surge in IFN-I, which aggravates hyperinflammation and may predispose to a severe clinical illness (49).

Recent COVID-19 and complete KD transcriptome dataset analysis has reported downregulated TLR7, IRF3 and stimulator of interferon genes (STING) expression in KD patients (50, 51). SARS-CoV-2 viral infection mediated RAS activation, *via* Ang-II and Angiotensin II type 1 receptor (AT1R), also triggers

TABLE 3 | Genetic loci associated with KD, MIS-C and severe COVID-19.

S. No	Study group	Disease	Associated host gene alterations	Function	Results	References
1	(103)	MIS-C	*SOCS1*	Negative regulator of IFN signaling	2/2 (100%)	(40)
2	(41)	MIS-C	*XIAP, CYBB, and SOCS1*	XIAP regulates cell death, and CYBB is essential in phagocytic NADPH-oxidase activity	5/18 (27.77%)	(41)
3	(140)	KD	*FCGR2A, ITPKC and rs2233152*	*FCGR2A*: Encodes IgG immunoglobulin Fc receptor ITPKC: Regulates calcium channels and controls the activated state of T cells	*FCGR2A: P* = 7.35 × 10 (−11), odds ratio (OR) = 1.32 *rs2233152: P* = 2.51 × 10 (−9), OR = 1.42 *ITPKC: P* = 1.68 × 10 (−12), OR = 1.52	(140)
4	(141)	KD	*FAM167A-BLK* (rs2254546) *HLA* (rs2857151), *CD40* (rs4813003), and *FCGR2A* (rs1801274)	BLK:B cell proliferation and differentiation HLA: Regulation of immune system CD40: co-stimulatory protein found on antigen-presenting cells	rs2254546: *P* = 8.2 × 10 (−21) rs2857151: *P* = 4.6 × 10 (−11) rs4813003: *P* = 4.8 × 10 (−8) rs1801274: *P* = 1.6 × 10 (−6)	(141)
5	(142)	KD	*IGHV3-66* variant	IG heavy chain variable gene	rs4774175; OR = 1.20, *P* = 6.0 × 10 (−9)	(142)
6	(143)	KD	HLA-DRB1	Regulation of immune system	Development of CAL in KD	(143)
7	(144)	Severe COVID-19	HLA-B*46:01	Regulation of immune system	Computer simulation study predicted vulnerability to COVID-19	(144)
8	(144)	Severe COVID-19	HLA-B*15:03	Regulation of immune system	Allele allows preferential presentation of highly conserved domains	(144)

CAL, coronary artery lesions; HLA, human leukocyte antigen; IGHV, immunoglobulin heavy variable; XIAP, X-linked inhibitor of apoptosis; CYBB, cytochrome b-245 beta.

the TLR4/MyD88/NFκB pathway resulting in elevated pro-inflammatory cytokines including TNF-α, IL-1β, IL-6 and IL-8 (22).

The cytokine profiling in MIS-C revealed down-regulation of tumor necrosis factor like weak inducer of apoptosis (TWEAK) (52), a negative regulator of IFN-γ. This indicates attenuation of IFN response and transition of innate to adaptive immunity (53). Lag in IFN response may result in delayed clearance of viral load and elevated inflammatory state (54) which may result in production of autoantibodies and alterations in self-tolerance. However, delay of 4–6 weeks in the development of MIS-C post-infection by SARS-CoV-2 indicates immune dysregulation may be the primary cause of MIS-C in predisposed children.

Clinically MIS-C overlaps with features observed in KD, TSS and secondary hemophagocytic lymphohistiocytosis (sHLH) (55). Similar to MIS-C, sHLH is characterized by immunological dysregulation, which includes immune hyperactivation, increased cytokine production, and severe systemic inflammation. Current HLH diagnostic criteria requires presence of at least five conditions including fever, splenomegaly, cytopenias, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in bone marrow or spleen or lymph nodes, reduced or absent NK cell activity, elevated ferritin and soluble CD25 (56). It is also critical to investigate the infectious trigger in case of sHLH. Elevated IFN-γ, and IL-10 are important biomarkers in the diagnosis of HLH (57). However various independent studies indicate that primary (genetic cause) and secondary (infectious, malignant or autoimmune mediated trigger) HLH can be differentiated based on the levels of IFN-γ (56, 58, 59).

In a recent study, Esteve-Sole et al. compared IFN-γ levels between healthy controls, KD, MIS-C, and MAS. The cytokine profile of MIS-C and KD overlapped with elevated IFN response markers (IFN-γ, IL-18 and IP-10) and monocyte activation markers (MCP-1, IL-1α and IL-1RA). However, a subset of MIS-C cases differentiated to form a subgroup with markedly elevated IFN-γ with incipient indication to MAS (60). As per previous studies, the MIS-C subgroup had elevated IFN-γ levels which indicate the involvement of an IFN-regulated mechanism.

Low erythrocyte sedimentation rate (ESR) and splenomegaly usually seen in sHLH, are not observed in MIS-C (61, 62). The cytokine profile of patients with COVID-19 and sHLH was similar with elevated serum levels of IL1, IL2, IL4, IL6, IL7, IL8, IL10, IL-18, TNFα, GCSF, IP-10, MCP1, MIP1α, CXCL9, CXCL-10, IFN-γ (63–66). A comparison of immunological perturbations seen in SARS, MERS, COVID-19, KD and MIS-C is tabulated in **Table 4**.

ROLE OF INFLAMMATORY CELLS IN COVID-19, KAWASAKI DISEASE AND MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

Neutrophils, Monocytes and Antigen Presenting Cells

In a recent multi-omic study, several immunological perturbations were documented in fatal SARS-CoV-2 infections. Peripheral neutrophils have upregulated genes which are

TABLE 4 | Immune mechanisms operative in SARS-MERS-COVID-19 infections and KD/MIS-C.

Immune component	SARS	MERS	COVID-19	KD	MIS-C
Entry into host cell	ACE-2 Co-receptors: DC-SIGN (CD209) L-SIGN (CD209L) (145)	CD26/Dipeptidyl peptidase-4 (DPP-4)	High affinity binding of ACE-2 (25). Alternate receptor: CD147-SP	Etiological agent not discovered yet	High affinity binding of ACE-2 (25)
Innate Immunity					
Inflammasome	NLRP3 inflammasome activation by SARS-CoV 3a protein (146)	NLRP3 inflammasome triggered by C5aR1	NLRP3 inflammasome IL-1β and IL-6 activation (147)Increased type 1 IFN STING/TBK1 (TANK-binding kinase 1)/IRF pathway	Dysregulated NLRP3 inflammasome (148) Downregulated STING expression	Upregulation of NLRP3 and Il-β signaling (14)
Monocytes	Poorly infect monocytes/ macrophages (149)	Poor replication in monocytes/ macrophages but significant anti-viral immune response (149)	Reduced monocyte subsets, lowered expression of HLA-DR, and elevated CD163 (150).	Elevated $CD14^+CD16^+$ monocytes in acute KD (151, 152)	Reduced CD14, elevated CD64 (FcRγ1) expression in non-classical $CD16^+$ monocytes (85)
IFN-γ	Delayed and diminished levels of IFN-I.	Delayed and diminished levels of IFN-I.	Reduced IFN- γ in COVID-19 generates cytokine storms	Differential response as per host IFN-I polymorphism (153)	Dysregulated IFN-γ (154)
Complement/coagulation	C3 factor CR1 in erythrocytes	C5a in the serum C5b-9 in the lung tissues	Thrombotic microangiopathy; increase in C5b-9 levels (99)	Classical pathway: C3 and B activation	sC5b-9 leading to microangiopathy
Adaptive Immunity					
B-Cells	Antibody dependent enhancement	Attenuated B cell response	Antibody dependent enhancement	IgA^+ peripheral B cells from acute KD (155) Elevated "activated" $CD86^+$ B cells (156)	Reduced total, effector and class switched memory B cells. Auto-antibodies including endoglins, exclusively to MIS-C: MAP2K2 and casein kinase family.
T Cell	Lymphopenia and suppressed T-cell activation; long-lived memory $CD4^+$ and $CD8^+$ T-cell responses—Polyfunctional $CD4^+$ and $CD8^+$ T cell responses.	Lymphopenia; $CD8^+$ T-cell response specific to MERS in severe disease; long-lived memory T-cell responses.	Lymphopenenia; reduction in functional diversity of T cells; higher exhaustion, reduced multi-functional $CD4^+$ T cells and higher $CD8^+$ T cell exhaustion	Increased $CD69^+$ natural killer and γδ T-cells (155) Decreased follicular helper T cells in children having COVID -19	Decreased naive $CD4^+$ T cells ($CD4^+CD45RA^+$) and elevated memory T cells ($CD4^+CD45RO^+$) Both CM and EM $CD4^+$ T cells are noted in MIS-C but not in KD (157). Higher levels of senescent T cells ($CD57^+$) were noted in MIS-C in comparison to pediatric mild COVID-19 cases, adults with COVID-19 and KD patients.
Cytokine Storm	Th17 mediated (158)	Th17 mediated (158)	Th17 mediated (158)	Elevated levels of Th17 mediated IL-17A in KD (160) compared to MIS-C patients	Consistent myeloid activation
Cytokines and chemokines	IFN TGF, IL1, IL6, IL8, IL-12, CCL2, CXCL3, CXCL5 CXCL9, CXCL10, MCP1	IFN TGF, IL1, IL6, IL8. CCL2, CCL3, CCL5, CXCL10	IL1, IL6, MCP1, IL-2, IL8, IL-7, IL-17, G-CSF, GM-CSF, MIP 1α	IL-6, IL-8, IL-1 and IL-17A levels	IFN-γ, IL-18, IL-1β, IL-8, IL-6, IL-10, IL17 and TNF

DC-SIGN, dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin.

involved in the synthesis of pro-inflammatory cytokines, enhance phagocytosis and degranulation (67). There is induction of interferon-stimulated genes, leukocyte recruitment and cytokine induction *via* the Ca^{+} binding proteins, S100A8/A9.

NETosis

Neutrophil extracellular traps (NETs) were also documented in severe COVID-19 infections (68). NETs are a combination of extracellular DNA, oxidase enzymes and microbicides released by neutrophils in order to contain the infection. The acetylation neutralizes positive charge on histones and allows the DNA to decondense which is crucial for NET formation. The Histone deacetylase2 (HDAC2) suppresses de-condensation and thus impairs NETs. The SARS-CoV-2 non-structural proteins, especially Nsp5, impact the formation of neutrophil extracellular traps (NETs). The viral protein, Nsp5 attenuates the HDAC2 and promotes NETs (69, 70). Along with S100A8/A9, peptidyl arginine deiminase-4 (PAD4) also facilitates NETosis *via* PAD4-mediated histone citrullination (67, 71). NET specific markers including myeloperoxidase-DNA (MPO-DNA), and citrullinated histone H3 (Cit-H3) have been found to be elevated in severe COVID-19 (68). NET formation has also been linked to vascular damage and organ dysfunction in COVID-19 (72). NETs are predictors of poor outcome in the patients with COVID-19 ARDS (51) and contribute toward increased mortality (68). Higher numbers of NETs have also been observed in acute KD compared to the convalescent KD indicating endothelial damage associated with this disease (73). Netosis may also be associated with enhanced vascular injury (74) and could be one of the pathogenic mechanisms of KD vasculitis. Considering the overlapping clinical and molecular features between KD and MIS-C, it was also hypothesized that the excessive NET formation may contribute to the severe cardiac manifestations in MIS-C (75). Seery et al. reported significantly elevated NETs in the MIS-C group compared to mild and moderate pediatric cases with COVID-19 (76). Hence, NET formation may act as critical indicator predicting vascular damage in MIS-C.

The elevated neutrophils also produces chemoattractants including CXCL2 and CXCL8 in bronchoalveolar lavage fluid (BALF) and PBMCs which signifies the role of neutrophil recruitment in severe COVID-19 (77, 78). Flow cytometry based study on monocytes from patients with severe COVID-19 demonstrated elevated levels of IL-6, IL-1, and TNF-α, indicating an inflammatory monocyte phenotype.

Monocytes/Macrophages

In severe SARS-CoV-2 infections, elevated numbers of monocyte-derived macrophages were observed in BALF comprising 80% of all infiltrated cells. Macrophage infiltrates have been previously observed in the post-mortem lungs from SARS-CoV affected patients. Due to similar cytokine profiles, it was hypothesized that mononuclear phagocytes may contribute to the hyperinflammation associated with COVID-19 (65). Histopathological assessment in autopsied KD cases reveals elevated monocyte/macrophage numbers in coronary arterial lesions (79, 80). These macrophages produce inflammatory chemokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-6, which result in increased recruitment of monocytes, macrophages and dendritic cells (81) and exacerbated immune response which may be associated with the cardiac manifestations. GM-CSF has also been observed to be critical in murine model of KD as it orchestrates cardiac inflammation (82). Thus, monocytes and neutrophils appear to play a central role in severe SARS-CoV-2 infections and KD. Monocytes induce cytokine storm and lung injury whereas neutrophils lead to enhanced chemotaxis, NETosis, and a hyper active immune response in severe SARS-CoV-2 infections.

MIS-C presents as a global activation of neutrophils and non-classical monocytes evidenced by increased CD64 (FcγRI) and CD54 (ICAM1) expression pointing toward consistent myeloid activation (83). There is an increase in immature neutrophils (low CD10 and CD62L) in the peripheral blood of MIS-C patients (84). Despite global activation of the myeloid lineage, HLA-DR and CD86 were found to be reduced on monocytes and dendritic cells. This was accompanied by a concomitant decrease in natural killer (NK) cells (CD56 low), plasmacytoid dendritic cells, $CD16^{+}$ monocytes, and γδ T lymphocytes (83, 85). Together, this may result in an impaired antigen presentation and a dysregulated immune response. Detailed immunopathogenesis mechanisms have been illustrated in **Figure 4**.

Dysregulated activation of neutrophils in addition to an enhanced expression of human neutrophil antigen 2 (HNA-2) encoded by the *CD177* gene, a specific activation marker of neutrophils, has also been noted in KD patients. CD177 enhances antimicrobial activity of neutrophils and an increased expression has also been associated with septic shock and inflammatory bowel disease. Abnormal methylation pattern of *CD177* gene and enhanced expression of CD177 in KD patients has been associated with intravenous immune globulin (IVIG) unresponsiveness (86). CD177 has also been associated with development of severe disease and mortality in COVID-19 (87).

NK Cells

Severe SARS-CoV-2 infections present with activated NK cells but in patients progressing to fatal COVID-19, the proliferation of NK cells is impaired. There is decrease in the cytotoxic effector perforin as compared to patients with severe COVID-19 (88). This indicates functional alterations of NK cells in patients who succumb to the disease. Patients with SARS-CoV-2 infections have decreased IFNγ production in NK cells when compared to healthy controls (89). Witkowski et al. reported higher levels of anti-inflammatory molecule transforming growth factor-β1 (TGF−β1) indicating altered antiviral defense mechanism by NK cells (90). The untimely enhancement of TGF-β1 alters NK cell function and negatively impacts early control of viral clearance.

Initial reports on MIS-C described NK cell cytopenia (91). Beckmann et al. reported aberrant NK cells in MIS-C using a transcriptome based approach. This study reported partially shared molecular etiology with KD but not with other inflammatory conditions. In patients with MIS-C and KD, exhausted effector $CD8^{+}$ T-cells and $CD56^{dim}CD57^{+}$ natural killer (NK) cells were reported (92). Another single-cell RNA sequencing-based study also reported enhanced expression of

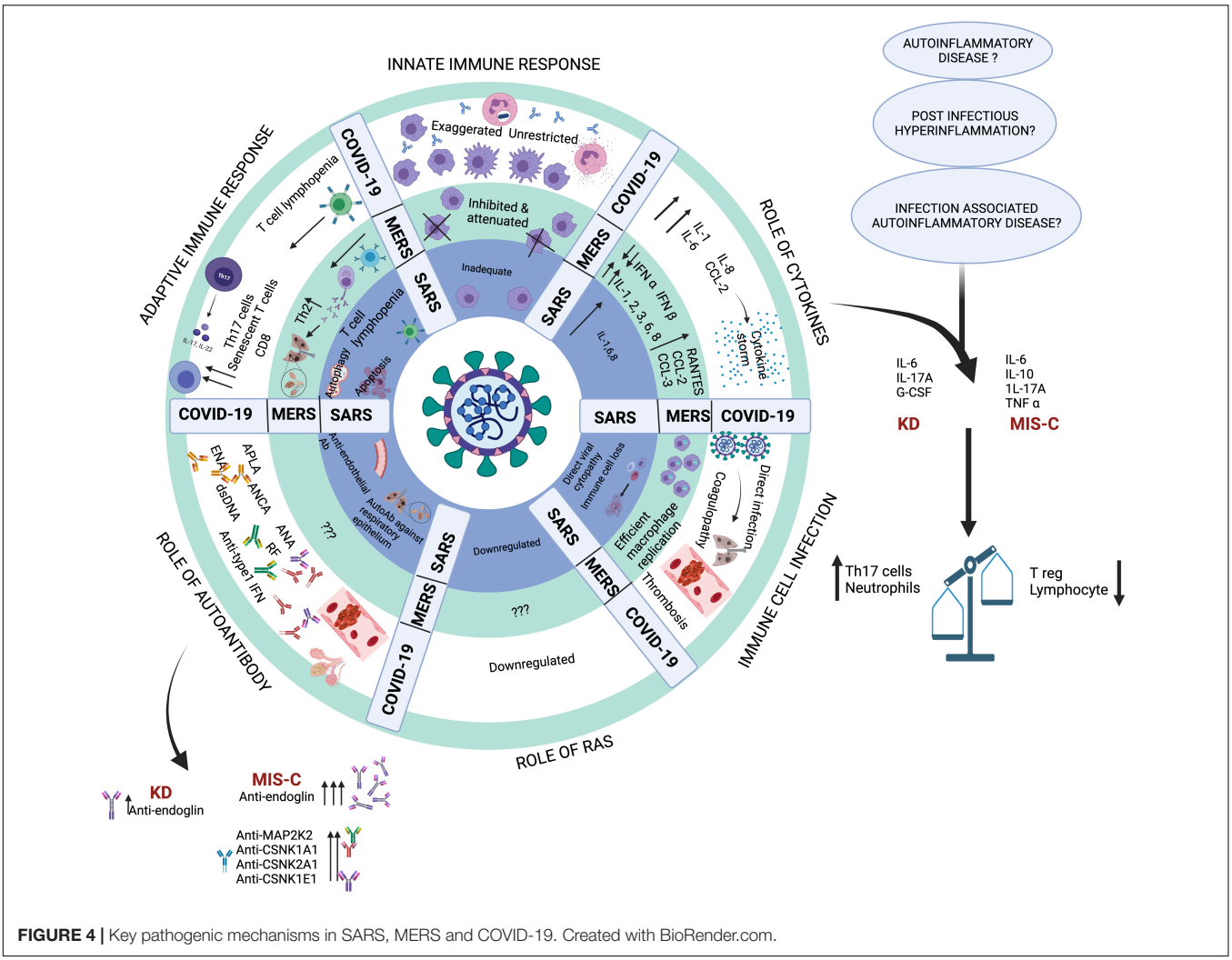

FIGURE 4 | Key pathogenic mechanisms in SARS, MERS and COVID-19. Created with BioRender.com.

cytotoxicity genes in NK and $CD8^+$ T cells (93). The elevated levels of cytolytic enzymes, such as perforin, granzyme A, and granzyme H may be responsible for tissue damage seen in MIS-C (93). These studies suggest sustained hyper inflammation may be due to depletion of NK cells leading to $CD8^+$ T-cell exhaustion. In a murine model, NK cells eliminated viral activated $CD8^+$ T-cells *via* Natural Cytotoxicity Receptor 1 (NCR1). This study indicated a cross-talk between these two cell types (94). The $CD8^+$ T-cells are crucial in resolving post-viral infection-associated pathology. Thus, in the event of NK cell depletion, increased senescent $CD8^+$ T-cells may be responsible for T cell-associated immunopathology observed in MIS-C patients (95, 96).

ROLE OF COMPLEMENT COMPONENTS

In SARS-CoV-2 infection, complement activation appears to play a key role (97). This is evidenced by endothelial deposition of complement and elevated levels of serum C5a in patients with severe COVID-19 (97). Yu et al. demonstrated the role of alternative complement pathway activation primarily mediated by SARS-CoV-2 spike proteins. They also reported that inhibition of C5 blocks the accumulation of C5b-9, but not C3c (98). Dorio et al. found increased levels of soluble C5b-9 (sC5b-9) in cases with MIS-C as well as severe COVID-19, but not in patients with milder forms of the disease (99). Elevations of sC5b-9, an activation product of the terminal complement cascade, have been linked to microangiopathy in a number of studies (100, 101). Surrogate markers of microangiopathy (as evidenced by burr cells and schistocytes) are seen in almost all patients with MIS-C and a significant proportion of patients with severe COVID-19 (99). Compared to healthy control and KD group, MIS-C reported highly enriched proteins associated with complement pathways specifically the components of classical complement cascade C1qA, C1qB, and C1qC (102). Hence, IVIg treatment is recommended to inhibit the complement deposition in MIS-C. Serum complement C3 is known to be elevated in KD (103). Role of C5a and C5b has also been implicated in the membrane damage associated in KD (104). The detailed comparison has been provided in **Table 4**.

ROLE OF T CELLS IN COVID-19, KAWASAKI DISEASE AND MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

Patients with COVID-19 have shown an unbalanced T cell homeostasis with reduction of multi-function $CD4^+$T cells and higher degree of $CD8^+$T cell exhaustion, leading to reduction in T cell subsets and an ineffective cellular immune response (105). In severe SARS-CoV-2 infections, elevated numbers of $CD8^+$ and Th17 cells were noted in peripheral blood and lung biopsy samples. This can explain lung injury seen in patients with severe COVID-19 (106). It appears that a strong Th17 mediated cytokine storm drives lung injury in COVID-19.

Patients with MIS-C and KD also present with decreased T cell counts and naïve $CD4^+$ T cells ($CD4^+CD45RA^+$) but increased memory T cells ($CD4^+CD45RO^+$). A subset of memory T cells, viz. Central memory (CM) and effector memory (EM) $CD4^+$ T cells were identified in MIS-C and pediatric SARS-CoV-2 cases in higher proportion when compared to KD (52). However, CD8 + effector memory cells were reduced in MIS-C compared to adult COVID-19 (107). Elevated CD4 + T cell proliferation was reported in MIS-C compared to the healthy subjects (93). A transcriptome based study revealed decrease in the CD8 + T cells and down-regulation of exhausted T (Tex) cells in the cases with MIS-C (92). It is crucial to emphasize the role of CD8 + T cells and NK cells which co-regulate one another to elicit cytolytic outcomes. A contrasting feature of MIS-C from COVID-19 is the T cells expressing fractalkine receptor (CX_3CR1 + CD8 + T cells) which homes the cells to endothelium. This may also explain the endothelium abnormalities observed in MIS-C. Moreover, expression of these cells reduces during the improvement in clinical course (108). Increased number of senescent T cells ($CD57^+$) had been noted in MIS-C, KD and in adults with mild COVID-19 infection (109). In contrast to senescent T cells, decreased numbers of follicular helper T cells were noted in children with SARS-CoV-2 infection and also in children who developed MIS-C.

A recent study on patients with MIS-C has shown polyclonal V21.3 T cell expansion directed toward SARS-CoV-2 antigenic peptides. This is unlike the lymphocyte phenotype seen in KD, TSS and COVID-19 patients. Alterations in T cell repertoire resolved after recovery from MIS-C (110). In another study, Porritt et al. have hypothesized the role of bacterial superantigens in development of MIS-C and observed T cell expansion of TCRβ variable gene 11-2 (TRBV11-2) (111). GM-CSF is also believed to have a role in pathogenesis of MIS-C. Previous studies had associated MIS-C with autoimmunity (85, 112). The study by Beckman et al., interrogated autoimmune signatures from transcriptome study databases but MIS-C was not associated with alternations in autoimmune pathways (92). This hints that novel autoimmune mechanisms may govern the predisposition and disease course for MIS-C. It has been noted that in KD patients, GM-CSF-activated myeloid cells release pro-inflammatory cytokines which may be associated with disease pathology. This also increases dendritic cell priming of T cells during antigen-specific immune responses (113).

MULTISYSTEM INFLAMMATORY SYNDROME IN ADULTS

Multisystem inflammatory syndrome in adults (MIS-A) was also reported, although only few cases were seen (114). The common pathogenic hallmarks associated with MIS-C/A could be macrophage hyperactivation, autoantibodies and antigen-antibody complexes. Moreover as emphasized earlier, MIS-C/A could be triggered in genetically predisposed individuals. Ronit et al. reported impaired Type I IFN (IFNα and IFNβ) and type III IFN (IFNλ) response in comparison to healthy controls, however, the response did not differ from severe COVID-19 cases admitted in ICU. Whole exome sequencing of MIS-A cases revealed variants in the genes associated with autophagy, Kawasaki disease, immune responses and viral restriction factors (115). In contrast to the cases with severe COVID-19 and MIS-C, IL-6 and IL-1β levels were normal in MIS-A cases (115, 116). Kawasaki disease in adolescent group is incredibly rare, however, KD-like features have been observed in MIS-A group.

B CELLS AND ANTIBODY RESPONSES IN COVID-19, KAWASAKI DISEASE AND MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

In most instances MIS-C results from an exaggerated inflammatory response that occurs several weeks after apparently asymptomatic or mild SARS-CoV-2 infection. Patients have neutralizing antibodies to SARS-CoV-2. In a recent study, MIS-C patients were immuno-profiled and B cell cytopenia was reported. Lower levels of B cell subsets, viz. effector B cells (plasma cells) and class switched memory B cells, were seen (117). SARS-CoV-2 infected infants had a lower number of follicular T helper (Tfh) cells which play crucial role in B cell maturation. However, alterations of Tfh cell frequencies were not observed in patients with KD (52). Woodruff et al. observed extrafollicular B-cell responses characterized by loss of germinal centers, expanded B cells and plasmablasts, and altered Bcl-6 expression in severe cases with COVID-19 (118). In acute KD, proportion of $CD138^+$ and IgG^+ antibody secreting plasmablast cells were increased while frequency of memory B cells was decreased (119, 120). T-box transcription factors T bet and eomesodermin expression was higher on plasmablasts in MIS-C compared to pediatric COVID-19. However, frequencies of plasmablasts were observed to be similar in both groups. This indicates an altered differentiation state of plasmablasts in MIS-C compared to pediatric COVID-19. MIS-C has also been associated reduced IgA responses and persistent IgG production leading to activation of monocytes (121).

Onset of MIS-C coincides with peak antibody production. A recent study reported presence of anti-spike (S) IgG, IgM,

and IgA antibodies, as well as anti-nucleocapsid (N) IgG antibodies in an adult COVID-19 cohort (122). Children with COVID-19 and MIS-C, on the other hand, displayed a restricted repertoire of anti-SARS-CoV-2 specific antibodies, generating predominantly IgG antibodies specific for the S protein but not the N protein. Moreover, lowered neutralizing activity was observed in both MIS-C and non-MIS-C groups in comparison to the adult COVID-19 cohort. Reduced anti-N antibodies correlate with the milder disease course in pediatric cohort, unlike adult cases with COVID-19 where higher levels of anti-N antibodies have been reported. Higher anti-N antibodies also correspond to higher viral cell lysis (122).

Autoimmunity is also implicated in pathogenesis of SARS. Autoantibodies against respiratory epithelial cells and endothelial cells are implicated in both cytotoxic injury of respiratory epithelium as well as systemic vasculitic pathology observed in SARS infection (123). Exposure of autoantigens due to organ injury or development of cross-reacting antibodies to SARS-CoV epitopes may be responsible for production of autoantibodies (124).

AUTOANTIBODIES IN COVID-19, KAWASAKI DISEASE AND MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

In severe COVID-19 there is multi organ involvement that may be accompanied by thrombotic lesions in heart and lungs. Several auto-antibodies have been associated with the thrombosis encountered in patients with COVID-19. These include anti-cardiolipin (a-CL), lupus anti-coagulant, and anti- β2GPI, anti-neutrophil cytoplasmic antibodies, anti-nuclear antigen, anti-rheumatoid factor, anti-cyclic peptide containing citrulline peptide, antibodies to extractable nuclear antigen and anti-double stranded DNA (125). Accumulating evidence of pre-existing autoantibodies against type I IFNs was first provided by Bastard et al. and a sharp increase in neutralizing type I IFNs autoantibodies was seen in the patients above 70 years (126, 127). This could be another factor favoring the hypothesis of genetic predisposition to severe COVID-19 and may explain the higher mortality in the geriatric population.

In a recent study, the levels of autoantibodies in COVID-19 cases were observed to be as high as 50% compared to 15% of healthy control group (128). This sporadic loss of self-tolerance may explain the mortality associated with severe COVID-19. Auto-antibodies targeting connective tissues and cytokines may be associated with the severity of COVID-19. The longitudinal production of IgG and auto-antibodies might be correlated with the viral genome and non-structural proteins of SARS-CoV-2 (128). In another study, Bastard et al. have reported anti-IFN auto-antibodies in 101 of 987 cases with severe SARS-CoV-2 infection. These included anti-IFN-ω in 18/101, anti-IFN-α in 36/101 and both anti-IFN-ω and anti-IFN-α in 56/101 cases. Patients with mild and asymptomatic infection, however, did not have measurable autoantibodies (125). Similarly, Goncalves et al. reported positive IFN-I auto-Abs in 18% severe COVID-19 cases, IFN subtypes IFN-ω and no measurable IFN-I auto-Abs in mild cases (129). In a French study, auto-Abs were observed in 20% severe COVID-19 cases (130). Studies have also reported the anti-cytokine antibody (ACA) blocking activity in severe COVID-19 (125, 131, 132). Moreover, presence of anti-IFN antibodies may significantly impair the immune response itself and may lead to a broader immune dysregulation. This was previously seen in inborn errors of immunity such as diseases of immune dysregulation presenting with monogenic and polygenic defects (*RAG1/2*, *AIRE*, auto-antibodies against *IL-17*, *IL-22*, *IFN-γ*, and GM-CSF) (133). ACAs have also been observed in SLE patients, thus they play a critical role in maintaining homeostasis of immune response. Similarly, ACAs play an important role in COVID-19 which may alter the immune response in these patients (128). On the other hand, the activation of pro-inflammatory markers and auto-antibodies may dampen T-cell responses resulting in altered self-tolerance.

Elevated levels of autoantibodies targeting endoglins were reported in several cases with MIS-C using proteomic arrays (52). Endoglin glycoprotein is expressed by endothelial cells and is critical in maintaining structural integrity of arteries. Autoantibodies against endoglin have also been reported in a small proportion of cases with KD (52). However, autoantibodies against *MAP2K2* and casein kinase family (viz. *CSNK1A1, CSNK2A1, CSNK1E1*) were only found in the cases with MIS-C. Gruber et al. have also reported the role of autoantibodies targeting endothelial, gastrointestinal, and immune-cell (85).

Mechanism of autoantibody clearance in MIS-C has not been explored thoroughly. As described earlier, low levels of TFH cells are reported in acute phase of MIS-C. Reduced TFH cells are associated with generation of low affinity antibodies. These, low affinity antibodies are cleared rapidly than the high affinity antibodies.

Clinical Management of Multisystem Inflammatory Syndrome in Children

As described above, immunopathogenic alterations in MIS-C have been reported that have prompted recommendations for diverse treatment strategies. Patients with MIS-C have an enhanced propensity to vascular damage and hyperinflammation, therefore, aggressive management of cardiac manifestations and immunomodulation is recommended (134). MIS-C patients with CAA require frequent echocardiograms. Cardiac MRI is indicated in cases with left ventricular (LV) dysfunction and in patients with suspicion of distal CAAs Cardiac CT is recommended. Immunomodulatory treatments are required in MIS-C cases with life-threatening complications. IVIg therapy in MIS-C accelerates auto-antibody clearance, inhibition of complement deposition, and increase

in T-regulatory cells (135). The use of biologics has been recommended for cases refractory to treatment with IVIG and corticosteroids (134, 136, 137).

CONCLUSION

In this manuscript, we have reviewed the putative immunopathogenic mechanisms operational in SARS, MERS, COVID-19, MIS-C and KD. SARS-CoV-2 is characterized by a modified spike (S1) polypeptide that has a higher binding affinity to host NRP1 receptors. This is responsible for the increased infectivity and tissue tropism seen with SARS-CoV-2 infections. Patients with COVID-19 appear to have delayed IFN responses that results in upregulation of the cytokines IL-6, IL-7 and TNF-α. This aggravates inflammation and may exacerbate clinical illness.

MIS-C, previously considered a KD-like disease, differs by age of presentation, ethnicity and immune response. Moreover, MIS-C is characterized by a differential cytokine production (IL6 and IL10), altered differentiation state of plasmablasts (T-bet, eomesodermin), and auto-antibodies to MAP2K2, CSNK1A1, CSNK2A1 and CSNK1E1. Host genetic factors also appear to play a crucial role in predisposition to MIS-C. Variations in *SOCS1, XIAP* and *CYBB* genes have been reported to be associated with pathogenesis of this disorder. These variations are different than the loci previously associated with development of KD.

There is concern about the long term cardiovascular sequalae of MIS-C as children present with acute myocardial injury/myocarditis and may develop coronary artery aneurysms. Differences in the immune response to CoVs between adults and children could partly explain the difference in the disease severity observed across age groups. Although the pathogenesis of MIS-C is not completely defined, it is reasonable that age related peculiarities in the immune response to CoVs could be involved to explain its prevalence in the pediatric population. Thus, MIS-C and KD are a spectrum of hyperinflammatory disorders arising as a sequel to known (MIS-C) and unknown (in KD) infections. Deeper understanding of these disorders is required to resolve the relationship between MIS-C and KD.

AUTHOR CONTRIBUTIONS

SS: conceptualization of the review, substantial contribution in drafting, and finalizing the draft. AR: substantial contribution in drafting and revising the draft. MD, RT, and PM: substantial contribution in drafting and revising the draft at various stages. PB, SL, JS, KS, and SM: substantial contribution in drafting the manuscript.

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Case Report: Anterior Scleritis Presenting as a Primary Ocular Manifestation in Multisystem Inflammatory Syndrome in Children With COVID-19

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Multisystem inflammatory syndrome in children (MIS-C) is a newly defined hyperinflammatory disease linked to antecedent coronavirus disease 2019. Patients with MIS-C present with various symptoms, and ocular findings such as mild bilateral conjunctivitis are relatively common. However, detailed descriptions of severe ocular reports associated with MIS-C are scarce in the current literature. Here we report a case of MIS-C in a Japanese boy, with severe eye manifestations in the form of anterior scleritis as the primary MIS-C symptom. Detailed ocular examinations by ophthalmologists may be key for clarifying the pathophysiology of MIS-C.

Keywords: multisystem inflammatory syndrome in children, COVID-19, scleritis, Kawasaki disease, conjunctivitis, fundus findings, ophthalmological examinations, case report

INTRODUCTION

Multisystem inflammatory syndrome in children (MIS-C) has emerged as a new hyperinflammatory disease linked to antecedent coronavirus disease 2019 (COVID-19) (1). MIS-C shares some clinical overlap with Kawasaki disease (KD), a systemic vasculitis, which is common in infants and young children (2). Although it is unclear whether MIS-C and KD are different syndromes or represent a common disease spectrum, both diseases manifest symptoms associated with systemic vascular involvement in various organs, such as the eye, skin, heart (including coronary arterial abnormalities), liver, and kidneys (2). Patients with MIS-C present with various symptoms among which ocular findings are relatively common, such as mild bilateral conjunctivitis (55%) (2). However, detailed descriptions of severe ocular reports associated with MIS-C are scarce in the current literature. Here we report a case of MIS-C in a Japanese boy with severe eye manifestations in the form of anterior scleritis as the primary symptom of MIS-C. The present case partially illustrates the pathophysiology of MIS-C.

CASE DESCRIPTION

A previously healthy 11-year-old Japanese boy was diagnosed with COVID-19 by nasopharyngeal polymerase chain reaction testing, attended with his parents. At the time, the delta variant was prevalent in Japan. The patient's only symptom was mild fever for 2 days. Five weeks later (day 1),

he experienced bilateral eye pain that disturbed his sleep, and photophobia. On day 5, he developed a fever of 38.5°C, bilateral red eyes, and general malaise, followed by abdominal pain, frequent vomiting, and watery diarrhea on day 6. During this period, he visited an ophthalmology clinic several times, and was diagnosed with severe anterior scleritis and conjunctivitis of unknown origin based on the slit-lamp examination; the examination showed microvascular dilatation in various layers, including not only in the conjunctiva, but also in the episclera and deep sclera. Topical steroids (0.1% fluorometholone) did not improve the ocular symptoms. Subsequently, the patient presented with a high fever of 40°C and his general condition deteriorated, which led to his admission in our hospital on day 10. His vital signs were stable, with a body temperature of 37.7°C, respiratory rate of 16/min, heart rate of 117/min, blood pressure of 121/70 mmHg, and SpO_2 of 98% on ambient air. Physical examination revealed cervical lymphadenopathy, abdominal tenderness, hypoactive bowel sounds, and rashes (dime-size annular plaques) on the inner thigh. Ophthalmological examination revealed anterior scleritis suggested by diffuse episcleral and deep scleral injection with microvascular dilatation, as well as bilateral conjunctivitis (**Figures 1A,B**). He did not show any discharges or matting of eyelashes. No uveitis, vitritis, or retinitis was observed. The visual acuity of the patient was normal. The fundal examination findings were unremarkable (**Figure 2**). Ocular ultrasonography was not performed. The film array showed no evidence of active viral infections, including those caused by SARS-CoV-2. **Table 1** shows the laboratory findings. The patient presented a normal range of leukocytes with decreased lymphocyte count (600/μL), hyperinflammatory state (C-reactive protein of 10.5 mg/dL, procalcitonin of 0.86 ng/dL, serum amyloid A of 1,219 μg/mL, ferritin of 252 ng/dL, and lactase dehydrogenase of 495 U/L), hypercoagulopathy (FDP of 12.1 μg/mL and D-dimer of 3.8 μg/mL), and elevated markers of cardiac stress/damage (brain natriuretic peptide of 47 pg/mL, N-terminal pro-brain natriuretic peptide of 704 pg/mL, and troponin T of 0.02 ng/mL). The patient also showed liver dysfunction (alanine aminotransferase of 213 U/L, and aspartate aminotransferase of 385 U/L), and dehydration with hyponatremia and hypoalbuminemia. Chest radiography and electrocardiography findings were unremarkable. Echocardiography demonstrated decreased cardiac function with a left ventricular ejection fraction (LVEF) of 48% (using a modified Simpson method). Although the patient showed some features compatible with KD, he was diagnosed as having MIS-C based on the definition by the Centers for Disease Control and Prevention and the World Health Organization (3, 4). Following intravenous immunoglobulin (2 g/kg) administration and heparinization on day 11, his fever subsided by the next day (day 12). Notably, the ocular manifestations improved dramatically after intravenous immunoglobulin administration, without additional topical steroids (**Figures 1C,D**). Serial echocardiography demonstrated gradual improvement in LVEF, and LVEF improved to normal by day 14. The patient's coronary arteries were normal. The patient was discharged on day 18 and had uneventful cardiac and ocular manifestations 6 months after discharge (**Figure 3**).

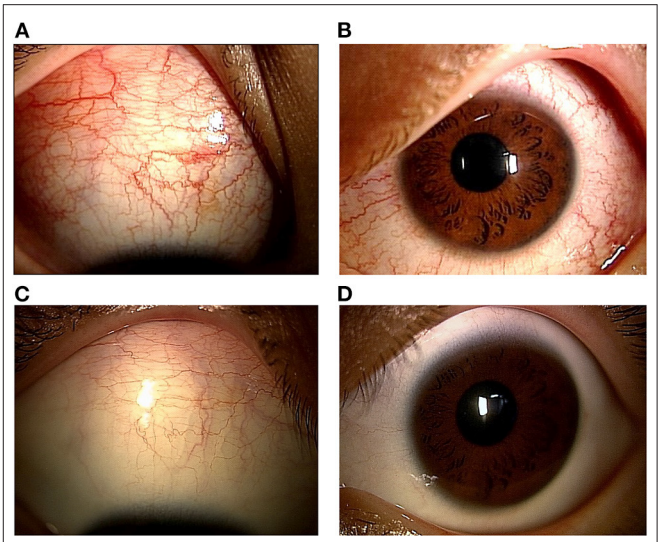

FIGURE 1 | Ophthalmological slit-lamp examination before and after the intravenous immunoglobulin (IVIG) administration. Right **(A)** and left **(B)** slit-lamp photographs show bilateral conjunctival, episcleral and scleral njection, suggesting scleritis and concomitant conjunctivitis. Right **(C)** and left **(D)** slit-lamp photographs after IVIG administration, showing the dramatic improvement in their ocular findings.

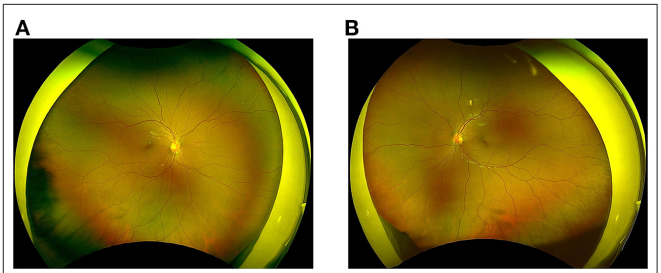

FIGURE 2 | Fundus findings before the IVIG treatment. Right **(A)** and left **(B)** wide-field fundus photographs show no abnormal findings.

DISCUSSION

MIS-C is defined as an individual aged less than 21 years who presents fever, laboratory evidence of inflammation, multisystem organ involvement (at least in 2 organ systems, such as ocular, dermatologic, gastrointestinal, and cardiac manifestations) and laboratory confirmed SARS-CoV-2 infection or epidemiologic link to a person with COVID-19 (3, 4). Therefore, MIS-C can present with various clinical features. While the literature is limited regarding ocular reports associated with MIS-C, anterior uveitis has recently been reported in addition to conjunctivitis (5–9). The present case was unique for the following two reasons: 1) the patient showed severe ocular manifestations as the primary symptom of MIS-C prior to other findings, such as fever or gastrointestinal manifestations, which could lead to delay in diagnosis, and 2) he suffered anterior scleritis, an unusual and severe form of inflammatory

TABLE 1 | Laboratory test at admission.

[Blood cell count]		
White blood cell	9,800	/μL
Neutrophil	85.7	%
Lymphocyte	0.1	%
Red blood cell	447 $\times 10^4$	/μL
Hemoglobin	12.8	g/dL
Platelets count	30.8$\times 10^4$	/μL
[Coagulation test]		
FDP	12.1	μg/mL
Fibrinogen	739	mg/dL
D-dimer	3.8	μg/mL
[Blood biochemistry]		
CRP	10.5	mg/dL
Total Protein	7.6	g/dL
Albumin	3	g/dL
BUN	24	mg/dL
Creatinine	0.64	mg/dL
Creatinine kinase	67	U/L
AST	385	U/L
ALT	213	U/L
LDH	495	U/L
Sodium	135	mmol/L
Potassium	4	mmol/L
Chloride	99	mmol/L
Procalcitonin	0.86	ng/dL
Ferritin	252	ng/dL
Serum Amyloid A	1,219	μg/mL
NT-pBNP	704	pg/mL
BNP	47	pg/mL
Troponin T	0.02	ng/mL

[Film array]	
Viruses	
Adenovirus	N/D
Coronavirus 229E	N/D
Coronavirus HKU1	N/D
Coronavirus NL63	N/D
Coronavirus OC43	N/D
SARS-CoV-2	N/D
Human metapneumovirus	N/D
Human Rhinovirus/Enterovirus	N/D
Influenza A, B	N/D
Parainfluenza Virus 1, 2, 3, 4	N/D
Respiratory Syncytial Virus	N/D
Bacteria	
Bordetella parapertussis	N/D
Bordetella pertussis	N/D
Chlamydia pneumoniae	N/D
Mycoplasma pneumoniae	N/D

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CRP, C-reactive protein; FDP, fibrinogen degradation products; LDH, lactase dehydrogenase; NT-pBNP, N-terminal pro-brain natriuretic peptide.

eye disease, rather than conjunctivitis. In addition, his detailed ocular examination provided us with clinical clues regarding the possible pathogenesis of MIS-C compared with KD.

To our knowledge, this is the first report of severe ocular manifestation as the primary symptom of MIS-C. Recently, several reports have demonstrated symptomatic anterior uveitis in a subset of patients with MIS-C (5–9). Notably, ocular symptoms associated with uveitis, such as blurring of vision or photophobia, became apparent at the subacute stage of disease, during or after the treatment of other MIS-C-related organ dysfunctions, such as myocarditis. The present case is unique in that the patient's severe ocular manifestation preceded other symptoms, such as fever, which could result in a delay in the diagnosis of MIS-C. We therefore recommend that pediatricians and physicians should keep in mind that severe ocular manifestations could be the first symptom of MIS-C, and MIS-C should be considered for a differential diagnosis, especially in COVID-19-prevalent areas.

The patient in the present case suffered from anterior scleritis as well as conjunctivitis. Ocular ultrasonography was not performed, and concurrent posterior scleritis was not fully ruled out. Since he first complained of bilateral eye pain and photophobia, followed by bilateral red eyes, scleritis could have preceded conjunctivitis. Scleritis is an inflammation in the episcleral and scleral tissues in both superficial and deep episcleral vessels, and can be vision-threatening. It is often associated with an underlying systemic disease (in up to 50% of patients), suggesting that the immune system may play a role in the pathogenesis of scleritis (10). To date, only one report has described bilateral anterior scleritis concomitant with anterior uveitis. In this report a 17-year-old boy with MIS-C complained of bilateral red eyes, eye pain, photophobia, and blurring of vision, with subsequent fever that occurred 1-week after post-admission, and after a 3-day course of intravenous methylprednisolone and tocilizumab administration (6). His eye condition required additional oral prednisolone and eye drops (0.1% dexamethasone) for up to a 6-week period. In contrast, in the MIS-C with scleritis case presented here, intravenous immunoglobulin was administered for MIS-C-related organ dysfunctions including

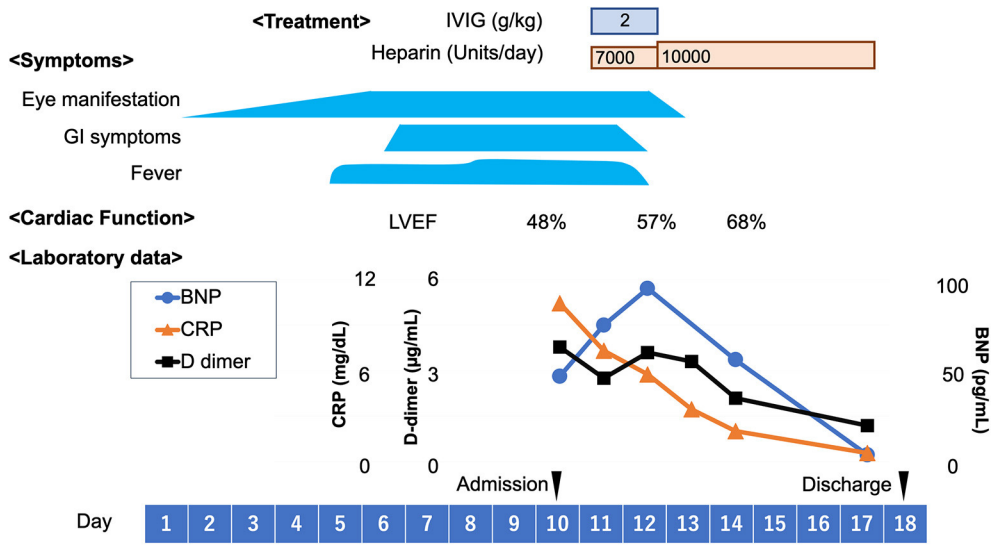

FIGURE 3 | Clinical course. BNP, brain natriuretic peptide; CRP, C-reactive protein; GI, gastrointestinal; IVIG, intravenous immunoglobulin; LVEF, left ventricular ejection fraction.

fever, gastrointestinal symptoms, myocardial dysfunction and ocular symptoms, as the patient had been refractory to a steroid eye drop before admission. Fortunately, intravenous immunoglobulin administration alone immediately relieved the patient's eye symptoms together with other symptoms. He showed no ongoing inflammation thereafter. The precise mechanism is unknown why the immunoglobulin was effective for scleritis in the present case with MIS-C, as therapeutic options usually include steroid and immunosuppressive drugs for non-infectious scleritis (10). However, it is reasonable to consider immunoglobulin administration as a first step therapeutic option if the patient with MIS-C show severe ocular manifestation refractory to a steroid eye drop. Moreover, a thorough ophthalmological examination should be performed to avoid misdiagnosing the potentially vision-threatening condition of scleritis/uveitis as common conjunctivitis.

To some extent MIS-C mimics KD, and 40% of MIS-C cases meet the criteria for either complete or incomplete KD (2). Compared with KD, MIS-C more often presents with gastrointestinal (92%) and cardiovascular (80%) symptoms, both of which were seen in the present case (2). Considering eye manifestations, both MIS-C and KD show similar ocular inflammation in the form of conjunctivitis and anterior uveitis (11, 12). The fundal findings in KD have not been fully examined in the currently available English literature, probably because of technical problems with examining infants/young children (usually younger than MIS-C patients). Posterior involvement in KD is rare and is usually limited to case reports (13). Similarly, fundus findings in MIS-C are scarce in the literature, but some reports have demonstrated normal findings, as described in this case (6, 7, 9). Considering that both MIS-C and KD mainly involve the anterior segment of the eyes, we speculate that MIS-C and KD have a similar pathogenesis. To prove this hypothesis, more information using multimodalities, such as histopathological examinations, is required.

Coronary arterial abnormalities were unique findings in both MIS-C and KD groups. In patients with KD, they may determine the long-term morbidity and mortality in 20–25% of untreated cases; therefore, early diagnosis and treatment are essential to prevent cardiac complications (14). When examining the eyes for small vessel changes, we could predict the condition of the coronary arteries in patients with KD. Lim et al. (15) demonstrated a significant association between the diameter of coronary arteries and retinal arteriolar geometric changes in 11 children with new-onset of KD and with a median age of 5.9 years. Similarly, a subset of patients with MIS-C present with coronary complications, although the precise underlying mechanism is unclear. Our future studies will evaluate the vascular condition, including that of the coronary arteries, through the eyes using noninvasive techniques; this research could lead to a deeper understanding of the pathophysiology of MIS-C. The relatively older-age-onset of MIS-C compared to KD would be advantageous for such ophthalmologic examinations.

In conclusion, MIS-C presents with a wide variety of clinical manifestations, with the present case showing severe ocular manifestations in the form of anterior scleritis as the primary MIS-C symptom. In addition, ocular scleritis could be sight-threatening, and therefore it may require specific treatment in MIS-C cases such as intravenous immunoglobulin. Detailed ocular examinations by ophthalmologists could refine and guarantee the diagnosis of MIS-C, and could possibly help in further clarifying the MIS-C pathophysiology.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

DM, DT, YK, YM, MH, and MS managed the patient, contributed to the conception of the study, and drafted the manuscript. YK and SM reviewed the manuscript from the ophthalmological perspective. TY critically reviewed the manuscript. All authors read and approved the final manuscript.

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Multisystem inflammatory syndrome in children related to COVID-19: Data from a Mexican national referral children's hospital

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Objectives: To describe characteristics of patients with the pediatric inflammatory multisystem syndrome, temporally associated with SARS-CoV-2 (PIMS-TS)/multisystem inflammatory syndrome in children (MIS-C) and to identify factors associated with admission to the pediatric intensive care unit (PICU) in the Mexican children without coronavirus disease 2019 (COVID-19) vaccination.

Methods: This was a cross-sectional study performed at Hospital Infantil de Mexico Federico Gomez, a referral children's hospital in Mexico. The study included all cases that met the criteria for PIMS-TS/MIS-C, unvaccinated, between March 2020 and January 2022. The primary outcome was the admission to PICU. Associations of PICU admission with demographic and clinical variables were estimated using logistic regression analyses.

Results: We identified a total of 90 cases, with a median age of 7.5 years old, 47 (52.2%) girls. A previously healthy status was recorded in 76 (85%) children. All patients had positive PCR, serology test, or COVID-19 exposure. PICU admission was reported in 41 (45.6%) children. No deaths were reported. Patients received as treatment only corticosteroids in 53.3% of the cases. In univariable analyses, baseline factors associated with PICU admission were older age, hypotension or shock, positive PCR test, hypoalbuminemia, elevated procalcitonin, ferritin, and lymphopenia. Age, shock at admission, and hypoalbuminemia remained independently associated in the multivariable analysis adjusted by gender and previously healthy status.

Conclusion: We found a high proportion of previously healthy children in patients with PIMS-TS/MIS-C in our center. Critical care attention was received by nearly half of the children. The main treatment used was steroids. Age, shock at admission, and hypoalbuminemia were factors associated with PICU admission.

KEYWORDS

pediatric inflammatory multisystem syndrome temporally associated with COVID-19, PIMS-TS, Multisystem Inflammatory Syndrome in Children (MIS-C), SARS-CoV-2, COVID-19, epidemiology, pediatrics

Introduction

In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was described as the causal agent of coronavirus disease 2019 (COVID-19) (1). Early in the pandemic, the main manifestations in children with COVID-19 were fever, cough, and mild pneumonia, and the epidemiology was obscured due to many asymptomatic cases (1). However, a severe multisystem inflammatory syndrome was described in children under 21 years old in Europe and the United States. This syndrome had similar features to Kawasaki disease and toxic shock syndrome (2). After noticing a gradual increase in cases of children with multisystem inflammation as a late response to SARS-CoV-2 infection, the definition of pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) was developed by The Royal College of Pediatrics and Child Health (RCPCH) and Multisystem Inflammatory Syndrome in Children (MIS-C) by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) (3).

At the beginning of the pandemic, the incidence of PIMS-TS/MIS-C was reported as 2 per 100,000 individuals younger than 21 years of age (4). As of March 2022, the CDC in the United States reported a total of 7,459 cases and 63 deaths (5). In a cohort study, the incidence was 5.1 cases per million persons-months and 316 per million persons with SAR-CoV-2 younger than 21 years old (6). In the latest epidemiological update of COVID-19 of the z(PAHO) and WHO on December 2nd, 2021, a total of 8,686 cumulative confirmed cases of PIMS-TS/MIS-C were reported, including 165 deaths with a fatality rate of 1.9% (7). In Mexico, as of March 2022, a total of 434,238 confirmed cases of COVID-19 and 1,078 deaths in children under 19 years of age were reported (8). However, there is currently no official report on the number of cases of PIMS-TS/MIS-C in the Mexican population.

Since the emergence of this new entity, a wide clinical spectrum of clinical signs and symptoms have been described, characterized by persistent fever and multisystem involvement, predominantly gastrointestinal, cardiac manifestations, and shock status (9, 10). Different clinical phenotypes have been described in order to standardize both diagnosis and treatment: Kawasaki disease-like presentation, undefined inflammatory presentation, and shock-like presentation (9). A significant proportion of patients experienced severe disease requiring admission to the Pediatric Intensive Care Unit (PICU) (11–13). Immunomodulatory therapies have been used to reverse the hyperinflammatory state, mainly immunoglobulin and corticosteroids (14, 15). In cases of refractoriness, biologics such as anakinra, infliximab, and tocilizumab have been used (16, 17). Anticoagulation and platelet antiaggregating treatment are described as adjuvant therapy (16). However, the response to treatment may vary due to genetic susceptibility (18). It is interesting to observe the clinical behavior in the context of the emergence of new SARS-CoV-2 variants and during the different pandemic waves. Considering this entity's relevance, it is necessary to carry out studies that contribute to the national and international epidemiology. The results of research studies may allow to develop guidelines focused on timely diagnosis and adequate treatment, in order to prevent complications that can lead to fatal outcomes in patients.

The aim of this study was to describe the clinical characteristics of patients with PIMS-TS/MIS-C and to identify the factors associated with admission to the PICU in a third-level hospital in Mexican children without COVID-19 vaccination.

Patients and methods

Patients and study outcomes

This was a cross-sectional study performed at Hospital Infantil de Mexico Federico Gomez, a national referral children's hospital in Mexico City. The study included all consecutive patients younger than 18 years old that met the criteria for PIMS-TS/MIS-C of the RCPCH, WHO, and/or CDC, who were hospitalized between March 2020 and January 2022. All patients were unvaccinated against SARS-CoV-2. Medical records were reviewed at the end of the hospitalization of each patient. The protocol was approved by the local ethics committee (Project Number HIM-2021-018). Since this was a study comprising a review of de-identified data, written informed consent was not required.

Variables assessed in the analysis were demographic data, clinical and laboratory data, such as age, sex, and clinical variables, including hospitalization days, symptoms duration, diagnosis at admission and all components of clinical criteria of WHO and CDC and treatment. We further analyzed levels of inflammatory markers, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin, and D-dimer. We included only patients with exposure to a suspected or confirmed COVID-19 cases within 4 weeks prior to the onset of symptoms. Treatment received during hospitalization was recorded. The primary outcome on this analysis was the admission to the intensive care unit (PICU).

The number of PIMS-TS/MIS-C cases registered by month at our center was graphically compared to the total number of COVID-19 cases by month in the Mexican general population reported by WHO throughout the pandemic (19).

Statistical analysis

Characteristics were examined for their association with admission to PICU using descriptive statistics; chi-squared or Fisher's exact test for categorical variables, *T*-student or Mann–Whitney *U*-test for continuous variables. In addition,

we computed odds ratios (*OR*) with 95% confidence intervals (*CI*) to examine the association between admission to PICU and covariates, using logistic regression analyses. We analyzed univariable and multivariable associations by adjusting for potential confounders, such as age, gender, and previously healthy status. The p-values < 0.05 were considered statistically significant. All analyses were performed with STATA 14.0 (Stata Corp LP, College Station, TX, USA).

Results

We identified a total of 90 cases. Children had a median age of 7.5 years old (interquartile range, IQR 2–11), the youngest being 2 months old and the oldest 17 years old, with 47 (52.2%) being female. Most of the children were previously healthy, 76 (85.4%).

Of all the above-mentioned cases, 41 (45.6%) were admitted to PICU, and 22 (24.4%) required mechanical ventilation. There was one documented case of macrophage activation syndrome (MAS), but no cases of disseminated intravascular coagulation (DIC) or deaths were reported.

Table 1 describes the demographic and clinical characteristics as well as the laboratory data at baseline in patients with PIMS-TS/MIS-C in children in our center by PICU admission status, from March 2020 to January 2022 of our studied population. No differences were noted based on sex. All of the patients had a history of positive PCR, serology test, or exposure to COVID-19.

Factors preceding admission significantly associated with the admission to PICU were age, *OR* 1.18 (95% *CI*: 1.1–1.3); hypotension or shock at admission, *OR* 21.1 (95% CI: 7.2–62.4); positive RT-PCR antigen test for COVID-19, *OR* 3.7 (95% *CI*: 1.5–9.3); CRP $\geq$ 7.4 (median in our population), *OR* 5.2 (95% *CI*: 1.9–13.8); elevated procalcitonin and ferritin (*OR* 4.0, 95% *CI*: 1.2–13.4 and *OR* 3.9, 1.3–11.7, respectively); lymphopenia, *OR* 4.3 (95% *CI*: 1.8–10.5) and hypoalbuminemia *OR* 4.5 (95% *CI* 1.4–14.9). In the multivariable analysis adjusted by gender and previously healthy status, age (*OR* 1.2, 95% *CI*: 1.1–1.5) and hypoalbuminemia (*OR* 13.4, 95% *CI*: 2.4–75.5), shock at admission (*OR* 23.7, 95% *CI*: 6.1–92.2) remained significantly associated with PICU admission.

Table 2 shows the management of 90 patients with PIMS-TS/MIS-C in Children in our center by PICU admission status from March 2020 to January 2022. In 53.3% of cases, only corticosteroids were used and the combination of intravenous immunoglobulin (IVIG) and corticosteroids was utilized in 40.0%. No children received extracorporeal membrane oxygenation (ECMO).

Figure 1 displays the number of PIMS-TS/MIS-C cases and the total number of COVID-19 cases in the Mexican general population by month reported by WHO (19). The first patient was registered in our database in June 2020. An increase in the number of cases of PIMS-TS/MIS-C after the peak of waves of COVID-19 in the general population in Mexico was observed.

Discussion

The present study focused on the description of characteristics of patients with PIMS-TS/MIS-C in a national referral center in Mexico and identification of factors associated with admission to PICU. The highest prevalence was observed in previously healthy school-aged children. This finding is in line with previous reports in the literature where MIS-C was described as predominantly affecting children between 6 and 12 years of age (20). The age range of presentation has been reported from 7 months to 20 years (21). The previous studies suggested a greater predilection for male gender; however, later studies did not reveal broad differences in this variable (11, 21, 22). The most frequent manifestations in our study were fever, mucocutaneous, gastrointestinal, and cardiovascular. These results are similar to those reported by different cohorts during the pandemic's course. In a meta-analysis including 27 studies with a large population of 917 patients, the most common symptoms were fever and gastrointestinal involvement (22). Another systematic review published by Hoste et al. reported that fever was documented in all patients during the first 5 days; 85.6% presented gastrointestinal symptoms such as diarrhea, abdominal pain, and vomiting; followed by cardiovascular disease in 79.3% (11).

Regarding laboratory findings, D-dimer elevation was reported in 97% of patients, and in all patients, inflammatory markers were considered within the aforementioned definition. These are related to the secretion of multiple inflammatory cytokines (20). Other biomarkers, such as ferritin, fibrinogen, and cardiac enzymes, have also been described (21). The elevation of procalcitonin and pro-BNP has been associated with admission to the PICU (13, 23). The first cases of PIMS-TS/MIS-C were described 4 weeks after acute SARS-CoV-2 infection (3). To complement the diagnosis, study tests such as PCR for SARS-CoV-2 and serology had been used. Approximately 75% of the children in the different published cut-offs had antibodies for SARS-CoV-2; and 52% had positive PCR (20). In our study, 36% had positive PCR tests for SARS-CoV-2 on admission. We found that PCR for SARS-CoV-2 was frequently positive in patients admitted to the PICU.

In a systematic review, a severe course of the disease was reported in up to 86% of patients. This was related to older age, gastrointestinal, and cardiovascular symptoms (11). A recent study found that the presence of anemia, diarrhea, hypoxia, altered mental status, and seizures or shock were risk factors for PICU admission (24). In our study, the associated factors were age, hypoalbuminemia, and shock at admission.

During the course of the pandemic, different clinical behaviors have been described, being denominated presentation phenotypes of MIS-C. In the MIS-C management guidelines in

TABLE 1 Demographic, clinical characteristics, and laboratory data at baseline in patients with Multisystem Inflammatory Syndrome in Children in Hospital Infantil de México Federico Gomez by PICU admission status, from March 2020 to January 2022.

Characteristics	Total $N = 90$	PICU 41 (45.6%)	NO PICU 49 (54.4%)	Univariable[a] OR (95% CI)	*p*
Age, median (IQR)	7.5 (2–11)	**10.0 (7–12)**	3.0 (2–8)	**1.18 (1.1–1.3)**	**0.001**
Female sex, *n* (%)	47 (52.2)	20 (48.8)	27 (55.1)	0.7 (0.3–1.8)	0.550
Overweight and/or Obesity (WHO), *n* (%)[b]	25 (31.7)	13 (38.2)	12 (26.7)	1.7 (0.7–4.4)	0.276
Previously healthy, *n* (%)	76 (85.4)	34 (82.9)	42 (87.5)	0.7 (0.2–2.3)	0.544
Hospitalization days, median (IQR)	6.0 (4–9)	7.0 (5–11)	5.0 (3–7)	1.1 (0.9–1.2)	0.087
Symptoms duration days, median (IQR)	6.0 (4–9)	6 (3–8)	7 (6–10)	0.9 (0.9–1.0)	0.092
Number of previous medical visits due to current illness	3.0 (2–4)	3 (2–4)	3 (2–4)	1.3 (0.9–1.9)	0.104
Kawasaki diagnosis at admission	19 (21.1)	6 (14.6)	13 (26.5)	0.5 (0.2–1.4)	0.174
PIMS diagnosis at admission	75 (83.3)	34 (82.9)	41(83.7)	1.1 (0.3–4.3)	0.908
RT-PCR antigen test for COVID-19	32 (36.4)	**21 (52.5)**	11 (22.9)	**3.7 (1.5–9.3)**	**0.005**
Positive serology for COVID-19[c]	19 (67.9)	11 (78.6)	8 (57.1)	2.8 (0.5–14.4)	0.232
Contact with patients with COVID-19 (4 weeks before)	74 (84.01)	30 (73.2)	44 (93.6)	0.2 (0.1–0.8)	0.185
Positive test or contact	90 (100)	41 (100)	49 (100)	-	-
WHO PIMS criteria, *n* (%)	90 (100)	41 (100)	49 (100)	-	-
Age 0–19 years					
Fever >3 days	72 (80.0)	31 (75.6)	41 (83.7)	0.6 (0.2–1.7)	0.343
Rash or bilateral non-purulent conjunctivitis or mucoutaneous inflammation signs	76 (84.4)	34 (82.9)	42 (85.7)	0.8 (0.3–2.5)	0.717
Hypotension or shock	41 (45.6)	**33 (80.5)**	8 (16.3)	**21.1 (7.2–62.4)**	**<0.001**
Features of myocardial dysfunction, pericarditis, valvulitis or coronary abnormalities	74 (82.2)	35 (85.4)	39 (79.6)	1.5 (0.5–4.5)	0.477
Elevated D dimer > 550 ng/ml	86 (95.6)	39 (95.1)	47 (95.2)	0.8 (0.1–6.2)	0.855
Acute gastrointestinal problems	70 (77.8)	33 (80.5)	37 (75.5)	1.3 (0.5–3.7)	0.572
Elevated markers of inflammation [ESR (>10), procalcitonin (>2), CRP (>0.3)]	88 (97.8)	40 (97.6)	48 (97.9)	0.8 (0.1–13.7)	0.899
Negative hemocultures[d]	80 (100)	38 (100)	42 (100)	-	-
CDC PIMS criteria, *n* (%)	90 (100)	41 (100)	49 (100)	-	-
Age < 21 years					
Fever > 38 ≥ 24 h	90 (100)	41 (100)	49 (100)	-	-
Elevated CRP[e]	74 (96.1)	32 (96.9)	42 (95.4)	1.5 (0.1–17.5)	0.736
Elevated ESR[e]	63 (84.0)	28 (84.8)	35 (83.3)	1.1 (0.3–3.9)	0.859
Elevated fibrinogen	63 (73.3)	28 (70.0)	35 (76.1)	0.7 (0.3–1.9)	0.525
Elevated procalcitonin[f]	20 (36.4)	**15 (50.0)**	5 (20.0)	**4.0 (1.2–13.4)**	**0.025**
Elevated ferritin[g]	34 (57.6)	**22 (73.3)**	12 (41.4)	**3.9 (1.3–11.7)**	**0.015**
Elevated HDL[g]	43 (70.5)	17 (60.7)	26 (78.8)	0.4 (0.1–1.3)	0.128
Lymphopenia	44 (49.4)	**28 (68.3)**	16 (33.3)	**4.3 (1.8–10.5)**	**0.001**
Hypoalbuminemia[b]	68 (77.3)	**36 (90.0)**	32 (66.7)	**4.5 (1.4–14.9)**	**0.014**
Glasgow Coma Scale, mean (SD)	14.8 (0.6)	14.7 (0.8)	14.9 (0.2)	0.3 (0.1–1.1)	0.06

[a]Logistic regression analysis.
[b]n = 79.
[c]n = 28.
[d]n = 80.
[e]n = 77.
[f]n = 55.
[g]n = 59.
IQR, interquartil range 25–75.
Bold values indicate statistically significant results.

TABLE 2 Management of 90 patients with Multisystem Inflammatory Syndrome in Children in Hospital Infantil de México Federico Gomez, by PICU admission status from March 2020 to January 2022.

Treatment, *n* (%)	**Total** ***N* = 90**	**PICU** **41 (45.6%)**	**NO PICU** **49 (54.4%)**	**Univariable** **(95% IC)**	***P***
Only corticosteroids	48 (53.3)	25 (60.9)	23 (46.9)	1.8 (0.8–4.1)	0.185
IVIG + corticosteroid	36 (40.0)	15 (36.6)	21 (42.9)	0.8 (0.3–1.8)	0.546
Vasopresors	37 (41.1)	36 (87.8)	1 (2.0)	**345.6 (38.7–3,088.3)**	**<0.001**
Biologic treatment (Infliximab)	2 (2.2)	1 (2.4)	1 (2.0)	1.2 (0.1–19.8)	0.899
Plasmapheresis	1 (1.1)	1 (2.4)	0	-	-
Replacement therapy	1 (1.1)	1 (2.4)	0	-	-
ECMO	0	0	0	-	-

Bold values indicate statistically significant results.

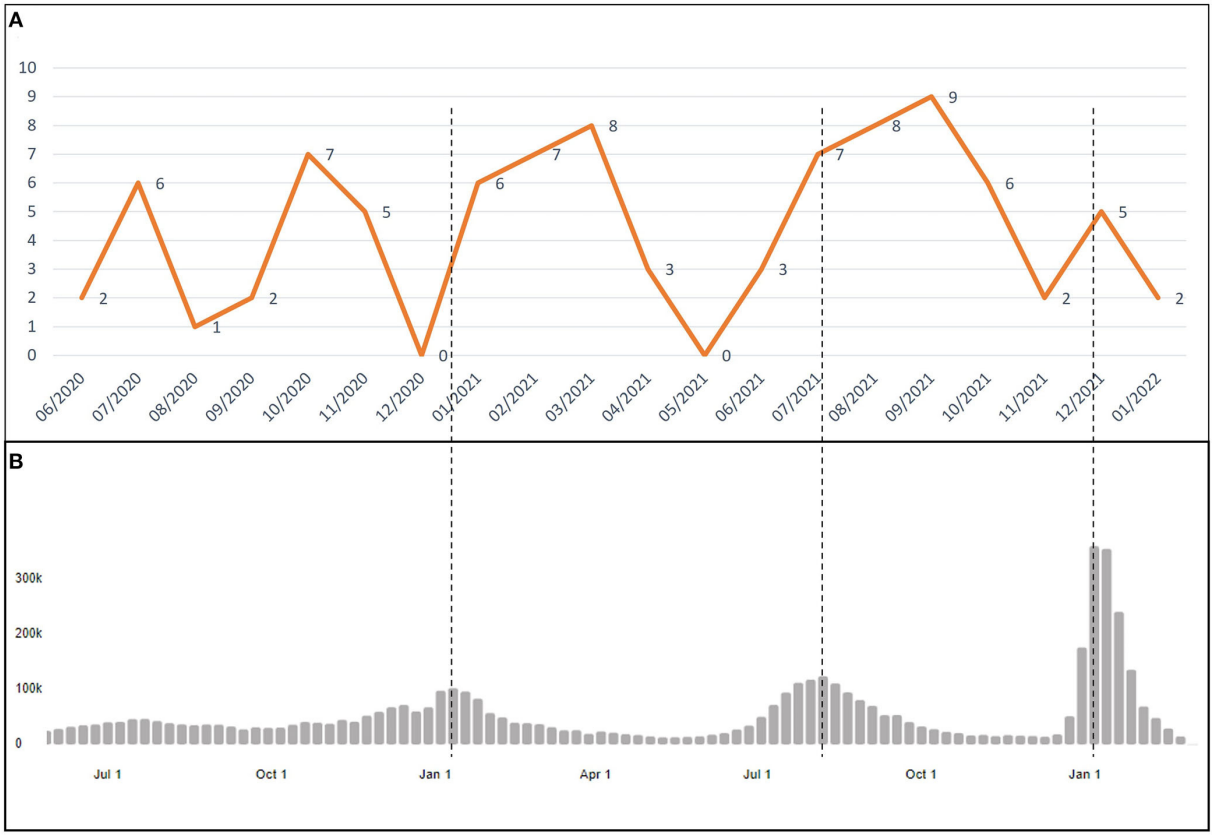

FIGURE 1
Temporal distribution of pediatric inflammatory multisystem syndrome, temporally associated with SARS-CoV-2 (PIMS-TS)/multisystem inflammatory syndrome in children (MIS-C) cases from March 2020 to January 2022. **(A)** Number of cases of PIMS-TS/MIS-C in "Hospital Infantil de Mexico Federico Gomez" by month and **(B)** COVID-19 cases in general population in Mexico by month reported by WHO.

Switzerland, these phenotypes were classified in the following presentations: shock, a presentation similar to Kawasaki disease and indefinite inflammatory (9). This classification was used for our analysis; from our patients, 46% had shock presentation, 21% had a presentation similar to Kawasaki disease, and the remaining had indefinite inflammatory presentation. Other publications describe presentations with characteristics similar to Kawasaki disease in 40% (25).

Regarding the treatment used, most of the patients in our study were treated only with corticosteroids with favorable results (26). Infliximab was used in two refractory cases with presentations similar to Kawasaki disease (26). Among

the comorbidities presented in our study, the relationship between overweight and obesity stands out in 31.7% (20). Other systematic reviews have found obesity as an associated comorbidity (11). Most of the patients in our study had no comorbidities.

We compared the number of PIMS-TS/MIS-C cases by month in our center and the total number of COVID-19 cases in the Mexican general population reported by WHO (19). We observed an increase in the number of cases of PIMS-TS/MIS-C after the peak of waves of COVID-19, which could be explained because PIMS-TS/MIS-C is a late immunology response after an acute SARS-CoV-2 infection.

Currently, with the spread of new variants among non-vaccinated pediatric populations, the spectrum of manifestations in children has changed. Among the last cases included for this analysis, we observed a higher incidence of similar to Kawasaki disease phenotype, compared to shock presentation.

A limitation of our study was the cross-sectional design. This was a single-center study. The small sample size has limited statistical power. However, this is one of the largest reports from a Latin American center and is the first report of PIMS-TS/MIS-C in exclusively Mexican population throughout the pandemic. Another strength of our study is the use of widely accepted definitions.

Conclusion

The present study depicts the experience of our institution with PIMS-TS/MIS-C. Our population was predominantly healthy without significant comorbidities. Nearly half of children received care in PICU, the associated factors were age, shock at admission, and hypoalbuminemia. The main treatment used was corticosteroids. We highlighted the null mortality.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

HM-A, PR-T, and EF-F performed data collection and data analysis. DA-R performed data analysis. EF-F conceptualized the study. All authors wrote and edited the manuscript and read and approved the final version of the manuscript.

Conflict of interest

DA-R is a scientific advisor for GSK unrelated to this study. EF-F has been speaker for Abbvie, Roche, and Pfizer unrelated to this study.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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