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A recently explored aspect of the iceberg named COVID-19: multisystem inflammatory syndrome in children (MIS-C)

Fatih Haslak, Mehmet Yıldız, Amra Adrovic, Sezgin Şahin, Kenan Barut, Özgür Kasapçopur

Department of Pediatric Rheumatology, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, Turkey

ABSTRACT

Humanity has recently gained a novel foe named coronavirus disease 2019. Although data so far mostly suggest that children are more likely to have a favorable disease course, new concerns have been raised because of recently reported pediatric cases with hyperinflammatory conditions resembling Kawasaki disease, toxic shock syndrome, and macrophage activation syndrome/hemophagocytic lymphohistiocytosis. Because the increasing evidence suggests that this recent hyperinflammatory condition emerged in the coronavirus disease 2019 era is a distinct clinical picture, the Centers for Disease Control and Prevention named this novel disease multisystem inflammatory syndrome in children. Even if this novel disease is rare, it seems to be highly fatal. Therefore, it is urgent to understand the pathogenesis of the disease to be able to establish the appropriate treatment regimes. Concerns regarding the diagnostic process and the management of the disease have been raised even among pediatricians. Therefore, we aimed to clarify this newly occurring enigma based on the current literature and our clinical insights.

Keywords: Coronavirus disease 2019 (COVID-19), hyperinflammatory syndrome, toxic shock syndrome, Kawasaki disease, multisystem inflammatory syndrome in children (MIS-C), pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 infection (PIMS-TS), pediatrics, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Introduction

Since December 2019, humanity has been suffering from a novel coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease caused by this virus, named coronavirus disease 2019 (COVID-19). The virus outbreak first emerged in Wuhan, China and spread all over the world rapidly. A global pandemic was declared by the World Health Organization on March 11, 2020 (1, 2).

Despite plenty of data regarding the clinical outcome of the infection accumulated from adults, the disease progression in children remains unclear, possibly because of higher asymptomatic carrier rates in pediatric age (3). Although data so far mostly suggest that children are more likely to have a favorable disease course, new concerns have been raised because of recently reported pediatric cases with hyperinflammatory conditions resembling Kawasaki disease (KD), toxic shock syndrome (TSS), and macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH) (4-6).

Although the first patient with concurrent COVID-19 and KD was described in June 2020 by Jones et al. (7), eight children were reported with severe hyperinflammatory findings similar to KD attributed to SARS-CoV-2 from the United Kingdom (UK) at the end of April 2020. These reports led clinicians to promptly investigate the potential linkage between the current pan-

Corresponding Author:
Özgür Kasapçopur
ozgurkasapcopur@hotmail.com
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demic and KD for the first time (8). Following those in the UK, similar case clusters have been reported from several European countries and the United States of America (9-12).

Because the increasing evidence suggests that this recent hyperinflammatory condition emerged in the COVID-19 era and is a distinct clinical picture from KD, TSS, and MAS/HLH, the Centers for Disease Control and Prevention (CDC) named this novel disease multisystem inflammatory syndrome in children (MIS-C) (13).

Our department is a tertiary pediatric rheumatology center, and we received hundreds of phone calls from the parents of our patients who previously experienced KD or MAS/HLH wondering whether their children are at increased risk of disease recurrence and severe COVID-19. Concerns regarding the diagnostic process and the management of the disease have been raised even among pediatricians. Therefore, we aimed to clarify this newly occurred enigma based on the current literature and our clinical insights.

Clinical and Research Effects

Pathogenetic and epidemiological aspects

It was previously shown that SARS-CoV-2 infects human cells via binding to angiotensin-converting enzyme 2 (ACE2) owing to its spike glycoproteins (S proteins) on the surface (14). The ACE2 serves as a cell receptor in a variety of human cells, such as lung, gastrointestinal tract, kidney, and heart cells (15). Even though this broad distribution of virus receptors among human cells is almost able to explain virus invasion of multiple organs, the exact organ damage mechanism, such as that in MIS-C, remains unclear.

A variety of mechanisms are currently suggested to explain the pathogenesis of MIS-C. However, it has not been precisely elucidated yet owing to a lack of data. Given the urgent need for understanding the action mechanism of the disease, prompt molecular studies involving a large number of patients are clearly required.

Although Tan et al. (16) suggested that direct viral invasion is the main mechanism responsible for the myocyte damage seen in COVID-19, preliminary data obtained from several countries present that SARS-CoV-2 antibody positivity is much more prevalent than SARS-CoV-2 polymerase chain reaction (PCR) positivity among patients with MIS-C (9, 17, 18). This immunological profile of the patients proposes a strong postinfectious etiology for the disease rather than a direct viral invasion.

In addition, it was confirmed that, just after the virus' entrance to human cells, antigen-presenting cells, such as infected macrophages and dendritic cells, induce a maladaptive immune response leading to a massive proinflammatory cytokine release (1). This cytokine storm causes vascular leakage of fluids and immune system cells by activating the coagulation and complement cascades and releasing inflammatory kinins (19).

Therefore, the main mechanism of the organ damage in patients with MIS-C seems to be a kind of antigen-antibody–mediated cytokine storm. For instance, based on the majority of the patients they reported who were SARS-CoV-2 antibody–positive, with elevated inflammatory markers such as interleukin (IL)-1 and IL-6 and without strong evidence supporting the cardiac tropism of the virus, Kaushik et al. (20) suggested that MIS-C is likely to develop predominantly because of an antibody-mediated cytokine storm.

Similarly, in a study from the UK describing 58 patients with MIS-C, the antibody test was positive, whereas the PCR test was negative, in most of the patients. Most of the patients had persistently elevated inflammatory markers, and anakinra (anti–IL-1 agent) was one of the treatment choices that provided clinical improvement. Therefore, it was postulated that possibly an abnormal immune response may induce the development of the disease (21). Furthermore, there are approximately 4 to 5 weeks between the time of peak incidence of pandemic and the time that the first patients with MIS-C occurred, and this interval is another hint supporting the idea of the disease mainly developing because of late and uncontrolled immune response (22-25).

An additional proposed mechanism of action of the virus causing multiorgan damage is endothelial dysfunction because of direct viral infection (26). Varga et al. (27) demonstrated endotheliitis findings caused by SARS-CoV-2 in three adult patients with several comorbidities. More recently, Colmenero et al. (28) examined the skin biopsies of seven children who presented with chilblains during the pandemic, and they demonstrated viroid particles of SARS-CoV-2 and immunohistochemical evidence of endotheliitis.

Because MIS-C shares remarkable similarities with TSS, several studies were performed to figure out the underlying molecular basis. It was previously shown that staphylococcal enterotoxin B (SEB) has a superantigen (SAg) motif that leads to tissue damage by activating T lymphocytes and inducing a massive release of inflammatory cytokines (29). Bittmann et al. (30) reported that SARS-CoV-2 encodes structurally very similar SAgs. Similarly, Cheng et al. (31) demonstrated that epitopes on the S proteins of SARS-CoV-2 contain a motif that has significant sequential and structural similarities with SEB SAg by structure-based computational models.

Another aspect of MIS-C that can present contributions for understanding the pathogenesis are the intriguing epidemiological findings of the disease. For instance, despite the many similarities between KD and MIS-C, the median age of the patients with MIS-C reported so far is older (22). It was previously demonstrated that there is a strong negative correlation between ACE2 enzyme activity and increasing age (32). This may present a reasonable explanation for the vulnerability of older children and adolescents to develop MIS-C compared with younger children.

It is well known that KD, as a differential diagnosis of MIS-C, is predominantly seen in the Asian population, and the SARS-CoV-2 pandemic originated from Far East Asia (4, 33). Nonetheless, MIS-C was mostly reported in children from western countries (8, 9, 11, 12). This paradoxical and asymmetric ethnic distribution is highly suggestive for a distinct genetic predisposition to MIS-C. Consistent with this hypothesis, a novel mutation at D839, which causes an increased binding ability of the SAg to T-cell receptors, was found in a European SARS-CoV-2

strain recently, and it may be a possible explanation of the geographical shift of the disease (30).

Considering an urgent need to better understand this novel disease called MIS-C, we tried to compose a pathogenetic picture summarizing previously suggested possible mechanisms from the current literature (Figure 1).

How do patients with MIS-C present?

According to the study by Riphagen et al. (8), which reported hyperinflammatory conditions in children because of COVID-19 for the first time, all eight children presented with similar symptoms such as fever, conjunctivitis, peripheral edema, extremity pain, diarrhea, vomiting, and abdominal pain. Refractory shock was seen in all patients, whereas significant respiratory involvement was seen in none of them. One had cardiac arrhythmia and required extracorporeal life support, but unfortunately the patient died.

In an Italian study, 10 patients were reported with Kawasaki-like presentations, such as fever, conjunctivitis, lymphadenopathy, mucositis, and polymorphic rash, during the pandemic; all had elevated inflammatory markers, eight had serological evidence of SARS-CoV-2 infection, six had diarrhea, five had pneumonia, five had hypotension, and four had meningeal signs (9). A study by Chiotos et al. (12) describes six pediatric patients with COVID-19 with hyperinflammation; in addition to Kawasaki-like features, all presented with gastrointestinal symptoms and shock.

Pediatric patients with refractory shock findings resembling TSS rather than KD because of COVID-19 were recently reported (34, 35). Because of the similar cytokine profiles, lymphocyte counts, levels of inflammatory markers, and clinical aspects such as fever and several organ damage findings, HLH was also emphasized in the differential diagnosis of these pediatric patients with COVID-19 with a hyperinflammatory state (19).

Finally, given the similarities and differences between children with COVID-19–induced hyperinflammation and patients with KD, TSS, and HLH, CDC put this clinical picture in a particular place, named MIS-C, and established the diagnostic criteria of this novel disease (Table 1) (13, 36).

A recent systemic review revealed that, although most of the patients reported as MIS-C so far had fever, gastrointestinal, cardiovascular, and mucocutaneous involvement, respiratory manifestations were observed only in a minority of patients (37).

In a study by Riollano-Cruz et al. (26), which described the first patients with MIS-C from New York City, seven were found positive by PCR, whereas positive antibodies were found in all 15 patients. Although fever was present in all of the patients, tachycardia and hypotension were present in 13 patients, severe cardiac involvement in 13, gastrointestinal complaints in 13, inotropic or vasopressor need in nine, rash in seven, respiratory symptoms in five, conjunctivitis in four, and edema in four patients. Lymphopenia, thrombocytopenia, hypoalbuminemia, and increased inflammatory markers were common. In another study from New York City including 33 patients with MIS-C, fever and vomiting were the most common symptoms. More than half of the patients had decreased left ventricular function, one third of the patients had shortness of breath, and one patient died (20).

In addition to features resembling KD, TSS, or MAS, patients with a variety of other tissue damages because of COVID-19 were recently reported. For instance, a distinct form of the disease was reported from Spain. Cabrero-Hernández et al. (10) reported five consecutive children with acute abdomen without evident respiratory symptoms; four had a proven SARS-CoV-2 infection. Screening tools revealed significant intestinal inflammation, and all patients recovered. In a study by Belhadjer et al. (11), SARS-CoV-2 infection was shown in 31 of 35 patients who were admitted to the pediatric intensive care unit because of acute heart failure and hyperinflammatory state. Stevens et al. (38) reported the first patient with MIS-C who initially presented with acute pancreatitis. In a study by Miller et al. (39) reporting 44 patients with MIS-C, although the gastrointestinal symptoms were the most common after fever, acute kidney injury was observed in seven of them. Given the pathogenesis of MIS-C, it is also possible to encounter patients with a variety of tissue damage findings because of COVID-19.

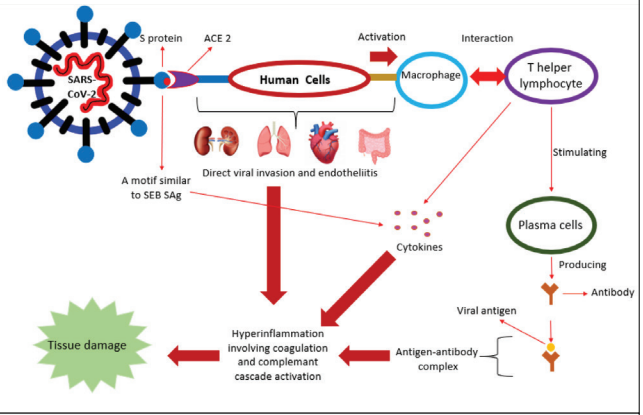

Figure 1. A summary of the possible pathogenetic mechanisms of MIS-C. ACE2, angiotensin-converting enzyme 2; MIS-C, multisystem inflammatory syndrome in children; SAg, superantigen; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SEB, staphylococcal enterotoxin B; S protein, spike glycoprotein.

Table 1. Diagnostic criteria of MIS-C

Case Definition for MIS-C (36)
• An individual aged <21 years presenting with fevera, laboratory evidence of inflammationb, and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); AND
• No alternative plausible diagnoses; AND
• Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test or COVID-19 exposure within the four weeks before the onset of symptoms.

COVID-19, coronavirus disease 2019; IL, interleukin; MIS-C, multisystem inflammatory syndrome in children; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
aFever ≥38.0°C for ≥24 hours or report of subjective fever lasting ≥24 hours.
bIncluding, but not limited to, one or more of the following: an elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase, or IL-6; elevated neutrophils; reduced lymphocytes; and low albumin.

In our daily practice, we also encountered pediatric cases with a broad spectrum of ages similar to those previously reported in the literature. They were mostly found to be serologically positive, whereas the PCR test was negative. In addition to Kawasaki-like features, TSS- and MAS-like findings were observed in a few. Most patients presented with significant gastrointestinal symptoms, but none required respiratory support and none died. Thrombocytopenia, lymphopenia, and increased inflammatory markers and cardiac enzymes were the most common laboratory findings.

What MIS-C is not

The first reported cases of MIS-C had Kawasaki-like features, and they were generally intravenous immunoglobulin (IVIG) responders. Therefore, this conundrum has been previously shown to cause a delay in the diagnosis of typical KD (40). However as a growing number of patients with a hyperinflammatory state because of COVID-19 occurred, it was seen that these patients did not generally fulfill the classic KD definition criteria. They were older, less likely to be Caucasians and Asians, and more likely to present with gastrointestinal symptoms and thrombocytopenia than children with KD. Additionally, the predominant cardiac presentation of these children was myocarditis, whereas it was coronary aneurysms in those with KD. Thus, it was clearly understood that this novel clinical picture was not typical KD (22).

It is well known that TSS is an acute, severe, and toxin-induced condition characterized by multiorgan failure owing to refractory shock. It was recently shown that children with hyperinflammation because of COVID-19 might present similar features to patients with TSS, such as fever, rash, mucous membrane involvement, conjunctivitis, gastrointestinal symptoms, hypotension, cytokine storm, thrombocytopenia, and multiorgan involvement (41-43). However, unlike patients with MIS-C, cardiac involvement, lymphopenia, and hyperferritinemia are not typical signs of TSS (42, 43). Thus, this novel hyperinflammatory condition was considered not to be TSS.

As mentioned previously, children with COVID-19–induced hyperinflammation generally presented with fever, signs of multiple organ damage, high ferritin levels, hypertriglyceridemia, and cytopenia, leading practitioners to consider HLH as a differential diagnosis when they first evaluated these cases (9, 19).

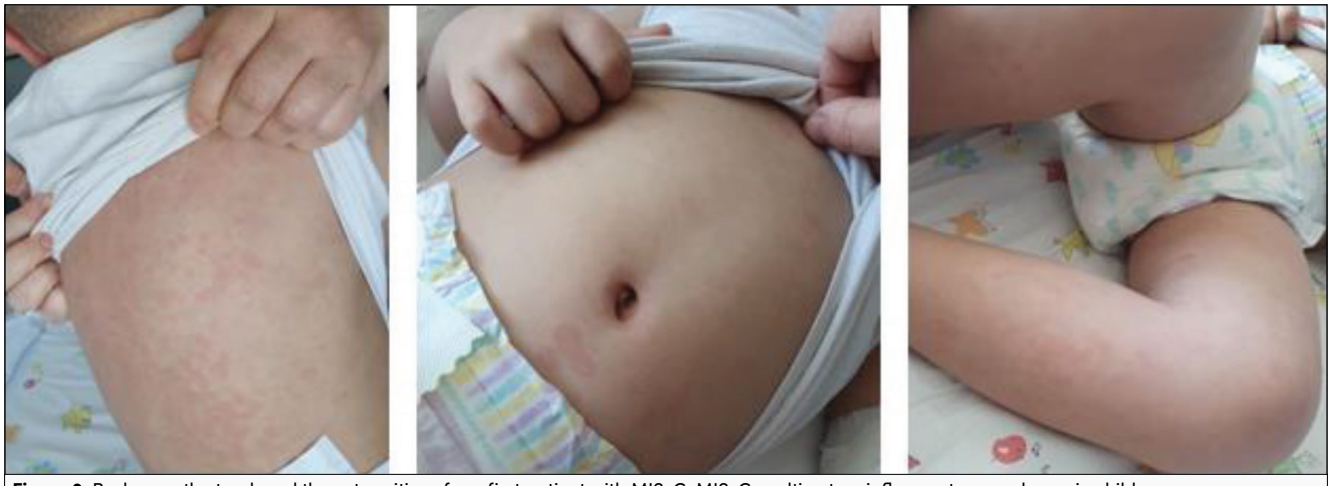

Figure 2. Rashes on the trunk and the extremities of our first patient with MIS-C. MIS-C, multisystem inflammatory syndrome in children.

Table 2. Differential diagnosis of MIS-C

	MIS-C	KD	TSS	HLH/MAS
Dominantly affected age group	School-age children and adolescents	Infants and toddlers	Any age	Any age
Prolonged fever	Yes	Yes	Yes	Yes
Fissured lips	Common	Typical	Possible	Insufficient data
Nonexudative conjunctivitis	Common	Typical	Possible	Possible
Hypotension	Common	Possible	Typical	Possible
GIS symptoms	Very common	Rare	Common	Rare
Coronary aneurysms	Possible	Common	Insufficient data	Insufficient data
Heart failure	Common	Possible	Rare	Rare
Neutrophilia	Yes	Yes	Yes	No
Lymphopenia	Yes	No	No	Yes
Thrombocytopenia	Yes	No	Yes	Yes
CRP	Elevated	Elevated	Elevated	Elevated
Ferritin	Elevated	Normal, or elevated	Normal	Elevated
Hypertriglyceridemia	Common	No	No	Typical

CRP, C-reactive protein; GIS, gastrointestinal system; HLH/MAS, hemophagocytic lymphohistiocytosis/macrophage activation syndrome; KD, Kawasaki disease; MIS-C, multisystem inflammatory syndrome in children; TSS, toxic shock syndrome.

However, contrary to what is observed in these patients, cardiac involvement, mucosal changes, gastrointestinal symptoms, and neutrophilia are extremely rare or absent in patients with HLH (44-47). Therefore, the diagnosis of these patients also was not HLH.

Although this hyperinflammatory condition originally was confused with KD, TSS, and HLH because of several similarities, it was realized that this condition has some prominent differences. Therefore, it was considered as a separate disease and named MIS-C. We tried to summarize these similarities and the differences in Table 2.

How do we treat?

At the beginning of May 2020, we admitted a 2-year-old boy. He presented with fever lasting for five days, nonexudative conjunctivitis, cervical lymphadenopathy, swelling of the ankles and wrists, fissured lips, and rash on the trunk and extremities (Figure 2). In his laboratory investigation, hemoglobin was 8.6 g/dL, white blood cell count was 7,800/mm^3, thrombocyte count was 160,400/mm^3, C-reactive protein was 215 mg/dL, alanine aminotransferase was 29.5 IU/L, aspartate aminotransferase was 25.5 IU/L, albumin was 2.91 g/dL, and, sodium was 138 mmol/L.

Although MIS-C had not been defined yet in May 2020, pediatric patients with COVID-19 with Kawasaki-like features were reported. Because of concerns regarding the unclear linkage between COVID-19 and KD, we performed SARS-CoV-2 PCR testing, and the results were negative. Antibody testing was not available when the patient was admitted. On the sixth day of the fever, echocardiography was performed, and a mild degree of coronary dilatation was seen.

IVIG (2 g/kg and 60 mg/kg/day) and acetylsalicylic acid were administered, with the diagnosis of KD. All of the symptoms, including fever, resolved rapidly. Echocardiographic findings also regressed in his next follow-ups. After 3.5 months, the patient was called back; antibody testing for SARS-CoV-2 was performed; and the results showed that, although immunoglobulin A was negative, immunoglobulin G was positive. Thus, we retroactively realized that he was our first patient with MIS-C with an excellent outcome.

Given that MIS-C is a rare but life-threatening multisystemic condition, there is an urgent need to plan available treatment options. However, because the disease has been recently described and rarely seen, there are scarce data regarding the most appropriate treatment regime.

Because sepsis could not be ruled out and several Kawasaki-like features were observed, the first reported cases were treated with IVIG, acetylsalicylic acid, and antibiotics, and the outcomes of these patients were mostly favorable (8). In subsequent cases, IVIG was widely used, and favorable effects, particularly on myocardial functions, were reported (11, 39).

As mentioned previously, MIS-C is a hyperinflammatory condition, and steroids are well known to be strong anti-inflammatory agents. Therefore, steroids are also used in the treatment of MIS-C. However, the efficacy and safety of these agents remains unclear (19).

Because it was previously shown that inflammatory cytokines such as IL-1 and IL-6 were found to be increased in patients with COVID-19–induced hyperinflammation, several immunomodulatory agents were also used in treatment (48). Both anakinra and tocilizumab were found to be effective in the treatment of most patients with MIS-C (20, 21, 39). Moreover, anakinra was considered in the treatment of patients with IVIG- and steroid-resistant MIS-C (49).

Recently, Minen et al. (50) reported two patients with MIS-C who required extracorporeal membrane oxygenation (ECMO); both of them had experienced thrombotic events, and unfortunately, one of them had died. Although there are scarce data regarding the utility of ECMO, considering the pandemic circumstances, it can be considered as a treatment option for patients with MIS-C with severe respiratory distress and refractory shock (19).

Conclusion

Although pediatric patients are thought not to be as vulnerable to SARS-CoV-2 as adults so far, new concerns have been raised because of recently reported pediatric cases with hyperinflammatory conditions, named MIS-C. Even if this novel disease is rare, it seems to be highly fatal. Therefore, it is urgent to understand the pathogenesis of the disease to be able to establish the appropriate treatment regimes. Moreover, there is a need for increased awareness among caregivers and further molecular and clinical studies because of scarce data and still unelucidated disease pathogenesis.

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