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Case Report

Clinical features of multisystem inflammatory syndrome in children-challenges for clinicians: a case report

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ABSTRACT

A variety of complications came to light after the SARS-CoV-2 pandemic of 2020. One such post-covid complication that manifests itself in the form of a hyperinflammatory syndrome in the pediatric population is multisystem inflammatory syndrome in children (MIS-C). It results in severe inflammation of a variety of organ systems, including the heart, lungs, brain, kidneys, gastrointestinal system, skin, and eyes. Surprisingly, clinicians can easily mistake this type of presentation for many other diseases due to overlapping features, especially Kawasaki disease (KD). An interesting case report on a patient admitted to the Grodno regional infectious diseases clinical hospital, Grodno, Belarus. The patient was initially diagnosed with enteroviral infection (EVI) at the time of admission. The clinicians in charge observed the underlying cause to be masked by Kawasaki-like presentation, how they diagnosed MIS-C, Kawasaki-like phenotype: exanthema, cheilitis, scleritis, infectious cardiopathy, gastrointestinal syndrome, coagulopathy and managed this patient is described in this scientific paper. Although the presenting signs and symptoms of MIS-C overlap with other diseases, certain additional features can be helpful in differentiation. Mainly MIS-C is present in a relatively older subgroup along with gastrointestinal symptoms that are uncommon for KD. The patient was treated with IVIG and steroids after which he attained full recovery. MIS-C associated with COVID-19 is serious, rare, and potentially fatal. Clinicians, primary care physicians, and emergency department pediatricians must be quick to recognize it and treat it at the earliest by deploying immunomodulatory strategies to subdue systemic injury caused by hyper-inflammation.

Keywords: Multisystem inflammatory syndrome in children, KD, SARS-CoV-2 hyperinflammatory syndrome

INTRODUCTION

The novel SARS-CoV-2, also referred to as COVID-19, caused a global pandemic that led to more than 6.8 million deaths and affected millions since its start in early 2020. Most of the cases were reported in the adult population while the rate of hospitalization, morbidity, and mortality was significantly lower in the pediatric population, compared with adults.[1] However, some patients went on to develop a rare, but severe complication of SARS-CoV-2 infection, referred to as MIS. It results in severe inflammation of a variety of organ systems, including the skin, gastrointestinal system, heart, lungs, brain, kidneys, and eyes.[2]

This condition is predominantly observed in the pediatric population as MIS-C but has now been reported in adults as well, Multisystem Inflammatory Syndrome in Adults (MIS-A).[3] As of now the actual global incidence of MIS-C is uncertain, but it appears to be rare. Reports have estimated the incidence in those under the of age 21 years to be 2 per 100,000 persons with an overall incidence among children with COVID-19 of 322 per 100,000 persons.[2] As of March 2023, 9445 cases of MISC have been reported in the United States, with 78 deaths related

to MIS-C.[4] Much remains unknown regarding the pathophysiology of MIS-C. Various hypotheses have been put forth, including-abnormal immune response, endothelial dysfunction associated with SARS-CoV-2 and cytokine storm, and SARS-CoV-2 spike protein directly activating the immune system and functioning as a superantigen, amongst many.[2]

Clinical features in patients with MIS-C include fever, mucocutaneous manifestations, abdominal symptoms, myalgias, and cardiovascular collapse. Gastrointestinal manifestations are very common and include abdominal pain, diarrhea, and vomiting. Respiratory symptoms include sore throat, neurological features (e.g., headache, meningeal signs, and altered sensorium) are also common. Severe cases may present with myocardial dysfunction, cardiogenic shock, multisystemic organ failure, and cytokine storm, which can overlap with presentations of KD, secondary hemophagocytic lymphohistiocytosis, EVI, septic shock, and toxic shock syndrome.[2,5] Therefore, the presentation of MIS-C is variable and can mimic a variety of other conditions, particularly KD. Whittaker et al identified three different types of clinical presentations: persistent fever and elevated inflammatory markers: these patients lacked the features of organ dysfunction, KD, septic shock, or toxic shock syndrome (TSS); fever, cardiovascular collapse, and elevated cardiac biomarkers: These patients had predominant cardiac manifestations, including left ventricular dysfunction and arrhythmias. Cardiac biomarkers like cardiac troponins and pro-BNP were significantly elevated in these patients; patients presenting as KD or KD shock syndrome (KDSS): These patients fulfilled the American Heart Association diagnostic criteria for KD.[6]

Thus, many aspects clinical presentation of MIS-C in the pediatric population closely resemble KD. In this case report we have described one such case of a boy that presented at the Grodno Regional Infectious Diseases Clinical Hospital with symptoms that were thought to be of KD due to overlapping features. Due to MIS-C being a dangerous pediatric complication of COVID-19, it becomes important for clinicians to know how to diagnose and manage this disorder.

CASE REPORT

In February 2022, a 7.5-year-old boy was brought to the Grodno Regional Infectious Diseases Clinical Hospital with complaints of increased body temperature, headache, weakness, and distributed maculopapular rashes on the trunk, extremities, and face. A child fell ill two days before admission. On the first day, the body temperature increased to 38.5℃, his parents did not seek medical help and gave him antipyretic medicines at home, and momentarily the temperature returned to normal. The next day body temperature rose to 38.7℃ and the mother noticed a small single maculopapular rash on the limbs and the trunk. On both days he had vomiting and passed liquid greenish stool.

On the third day, the rash appeared on the face, and elements of the rash increased in size and became confluent on the skin of the thighs (Figure 1). The patient was rushed to the hospital at this time. The patient had no surgical, travel, or hereditary history. The child was examined by the doctor on duty at the pediatric hospital, who diagnosed enterovirus infection and the child was taken to the infectious disease hospital with this diagnosis. The epidemiological history stated that in school six of his classmates were absent due to the disease, but there was no history of contact. Over the past week, the mother had symptoms of a cold (during this period the mother was on a business trip). All other members of the family contact with the child were healthy. It was noted that in January 2022, the child had an Acute Respiratory Infection (ARI) (with rhinitis, without fever).

On admission, the body temperature was 37.6 °C. The general condition was severe. The child was conscious. The Glasgow coma scale (GCS) level of consciousness was 15 points. Muscle tone was preserved. Meningeal symptoms-neck stiffness: negative. Kernig's sign: is negative, on both sides; Brudzinsky's sign: negative, on both sides. There were elements of a rash of different sizes with a tendency to merge an urticarial character on the face, ears, upper and lower extremities, feet and hands, trunk, and buttocks; on the skin of the thighs, rashes were confluent (Figure 1).

The phenomenon of cheilitis was presented as bright red color border over the lips, the skin of the lips is rough and dry, and along the edge of the border, there is a rash of the same nature. Conjunctivitis and scleritis were also present. Lymph nodes were not palpable. Cardiovascular system: the heart sounds were loud without the presence of any murmur. Tachycardia was present (heart rate:115 per minute) BP: 120/70 mmHg. Respiratory system: wheezing was absent. Respiratory rate: 26 per min. SpO^2: 98% when breathing atmospheric air. Breath sounds were vesicular. Gastrointestinal tract: the tongue was moderately moist, and covered with a white coating. Hyperemia of the posterior pharyngeal wall, tonsils were loose, hypertrophied, no membranes. The abdomen was soft, slightly inflated, and sensitive on palpation along the bowel, liver, and spleen were not enlarged. Based on the initial examination findings an initial diagnosis of EVI was placed.

The electrocardiography showed slight changes in myocardium and tachycardia while the echocardiogram showed mitral regurgitation (grade I) as per Effective Regurgitant Orifice Area (EROA). Ultrasound of the abdomen showed signs of splenomegaly, mesenteric lymphadenitis, and intestinal infection. The patient’s condition continued to deteriorate.

PCR for EVI. PCR for RNA SARS-CoV-2 turned out to be negative. Results of laboratory data, leukocytosis (11.6×109) with neutrophilia (81%), increased levels of CRP- 62.6 mg/l, procalcitonin -1.6 ng/ml, D-dimer: 1.37 mg/l. The patient suffered a mild form of COVID-19 a month ago. Based on the subtle anamnesis reporting, a month ago child had acute respiratory symptoms (about rhinitis, without fever). In the blood IgG to SARS-COV-2 were detected.

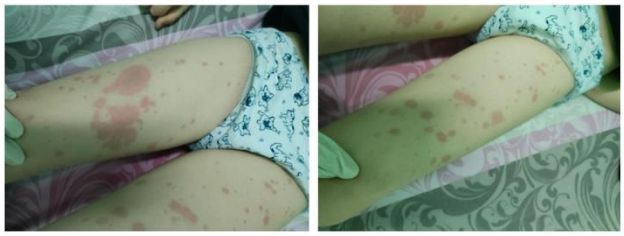

Figure 1: Kawasaki-like rash in a patient of MIS-C.

Table 1: Cardinal features of distinguishing between MIS-C and Kawasaki disease.[24]

MIS-C	KD
More commonly affects older children and adolescents (>7 years)	More commonly affects younger children and infants (<5 years)
GI symptoms are very common	GI symptoms are not common
Myocardial dysfunction and shock are more common	Myocardial dysfunction and shock are less common
Inflammatory markers [CRP, ferritin, D-dimer] are significantly elevated	Inflammatory markers (CRP, ferritin, D-dimer) minimally elevated
Absolute lymphocyte count and platelet counts are low	Leukocytosis and thrombocytosis are common

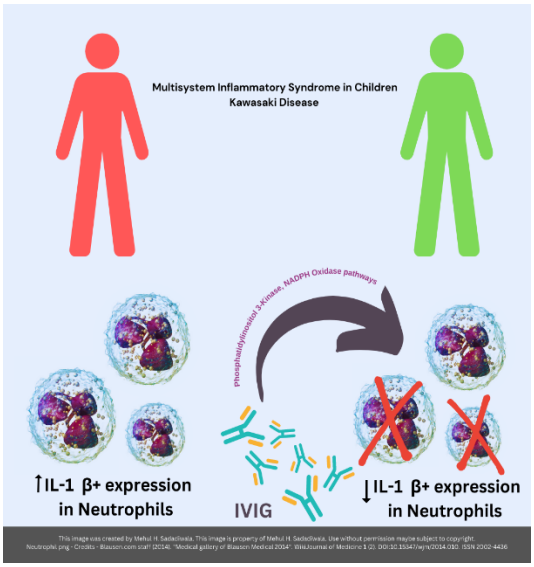

Figure 2: Role of IVIG in MIS-C and KD.

Taking into account the development of severe clinical and laboratory inflammatory manifestations, anamnestic data, and a multisystem nature of the disease after a mild form of COVID-19 made it possible to establish a diagnosis of MIS-C, Kawasaki-like phenotype: exanthema, cheilitis, scleritis, infectious cardiopathy, gastrointestinal syndrome, coagulopathy. He was administered octagam (IVIG-intravenous immune-globulins) 60 ml (1 g/1kg) IV, methylprednisolone (32 mg q.d.), and cefotaxime (1000 mg t.i.d.) IV, aspirin (45 mg b.i.d.) orally and omeprazole (20mg q.d.) orally.

After that patient was transferred to Regional Paediatrics Hospital, these same medications were continued along with acetylsalicylic acid (0.075 mg q.d.), carniton-L-arginine+L-carnitine and co-enzyme Q10 (0.5 mg q.d.), fish oil (q.d.), and magnesium citrate + pyridoxine (1 sachet b.i.d.). Following this treatment, the patient attained full recovery after 12 days.

DISCUSSION

Following the COVID-19 pandemic, in April 2020, a new post-covid complication in the form of a hyper-inflammatory syndrome was described in the United Kingdom. It was found predominantly in the pediatric population.[7] These cases attracted attention because they were associated with COVID-19 infection and overlapped with KD, the leading cause of acquired heart disease in children.[8] Patients with MIS-C showed very similar symptoms mimicking KD like fever, scleritis, maculopapular rashes on extremities, and oral erythema. With these symptoms, it is easy to get tricked while drawing differentials between KD and MIS-C. However, the two syndromes have also found obvious differences in clinical presentations, diagnosis, and treatment. Therefore, it becomes necessary to have a proper distinction between MIS-C and KD.

Ultimately, age has been recognized as one of the essential demographic differences. Similar to the current study, Kawasaki disease typically affects young children under the age of five, whereas MIS-C has been reported in children ranging from 1.6 to 20 years, with a median age of 6-11 years.[9-11] Male predominance was observed in other MIS-C studies.[12] Based on these findings clinicians should bear in mind the possibilities. Further laboratory tests should be carried out for a definitive diagnosis, as the rise in inflammatory markers is out of proportion to the presentation. Additionally, it should also be kept in mind that if a patient presents with Kawasaki-like signs and symptoms but has simultaneous gastrointestinal symptoms then it being MIS-C is a strong possibility. The delayed post-viral onset and clinical manifestations are the keys features of the diagnostic evaluation of suspected MIS-C, and thus confirmation by SARS-CoV-2 polymerase chain reaction (PCR) and/or serologies should be at the helm of it when it comes to differentiating MIS-C from KD. Thereby, asking about a

recent history of acute respiratory illness from the very onset of admission or hospitalization can be of great help.

Simultaneously the same presenting signs and symptoms of MIS-C phenotype: exanthema, cheilitis, scleritis, infectious cardiopathy, gastrointestinal syndrome, and coagulopathy can also be mistaken with EVI. Enteroviruses (EVs) are a common cause of self-limiting febrile illnesses in infants and young children but can occasionally cause severe diseases including meningoencephalitis, myelitis, paralysis, myocarditis, sepsis-like syndrome, respiratory disease, and acute hepatitis.[13] Whereas, here in EVI as well, the age (<4 years old) and presence of neurological symptoms, sepsis, respiratory distress, and vesicular rash remain prominent findings.[14]

The diagnostic evaluation of suspected MIS-C in a toxic-appearing patient (e.g., dehydration, shock, respiratory distress, neurologic changes) should include a complete blood cell count (CBC), renal and liver function, electrolytes, inflammatory markers [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)], coagulogram, D-dimer, albumin, SARS-CoV-2 testing (PCR and/or serologies if available), troponin, and brain natriuretic peptide (BNP). Due to the overlapping presentation with sepsis, blood cultures should also be obtained. If available, ferritin, fibrinogen, and procalcitonin can be useful as well. For patients who are otherwise well-appearing, the American College of Rheumatology recommends a tiered system of testing.[15] In this testing strategy, those who appear well but in whom MIS-C is a consideration should be tested with CBC, electrolytes, renal and liver function, CRP, and ESR. If CRP ≥5 mg/dl or ESR ≥40 mm/h is found on testing combined with one of the following other laboratory abnormalities (absolute lymphocyte count <1.5, platelet count <150,000, sodium <135 mmol/l, neutrophilia, or hypoalbuminemia), then full testing as described above is recommended.[15] To avoid repeat blood draws in this population, it is recommended to obtain extra blood tubes for this additional testing if they are otherwise well appearing, but MIS-C is suspected.

Resuscitation and hemodynamic stabilization in individuals who show symptoms of shock should be the first steps in the treatment of patients with MIS-C. Broad-spectrum antibiotics are advised, and if essential, blood cultures should be obtained before antibiotic therapy as these individuals frequently have toxic appearances and present similarly to those who have septic shock. Before beginning aggressive volume resuscitation, point-of-care ultrasonography should be conducted due to the possibility of cardiogenic versus vasodilatory shock.[2] Patients may require to be supported by vasopressors that contain substances like adrenaline or norepinephrine. However, if cardiac dysfunction is present, epinephrine could potentially be chosen. Prednisolone 2 mg/kg/day given intravenously or orally in three separate doses for 10 days has also been linked to promising outcomes in recent retrospective data, notably in critically sick children and those using numerous vasoactive medicines.[12,15,16]

According to one study, the MIS-C can be treated with IVIG, which targets IL-1+ neutrophils to have anti-inflammatory effects.[17] As MIS-C and KD patients exhibit increased frequency of IL-1+ neutrophils with upregulated activation and adhesion markers, these IVIG are also helpful in the treatment of KD (Figure 2).[17] According to the latest guidelines of the Order of the Ministry of Health of the Republic of Belarus "On approval of recommendations (temporary) on the specifics of providing medical care to patients under the age of 18 with COVID-19 infection" dated 24 June 2022-remdesivir, a SARS-CoV-2-specific antiviral agent is not routinely indicated, but it can be given to children who retain virus isolation by the presence of positive SARS-CoV-2 RNA (by PCR method) in a nasopharyngeal swab. With the rising frequency of MIS-C reported in recent studies, it was also discovered that anti-inflammatory drugs other than remdesivir had received attention in recent clinical investigations, including corticosteroids, intravenous immunoglobulin, tocilizumab, and interferon.[18] IL-6 inhibitors like tocilizumab or siltuximab were reported to be used in MIS-C in children. The role of tocilizumab is to manage the cytokine storm that may occur in MIS-C.[19] Tocilizumab is administered intravenously. Tocilizumab dose in children over 2 years old weighing up to 30 kg-12 mg/kg once, children and adolescents weighing ≥30 kg-8 mg/kg once (maximum dose 800 mg).

Studies have proven that combined IVIG with methylprednisolone results in a better outcome for fever than merely utilizing IVIG.[20] While there is still controversy regarding the evidence proving these results. Studies found that two doses of the COVID-19 vaccine resulted in an estimated efficiency of more than 90% for avoiding MIS-C, further demonstrating the efficacy of COVID-19 vaccination in lowering the risk of MIS-C.[21,22] Given the complexity of management, patients presenting to non-pediatric centers should be transferred to a pediatric tertiary care center once stabilized.[23] Due to the risk of significant and severe complications and the necessity for close monitoring, the majority of patients (60-80%) with MIS-C will require admission to an intensive care setting.

CONCLUSION

A 7.5-year-old boy presents to the Grodno Regional Infectious Diseases Clinical Hospital with the symptoms like EVI, which was ruled out immediately due to negative PCR. The older age of presentation, a disproportionate rise in the inflammatory markers, and symptoms of GIT helped us arrive at the final diagnosis of MIS-C, Kawasaki-like phenotype: exanthema, cheilitis, scleritis, infectious cardiopathy, gastrointestinal syndrome, coagulopathy. Which was confirmed by the

presence of IgG to SARS-CoV-2 in blood serum. As per the treatment plan, he was started on IVIG plus Methylprednisolone, and other medications which yielded positive results and in full recovery. MIS-C associated with COVID-19 is serious, rare, and potentially fatal. Clinicians, primary care physicians, and emergency department pediatricians should have a high level of clinical suspicion in this type of presentation, especially in the post-COVID era, recognize it and treat it early using immunomodulatory strategies (IVIG+methyl-prednisolone) to reduce systemic injury. KD and MIS-C both are caused by enhanced neutrophilic activity therefore implementing the use of IVIG is a safe treatment option to start the therapy at the earliest which can be modulated with a confirmed diagnosis.

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