Multisystem inflammatory syndrome in children associated with SARS-CoV-2 in an 8-week old infant

Esther Orlanski-Meyer, MD[1,6]*, Dotan Yogev, MD[1,6,8]*, Adi Auerbach, MD[2,6], Orli Megged, MD[3,6,8], Daniel Glikman, MD[7], Philip J. Hashkes, MD[4,6,8], Maskit Bar-Meir, MD[3,6,8]

* Contributed equally as co-first authors

1- Institute of Pediatric Gastroenterology and Nutrition; 2 - Pediatric Endocrinology unit; 3 - Pediatric Infectious Diseases unit; 4 - Pediatric Rheumatology Unit; 6 - Shaare Zedek Medical Center, Jerusalem, Israel; 7 - Padeh-Poriya Medical Center and The Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel; 8 - Hadassah Hebrew University Medical School

Corresponding Author:
Esther Orlanski-Meyer, MD
Tel: 972-52-802-0855
Email: eomeyer@szmc.org.il

Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.

Funding Source: No financial support.

Potential Conflicts of Interest: The authors have no conflicts of interest relevant to this article to disclose.

Abbreviations: SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; MIS-C: multisystem inflammatory syndrome in children; COVID-19: Coronavirus disease 2019; PIMS: pediatric inflammatory multisystem syndrome; KD: Kawasaki Disease; GI: gastrointestinal; MAS: macrophage activating syndrome; PCR: polymerase chain reaction; CRP: C-reactive protein; BNP: B-type natriuretic peptide; TPN: Total parenteral nutrition; NPO: Nil per os; IL: interleukin; IVIG: intravenous immunoglobulin

Table of contents summary: An 8-week old infant with severe gastrointestinal involvement and mild carditis was diagnosed with multisystem inflammatory syndrome associated with SARS-CoV-2 following asymptomatic infection.

Contributors' Statement Page

Drs Yogev and Orlanski-Meyer collected data, reviewed the literature, and drafted and revised the manuscript; Drs Auerbach, Glikman, and Megged contributed intellectual content and revised the manuscript; Drs Bar-Meir and Hashkes supervised data collection, revised the manuscript 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.

Abstract

We describe an 8-week-old infant with severe gastrointestinal symptoms, significant hypoalbuminemia, and mild carditis following asymptomatic infection with SARS-CoV-2. The infant's symptoms, including their temporal appearance, were consistent with multisystem inflammatory syndrome in children (MIS-C). A unique finding on colonic histology which may shed light on the pathogenesis of MIS-C was identified. The patient improved significantly following several anti-inflammatory treatments. The lag between the presentation of MIS-C and initial SARS-CoV-2 exposure, which may often be asymptomatic, together with the young age of our patient, make this a challenging diagnosis. Clinicians should be aware of this entity, even in the neonatal and infantile age groups, to facilitate timely identification and treatment.

Introduction

During April-May 2020, in the midst of the Coronavirus disease 2019 (COVID-19) pandemic, several publications described a pediatric systemic hyper-inflammatory syndrome associated with COVID-19. This new condition, pediatric inflammatory multisystem syndrome (PIMS) or multisystem inflammatory syndrome in children (MIS-C), has received case definitions from several organizations with almost 1000 cases reported to date[1]. Clinical features of this syndrome are reminiscent of Kawasaki Disease (KD), but with some striking differences: the mean age of PIMS/MIS-C is approximately 10 years; it has rarely been reported in Asian countries, and Blacks appear to be at higher risk. The majority of patients have prominent gastrointestinal (GI) symptoms, cardiac involvement is mainly myocardial, and laboratory features resembling macrophage activating syndrome (MAS) or the cytokine storm of COVID-19 in adults rather than classic KD[2].

Herein, we describe one of the youngest patients fulfilling the case definition of PIMS/MIS-C and highlight unique aspects of this syndrome.

Case Presentation

An 8-week-old infant presented with a 7-day history of diarrhea, heralded by transient bloody stool, followed by vomiting, fever up to 38.5^{o}C, and profuse watery diarrhea two days prior to admission. Pregnancy and delivery were normal.

At 2 weeks of age, following exposure to the infant's uncle, both parents tested positive for SARS-CoV-2 by polymerase chain reaction (PCR) from nasopharyngeal swabs. The family stayed at a quarantine center (“corona hotel”) and the infant was asymptomatic. Her first PCR test was misplaced, subsequent testing was negative. Family history was remarkable for Crohn's disease among 2nd degree relatives. On admission to a local hospital, the infant was lethargic and tachycardic (heart rate 150 beats per minute). Notable laboratory findings included leukocytosis, thrombocytosis, hypoalbuminemia, elevated C-reactive protein (CRP),

metabolic acidosis and elevated B-type natriuretic peptide (BNP) (**Table 1**). Blood, cerebrospinal fluid, urine, stool cultures, and stool multiplex PCR (Biofire GI panel®, Biomérieux) for bacterial, parasitic, and viral pathogens, were negative. There was no clinical or laboratory improvement despite dietary switch from breastfeeding to amino acid-based formula and a course of antibiotics. She transferred to our hospital on day 10 with continued fever and profuse diarrhea.

On admission, she had cracked lips but no other signs of KD. Total parenteral nutrition (TPN) was initiated with nil per os (NPO), however diarrhea persisted with worsening hypoalbuminemia. Abdominal sonograms showed worsening nonspecific intestinal wall changes and mucosal flattening, consistent with stomach and intestinal edema. Splenomegaly was found. Protein-losing gastropathy or enteropathy were considered but alpha-1 antitrypsin was negative. Initial immunologic work-up did not support immunodeficiency. Congenital diarrhea syndromes and neonatal inflammatory bowel disease were considered. Gastroscopy was nonspecific, colonoscopy showed patchy erythema and scattered pinpoint erosions, consistent with colitis. Colonic pathology showed patchy active colitis with neutrophils, crypt abscesses, minimal plasma cells, and crypt atrophy(**Figure 1)**. Additional biopsies were taken pending further analysis with electron microscopy.Worsening laboratory values included severe anemia of 5.9 g/dL requiring blood transfusion, elevated D-dimer and ferritin levels and thrombocytopenia. Echocardiogram showed mild-moderate mitral regurgitation with normal coronary arteries and systolic function. Nasopharyngeal SARS-CoV-2 PCR was negative, however SARS-CoV-2 IgG was positive (Abbot Architect, 4 s/co, positive>1.4) and interleukin (IL)-6 level was elevated. As the parents' time of diagnosis was well documented and their exposure to a COVID-19 patient occurred at 2 weeks of age, the positive serology was unlikely to represent passive transfer of maternal antibodies.

The infant therefore fulfilled the World Health Organization case definition for PIMS/MIS-C[3]. She was treated with intravenous immunoglobulins (IVIG) 2 gr/kg with improved well-being and a decrease in CRP levels. However, profuse diarrhea continued as well as progressive anemia. Due to the clinical and laboratory picture suggestive of severe cytokine storm, pulse methylprednisolone therapy (30 mg/kg/d) was given for 3 days (**Figure 2)** with good response including rapidly increasing albumin levels up to 3 g/dL, decreasing CRP and D-dimer, normalization of fibrinogen, and decreasing stool output. Oral breastfeeding was resumed and TPN discontinued. Treatment was changed to prednisolone 2 mg/kg/d. Despite this convincing clinical and laboratory improvement, liver enzymes increased (alanine-aminotransferase 173 IU/L, aspartate-transaminase 140 IU/L, gamma-glutamyltransferase 274 IU/L) and ferritin levels continued to rise. The infant was treated with 4 doses of Anakinra (IL-1 receptor antagonist) 3.5 mg/kg/d for 3 days. D-dimer normalized and ferritin levels decreased by about 50%. She was discharged on a weaning course of oral prednisolone and later developed a minor flare of diarrhea with no fever or elevation in inflammatory markers at a prednisolone dose of 0.15 mg/kg. Corticosteroid wean was slowed but was completed successfully one-month post-discharge.

Discussion

In this report, we present one of the youngest PIMS/MIS-C cases described to date. Our report emphasizes the central role of GI symptoms in the presentation of PIMS/MIS-C, as well as the differences from classic KD. In line with current case definition criteria[3], our patient had fever for more than 3 days, mitral valve regurgitation, cardiac dysfunctionas indicated by elevated BNP levels (albeit with normal systolic function), severe GI involvement, evidence of coagulopathy (elevated D-dimer and prolonged prothrombin time), and elevated CRP/ferritin levels, with serologic evidence of prior COVID-19 infection and no other obvious microbial cause of inflammation. Notably, this infant had features of MAS:

splenomegaly, new thrombocytopenia, elevated liver enzymes and ferritin levels. Our patient did not fulfill criteria for KD as only 1 clinical criterion (cracked lips) was met. Additionally, echocardiogram did not show coronary artery involvement or 3 other suggestive features required for diagnosis of incomplete KD at this age group.

While knowledge regarding COVID-19 infection is continuously evolving, it appears that primary infection is milder in children compared with adults. The PIMS/MIS-C entity tends to occur in children who did not manifest symptoms of acute COVID-19 infection. Only a few case reports of this entity in infancy exist. Moreover, there is a delay, often more than 3 weeks long, between COVID-19 infection and the inflammatory syndrome as manifested by PCR negativity and positive serology in these patients.[4] These data support a post-infectious process, with COVID-19 infection serving as a trigger[2].

Almost all PIMS/MIS-C patients described had prominent GI symptoms[4], compared with approximately a third of KD patients. Our patient presented with severe symptoms leading to TPN dependence and extensive initial investigation did not support allergic, immunologic, infectious, or congenital etiologies. Colonic biopsies showed marked crypt atrophy, a finding which may be compatible with post-infectious, hyper-immune mediated damage,[5] possibly providing insight into the mechanism of the abundant GI involvement in PIMS/MIS-C. Further research is needed to clarify this finding.

Our patient developed hypoalbuminemia, with negative alpha-1 antitrypsin, making losses less likely. Mechanisms such as capillary leak, decreased liver synthesis, increased scavenging, and degradation of albumin are well established in the pathophysiology of hypoalbuminemia in inflammatory conditions. The lack of improvement despite adequate protein supplementation and the rapid recovery of normal albumin levels following corticosteroids (**Figure 2**), further support this hypothesis.

The optimal care of children with PIMS/MIS-C is multidisciplinary with most children receiving treatment in the intensive care unit. Medical therapy aims to modulate the cytokine storm. IVIG and steroids have been suggested as first line therapy for PIMS, with IVIG being particularly effective in patients with a KD phenotype. The use of other immune-modulating agents particularly anakinra or tocilizumab (anti IL-6 receptor monoclonal antibody) may be considered for refractory patients.[6] Our patient responded remarkably to corticosteroids, allowing TPN withdrawal. However, persistent elevation of liver enzymes, ferritin, and D-dimer levels led to a short therapeutic course with anakinra. We chose anakinra as it is labelled for use in neonatal inflammatory conditions such as neonatal onset multisystem inflammatory disease (NOMID) and is used in deficiency of the IL-1 receptor antagonist (DIRA). Following anakinra the infant was gradually weaned from corticosteroids and is gaining weight.

The new entity of PIMS/MIS-C is an evolving pediatric challenge and as such is still surprising clinicians with its varied systemic presentations. The present case of a very young infant with severe GI manifestations requiring parenteral nutrition and myocardial dysfunction broadens our clinical understanding and highlights possible effective therapies for this newly described condition even at this young age.

Acknowledgments: The authors wish to thank Dr. Eli Brazowski for his input and review of the biopsies and Dr. Elena Rachman for her input on patient management.

References

1. Levin M. Childhood Multisystem Inflammatory Syndrome - A New Challenge in the Pandemic. *N Engl J Med*. 2020;383(4):393-395. doi:10.1056/NEJMe2023158
2. Shulman ST. Pediatric Coronavirus Disease-2019-Associated Multisystem Inflammatory Syndrome. *J Pediatric Infect Dis Soc*. 2020;9(3):285-286. doi:10.1093/jpids/piaa062
3. Whittaker E, Bamford A, Kenny J, et al. Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2 [published online ahead of print, 2020 Jun 8]. *JAMA*. 2020;e2010369. doi:10.1001/jama.2020.10369
4. Toubiana J, Poirault C, Corsia A, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. *BMJ*. 2020;369:m2094. Published 2020 Jun 3. doi:10.1136/bmj.m2094
5. Cerilli LA, Greenson JK. The differential diagnosis of colitis in endoscopic biopsy specimens: a review article. *Arch Pathol Lab Med*. 2012;136(8):854-864. doi:10.5858/arpa.2012-0205-RA
6. Clinical Guidance for Pediatric Patients with Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 and Hyperinflammation in COVID-19. 2020. at https://www.rheumatology.org/Portals/0/Files/ACR-COVID-19-Clinical-Guidance-Summary-MIS-C-Hyperinflammation.pdf. Published and accessed june 2020.

Legend to figures

Figure 1. Colonic biopsy showing patchy active colitis with crypt abscess (thick arrow) and crypt atrophy (thin arrows)

Figure 2. Timeline of symptoms, medical interventions, and inflammatory laboratories. CRP - C-reactive protein, IL-6 - Interleukin-6, TPN - total parenteral nutrition, IVIG - Intravenous Immunoglobulin

Table 1. Laboratory values throughout hospitalization

	Reference values	Presentation to 1st medical center	Pre-treatment	Discharge
Hemoglobin	9-11g/dL	10.5	7.2	11.4
WBC	4-15 10^3/μL	22.7	14.2	14.2
Platelets	150-450 10^3/μL	958	150[1]	719
Albumin	3.2-5.2 gr/dL	2.4	1.4	4.2
CRP	0-0.5 mg/dL	13.5	6.4	<0.1
BNP	0-124 pg/mL	1011	37.3	NA
INR	0.84-1.14	NA	3.31	0.84
Ferritin	11-205 ng/mL	NA	385[2]	1134
D-dimer	0-500 ng/mL	NA	722[3]	419
Fibrinogen	200-500 mg/dL	NA	393	267
C3/C4	86-186 mg/dL / 16-47 mg/dL	NA	130 / 60	NA
IL-6	0-7 pg/mL	NA	37.5	2.44

[1]Lowest platelet count 80 10^3/μL1 day after IV immunoglobulin treatment
[2]Peak ferritin 2788 ng/mL 9 days following IV methylprednisolone treatment
[3]Peak D-dimer 1084 ng/mL 3 days following IV immunoglobulin treatment

WBC-White blood cells; CRP- C-reactive protein; BNP- B-type natriuretic peptide; NA- not applicable; IL-6- Interleukin-6; INR-international normalized ratio; IV-intravenous

Figure 1

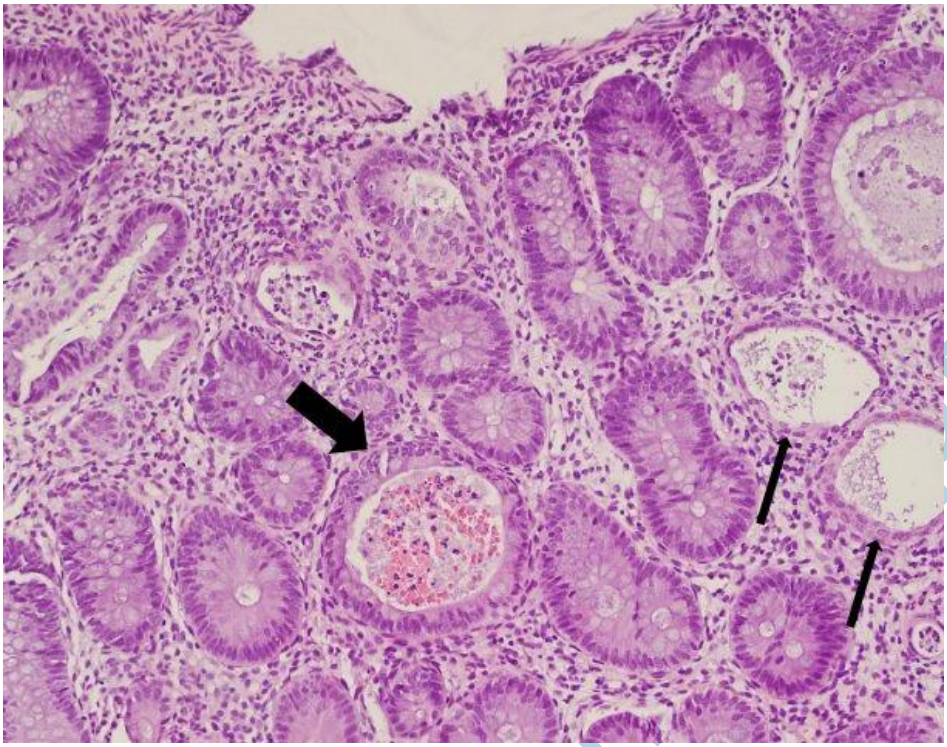

Figure 2