Inflammatory Bowel Disease Presenting With Concurrent COVID-19 Multisystem Inflammatory Syndrome

Katherine F. Sweeney, MD, Yanjia Z. Zhang, MD, PhD, Bonnie Grume, MD, Colin A. Martz, MD, PhD, Melissa M. Blessing, DO, Stacy A. Kahn, MD

Coronavirus disease 2019 (COVID-19) is associated with a postinfectious multisystem inflammatory syndrome in children (MIS-C). This syndrome is marked by cytokine storm and multiorgan dysfunction, often affecting the gastrointestinal tract, the heart, and the hematopoietic system. We describe the case of a 16-year-old boy with an initial presentation of severe inflammatory bowel disease and concurrent MIS-C. He presented with abdominal pain, diarrhea, and hematochezia and met criteria for the systemic inflammatory response syndrome. Laboratory inflammatory profiling revealed markedly elevated ferritin, D-dimer, C-reactive protein, soluble interleukin 2, and interleukin 6 levels. Endoscopy and colonoscopy revealed severe active gastroduodenitis, patchy colitis, and a normal-appearing terminal ileum. The patient was treated with a combination of steroids, intravenous immunoglobulin, and inﬂiximab, and his symptoms slowly resolved over a 3-week period. In this case, we describe coincident MIS-C with a remarkably severe and difﬁcult-to-treat initial presentation of inﬂammatory bowel disease and highlight the need to investigate the effect of coronavirus disease 2019 and MIS-C on inﬂammatory disorders.

Coronavirus disease 2019 (COVID-19) is increasingly associated with multisystem inﬂammatory syndrome in children (MIS-C). MIS-C is a serious postinfectious syndrome resulting in cytokine storm and multiorgan dysfunction often affecting the heart, the hematopoietic system, and the gastrointestinal (GI) tract. Here, we describe a novel and timely case of an adolescent boy with an initial presentation of severe inﬂammatory bowel disease (IBD) and concurrent MIS-C.

CASE

A 16-year-old African American boy of Cape Verdean descent with no signiﬁcant past medical history presented to an outside hospital emergency department with a chief complaint of 3 weeks of hematochezia and worsening abdominal pain. He was in his usual state of good health until 6 weeks before, when he developed mild rhinorrhea. The rhinorrhea resolved, and ~2 weeks later, he developed intermittent abdominal discomfort and diarrhea, which progressed to 6 bloody stools per day with severe generalized abdominal pain. He denied fevers, oral ulcers, myalgia, arthralgia, respiratory symptoms, rash or headaches. Family history was remarkable for a father diagnosed with colonic cancer at age 43, currently in remission. There was no history of travel, trauma, or sick contacts. Family history was negative for autoimmune diseases or COVID-19.

On physical examination, the patient was thin, ill appearing, and met clinical
erythrocyte sedimentation rate was 21

2.5 SWEENY et al.

Laboratory evaluation was significant for systemic inflammatory response syndrome. He had a fever with a maximum temperature of 38.0°C and remained febrile on the first day of hospitalization; he had a heart rate of 165 beats per minute, a blood pressure of 110/60 mm Hg, a respiratory rate of 22, and an oxygen saturation of 98% on room air. He received 3 L of normal saline boluses but remained tachycardic with a heart rate of ~120 beats per minute. He had severe diffuse abdominal tenderness to palpatation with involuntary guarding but no rebound or focal tenderness and no hepatosplenomegaly. He had no cough, shortness of breath, rashes, lymphadenopathy, icterus, conjunctivitis, joint tenderness or swelling, and a normal perianal examination.

The patient was stabilized, and on hospital day 5, he underwent esophagogastroduodenoscopy and colonoscopy with biopsies. Esophagogastroduodenoscopy revealed severe gastritis and duodenitis. Colonoscopy revealed patchy moderate to severe colitis with a normal-appearing terminal ileum (Fig 1A). Pathology from the upper GI tract revealed severe, chronic active duodenitis as well as chronic active gastritis. Notably, in the duodenum, there was an inflammatory infiltrate focally involving medium-sized blood vessels. Although the computed tomography revealed mild ileitis, the terminal ileum histopathology was normal. There was moderately to severely active colitis in the ascending, transverse, descending, and sigmoid colon and mildly active colitis in the rectum (Fig 1B). Immunostaining results for cytomegalovirus, Helicobacter (stomach), and SARS-CoV-2 were negative. Features of chronicity were seen in the duodenum, antrum and corpus, and in several colon biopsies; granulomata were not identified. The diagnostic possibilities included IBD, MIS-C, infection, or a combination thereof. The Prometheus IBD sig Diagnostic test was sent, and results were consistent with Crohn disease, with serology revealing an elevated anti-Saccharomyces cerevisiae antibody immunoglobulin A enzyme-linked immunosorbert assay level of 13.5 EU/mL (reference <9.2 EU/mL), heterozygous ECM1 and STAT3 single-nucleotide polymorphisms.

On hospital day 7, the patient had acute worsening, with increasing large-volume bloody stools, and the methylprednisolone was increased to 60 mg intravenous daily. Exclusive enteral nutrition (EEN) was initiated. On hospital day 10, because of severe ongoing symptoms unresponsive to parenteral corticosteroids and EEN in the setting of MIS-C, he was given 1 g/kg of intravenous immunoglobin (IVIg). Within 24 hours, his serum inflammatory markers and coagulation laboratories began to downtrend (Fig 1C). Two days after receiving IVIg, he developed chest pain, a fever of 40.0°C, and hypotension (blood pressure of 95/36 mm Hg) and was transferred to the ICU. He received a packed red blood cell transfusion for a hemoglobin level that had dropped from 11.5 to 8.8 g/dL and additional crystalloid resuscitation. Within 24 hours, he had stabilized and was transferred back to the gastroenterology service.

The patient’s serum inflammatory markers improved significantly on steroids and IVIg. His CRP level decreased from 22.14 to 2.9 mg/dL, and his D-dimer level decreased from 9.14 to 1.62 μg/mL or FEU, but he continued to have significant diarrhea and hematocrit (Fig 1C). Magnetic
resonance enterography performed at that time revealed colonic wall thickening with a normal-appearing small bowel. With ongoing input from the immunology, infectious diseases, and IBD services, on hospital day 17 he was treated with infliximab 10 mg/kg, which resulted in rapid improvement in his GI symptoms. He was discharged on day 24 and has continued to improve in the outpatient setting on infliximab monotherapy.

DISCUSSION
In this case, we describe an unusual presentation of new-onset IBD, likely Crohn disease, with overlapping features of MIS-C related to COVID-19 in an adolescent boy. In several MIS-C case series, researchers now describe significant GI symptoms in many children, especially older children, but endoscopic and histologic features consistent with IBD appear to be rare.1,2 The overlap in our patient of new-onset IBD and MIS-C

FIGURE 1
A. Severe gastritis in the body of the stomach (left), severe duodenitis in the duodenal bulb (middle), and severe colitis in the sigmoid colon (right) noted on endoscopy. B. Corpus mucosa with active gastritis and expansile lamina propria lymphoplasmacytic infiltrate (left, arrow), ulcerated duodenal mucosa with vasculitis-like involvement of a blood vessel (middle), and severe active colitis with mucosal ulceration (right) (original magnification ×400). C. Course of laboratory inflammatory markers (green: ferritin, blue: D-dimer, yellow: CRP), stool output (maroon bars), and treatment (gray bars and arrows). IV, intravenous.
ultimately responded to anti-inflammatory therapies, consistent with our growing understanding of MIS-C. First, and were more consistent with our course were unusual for new-onset IBD. The biopsy is not expected in IBD and is typically reserved for cases of established IBD, which was not true for our patient when IVIg was initially administered. Multiple providers thought that his GI findings could be explained by MIS-C alone. His lymphopenia, elevated ferritin level, elevated D-dimer level, and cytokine profile were suggestive of MIS-C. Fourth, it is unusual for a case of pediatric IBD to present with coagulopathy. Studies of coagulation factors during active IBD exacerbations have revealed elevations in fibrinogen levels but normal D-dimer and INR levels. Even in studies in which a statistically significant difference was found in D-dimer and INR levels between patients with Crohn disease and controls, the D-dimer and INR levels of patients with Crohn disease were within normal ranges. Fifth, it is uncommon for children with IBD without fulminant colitis to present in compensated shock as our patient did on admission. Finally, our patient had no personal or family history of IBD or autoimmune conditions. On the contrary, his familial background may confer higher MIS-C risk because early case series of MIS-C note an overrepresentation of children of African-Caribbean descent. These features, in the setting of a positive SARS-CoV-2 immunoglobulin G antibody titer, support the hypothesis that this patient had concurrent MIS-C related to COVID-19 and new-onset IBD. Altogether, he meets the positive criteria in the Centers for Disease Control and Prevention (CDC), Royal College of Pediatrics and Child Health (RCPCH), and WHO case definitions of MIS-C, including (1) fever; (2) multisystem involvement (including coagulopathy and GI symptoms), and (3) positive SARS-CoV-2 serology results. The case definitions include different exclusion criteria. The WHO and RCPCH exclude patients with other microbial causes of inflammation, whereas the CDC excludes patients with other plausible alternative diagnoses. Thus, despite our hesitancy to ascribe all our findings to IBD, our patient technically meets the WHO and RCPCH but not the CDC definition of MIS-C. Because this pandemic is now entering its third and most severe wave, it is likely that we will see more cases of MIS-C and further refine our definitions and inclusion and exclusion criteria.

Our understanding of the pathophysiology of MIS-C related to COVID-19 is rapidly evolving; however, its relationship to triggering predisposed autoimmune conditions has not been established. It may be that the inflammatory dysregulation of the immune system triggered by viral infection of immune cells led to the presentation of IBD in a genetically susceptible host. Dolinger et al described a case of a patient with known Crohn disease who had contemporaneous IBD exacerbation and MIS-C. The virus-as-trigger hypothesis could apply to that case as well, although, notably, our patient did not have a previous diagnosis of IBD. Alternatively, it may be that this patient presented with GI symptom–predominant MIS-C related to previous SARS-CoV-2 infection because of a genetic predisposition to GI inflammation, but he will not continue to have chronic GI disease suggestive of a primary diagnosis of IBD. Further study of the impact of COVID-19 infection and MIS-C on the presentation of autoimmune diseases is indicated.

ACKNOWLEDGMENTS

We thank Drs Pui Lee and Craig Platt for their discussions and suggestions, particularly with the immunologic and rheumatologic aspects of this case. We also thank Dr Lisa Teot for her discussions and suggestions of...
the pathologic findings presented in this article.

ABBREVIATIONS

CDC: Centers for Disease Control and Prevention
COVID-19: coronavirus disease 2019
CRP: C-reactive protein
EEN: exclusive enteral nutrition
FEU: fibrinogen-equivalent units
GI: gastrointestinal
IBD: inflammatory bowel disease
INR: international normalized ratio
IVIg: intravenous immunoglobulin
MIS-C: multisystem inflammatory syndrome in children
RCPCH: Royal College of Pediatrics and Child Health
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

REFERENCES

Inflammatory Bowel Disease Presenting With Concurrent COVID-19 Multisystem Inflammatory Syndrome

Katherine F. Sweeney, Yanjia J. Zhang, Bonnie Crume, Colin A. Martz, Melissa M. Blessing and Stacy A. Kahn

*Pediatrics* 2021;147;
DOI: 10.1542/peds.2020-027763 originally published online January 7, 2021;

Updated Information & Services
including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/147/4/e2020027763

References
This article cites 9 articles, 0 of which you can access for free at:
http://pediatrics.aappublications.org/content/147/4/e2020027763#B1B1

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Gastroenterology
http://www.aappublications.org/cgi/collection/gastroenterology_sub
Infectious Disease
http://www.aappublications.org/cgi/collection/infectious_diseases_sub
Immunologic Disorders
http://www.aappublications.org/cgi/collection/immunologic_disorders_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.aappublications.org/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
http://www.aappublications.org/site/misc/reprints.xhtml

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN®
Inflammatory Bowel Disease Presenting With Concurrent COVID-19 Multisystem Inflammatory Syndrome

Katherine F. Sweeny, Yanjia J. Zhang, Bonnie Crume, Colin A. Martz, Melissa M. Blessing and Stacy A. Kahn

Pediatrics 2021;147;
DOI: 10.1542/peds.2020-027763 originally published online January 7, 2021;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/147/4/e2020027763