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

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Abbreviations: COVID-19: Coronavirus disease 2019; MIS-C: multisystem inflammatory syndrome in children; IBD: inflammatory bowel disease; SIRS: systemic inflammatory response syndrome; IVIG: intravenous immunoglobulin; EGD: esophagogastroduodenoscopy; GI: gastrointestinal; TNF: tumor necrosis factor.

Article Summary: COVID-19 multisystem inflammatory syndrome (MIS-C) and its sequelae are still being defined. We present an MIS-C case with concurrent new diagnosis of inflammatory bowel disease.

Contributors' Statement Page

Drs. Zhang, Sweeny and Kahn conceptualized the report, drafted the initial manuscript, and reviewed and revised the manuscript.

Drs. Crume, and Martz collected patient data, analyzed data trends, reviewed and revised the manuscript.

Dr. Blessing collected and analyzed histopathologic data, reviewed and revised the manuscript.

Abstract

Coronavirus disease 2019 (COVID-19) is associated with a post-infectious multisystem inflammatory syndrome in children (MIS-C). This syndrome is marked by cytokine storm and multi-organ dysfunction, often affecting the gastrointestinal tract, the heart and the hematopoietic system. We describe the case of a 16-year-old male with an initial presentation of severe inflammatory bowel disease (IBD) and concurrent MIS-C. He presented with abdominal pain, diarrhea and hematochezia, and met criteria for the Systemic Inflammatory Response Syndrome (SIRS). Laboratory inflammatory profiling revealed markedly elevated ferritin, D-dimer, C-reactive protein, soluble interleukin (IL)-2 and IL-6. Endoscopy and colonoscopy showed severe active gastroduodenitis, patchy colitis and a normal appearing terminal ileum. He was treated with a combination of steroids, intravenous immunoglobulin (IVIG) and infliximab, and his symptoms slowly resolved over a 3-week period. This case describes coincident MIS-C with a remarkably severe and difficult-to-treat initial presentation of IBD, and highlights the need to investigate the effect of COVID-19 and MIS-C on inflammatory disorders.

Introduction

Coronavirus disease 2019 (COVID-19) is increasingly associated with multisystem inflammatory syndrome in children (MIS-C). MIS-C is a serious post-infectious syndrome resulting in cytokine storm and multi-organ dysfunction, often affecting the heart, the hematopoietic system and the gastrointestinal tract¹. Here we describe a novel and timely case of an adolescent male with an initial presentation of severe inflammatory bowel disease (IBD) and concurrent MIS-C.

Case

A 16-year-old African-American male 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 prior, when he developed mild rhinorrhea. The rhinorrhea resolved and approximately 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 exam, he was thin, ill appearing, and met clinical criteria for the Severe Inflammatory Response Syndrome (SIRS). He had a fever with a maximum temperature (T_m) of 38.0° Celsius and remained febrile on the first day of hospitalization, heart rate (HR) 165, blood pressure 110/60 mmHg, respiratory rate of 22, and an oxygen saturation of 98% on room air. He received 3 liters (L) of normal saline boluses, but remained tachycardic with a HR in the 120s. He had severe diffuse abdominal tenderness to palpation 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 exam.

Laboratory evaluation was significant for leukocytosis to 21,660 cells/uL (range 5,240 – 9,740 cells/uL), neutrophilia with an absolute neutrophil count of 20,530 cells/uL (range 2,730 – 6,6680 cells/uL) and lymphopenia with an absolute lymphocyte count of 560 cells/uL (range 1,030 -2,180 cells/uL). His was mildly anemic with a hemoglobin of 10.4 g/dL, (range 11.0 – 14.3 g/dL) with a mean corpuscle volume (MCV) of 83.4 fL (range 80.8 – 86.6 fL). His C-reactive protein (CRP) was 22.14 mg/dL (range <0.50 mg/dL) and his erythrocyte sedimentation rate (ESR) was 21mm/hr (range 0 -30 mm/hr). His albumin was normal at 4.0 g/dL. He was mildly coagulopathic with an INR of 1.45 seconds. An abdominal Computed Tomography (CT) scan revealed trace free fluid, mild ileitis, significant ascending and descending colitis with

relative sparing of the transverse and sigmoid colon and rectum. Infectious studies including stool cultures, *Clostridium difficile* testing, blood cultures, and nasal swab for SARS-CoV-2 antigen testing were negative. Additional labs revealed an elevated ferritin at 1116.0 ng/mL (range 10.0 -320.0), a significantly elevated D-dimer of 9.14 mcg/mL FEU (range \leq 0.50), and an elevated procalcitonin of 0.65ng/mL (range \leq 0.09). He was admitted to the gastroenterology service for further evaluation and treatment. Infectious diseases, rheumatology and immunology were consulted. He received Vitamin K and was started on 40 mg of intravenous (IV) methylprednisolone daily.

He was stabilized and on hospital day 5, he underwent esophagogastroduodenoscopy (EGD) and colonoscopy with biopsies. EGD revealed severe gastritis and duodenitis. Colonoscopy revealed patchy moderate to severe colitis with a normal appearing terminal ileum (Figure 1A). Pathology from the upper gastrointestinal (GI) tract demonstrated 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 CT showed 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 (Figure 1B). Immunostains for cytomegalovirus (CMV), Helicobacter (stomach) and SARS 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. Prometheus® IBD sgi Diagnostic® was sent and was consistent with Crohn disease with elevated ASCA IgA ELISA 13.5 EU.mL (reference $<$ 9.2 EU/mL) serology and homozygous ATG16L1, NKX2-3 and heterozygous for ECMI and STAT3 single nucleotide polymorphisms (SNP).

Immune work-up demonstrated an elevated interleukin (IL)-2 receptor level at 1550 pg/mL (normal low < 1033) and IL-6 levels at 8 pg/mL (normal range <5). Subsequently, SARS-CoV-2 IgG returned positive with a titer of 12 (upper limit of normal 9) and with a repeat with a titer of 16, and a negative IgM. Due to concern for MIS-C, an electrocardiogram, an echocardiogram, troponin and N-terminal-pro-hormone brain natriuretic peptide (NT-proBNP) were performed and were all within normal limits.

On hospital day 7, he had acute worsening, with increasing large volume bloody stools and the methylprednisolone was increased to 60 mg IV daily. Exclusive enteral nutrition (EEN) was initiated. On hospital day 10, due to severe ongoing symptoms unresponsive to parenteral corticosteroids and EEN in the setting of MIS-C, he was given 1 gm/kg of intravenous immunoglobulin (IVIg). Within 24 hours, his serum inflammatory markers and coagulation laboratories began to downtrend (Figure 1C). Two days after receiving IVIg, he developed chest pain, fever Tm 40.0° Celsius and hypotension, with blood pressure 95/36 mmHg and was transferred to the intensive care unit (ICU). He received packed red blood cell transfusion for a hemoglobin 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.

His serum inflammatory markers improved significantly on steroids and IVIg; CRP decreased from 22.14 to 2.9 mg/dL and D-dimer decreased from 9.14 to 1.62 mcg/mL FEU, but he continued to have significant diarrhea and hematochezia (Figure 1C). Magnetic resonance enterography (MRE) performed at that time showed 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 gastrointestinal symptoms. He was discharged on day 24 and has continued to improve in the outpatient setting on infliximab monotherapy.

Discussion

This case describes an unusual presentation of new onset IBD, likely Crohn disease, with overlapping features of MIS-C related to COVID-19 in an adolescent male. Several MIS-C case series now describe significant gastrointestinal 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 represents an important and novel pediatric presentation during the still-unfolding COVID-19 pandemic.

The successful evaluation and management of this patient was delivered via a multi-disciplinary team involving the gastroenterology, infectious diseases, immunology, and critical care physicians. This allowed for a comprehensive evaluation of his gastrointestinal illness as well as his SIRS physiology, in the setting of severe inflammation and immune dysregulation. This team approach facilitated the development of a treatment plan that included medical therapies not commonly used to treat IBD, and that may not have otherwise been considered.

Many features of this case are consistent with IBD. These include predominant gastrointestinal symptoms for 4 weeks with associated laboratory, imaging, biomarker and ultimately histologic evidence of chronic gastrointestinal inflammation. Histologically, the presence of chronic changes supports IBD. His gastrointestinal symptoms ultimately responded to anti-tumor necrosis factor (TNF) therapy, the mainstay treatment for moderate to severe IBD.

However, several aspects of his course were unusual for new-onset IBD and were more consistent with our growing understanding of MIS-C. First, the finding of submucosal vasculitis

on biopsy is not expected in IBD, and is rather a finding consistent with MIS-C. Sahn and colleagues describe vascular inflammation in MIS-C patients³. Second, the patient's symptoms only began one month prior to admission with mild rhinorrhea in the midst of the COVID-19 outbreak in his community, rather than prolonged gastrointestinal symptoms, growth failure, anemia or other common extra-intestinal manifestation of inflammatory bowel disease. His MCV and albumin levels were normal, which is unusual in the setting of chronic gastrointestinal inflammation and gastrointestinal bleeding. Third, his evolving biochemical laboratory profile showed severe ongoing inflammation despite typically effective treatment for IBD with steroids, bowel rest, and EEN. He had biochemical improvement in his systemic inflammation after receiving IVIG, a treatment which has shown efficacy for MIS-C². After our patient's hospital course, a case report noted resolution of both IBD and MIS-C features in a patient treated with infliximab. Infliximab 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, elevated D-dimer, and cytokine profile were suggestive of MIS-C⁴. Fourth, it is very unusual for a case of pediatric IBD to present with coagulopathy. Studies of coagulation factors during active IBD exacerbations have shown elevations in fibrinogen, but normal D-dimer and INR^{5,6}. Even in studies where a statistically significant difference was found in D-dimer and INR levels between Crohn disease patients and controls, the Crohn patient D-dimers and INR levels were within the laboratory's normal range⁶. Fifth, it is very uncommon for children with IBD without fulminant colitis to present in compensated shock as our patient did on admission. Finally, there was no personal or family history IBD or other autoimmune conditions. On the contrary, his familial background may confer higher MIS-C risk, as early case series of MIS-C note an overrepresentation of

children of Afro-Caribbean descent. These features, in the setting of a positive SARS-CoV-2 IgG 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 CDC, Royal College of Pediatrics and Child Health (RCPCH) and WHO case definitions of MIS-C, including 1.) fever, 2.) multi-system involvement including coagulopathy and gastrointestinal symptoms and 3.) positive SARS-CoV-2 serologies⁷. The case definitions include different exclusion criteria. The WHO and RCPCH exclude patients with “other microbial causes” of inflammation while the CDC excludes patients with “other plausible alternative diagnoses.” Thus, despite our hesitancy to ascribe all of his findings to IBD, our patient technically meets the WHO and RCPCH but not the CDC definition of MIS-C. As this pandemic is now entering its most severe and third wave it is likely that we will see more cases of MIS-C and further refine our definitions and inclusion/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 host⁸. Dolinger et al. described a case of patient with known Crohn disease who had contemporaneous IBD exacerbation and MIS-C⁹. The virus-as-trigger hypothesis could apply to that case as well, though notably our patient did not have a previous diagnosis of IBD. Alternatively, it may be that this patient presented with gastrointestinal symptom predominant MIS-C related to previous SARS-CoV-2 infection due to a genetic predisposition to gastrointestinal inflammation, but he will not continue to have chronic gastrointestinal disease

suggestive of a primary diagnosis of inflammatory bowel disease. Further study on the impact of COVID-19 infection and MIS-C on the presentation of autoimmune diseases is indicated.

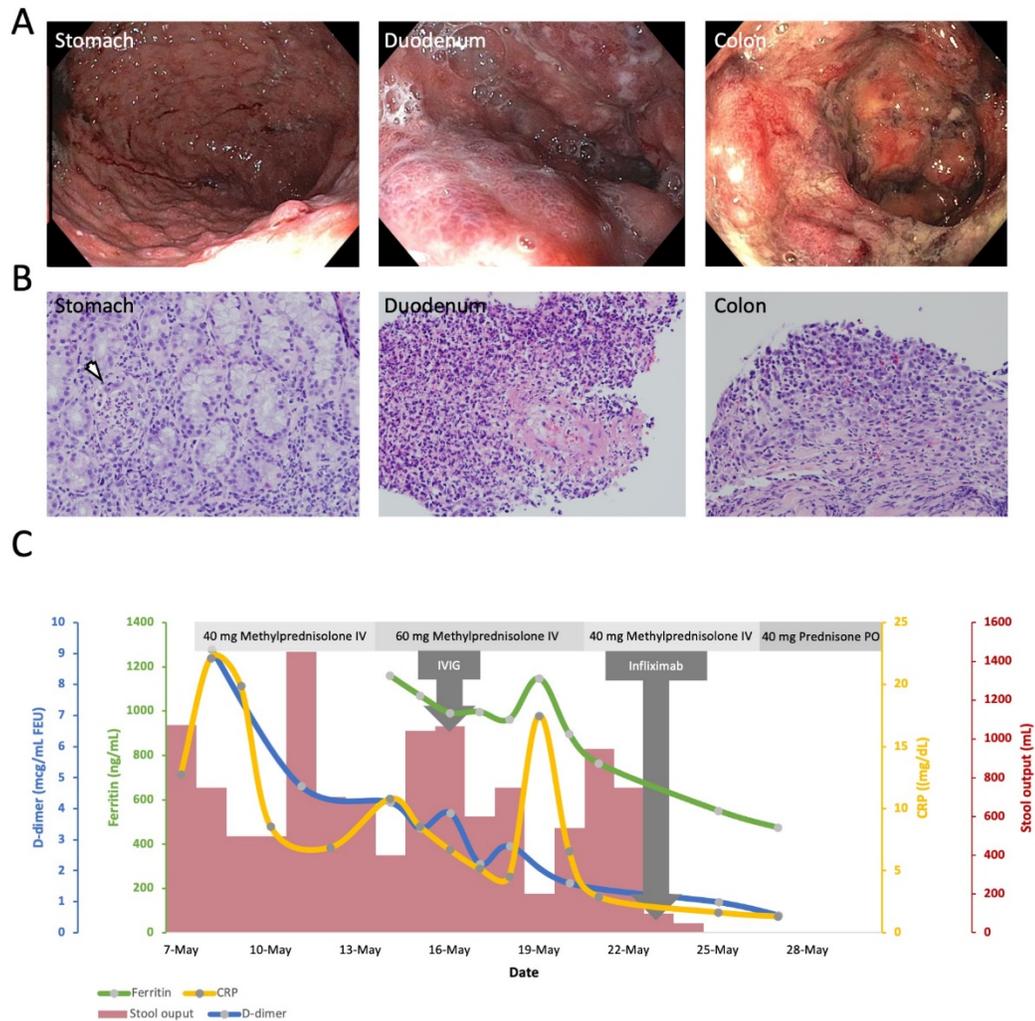
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Figure

A. Severe gastritis in the body of the stomach (left, arrow), severe duodenitis in the duodenal bulb (middle) and severe colitis in the sigmoid colon (right) noted on endoscopy. B. Corpus mucosa with active gastritis with expansile lamina propria lymphoplasmacytic infiltrate (left), ulcerated duodenal mucosa with vasculitis-like involvement of a blood vessel (middle), and severe active colitis with mucosal ulceration (right), all 400x magnification. C. Course of laboratory inflammatory markers (Green: Ferritin, Blue: D-dimer, Yellow: CRP), stool output (maroon bars), and treatment (grey bars and arrows).

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