Suspected Case of Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 Infection Presenting as Acute Pancreatitis in a Child With Leukemia

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Abstract: Multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 may present with fever, elevated inflammatory markers, and multiorgan involvement. Although the gastrointestinal system is commonly affected in MIS-C patients, associated necrotizing pancreatitis is rare. We present an 11-year-old boy with B-cell acute lymphoblastic leukemia in remission undergoing maintenance chemotherapy presenting with acute necrotizing pancreatitis. He developed fevers, fluid and electrolyte imbalance, respiratory distress, cytopenias, and coagulopathy, and was found to have markedly elevated inflammatory markers and positive SARS-CoV-2 antibodies. The patient met criteria for MIS-C and was treated with intravenous immunoglobulin with significant clinical improvement. This is the first known reported case of a child with B-cell acute lymphoblastic leukemia who met criteria for MIS-C presenting as acute pancreatitis, and highlights the importance of considering a broader differential for pancreatitis in children given the current SARS-CoV-2 pandemic.

Key Words: MIS-C, B-ALL, SARS-CoV-2, pancreatitis

(*Infect Dis Clin Pract* 2021;29: e465–e467)

In December 2019, a novel coronavirus (SARS-CoV-2) was discovered and soon after was deemed a global pandemic by the World Health Organization. Initially, SARS-CoV-2 infection was reported to be milder in children, and deaths were rare.[1] However, by May 2020, reports of a multisystem inflammatory syndrome in children (MIS-C) related to SARS-CoV-2 infection began to surface. Multisystem inflammatory syndrome in children was initially described as a "Kawasaki disease-like illness" with features of toxic shock syndrome, including fever, shock, myocardial dysfunction, conjunctivitis, edema, mucosal membrane changes, gastrointestinal symptoms, and rash. Most children affected had negative SARS-CoV-2 polymerase chain reaction (PCR) on nasal swab, but had significantly elevated inflammatory markers and positive SARS-CoV-2 antibodies. Case reports have shown that intravenous immunoglobulin (IVIG) and methylprednisolone were successful in reducing systemic inflammation.[2]

As of October 30, 2020, 1163 cases of MIS-C have been reported in the United States.[3] The Centers for Disease Control and Prevention criteria for MIS-C include patients younger than 21 years presenting with fever, laboratory evidence of inflammation, and involvement of at least 2 organ systems. Suspected patients must have a positive SARS-CoV-2 infection by PCR or antigen testing, or a history of exposure to SARS-CoV-2 within 4 weeks before onset of symptoms.[4]

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The authors have no conflicts of interest to disclose.

ISSN: 1056-9103

The gastrointestinal system is one of the commonly affected organ systems in MIS-C, primarily manifesting as abdominal pain, nausea, vomiting, or diarrhea. Pancreatitis is reported in 7% of MIS-C patients aged 5 to 12 years.[5] In general, pancreatitis is relatively rare in children with an estimated 2 to 13 new cases per 100,000 children annually.[6] There are limited data on drug-induced pancreatitis; however, it is well documented that children with acute lymphoblastic leukemia (ALL) are at risk for acute pancreatitis related to their cancer treatment, particularly asparaginase formulations.[7,8]

Here, we present the first case report of a child with leukemia who presented with acute necrotizing pancreatitis and met criteria for MIS-C. This case highlights the importance of considering novel causes of pancreatitis, even in children with known risk factors, given the current pandemic.

CASE PRESENTATION

The patient is an 11-year-old boy diagnosed at age 10 years with B-cell ALL (B-ALL), classified as high risk because of his age. He had favorable cytogenetics of his leukemic blasts with Trisomy 4 and 10, and his central nervous system was negative for disease involvement. He was treated as per the Children's Oncology Group high-risk protocol AALL1131 and achieved remission by the end of induction. He completed 9 months of intensive chemotherapy. Early in maintenance chemotherapy, he presented with 1 day of epigastric abdominal pain and vomiting. His laboratory evaluation showed a markedly elevated amylase of 825 U/L and lipase of 1623 U/L, as well as neutrophilia and lymphopenia on complete blood count (Table 1). His oral chemotherapy medications included daily 6-mercaptopurine (6-MP), weekly methotrexate, and monthly 5-day prednisone 40 mg/m^2/day pulses (last completed 2 days before presentation). He had not received any asparaginase for 5 months. He also received monthly intravenous pentamidine prophylaxis (last administered 8 days before presentation). Magnetic resonance imaging and magnetic resonance cholangiopancreatography showed necrotizing pancreatitis with acute peripancreatic fluid collection and associated retroperitoneal edema, ascites, and pleural effusion. Within the first 48 hours of hospital admission, he developed hypoalbuminemia with third spacing, respiratory distress with desaturations secondary to pleural effusions and pulmonary congestion, anemia, thrombocytopenia, leukopenia, and coagulopathy. He was managed in the intensive care unit with albumin infusions and diuretics, oxygen supplementation, nasogastric tube decompression, empiric antibiotics, blood products, and pain control.

On hospital day 1, the patient started spiking fevers to a maximum temperature of 39.5°C, which persisted despite clinical improvement from pancreatitis. Blood cultures and a respiratory viral panel were negative, and SARS-CoV-2 was negative by nucleic acid amplification test. However, there was a history of SARS-CoV-2 infection in the patient's father 1 month prior and the patient's SARS-CoV-2 IgG resulted positive at a titer of 2.0 S/C (negative is <1.4 S/C), confirmed on repeat analysis at

TABLE 1. Laboratory Measures From Office Visit Before Admission Until HD10

	Clinic	HD0	HD1	HD2	HD3	HD4	HD5	HD6	HD7	HD8	HD10
Amylase, U/L	831	1607	1153	831	425	197	141	108	89	77	73
Lipase, U/L	1623	2434	2398	1263	498	184	146	142	127	62	107
CRP, mg/L					194	199	278	348	318		155
ESR, MM/1 h							19	24	22		
LDH, IU/L	240						389	354	288		
Fibrinogen, mg/dL				<150	216	274					
D-Dimer, ng/mL							10,489	8764			5775
Ferritin, ng/mL							2117	2267	2382		
Albumin, g/dL		4.1	2.9	3.8	3.8	3.4	3.2	3.3	3.2	3.1	3.3
WBC, $10^3/\mu L$	5.9	6.7	3.2	2.1	2.4	2.5	1.6	3.7	5.5	7.0	7.7
Hgb, g/dL	11.6	12.8	9.5	8.7	7.6	9.0	10.8	10.1	9.1	9.9	8.6
Platelets, $10^3/\mu L$	154	152	62	45➔98*	102	98	92	99	99	117	157
PT, s				22.8	14.5	14					
PTT, s				43	31.7	32.0					
INR				1.97	1.26	1.21					

*Transfused unit of platelets.

HD indicates hospital day; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time.

2.4 S/C (Abbott chemiluminescent microparticle immunoassay). Because of the concern for MIS-C, further laboratory workup was sent, revealing a markedly elevated CRP, ferritin, d-dimer, and IL-6 (Table 1). Troponin and B-type natriuretic peptide were normal, and echocardiogram was normal. The patient was determined to meet the criteria for MIS-C and on day 6 of fever was treated with IVIG at a dose of 2 g/kg with resolution of fever. He had recurrence of fever 48 hours later that resolved without intervention. The fever resolved by hospital day 9. He recovered completely and was discharged home on hospital day 11.

After discharge, he restarted his oral chemotherapy with 6-MP, methotrexate, and prednisone, which he tolerated well. At 11 weeks postdischarge, the patient was readmitted to the hospital with a mild recurrence of pancreatitis, 6 days after completing a steroid pulse. He recovered completely with conservative management and resumed oral chemotherapy with the omission of steroids.

DISCUSSION

To our knowledge, this is the first reported case of a child with leukemia presenting with acute necrotizing pancreatitis and evidence of MIS-C.

In an epidemiological study of 186 patients in the United States meeting diagnostic criteria for MIS-C, 92% of patients had gastrointestinal system involvement. In this study, pancreatitis was diagnosed in 7% of patients aged 5 to 12 years (n = 75), and 2% of patients aged 13 to 20 years (n = 45).[5] Similarly, in a study of 44 children diagnosed with MIS-C in the United States, 84.1% of patients presented with GI symptoms (abdominal pain, vomiting, and/or diarrhea), with 1 patient exhibiting a significant elevation in lipase suggestive of pancreatitis.[9] Furthermore, in a retrospective multiinstitutional European study, of 35 children admitted for cardiac compromise related to MIS-C, 80% had associated GI symptoms.[10] There have been 5 cases of otherwise healthy children with SARS-CoV-2–associated pancreatitis, 4 of whom had a positive SARS-CoV-2 PCR, with 3 of the 4 expressing SARS-CoV-2 symptoms 1 week prior, and the other with clinical evidence of MIS-C and positive SARS-CoV-2 antibodies. All patients recovered completely with supportive care and with IVIG and aspirin for the patient with evidence of MIS-C.[11–13]

Research is currently underway to better understand the pathophysiology of acute SARS-CoV-2 infection and its clinical manifestations. There is evidence to suggest that SARS-CoV-2, similar to the previously studied SARS-CoV, uses the receptor angiotensin-converting enzyme 2 to enter cells and uses the protease TMPRSS2 for S protein priming.[14] Researchers believe that there is ubiquitous expression of the angiotensin-converting enzyme 2 receptor in human organ systems, including the exocrine and islet cells of the pancreas, rendering the pancreas vulnerable to infection.[15–17]

Multisystem inflammatory syndrome in children is thought to be a delayed inflammatory response provoked by SARS-CoV-2 infection. Nakra et al[18] explain that early infection may be mild or asymptomatic in children and triggers macrophage activation and T-helper cell stimulation. Subsequent cytokine release and antibody production lead to a hyperimmune response, manifesting in symptoms consistent with MIS-C.

It is important to note that drug adverse reactions are common causes of pancreatitis in children, and although our patient met criteria for MIS-C, we cannot entirely rule out this etiology. In children being treated for leukemia, pancreatitis has been associated with PEG-asparaginase, steroids, and 6-MP and has also been rarely reported in association with pentamidine. In 1 review, the incidence of asparaginase-associated pancreatitis was reported to range from 2% to 18%.[19] In a cohort study of 271 pediatric patients admitted to the hospital for pancreatitis, most of whom had underlying medical conditions, including seizure disorders, ALL, and Crohn disease, 25.6% (n = 55) of pancreatitis episodes were drug-associated with steroids and valproic acid as the leading causes and pentamidine as the least common.[20] Our patient had not received asparaginase in 5 months, ruling out this drug as the causative agent. Although pentamidine-associated pancreatitis is rare, pentamidine was discontinued for the patient, because there are suitable alternate antibiotics. Our patient tolerated reexposure to steroids and 6-MP after recovery from his initial episode, however after his recurrence, steroids were discontinued from his therapy and he continues to tolerate 6-MP well.

As noted, the recurrence of pancreatitis in our patient raised further concern about a drug-related etiology. However, studies have shown that patients may have a spontaneous idiopathic

recurrence of pancreatitis, termed acute recurrent pancreatitis (ARP) and that as many as 75% of pediatric cases of ARP are idiopathic without an obvious cause.[21–23]

With our patient's clinical picture of systemic inflammation with multisystem involvement, the presence of SARS-CoV-2 antibodies, and resolution of fever after IVIG, we believe that our patient most likely had MIS-C presenting as pancreatitis with a subsequent episode of idiopathic ARP. The patient's improvement in pancreatitis with supportive care, but persistence of fevers, is indicative of ongoing systemic inflammation and supports the diagnosis of MIS-C. Although first-tier recommendations include IVIG and/or steroids for immunomodulatory treatment, and aspirin as an antiplatelet agent, steroids were avoided out of concern for the differential diagnosis of steroid-induced pancreatitis and aspirin was omitted because of risk of bleeding in the setting of thrombocytopenia.[24]

This case report suggests that SARS-CoV-2–related diseases should be in the differential diagnosis in a patient with B-ALL and pancreatitis. Although drug adverse reactions in these patients remain a leading differential, we must now look more broadly due to the current pandemic. We advise that SARS-CoV-2 is routinely screened for, and past or present exposures to SARS-CoV-2 are thoroughly investigated in the setting of a B-ALL patient with new and acute gastrointestinal symptoms.

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