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CASE REPORT

Pancreatology

Multisystem inflammatory syndrome in children presenting as acute severe necrotizing pancreatitis: A case report

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Abstract

We report a case of moderately severe acute pancreatitis, hyperglycemia, acidosis, splenic, superior mesenteric, and portal vein thrombosis in relation to multisystem inflammatory syndrome in children (MIS-C). The patient responded well to intravenous immune globulin, corticosteroids, antibiotics, systemic anticoagulation, and drainage of peripancreatic fluid. The case highlights the polymorphic presentation of MIS-C and advises high level of suspicion for unusual, severe cases unresponsive to routine care.

KEYWORDS

MIS-C, SARS-CoV-2, Spike protein, thrombosis

1 | INTRODUCTION

Multisystem inflammatory syndrome in children (MIS-C) is an inflammatory sequela presenting 2–6 weeks after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Development of MIS-C is not necessarily related to the severity of the initial SARS-CoV-2 infection and can be seen following mild or even asymptomatic infections. Surveillance definition initially proposed by the Centers for Disease Control and Prevention in May 2020 included age less than 21 years, fever for at least 24 h, evidence for current or recent SARS-CoV-2 infection, elevated inflammatory markers, more than two organs involved, severe illness requiring hospitalization, and no other plausible diagnosis.[1] This definition was later modified in December 2022 to improve specificity.[2] The five areas of modification in the new definition include: acceptance of any duration of fever as a valid criterion; elevated C-reactive protein (>3.0 mg/dL) as the favored marker of systemic inflammation; exclusion of renal, respiratory, and neurologic system (given their lack of specificity) as part of the multiorgan criterion; addition of shock (besides cardiac) as a separate organ involvement; and more clarity on timing of molecular or serologic testing of SARS-CoV-2 infection.[3] Of note, gastrointestinal involvement remains a prominent criterion in the new definition.[2]

While the cases of MIS-C initially reported resembled Kawasaki Disease,[4] progression of the pandemic has witnessed unusual and diverse presentations. Here, we describe a child with necrotizing pancreatitis, hyperglycemia, acidosis, and multiple splanchnic vessels thrombosis as the presenting form of likely MIS-C.

2 | CASE REPORT

A 14-year-old female with overweight (body mass index [BMI]: 29 kg/m^2) and acne, recently started on oral contraceptive pills (OCP) and isotretinoin, presented in

January 2022 with 3 days of worsening epigastric pain and vomiting. On presentation, she had mildly elevated alanine aminotransferase and aspartate aminotransferase, normal bilirubin, elevated lipase, glucose, and beta-hydroxybutyrate with low total carbon dioxide (Table 1). Magnetic resonance cholangiopancreatography on hospital day (HD) 2 showed ascites, edema of the pancreas, and potential thrombosis of the splenic vein (Figure 1); also noted were liver steatosis, patent gallbladder, and nondilated biliary system; the pancreatic duct was not visualized. Similarly, abdominal ultrasound (HD 3) showed enlarged pancreas with ascites and septated fluid of upper abdomen. Computerized tomography scan (HD 4) confirmed edema of the pancreas with a necrotic collection (size 9.9 × 12.1 × 6.2 cm) anterior to the pancreatic body consistent with necrotizing pancreatitis. Complete thrombosis of the splenic, superior mesenteric, and portal veins was also noted.

Infectious work-up for Cytomegalovirus, Epstein-Barr Virus, and Herpes Simplex Virus were negative; plasma microbial cell-free DNA next-generation sequencing (Karius Test®) was positive for *Escherichia coli* but blood and urine cultures were negative. Afebrile on admission, the patient then developed fever on HD 2 and was started on meropenem and linezolid, but fever persisted. The possibility of MIS-C was then entertained due to persistent fevers unresponsive to antibiotics and the ongoing COVID-19 pandemic. History review disclosed that she was not vaccinated against SARS-CoV-2 and had no documented SARS-CoV-2 infection, but 4 weeks before presentation her whole family, including the patient, had had "cold-like" symptoms. Her admission tests were negative for SARS-CoV-2 Nucleic Acid Amplification (Thermo Fisher Scientific™) and antibody against Nucleocapsid protein (Abbott Architect CMIA),[5] but positive for SARS-CoV-2 Spike protein (Roche EIA)[6] at 1557 U/mL on HD 4 and repeat 1670 U/mL on HD 5. Other pertinent laboratory results showed elevated white blood cell count, with neutrophilia and lymphopenia, elevated C-reactive protein, and procalcitonin (Table 1). Intravenous immune globulin (IVIG) (2 g/kg body weight) was administered on HD 6 and methylprednisolone started the same day (2 mg/kg/day for 10 days and tapered over 21 days), with prompt resolution of fever and subsequent decrease in inflammatory markers (Table 1). Antibiotics were administered for 10 days. Heparin drip was started on HD 5 and transitioned to enoxaparin on HD 10. There were no renal, respiratory, or cardiac dysfunction noted; cardiac echocardiograms performed on HD 5 and HD 16 were normal.

At discharge on HD 27, the patient's necrotic peripancreatic fluid had grown slightly in size to 11.9 × 14.6 × 10.3 cm. It was initially managed conservatively and followed sonographically but ultimately drained 3 months after initial hospitalization when it was not decreasing in size and there was concern for possible superinfection, given new fevers and abdominal pain. Purulent fluid was drained by endoscopic cyst gastrostomy; culture grew "rare" methicillin sensitive *Staphylococcus aureus, Granulicatella adiacens, Veillonella* spp. and *Gamella morbillorum*. Initial empiric treatment was with meropenem plus linezolid, then narrowed to cefazolin plus clindamycin and finally oral cephalexin plus clindamycin on discharge. Follow-up imaging showed resolution of the fluid collection. For anticoagulation, the patient was continued on enoxaparin for 3 months after discharge with resolution of thrombosis in the right portal and splenic veins. Insulin requirements progressively decreased, and presently on low dose, long-acting insulin (glargine) 5U daily. Despite abnormal fecal elastase (66 µg/g), the patient did not show clinical evidence of exocrine pancreatic insufficiency and did not require pancreatic enzyme replacement therapy.

3 | DISCUSSION

Gastrointestinal symptoms are well documented during SARS-COV-2 infection and MIS-C. In one review of 101 children hospitalized with laboratory-confirmed SARS-CoV-2 infection, 58 (57%) presented gastrointestinal symptoms during their illness, in 14 (14%) as first manifestation; importantly, the presence of gastrointestinal symptoms increased the chances of intensive care admission (odds ratio [OR]: 5.9).[7] Pancreatitis,[8] is seen much less frequently in patients with COVID-19, and was reported in 2 (1.8%) of 112 children admitted with COVID-19 in New York.[9] Regarding MIS-C, pancreatitis has been described since the beginning of the epidemic in 2020, but the true incidence is hard to discern since most have been single case reports.[10–12] A multicenter series of 186 cases of MIS-C collected in early 2020 in the United States, found 171 (92%) of them with gastrointestinal symptoms, and nine (5%) diagnosed with pancreatitis.[13] Conversely, a small series of 17 children with MIS-C, at a single-, referral-center in India diagnosed pancreatitis (using the Atlanta Criteria) in about 50% of cases[14]; and, a second series in Italy of 55 children hospitalized with MIS-C, reported 24 (44%) with increased pancreatic enzymes, and 2 (3.6%) with enlarged pancreas by ultrasound.[15] In most of those cases, MIS-C was clinically evident at presentation and pancreatitis manifested as part of a systemic inflammatory process.

In that context, our patient's case was unusual in that MIS-C presentation was cryptic—initially manifesting only as moderately severe acute pancreatitis (AP).[16] Mucocutaneous signs were never present, and fever did not develop until 4 days after initial symptoms, delaying diagnosis and interventions.

TABLE 1 Select laboratory results and maximum daily temperature days before and after treatment for MIS-C started on hospital day 6.

		Hospital day												
Test	**Normal values**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**16**	**22**	**27**
Glucose	70–99 mg/dL	248	>500	170	131	150	130	190	129	141	176	134	110	81
HbA1c	0%–5.6%	5.6												
BHB	0.02–0.27 mmol/L	1.11												
CO_2	21–30 mEq/L	14												
Lipase	18–71 IU/L	2899	585	225		96		70	65	104	147	111	164	106
AST	13–38 U/L	96	55								161	39	39	
ALT	9–48 U/L	47	22								48	49	39	
Bilirubin (total)	0–1.2 mg/dL	0.4									0.7	0.4		
Triglyceride	<150 mg/dL		81									116		
Fecal elastase	>200 µg/g											66		
WBC	$3.8–11.2 \times 10^9$/L	22.8	18.5	15.1	18.3	17.8	26.2	24.3	25		22.3	28.4	23	9.5
Platelets	$150–450 \times 10^9$/L	312	230	203	251	298	408	403	407	464	483	586	644	507
ANC	$1.9–9.8 \times 10^9$/L	19.4	15.0	12.2	15.6	15.0	22.0	23.8	22.3	27.7	35.2	26.7	21.6	5.98
ALC	$0.7–4.5 \times 10^9$/L		1.32	1.26	1.46	1.42	2.36	0.24	1.5	2.25	0.89	1.09	0.92	3.12
ESR	0–20 mm/h						58				62	102	78	59
CRP	<5.0 mg/dL	257					298	247	149	84	77.2	39.5	19.4	4.8
PCT	<0.10 ng/mL						0.48				0.13	0.13		
Ferritin	8–364 ng/mL						892				1848	1,184		616
PT	11.6–14.2 s		15.9			17.2	15	16.2	16.3	16.5	16.0	13.4	13.2	
PTT	25–36 s		32			46	66				37	35		
T_{max}	36–38°C	37.1	39.4	39.3	39.5	38.9	39.5	37.6	36.6	37.1	38.0	37.4	37.1	36.8

Abbreviations: ALC, absolute lymphocyte count; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BHB, beta-hydroxybutyrate; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MIS-C, multisystem inflammatory syndrome in children; PCT, pro-calcitonin; PT, prothrombin time; PTT, partial thromboplastin time; T_{max}, maximum recorded daily temperature; WBC, white blood cell count.

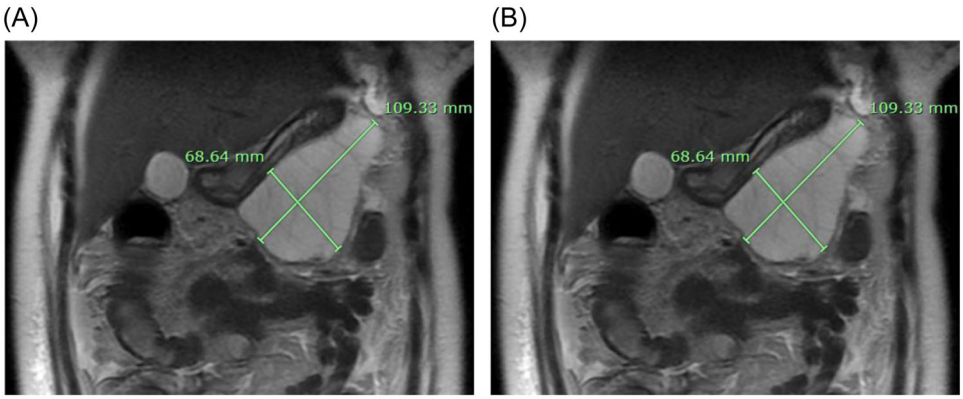

FIGURE 1 Magnetic resonance cholangiopancreatography obtained on hospital Day 2. Axial (A) and coronal (B) views T2 images showing enlarged and heterogeneous pancreas consistent with pancreatitis. Focal fluid is seen anterior to the pancreas and likely within the lesser sac measuring 5.8 × 6.9 × 10.9 cm in dimension and with mild septations. Decrease prominence to the flow void within the distal portion of the splenic vein is noted.

Eventually, the presence of fever, systemic inflammation, presence of SARS-CoV-2 antibodies, absence of an alternative diagnosis, and—more importantly—prompt response to IVIG infusion, highly suggested the diagnosis of MIS-C. Hence, the case here presented not only reaffirms the association of MIS-C with pancreatitis but extends the spectrum of presentation to more subtle forms, emphasizing the need for increased awareness. We should mention that two cases in the literature mimic some aspects of our case, in that they also presented prominently with manifestations of AP; the diagnosis of MIS-C was eventually entertained due to persistent fever and high inflammation, and reinforced by prompt response to IVIG and/or steroids.[17,18] While there are many similarities between our case and these two cases, there are some differences. One presented acute inflammation but no necrosis of the pancreas and recovered promptly[17]; and the other,[18] similar to ours, presented with necrotizing pancreatitis requiring drainage, but had more obvious clinical and radiological pulmonary findings, which assisted with the diagnosis and, again, highlights the unusual cryptic presentation of our case.

The SARS-CoV-2 antibody tests used here are reported to have high sensitivity and specificity.[5,6] The high and twice positive Spike antibody result, along with the history of "cold," suggest a real and recent infection. The negative Nucleocapsid antibody result (also twice) is puzzling and cannot be fully explained. While there is limited data on Nucleocapsid antibody kinetics following SARS-CoV-2 infection, the evidence suggests children (with or without MIS-C) may have a better antibody response to Spike than to Nucleocapsid protein.[19] We identified other potential aggravating factors for pancreatitis, such as overweight, use of isotretinoin and OCPs; while we believe they played an important role, they alone unlikely explain the full constellation of presentation and the response to therapy. There is always the possibility that the occurrence of pancreatitis and SARS-CoV-2 was coincidental and the improvement seen represented natural progression of the disease, but we believe that explanation is also of low probability. The moderately severe AP in our patient was complicated by multiple vessels splanchnic thromboses; fortunately, a favorable outcome was seen with use of anticoagulation.

Our case illustrates the varied and evolving manifestations of MIS-C, beyond the proposed limited diagnostic criteria. Our patient's unique presentation shows that MIS-C can be a cryptic diagnosis and should be entertained in critically ill patients. Clinicians are well-advised to keep an open mind and consider the possibility of MIS-C in unusual, especially severe cases that do not follow a predictable course. Our case adds to the mounting literature of severe pancreatitis as a manifestation of MIS-C.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

Informed patient consent was obtained for publication of the case details.

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