



Management of acute abdomen during the active disease course of COVID-19 and multisystem inflammatory syndrome in children

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Abstract

Purpose To evaluate the management of children with severe gastrointestinal symptoms during the disease course of COVID-19 and multisystem inflammatory syndrome (MIS-C).

Methods After ethical approval, we reviewed the medical records, retrospectively, of children with COVID-19 or MIS-C requiring surgical consultation for severe gastrointestinal symptoms.

Results The subjects comprised 15 children, 13 with MIS-C and 2 with COVID-19. Twelve children (80%) had been in known close contact with a person with SARS-CoV-19 and 13 were positive for Anti-SARS-CoV-2 IgG. All the children had experienced fever for at least 1 day and had signs of involvement of two or more systems. Three patients required surgical intervention: one underwent surgical exploration with a presumptive diagnosis of acute appendicitis in the referring center and was transported to our center following clinical deterioration, where a diagnosis of MIS-C was confirmed; and the remaining two developed appendicitis during hospitalization for COVID-19. All three patients had a longer duration of abdominal pain, a higher number of lymphocytes, and a lower level of inflammatory markers than the non-surgically managed patients. None of the patients presenting with MIS-C underwent surgical exploration.

Conclusion Gastrointestinal involvement may mimic acute abdomen in children with COVID-19. Thus, children presenting with acute abdomen in the pandemic era require careful evaluation and prompt diagnosis to avoid unnecessary surgical intervention.

Keywords Abdominal pain · Gastrointestinal symptom · MIS-C · COVID-19 · Pandemics · Children

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been impacting the whole world since the corona virus disease-19 (COVID-19) pandemic began. SARS-CoV-2 spread rapidly in our country as it did in other countries [1]. According to reports from the Center for Disease Control (CDC), children constitute only about 2% of infected people [1, 2]. Despite all the uncertainties about the epidemiology and clinical course of the disease in children, the first reports indicated a favorable clinical course

and prognosis for affected children [3–5]. However, recent studies show that SARS-CoV-2 can cause severe disease requiring intensive care in a small percentage of infected children [1, 6]. As the pandemic continued, another severe clinical situation emerged. In April, 2020, a critical illness associated with hyper-inflammation syndrome secondary to SARS-CoV-2 infection was defined in children and adolescents [7]. Subsequently, this was reported to be related to SARS-CoV-2 infection and termed ‘multisystem inflammatory syndrome in children’ (MIS-C) [8, 9].

The clinical presentation of MIS-C is clustered in three groups, with Kawasaki-like symptoms in about 20%, cardiac dysfunction in 70%, and gastrointestinal symptoms in 90% [9, 10]. Because of this clinical diversity, the CDC has proposed the diagnostic criteria for MIS-C [11]: age < 21 years, persistence of fever, involvement of at least two organ systems, elevated inflammatory biomarkers, laboratory or epidemiologic evidence of SARS-CoV-2 infection, and

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exclusion of other clinical etiologies. Among all clinical presenting symptoms, gastrointestinal symptoms are not only the most frequently seen in MIS-C but also very commonly seen as the presentation of COVID-19 disease [6, 9, 10]. This frequent occurrence of gastrointestinal symptoms may cause diagnostic challenges, such as delayed diagnosis even after surgery for acute abdomen [9, 12, 13]. Moreover, the abdominal pain may mimic appendicitis, gastroenteritis, or inflammatory bowel disease, causing more diagnostic challenges [12–14]. Therefore, careful evaluation of abdominal pain and other gastrointestinal symptoms has become more important in children when we consider today's conditions. Based on this issue, we conducted a retrospective analysis of children presenting with gastrointestinal symptoms during the disease course of COVID-19, with a subsequent diagnosis of MIS-C.

Materials and methods

This study was approved by the Institutional Ethical Review Board (GO 21/376–2021/06–39) and performed under the guidelines of the Helsinki declaration of human rights. All patients and their families were informed about the study and informed consent was obtained.

Patients under 18 years of age who were confirmed as having COVID-19 and MIS-C according to CDC criteria [11] and who were referred to the pediatric surgery department for investigation of gastrointestinal symptoms were included in the study. The medical records of patients with COVID-19 and MIS-C with gastrointestinal symptoms encountered between May 1st, 2020 and March 1st, 2021 were evaluated retrospectively. Medical data including demographic features, admission weight percentiles, presenting symptoms, duration of symptoms, epidemiologic data regarding SARS-CoV-2 infection, associated medical conditions, laboratory investigation results, radiological and clinical findings, medical management, surgical interventions, and outcomes were collected from the hospital patient records.

The inclusion criteria met the CDC criteria for MIS-C cases, but we included hospitalized patients younger than 18 years of age, since pediatricians are allowed to treat patients up to 18 years of age in our hospital. Apart from age, all other criteria of the CDC were met; namely, persistence of fever, involvement of two or more organ systems, elevated inflammatory biomarkers, laboratory or epidemiologic evidence of SARS-CoV-2 infection, and exclusion of other clinical etiologies. We also included children with gastrointestinal symptoms in the analysis. All patients were tested for SARS-CoV-2 infection via nasopharyngeal swap samples with reverse transcriptase-polymerase chain reaction test (RT-PCR) for COVID-19. In addition, all patients

were questioned about epidemiologic data regarding possible close contact with a PCR (+) COVID-19 case and tested for Anti-SARS-CoV-2 IgG with Euroimmun anti-SARS-CoV-2 ELISA IgG test.

Statistical analysis

For statistical analysis, Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM, USA) was used. The normally distributed descriptive values are calculated as means and standard deviation. The non-normally distributed descriptive values are calculated as medians and interquartile range. Categorical variables are given as frequency in percentages. The X^2 test was used to compare categorical data. P values < 0.05 were considered significant.

Results

The subjects comprised 15 patients: 13 with MIS-C and 2 with COVID-19. All patients had been referred to the pediatric surgery department for investigation of gastrointestinal symptoms to rule out any surgical pathology. The male-to-female ratio was 9:6 and the mean age was 9.2 years (range, 5–15 years). The weight percentiles on admission were above the 75th percentile for five children and five children had co-morbidities; namely, familial Mediterranean fever, G6PD deficiency, ependymoma, and asthma (Table 1). An epidemiological review revealed that 12 children (80%) had a history of close contact with a confirmed COVID case, all being relatives in the last 1 month. All children were tested for Anti-SARS-CoV-2 IgG and all but two were found to be positive for Anti-SARS-CoV-2 IgG.

Table 1 summarizes the demographic features and presenting symptoms of the patients. All the children had experienced fever for at least 1 day prior to presentation and had signs of involvement of two or more systems. Table 2 lists the results of laboratory investigations, including complete blood count, serum biochemistry, and all inflammatory markers. There were no pathologic findings on the abdominal X-rays of 13 patients, but an air-fluid level was seen in two patients, who were managed surgically. Abdominal ultrasound (USG) was performed for 12 patients, revealing terminal ileum wall thickening in 3 patients and duodenum wall thickening in 1 patient who was vomiting on admission. Abdominal USG also revealed pelvic abscess in two patients and inter-loop free fluid in two patients. Abdominal CT or MRI was performed for persistent abdominal pain and tenderness in nine patients. A diagnosis of appendicitis was made by abdominal MRI in two patients found to have a pelvic abscess on abdominal USG. Terminal ileal wall-thickening and mucosal enhancement was found by abdominal CT/MRI in six patients, two of whom had not had prior

Table 1 Demographic features and presenting symptoms of the patients

Characteristics	Values
Patients	<i>N</i> = 15
Age	9.2 ± 3.96 years (5–15 years)
Sex (%)	Male: 9 (60%) Female: 6 (40%)
Body weight (percentile for age)	< 3 percentile: (<i>N</i> = 3) 25–50 percentile: (<i>N</i> = 2) 50–75 percentile: (<i>N</i> = 5) 75–95 percentile: (<i>N</i> = 3) > 95 percentile: (<i>N</i> = 2)
Co-morbidities ^a	<i>N</i> = 5 (33%)
Presenting GIS symptoms	
Abdominal pain	<i>N</i> = 12 (80%)
Duration of abdominal pain	2 days (range: 0–5 days)
Nausea/vomiting	<i>N</i> = 9 (60%)
Diarrhea	<i>N</i> = 7 (46%)
Presenting other system symptoms	
Fever	<i>N</i> = 15 (100%)
Duration of fever	5 days (range: 1–7 days)
Respiratory deficiency	<i>N</i> = 3
Conjunctivitis	<i>N</i> = 5
Rash	<i>N</i> = 6
Strawberry tongue	<i>N</i> = 2
Cardiac dysfunction	<i>N</i> = 7
Other	hypotension <i>N</i> = 6 pretibial edema <i>N</i> = 1 pneumothorax <i>N</i> = 1
SARS-CoV-2 screening	
History of SARS-CoV-2 in the last month ^b	<i>N</i> = 6 (40%)
Close contact with a confirmed case in the last month	<i>N</i> = 12 (80%)
Anti-SARS-CoV-2 IgG positivity	<i>N</i> = 13 (86%)

^aFamilial Mediterranean fever (*N* = 2), G6PD (*N* = 1), ependymoma (*N* = 1), and asthma (*N* = 1)

^bSARS-CoV-2 confirmed with PCR test

abdominal USG, two had normal findings on abdominal USG, and two had thickened bowel wall and inter-loop free fluid on abdominal USG.

The medical management of MIS-C was based on recommendations of the pediatric infectious disease committee, which is consistent with the literature. Favipiravir, methylprednisolone, anticoagulants (low-molecular-weight heparin), antibiotics, and intravenous immunoglobulin (IVIG) were given to all patients. Immune modulators (Anakinra) were given to nine patients, adrenalin infusion and vasopressin treatment were given to six, and plasma exchange was performed in three. Two patients needed endo-tracheal intubation and ventilator support and one was ventilated with non-invasive mechanical ventilation. The median duration for ventilator support was 0 (0–20) days and the median duration of total hospitalization was 7 (3–90) days.

Three patients required surgical management, after at least 3 days of abdominal pain and persistent fever. The first

patient underwent surgery for suspected appendicitis in the referring center. Although the pathology had revealed signs of acute inflammation, the fever and gastrointestinal symptoms persisted and signs of cardiac dysfunction developed. The patient was transferred to our center, where MIS-C was diagnosed and managed accordingly. The second patient was admitted with high fever, nausea, and abdominal pain. He had been in close contact with a PCR (+) relative and his COVID-19 PCR test was found to be positive. During his hospitalization, abdominal tenderness developed, and a second abdominal CT scan revealed appendicitis. The patient underwent appendectomy, and his postoperative course was uneventful. The third patient presented to another medical center with abdominal pain and was hospitalized for suspected MIS-C. He was referred to our center, because the symptoms persisted, where abdominal MRI scans showed perforated appendicitis. After appendectomy, his fever recurred. His care-giver and he were tested and found to be

Table 2 Results of laboratory and radiological investigations on admission

Parameter	Values
Hemoglobin (Normal range: 11.5–14.5 gr/dL, varies by age)	11.3 (9.9–16.2)
White blood cell count (Normal range: 5–13 × 10 ³ /μL)	7.4 × 10 ³ (4.1 × 10 ³ –27.6 × 10 ³)
Absolute lymphocyte count (Normal range: 1–5 × 10 ³ /μL)	0.75 × 10 ³ (0.45 × 10 ³ –1.23 × 10 ³)
Platelet count (Normal range: 180–400 × 10 ³ /μL)	139 × 10 ³ (47 × 10 ³ –342 × 10 ³)
Erythrocyte sedimentation rate (Normal range: 0–20 mm/h)	29 (9–86)
CRP (Normal range: 0–0.5 mg/dL)	12.55 (2.2–30.54)
Procalcitonin (Normal range: 0–0.1 ng/mL)	7.07 (0.22–111)
Lactate dehydrogenase (Normal range: 110–295 U/L)	305 (174–822)
ALT (Normal range: <39 U/L)	15 (10–62)
AST (Normal range: <51 U/L)	30 (15–96)
Ferritin (Normal range: 11–307 μg/L)	467 (77.3–1661)
Fibrinogen (Normal range: 180–350 mg/dL)	479 (235.79–806)
Interleukin-6 (Normal range: <6.4 pg/mL)	47.91 (8.5–3314)
Gastrointestinal imaging	
Abdominal X-ray (N=15)	Air-fluid level: N=2 Normal findings: N=13
Abdominal USG (N=12)	Thickened bowel wall: N=4 ^a Free fluid: N=2 Pelvic abscess: N=2 Normal findings: N=4
Abdominal CT/MRI (N=9)	Thickened bowel wall: N=6 Pelvic abscess and appendicitis: N=2 Normal findings: N=1

^aLevel of bowel-wall thickening: terminal ileum (N=3), duodenum (N=1)

positive for COVID-19 on postoperative day 4. He was managed accordingly and discharged uneventfully.

The 12 patients managed non-surgically were all examined by pediatric surgeons. MIS-C was diagnosed in all, and none underwent surgical exploration. After exclusion of surgical pathology, all were managed with intravenous hydration without oral feeding for 2 days (range 1–3 days) and resumed oral intake after the abdominal tenderness had resolved. One patient continued to experience nausea and vomiting, which delayed oral intake by a day. Later he suffered pneumothorax and required tube thoracostomy insertion. He was followed up for 14 days after tube removal.

If we exclude this case, the median duration of follow-up for gastrointestinal symptoms was 2 days (range 1–3 days). Table 3 summarizes the surgically and non-surgically managed patients. Although statistical analysis was not possible because of the small number of cases in the surgical group, several differences were evident between the two groups. First, the duration of abdominal pain was longer in the surgically managed patients. Second, the absolute lymphocyte count was higher in surgically managed patients, whereas the levels of inflammatory markers were higher in the non-surgically managed patients. Abdominal USG and CT/MRI seem to be descriptive in such cases. Finally, although the duration of hospitalization varied, follow-up was longer for the surgically managed patients, probably because of the postoperative follow-up.

Discussion

Early in the pandemic, it was thought that the clinical course of SARS-CoV-2 infection in children was favorable [1]. However, a small number of children become critically ill approximately 2–3 weeks after exposure to COVID-19, even if they were asymptomatic at the time of exposure. This condition was explained by a post-infectious hyperinflammation syndrome secondary to COVID-19 infection; later called multisystem inflammatory syndrome in children (MIS-C) [7–9]. Although the clinical course is generally favorable, the gastrointestinal system is involved in 20% of COVID-19 cases and may be severe in children [6, 12]. Several reports from all over the world have identified gastrointestinal symptoms as the most common presentation of MIS-C, seen in 70% to 90% of cases [9, 10]. The gastrointestinal symptoms of MIS-C may be so severe that they are confused with acute surgical pathologies, or they may mimic a chronic bowel disease such as inflammatory bowel disease. This heterogeneity in presentation highlights the importance of every piece of knowledge about the various clinical presentations, so that this new clinical entity is managed appropriately. We conducted this study to analyze children with gastrointestinal complaints subsequently diagnosed as MIS-C as well as COVID-19. Now, we identify if any children presenting with abdominal pain have a history of COVID-19 infection or close contact with a COVID-19 positive person. This epidemiologic evaluation has become routine in our department even for patients who have only gastrointestinal symptoms. On the contrary, early consultation with the pediatric surgery department is considered for all children with a diagnosis of COVID-19 or MIS-C in our center.

In the present series, three patients were managed surgically. The first one underwent surgery for suspected appendicitis in another center and MIS-C was diagnosed later in our

Table 3 Comparison of the patients managed surgically and those managed non-surgically

Characteristic	Patients managed surgically	Patients managed non-surgically
Patients	<i>N</i> = 3	<i>N</i> = 12
Age	9.6 ± 3.5 years	9.08 ± 4.2
Presenting GIS symptoms		
Abdominal pain	<i>N</i> = 3	<i>N</i> = 11
Duration of abdominal pain	4 ± 1 days	2.25 ± 1.55 days
Presenting other symptoms		
Fever	<i>N</i> = 3	<i>N</i> = 12
Duration of fever	4 ± 3 days	4.75 ± 1.65 days
Laboratory results		
Hemoglobin (gr/dL)	12.3 (9.9–16.2)	11.3 (9.3–14.4)
White blood cell count (× 10 ³ /μL)	8.9 (6.1–9.3)	7.35 (4.1–27.6)
Absolute lymphocyte count (× 10 ³ /μL)	0.98 (0.80–1.12)	0.675 (0.45–1.23)
Platelet count (× 10 ³ /μL)	186 (136–284)	137.5 (47–342)
ESR (mm/h)	29 (12–50)	26.5 (9–86)
CRP (mg/dL)	7.96 (6.58–19)	12.85 (2.2–30.54)
Procalcitonin (ng/mL)	2.84 (0.22–7.57)	7.07 (0.82–111)
Lactate dehydrogenase (U/L)	175.5 (174–177)	309 (255–822)
ALT (U/L)	11 (10–15)	24.5 (11–62)
AST (U/L)	19 (15–25)	35 (24–96)
Ferritin (μg/L)	682.5 (258–1107)	467 (77.3–1661)
Fibrinogen (mg/dL)	606.48 (239.94–806)	441.22 (235.79–686.69)
Interleukin-6 (pg/mL)	20.28 (10.78–29.79)	70.52 (8.5–3314)
Gastrointestinal imaging		
Abdominal X-ray	Air-fluid level: <i>N</i> = 2 Normal findings: <i>N</i> = 1	Normal findings: <i>N</i> = 12
Abdominal USG	Free fluid: <i>N</i> = 1 Pelvic abscess: <i>N</i> = 2	Thickened bowel wall: <i>N</i> = 4 Free fluid: <i>N</i> = 1 Normal findings: <i>N</i> = 4
Abdominal CT/MRI	Pelvic abscess and appendicitis: <i>N</i> = 2	Thickened bowel wall: <i>N</i> = 6 Normal findings: <i>N</i> = 1
Management details		
Duration of hospitalization	12 (10–19) days	7 (3–90) days
Surgical follow-up duration	10 (3–10) days	2 (1–14) days ^a

^aIf the patient who required tube thoracostomy was excluded, the median duration would have been 2 (1–3) days

center; the second patient suffered appendicitis during his hospitalization for COVID-19; and the third was hospitalized for abdominal pain and referred to our center because of the persistence of symptoms, where perforated appendicitis was diagnosed and a positive PCR test for COVID-19 was confirmed postoperatively. These three patients had a longer duration of abdominal pain, a higher lymphocyte count, and lower levels of inflammatory markers in contrast to the non-surgically managed cases. Malhotra A et al. compared the findings of patients with appendicitis and those with abdominal pain related to COVID-19 [15]. They found that the patients with appendicitis had more acute abdominal pain, higher neutrophils, and lower levels of inflammatory markers than those with COVID-19; consistent with our results. The small number of cases in the present series made

statistical analysis impossible, so further comparative studies on more patients are needed to reach a firm conclusion. Nevertheless, each case is a unique representation of the diversity of the clinical presentation of MIS-C and COVID-19, which may mislead physicians to perform unnecessary diagnostic examinations and interventions.

The etiology of the higher frequency of gastrointestinal involvement in COVID-19 and MIS-C is not understood well. The most likely mechanism is thought to be that angiotensin converts the enzyme 2 receptor (the entry site for the COVID-19 virus) at great density in the small intestine and colonic enterocytes [16]. This mechanism may also explain why obesity is a risk factor for critical illness in these patients [14]. Five of the patients in the present series were obese, and one needed mechanical ventilation and intensive

care. The small intestine and colon involvement can also be detected with imaging techniques such as abdominal USG, BT, or MRI. The most prominent radiological findings are bowel-wall thickening, mucosal enhancement, and edema [9, 13, 14]. When a diagnosis cannot be made with abdominal USG, abdominal CT/MRI can be performed. We performed abdominal CT/MRI for nine of our patients, six of whom had no abdominal USG findings.

The involvement of terminal ileum in MIS-C may also be responsible for confusing the diagnosis with appendicitis [15]. There are several reports of undiagnosed acute surgical abdomen or MIS-C attributed to acute surgical pathology such as appendicitis or intussusception [12, 15, 17, 18]. Moreover, the abdominal pain in children with COVID-19 and MIS-C may mimic appendicitis, gastroenteritis, or inflammatory bowel disease, causing more diagnostic challenges [13, 14]. In the present study, the patients with MIS-C that was not managed surgically were also examined by a pediatric surgeon for possible acute surgical pathology. Bowel-wall thickening was confirmed on radiological images, and all resolved with medical management. However, as this bowel-wall thickening has been reported to cause progressive intestinal obstruction requiring bowel resection in some cases, stopping oral feeding, frequent physical examinations, and further radiological examinations if the abdominal signs worsen can prevent under-diagnosis of such pathology [16].

Despite the limitations of our study, including its retrospective design and the small number of cases, it includes important data on these conditions that are affecting the whole world. Each of the cases in this series is a representative example of the diagnostic challenges associated with MIS-C and COVID-19 with gastrointestinal symptoms. Although further studies are needed, we observed that our surgically managed patients had a longer duration of abdominal pain, a higher lymphocyte count, and lower levels of inflammatory markers than our non-surgically managed patients. In addition to clinical and laboratory results, radiological images are also valuable for making a differential diagnosis, as they can generally confirm confirm appendicitis regardless of COVID-19, whereas diffuse bowel-wall thickening will be seen in MIS-C related gastrointestinal involvement. Until confirmative data are published, careful evaluation of children with abdominal pain and early surgery consultation for those with MIS-C and COVID-19 will assist with early and accurate diagnosis. Therefore, the present study is important for raising awareness of gastrointestinal involvement and the diagnostic challenges of COVID-19 in addition to MIS-C.

In conclusion, gastrointestinal involvement is a common finding in MIS-C and in some children with COVID-19, although most do not require surgical management. Careful evaluation and prompt diagnosis of children with suspected

COVID-19 and MIS-C, who present with persistent abdominal pain, are important to prevent unnecessary surgical intervention.

Declarations

Conflict of interest We have no conflicts of interest to declare.

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