Simil-appendicitis presentation may precede cardiac involvement in MIS-C patients

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Case report

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Abstract

Background

Multisystem inflammatory syndrome in children (MIS-C) is a new clinical entity characterized by a systemic hyperinflammation triggered by SARS-CoV-2 infection in children and adolescents. This condition could potentially involve all organs with main complications concerning cardiovascular system. Despite up to 90% of patients complain gastrointestinal symptoms (nausea, vomit and diarrhea), a presentation mimicking acute appendicitis has rarely been reported, and can be the presenting feature of the disease, potentially leading to misdiagnosis and delayed treatment.

Case presentation

A 15-year-old boy presented to the Emergency Department for a two-day history of fever, vomiting and mild abdominal pain. One month before, the patient complained ageusia and anosmia while his mother tested positive for Sars-CoV2 nasopharyngeal swab. At admission, laboratory tests showed leukocytosis with lymphopenia and elevation of inflammatory markers, while cardiac enzymes, electrocardiogram and echocardiography were unremarkable. An abdominal ultrasound displayed a thickening of terminal ileus and cecum with ascites. Because of the worsening abdominal pain and a physical examination suggestive of acute appendicitis, a laparoscopy was performed but no surgical condition was found. After surgery, fever and generalized malaise persisted, so a cardiac evaluation was repeated, showing a relevant increase in inflammatory markers and cardiac enzymes. Electrocardiogram demonstrated a QTc prolongation with mild decrease in left ventricular ejection fraction at echocardiogram. A MIS-C was diagnosed and intravenous immunoglobulin along with a steroid treatment started. After 36 hours, the patient presented a complete clinical recovery with fever cessation. Cardiac anomalies normalized in three weeks.

Conclusion

MIS-C has been defined as a systemic inflammation, involving at least two organs, after a previous SARS-CoV2 infection in children and adolescents. Physicians should be aware that while gastrointestinal manifestations are common, a pseudo appendicitis presentation may also occur, leading to misdiagnosis and delayed treatment. This report suggests that in patients with symptoms suggestive of an acute appendicitis, the presence of lymphopenia, hypoalbuminemia and ultrasound images of terminal ileus inflammation, should raise the suspect for MIS-C even without initial overt signs of cardiac involvement.

Background

Multisystem inflammatory syndrome in children (MIS-C), firstly described by Riphagen and colleagues, is characterized by a systemic hyperinflammation triggered by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents (1, 2). According to the Centre of Disease Control and Prevention (CDC), case definition of MIS-C includes age of less than 21 years, fever

for at least 24 hours, elevation of inflammatory markers, serious illness leading to hospitalization or at least two organs involvement (cardiac, renal, respiratory, hematological, gastrointestinal, dermatological, or neurological) with a history of possible SARS-CoV2 infection (positive real time-polymerase chain reaction, positive serology or contact with COVID-19 in the past 4 weeks). Usually developed after 4–6 weeks from primary infection, MIS-C is the most dangerous complication of SARS-CoV2 infection in children (2, 3).

While adult patients with COVID-19 present gastrointestinal symptoms in only 15% of cases, up to 90% of MIS-C patients complain abdominal pain, diarrhea and vomiting. Gastrointestinal symptoms may be the first symptoms in MIS-C patients mimicking other conditions such as gastrointestinal infections or inflammatory bowel diseases (2, 4–6). For this reason, laboratory exams and abdominal ultrasound can be helpful in differential diagnosis, though at the onset they can be indeterminate or unremarkable (2, 4, 6, 7).

Cardiovascular involvement is present in up to 80% of MIS-C patients, usually arising after 6–8 days of fever, with cardiogenic shock as its most life-threatening manifestation (2, 8). Due to a high prevalence of intensive care needs, directly associated to the elevation of myocardial and inflammatory markers, a prompt recognition and treatment of MIS-C patient is mandatory (9). Up to now, immunomodulant treatment seems effective to recover from cardiac damage, but no studies evaluated long-term cardiovascular sequalae (2, 10–12).

Here, we report a case of MIS-C in an adolescent boy with pseudo-appendicitis symptoms followed by myocarditis and heart conduction abnormalities.

Case Presentation

We report the case of a 15-year-old adolescent who presented to the pediatric emergency department with a two-day history of fever, vomiting and diarrhea and mild abdominal pain. His history was remarkable for a period of anosmia and ageusia experienced one month before presentation. In that occasion, two nasopharyngeal swabs for SARS-CoV-2 tested negative, while his mother's one tested positive.

At admission, he was febrile and reported a severe asthenia. Vital signs were normal, except for mild tachycardia (hearth rate 140 beats/min) and fever of 39°C. Refill time was lower than 2 seconds. The cardio-thoracic examination was unremarkable, while a mild diffuse tenderness on abdominal palpation was elicited. Laboratory tests showed mild leukocytosis (white blood cells 10480 mm^3), with lymphopenia (550 mm^3), elevation of C-reactive protein (CRP 137 mg/L, normal value < 5 mg/L), mild elevation of D-dimer (1249 ng/mL; n.v. < 500 ng/mL) and fibrinogen within the normal values (430 mg/dL, n.v. 174–434 mg/dL). Considering the history of recent ageusia and anosmia, the presence of fever, asthenia and gastrointestinal symptoms within elevation of inflammatory markers and lymphopenia, a diagnosis of MIS-C was suspected. Nevertheless, no signs of cardiac involvement were noted: myocardial markers were in normal range (cardiac troponin 2 ng/L [n.v. <19 ng/L] and brain

natriuretic peptide BNP 200 pg/mL [n.v. <300 pg/mL]) with normal electrocardiogram and echocardiography.

Twenty-four hours after admission the patient developed a progressive worsening abdominal pain in the right lower quadrant, with local guarding and rebound tenderness. Abdominal ultrasound showed a thickening of the terminal ileus with ascites and mesenteric lymphadenopathy, while the appendix was not detected (Fig. 1).

A laparoscopic exploration was performed to rule out acute appendicitis. The ileus and cecum appeared thickened and inflamed, while the appendix was normal. Broad spectrum antibiotic treatment was started.

Four days after admission and two days after surgery, despite antibiotic therapy the patient was still febrile and markedly asthenic. Thus, a second cardiological evaluation was performed, showing increased inflammatory and myocardial markers (CRP 250 mg/L, cardiac troponin 65 ng/L, BNP 9195 pg/mL), negative T waves along with prolonged QT interval (490msec) at ECG (Fig. 2) and a reduced left ventricular ejection fraction (LVEF 55%) with a tricuspid regurgitation at echocardiography. According to the simultaneous presence of cardiac and abdominal involvement, a diagnosis of MIS-C was made and treatment with intravenous immunoglobulins (2 gr/kg) and steroids (methylprednisolone 2 mg/kg) was started. Due to the concomitant myocarditis, he received a prophylactic anticoagulation and antiplatelet therapy. After 24 hours the patient had a prompt recovery with cessation of fever, abdominal pain and malaise. In few days inflammatory and cardiac markers progressively decreased to normal values, while ECGs and echocardiogram normalized in three weeks. Exercise restriction was recommended for 6 months, when the patient will undergo cardiac magnetic resonance imaging (MRI).

Discussion And Conclusions

Here, we reported the case of an adolescent with MIS-C in which gastrointestinal symptoms resembled an acute appendicitis. This simil-appendicitis presentation led to an unnecessary explorative laparoscopy and treatment delay. The subsequent cardiovascular involvement and the increasing inflammatory markers allowed the right diagnosis and treatment with prompt and complete recovery.

Despite gastrointestinal symptoms (abdominal pain, emesis and diarrhea) are common features in MIS-C patients, only in a few cases these manifestations resemble an acute appendicitis (5, 6, 13–15). Moreover, when these manifestations precede other organ involvement a differential diagnosis between inflammatory bowel disease, abdominal surgical conditions or severe infections could be difficult (13–16). Typical laboratory findings in MIS-C patients are lymphopenia with neutrophilia, increased PT and D-dimer, hypoalbuminemia, hypertransaminasemia, elevation of inflammatory (CRP, ESR, ferritin and fibrinogen) and cardiac (troponin and BNP) markers (2). As in our case, among all these values, increased inflammatory markers, lymphopenia and hypoalbuminemia are common findings in patients with gastrointestinal symptoms (4, 6). In addition, reviewing abdominal imaging in MIS-C patients, common US findings are ascites, acalculous cholecystitis, bowel wall thickening and mesenteric adenitis (4, 6, 7).

Nevertheless, as in our case, Tullie et al. described eight patients affected by MIS-C with acute abdomen presentation, in some cases simultaneous with cardiac involvement, for whom symptoms and ultrasound imaging were misleading. Notably, pseudo-appendicitis presentation may be associated to the finding of terminal ileitis or typhlitis on abdominal imaging or laparoscopy (6, 13). Therefore, in the first week of disease, gastrointestinal symptoms, laboratory exams and abdominal US could be misleading, especially if no other organ involvement is already present. In our case, retrospectively, the persistent asthenia could be seen as an early marker of cardiac involvement. Indeed, asthenia is almost ever present in MIS-C patient with cardiac manifestation (12). Nevertheless, no elevation of cardiac enzymes or decreased ventricular function were noted in the patient until the second week of disease.

In regard to the risk of intensive care admission and inotropic support in MIS-C patient, a prompt and right diagnosis is mandatory. Up to 80% of patients develop cardiovascular involvement ranging from only mild elevation of cardiac markers (troponin and pro-BNP) to cardiogenic shock. If MIS-C shares some Kawasaki's disease features, the former usually results in more severe ventricular dysfunction and myocarditis. Cardiogenic shock has been proposed to be the result of either myocardial viral damage or "cytokine storm" vasodilatation. Other cardiovascular complications encompass coronary artery aneurism/dilatation and conduction abnormalities. According to a review of cardiac involvement in MIS-C, coronary artery dilatation is reported in up to 25% of patients, while heart conduction abnormalities showed a 7–60% prevalence. Typical arrhythmias are first-degree atrioventricular block, QTc prolongation and ST segment changes. The American Heart Association suggests repeated ECG during the acute phase, but telemetry is needed if any arrythmias occur. From several large studies, early immunomodulatory treatment seems to resolve cardiac damage in most of all cases, but little is known about cardiac sequelae in MIS-C patients. Once myocardial damage occurs, an expert consensus recommends exercise restriction for 6 months with a cardiac MRI at 3 or 6 months to evaluate heart function.

Up to now, no randomized trials have been developed for treatment and management of MIS-C, but due to the similarities between Kawasaki disease and MIS-C, an immunomodulatory approach with IVIG and steroids is recommended. Moreover, antiplatelet treatment and prophylactic anticoagulation are suggested once myocardial or coronary involvement are present. As in our case, several retrospective studies reported, in the majority of patients, normalization of myocardial markers, ECGs abnormalities and ventricular dysfunction after immunomodulatory treatment (10, 12). Nevertheless, longer studies and trials are needed to evaluate treatments and chronic sequalae.

In conclusion, our case highlights how gastrointestinal involvement in MIS-C could mimic acute appendicitis, and this presentation may precede cardiac involvement, leading to possible misdiagnosis and delayed treatment.

In patients with a recent exposure to SARS-CoV-2 a clinical presentation with fever, asthenia and gastrointestinal symptoms should be seen as highly suggestive of MIS-C. This suspect may be supported by the presence of an increased inflammatory markers, lymphopenia and hypoalbuminemia and images

suggestive of terminal ileitis on ultrasound. Even in the absence cardiac involvement at presentation the diagnosis of MIS-C should not be ruled-out and a strict cardiological follow-up should be performed.

Abbreviations

BNP
Brain Natriuretic Peptide
CDC
Center for Disease Control and Prevention
CRP
C-Reactive Protein
ECG
Electrocardiogram
ESR
Erythrocyte Sedimentation Rate
IVIG
Intravenous Immunoglobulin
LFEV
Left Ventricular Ejection Fraction
MIS-C
Multisystem Inflammatory Syndrome in Children
MRI
Magnetic Resonance Imaging
N.V.
Normal Value
US
Ultrasound

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: The authors obtained a written consent form to publish the case report and its radiological image.

Availability of data and materials: No supporting data are available.

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Figures

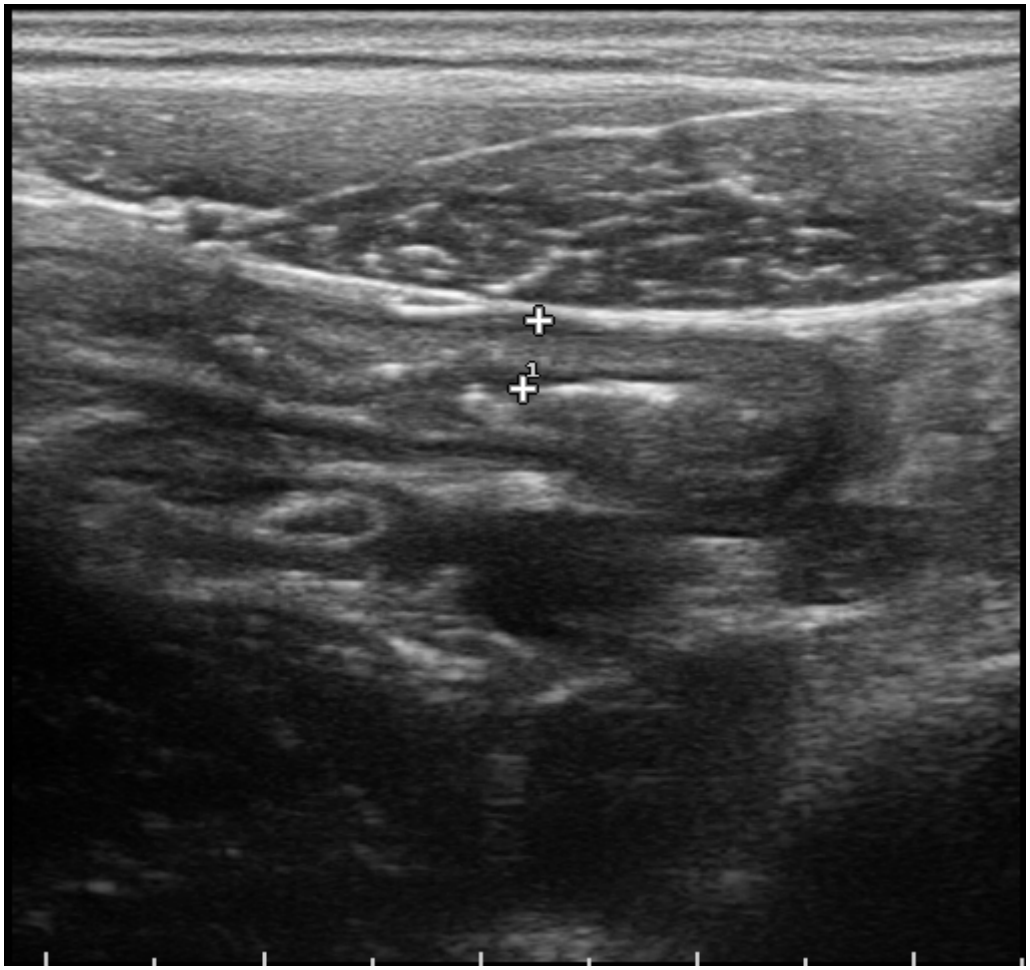

Figure 1

Abdominal ultrasound showing transmural thickening of the terminal ileus.

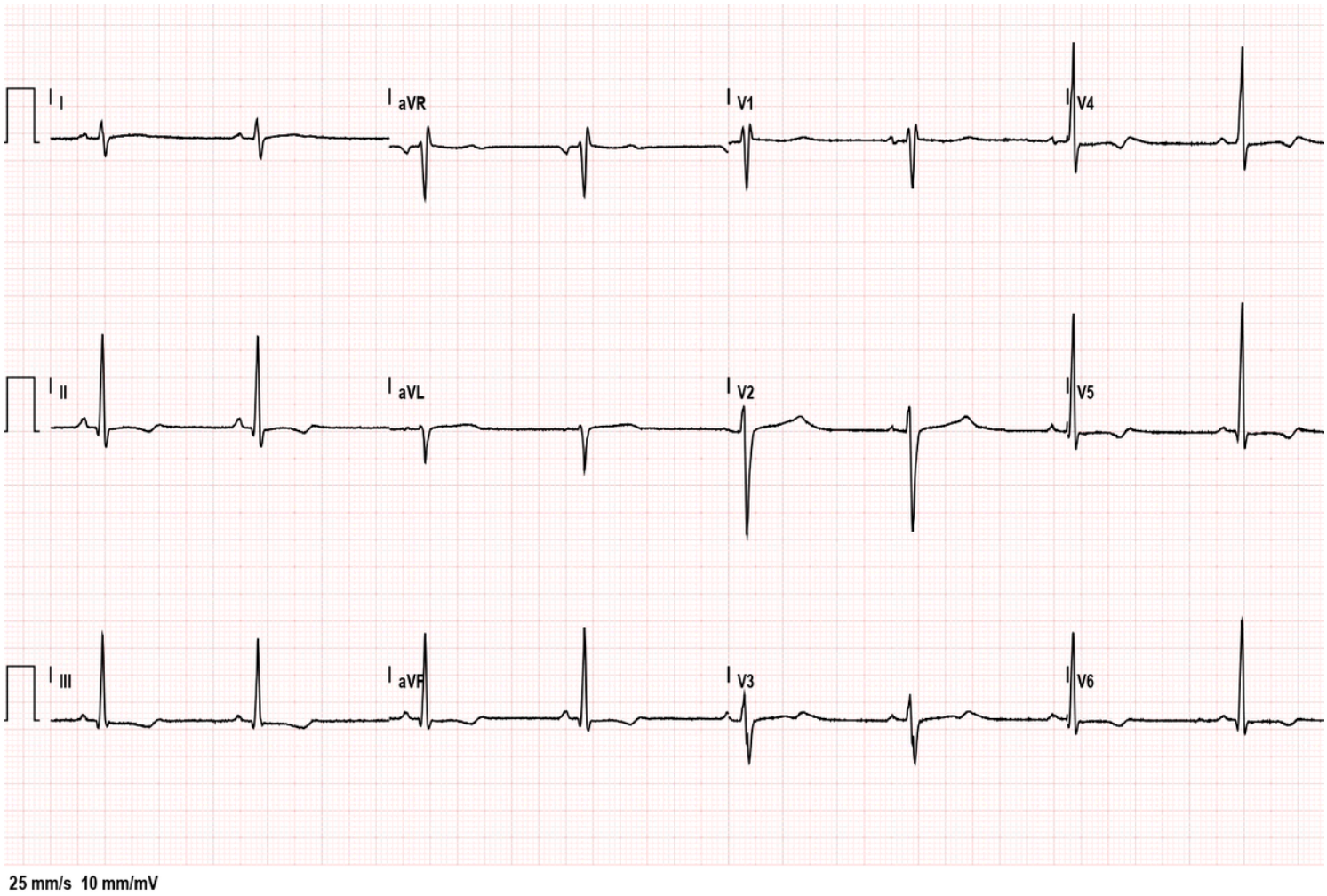

Figure 2

Electrocardiogram showing sinus bradycardia (HR 50 beats/min) with QT tract prolongation of 494 msec, diffuse T-waves alteration and minimal right branch block.