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Severe cardiac dysfunction in a patient with multisystem inflammatory syndrome in children associated with COVID-19: Retrospective diagnosis of a puzzling presentation. A case report

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ABSTRACT

We report one of the earliest known U.S. cases of multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C). This adolescent male presented prior to any known association between COVID-19 and immune mediated inflammatory syndrome in children. He presented in stable condition and without significant multisystem involvement. During hospitalization, he developed severe left ventricular dysfunction and mixed hypovolemic, distributive and cardiogenic shock. Clinical features overlapped with Kawasaki disease, acute rheumatic fever, and toxic shock syndrome. After centers in Europe began reporting a multisystem inflammatory condition in children with COVID-19, the patient's clinical course and laboratory findings were revisited. He underwent newly available antibody testing and was diagnosed as one of the first known cases of MIS-C in the United States.

1. Introduction

In December 2019, an outbreak of a severe respiratory illness caused by a novel strain of coronavirus, subsequently named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in Wuhan, China [1]. The disease caused by SARS-CoV-2 was termed COVID-19 and the World Health Organization declared the COVID-19 outbreak a public health emergency of international concern on January 30th, 2020. It was labeled a pandemic on March 11th, 2020 [1]. Initial data suggested that severe illness in children was far less frequent than adults [2]. However, in April 2020, reports from the United Kingdom noted a number of children of all ages presenting with a multisystem inflammatory state requiring intensive care. Many of these patients presented with gastrointestinal symptoms and cardiac inflammation and some shared features of Kawasaki disease. The term multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C) was coined to describe this novel presentation and diagnostic criteria were established. Here we describe a patient who presented prior to the case definition and who was retrospectively diagnosed by putting together his clinical and laboratory findings with newly available antibody testing.

2. Case presentation

A 14-year old multiracial (Caucasian and Hispanic) male with prior medical history of constipation and eczema presented on April 12th, 2020 to the emergency department with a four day history of fever, fatigue, and abdominal pain. Family history was remarkable for ulcerative colitis in the father. Emergency department physical examination was significant for sinus tachycardia and diffuse abdominal tenderness. Computed tomography scan of the abdomen revealed thickening of the distal ileum and diffuse lymphadenopathy. Initial lab findings were significant for a normal white blood cell count of 11.5 K/μl with absolute lymphopenia of 690 lymphocytes, elevated c-reactive protein of 14 mg/dl, elevated erythrocyte sedimentation rate of 48 mm/h, and negative polymerase chain reaction testing for gastrointestinal and respiratory pathogens, including SARS-CoV-2 RNA.

The patient was initially admitted to the general pediatric ward. He subsequently developed severe diarrhea, a maximum temperature of 40.4 degrees Celsius, and an erythematous, blanchable, macular

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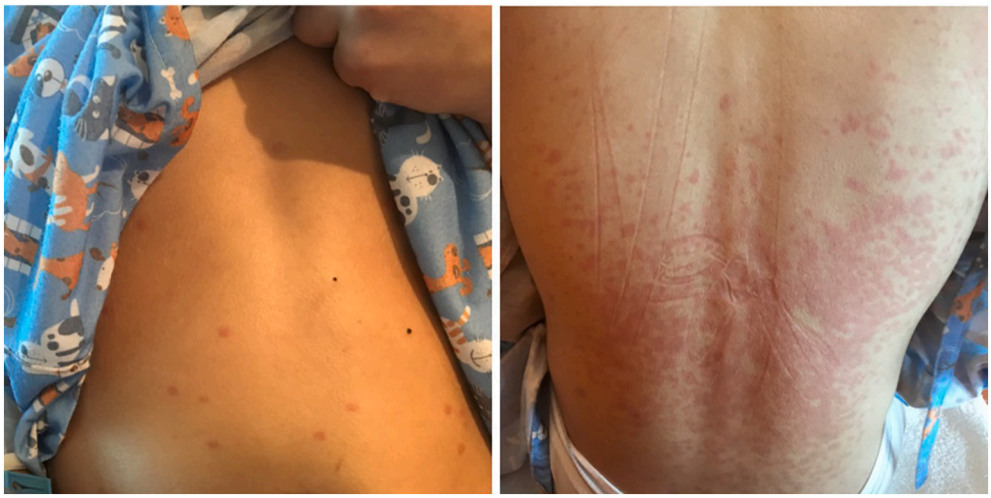

Fig. 1. Exantham on abdomen and back.

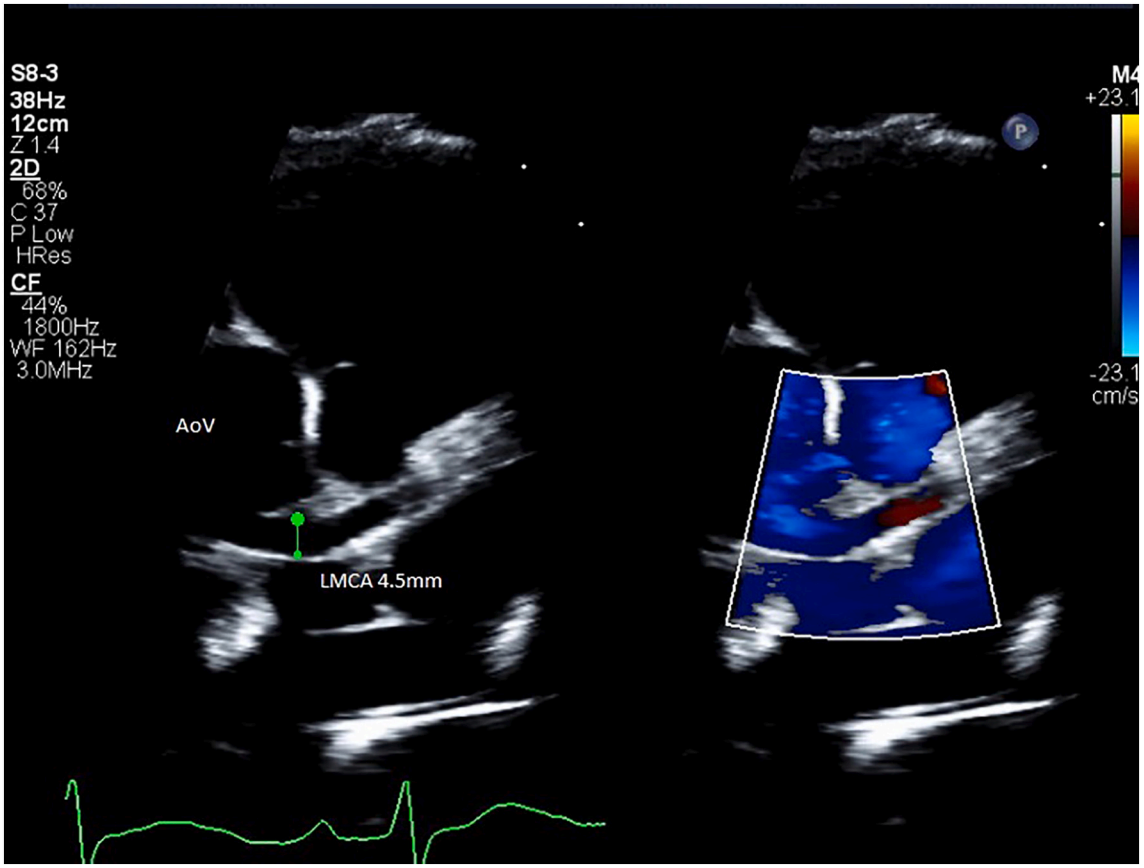

Fig. 2. Echocardiogram showing trivial dilation of left coronary artery. AoV: aortic valve; LMCA: left main coronary artery.

exanthem on his abdomen and back that rapidly coalesced and spread to his extremities (Fig. 1). Pharyngeal group A Streptococcus polymerase chain reaction testing was positive. Intravenous fluids were initiated due to profuse diarrhea, a blood culture was obtained, and he was started on intravenous ceftriaxone. In the evening of his second day of hospitalization, the patient developed chest pain and fluid-refractory hypotension. Chest x-ray and electrocardiogram (ECG) were obtained and were within normal limits. The patient was transferred to the intensive care unit for norepinephrine infusion, and addition of clindamycin due to suspicion of toxic shock syndrome. He subsequently developed respiratory distress with continued hypotension, and additional blood work and an echocardiogram were obtained. Brain natriuretic peptide was elevated to 670 pg/mL (normal 0–100 pg/ml), troponin I was elevated to 10.6 ng/L (normal 0–0.03 ng/ml), and echocardiogram demonstrated severely decreased biventricular systolic function with left ventricular fractional shortening of 19.9%, mild to moderate tricuspid and mitral regurgitation, and trivial dilation of the left coronary artery (Fig. 2). Repeat chest x-ray demonstrated slight cardiomegaly and pulmonary edema (Fig. 3). Norepinephrine was discontinued, and milrinone and low-dose epinephrine were initiated. He was transferred to the cardiac intensive care unit, intubated and placed on mechanical ventilation, and initiated on diuretic therapy. Due to the

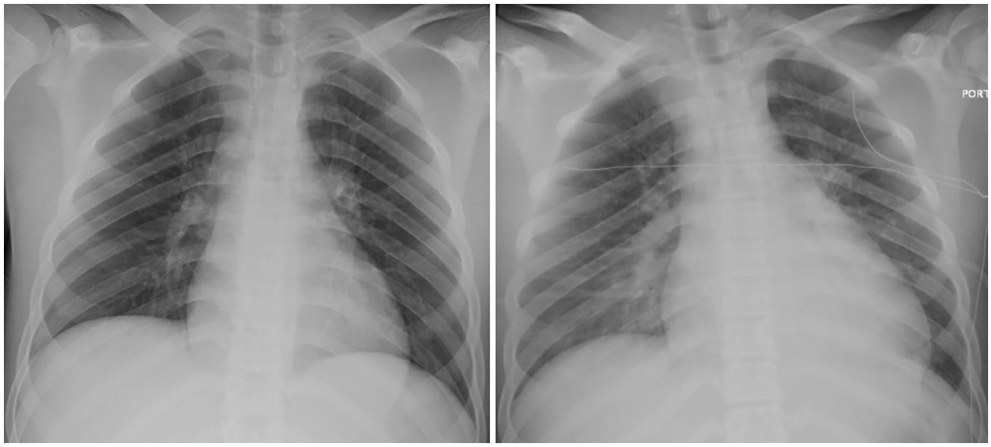

Fig. 3. Chest x-ray changes.

carditis, fever, elevated inflammatory markers, and positive group A Streptococcus testing, he received penicillin G intramuscularly to treat for suspected acute rheumatic fever.

Repeat echocardiogram 24 h later revealed improved systolic function with fractional shortening of 38%, but blood pressures remained persistently low, so phenylephrine was added. The patient was extubated on the fifth day of hospitalization. Epinephrine, phenylephrine, and milrinone were discontinued on the fifth, sixth, and ninth day of hospitalization respectively. On hospital day six, the patient was treated with intravenous immune globulins and high-dose aspirin to cover for atypical Kawasaki disease as left coronary artery z-score had increased from 1.6 to 2.1 and his right coronary z-score had increased from 0.2 to 1.5. He completed seven days of ceftriaxone. Serology was negative for various viral causes of myocarditis. AntiDNAse B and multiple antistreptolysin O titers remained in normal range. The patient was discharged after a twelve day hospital course, on low dose aspirin for a presumptive diagnosis of atypical Kawasaki disease. He was initially continued on monthly penicillin G prophylaxis for possible rheumatic fever, though with a low index of suspicion. Outpatient echocardiogram at 12 and 28 days after discharge revealed normal biventricular function and no coronary artery abnormalities. On April 24th, the National Health Service in the United Kingdom circulated a memo to health care providers, alerting them of an emerging Kawasaki-like syndrome in older children, with a predominance of gastrointestinal symptoms. Serology for SARS-CoV-2 was obtained three weeks after initial presentation and was positive for IgG, and the patient was retrospectively diagnosed with MIS-C.

3. Discussion

On May 4th, 2020, the New York City Health Department issued an alert to health care providers in the United States after identifying 15 patients aged 2–15 years, who had been hospitalized from April 17th to May 1st, 2020 with illnesses compatible with a multisystem inflammatory syndrome [3]. The patient in this case presented on April 12th, 2020 in Wilmington, Delaware, and is one of the earliest cases to be reported in the United States. Although presenting prior to the guidelines established by public health agencies, the patient retrospectively met both Center for Disease Control [4] and World Health Organization [5] criteria for MIS-C due to fever, elevated inflammatory markers, multi-organ involvement, absence of another plausible diagnosis, and positive SARS-CoV-2 serology. We believe this case offers several important lessons regarding this novel disease.

Cardiac involvement has been commonly noted in children diagnosed with MIS-C [6–8]. Fever along with rash or diarrhea are common presenting symptoms [9]. In this case, many of the patient's symptoms such as diarrhea, rash, hypotension, and cardiac dysfunction did not emerge until already hospitalized. Once hospitalized, symptoms progressed rapidly, and the patient acutely decompensated when treated with fluids and peripheral vasoconstrictors, which are standard therapies for hypovolemic and distributive shock. However, while the patient did improve with traditional therapies for cardiogenic shock such as diuretics, inotropes, and mechanical ventilation, the patient still ultimately required re-initiation of vasoconstrictors to maintain adequate blood pressure, highlighting the mixed cardiogenic, hypovolemic, and distributive shock. This multi-shock picture may be due to a combination of cardiac dysfunction, volume loss through diarrhea, insensible losses due to fever, and vasodilation due to elevated inflammatory state, all which have been reported with MIS-C [10]. Despite likely volume depletion, fluid resuscitation should proceed cautiously as excess fluid therapy may result in worsening of underlying cardiac dysfunction.

Additionally, physicians need to have a high index of suspicion for the condition as several alternative diagnoses may appear viable. In our case, the patient did not meet diagnostic criteria on admission and the presence of positive group A Streptococcus testing raised suspicion for both toxic shock syndrome as well as acute rheumatic fever. However, antistreptolysin O and antiDNAse B titers ultimately remained negative throughout the hospital course. While myocardial involvement was severe, there was no significant valvulitis, further arguing against acute rheumatic fever. Therefore those diagnoses were subsequently ruled out [11]. The patient was discharged on penicillin prophylaxis, but after this was discontinued after positive SARS-CoV-2 serology. Similarly, Kawasaki disease was entertained as an alternative diagnosis given the prominent coronary arteries on echocardiography. However, the patient met neither physical exam nor laboratory criteria for typical nor incomplete Kawasaki disease [12]. The predominance of gastrointestinal symptoms, older age, and extent of myocardial dysfunction were also unusual for Kawasaki disease. Emerging data suggests that children with MIS-C are not typically noted to have residual coronary artery aneurysms [8].

After reviewing data from several centers in Europe and United States, as well as this and subsequent cases presenting to us, our hospital has instituted a clinical pathway for early recognition and treatment of MIS-C (Appendix 1). We urge providers to have a high index of suspicion for these cases and strongly consider addition of c-reactive protein, troponin, and brain natriuretic peptide to initial set of screening labs for a patient presenting with a fever and signs of inflammation. The presence of normal initial chest x-ray and ECG may be falsely reassuring as these are frequently abnormal in myocarditis [13] and reports of MIS-C have noted ECG is frequently normal [8]. It is also important to be aware that while patients may present volume depleted and with symptoms that represent distributive and/or hypovolemic shock, aggressive fluid rehydration may prove to be detrimental and

should be judiciously administered. Patients may present with features of cardiogenic, hypovolemic, or distributive shock and may develop features of all. MIS-C is a new clinical presentation of novel COVID-19, and further studies are needed to determine optimal treatments and surveillance.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ppedcard.2020.101270.

CRediT authorship contribution statement

Daniel Vari: Conceptualization, Investigation, Writing - original draft, Visualization.**Jonathan M. Miller:**Conceptualization, Investigation, Writing - review & editing, Supervision.**Neil Rellosa:**Conceptualization, Writing - review & editing.**Shubhika Srivastava:**Conceptualization, Writing - review & editing.**Meg Frizzola:**Conceptualization, Writing - review & editing.**Deepika Thacker:**Conceptualization, Investigation, Writing - review & editing, Supervision, Visualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary material: Pathway for evaluation and management of patient with suspected MIS-C.

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