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MIS-C frenzy: The importance of considering a broad differential diagnosis

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Abstract

We report a case of a 3 year-old boy with possible typhoid fever with recent travel to a typhoid endemic area who was primarily managed as a case of multisystem inflammatory syndrome in children (MIS-C). The patient was initially treated for tonsillitis after a 3 day history of persistent fever, sore throat, and constipation. The patient presented later when he deteriorated. Severe acute respiratory syndrome coronavirus (SARS-CoV-2) viral RNA was not detected but the antibodies were positive. The patient went on to develop mucosal, cardiac, and gastrointestinal manifestations and was subsequently treated with immunoglobulins and corticosteroids for MIS-C. Despite the rarity of MIS-C as a complication of COVID-19 infection, the endemic typhoid fever which is relatively more common was not ruled out. The patient additionally received antibiotics for a total of 5 weeks given his unremitting fever. Even during the COVID-19 pandemic, healthcare professionals should carry out timely testing to exclude more probable differential diagnoses, with area-specific common diseases given due diligence.

Keywords

PIMS, COVID-19, pediatric inflammatory multisystem syndrome, fever of unknown origin, typhoid fever, multisystem inflammatory syndrome, Multisystem Inflammatory Syndrome temporarily associated with Covid-19, MIS-TS

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Introduction

Multisystem inflammatory syndrome in children (MIS-C) is a potentially fatal yet rare complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[1–3] In May 2020, the U.S. Centers for Disease Control and Prevention (CDC) published a case definition of the newly recognized MIS-C as an acute febrile state presenting nonspecific symptoms and signs of multiple organ affection.[4] Due to the nonspecific nature of MIS-C, its presentation shares many similarities with typhoid fever—a common pediatric infection in Egypt.[5,6] Typhoid fever is an acute febrile illness caused by the Salmonella enterica serotype Typhi or Paratyphi bacteria.[5] Typhoid fever presents as a flu-like illness including a fever, sore throat, diffuse abdominal pain, hepatomegaly, constipation, or diarrhea with a median age of 5 years old.[5,7] Up to 30% of patients present with a maculopapular rash, which is commonly found on the chest and abdomen.[5] Both typhoid fever and MIS-C may present with fever, sore throat, abdominal pain, or constipation.[2,5] Over a quarter of the patients evaluated for MIS-C had non-SARS-CoV-2 infections.[8] We report a 3 year-old child's case that was managed as MIS-C without full consideration of other diagnoses which led to longer-duration use of antibiotics and immunomodulators.

Case report

A 3-year-old Egyptian boy had a past medical history of recurrent attacks of acute tonsillitis (twice/year) since the age of 2 months. The tonsillitis attacks were managed conservatively with antibiotics and antipyretics. The patient is an otherwise healthy child.

The patient complained of sore throat and a 3-day persistent fever of 39.5°C, which failed to improve on cefoperazone, diclofenac, paracetamol, and intravenous (IV) corticosteroids (1 cm 50 mg/ml). Seven days later, he was referred to a secondary care center as he developed lower limb edema, conjunctivitis, bilateral macular erythema on

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Table 1. Daily laboratory investigations of the patient up till 9 days after tertiary care hospital admission.

Day since admission	1	2	3	4	5	6	7	8	9
Hematology									
RBC (4.0-5.2,10^6/µl)	5.6		4.72		4.85		4.53		
HGB (11.0-14.0, g/dl)	14.3	14.3	12.2		12.9		12.4		
HCT (34.0-40.0, %)	43		36.9		39.8		36.2		
WBC (5.0-15.0, 10^3/µl)	11.5		12.3		25.3		27.1		
Neutrophils, Absolute (1.50-8.0, 10^3/µl)	9.4		5.6		14.8		16.69		
Lymphocytes, Absolute (3.5-8.0, 10^3/µl)	1.6	1.6	6.1		9.1		7.83		
PLT (200.0,490.0, 10^3/µl)	304	304	1008		910		693		
D-Dimer (0-0.5, mg/l)						0.50			
Chemistry									
CRP (Up to 6.0, mg/l)	163	163			8.2				
ESR (2.0-20.0, mm/hr.)						90	60		
Ferritin (6.0-80.0, ng/mL)	122.4	122.4						336.3	
Uric acid (3.5-7.2, mg/dl)					2.8				
Potassium (3.4-4.7, mmol/L)				5.9	6.0				
Troponin I (0.0-0.04, ug/l)						0.01			
Hormonal Profile									
FT3 (2.40-5.50, pg./ml)									3.54
FT4 (0.96-1.77, ng/dl)									2.06
TSH (0.70-5.90, uIU/ml)									1.61

RBC: Red Blood Cell count. HGB: Hemoglobin. HcT; Hematocrit. WBC: White Blood Cells count. PLT: platelets. CRP: C-Reactive Protein. ESR: Erythrocyte Sedimentation Rate. FT3: Free triiodothyronine. FT4: Free thyroxine. TSH: Thyroid-stimulating hormone.

both upper limbs, and constipation that required glycerin suppositories. The patient had signs of confusion on admission at the secondary care center. Apart from the persistent fever, his vitals were within the normal range for age. Other systems review was unremarkable.

SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) test was negative, but IgM and IgG antibodies were positive. Laboratory investigations revealed elevated C-reactive protein (CRP) level of 163 mg/l (reference: up to 6.0 mg/l), polycythemia, erythrocytosis, mild neutrophilia, lymphopenia, and a negative Widal test (Table 1). The patient's ferritin level more than doubled within a week. A chest X-ray revealed mild left ventricular dilatation and colonic distension. The patient was admitted to the infection isolation unit and was managed with antipyretics. Two days later, he was transferred to a tertiary care hospital as a suspected case of MIS-C.

On initial examination at the tertiary care hospital the child was inconsolable with persistent fever. He received IV corticosteroids (30 mg/kg/day). The following day he received his first dosing of intravenous immunoglobulins (IVIG; 1 gm/kg (20 gm over 8 divided doses)).

A day later the patient's fever subsided but he had developed distended abdomen, hepatomegaly, tachycardia, and oral thrush. He had a resting heart rate of 140bpm. He was not hypertensive, dyspneic, tachypneic, or cyanotic. Fever attacks every 4 to 6 h` lasting 10 min each, conjunctival injection, and macular rash on the neck and extremities were observed over the following days (Figure 1). Investigations

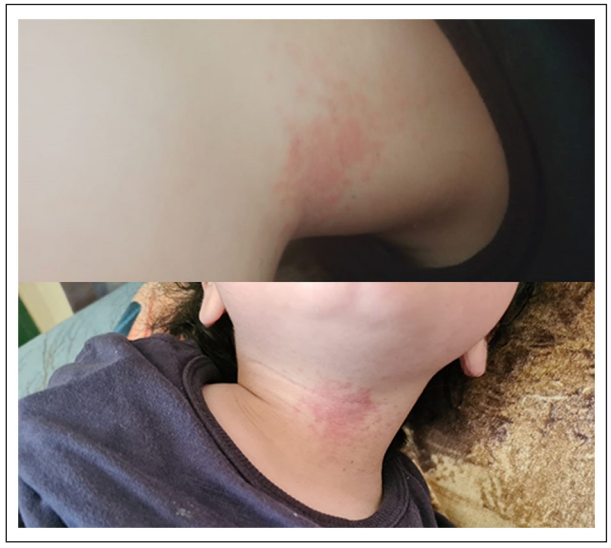

Figure 1. photograph showing macular rash on the right arm (top) and on the neck (bottom) of the patient.

revealed moderate thrombocytosis, hyperkalemia, hypouricemia, and otherwise normal kidney and liver function tests. An electrocardiogram revealed sinus tachycardia. An echocardiogram was remarkable for mild left ventricular enlargement with normal ejection fraction and minimal pericardial effusion with no evidence of coronary abnormalities or valvular dysfunction. Pelviabdominal ultrasound revealed mild hepatomegaly and remarkable colonic distention.

Table 2. Comparison of the common clinical features of typhoid fever and multisystem inflammatory syndrome in children (MIS-C).

Clinical presentation	Typhoid fever	MIS-C
Incidence	59 per 100,000 person-years[a,b]	6.1 per 100,000 person-years[a,b]
Median age	5 years[a]	9 years[a]
Duration of symptoms pre-hospitalization	9.4 days[a]	4 days[a]
Fever	Stepwise pattern with diurnal variation[a]	Persistent fever[a]
Signs & Symptoms	Malaise, poorly localized abdominal pain, distended abdomen, constipation[a], diarrhea, and/or hepatosplenomegaly[a] Tachycardia or relative bradycardia Rose spots (blanching erythematous maculopapular rash with lesions 2 to 4 mm in diameter)	Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain) Features of myocardial dysfunction, pericarditis, valvulitis, coronary abnormalities, mild or moderate decreased left ventricular ejection fraction, and/or hypotension Nonpurulent conjunctivitis and/or periorbital edema Polymorphous exanthema Swelling of hands & feet
Mortality rate	2.0%	1.5%
Laboratory		
WBC	Normal, leukocytosis, eosinopenia[a]	Neutrophilia, lymphocytopenia
Coagulation markers	Elevated PT and PTT seen in case of DIC as a complication	Evidence of coagulopathy (Elevated PT, PTT, and D-Dimer)
Inflammatory markers (ESR, CRP, Ferritin)	Increased	Significantly increased
Myocardial Injury markers	Not typically elevated	Frequently elevated (troponins[a], brain natriuretic peptide[a])

[a]Points of significant difference.
[b]Incidence of typhoid was from Egypt and that of MIS-C was from the United States.
MIS-C: multisystem inflammatory syndrome in children. PT: prothrombin time. PTT: partial thromboplastin time. DIC: disseminated intravascular coagulation.

IV corticosteroids (1 mg/kg twice a day) and cefuroxime were added for 2 weeks in addition to the IVIG (14 gm in 5 divided doses). The patient's hyperkalemia normalized after 2 sessions of salbutamol inhalation therapy. Four days later, corticosteroids were switched to oral, amoxicillin/clavulanic acid and antifungal oral gel were added. Fever subsided and the patient's general condition improved except for the persistent isolated sinus tachycardia. Cardiac troponins and D-dimer levels were normal. Five days later, thyroid hormone tests revealed elevated free thyroxine (T4) with normal thyroid-stimulating hormone level (TSH) (Table 1). Beta-blocker and aspirin were added.

17 days after the first admission, the patient was discharged on low dose aspirin once daily to be continued for six months. The patient was placed on corticosteroids syrup, cefepime hydrochloride, and linezolid pending echocardiogram follow-up. One week after discharge, the echocardiogram was unremarkable.

Discussion

We report a case of a 3 year-old boy with a presentation highly suggestive of typhoid fever. The patient had a long and complicated course as he was diagnosed as multisystem inflammatory syndrome in children (MIS-C), which we believe the healthcare team may have been anchored on and missed the more common endemic bacterial infection. The patient received treatment for both MIS-C and a bacterial infection, neither of which were confirmed. We reported the daily laboratory investigations of the patient up till 9 days after admission to the tertiary care hospital (Table 1). Lymphocytes were lowest in the first 2 days post-admission. White blood cells were highest on day 7 post-admission. There was persistent thrombocytosis with a peak on day 3 post-admission. Hyperkalemia noted on the 4th and 5th day. Troponin and D-Dimer levels were within normal limits.

As MIS-C is increasingly reported in the literature, we expect that clinicians are developing a high index of suspicion for the syndrome. This might lead to overdiagnosis of MIS-C. While identifying MIS-C is critical given the complications associated with the disease, other more common and serious febrile illness diagnoses like typhoid fever might be overlooked.[8] There are some differences worth noting in the clinical pictures of typhoid fever and MIS-C (Table 2). The incidence of typhoid fever in Egypt is 59 per 100,000 person-years while the incidence of MIS-C was found to be 6.1 per 100,000 person-years in a US study.[3,6] The median age of onset of typhoid fever is 5 years old while in MIS-C it is 9 years old.[1,7] Constipation and malaise are common features of typhoid fever while diarrhea and vomiting are common in MIS-C.[1,5] Both conditions could exhibit a rash while non-purulent conjunctivitis is commonly found in MIS-C.[5,9] Eosinopenia is common in typhoid fever while

lymphocytopenia is common in MIS-C.[5,10] Cardiac markers are commonly elevated in MIS-C.[1]

MIS-C diagnostic criteria requires the exclusion of other causes.[4] Given the heterogeneity of its presentation and the extensive list of differential diagnoses,[10] this might not always be possible. This is especially highlighted in low-resource areas where diagnostic tests that are considered standard in high-resource areas may not be as readily available.

Egypt is one of the endemic areas of typhoid fever.[6] Our patient presents with a history of travel to a typhoid endemic area along with prolonged fever and constipation, two frequent complaints of typhoid fever;[5] however, satisfactory ruling out of typhoid fever was not achieved. First, blood cultures are the mainstay of diagnosis in typhoid fever[5] but instead only a one-time serology testing—the Widal test—was carried out given that the Widal test is relatively rapid and inexpensive. The Widal test was designed to be positive after a 4-fold increase in antibody titer but in practice a single sample is usually used and compared to base levels of antibodies in the local population.[5] It is highly inaccurate with common false positive and false negative results and thus its use is usually discouraged.[5] Our patient's blood cultures—the more accurate diagnostic method—were not obtained upon arrival at either the secondary or tertiary care centers.

Second, the patient was initially self-managed with antibiotics, antipyretics, and corticosteroids which might have altered the clinical presentation and laboratory testing results.[5] Third, both MIS-C and typhoid fever would require empirical use of antibiotics with close follow up for possible medications' adjustments.[5,11] However, our patient was diagnosed as a suspected case of MIS-C when he had only fulfilled two criteria of MIS-C diagnosis: multiorgan involvement coupled with positive SARS-CoV-2 IgG and IgM antibodies.[4] Antibody titers used as part of the diagnosis may now be more ubiquitous as more and more individuals succumb to the infection. An MIS-C diagnosis was reached despite the fact that other features were unusual for MIS-C. Namely, the duration of symptoms before our patient was admitted lasted longer than the 4 days expected in MIS-C[9] and closer to the 9 days of symptoms pre-hospitalization in typhoid fever.[12]

Our patient was discharged on prophylactic aspirin for his persistent cardiovascular symptoms. Aspirin is prescribed in over 50% of MIS-C patients[1] and its use in this case indicates that the healthcare team still considered MIS-C as a possible diagnosis.

Our patient was subjected for about 5 weeks to various broad-spectrum antibiotics in the form of second, third, and fourth generation cephalosporins in addition to a high dose of corticosteroids. Antibiotics were maintained for this prolonged duration given that an infectious cause was still a possibility. Blood cultures were not obtained since the patient had already started antibiotic treatment, rendering the blood culture less valid. We contrast this prolonged antibiotic course with the standard oral chloramphenicol antibiotic for 4–6 days duration for typhoid fever.[5] We believe that such a prolonged exposure to antibiotics and immunosuppressants was unnecessary and could have been avoided with a more diligent approach to diagnosing common diseases.

Our study's limitations are due to the nature of case reports: it is an observational study on one person without a comparison group. It cannot be used to inform practice but rather to raise potential hypotheses to be tested. Since the final diagnosis remains unconfirmed, we cannot ascertain whether it was a medical error. Still, our study adds an often-untold perspective of the developing countries, where healthcare access and resources are vastly different.

Conclusion

An increasing number of children are expected to have positive SARS-CoV-2 antibodies as the pandemic progresses which might lead clinicians to be anchored toward an MIS-C diagnosis. This is especially important in low resource settings where standard tests may not be as readily available, and more emphasis is placed on clinical judgment. Our report highlights the importance of following a systematic evaluation approach in the diagnosis of pediatric febrile illness in the era of Coronavirus disease of 2019 (COVID-19) pandemic to avoid potentially overlooking an endemic infection and overprescribing broad-spectrum antibiotics. That is particularly worrisome as antibiotic resistance remains on the rise. Given the excessive costs of unnecessary care on both the patient and the healthcare system, international guidelines and diagnostic definitions may not always be suitable for low resource settings.

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Author contributions

R.A.L. took the patient history, drafted the case report, and maintained clinical correspondence with the patient. A.E. contributed to the design, discussion, and conclusion of the case report. E.O.S. contributed to the writing of the introduction and discussion. All authors critically revised the manuscript and gave their final approval of this work.

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Ethics approval

Our institution does not require ethical approval for reporting individual cases without patient identifying information.

Informed consent

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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