BRIEF REPORT

Murine Typhus in 5 Children Hospitalized for Multisystem Inflammatory Syndrome in Children

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ABSTRACT

Multisystem inflammatory syndrome in children (MIS-C) is an emerging disease described in children in association with infection or epidemiological link to severe acute respiratory syndrome coronavirus 2. Signs and symptoms include fever, rash, and cardiac dysfunction; US Centers for Disease Control and Prevention have put forth broad criteria for diagnosis. The illness is serious and can progress rapidly to heart failure and death. However, findings in MIS-C are nonspecific, and there is significant overlap with other systemic illnesses, including Kawasaki disease and several viral and bacterial infections. We present 5 children admitted to a teaching hospital within an 11-day period in May 2020 for MIS-C evaluation who were later diagnosed with murine typhus. Typhus is a rickettsial infection that presents with fever and rash, and, although usually self-limited, responds well to treatment with doxycycline to shorten the course of illness. Clinical and laboratory characteristics of these children are presented to illustrate similarities to MIS-C, which can also be shared with viral, bacterial, or other regional endemic infections, as well as noninfectious inflammatory diseases. This case series serves to remind pediatric hospitalists to be vigilant to avoid premature closure on MIS-C for children admitted with fever and systemic inflammation. Maintaining a wide differential diagnosis in approaching such patients is of utmost importance as community exposure to severe acute respiratory syndrome coronavirus 2 is likely and evidence of past infection becomes commonplace.

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Multisystem inflammatory syndrome in children (MIS-C) presents with fever, fatigue, elevated inflammatory markers, and either a history of exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or positive antibodies to SARS-CoV-2.[1] Pediatricians and hospitalists remain on high alert for this disease, which is associated with multiorgan involvement, including rapid progression of myocardial dysfunction requiring inotropic support.[1–4] Importantly, diagnosis of MIS-C requires the absence of a plausible alternative diagnosis.[1]

The case definition provided by the US Centers for Disease Control and Prevention is broad to identify all potential cases of this disease. However, it has been noted that this case definition may be problematic because of its significant crossover with other childhood illness.[1–3,5–7] Dr Anne Rowley[5] describes the concern of premature diagnostic closure on MIS-C for children who in reality have a potentially life-threatening, non–MIS-C illness, namely, Kawasaki disease (KD).[6] In addition to delaying the diagnosis of other treatable conditions, concern for MIS-C has the potential to lead to overuse of health care services, including testing and transfers to tertiary care centers.

As the pandemic continues and more children are infected with SARS-CoV-2, the prevalence of MIS-C will likely continue to rise. However, exposure to SARS-CoV-2 and the presence of antibodies in children hospitalized with other illnesses will also become common and may further complicate the diagnostic process. We present 5 children admitted within an 11-day period for evaluation of MIS-C who were subsequently diagnosed with murine typhus, a disease caused by infection with *Rickettsia typhi*. In this case series, we aim to highlight the broad differential pediatric hospitalists must maintain when approaching a child with fever, nonspecific symptoms, and elevated inflammatory markers when MIS-C is within the differential.

METHODS

We describe a case series of 5 children managed in a single institution in Southeast Texas during May 2020. All 5 presented with fever, were admitted to the pediatric hospital medicine service for further evaluation for MIS-C and were discharged with a diagnosis of murine typhus. The local institutional review board approved the study, and parents provided verbal consent to be included. Basic demographic information, clinical features, laboratory and imaging findings at time of presentation, and clinical course were extracted from the electronic medical record. The postdischarge course was obtained from phone calls to parents and the electronic medical record when available.

RESULTS

Case 1

A 17-year-old boy presented with a 5-day history of fever associated with rash (Table 1). Because of high inflammatory markers (Table 2), the rheumatology department was consulted to evaluate for MIS-C and agreed an infectious etiology was more likely. His fever resolved and he clinically improved with empirical doxycycline.

Case 2

A 16-year-old girl presented with 10 days of fever accompanied by headache and abdominal tenderness (Table 1). In addition to significant elevation of liver enzymes (Table 2), she had elevated prothrombin time, partial thromboplastin time, and creatinine kinase. She showed clinical and laboratory improvement with doxycycline.

Case 3

A 12-year-old boy presented with 6 days of fever associated with headache and rash (Table 1). The initial examination was notable for dry lips, conjunctival injection, and an eczematous rash. Laboratories revealed mildly elevated C-reactive protein (CRP) as well as hyponatremia and thrombocytopenia (Table 2). Additionally, he had sterile pyuria and mildly elevated prothrombin time. He was treated with empirical doxycycline, and the fever resolved over the next 24 hours.

An echocardiogram performed as part of his initial evaluation revealed mild dilation of the left anterior descending and right coronary arteries, which, despite resolution of fever by the time it was resulted, prompted treatment with intravenous immunoglobulin and aspirin for atypical KD versus MIS-C. He developed a doxycycline-associated rash and completed treatment against *R typhi* infection with azithromycin. His coronary-artery dilation resolved on subsequent outpatient echocardiograms.

Case 4

A 10-year-old girl presented with 10 days of fever associated with headache, rash, and abdominal tenderness on examination (Table 1). Laboratory findings are noted in Table 2. Her fever and headache resolved with empirical doxycycline treatment.

Case 5

An 8-year-old girl presented with 9 days of fever accompanied by headaches. Her examination was largely normal aside from fever. Her mother had known coronavirus disease 2019 exposure. Laboratories revealed leukocytosis with an elevated absolute neutrophil count (Table 2). Multiple SARS-CoV-2 polymerase chain reaction results were negative and antibodies were nonreactive. Her fever resolved with empirical doxycycline.

DISCUSSION

Murine typhus, also known as endemic typhus, is an inflammatory vasculitis caused by infection with *R typhi*. The disease is present along the southeastern Gulf Coast, Southern California, and Hawaii and is transmitted to humans via bites from fleas with rodent reservoirs. However, many patients will not report known flea exposure,[8,9] as seen in 2 children in our series. Although thought of as a rare disease, murine typhus incidence is underestimated[8] and rising in South Texas.[9] Anecdotally, we have noted a particular increase in hospitalized children in spring 2020, including the period of this study. Although it is yet unclear whether this represents a true increase in prevalence, we postulate that school closures and social distancing may have increased exposure because of time spent outdoors or with pets. Alternatively, parental concern for SARS-CoV-2 infection could mean children

TABLE 1 History, Physical Examination, and Clinical Course of 5 Children With Murine Typhus

	Case 1	Case 2	Case 3	Case 4	Case 5
Age in y	17	16	12	10	8
Days of fever	5	10	6	10	9
Headache	No	Yes	Yes	Yes	Yes
Rash	Yes	No	Yes	Yes	Yes
Abdominal pain	No	Yes	No	No	No
Other symptoms	Malaise	Diarrhea	Fatigue	Fatigue	Decreased appetite
	Dizziness	Myalgias	Chills	Myalgias	—
	—	—	Eye redness	Vomiting	—
	—	—	Decreased appetite	Cough	—
	—	—	Vomiting	Neck stiffness	—
	—	—	—	Eye redness	—
Exposure	Multiple animals, including puppy with fleas	Dogs	2 cats and 1 dog previously treated for fleas	2 dogs	1 dog
	—	Rats	—	1 cat	No known fleas
	—	Home treated for fleas	—	No known fleas	—
Physical examination at presentation	Fever	Fever	Dry lips	Abdomen tender to palpation in the right upper quadrant and epigastric area	Fever
	Tachycardia	Tachycardia	Eczematous patches and excoriations	Few scattered macules	Tachycardia
	Maculo-papular rash on trunk, back, and extremities	Tachypnea	Injected conjunctivae	—	—
	—	Conjunctival injection	—	—	—
	—	Abdominal tenderness	—	—	—
Days to fever resolution after doxycycline initiation	3	2	1	2	2
Recurrence of symptoms after discharge	None	None	None	None	None

—, not applicable.

TABLE 2 Laboratory Features of 5 Children With Typhus

Test (Reference Range With Units)	Case 1	Case 2	Case 3	Case 4	Case 5
White blood cell count[a] (4500–13 000 per μL)	6.7	7.7	5.3	4.5	15.2
Lymphocyte % per absolute (1200–5200 cells per μL)	16 of 1080	34 of 2620	23 of 1210	38 of 1720	24 of 3620
Neutrophils % per absolute (1800–8000 cells per μL)	78 of 5200	56 of 4280	29 of 3620	52 of 2380	67 of 10 190
Hemoglobin (12.0–16.9 g/dL)	12.8	9.9	13.4	13.3	11.7
Platelets (140 000–400 000 per μL)	151	157	136	161	280
Sodium (135–146 mmol/L)	134	137	131	134	135
CRP (<1.0 MG/DL)	17.1	16.9	3.1	5.9	5.4
ESR (0–20 mm/h)	19	13	11	17	33
AST (10–45 U/L)	73	396	78	128	122
ALT (11–26 U/L)	70	344	43	73	236
LDH (340–670 U/L)	938	1506	N/A	1746	1378
D-dimer (≤0.40 μg/mL)	2.68	3.18	3.42	2.41	1.88
Ferritin (18–464 ng/mL)	383	535	454	271	101
Fibrinogen (220–440 mg/dL)	422	278	273[a]	414	382
Procalcitonin (0.05–2.00 ng/mL)	N/A	0.77	N/A	0.44	0.54
BNP (<100.0 pg/mL)	<10	20.7	89.1	72.6	N/A
Troponin (<0.030 ng/mL)	0.025	<0.010	0.015	0.011	N/A
Electrocardiogram	Normal	Normal	Mild PR interval prolongation	N/A	N/A
Echocardiogram	Normal	Normal	Mild coronary-artery dilation	Normal	Normal
R typhi antibodies	IgM 1:64	IgM >1:1024	IgM 1:128	IgM 1:512	IgM >1:1024
	IgG <1:64	IgG >1:64	IgG <1:64	IgG 1:512	IgG 1:1024
SARS-CoV-2 PCR	Negative	Negative	Negative	Negative	Negative
SARS-Co2-2 IgM and IgG	Nonreactive	Nonreactive	Nonreactive	Nonreactive	Nonreactive

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; N/A, not applicable; PCR, polymerase chain reaction.
[a] Obtained after admission.

with symptoms are presenting to care and being referred or admitted to the hospital more frequently because of provider concern for MIS-C.

Murine typhus disease is classically described as triad of fever, headache, and rash, but this triad only occurs in 41.6% to 42.7% of children.[8,9] Instead, there is a broad spectrum of disease, as demonstrated in this series; 3 of 5 had the triad, and other symptoms included abdominal pain, vomiting, cough, myalgias, fatigue, and malaise, all of which have been previously described.[7–10] The rash in murine typhus can vary.[8–10] Laboratory findings are nonspecific, as is reflected in this case series, and most commonly include transaminemia, lactate dehydrogenase elevation, hypoalbuminemia, elevated inflammatory markers, hyponatremia, anemia, and thrombocytopenia.[7–10] The pattern and degree of derangements also vary. For example, although transaminases are usually mildly elevated, in a review of cases, one-quarter of the patients had normal levels, and one-quarter had a significant (greater than fourfold) increase in levels,[8] as seen in cases 2 and 4.

After presenting with fever, a range of laboratory tests was undertaken in these children, in accordance with Centers for Disease Control and Prevention recommendations to evaluate for MIS-C.[1] In these 5 children, CRP and D-dimer were elevated in all 5, the erythrocyte sedimentation rate and lactate dehydrogenase were elevated in 4, ferritin was elevated in 1, and procalcitonin and fibrinogen were not elevated. Interleukin-6 was not assessed. This series serves as a reminder that these laboratory findings are nonspecific and, although rarely obtained, would likely be abnormal in a variety of non–MIS-C infectious and inflammatory conditions.

Additionally, we postulate that mild cardiac involvement in non–MIS-C and non-KD diagnoses may also be underappreciated. Although troponin and B-type natriuretic peptide levels in our selected cases were within normal range, the patient in case 3 had mild coronary-artery dilation. Although KD cannot be definitively ruled out in this child, his fever resolved on doxycycline alone, and he had hyponatremia and thrombocytopenia, features not typical in KD. Indeed, although true coronary aneurysms are specific to KD, there is evidence that coronary-artery dilation can result from other febrile illnesses because of interleukin-6 cytokine storm.[11,12] Again, because cardiac enzymes and imaging have, until now, not been routinely included in the

evaluation of febrile illness, the specificity of mild abnormalities is unclear. During this time of uncertainty and heightened awareness of SARS-CoV-2, interpretation of results may contribute to premature closure and, possibly, overtreatment for MIS-C.

Untreated, the fever in murine typhus persists for 12 to 24 days.[8] However, most patients defervesce within 72 hours on appropriate antibiotics.[8,9] In describing our cases, it is important to note that the gold standard to diagnose murine typhus is convalescent antibody titers 2 to 4 weeks apart to show a fourfold increase in anti–*R typhi* immunoglobulin G (IgG), which differentiates present and past infection.[7] Because antibody testing takes several days to result, providers at our institution rely on surrogate factors for diagnosis, namely, rapid response to doxycycline, as seen in all 5 of these cases. Convalescent titers were not feasible because of the retrospective nature of this study. However, elevated immunoglobulin M (IgM) in all 5 children, which resulted after discharge, supports acute infection with *R typhi*, and none had a recurrence of symptoms. Brief observation periods on empirical antibiotics were sufficient to make a presumptive diagnosis of murine typhus, avoiding intravenous immunoglobulin and other anti-inflammatory therapies in 4 out of 5 cases.

CONCLUSIONS

With this case series of children evaluated for MIS-C, we emphasize the wide differential diagnosis hospitalists must maintain when approaching a child with prolonged fever and evidence of systemic inflammation. In addition to common viral, bacterial, and noninfectious diagnoses, a range of regional endemic rickettsial and parasitic infections must be considered as alternative diagnoses to MIS-C, including murine typhus. Many of these diseases cannot be reliably differentiated from MIS-C on presentation, and, as community exposure to SARS-CoV-2 grows, hospitalists should be prepared to admit febrile children with evidence of systemic inflammation for brief observation periods to evaluate for MIS-C. When appropriate, empirical treatment of common or even uncommon infectious diseases, such as murine typhus, may avoid overdiagnosis and overtreatment of MIS-C as well as improve patient outcomes.

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