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

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Dr. Dean conceptualized and designed the study, performed chart review, drafted the initial manuscript, revised the manuscript, and approved the final manuscript as submitted.

Dr. Asaithambi performed chart review, reviewed and revised the manuscript, obtained consent from families, and approved the final manuscript as submitted.

Dr. Neubauer conceptualized and designed the study, performed chart review, carried out analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted.

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 (SARS-CoV-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 non-specific, and there is significant overlap with other systemic illnesses, including Kawasaki disease and several viral and bacterial infections. We present five 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, though 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 non-infectious 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 SARS-CoV-2 is likely and evidence of past infection becomes commonplace.

Introduction

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 multi-organ 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 (CDC) is broad in order to identify all potential cases of this disease. However, it has been noted that this case definition may be problematic due to its significant crossover with other childhood illness.^{1-3,5-7} Dr. Anne Rowley 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).^{5,6} In addition to delaying diagnosis of other treatable conditions, concern for MIS-C has the potential to lead to overutilization 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 five 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*. This case series aims to highlight the broad differential pediatric hospitalists must maintain when approaching a child with fever, non-specific 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 five 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 (EMR). Post-discharge course was obtained from phone calls to parents and EMR when available.

Results:

Case 1

A 17-year-old male presented with a five-day history of fever associated with rash (Table 1). Due to high inflammatory markers (Table 2), rheumatology was consulted to evaluate for MIS-C

and agreed an infectious etiology was more likely. His fever resolved and he clinically improved with empiric doxycycline.

Case 2

A 16-year-old female presented with ten 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 (PT), partial thromboplastin time (PTT) and creatinine kinase. She showed clinical and laboratory improvement with doxycycline.

Case 3

A 12-year-old male presented with six days of fever associated with headache and rash (Table 1). Initial exam was notable for dry lips, conjunctival injection, and an eczematous rash. Labs showed mildly elevated c-reactive protein (CRP) as well as hyponatremia and thrombocytopenia (Table 2). Additionally he had sterile pyuria and mildly elevated PT. He was treated with empiric doxycycline and fever resolved over the next 24 hours.

Echocardiogram performed as part of his initial evaluation, showed 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 (IVIG) 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 female presented with 10 days of fever associated with headache, rash and abdominal tenderness on exam (Table 1). Lab findings are noted in Table 2. Her fever and headache resolved with empiric doxycycline treatment.

Case 5

An 8-year-old female presented with 9 days of fever accompanied by headaches. Her exam was largely normal aside from fever. Her mother had known COVID exposure. Labs showed leukocytosis with elevated absolute neutrophil count (Table 2). Multiple SARS-CoV-2 PCRs were negative and antibodies were nonreactive. Her fever resolved with empiric 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 fleas with rodent reservoirs. However, many patients will not report known flea exposure,^{8,9} as seen in two children in our series. While thought of as a rare disease, murine typhus incidence is underestimated⁸ 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. While it is yet unclear whether this represents a true increase in prevalence, we postulate that school closures and social distancing may have increased exposure due to time spent outdoors or with pets. Alternatively, parental concern for SARS-CoV-2 infection could mean children with symptoms are presenting to care and being referred or admitted to the hospital more frequently due to provider concern for MIS-C.

Murine typhus disease is classically described as triad of fever, headache, and rash, but this triad only occurs in 41.6-42.7% of children.^{8,9} Instead, there is a broad spectrum of disease as demonstrated in this series; three of five 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 Lab findings are nonspecific, as is reflected in this case series, and most commonly include: transaminemia, lactate dehydrogenase elevation, hypoalbuminemia, elevated inflammatory markers, hyponatremia, anemia, thrombocytopenia.⁷⁻¹⁰ The pattern and degree of derangements also vary. For example, though transaminases are usually mildly elevated, in review of cases, a quarter had normal levels and a quarter had a significant (greater than 4-fold) 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 CDC recommendations to evaluate for MIS-C.¹ In these five children, CRP and D-dimer were elevated in all five, erythrocyte sedimentation rate (ESR) and LDH were elevated in four, ferritin was elevated in one, and procalcitonin and fibrinogen were not elevated. IL-6 was not assessed. This series serves as a reminder that these lab findings are nonspecific and,

though 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. Though troponin and B-type natriuretic peptide (BNP) levels in our selected cases were within normal range, Case 3 had mild coronary artery dilation. While 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, while true coronary aneurysms are specific to KD, there is evidence that coronary artery dilation can result from other febrile illnesses due to IL-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 12-24 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 2-4 weeks apart to show a 4-fold 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 five of these cases. Convalescent titers were not feasible due to the retrospective nature of

this study. However, elevated IgM in all five children, which resulted after discharge, supports acute infection with *R. typhi* and none had a recurrence of symptoms. Brief observation periods on empiric antibiotics were sufficient to make a presumptive diagnosis of murine typhus, avoiding IVIG and other anti-inflammatory therapies in four out of five cases.

Conclusion:

This case series of children evaluated for MIS-C emphasizes 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 non-infectious 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, empiric treatment for common or even uncommon infectious diseases, such as murine typhus, may avoid over diagnosis and overtreatment of MIS-C as well as improve patient outcomes.

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Table 1. History, physical exam and clinical course of five children with murine typhus

	Case 1	Case 2	Case 3	Case 4	Case 5
Age in years	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
Abd Pain	No	Yes	No	No	No
Other Symptoms	<ul style="list-style-type: none"> • Malaise • Dizziness 	<ul style="list-style-type: none"> • Diarrhea • Myalgias 	<ul style="list-style-type: none"> • Fatigue • Chills • Eye redness • Decreased appetite • Vomiting 	<ul style="list-style-type: none"> • Fatigue • Myalgias • Vomiting • Cough • Neck stiffness • Eye redness 	<ul style="list-style-type: none"> • Decreased appetite
Exposure	Multiple animals including puppy with fleas	<ul style="list-style-type: none"> • Dogs • Rats • Home treated for fleas 	2 cats and 1 dog previously treated for fleas	<ul style="list-style-type: none"> • 2 dogs • 1 cat • No known fleas 	<ul style="list-style-type: none"> • 1 dog • No known fleas
Physical Exam at Presentation	<ul style="list-style-type: none"> • Fever • Tachycardia • Maculo-papular rash on trunk, back, and extremities 	<ul style="list-style-type: none"> • Fever • Tachycardia • Tachypnea • Conjunctival Injection • Abdominal tenderness 	<ul style="list-style-type: none"> • Dry lips • Eczematous patches and excoriations • Injected conjunctivae 	<ul style="list-style-type: none"> • Abdomen tender to palpation in the right upper quadrant and epigastric area • Few scattered macules 	<ul style="list-style-type: none"> • Fever • Tachycardia
Days to fever resolution after doxycycline initiation	3	2	1	2	2
Recurrence of symptoms after discharge	None	None	None	None	None

Table 2. Laboratory Features of Five Children with Typhus

Test (Reference range with units)	Case 1	Case 2	Case 3	Case 4	Case 5
White Blood Cell Count* (4.5 - 13.0 Thousand/uL)	6.7	7.7	5.3	4.5	15.2
Lymphocyte % / absolute (1,200 - 5,200 cells/uL)	16 / 1080	34 / 2620	23 / 1210	38 / 1720	24 / 3620
Neutrophils % / absolute (1,800 - 8,000 cells/uL)	78 / 5200	56 / 4280	29 / 3620	52 / 2380	67 / 10190
Hemoglobin (12.0 - 16.9 g/dL)	12.8	9.9	13.4	13.3	11.7
Platelets (140 - 400 Thousand/uL)	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/hr)	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 UG/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*	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 prolongation	N/A	
Echocardiogram	normal	normal	mild coronary artery dilation	normal	normal

Prepublication Release

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 / IgG	Nonreactive	Nonreactive	Nonreactive	Nonreactive	Nonreactive

* Obtained after admission

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