CASE SERIES

Pediatric Scrub Typhus Manifesting with Multisystem Inflammatory Syndrome: A New Cause for Confusion or Concern—A Case Series

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Abstract

The pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has discovered a new disease called multisystem inflammatory syndrome in children (MIS-C). In developing nations, pediatricians must be mindful of the similarities between MIS-C and other tropical fevers such as scrub typhus. Not only should such patients be kept on high alert to rule out tropical diseases and receive appropriate treatment, such as steroids or immunomodulatory medications, but this is also concerning because, if rickettsial or bacterial infection is not detected through cultures and serology, steroid, or immunomodulatory treatment alone can be fatal.

Keywords: Child, Multisystem inflammatory syndrome in children, Rickettsia, Scrub typhus, Severe acute respiratory syndrome.

Indian Journal of Critical Care Medicine (2022): 10.5005/jp-journals-10071-24200

Introduction

Scrub typhus is a febrile infection caused by Orientia tsutsugamushi, a gram-negative coccobacillus, transmitted by the bite of an infected larval trombiculid mite.[1] It has been reported worldwide,[2] including India[3,4] during the summer and autumn in rural areas. Close differential diagnosis is other endemic febrile illnesses and correlated with compatible clinical signs, symptoms, laboratory findings along with epidemiologic indicators (e.g., recent exposure to locations where chiggers are suspected to be present). A lymphohistiocytic vasculitis with extensive vascular dysfunction and endothelial damage is the histological hallmark of the disease.

Recently, a serious condition multisystem inflammatory syndrome in children (MIS-C) has been diagnosed among patients who tested positive for coronavirus disease-2019 (COVID-19) (by PCR or serology) or showed epidemiological linkages to COVID-19.[5,6] MIS-C appears to be an excessive immune response related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with symptoms of persistent fever and hyperinflammation, as well as cardiac, gastrointestinal, renal, hematologic, dermatologic, and neurologic problems. We describe the clinical characteristics, laboratory data, and treatment management of pediatric scrub typhus patients manifesting as MIS-C in a northern Indian hospital.

Case Series

Between August and October 2021, children admitted into pediatric intensive care unit (PICU) of a tertiary care teaching hospital in northern India with unexplained fever and symptoms of multisystemic involvement were investigated for COVID NAAT as well as serology, tropical infections scrub, dengue, typhoid, malaria, and blood and urine cultures. The hospital records of all patients who had a positive Scrub IgM ELISA serology and symptoms, signs, and laboratory markers consistent with systemic hyperinflammatory disease were reviewed retrospectively.

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How to cite this article: Bhardwaj P, Sood M, Singh R. Pediatric Scrub Typhus Manifesting with Multisystem Inflammatory Syndrome: A New Cause for Confusion or Concern—A Case Series. Indian J Crit Care Med 2022;26(6):723–727.

Source of support: Nil

Conflict of interest: None

Clinical Characteristics, Laboratory Findings, Treatment, and Outcome

Table 1 displays clinical characteristics, laboratory, and treatments of all patients with outcomes. Table 2 displays the echocardiogram (ECHO) findings of all patients. Three of the nine patients were males, with a median age of 11.2 years (range 6.6–15.8 years). Mean weight was 34.1 kg (±15.4), mean height 133.5 cm (±32.3). All the three females who were underweight died. None of the patients tested COVID NAAT positive, while two with positive COVID serology survived.

At the time of admission, erythematous rash without an eschar (ESCHAR) was present in seven (77.8%), gastrointestinal involvement in eight (88.9%), shock in eight (88.9%), altered sensorium in three (33.3%), eight (88.9%) developed acute respiratory distress syndrome(ARDS) within 24 hours of admission, three (33.3%) patients had cardiac involvement, one had ECHO finding suggestive of myocardial dysfunction, and ejection fraction of 40%. None had coronary vessel abnormalities. Laboratory tests revealed anemia in all patients, range of Hb 8–10.7 gm/dL, low total leucocyte count (TLC) in three (33.3%) with lowest value 1200. Lymphopenia was present in five (55.5%) with lowest count 200 and all patients had

Table 1: Demographic characteristics, laboratory values, treatment, and outcome of patients

Baseline characters	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
Name, Sex	*J, Male*	*P, Male*	*S, Female*	*V, Female*	*R, Male*	*M, Female*	*P, Female*	*A, Female*	*A, Female*
Age in months	23	168	192	156	72	204	34	164	200
Weight in kg	12	45	45	40	18	50	12	45	40
Height in cm	80	154	140	135	113	157	90	168	165
Scrub IgM	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
COVID PCR/RAT positive	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
COVID serology	Positive	Negative	Negative	Negative	Negative	Positive	Negative	Negative	Negative
Rash	Present	Present	Absent	Present	Present	Present	Present	Present	Absent
Conjunctivitis	Absent	Absent	Absent	Absent	Absent	Present	Present	Present	Absent
Oral ulcers	Absent	Present	Absent	Absent	Absent	Present	Present	Present	Absent
Gastrointestinal involvement	Absent	Present	Present	Present	Present	Present	Present	Present	Present
Shock	Absent	Present	Present	Present	Present	Present	Present	Present	Present
Altered sensorium	Absent	Absent	Absent	Absent	Present	Absent	Absent	Present	Present
Respiratory symptoms	Present	Present	Present	Present	Present	Absent	Present	Present	Present
Cardiac involvement (either Lab/ECHO)	Absent	Present	Absent	Absent	Present	Absent	Present	Absent	Absent
LVEF %	70	60	70	70	50	70	60	40	65
Preexisting comorbidities	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Duration of fever/illness in days	7	5	7	7	8	6	7	7	4
Duration of hospital stay in days	7	12	15	10	15	6	15	3	13
Laboratory									
Hemoglobin (gm/dL)	9.5	10.2	10.7	10	9.5	10.3	9	8	8.2
Total leukocyte counts (mm^3)	13,700	8,300	9,500	4,500	1,200	7,000	1,400	2,700	5,500
Lymphocyte count (mm^3)	4,523	3,732	4,655	1,350	200	980	1,120	840	1,390
ANC (mm^3)	9,070	4,560	4,838	3,150	1,000	6,020	260	1,850	4,100
Platelet count (mm^3)	1,11,000	80,000	39,000	81,000	29,000	57,000	19,000	25,000	39,000
ESR (mm/hour)	25	48	29	48	38	50	30	30	50
CRP (mg/dL)	54	165	159.5	158	164	138.5	111.9	189	65
Serum ferritin (ng/mL)	1,324	More than 2,000	More than 2,000	More than 2,000	More than 2,000	More than 2,000	More than 2,000	More than 2,000	1,678
NT-proBNP (pg/mL)	Not done	Not done	Not done	Not done	Not done	Not done	Not done	Not done	Not done
D-dimer (ng/mL)	Less than 0.5	2–4	1–2	2–4	4–8	1–2	2–4	4–5	3–4

PaO_2/FiO_2 ratio	400	110	115	250	124	250	290	135	150
PT/INR/APTT	14.7/1.1/30	17.8/2.1/45.4	14.8/1.12/38.9	14.6/1.2/34.6	13.7/1.01/37	13.7/1.2/40.1	25.7/2/62.8	30.2/3/71.2	24/2.2/68
Urea/Cr	10/0.38	42/1.02	22/0.7	20/0.68	16/1.0	12/0.7	7/0.3	26/1.1	20/0.67
Albumin/ALT/AST	3.5/23/52	1.9/158/120	2.2/129/61	3/68/54	3/47/54	2.5/39/72.5	2.2/21/44	2.3/98/108	2/70/70
Treatment									
Duration of inotropic support in hours, type	20, noradrenaline	44, noradrenaline	62, noradrenaline and adrenaline	60, noradrenaline	110, noradrenaline and adrenaline	48, noradrenaline	24, noradrenaline	72, noradrenaline	120, noradrenaline
Duration of mechanical ventilation	Not required	6 days	5 days	Not required	10 days	Not required	1 day	3 days	11 days
IVIg with dose	Not given	Not given	Not given	1 dose @ 2 g/kg	1 dose @ 2 g/kg	Not given	1 dose @ 2 g/kg	1 dose @ 2 g/kg	Not given
Duration of steroids, type, and dose	7 days methyl-prednisolone @30 mg/kg/day for 3 days, tapered over 4 weeks	7 days methyl-prednisolone @10 mg/kg/day then shifted to oral prednisolone @2 mg/kg/day	7 days methyl-prednisolone @30 mg/kg/day then shifted to oral prednisolone @2 mg/kg/day	7 days methyl-prednisolone @10 mg/kg/day then shifted to oral prednisolone @2 mg/kg/day	7 days methyl-prednisolone @30 mg/kg/day for 3 days, tapered over 4 weeks	5 days, methyl-prednisolone @30 mg/kg/day	7 days, methyl-prednisolone @30 mg/kg/day	3 days, methyl-prednisolone @30 mg/kg/day	7 days, methyl-prednisolone @30 mg/kg/day
Duration of antibiotics, name	Doxycycline × 7 days, Ceftriaxone × 7 days	Doxycycline × 10 days, Ceftriaxone × 10 days	Doxycycline × 10 days, Ceftriaxone × 12 days	Doxycycline × 7 days, Ceftriaxone × 10 days	Doxycycline × 7 days, Linezolid × 15 days	Doxycycline × 6 days, Ceftriaxone × 6 days	Doxycycline × 6 days, Piperacillin × 13 days	Doxycycline × 3 days, Ceftriaxone × 3 days	Doxycycline × 6 days, Ceftriaxone × 13 days
Outcome	Discharged alive	Discharged alive	Discharged alive	Discharged alive	Discharged alive	Discharged alive	Death	Death	Death

ALT/AST, alanine aminotransferase/aspartate aminotransferase; ANC, absolute neutrophil count; CRP, creative protein; Cr, creatinine; ESR, erythrocyte sedimentation rate; IVIg, Intravenous immune globulin; LVEF, left ventricle ejection fraction; NT-proBNP, N-terminal pro b-type natriuretic peptide; PCR/RAT, polymerase chain reaction/rapid antigen test; PT, prothrombin time and partial thromboplastin time

Table 2: ECHO findings of patients

Cardiac parameter	*J, Male*	*P, Male*	*S, Female*	*V, Female*	*R, Male*	*M, Female*	*P, Female*	*A, Female*	*A, Female*
LVEF %	70	60	70	70	50, MR, TR with mild PAH present	65	60	40	60
LCA @ baseline coronary	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Coronary dilation	No	No	No	No	No	No	No	No	No
Coronary aneurysm	No	No	No	No	No	No	No	No	No
LAD @ baseline coronary	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Coronary dilation	No	No	No	No	No	No	No	No	No
Coronary aneurysm	No	No	No	No	No	No	No	No	No
RCA @ baseline coronary	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Coronary dilation	No	No	No	No	No	No	No	No	No
Coronary aneurysm	No	No	No	No	No	No	No	No	No

LAD, left anterior descending artery; LCA, left coronary artery; LVEF, left ventricle ejection fraction; MR, mitral regurgitation; PAH, pulmonary arterial hypertension; RCA, right coronary artery; TR, tricuspid regurgitation

thrombocytopenia with lowest count 19,000: elevated erythrocyte sedimentation rate(ESR) and C-reactive protein (CRP). Seven (77.8%) had elevated ferritin and D-dimer value, all except one had PaO_2/FiO_2 ratio less than 300, and four (44.4) had coagulopathy. All patients had more than 3 days of fever before admission, (range 4–8 days). Total hospital duration ranges from 3 to 15 days, with a median of 10.6 days.

All patients required inotropic support and remained on noradrenaline infusion, median time 62 hours (range 20–120 hours), two patients required adrenaline infusion in addition. Eight patients required mechanical ventilation for median 4 days (range 1–11 days), four (44.5%) were given 2 g/kg IVIg within 48 hours of admission. Two parents refused for IVIg citing financial reasons. In addition, all patients received high-dose methylprednisolone for 3–7 days and were tapered off subsequently. All patients received antibiotics, including doxycycline in accordance with the ICU protocol. Three (33.3%) patients died. There was no significant correlation with any particular symptom, COVID serology positivity, duration of fever, laboratory values, intravenous Immunoglobulin (IVIg) and steroids, choice, and duration of antibiotics with death ($p > 0.05$) (Table 4).

Discussion

According to early reports of SARS-CoV-2 patients, the sickness was more common and severe in elderly persons and people with comorbidities compared to children.[7] However, incidences of severe multisystem hyperinflammatory syndrome in children were shortly reported from a number of countries.[5] The World Health Organization (WHO) provided a case definition for MIS-C which include patients under 19 years of age with ≥3 days fever, laboratory evidence of inflammation, and involvement of two or more organ systems (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological), with positive testing for SARS-CoV-2 indicating current or recent infection or COVID-19 exposure; and no other alternative plausible diagnoses.[8] With the ongoing COVID-19 pandemic, clinicians have been on the lookout for MIS-C; and in countries like ours, many tropical infections such as scrub typhus, leptospirosis, malaria, dengue, Kawasaki syndrome, and toxic shock syndrome have been close differential diagnoses in the initial 2–3 days when laboratory investigations for alternative diagnosis are not available.

Table 3: Similarities between clinical and laboratory features of MIS-C and pediatric scrub typhus

Clinical features	*MIS-C*	*Scrub typhus, N = 9*
High fever	++	9 (100%)
Skin rash	++	7 (77.8%)
Nonpurulent conjunctivitis	++	3 (33.3%)
Mucocutaneous inflammation (oral, hands, or feet)	++	4 (44.4%)
Hypotension	++	8 (88.9%)
Features of myocardial involvement (dysfunction)	++	3 (33.3%)
Coronary abnormalities	++	Nil
Gastrointestinal problems (diarrhea, vomiting, or abdominal pain)	++	8 (88.9%)
Renal problems	++	Nil
Neurological problems (altered mental status and headache)	++	3 (33.3%)
Respiratory problems (pneumonia and ARDS)	++	8 (88.9%)
High CRP	++	9 (100%)
High ESR	++	9 (100%)
High ferritin	++	7 (77.8%)
High D-dimers	++	8 (88.9%)
Coagulopathy	++	4 (44.4%)
Low albumin	++	6 (66.7%)
Lymphopenia	++	6 (66.7%)
Reduced platelet count	++	9 (100%)
Increased aspartate aminotransferase (AST) and alanine transaminase (ALT)	++	6 (66.7%)

In Himachal Pradesh, postmonsoon months always see a spike in cases of scrub typhus among adults and children. Few critically sick children presented in shock with multiple organ dysfunction syndrome (MODS) and during the initial 2–3 days satisfied the case definition of MIS-C pending IgM enzyme linked immunoassay (ELISA) report for scrub typhus (Table 3). We treated these children according to MIS-C protocol,[9] in addition to antibiotics for tropical infections including scrub.[10] Recently, a case report of dengue presenting as

Table 4: Correlation of various variables with mortality among scrub typhus patients presenting as MIS-C

	Alive	*Dead*	*p value*
COVID serology –ve	4	3	0.25
COVID serology +ve	2	0	
Rash –ve	1	1	0.57
Rash +ve	5	2	
GIT symptoms –ve	1	0	0.45
GIT symptoms +ve	5	3	
Shock –ve	1	0	0.45
Shock +ve	5	3	
Altered sensorium –ve	5	1	0.13
Altered sensorium +ve	1	2	
Respiratory symptoms –ve	1	0	0.45
Respiratory symptoms +ve	5	3	
Cardiac involvement –ve	4	3	1.0
Cardiac involvement +ve	2	0	

GIT, gastrointestinal symptoms

MIS-C has also been published; therefore, tropical fevers in children should always be its close differential.[11]

However, our case series also has two patients with positive COVID serology, complicating the final diagnosis. The community transmission of COVID infection could explain the positive SARS-CoV-2 antibodies among scrub typhus patients, with many children with asymptomatic infections during peak of COVID pandemic may be showing serological evidence now. This is concerning because, if rickettsia or bacterial infection is not detected through cultures and serology, steroid or immunomodulatory treatment alone can be fatal.[9] We need to be vigilant and rule out tropical infections and administer appropriate treatment, along with steroids or immunomodulatory drugs among such patients. In the previous years too, scrub typhus patients had presented with shock and MODS, but we were not giving steroids and immunomodulatory treatment for associated hyperinflammation, due to concern about worsening of the infection.

In this case series, we had favorable prognosis among scrub typhus patients with hyperinflammation when steroids and IVIg were combined with doxycycline. We recommend randomized controlled trials to establish definitive role of steroids and immunomodulatory treatment in improving the outcome of scrub typhus children presenting with hyperinflammation.

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