



A Case Series

SARS-CoV-2 Induced Multisystem Inflammatory Syndrome in Children (MIS-C) with Seropositive Scrub Typhus: A Case Series.

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Abstract:

Statement of the problem: Pediatric patient with history of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was diagnosed with a serious condition called Multisystem Inflammatory Syndrome in Children (MIS-C). It is a post infectious excessive immune response differing from cytokine storm of SARS-CoV-2. MIS-C ranges from mild to severe form, with multiorgan involvement viz, cardiac, gastrointestinal, renal, neurological, hematological etc.; and laboratory evidence of hyperinflammation. Scrub Typhus (ST), a mite borne rickettsial febrile zoonosis; has been reported in India and worldwide. It is caused by a gram-negative coccobacillus called *Orientia tsutsugamushi* and transmitted by the bite of chiggers, the infected larva of trombiculid mites (genus *Leptotrombidium*). ST present as a febrile illness with eschar and rash, but can manifest with a myriad of unusual presentations involving different organ system. Incidence of different organ involvement with rarity of association between these two conditions grew our interest on this case series.

Methodology and Theoretical orientation: The study was conducted in the Pediatrics department of Malda Medical College and Hospital for a period of 6 months. All the subjects (age < 12 years) with complain of fever was evaluated for all tropical causes and among them the 3 child with

a) Scrub Typhus IgM Ab Positive

b) SARS-CoV-2 RTPCR Negative

c) SARS-CoV-2 IgG antibody Positive

d) MIS-C Positive (as per WHO's definition) was included in the study. The 3 cases was clinically evaluated in details with signs, symptoms, laboratory parameters and treatment given.

Findings: The CASE 1 and CASE 2 came with a neurological presentation on admission where as the CASE 3 presented with gastrointestinal one, fever being common in both. IV steroids, IVIg, Enoxaparin s/c were given to the patients but fever subsided with introduction of doxycycline after they became seropositive for scrub typhus. After thorough investigation it was found that both of them were positive for SARS-CoV-2 IgG antibody and Scrub Typhus IgM antibody with features of MIS-C.

Conclusion and Significance: Recently a seroprevalence study also reported a 5% co-infection of Scrub Typhus with seropositive MIS-C. The attribution of the co-infection in the Tsutsugamuschi Triangle with this clinical scenario and febrile presentation mimicking tropical diseases make this condition a circumstantial challenge. Pediatrician should be more vigilant while dealing with the febrile illness for early diagnosis and proper treatment of this condition.

Introduction

Pediatric population with history of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (2 to 6 weeks back) was recently diagnosed with a serious condition called Multisystem Inflammatory Syndrome in Children (MIS-C)^{1,2}. It is a post infectious excessive immune response differing from cytokine storm of SARS-CoV-2³. MIS-C ranges from mild to severe form, with multiorgan involvement viz, cardiac, gastrointestinal, renal, neurological, hematological etc.; and laboratory evidence of hyperinflammation.

Scrub Typhus (ST), a mite borne rickettsial febrile zoonosis; has been reported in India and worldwide^{4,5}. It is caused by a gram-negative coccobacillus called *Orientia tsutsugamushi* and transmitted by the bite of chiggers, the infected larva of trombiculid mites (genus *Leptotrombidium*)⁶. ST present as a febrile illness with eschar and rash, but can manifest with a myriad of unusual presentations involving different organ system⁷.

In this case series, we have described 4 cases of SARS-CoV-2 induced MIS-C with seropositive Scrub Typhus. Tenacity of different organ involvement with rarity of association between these two conditions grew our interest on this case series.

Materials and Methods

4 cases of pediatric population with Scrub Typhus IgM Ab Positive & MIS-C Positive (as per WHO's definition¹) in the department of pediatrics, of a Tertiary Care Centre from June'21 to December'21, were studied. Details of clinical presentation (symptoms, signs), investigations (CBC, inflammatory markers, LFT, RFT, routine urine test, serology, imaging) and treatment modalities with outcome were noted.

Case 1: A 2 years 6 months old male child weighing 10 kg was admitted in a Tertiary Care Center, Malda with chief complaints of high-grade fever for 2 weeks and convulsion. On examination, temperature – 102.4°F, SpO₂- 95%, heart rate- 108/min, CBG- 150mg/dl, no papilledema, no cervical lymphadenopathy, abdomen- soft, heart sounds- S1 and S2 were audible with no murmurs. His positive clinical findings were altered sensorium with active focal convulsion, neck rigidity, nystagmus, conjunctival injection, increased muscle tone and chest-bilateral basal crepitations. Empirical therapy was started with a provisional diagnosis of acute meningoencephalitis with ceftriaxone and amikacin with paracetamol infusion. He had a low hemoglobin of 7.5g/dl, with raised CRP (4.5mg/dl), ESR (55mm/1sthr.) and d-

Dimer(1.31microgram/ml).Arterial blood gas analysis on the day of admission reported ↑pH(7.613), ↓pCO₂(26.5mmHg), ↑pO₂(194.6mmHg), ↓Na⁺(127mmol/L), ↑K⁺(4.69mmol/L), ↓Cl⁻ (92 mmol/L). Renal function test (RFT) was within normal range whereas liver function test (LFT) showed decrease in serum albumin (2.7 g/dl), serum total protein(6.0 g/dl) level with increase in serum SGPT (52 IU/L), serum SGOT (64 IU/L) and serum Alkaline phosphatase(392IU/L). Blood for routine fever profile (MPDA-negative, DengueNS1 & IgM -negative, Japanese encephalitis IgM -negative, Widal test - negative) was done to rule out the differential febrile causes, out of which SARS-CoV-2 IgG antibody and ScrubTyphus IgM antibody came positive (on Day-2 of admission). Doxycycline, I/V Ig, s/c Enoxaparin and Dexamethasone were started after the child became seropositive for SARS-CoV-2IgG antibody->250 U/ml(Positive-≥0.80U/ml) and Scrub Typhus IgM antibody, and became afebrile on Day-4 with active convulsions. Radiological findings of chest X-ray(PA view) were within normal range, whereas Phase Contrast Magnetic Resonance Imaging(PC-MRI) showed intensity changes at posterior temporal, parietal, para-sagittal location(right > left) and both medial temporal region without contrast enhancement. 2D-Echocardiography showed dilatation of left main coronary artery (LMCA) and left anterior descending (LAD) artery with mild pericardial effusion and LVEF- 42%. The child was shifted to PICU on day 6 and put on vancomycin, sodium valproate and phenytoin along with ventilatory support. A diagnosis of SARS-CoV-2 induced MIS-C like presentation with seropositive Scrub Typhus was made and after 16 days of hospital stay the patient was afebrile with no convulsions and stable vitals, and discharged with oral aspirin, cefotaxime and prednisolone.

Case 2: A 3 years 3 months old male child weighing 12 kg was admitted to Tertiary Care

Centre, Malda with chief complaints of fever, cough, cold for 10 days, and pain in the abdomen with 2 episodes of loose stool for 1 day. On examination, temperature - 101.4°F, SpO₂- 96%, heart rate- 104/min, CBG- 168mg/dl, no papilledema, no cervical lymphadenopathy heart sounds-S1 and S2 were audible with no murmurs. His positive clinical findings were extensive maculopapular rash, significant cervical lymphadenopathy, Abdomen - soft, tender and chest-bilateral basal crepitations with ronchi. Empirical therapy was started with ceftriaxone and amikacin with paracetamol infusion. He had a low hemoglobin of 8.8g/dl, with raised CRP (12.10mg/dl), ESR (28mm/ 1st hr.) and d-Dimer (6.8 microgram/ml). Routine and microscopic urine examination showed mild proteinuria (+) with pus cells-2-4/hpf. LFT and RFT was within normal range, with ↑K⁺(5.1mmol/L) and ↓Na⁺ (132mmol/L). Blood for routine fever profile (MPDA-negative, Dengue NS1 & IgM -negative, Japanese encephalitis IgM -negative, Widal test - negative) was done to rule out the differential febrile causes, out of which SARS-CoV-2 IgG antibody- - >250 U/ml(Positive-≥0.80 U/ml) and Scrub Typhus IgM antibody came positive (on Day-2 of admission). The following reports along with clinical examination directed the diagnosis to MIS-C following SARS-CoV-2 with seropositive Scrub Typhus. Radiological findings of chest X-ray (PA view) and straight X-ray abdomen (erect posture) with USG whole abdomen was within normal range. The 2D-Echocardiography findings were also within normal range. After ruling out the possible tropical infections the child was put on methylprednisolone. He was given Doxycycline after he became seropositive for Scrub typhus; with IVIg, Enoxaparin and ofloxacin. The child became afebrile on Day-3 and condition improved gradually with a decrease in d-Dimer (to 0.43 microgram/ml on Day-6). After a hospital stay of 9 days the child

became a febrile with stable vitals and was discharged with oral prednisolone.

Case 3: A 1 year 8 months old female child weighing 9 kg was admitted in a Tertiary Care Centre, Malda with chief complaints of multiple episodes of convulsions with fever for 10 days. On examination, temperature – 102.7°F, SpO₂- 99%, heart rate- 111/min, CBG-133mg/dl, no papilledema, no cervical lymphadenopathy, abdomen- soft, heart sounds- S₁ and S₂ were audible with no murmurs. His positive clinical findings were altered sensorium with active convulsion, neck rigidity, increased muscle tone and chest-bilateral basal crepitations. Here also empirical therapy was started in the line of management of acute meningoencephalitis with ceftriaxone and amikacin with phenytoin. She had a low hemoglobin of 9.65g/dl, with raised CRP (21.64mg/dl), ESR (51mm/ 1sthr.) and d-Dimer(3.55 microgram/ ml). Electrolytes were within normal range with increased urea (29 mg/dl), and normal creatinine (0.5). LFT showed a similar pattern like case 1 i.e., decrease in serum albumin (2.8 g/dl), serum total protein (5.3 g/dl) level with increase in serum SGPT (74IU/L), serum SGOT (248 IU/L) and serum Alkaline phosphatase (679 IU/L). Blood for routine fever profile ruled out other tropical causes of fever except SARS-CoV-2 IgG antibody and Scrub Typhus IgM antibody, which came positive (on Day-2 of admission). SARS-CoV-2 induced MIS-C like presentation with seropositive Scrub Typhus was suspected and the patients were put on medications like IV methylprednisolone, S/c Enoxaparin was given, but fever only subsided with introduction of oral Doxycycline. Radiological findings (chest X-ray PA view and NCCT brain) and 2D-Echocardiography were within normal range. On follow up patient became afebrile with clear chest and d-Dimer

was reduced to 0.5 microgram/ ml. After 9 days of hospital-stay she was discharged with oral aspirin, and prednisolone.

Case 4: A 3 years 6 months old female child weighing 14 kg was admitted in Tertiary Care Centre, Malda with chief complaints of fever 4 days with pain in the abdomen and generalized body swelling and decreased urine output. On examination, temperature–100.4°F, SpO₂-99%, heart rate- 100/min, CBG- 152mg/dl, no papilledema, no cervical lymphadenopathy heart sounds- S₁ and S₂ were audible with no murmurs. Her positive clinical findings were Abdomen – soft, tender with chest- bilateral basal crepitations. Empirical therapy was started with ceftriaxone with provisional diagnosis of Nephrotic syndrome. She had a low hemoglobin of 8.3g/dl, with raised CRP (7.8mg/dl), ESR (12mm/ 1st hr.) and d-Dimer (1.1microgram/ml). Routine and microscopic urine examination showed moderate proteinuria (++) with pus cells (2-4/hpf) and epithelial cells (2-4/hpf). RFT was within normal range, with normal K⁺ (4.3 mmol/L) and ↓ Na⁺ (134mmol/L). LFT showed increase in SGOT (104IU/L), SGPT (85 IU/L), serum Alkaline Phosphatase (242 IU/L) with decrease in serum albumin (2.2 gm/dl) and serum total protein (6.1 gm/dl). Blood for routine fever profile was done to rule out the differential febrile causes, out of which SARS-CoV-2 IgG antibody and Scrub Typhus IgM antibody came positive(on Day-2of admission). MIS-C following SARS-CoV-2 with seropositive Scrub Typhus was diagnosed and patient was put on I/V Methylprednisolone, S/C Enoxaparin, ofloxacin and Doxycycline after which the patient became afebrile with clear chest. Chest X-ray (PA view), USG whole abdomen, 2D-Echocardiography all was within normal range. Patient was discharged after 5 days of hospital-stay with oral prednisolone.

RESULTS

Table 1: Clinical features of the cases.

Clinical Features	CASE 1	CASE 2	CASE 3	CASE 4
<i>Basic information</i>				
1.Age	2 years 6 months	3 years 3 months	1 year 8 months	3 years 6 months
2.Sex	Male	Male	Female	Female
3.Body weight	10 kg	12 kg	9 kg	14 kg
4.History of contact to COVID-19 positive individual	Nil	Nil	Nil	Nil
5.Hospital Stay	16 days	9 days	9 days	5 days
6.Outcome	Discharged Alive	Discharged Alive	Discharged Alive	Discharged Alive
<i>Symptoms</i>				
1. Fever Duration (in days)	14 days	10 days	10 days	4 days
2.Disorientation	Present	Absent	Present	Absent
3.Vomiting	Absent	Absent	Absent	Absent
4.Loose stool	Absent	Present	Absent	Absent
5.Pain abdomen	Absent	Present	Absent	Present
6.Headache	Absent	Absent	Absent	Absent
7.Convulsion	Present	Absent	Present	Absent
8.Shortness of Breath	Absent	Absent	Absent	Absent
<i>Signs</i>				
1.Altered sensorium	Present	Absent	Present	Absent
2.Hypotension (Shock)	Absent	Absent	Absent	Absent
3.Non purulent conjunctivitis	Present	Absent	Absent	Absent
4.Maculopapular rash	Absent	Present	Absent	Absent
5.Eschar	Absent	Absent	Absent	Absent
6.Neck rigidity	Present	Absent	Present	Absent
7.Lymphadenopathy	Absent	Present	Absent	Absent
8.Hepatomegaly	Absent	Absent	Absent	Absent
9.Splenomegaly	Absent	Absent	Absent	Absent
10.Respiratory findings	Present	Present	Present	Present
11.Direct Ophthalmoscopy	Absent	Absent	Absent	Absent

Table 2: Investigatory findings of the cases.

Investigation Parameters	CASE 1	CASE 2	CASE 3	CASE 4
<i>Baseline investigation on admission</i>				
1.Temperature	102.4°F	101.4°F	102.7°F	100.4°F
2.SpO2	95%	96%	99%	99%
3.Heart rate	108 beats/min	104 beats/min	111 beats/min	100 beats/min
4.CBG	150 mg/dl	168 mg/dl	133 mg/dl	152 mg/dl
<i>Hematological Parameters</i>				
1.Hb%	7.5%	8.8%	9.65%	8.3%
2.Total count(WBC)	8.23×10 ⁹ /L	10.4×10 ⁹ /L	4 ×10 ⁹ /L	×10 ⁹ /L
3.Platelet	243×10 ⁹ /L	181×10 ⁹ /L	166×10 ⁹ /L	×10 ⁹ /L
4.ESR	55mm / 1 st hour	28mm/ 1 st hour	51/1 st hour	12/1 st hour
5.CRP	4.5 mg/dl	12.1 mg/dl	21.64mg/dl	7.8 mg/dl
6.Serum LDH	2120 IU/L	867 IU/L	1997 IU / L	504 IU / L
7.Serum Ferritin	393 ng/dl	337 ng/dl	362.3 ng/dl	238.7 ng/dl
8.Na+	132mmol/ L	132mmol/ L	140 mmol/L	134 mmol/ L
9.K+	5.2mmol/ L	5.1mmol/ L	4.3 mmol/ L	4.3 mmol/ L
10.Urea	18 mg/dl	22 mg/dl	29 mg/dl	15 mg/dl
11.Creatinine	0.6 mg/dl	0.9 mg/dl	0.5 mg/dl	0.6 mg/dl
12.SGOT	52 IU / L	21 IU/ L	248 IU / L	104 IU / L
13.SGPT	64 IU / L	33 IU/ L	74 IU / L	85 IU / L
14. Serum Alkaline Phosphatase	392 IU / L	123 IU / L	679 IU / L	242 IU / L
15.Serum Albumin	2.7 gm/dl	4.0 gm/dl	2.8 gm/dl	2.2 gm/dl
16.Serum Total Protein	6.0 gm/dl	7.8 gm/dl	5.3 gm/dl	6.1 gm/dl
17.d-Dimer	1.31 μ /ml	6.8 μ /ml	3.55 μ /ml	1.1 μ /ml
<i>Serology for fever profile</i>				
18.Widal test	Negative	Negative	Negative	Negative
19.NS1 antigen	Negative	Negative	Negative	Negative
20.RK 39	Negative	Negative	Negative	Negative
21.MPDA	Negative	Negative	Negative	Negative
22.Scrub Typhus IgM Ab	Positive	Positive	Positive	Positive
23.SARS-CoV-2RTPCR	Negative	Negative	Negative	Negative
24.SARS-CoV-2 IgG antibody	Positive	Positive	Positive	Positive
<i>Imaging Parameters</i>				
25.Chest XRay (PAview)	WNL	WNL	WNL	WNL
26.Straight X ray Abdomen (erect posture)	-	WNL	-	-
27.USG wholeabdomen	-	WNL	-	WNL

28.PC-MRI	Intensity changes at posterior temporal, parietal, parasagittal location (right >left) and both medial temporal region without Contrast enhancement	-	-	-
Others				
29.2d-Echocardiography	Dilatation of left main coronary artery (LMCA) and left anterior descending (LAD) artery with mild pericardial Effusion and LVEF-42%	WNL	WNL	WNL
30.CSF study	Lymphocytic pleocytosis with elevated protein.	-	-	-
31.Urine	-	Mild proteinuria (+) with pus cells – 2-4/hpf	-	Moderate proteinuria (++) with pus cells – 2-4/hpf, epithelial cells-2-4/hpf.

*WNL- within normal limit

Table 3: Treatment received by the cases.

Treatment Received	CASE 1	CASE 2	CASE 3	CASE 4
1.Ceftriaxone	+	+	+	+
2.Amikacin	+	+	+	-
3.Oral Doxycycline	+	+	+	+
4.IV steroids(Methylprednisolone/Dexamethasone)	+	+	+	+
5.Enoxaparin S/C	+	+	+	+
6.IV Ig	+	+	+	+
7.Oral Prednisolone	+	+	+	+
8.Oral Aspirin	+	-	-	-
9.Vancomycin	+	-	-	-
10.Ofloxacin	-	+	-	+
11.Ventilator support	+	-	-	-

Discussion

Table 4: Diagnosis of MIS-C in the 2 cases

Criteria for diagnosis of MIS-C according to WHO definition. ⁸	Case 1	Case 2	Case 3	Case 4	Fulfilment of the criteria.	
<i>Criteria 1- Age 0 to 19 years</i>	✓	✓	✓	✓	✓	
<i>Criteria 2- Fever for ≥ 3 days.</i>	✓	✓	✓	✓	✓	
Criteria 3- Clinical signs of multisystem involvement (at least two of the following five)	Rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet)	✓	✓	-	-	✓
	Hypotension or shock	-	-	-	-	
	Features of myocardial dysfunction, pericarditis, valvulitis or coronary abnormalities (including echocardiographic)	✓	-	-	-	

	findings or elevated troponin/ NT-BNP)					
	Evidence of coagulopathy (prolonged PT, PTT, elevated d-Dimer)	✓	✓	✓	✓	
	Acute gastrointestinal symptoms (diarrhoea, vomiting or Abdominal pain)	-	✓	-	✓	
Criteria 4- elevated markers of inflammation	Prolonged PT	-	-	-	-	✓
	Prolonged aPTT	-	-	-	-	
	Elevated d-Dimer	✓	✓	✓	✓	
Criteria 5- No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/streptococcal toxic shock syndromes	✓ (except for scrub typhus)	✓ (except for scrub typhus)	✓ (except for scrub typhus)	✓ (except for scrub typhus)	or ✓ (An ongoing controversy)	
Criteria 6- Evidence of SARS-CoV-2 infection (RT-PCR, antigen test or serology positive) or contact with an individual with COVID-19 present.	✓	✓	✓	✓	✓	

We have diagnosed the Multisystem Inflammatory Syndrome- in Children (MIS-C) in these 4 cases according to WHO's definition⁸. The CASE 1 and 3 came with a neurological presentation on admission whereas the CASE 2 and 4 presented with gastrointestinal and urinary feature respectively, fever being common in all. The duration of fever was between 7-14 days and crepitations were present in all without significant difficulty in breathing. All of them were anemic with raised inflammatory markers like CRP, ESR, d-Dimer, serum ferritin and LDH. RFT was within normal range with mild dyselectrolytemia. But LFT showed a noticeable pattern of hypoproteinemia and hypoalbuminemia with increased SGOT, SGPT and ALP. IVsteroids, IVIg, Enoxaparin s/c were given to the patients but fever subsided with introduction of Doxycycline.

Literature review also supported this finding⁹. After thorough investigation it was found that all of them were positive for SARS-CoV-2 IgG antibody and Scrub Typhus IgM antibody with features of MIS-C. Here lies the diagnostic dilemma as stated by Mandal A et al that whether should we diagnose it as post COVID-19 MIS-C with association of scrub typhus or an exaggerated immune response of scrub typhus on the background of SARS-CoV-2⁹. As per the WHO's diagnostic criteria for MIS-C, all obvious causes of microbial infection should be ruled out. So, should we discard the diagnosis of MIS-C on the basis of the guideline or are there chances of co-infection or true cross-reactivity?

Indian guidelines suggest that there are possibilities of co-infection of other tropical illness with SARS-CoV-2¹⁰. So, can we

consider the same for post-COVID-19 MIS-C? Recently a seroprevalence study also reported a 5% co-infection of Scrub Typhus with seropositive MIS-C¹¹. The attribution of the co-infection or cross-reactivity with this clinical scenario and febrile presentation mimicking tropical diseases makes this condition a circumstantial challenge.

Conclusion

The case series deals with the rarely reported cases of MIS-C with concomitant scrub typhus infection. This study reveals a close and overlapping clinical and laboratory picture of MIS-C and Scrub typhus infection, along with its mimicking potential of different tropical diseases which makes this a circumstantial challenge. Moreover, the management modality also reflects light on the preferable line of treatment for this febrile condition. The pediatrician should be more vigilant while dealing with the febrile illness for early diagnosis and proper treatment of this condition.

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