CASE REPORT

Multisystem Inflammatory Syndrome in a Child with Scrub Typhus and Macrophage Activation Syndrome

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ABSTRACT

Kawasaki disease (KD), multisystem inflammatory syndrome in children (MIS-C) and macrophage activation syndrome (MAS) have been speculated as three distinct phenotypes of hyperinflammation seen in children during coronavirus disease (COVID-19) pandemic. KD has been reported in association with dengue, scrub typhus and leptospirosis. COVID-19 and dengue coinfection has also been described. However, MIS-C with concomitant infection has rarely been reported. We report an adolescent girl with clinical and laboratory parameters of MIS-C resembling KD with positive serology for scrub typhus at presentation. Clinical manifestations resolved and laboratory parameters improved with IVIG, azithromycin and corticosteroids. However, she developed fever recurrence with thrombocytopenia, elevated inflammatory markers, hypofibrinogenemia and hypertriglyceridemia which were consistent with MAS. With the emergence of MIS-C and increase in the number of such cases being reported throughout world, physicians should be aware of different phenotypes of hyperinflammation associated with COVID-19 and the possibility of coexistence of MIS-C with other infections.

LAY SUMMARY

Clinical and laboratory parameters of multisystem inflammatory syndrome in children (MIS-C) mimic Kawasaki disease (KD). KD has been described in association with dengue, scrub typhus and leptospirosis. However, MIS-C with concomitant infection has rarely been reported in literature. A 14-year-old-girl presented with fever and rash with history of redness of eyes, lips and tongue. Investigations showed anemia, lymphopenia, thrombocytosis with elevated erythrocyte sedimentation rate, C-reactive protein, pro-brain natriuretic peptide, Interleukin-6, ferritin and d-dimer. Scrub typhus immunoglobulin M was positive. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulin G (IgG) level was also elevated. A diagnosis of MIS-C with concomitant scrub typhus was proffered. Child received azithromycin, intravenous immunoglobulin and methylprednisolone. After an afebrile period of 2.5 days, child developed unremitting fever and rash.
Repeat investigations showed anemia, worsening lymphopenia, thrombocytopenia, transaminitis, hypertriglyceridemia, hyperferritinemia and hypofibrinogenemia which were consistent with a diagnosis of macrophage activation syndrome (MAS). KD, MIS-C and MAS represent three distinct phenotypes of hyperinflammation seen in children during coronavirus disease pandemic. Several tropical infections may mimic or coexist with MIS-C which can be a diagnostic challenge for the treating physician. Identification of coexistence or differentiation between the two conditions is important in countries with high incidence of tropical infections to guide appropriate investigations and treatment.

**KEYWORDS**: COVID-19, Kawasaki disease, PIMS, MIS-C, Scrub typhus, Macrophage activation syndrome

**INTRODUCTION**

Children constitute only a small number of cases of coronavirus disease (COVID-19) compared to adults. However, a hyperinflammatory syndrome is increasingly being reported from several countries [1–3] with overlapping features of Kawasaki disease (KD) and toxic shock syndrome [4]. KD, multisystem inflammatory syndrome in children (MIS-C) and macrophage activation syndrome (MAS) have been speculated as three distinct phenotypes of hyperinflammation seen in children during COVID-19 pandemic [4]. Various organisms and bacterial superantigens have been implicated in the pathogenesis of KD [5]. However, the role of infectious organisms has not been explored in the pathogenesis of MIS-C. We report an adolescent girl with clinical and laboratory parameters of MIS-C resembling KD with positive serology for scrub typhus who subsequently developed MAS.

**CASE PRESENTATION**

A 14-year-old girl presented with fever for 10 days, non-pruritic rash over chest and neck, with history of redness of eyes, lips and tongue on day 5 of illness. Grandparents had a history of flu-like illness 3 weeks prior to symptom onset. There was no improvement after 3 days of oral amoxicillin-clavulanate (40 mg/kg/day) and azithromycin (10 mg/kg/day) followed by 4 days of intravenous ceftriaxone (50 mg/kg/day) received elsewhere for prolonged fever. The child was febrile at presentation with nontender right cervical lymphadenopathy (2.0 × 1.5 cm) and erythematous maculopapular rash over neck and chest. Systemic examination was unremarkable. She had anemia (hemoglobin 102 g/l, normal: 115–155 g/l), lymphopenia [total leukocyte count (TLC) 19.4 × 10⁹/l, neutrophils 87%, lymphocytes 10%] and thrombocytosis (platelet count 674 × 10⁹/l, normal: 170–450 × 10⁹/l). Her inflammatory markers were elevated with erythrocyte sedimentation rate (ESR) 88 mm in first hour, C-reactive protein (CRP) 107.07 mg/l (normal: <1.0 mg/l), probrain natriuretic peptide (NT-pro BNP) 787 pg/ml (normal: <125 pg/ml), Interleukin-6 (IL6) 86.87 pg/ml (normal: 0–7 pg/ml), ferritin 782 ng/ml (normal: 11–306 ng/ml) and d-dimer 1173 ng/ml (normal: <243 ng/ml) with normal fibrinogen (424 mg/dl, normal: 248–498 mg/dl) levels. Procalcitonin (0.18 ng/ml), urine examination, renal and liver functions, chest X-ray, ultrasound abdomen were normal and blood culture was sterile. Scrub typhus immunoglobulin (Ig) M was positive (2.46, negative: <1.2). Investigations for typhoid, dengue, malaria and chikungunya were negative. Real-time polymerase chain reaction for SARS-CoV-2 was also negative. SARS-CoV-2 IgG level was elevated at 60.7 AU/ml (>12 indicates exposure to the pathogen). Echocardiography showed minimal pericardial effusion with no coronary artery abnormality.

A diagnosis of MIS-C mimicking classic KD with concomitant scrub typhus was proffered. Child received oral azithromycin (10 mg/kg/day), intravenous immunoglobulin (IVIG 2 g/kg), aspirin (3 mg/kg) and methylprednisolone (20 mg/kg/day for 3 days), following which fever subsided, CRP (9.3 mg/l) and d-Dimer (737 ng/ml) decreased while lymphopenia persisted (TLC 11.8 × 10⁹/l, neutrophils 83%, lymphocytes 12.2%).

After an afebrile period of 2.5 days, child developed fever with recurrence of erythematous, non-pruritic rash over face, left ear (Fig. 1A), chest and abdomen. Repeat investigations showed anemia...
hemoglobin 111 g/l), rise in leukocyte count with worsening lymphopenia (TLC 18.4 × 10⁹/l, neutrophils 92%, lymphocytes 3.9%) and decrease in platelet count (292 × 10⁹/l). CRP had increased to 45.08 mg/l and child developed hyponatremia (serum sodium 128.6 mmol/l, normal: 136–146 mmol/l), hypocalcemia (serum calcium 8.5 mg/dl, normal: 8.8–10.6 mg/dl) and transaminitis (alanine transaminase 153.8 U/l, aspartate transaminase 81.3 U/l). Urine examination and procalcitonin (0.26) were normal, blood culture was sterile, and dengue IgM was negative. Repeat echocardiography was also normal. Rapid deterioration in clinical (persisting fever, progressive rash, irritability) and laboratory parameters necessitated the use of tocilizumab (8 mg/kg) and methylprednisolone (20 mg/kg/day, total 1 g). However, child continued to have unremitting fever with progression of rash to bilateral upper (Fig. 1B) and lower limbs. Further investigations showed increase in NT pro-BNP (3890 pg/ml), ferritin (13 167 ng/ml) and d-dimer (11 960 ng/ml) with decrease in fibrinogen (243 mg/dl) and IL6 (48.72 pg/ml) compared to baseline. Platelet count dropped to 100 × 10⁹/l and hypertriglyceridemia (fasting triglyceride 247.4 mg/dl) was also noted. Highly elevated ferritin and hypertriglyceridemia with hypofibrinogenemia and thrombocytopenia raised the suspicion for MAS. Child was continued on methylprednisolone for 5 days followed by gradual tapering by 250 mg every 2 days along with subcutaneous low molecular weight heparin (1 mg/kg/day) for 5 days. Repeat IVIG could not be given. Child showed improvement with resolution of fever, decrease in CRP (1.57 mg/l), rise in platelet (241 × 10⁹/l), lymphocytes (TLC 7.2 × 10⁹/l, lymphocytes 16.7%) and serum sodium (135.9 mmol/l). She was shifted to oral prednisolone (2 mg/kg/day) which was gradually tapered by 5 mg every 7 days.

DISCUSSION

Clinical and laboratory parameters of MIS-C mimic KD (Table 1) which is the most common childhood vasculitis with predilection for coronary arteries. Although, an association with several organisms (Streptococcus pyogenes, Staphylococcus aureus, Epstein–Barr virus, Coronavirus and Parvovirus) has been reported, exact etiology of KD remains unknown [5]. KD has been described in association with dengue, scrub typhus and leptospirosis [6–8] while COVID-19 and MIS-C have been reported with dengue [9, 10]. However, MIS-C with concomitant scrub typhus has not been described in literature. Index child fulfilled the clinical and laboratory parameters of MIS-C mimic KD (Table 1) which is the most common childhood vasculitis with predilection for coronary arteries.
| Characteristic                          | KD [5]                              | MIS-C [3]                                    | MAS [4]                                      | Index child |
|----------------------------------------|--------------------------------------|----------------------------------------------|----------------------------------------------|-------------|
| Age in years                           | Usually <5                           | Older children and adolescents               | Usually adolescents, but may affect any age group | 14          |
| Fever duration                         | Usually >5 days                      | Variable, ranging from ≥24 h to ≥3 days according to various case definitions | Unremitting fever                             | 10 days     |
| Mucocutaneous manifestations           | Rash, bilateral non-purulent conjunctivitis, erythema and cracking of lips, periungual desquamation, strawberry tongue, cervical lymphadenopathy | Classic or incomplete KD                     | –                                             | Classic KD  |
| Organ involvement                      | Coronary artery abnormalities        | Single or multiorgan dysfunction (shock, cardiac, respiratory, gastrointestinal, renal or neurological) | Hepatosplenomegaly, other organ dysfunction    | Myocardial (raised NT-pro BNP), pericardial effusion |
| Laboratory parameters                  | Anemia, neutrophilia, thrombocytosis; elevated ESR (≥40 mm/h) and/or CRP (≥30 mg/l). | Neutrophilia, lymphopenia; low albumin; elevated ESR, CRP, d-Dimer, ferritin, LDH, NT-pro BNP, IL-6, fibrinogen | Cytopenia affecting two cell lines; elevated ferritin, triglyceride and transaminases; hypofibrinogenemia | At presentation: Anemia, neutrophilia, lymphopenia, thrombocytosis; elevated ESR, CRP, IL-6, d-dimer, ferritin and NT-pro BNP. At fever recurrence: Anemia, thrombocytopenia; elevated CRP, ferritin, triglyceride, transaminases; decreased fibrinogen. |
parameters of MIS-C [4] and had positive scrub typhus IgM with negative serology for other tropical infections (dengue, typhoid, malaria, chikungunya).

MAS is characterized by uncontrolled proliferation and activation of macrophages. Immune dysregulation characterized by macrophage activation with increased production of circulating cytokine and chemokines (tumor necrosis factor, IL6) is central to the pathogenesis of MAS, KD as well as MIS-C [11]. Index child fulfilled the criteria for classic KD [5] and MIS-C [4] at presentation (fever and mucocutaneous manifestations with neutrophilia; lymphopenia; elevated inflammatory markers-ESR, CRP, ferritin, fibrinogen, IL6, D-dimer; and positive SARS-CoV IgG). Recurrence of fever episodes coupled with thrombocytopenia, elevated inflammatory markers, hypofibrinogenemia and hypertriglyceridemia was consistent with a diagnosis of MAS. MAS in our patient is more likely to have been triggered by KD phenotype as she was adequately treated with oral azithromycin (10 mg/kg/day for 7 days) for scrub typhus.

Several tropical infections may mimic or coexist with MIS-C which can be a diagnostic challenge for the treating physician. Identification of co-existence or differentiation between the two conditions is important in countries with high incidence of tropical infections to guide appropriate investigations and treatment. With the emergence of MIS-C and increase in the number of such cases being reported throughout the world, physicians should be aware of the different phenotypes of hyperinflammation associated with COVID-19 and the possibility of coexistence of MIS-C with other infections, as reported with KD.

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