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CASE REPORT

PEDIATRIC INFLAMMATORY MULTISYSTEM SYNDROME TEMPORALLY ASSOCIATED WITH SARS COV 2 (PIMS-TS): A CASE REPORT FROM ETHIOPIA AND A REVIEW OF LITERATURE

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ABSTRACT

Many thousands of children have so far been diagnosed with SARS-CoV-2 infection. An uncommon presentation of pediatric Coronavirus Disease COVID-19 is the Pediatric inflammatory multisystem syndrome temporally associated with SARS CoV 2 (PIMS-TS), also referred to as Multisystem Inflammatory Syndrome in Children (MIS-C). Though more than 35 countries have reported this syndrome, there have been very few reports from low- and middle-income countries, including Ethiopia. We are reporting the first child from Ethiopia affected by PIMS-TS and a review of the literature on its presentation, diagnosis, and management.

INTRODUCTION

The COVID-19 pandemic caused by the SARS-CoV-2 virus had led to more than 100 million cases worldwide one year after its onset in December 2019, claiming the lives of close to 2.5 million people (1). The first child diagnosed with COVID-19 was reported from Shenzhen, China, on 20th January 2020 (2). In March 2020, pediatricians in Europe began reporting children infected with SARS-CoV-2 and presenting with fever and multisystem inflammation (3). Even though hundreds of more cases have subsequently been diagnosed with this syndrome, now known as Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) – very few has been reported from low- and middle-income countries (4). Its commonest presentations include fever, hypoxia and/or hypotension, less often abdominal pain, conjunctivitis, cough, diarrhea, headache, mucositis, lymph node swelling and rash (5). We are reporting here the first child from Ethiopia affected by PIMS-TS.

CASE PRESENTATION

A four years and eight months old boy presented with a high grade fever of five days. He also had a reddish-colored rash behind his right ear and trunk in the preceding few hours, which did not follow a contiguous spread. He also complained of poor appetite, intermittent mild abdominal, dysuria, groin pain, and intermittent cough. His parents reported red eyes and swollen lips, which started a day prior to the presentation. He had no runny nose.

He was vaccinated with a single dose of the Measles vaccine at nine months of age and was up-to-date for his age on the rest of his vaccines. An asymptomatic close contact (of a patient who tested positive for PCR of SARS-CoV-2 three weeks ago) had spent two nights with the boy and his family a fortnight ago. His parents reported no history of allergies to medication and food. He had received antipyretics, oral Amoxicillin for one day, and oral Cefpodoxime for three days for presumed acute pharyngitis but his symptoms failed to improve. He had no travel history outside of his hometown – Addis Ababa – a city 2400 meters above sea level in Ethiopia's central highlands – a malaria-free area.

On physical examination, his temperature was 36.3°C, pulse rate 160 beats per minute, respiratory rate 28 per minute, and blood pressure 80/40 mmHg. He had bilateral injected bulbar conjunctivae sparing the limbs, strawberry tongue, swollen erythematous and cracked lips, anterior cervical lymphadenopathy (largest having a diameter of 1.5 cm), erythematous palms with macules (blanching), and an erythematous maculopapular rash over the right posterior auricular region, right axilla, left leg as well as the trunk (Figure 1).

His admission lab work-up showed a white blood cell count of 11000/mm^3 with neutrophils of 9770/mm^3 and platelets of 111,000/mm^3. The rest of his complete blood count was within normal ranges for his age. His serum C-reactive protein (CRP) was elevated (118 mg/l). His urinalysis showed 1 – 2 white blood cells and 0 – 1 red blood cells per high power field with no proteins.

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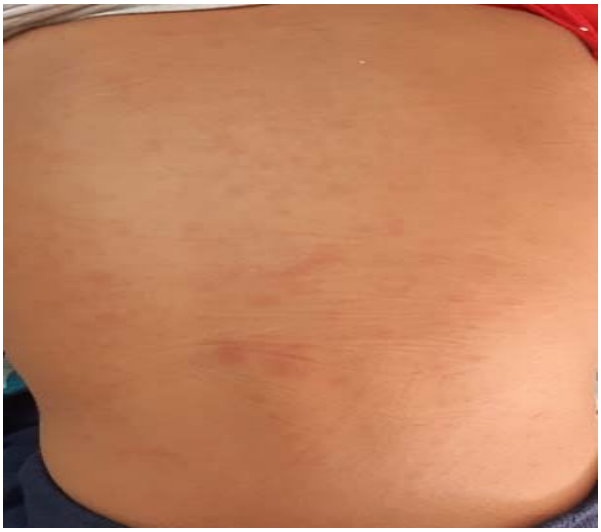

Figure 1: Erythematous maculopapular rash over the child's back

His serum urea nitrogen and creatinine were 15 mg/dl and 0.5 mg/dl, respectively, while liver enzymes were elevated two times (Alanine transaminase 85 U/l and Aspartate transaminase 98 U/l). His seromarkers for hepatitis B and C were negative, while his group A rapid streptococcal antigen test was negative. His serum albumin was 3.1 g /dl (normal: 3.8 – 5 g/dl).

His SARS-CoV-2 PCR (nasopharyngeal and oropharyngeal samples) was negative, while his SARS-CoV-2 specific IgM and IgG were positive. Echocardiography done at admission (day five of fever) showed acute mild mitral regurgitation with no evidence of coronary artery lesions and pericardial or myocardial abnormalities. His troponin could not be determined. His chest X-ray did not show any abnormalities. An abdominal ultrasound showed mild terminal thickening with enlarged mesenteric lymph nodes, the largest having central necrosis and measuring 0.88 cm x 1.27 cm.

He met the diagnostic criteria for Kawasaki disease (KD): fever of five days, bilateral injection of the bulbar conjunctivae with limbic sparing and without exudate, erythematous swollen cracked mouth and lips, strawberry tongue, erythematous maculopapular rash, palmar erythema, and anterior cervical lymphadenopathy. In addition, he had abdominal pain with ultrasound findings of ileitis and mesenteric lymphadenopathy, urethritis, neutrophilia and lymphopenia, abnormal inflammatory markers (elevated serum CRP, hypoalbuminemia) and positive SARS-CoV-2 specific serum IgM and IgG, which led to a final diagnosis of Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS).

The boy was given a first dose of IV immunoglobulin (IVIG) infusion at 2 g/kg over 12 hours and also started on Aspirin per os (PO) at 40 mg/kg/day divided into four doses. He was given oral paracetamol for fever records of more than 37.8^{o}C. Nearly two days (44 hours) after completing his IVIG dose, he became afebrile and the redness of his eyes started to subside. The abdominal pain and dysuria also lessened. His rash started to fade after 60 hours IVIG completion and disappeared within the ensuing 24 hours. His pulse rate dropped to 105 beats per minute while his blood pressure elevated to 90/50 mmHg.

His serum CRP dropped to 50.4 mg/L after 24 hours of admission and to 5 mg/L by the 14th day of illness. A repeat echocardiography on his 14th day of illness showed very mild mitral regurgitation with normal coronary arteries. His liver enzymes normalized within 48 hours of starting treatment. On his 14th day, his complete blood count (CBC) abnormalities had corrected to normal ranges for age (absolute neutrophil count being 2190/mm^3 and platelets 332,000/mm^3). Though he did not require a second dose of IVIG, he continued taking aspirin at 4 mg/kg/day as a single dose after 48 hours lapsed without fever until six weeks after onset of illness. Echocardiography, CBC, and CRP done at the end of the sixth week of follow-up showed normal findings and aspirin was stopped.

DISCUSSION

The World Health Organization defines the PIMS-TS as seen in a patient aged 19 years or less with a fever of more than three days and two, or more of the following signs (6):

- 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-proBNP)
- Evidence of coagulopathy (by prothrombin time (PT), partial thromboplastin time (PTT), elevated D-dimers)
- Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain)

This should be accompanied by elevated markers of inflammation such as erythrocyte sedimentation rate (ESR), CRP, or procalcitonin in the absence of an alternative diagnosis and evidence of COVID-19 (RT -PCR, antigen test or serology positive), or likely contact with patients with COVID-19. Our patient fulfilled the criteria through his fever, typical rash, echocardiographic evidence of valvulitis, abdominal pain, elevated CRP and serologic evidence of a recent COVID19 infection (positive SARS-CoV-2 specific immunoglobulin (Ig) M and IG (6) .

The proposed mechanisms for PIMS-TS are post-viremia aberrant immune response mediated by enhanced non-neutralizing IgG antibodies (7,8) and delayed and excess cytokine storm caused by a high SARS CoV 2 viral load leading to impaired types I and III interferon responses (7,9). Clinical signs of PIMS-TS resemble that of KD. In their review of 21 children with PIMS-TS, Toubiana et al. noted the fulfillment of diagnostic criteria for KD in all of their cases while Feldstein et al. reported overlapping features of KD with PIMS-TS in 43% of patients (10,14). In PIMS-TS with presentations mimicking KD, treatment with IVIG, and aspirin should be initiated (12). The mean age at presentation of PIMS-TS is eight years with males, and black children disproportionally affected. The commonest presentations are fever (99%), gastrointestinal (86%) and cardiovascular symptoms (80%). Children with isolated KD (not associated with SARS CoV 2) are younger with a peak age at presentation being 18 – 24 months, and manifest with myocarditis less frequently (< 5%) while gastrointestinal symptoms frequently occur in both PIMS-TS and KD (11,12).

The syndrome is postulated to be due to a post-viremia hyperinflammatory response and as such, a recent COVID19 diagnosis is more likely to be made with serologic tests rather than RT-PCR tests. A study from the United Kingdom (U.K.) showed that of a cohort of 78 children with PIMS-TS, only 17 tested positive for RT-PCR from nasopharyngeal and oropharyngeal samples while 33 and 35 respectively had positive IgM and IgG (8).

SARS-CoV-2 serologic tests show no cross-reactivity with other respiratory viruses and are better diagnostic tests for acute (positive IgM and IgG) and resolved (negative IgM and positive IgG) beyond five days of illness (13). Elevated inflammatory markers are a hallmark feature in PIMS-TS, with 92% of affected children having high ESR, C-reactive protein, or procalcitonin levels (14). While coronary aneurysms are a recognized complication of KD, they are infrequently seen in PIMS-TS.

Only three children of a total 58 presenting with PIMS-TS in the U.S. were found to have coronary aneurysms on Echocardiography (15).

A large proportion of children may need ICU care with mechanical ventilation rarely needed. Mortality due to PIMS-TS is rare, with death rates of 0 – 2.5% recorded among cohorts in Italy, the U.S., U.K., Switzerland, and France and average length of admission of 7 days (8,10,14-17).

The foundation of treatment for PIMS-TS is immune -modulation with IVIG being the preferred therapy among many reports (8,10,14-17). Other treatment options used with less frequency include corticosteroids, interleukin 6 inhibitors (Tocilizumab), interleukin 1 receptor antagonist (Anakinra) and anti-TNF inhibitors (Infliximab) (14-15, 18).

Our patient was successfully treated with IVIG alone with clinical and echocardiographic resolution and with his inflammatory markers subsiding to normal levels. He did not require respiratory support or inotropes. Accessing IVIG is difficult in Ethiopia and when available, it's expensive. Corticosteroids like Methylprednisolone were used in 31 – 80% of cohorts of PIMS-TS globally (8,10,14-17) and adding steroids to IVIG was associated with recovery of cardiac function in PIMS-TS according to one report (19). In the absence of alternatives, steroids alone should be used to treat PIMS-TS in addition to supportive care.

In conclusion, we are reporting the first case of Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) from Ethiopia as a useful communication to manage similar cases amidst the ongoing COVID19 pandemic.

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Competing of interest

The authors report no conflicts of interest.

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