Case Report

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Multisystem Inflammatory Syndrome In Children (MIS-C) with Seropositivity for Scrub Typhus and Leptosipra: A Case Report

Bibechan Thapa[1], Prabha Devi Chhetri[1], Sagun Ghimire[2]

[1]Department of Pediatrics, KIST Medical College and Teaching Hospital, Mahalaxmi-1, Lalitpur, Nepal

[2]Medical Student, KIST Medical College and Teaching Hospital, Mahalaxmi-1, Lalitpur, Nepal

ABSTRACT

Multisystem inflammatory syndrome in children (MIS-C) is rare phenomenon that presents after corona virus disease 2019 (COVID-19). According to The Centres for Disease Control and Prevention, one important criterion in diagnosing MIS-C is to exclude other obvious microbiological causes. An 11-year-old boy presented with septic shock, elevated inflammatory markers and multisystem dysfunction. He had antibodies to SARS-CoV-2, Scrub typhus and Leptospira. The patient was initially treated with antibiotics, and other supportive treatments. Patient clinically improved before confirmation of MIS-C thus immunoglobulin and steroid therapy was not instituted. Diagnostic criteria of MIS-C includes absence of other alternative plausible diagnoses but in an endemic area for tropical febrile illness like Nepal, there is the possibility that MIS-C can co-exist with other infectious condition. Therefore there is need of re-evaluation of diagnostic criteria of MIS-C.

Keywords: Co-infection; COVID-19; Leptospira; MIS-C; Scrub typhus

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Correspondence:

Dr. Bibechan Thapa

KIST Medical College and Teaching Hospital, Imadol, Lalitpur, Nepal

Email:bibechanthapa@gmail.com,

Mobile:+977-9841606316

https://orcid.org/0000-0002-4783-6572

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection despite being aggressive in certain groups, is typically mild and often asymptomatic in children.[1, 2] However, a rare phenomenon described as the multisystem inflammatory syndrome in children (MIS-C)[3, 4] can occur which predominantly affects children around 8.6 years.[4]

MIS-C ranges from mild illness to severe involvement of two or more organ systems with shock, with laboratory evidence of inflammation and laboratory or epidemiologic evidence of SARS-CoV-2 infection.[2,3]Severe physiological impairments necessitating an intensive care (ICU)is observed in the majority.[4] A surge in MIS-C has raised questions about the unique effects of SARS-CoV-2 in children.[5] The relationship of MIS-C to SARS-CoV-2 infection suggests that the pathogenesis involves post-infectious immune dysregulation.[3] However the inflammatory response in MIS-C differs from the cytokine storm of severe acute COVID-19.[2] Here, we report a child with typical features of MIS-C but had seropositivity for Scrub typhus and Leptospira.

CASE REPORT

An 11-years-old male child presented to outpatients (2021/01/17) with fever and neck swelling for five days. There were no other localising symptoms and signs and the vitals were normal. He had history of exposure to corona virus disease 2019 (COVID-19) positive individual but reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 was negative. Ultrasonography (USG) of neck showed significant cervical lymphadenopathy (largest node 17mm X 8.7mm) which was thought to be reactive lymphadenitis secondary to bacterial infection. Hence child was prescribed Cloxacillin empirically but the fever persisted even after five days of the oral antibiotic.

Subsequently, he developed new symptoms: myalgia, headache, mild pain abdomen, anorexia, occasional vomiting with persistence of cough however the cervical lymph nodes had decreased in size. There was no history of chest pain, shortness of breath, or rashes. He was toxic looking, febrile, and had tachycardia, tachypnea and blood pressure less than third percentile (80/50 mmHg) for his age and sex. He also had decreased urine output for past 24 hours and warm peripheries. There was epigastric tenderness and tender hepatomegaly (liver palpable 5cm below subcostal margin with span of 14cm). There were no signs of meningeal irritations nor splenomegaly. The child was admitted to an ICU with septic shock (differential diagnosis; enteric fever, bacterial sepsis, MIS-C). He was resuscitated with fluids and nor-adrenaline support (0.1mcg/kg/min) following which blood pressure stabilized. He was treated with Meropenem 20mg/kg /dose (8 hourly) in view of severe sepsis and Azithromycin (20mg/kg) to cover rickettsial diseases empirically.

There was leucopenia (3200/cumm with neutrophil 57% and lymphocyte 43%), with normal haemoglobin and platelets. Repeat RT-PCR for SARS-CoV-2 was negative. Chest X-ray showed infiltrates on lower zone of right lung. Liver function was deranged (bilirubin total 1.8 mg/dl, bilirubin direct 1 mg/dl, aspartate aminotransferase 522 IU/L, alanine aminotransferase 371 IU/L) however renal function test, prothrombin time and international

normalized ratio was normal. The inflammatory markers:C-reactive protein (CRP) (156.34 mg/L), erythrocyte sedimentation ratio (ESR) (11mm/hr), procalcitonin (3.78ng/ml), D-dimer (8.2 ug/dl), serum ferritin (950ng/ml) and lactic acid dehydrogenase (LDH) (1719 IU/L) were all elevated. Serum Anti SARS-CoV-2 total antibody serum was detected (41.31 COI), which with other features confirmed diagnoses of MIS-C. The child had persistent epigastric pain with tenderness but serum amylase was normal (63 IU/L) and USG showed only thicken gall bladder wall. The child had intermittent episodes of asymptomatic bradycardia which resolved spontaneously. Electrocardiography and creatinine phosphokinase myocardial band was normal. Echocardiography showed normal left ventricular function and normal coronaries. Blood and urine cultures was negative. The child had persistent high grade fever for 3 days refractory to antipyretics therefore tests for tropical illness were sent. Malaria and dengue were negative. The child improved clinically after fourth day. Inotrope was gradually tapered. The child became afebrile and inflammatory markers were normalized by the time the report of serum Anti SARS-CoV-2 total antibody test was received. Therefore, immunoglobulin or steroids therapy was not instituted, moreover echocardiography was normal. Similarly reports for Scrub typhus and Leptospira was received after significant clinical improvements. Scrub typhus IgM (immunoglobulin) serum (ELISA-enzyme-linked immunosorbent assay) was positive (4.2 U/ml) and Leptospira IgM serum (ELISA) was positive (16 U/ml). Further interventions was not carried out as patient was already being treated with Azithromycin and was clinically better. The child was discharged on tenth day of admission and followed up closely for three month. Repeat echocardiography was normal. Child didn't showed any residual effects, though chest computerized tomography (CT) scan was never done.

DISCUSSION

The Centres for Disease Control and Prevention (CDC) has provided a case definition for MIS-C and one of the criteria is that there should be no other alternative plausible diagnoses.[6]

Our case was 11-year-old boy with high grade fever and elevated inflammatory markers. He had dysfunction of cardiac (tachycardia and hypotension requiring inotrope support), gastrointestinal (loose stool, vomiting, and severe abdominal pain), respiratory (tachypnea, cough), and renal system (decrease urine output) thus was admitted in ICU. Our patient had detectable antibody for SARS-CoV-2 however, IgM for Scrub typhus and Leptospira were also positive. In diagnostic criteria of MIS-C, one important criterion is to exclude other obvious microbiological causes. But in our patient, it was a diagnostic dilemma as all the criteria were met except for absence of other microbiological causes. Should diagnosis of MIS-C be completely discarded based on the given definition and treatment only focused on alternate infectious condition? Or was this case incidental co-infection? Or this was case of false seropositivity with Scrub typhus or Leptospiral antibodies. Therefore focusing in treating MIS-C is a clinical and circumstantial challenge. Could this clinical condition be attributed to serological cross-reactivity, incidental co-infection, or perhaps signifies serological positivity of Scrub typhus and Leptospira in endemic regions that poses unique challenge of differentiating and managing these disease entities together.

There are no literature that advocates cross-reactivity of MIS-C with Scrub typhus and Leptospira therefore it can't be said with certainty that this was the case of cross-reactivity. But cross-reactivity between the dengue virus and SARS-CoV-2 has been reported to be possible and has been attributed to false-positive serology among COVID-19 patients and vice versa.[7] Serological cross-reactivity between SARS-CoV-2 and Zika virus was also observed. [8]

An Indian guideline suggest possibility of co-infection of COVID-19 with Scrub typhus, Leptospira, Chikungunya, Dengue, Malaria and even bacterial infection.[9] If co-infection with COVID-19 is possible then why should we not consider same in MIS-C? Can co-infection with COVID-19 result into MIS-C with persistence of antibodies for infectious condition like Scrub typhus and Leptospira. These seasonal epidemic-prone diseases, may all present as a febrile illness, with symptoms mimicking COVID-19 [9], and they also have multisystem manifestation thus may also mimic MIS-C which also presents as febrile illness.

As Nepal is an endemic region for tropical and shares border with India, Indian guideline can be adapted in absence of local guideline. Therefore MIS-C should be considered when symptomology similar to tropical febrile illness appears.[10] In an seroprevalence study in India which is also endemic region for similar tropical illness like Nepal, among 91 COVID-19 seropositive patient, 11 has co-infections of which 5 had co-infection with Scrub typhus. Among 44 seropositive MIS-C, 11% (5) had co-infection. [11]

It is paramount to be familiar with MIS-C owing to its severity and consider it as differential diagnosis, even in cases where classic diagnostic criteria are not initially fulfilled.[12] This case report aims to showcase that MIS-C may mimic a more routine diagnosis. Pediatricians in developing countries need to be aware of the overlapping feature of MIS-C with tropical fevers in order to early recognize and treat the condition.[10]

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