Case Study

MULTI-SYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C) WITH COVID-19 INFECTION IN BANGLADESH: A CASE REPORT

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INTRODUCTION

An outbreak of pneumonia of unknown etiology developed in Wuhan of Hubei Province, China in December 2019.[1-3] Chinese scientists reported on 7th January, 2020 that the outbreak was caused by a novel Coronavirus, Severe Acute Respiratory Syndrome-related coronavirus 2 (SARS-CoV-2) and the disease is now termed as Coronavirus Disease 2019 (COVID-19).[4] In response to the rapid development of the outbreak on January 30, 2020, WHO declared a public health emergency of international concern (PHEIC) and was declared as pandemic on 11 March 2020.[5]

A surprising feature of the disease is that children might be immune from the worst of it, although the global coronavirus crisis worsens in adult.COVID-19 has affected old age persons particularly those with chronic comorbidities.[6] The initial stage of the COVID-19 epidemic has mainly affected adults usually older than 15 years.[6, 7] Fewer infections with COVID-19 in children have been reported. In Bangladesh 3% of children <10 years were identified as COVID-19 positive.[8] The reason behind this could be lower risk of exposure or less notification due to asymptomatic or mild manifestation of the disease, rather than resistance to infection.[9]

A new COVID-19 related clinical syndrome, with hyper-inflammatory manifestation as like Kawasaki disease (KD), recently noticed in children. Few children had clinical manifestation of toxic shock syndrome, myocarditis or cardiogenic shock. Clinical reports have recently been published from the United States[10], Italy[11], the United Kingdom[12], France and Switzerland[13] and the Center for Disease Control (CDC) has issued an emergency.[14] In May 2020, Evercare Hospital in Dhaka first reported MIS-C in children in Bangladesh.[15]

Clinical manifestations of COVID-19 are variable. Various publications have reported following clinical manifestations, significant respiratory symptoms, gastrointestinal (GI) symptoms, cardiac involvement, rash, red eyes, and oral mucous membrane changes. A number of nomenclature have been used to identified this clinical syndromes such as "Kawashocky", "Coronasacki", hyper-inflammatory shock in children with COVID-19, Pediatric COVID-19 Associated Inflammatory Disorder (PCAID), Pediatric Multisystem Inflammatory Syndrome (PMIS) and Multisystem Inflammatory Syndrome in Children (MIS-C). This may be due to a primary complication of infection with SARSCoV-2 or post-infectious complication. The initial epidemiologic presentation is highly suggestive of a correlation. We categories this clinical syndrome herein as MIS-C, the moniker adopted by the CDC. CDC classified Multisystem Inflammatory Syndrome in Children (MIS-C) as: An individual aged <21 years presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); and no alternative plausible diagnoses; and positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, antigen test or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.[14]

CASE

Master X, a 3 year old child got admitted in Dhaka Shishu (Children) Hospital, a Covid dedicated tertiary care hospital with high grade continuous fever for 5 days & breathing difficulty for 1 day. Family resides in Gajipur district which is endemic for COVID-19. His father is a garments worker & had history of COVID-19 infection 2 weeks back. The child was febrile, dyspneic, having chest retraction, tachypnea, tachycardia with normal heart sound. Breath sounds were vesicular with crepitation over both lateral chest walls. Liver was just palpable. He was diagnosed as a case of suspected COVID-19 infection with pneumonia.

Laboratory investigation showed leucocytosis with lymphopenia and thrombocytopenia, raised CRP, CXR revealed bilateral patchy opacities over lung fields.[Fig-2] Initial nasopharyngeal swab for RT-PCR for COVID-19 was negative. After 3 days of antibiotic treatment the child was still febrile, toxic, developed puffy eyelids and leg edema. Repeat investigations showed leucocytosis with lymphopenia and thrombocytopenia, raised CRP, hypoalbuminemia, raised ALT, urine albumin was nil. After 7 days of antibiotic treatment the child was still febrile, developed erythematous rash, conjunctival congestion, redness over tongue. Lab investigations re-evaluated which showed raised LDH, hyperferritinemia and raised D-Dimmer. Color Doppler Echocardiogram revealed prominent dilated coronaries with perivascular brightness involving LMCA, LAD and LCX suggestive of Kawasaki disease.[Fig-3]

Fig-1: Master X having strawberry tongue

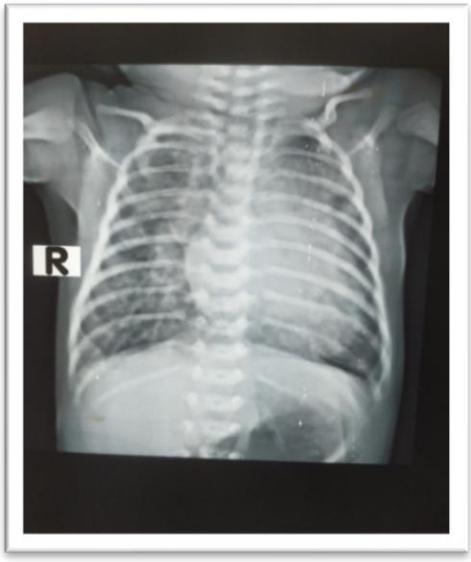

Fig-2: CXR showing cardiomegaly with bronchopneumonia.

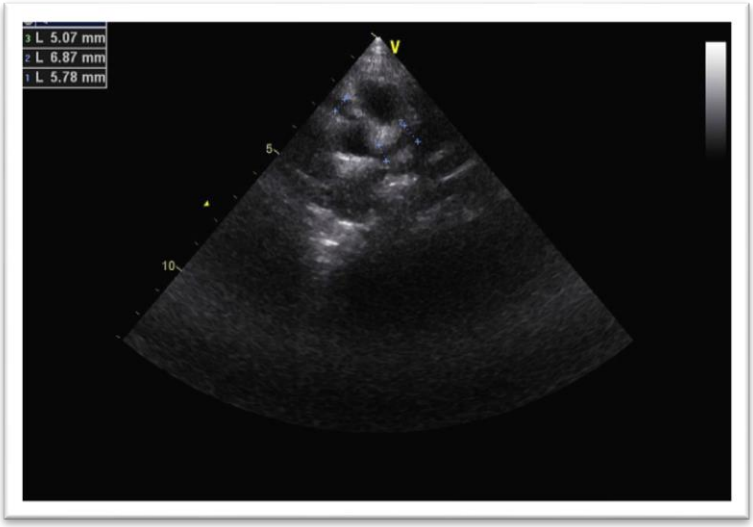

Fig-3: Echocardiogram revealed prominent dilated coronaries with perivascular brightness involving LMCA, LAD and LCX suggestive of Kawasaki disease

Then nasopharyngeal swab for RT-PCR for COVID-19 infection was repeated and found to be positive. The child was finally diagnosed as COVID-19 infection with MIC-S. IVIG was started at a dose of 2gm/kg along with oral antiplatelet. His condition gradually became stable 2 days after starting IVIG. When asymptomatic, he was discharged from the hospital after two subsequent nasopharyngeal swab samples became negative by PCR. We suggest for home quarantine for the next 14 days and advice for follow-up Echocardiogram after 1 month.

DISCUSSION

In April 2020, a group of children with hyper-inflammatory syndrome, features consistent with Kawasaki disease and toxic shock syndrome was reported in England. Although the signs and symptoms of these patients were temporally associated with COVID-19 but presumed to have developed 2-4 weeks after acute COVID-19 infection. All of them had serologic evidence of SARS-CoV-2 infection. The initial clinical manifestation includes breathing difficulty, loose stool, fever, rash, conjunctivitis, peripheral edema, shock, and elevated markers of inflammation and cardiac damage.[12] On May 14, 2020, CDC published an online Health Advisory that summarized the manifestations of reported multisystem inflammatory syndrome in children (MIS-C), outlined a case definition, and asked clinicians to report suspected US cases to local and state health departments.[14] A total 570 US MIS-C patients who met the case definition had been reported to CDC by July 29.[16] Our case fulfills the suggested case definition.

Close contact with person outside the family with COVID-19 infection was rarely published; among affected children, 67.3% (113/168) had at least one parent who was tested positive for SARS-CoV-2 infection.[17] Our case has history of contact with his father who had recent COVID-19 infection. Most of child with SARS-CoV-2 infection developed fever, myalgia, cough, respiratory distress or gastrointestinal symptoms at the onset of the illness. The novel coronavirus infection mostly presents with mild symptoms in children; however, in few cases developed fatal consequences.[18] Our case also presented initially with fever, coughs and then developed breathing difficulty.

Variable clinical signs and symptoms at initial evaluation reported in MIS-C patients, but most of them had features of shock, myocarditis, gastrointestinal and clinical features that overlapped with Kawasaki disease. Sometimes difficult to distinguishing cases from those with classical Kawasaki disease.[11] Increases in COVID-19 incidence resulting in more notification of MIS-C which is usually notched 2-4 weeks after acute SARS-CoV-2 infection.[19] Rarely the child with coronavirus infection may developed generalized edema and

hypoalbuminemia.[20] Our case also presented at 2nd week of infection and during hospitalization also developed edema and hypoalbuminemia.

A cytokine storm syndrome (CSS) develop in response to the virus in some critically ill children which is characterized by an excessive production of pro-inflammatory cytokines such as TNF, IL-6, and IL-1β which results in clinical features of fevers, rashes, coagulopathy, shock, myocarditis, multiorgan failure and death.[21] Laboratory investigation revealed thrombocytopenia, lymphopenia, raised transaminase levels, D-dimmers, lactate dehydrogenase (LDH), coagulation times, CRP, and ferritin. This clinical syndrome and laboratory abnormalities are very close to macrophage activation syndrome (MAS) or secondary hemophagocyticlymphohistiocytosis (HLH).[22] Our child had elevated liver enzymes, D-dimmers, CRP, LDH and hyperferritinemia.

Children diagnosed as KD rarely reported to develop shock or myocarditisprior to the COVID-19 pandemic.[23] Cardiac involvement in KD usually present with coronary artery dilatation with perivascular brightness, thrombus in the coronary artery or aneurysm formation and rarely with ventricular dysfunction. Several authors published MIS-C with COVID-19 cases presented with myocarditis, coronary artery involvement, AV valve regurgitation and pericardial effusions.[10, 13, 24] Early reports of MIS-C suggest that the child with classic criteria of KD generally had less myocardial manifestation and usually respond promptly to care directed at KD.[25] Our patient had some clinical, laboratory as well as echocardiographic evidence of cardiac involvement in the form of coronary dilatation with perivascular brightness with loss of distal tapering.

Use of adjuvant therapies like intravenous immunoglobulin (IVIG), corticosteroids, anakinra (an interleukin-1 receptor antagonist), and to cilizumab (an anti-interleukin-6 receptor monoclonal antibody) has been reported to treat COVID infection with MIS-C presenting with hyper-inflammatory condition and KD-like clinical manifestation. Teresa et al26 suggest to give IVIG 2 g/kg and aspirin 20-25 mg/kg/dose every 6 hourly (80-100 mg/kg/day) for all patients with evidence of hyper-inflammatory syndrome such asferritin >700 ng/ mL, CRP >30 g/dL, or multi organ failure or myocarditis or KD like manifestation. We gave IVIG 2g/kg along with aspirin 80 mg/kg/day and there was significant clinical improvement after starting anti-inflammatory therapy.

Differentiating MIS-C from acute COVID-19 is critical. As the COVID-19 pandemic continues, awareness of MIS-C among health care provider along with clinical and laboratory suspicion will help early diagnosis, early treatment and successful outcomes.

CONCLUSION

There is a growing concern over emerging cases of MIS-C worldwide. The children with COVID-19 associated MIS-C can deteriorate quickly, so high index of suspicion and early intervention could be effective to save lives.

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