Kawasaki disease like presentation of Multisystem inflammatory syndrome in children - A Case report

Dr Gargi H Pathak[1], Dr Anuya V Chauhan[2], Dr Priyanka Goswami[3*]

[1] Professor and Head of the unit, Department of Pediatrics, BJMC
[2] Assistant professor, Department of Pediatrics, BJMC
[3] Third year resident , Department of Pediatrics, BJMC

Corresponding Author: Dr Priyanka Goswami

Email: goswamipriyanka1993@gmail.com

Abstract

A new COVID-19 related clinical syndrome in children called Multisystem inflammatory syndrome in children (MISC) has been reported, with significant inflammation and similarities to Kawasaki disease (KD) with concurrent SARS-CoV-2 in Europe and in USA since 7 April 2020. On 25th April, concerns were initially raised in the United Kingdom regarding a cluster of children of various ages, presenting with a Multisystem inflammatory state who required intensive care, and who all displayed "overlapping features of toxic shock syndrome and atypical Kawasaki disease with blood parameters consistent with severe COVID 19 in children. Clinical presentations were variable, with significant gastrointestinal (GI) symptoms, cardiac disease, mild or absent respiratory symptoms, and variable incidence of rash, red eyes, oral mucous membrane changes. Later on this was diagnosed as part of a post covid Multisystem inflammatory disease (MISC). We report one patient admitted in Civil hospital, Ahmedabad with high grade fever for more than three days along with manifestations of multisystem disease involving cardiovascular system with myocarditis,and gastrointestinal system in form hepatitis, widespread blanchable rashes and respiratory distress due to pleural effusion.The clinical features had similarly to features of Kawasaki disease. Patients also had raised inflammatory markers in form of increased CRP, ESR, PT, APTT. Covid IgG antibody was found positive and patient was treated as per MISC protocol with steroid, IVIG and aspirin together with proper supportive management in form of oxygen through High flow nasal cannula and ionotropes for shock. Multiple theories on pathogenesis have been suggested in form of Antibody dependent enhancement precipitating kawasaki like illness due to cytokine storm provoked by type 1 and 3 interferon. Role of STING (Stimulator of interferon gamma) pathway has been found to be involved in MISC. With proper treatment as per protocol it is possible to successfully discharge patients with MISC admitted in decompensated states.

Keywords: MISC, Kawasaki, steroids, PIMS-TS, blanchable rashes, COVID 19 antibody

Introduction

A hyperinflammatory syndrome with multiorgan involvement similar to Kawasaki disease shock syndrome was reported in the Lancet which was given nomenclature of MIS-C: Multisystem

Inflammatory Syndrome in Children. Till now almost 3000 cases of MIS-C have been reported.As this is an emerging condition, a number of other names have been used like, "Kawashocky", "Coronasacki", hyperinflammatory 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) The pathogenesis [1] is unknown. SARS-CoV-2 could have one of several roles; it could act as an environmental trigger for the condition either directly or indirectly (by somehow paving the way for a different trigger).

As with Kawasaki disease[2], antibody dependent enhancement whereby development of antibodies could facilitate viral entry into host cells, has been proposed as a memechanism. A post-infectious mechanism seems likely, possibly coinciding with the development of acquired response to the virus. The ability of coronaviruses to block type I and type III interferon responses could help explain a delayed cytokine storm in children whose immune systems struggle to control SARS-CoV-2 viral load. Hyperimmune response could involve early viral triggering of macrophage activation, followed by T helper cell stimulation, leading to cytokine release, stimulation of macrophages, neutrophils,in conjunction with B cell & plasma cell activation,and antibody production. The frequent GIT presentation and mesenteric lymph node inflammation are due to SARS-CoV-2 replication in enterocytes. Association of Kawasaki-like disease with COVID-19 could support the view that SARS-CoV-2 can cause systemic vasculitis by targeting endothelial tissue via angiotensin converting enzyme2 (ACE2). A role of the STING pathway (stimulator of interferon-gamma) encoded by TMEM173 (transmembrane protein) and expressed in alveoli, endothelial cells, and spleen may be also involved

Case report

Case: A 4.5 year old male child presented to our institute with complaint of high grade, intermittent fever for 8 days associated with difficulty in breathing with severe subcostal indrawing, gradually increasing in severity for 7days. Patient had rashes all over the body, maculopapular,blanchable and involving palms and soles. He also had complaint of increased frequency of stool 6-7 times a day with colicky abdominal pain around epigastrium for 3 days.Patient had no past history of any hospitalization or any chronic disease and neither had any history of covid contact. Patient was initially taken to some private hospital and some intravenous injections given and referred for further management to our institute.

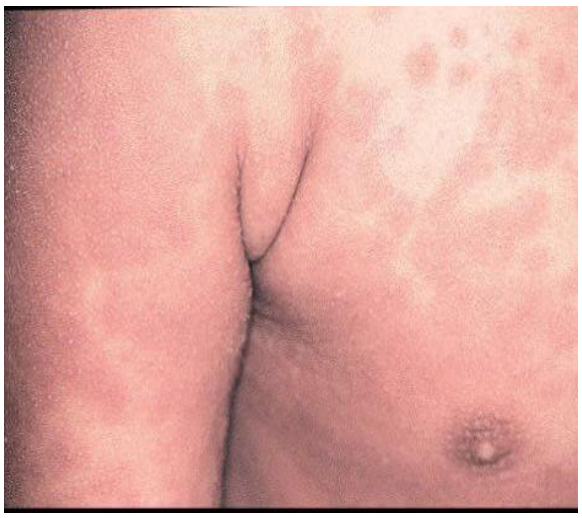

Figure 1: Rash in the MISC patient

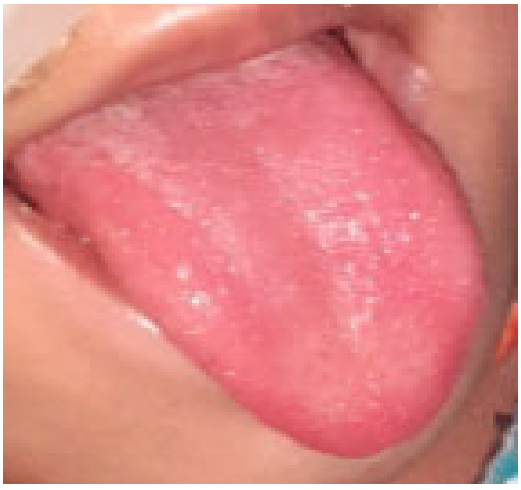

Figure 2: strawberry tongue in case of MISC

On examination the patient was irritable, but conscious with a low volume, thready pulse with cold peripheries. Patient had hypotension with blood pressure of 80/54 mm of Hg that was less than 50th

centile. Patient was having severe respiratory distress and impending respiratory failure with respiratory rate of almost 90/min and spo2 of 70% on room air. Generalised edema with blanchable maculopapular rashes were documented with features of mucosal ulceration in mouth, bilateral conjunctival congestion and strawberry tongue. Per abdominal examination suggested mild distension with dull percussion note and shifting dullness suggestive of ascites. Investigations were sent which revealed moderate normocytic normochromic anemia with Hemoglobin of 7.8 gm/dl, total counts 16,500/mm³ with differentials of neutrophils and lymphocytes were 45/54, Plateletes 1,32,000/mm³. Patient had elevated levels of D-Dimer 5.606ug/ml (0.2-0.7ug/ml), fibrinogen 482mg/dl (150-370mg/dl), CRP 23, 66 mg/dl (0-2.4mg/dl) and procalcitonin >100ng/ml(0-5 ng/ml), ESR 58mm/h(upto 25mm/h). PT, APTT, INR, RFT AND LFT were normal. Cardiac markers were elevated with troponin I 200.20 pg/ml (upper reference limit of 25pg/ml). Dengue NS1 and IGM and Covid 19 RTPCR were negative.In view of elevated markers in form of fibrinogen, D-Dimer, CRP, ESR, cardiac markers in our patient a diagnosis MISC was considered. Patient's CXR showed cardiomegaly with bilateral pleural effusion. For persistent tachypnea pleural fluid tapping was done which was serous in nature.2DECHO revealed LVEF of 55% with mild LV dilatation and mild pericardial effusion. Blood culture was negative. Finally with clinical picture satisfying criteria of MISC with rashes, hypotension,coagulopathy in form of altered D-dimer , myocarditis and elevated inflammatory markers -Covid 19 IgG antibody titre was done which showed a value of >183mg/dl(upper limit upto 20mg/dl) which confirmed diagnosis of MISC.

Patient was treated thereafter as per protocol of MISC. Taking the severe respiratory distress in view patient was put on High flow nasal cannula with adequate head end elevation and cardiac bed. Injection IVIG was given at dose of 2g/kg as per recommendation and MPS started at pulse therapy of 10mg/kg/day with coverage of higher antibiotic. Ionotropes were started for shock but total fluid restriction was done in background of acute myocarditis and impending cardiac failure. Later on oral furosemide was started to prevent congestive failure. Patient was also put on aspirin in view of cardiomyopathy at 3mg/kg/ day. Gradually the patient improved over 2-3 days, and was successfully discharged after 20 days of hospital stay and regular follow up done.

For considering MISC, we ruled out dengue by a dengue IGM and NS1 test, blood culture of the patient was negative ruling out any sepsis, masquareding as MISC and above all a positive high titre of covid antibody turned supportive to stamp the diagnosis of MISC.

Patient was thereafter followed up in OPD regularly at 2 weeks interval. Follow up echocardiogram done was suggestive of improvement as well.

Discussion

In MISC different types of presentations have been described with Kawasaki like presentation (35%), ARDS like picture (35%), GIT manifestations, toxic shock syndrome like features, some patients may have thrombosis as well.

Diagnostic Criterias (By AAP and MOHFW) of MISC[3] Initially CDC designed the diagnostic criteria which was later on adapted by American academy of pediatrics and also by Ministry of health and family welfareelfare of India.

The diagnostic criteria are as follows-

Fever since >3 days in children of 1-18years AND two of the following-

- Rashes or bilateral nonpurulent conjunctivitis, mucocutaneos inflammation signs (hands, foot, oral)
- Hypotension or shock
- Features of myocardial dysfunction
- Evidence of coagulopathy (by PT, APTT, elevated D Dimer)
- Acute GIT problems (diarrhoea, nausea, vomiting)
  And
- Elevated markers of inflammation such as ESR, CRP or PCT.

And

- No other obvious signs of bacterial disease or staphylococcal infection

And

- Covid 19 RTPCR positive or RAT positive or covid 19 antibody titre elevated.

The patient admitted under our care was having a high grade fever more than three days as well as rashes, gastrointestinal involvement, cardiomyopathy and covid antibody positive which fitted the diagnostic criteria of MISC.

MIS-C/PIMS-TS is a systemic disorder involving persistent fever, extreme inflammation (hyper-inflammation), and organ dysfunction, which is temporally associated with exposure to COVID-19. Onset may be delayed or contemporary with ongoing SARS-CoV-2 infection, which may pass without symptoms. The time the syndrome takes to appear following the initial viral infection is debated, though it may develop between the first and second week. Epidemiological data suggest that recognition of the disease may typically be delayed by 2–6 weeks, and usually by 3–4 weeks. By the time of presentation children have often developed antibodies to SARS-CoV-2, but test negative for the virus by RT PCR.

The condition may match some or all of the diagnostic criteria for Kawasaki disease[4,5] i.e. the 'complete' or 'incomplete'/'atypical' subtypes or for Kawasaki disease shock syndrome. It can a share clinical features with other inflammatory conditions toxic shock syndrome, and secondary macrophage lymphohistiocytosis syndrome .In contrast to covid 19 infection most children have gastrointestinal symptoms,muscle pain and tiredness of various severity which was seen in our patient. Some Kawasaki like symptoms in children of less than 5 years include mucosal changes[6] around mouth (strawberry toungue, cracked lips etc), red eyes, widespread rashes (consistent with leucocytoclastic vasculitis), red or swollen hand or feet and enlarged lymph nodes A similar clinical presentation was seen in our patient. Features of meningitis with severe headache as well as encephalopathy, stroke, Guillian Barre syndrome have also been documented.[7] Cardiovascular involvement with Acute heart failure is common in the form of LV dysfunction and a LV ejection fraction under 60%. Shock is often of myocardial– mainly left ventricular – origin. Cytokine storm including extremely high serum interleukin6 (IL-6) levels,] are seen and patient need ionotropic support to maintain cardiac output. Coronary artery abnormalities, such as dilatation and aneurysms are common. Other features include valvulitis, pericarditis and pericardial effusion. Echocardiographic and ECG features of myocarditis (inflammation of the heart muscle) have been recorded. Our patient had blanchable maculopapular rashes with mucosal ulceration in mouth, bilateral conjunctival congestion, strawberry tongue, red and swollen palms and soles, which was consistent with a Kawasaki disease like presentation of MISC.

Conclusion

The diagnosis and treatment of MISC may be challenging but proper management according to protocol can change the clinical course and lead to a positive outcome. With the vaccination in children of 12-18years age group, there remains a bright hope to encounter a falling trend of this disease.

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