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Case Report

Old wine in new bottle

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ABSTRACT

For the last one and half years, COVID-19 pandemic has become a medical challenge all over the world. Patients fulfill criteria for Kawasaki disease in a substantial proportion of cases. MIS-C tends to occurr in previously healthy patients. MIS-C tends to affect black and Hispanic individuals. On the other hand Kawasaki disease tends to affect more of Asian population. The author reports a case of post COVID MIS-C in a 13 years child who presented with fever for 4 days and hypotension. Physical examination revealed left sided lymphadenopathy in neck, tachycardia and tachypnea. Investigations showed elevated CRP, ESR, D-dimer, PT-INR, ferritin, procalcitonin, very high antibody titer of SARS COV-2 IgG and low platelet count. Patient was treated with IV methylprednisolone, IV immunoglobulin, IV meropenem, SC enoxaparin and Tab aspirin. His condition gradually improved, BP normalised, and heart rate decreased and fever subsided. This case report emphasises that early recognition and concomitant treatment of COVID related MIS-C can enhance good outcome and negate potentially life threatening complications.

1. Introduction

The SARS-CoV-2 (COVID-19) pandemic has emphasised a huge range of clinical features, ranging from asymptomatic patients on one spectrum to acute respiratory distress syndrome and death on the worst spectrum. Disease severity is however less in pediatric populations.

A new terminology affecting younger patients with COVID-19, multisystem inflammatory syndrome in children (MIS-C), has been defined recently.[1] The clinical conundrum of MIS-C is manifested by an unopposed inflammation which may move on to multiorgan failure. Young patients with MIS-C present with persistent pyrexia (100%), conjunctival inflammation (68%), rash (45-76%), increased inflammatory markers (100%), coagulation disorders (100%), gastric and intestinal complaints (60-100%), acute kidney injury (8-52%) and cardiac abnormalities (51-90%).[2] The relation between multi system inflammatory syndrome, Kawasaki disease and macrophage activation syndrome points MIS-C to be linked to SARS-CoV-2 infection.[3] The multiinflammatory disease in children associated with COVID-19 infection occurs weeks after infection and may go unnoticed.[4] although the side effects of COVID-19 in adult patients are recognised, the outcome quality in paediatric patients have become apparent.[5]The initial reports came from United Kingdom in April 2020.[6,7] Gradually countries such as European nation, Canada, US and Africa started reporting with few case reports from Asia and China inspite of increased COVID-19 burden.[8]Literature suggests. Patients with MIS -C have IgG with increased propensity to stimulate monocytes, T cell lymphopenia and more CD8+ T cell activation.[9]Most patients have COVID-19 negative polymerase chain reaction (PCR) reports but have positive serology, supporting the hypothesis that the disease process is controlled by dysregulation of immune

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system days to weeks after infection have subsided. Few patients do have positive PCR testing. The background of cardiac injury in MIS-C are include inflammatory cascade, stress related cardiomyopathy, coronary ischemia and acute virus driven myocardial injury.[10]The differential diagnosis of MIS-C include acute COVID-19, bacterial infection, hemophagocytic lymphohistiocytosis, systemic lupus erythematosus, toxic shock syndrome and vasculitis. Treatment involves supportive care, aspirin, low molecular weight heparin to selected patients, antibiotics, intravenous immunoglobulin, and glucocorticoids in moderate to severe cases. Patients should be risk stratified and strict follow up protocols should be adopted for weeks after clinical recovery.

The documentation of positive COVID virus antigen by PCR, testing for antibodies or report of close contact with a patient diagnosed with COVID-19 helps differentiate MIS-C from other diseases. Patients suffering from moderate to severe diseases are benefitted from intensive care support and by treatments targeted to specific part of virus or malregulated immunity affecting positive outcomes.

Physicians are knowing gradually regarding the spread of MIS-C as the incidence rises, which has emphasised on global interaction to define the disease and risk factors associated with poor outcomes. We have tried to present the case report of MIS-C where the patient was thought of as a case of septic shock during emergency admission in a way to help health care providers to be very updated and be cautious regarding the diagnosis in order to rule in or out the disease at the very early presentation.

2. Case Report

A seemingly well to do,13 yrs old Indian boy, residing in Sonarpur, 24 PGs (south), West Bengal, presented to emergency department of Ramakrishna Mission Seva Pratisthan with fever unresponsive to antipyretics and doxycycline (prescribed outside by local physician) for 4 days. There was no history of any other symptoms at that point of time. There was a preceeding occurence of fever one month back which subsided spontaneously within 1-2 days. No history of headache, oral ulcers, retroorbital pain, cough, shortness of breath, dysuria, abdominal pain, polyarthritis or recent travel were present. No history of recent vaccination. Family history was insignificant also. Physical examination showed hypotenstion (BP 80/60 mm of Hg), multiple, tender lymph nodes in left posterior triangle of neck and elevated temperature (103^0F). Thorough clinical examination was negative for any eschar, conjunctivitis, muco-cutaneous inflammation (oral, hands or feet). No signs of cardiac dysfunction like pedal oedema, elevated JVP, lung crepitations were present.

Patient was initially admitted in general ward, but later was shifted to intensive care unit due to progressive hypotensionAs per the rules prevailing in hospital as per national guidelines we tested for COVID by appropriate swabs from oropharynx and nasopharynx and the results were negative. Although faint erythematous rash with lymphadenopathy was noted on neck. (Figure 1 → arrow showing faint erythematous rash over posterior triangle of neck with lymphadenopathy)

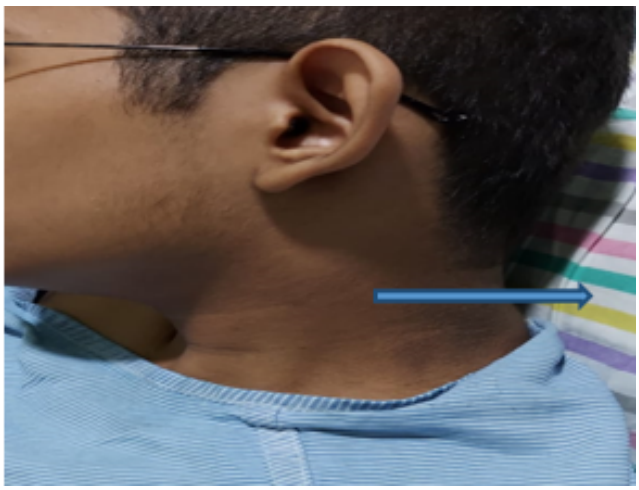

Figure 1: Rash over posterior triangle of neck

Routine blood investigations revealed decreased haemoglobin and platelet count, normal total count with elevated neutrophil percentage. Prothrombin time, D-dimer, CRP, ferritin, NT-proBNP, Troponin-I were all elevated. (Table 1)

Chest X ray was within normal limit and echocardiography showed mild pericardial effusion. The next morning, inspite on appropriate antibiotics and judicious fluid administration the patient still developed high temperatures along with rise in pulse rate. Ultrasonography showed bilateral mild pleural effusion and CT neck showed bilateral multiple lymphadenopathy. Electrocardiogram showed tachycardia sinus in nature, and there was worsening of erythrocyte sedimentation rate, C reactive protein, prothrombin time, activated partial thromboplastin time and markers of cardiac injury. Blood and urine cultures showed no growth.

As we were thinking about myocarditis viral in origin, cardiology was consulted.

Blood tgests for SARS COV-2 was ordered provided the history of fever 1 month back. Repeat echocardiogram showed no aneurysm, normal systolic function and mild pericardial effusion. He was tested positive for SARS COV-2 IgG in high titre (1320 AU/ml – negative < 50). After about a day after admission, we kept atypical KD, COVID-19 related multisystem inflammatory syndrome in children, myocarditis of viral aetiology and macrophage activation syndrome. The patient had negative test result for COVID virus but the rest of symptomatology and reports of laboratory were suggestive of MIS-C. The rise in NT

Table 1: On admission report profile of patient

Parameters	Hemoglobin	Total count	Platelet count	Prothrombin time	D dimer	CRP	Ferritin	Troponin I
Values	10 gm/dl (12-13 gm/dl)	10,300 / ul (4,000-11,000/ul)	68,000/ul (1,50,000 – 4,50,000/ul)	28.7 seconds (control 11 seconds)	10,000 ng/ml (< 500 ng/ml)	129 mg/L (<10 mg/L)	2204 mg/ml (261-462 mg/ml	825.3 mg/L (< 19 mg/L)

Table 2: Case definition of MIS

1.	Age ranging from 0 to 19 years
2.	Fever ≥ 3 days
3.	Multisystem involvement – atleast 2 of rash, inflammation of mucosa / shock / cardiac issues, pericarditis, valvular inflammation, coronary issues or conjunctival inflammation bilaterally including troponin or NT pro BNP / coagulopathy / gastrointestinal symptoms
4.	Elevated inflammatory markers
5.	No microbial cause or toxic shock syndromes
6.	Evidence of COVID virus infection – positive RT PCR or antibody or antigen or recent contact with positive patient

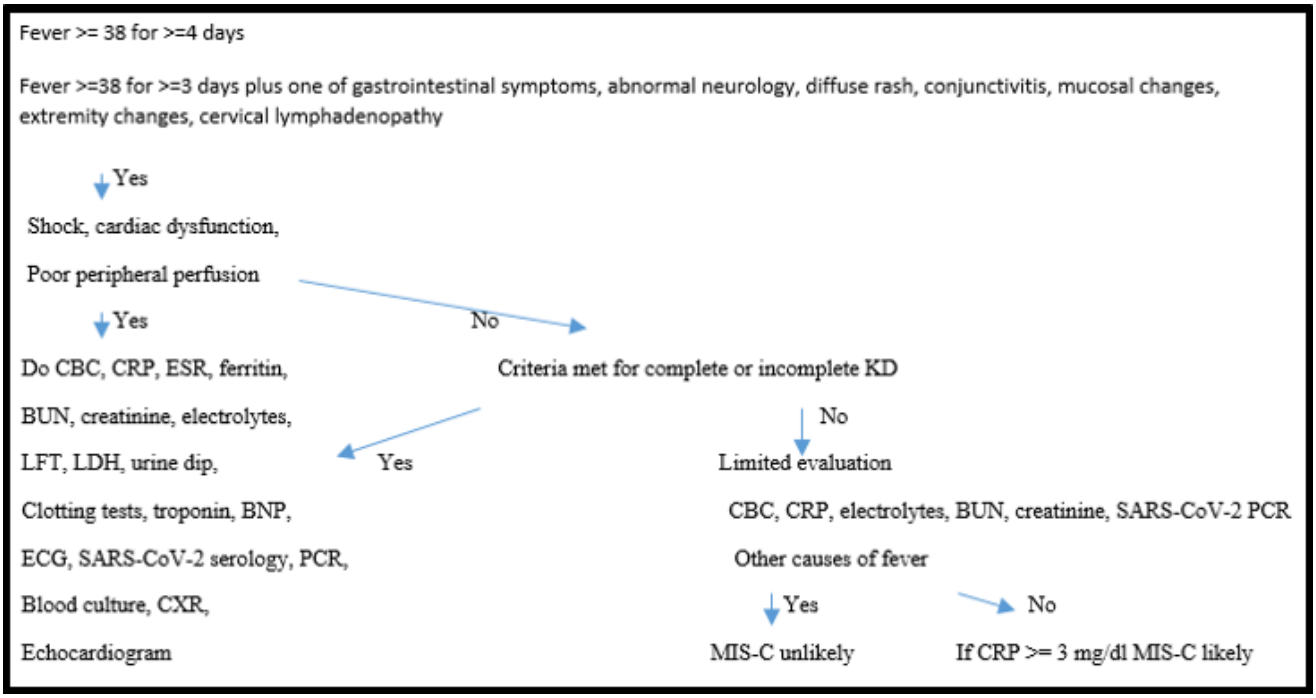

Figure 2: Algorithm to work up of MIS-C

pro BNP and heart rate were indicators of myocarditis and MAS (macrophage activation syndrome) was ruled out for not fulfilling all the criterias.

In the ICU, patient rapidly deteriorated despite treatment with IV fluids, inotropes (noradrenaline) and IV antibiotics (meropenem and doxycycline). So after checking the COVID-19 IgG report, he was started on high dose intravenous methylprednisolone, intravenous immunoglobulin and low molecular weight heparin. On suspicion of cytokine storm, interleukin-6 level was ordered which came out as normal. 12 hours after starting intravenous immunoglobulin, patient started improving, pulse rate normalized, BP stabilized and he was gradually taken off inotrope support on the next day.

3. Discussion

Though the occurrence frequency of MIS – C is unknown it is still as not a known complication of covid 19 in younger patients. MIS C can occur from children and may extend upto adolescence. Cases typically occur several weeks after covid 19 surge in community. WHO case definition[11] includes – (Table 2)

Multi system inflammatory syndrome and Kawasaki disease are similar in many respects. Major differences being MIS-C elderly children and adolescents, affects black and Hispanic children more, gastrointestinal involvement is more, myocardial dysfunction and shock occurs more commonly and elevation of inflammatory markers are more in comparison to KD which typically affects infants and young children, Asian children more affected and gastrointestinal and myocardial dysfunction are less common.[12] The typical manifestation of MIS-C include persistent fever, pain inj abdomen, vomitting, loose motions, rash and conjunctival involvement often followed by multiorgan involvement and shock. Laboratory tests may show lymphopenia, raised C-reactive protein, erythrocyte sedimentation rate, D dimer, troponin I and BNP (B type natriuretic peptide).[13] The differential diagnosis includes sepsis, COVID -19 infection, toxic shock syndrome and intraabdominal infection.

An algorithm for work up of suspected MIS patient has been formulated. (Figure 2)

Patients require multidisciplinary care with input from various specialities. Patients should generally receive prompt antimicrobials as per hospital policy judged by clinical scenario. Patients with moderate or severe features of shock are treated with intravenous immunoglobulin plus a glucocorticoid.[14]Patient with milder features are treated with intravenous immunoglobulin alone. Anakinra, canakinumab and tocilizumab are used when disease is refractory to glucocorticoids. Thromboprophylaxis is done by aspirin in low dose for all, usage of low molecular weight heparin (LMWH) in persons with current or previous venous thromboembolism.[15]Therapeutic anticoagulation is used for severe left ventricular dysfunction and giant co0ronary artery aneurysms. The overall mortality is 1 to 2 %.[16] Most patients with cardiac involvement have functional recovery by hospital discharge. Young patients with cardiac involvement should be followed up by cardiac team post discharge. In patients who do not have any myocardial or coronary artery related issues, follow-up imaging of heart by echocardiography is done after 2 weeks to assess coronary artery size. In patients with coronary artery involvement the imaging is done every 3 days until size is stable and after that every 2 weeks for the next 4 – 6 weeks.

For patients with abnormalities of pump function and normal coronaries the echocardiogram is repeated as necessary including repeat imaging of the coronary artery. Cardiac imaging by MRI can be thought of at 2 – 6 months after the acute disease to assess function of ventricles.

4. Conclusion

Post covid era we should be cautious about any patient presenting with rash, fever and multisystem involvement with shock about MIS as definite treatments are available. Long term monitoring of patient is required to look for developing coronary artery aneurysms which can lead to premature myocardial infarction. Our case highlights the above findings of meticulous history and clinical examination to decipher MIS in such patients.

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None.

6. Conflict of Interest

None.

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