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CASE REPORT

Treatment Failure with IVIG in a Case of Multisystem Inflammatory Syndrome in Children Managed by Tocilizumab

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has rapidly spread around the world from the time when it was first identified in China in December 2019.[1,2] Among initial reports from China on corona virus disease 19 (COVID-19) in paediatric age group, very few have sporadically described critically ill children.[3] Most children with this disease are asymptomatic or exhibit a mild upper respiratory illness, and recover within 1 to 2 weeks.[4] However, reports have begun to emerge of multiple system involvement with circulatory shock and systemic inflammation that has presented predominantly in children with COVID-19. The first such report was from the United Kingdom involving a cohort of 8 children with evidence of severe inflammation and Kawasaki disease-like features.[5] Thereafter, similar reporting continued from Italy describing 10 children, and from France and Switzerland describing 35 children.[6,7] On 14 May, the US Centers for Disease Control and Prevention (CDC) formally termed this entity as multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 and introduced a case definition.[8]

Epidemiologic evidence implicates SARS-CoV-2 as the likely cause of the newly recognized MIS-C, even though causation has not yet been established. The occurrence of clusters of MIS-C cases in places that have been heavily impacted by COVID-19 such as Italy, the UK, and New York City, is highly suggestive of an association to infection with SARS-CoV-2. While the incidence of MIS-C is uncertain, it appears to be an uncommon complication of COVID-19 in children. In one report, the estimated incidence of laboratory-confirmed SARS-CoV-2 infection in individuals less than 21 years old was 322 per 100,000 and the incidence of MIS-C was 2 per 100,000.[9]

CDC data on tracking reports of MIS-C cases shows strong evidence of its linkage with COVID-19. Almost all (98 %) cases were positive for antigen or antibody of SARS-Cov-2.[8] The majority of published cases with this syndrome were positive for serologic testing for SARS-CoV-2 (60/69, 87%) and less commonly positive for RT-PCR testing from nasopharyngeal swab (23/70, 32%), which suggests that this syndrome may be post-infectious rather than related to acute early infection.[10] The clinical presentation of MIS-C includes fever with severe illness, and the involvement of two or more organ systems, along with laboratory evidence of inflammation and laboratory or epidemiologic evidence of SARS-CoV-2 infection.[8] Laboratory findings include lymphopenia, hypoalbuminaemia, elevation in serum troponin, liver enzymes, D-dimer, and ferritin. C-reactive protein (CRP) and ESR are also elevated, along with cytokines elevation such as tumor necro-sis factor alpha, interleukin (IL)-4, IL-6, and IL-10.[11]

Specific immunomodulatory therapy depends on the clinical presentation of this severe illness. The goals of treatment for MIS-C are to reduce systemic inflammation and restore organ function, in order

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to decrease mortality and reduce the risk of long-term sequelae, such as the development of coronary artery aneurysm (CAAs) or persistent cardiac dysfunction.[10] Overall, children will survive this hyperinflammatory condition with IVIG administration, steroids, a multidisciplinary team of relevant healthcare providers, and in few cases immunomodulatory agents.[12] In a very few reported cases where IVIG response was unsatisfactory, Interleukin-6 inhibitors, an immunomodulatory agent was found beneficial while given during the cytokine storm associated with COVID-19.[13] We are reporting a case of MIS-C from a tertiary care hospital (Evercare Hospital Dhaka), from Capital Dhaka, Bangladesh, who was successfully treated with IL-6 inhibitor (Tocilizumab), as a second line therapy after failed treatment with adequate dose of IVIG and steroid.

Case Report

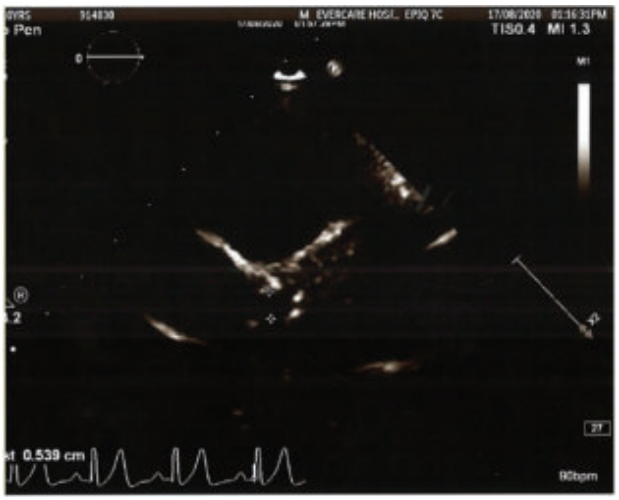
A 10 years 10 months old previously healthy boy was admitted through emergency room with the complaints of high-grade fever (maximum peak 106°F) for 2 days, repeated vomiting, severe abdominal pain and dry cough. Both his parents and the patient were positive for SARS-CoV-2 RT-PCR nasopharyngeal swab test three weeks prior to this illness. At that time, he had fever (102°F for about 2.5 days) with mild cough, which was managed conservatively at home.

On arrival, the boy was febrile with temperature 104°F, sick looking, mildly tachypneic with normal oxygen saturation. His heart rate was 128/min and he was normotensive with BP 90/60 mmHg. His chest was clear on auscultation, abdomen was soft with diffuse tenderness, and bowel sound was normal. Skin survey was normal and no signs of meningism were noted. Investigations on admission showed, neutrophilic leukocytosis with lymphopenia, slightly raised CRP and SGPT. His SARS-CoV-2 (RT-PCR) test came negative and chest radiograph was normal. Ultra-sonogram of whole abdomen showed trace free fluid. On suspicion of sepsis, Inj. Amoxycillin with Clavulanic acid was started empirically. On the following day, he also developed new symptom of intermittent delirium with irritability and complained of getting smell in everything around. After 36 hours of admission, on day 4 of illness, as there was no change of clinical condition, repeat investigations were done, which revealed thrombocytopenia and markedly raised inflammatory markers including S. ferritin, D-Dimer, LDH and ESR. He also had low S. albumin, proteinuria and normal troponin-I (1.9 ng/ml). Multisystem inflammatory syndrome in children (MIS-C) has been suspected and inj. Methyl-prednisolone (2 mg/kg/day) 12 hourly IV was added in treatment.

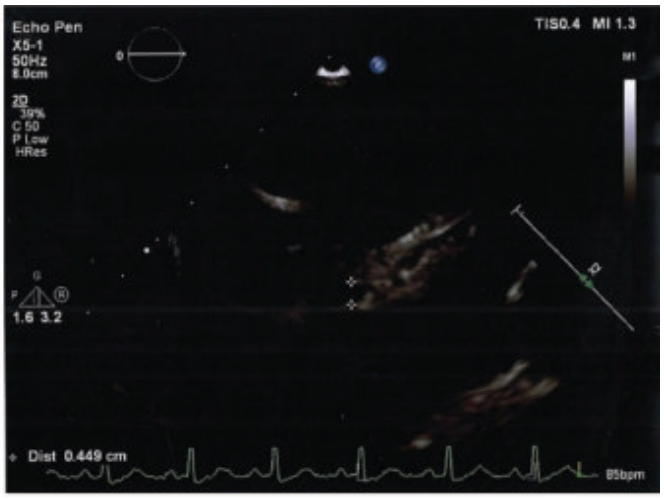
Next day, his general condition further deteriorated with continued high fever along with cough induced vomiting and persisting abdominal pain. Repeat investigations revealed persisting lymphopenia, markedly raised C-reactive protein (127 mg/L), raised procalcitonin, normal Widal titre, further increasing D-Dimer and high fibrinogen level (717.2 mg/dl) with negative septic screen. 2D colour doppler echocardiography (Fig. 1) revealed medium aneurysmal dilation of coronary arteries [LMCA (Z-score +5.95) and LAD (Z -score +5.26)] with irregular and distorted vascular wall and electrocardiogram (EKG) showed sinus tachycardia. Our patient fulfilled the CDC case definition of MIS-C.[8] We have started IVIG (1.5 g/kg) continuous infusion over 24 hours. Antibiotic was switched to Meropenem. Inj. Enoxaparin S/C and low dose Aspirin were also started. He became afebrile day after IVIG infusion and started showing general wellbeing. His cough as well as vomiting and abdominal pain also subsided.

However, 72 hours after IVIG infusion (on Day 9 of illness), his fever recurred with increasing peak along with excessive dry cough, anorexia and repeated vomiting. His ESR further raised along with raised inflammatory markers, and he also developed hyponatraemia. On day 11 of illness, 48 hours after new onset fever, he also developed macular rash on both palms, bilateral conjunctival injection (Fig. 2) and erythematous throat with mildly tender left cervical lymphadenopathy. His blood pressure and oxygen saturation remained within normal range. Antifungal Tab. Fluconazole was added. His subsequent lab test showed very low S. albumin, further rising inflammatory markers with markedly high CRP, D-dimer as well as ESR. His 2nd set of septic screen also came negative and repeat chest radiograph also revealed normal. On day 12 of illness, Inj. Tocilizumab (8 mg/kg) single dose was infused. Shortly after the infusion, 2 hours later, his fever subsided and there was significant improvement of wellbeing along with

resolution of cough and vomiting. Four days after Tocilizumab infusion, investigations were repeated and yielded normal lymphocyte count, improving CRP and ESR, near normal procalcitonin and normal D-dimer (Fig. 3). He developed thrombocytosis (455 10^9/L), further rising S. ferritin & SGPT (422 IU/L). 2-D echo (Fig. 1) before discharge revealed reduction in aneurysmal dilation of LMCA (Z- score +3.13) and LAD (Z- score +3.38) with irregular vascular wall. He was discharged in vitally stable state after 15 days of hospital stay with advice of tapering oral steroid and low dose aspirin. All his relevant laboratory tests during admission and subsequent follow up are shown in the Table I and trend of inflammatory markers during hospital stay in (Fig. 3). He attended follow-up visits in outpatient clinic after 1, 3 and 6 weeks of discharge, where he was found vitally stable with normalization of his inflammatory markers, but he had persisting small aneurysmal dilatation of LMCA and LAD with irregular vascular wall in 2-D echocardiogram even at 3 weeks after discharge. On further follow up, at 7 weeks, all coronary arteries became normal.



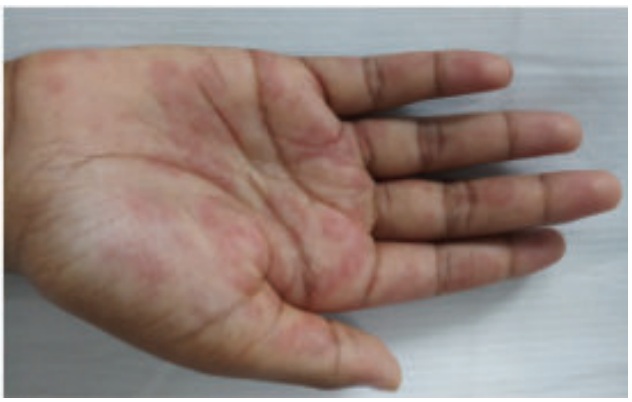
1st 2D-Echocardiogram showing medium aneurysmal LMCA dilation on day 5 of illness



2nd 2D-Echocardiogram showing small aneurysmal LMCA dilation on day 15 of illness

Fig 1 *1st and 2nd echocardiogram images showing aneurysmal dilation of coronary arteries with irregular and distorted vascular wall*

Conjunctival injection



Palmer rash

Fig 2 *Changes in eyes and hands on day 11 of illness*

Table I
Laboratory findings during hospital stay and follow-up

Laboratory test	During Hospitalization								1st F-up	2nd F-up
	Day of illness of specific treatment									
	1	4	5	7	10	12	14	17	24	56
			IVIG			Tocilizumab				
TLC 10^9/L (normal: 5-13)	13.93	7.71	6.42	4.65	9.67	14.82		15.59	12.97	6.13
Absolute Neutrophil count 10^9/L (normal: 2-7)	12.79	6.37	5.74	3.18	8.23	12.96		11.3	9	3.71
Absolute Lymphocyte count 10^9/L (normal: 1-3)	0.87	1.13	0.61	0.97	0.85	1.34		3.31	3.68	1.83
Platelets 10^9/L (normal 150-400)	161	139	165	244	292	284		4.55	319	257
CRP mg/L (normal <3.3)	5.2		127	70.9	53.7	178		162	28.6	<2.9
Procalcitonin ng/mL (normal <0.05)	0.75		2.97	0.7	0.38			0.14		
ESR mm in 1st hour	80			121	134			110	41	11
Ferritin ng/ml (12-140)	148	239		349		454		796	259	86
D-Dimer µg/L (<500)	462	2314	2646	1618	1422	1917		923	305	184
Fibrinogen mg/dL (180-350)			717	358						
LDH U/L (normal <250)		264					194			
Troponin ng/mL, (normal 3-17)		1.9								
SGPT IU/L (normal 14-63)	73		50		75	44		422	140	64
S. Albumin g/dL (normal 3.5-5)		3.3			2.9	2.2		2.6	3.3	
S. Sodium mmol/L (normal 135-145)	135	136			130	134				136
Urine Protein		Trace			Trace			NIL		
Aerobic C/S blood		No growth				No growth				
Aerobic C/S urine		No growth				No growth				

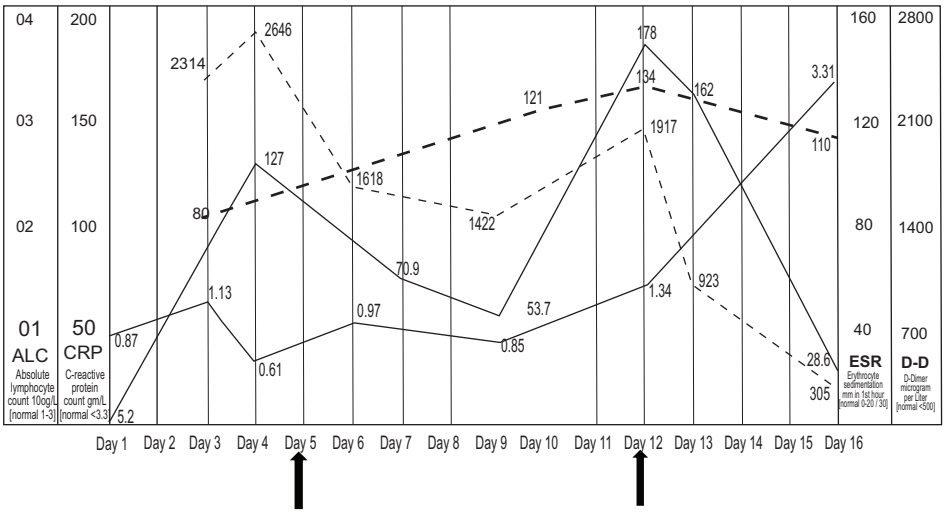


Fig 3 *Trend of inflammatory markers with effect of IVIG and tocilizumab during hospital stay*

Discussion

Multisystem inflammatory syndrome in children (MIS-C) is a rare but severe inflammatory condition that has been reported in previously healthy pediatric patients having SARS-CoV-2 exposure.[14] Evidence supporting an underlying link with SARS CoV- 2 includes a strong historical association with COVID-19 activity, diagnosis of SARS-CoV-2 infection through RT-PCR or antibody testing in most patients, and hyper inflammatory manifestations like COVID-19 infected adults.[15-17] We report a previously healthy boy, who fulfilled the CDC case definition[8] of MIS-C and was positive for SARS-CoV-2 RT PCR nasopharyngeal swab test three weeks prior to his illness. MIS-C is speculated to be a delayed immunological phenomenon associated with

inflammation (stage III hyperinflammation phase) following either symptomatic or asymptomatic COVID infection.[10]

There is resemblance between MIS-C and atypical Kawasaki disease (KD); however, there are some noticeable clinical differences, such as presentation at older age, a higher frequency of gastrointestinal symptoms on presentation, and a higher rate of cardiac involvement in MIS-C.[6-8,18]

Our reported case had several systemic involvements including cardiac, gastrointestinal, hematological, hepatic and nervous system. He presented very early within 2 days of illness, and we could record the evolution of clinical and laboratory features. His brief mucocutaneous manifestations with cervical lymphadenitis resembling features of incomplete KD developed late in the disease course on 11th day of illness during second peak of febrile episode.

Current management of MIS-C emphasizes on supportive care and treatment of the underlying inflammatory process to reverse organ dysfunction and prevent further complications. Although there are no specific therapies approved by the U.S. Food and Drug Administration (FDA) for this condition, several agents are being used in different clinical trials and under institutional protocols based on their clinical benefit in similar conditions.[8,18] Stepwise immunomodulatory treatment in MIS-C is recommended with intravenous immunoglobulin (IVIG) and/or glucocorticoids as first line agents. This immunomodulatory approach is the most commonly used treatment reported to date in patients with MIS-C.[5-7,19-24] We have seen brief positive clinical response in our patient after treatment with IVIG and steroid. But after 3 days of IVIG infusion, his fever recurred along with clinical deterioration and rapidly rising inflammatory markers. Verdoni et al[6], reported that, the KD cases who presented during the COVID-19 pandemic showed high rate of IVIG resistance, as compared to that in a past cohort of KD patients, suggesting a role for glucocorticoids in MIS-C.

In case of patients not responding or partially responding to IVIG and/or steroid, alternative agents have been used in different centers. Considering the cytokine release syndrome as the important contributor to severe inflammation in some patients with MIS-C.[25] American College of Rheumatology guidance recommended anakinra (Interleukin-1 antagonist) in patients with MIS-C who are refractory to IVIG and/or glucocorticoids.[26]

This recommendation is based on the relative safety of anakinra in pediatric patients with hyperinflammatory syndromes even with active infection, and the outcomes mentioned in the literature in some of MIS-C patients.[13,14,24,27-30] IL-6 is an important cytokine in this inflammatory process and a few studies suggest that CS is certainly correlated with disease severity.[31] IL-6 is a proinflammatory cytokine that is involved in T-cell activation, immunoglobulin secretion induction, acute-phase protein synthesis initiation in liver, and stimulation of hematopoietic precursor cell proliferation and differentiation.[32] Assuming the relationship between increased IL-6 levels and negative outcomes in COVID-19, IL-6 neutralization with tocilizumab can be a potential treatment option.[16,33,34] This monoclonal antibody blocks IL-6-mediated signaling by competitively binding to both soluble and membrane-bound IL-6 receptors, and it is approved by the US FDA for treating cytokine release syndrome (CRS). [6]

Our reported patient was declared as treatment failure with IVIG and was labeled as an IVIG refractory case of MIS-C. We chose tocilizumab (IL-6 inhibitor) empirically as the second line treatment considering role of IL-6 in cytokine storm, as anakinra (IL-1 inhibitor) is not available in commercial market, and we lack laboratory facility for doing IL-6 assay. He demonstrated quick and significant as well as sustained clinical remission and improvement in laboratory parameters after treatment with inj. tocilizumab.

Children's Hospital of the King's Daughters (CHKD) protocolized tocilizumab for patients with continued fever for 24 hours after IVIG and/or steroids or moderate to severe presentation. They recommended a single dose of tocilizumab 12 mg/kg IV in patients less than 30 kg and 8 mg/kg IV (Max: 800 mg) in patients 30 kg or more and mentioned the typical response time within 48 to 72 hours.[35] We have used 8 mg/kg single dose in our patient. In 3 New York City tertiary care children's hospitals, (n = 33; age 2 months to 20 years), Kaushik et al[28] treated 12 (36%) patients with tocilizumab along with IVIG or methylprednisolone. Tocilizumab was given to patients with high IL-6 concentrations.[36] In another 3 systematic reviews of MIS-C patients (n =

662 to 783), interleukin-6 inhibitors were administered to 6% to 6.5% of patients. Sixty eight to seventy one percent of patients were in the intensive care unit and there was 1.5% to 1.7% mortality rate.[37-39] In an observational study (n=27; median age 6 years) tocilizumab was administered to 2 patients with suspected cytokine storm syndrome with no mortality.[40]

Fourteen percent of patients among 186 MIS-C cases reported to receive tocilizumab or siltuximab in addition to IVIG and other therapies. Eighty percent of patients were in the critical care unit and 20% received mechanical ventilation.[14] Gruber et al[40] reported in a case series of 8 patients with median age 11.5 years, all patients received 1 to 3 doses of tocilizumab within 1 day of admission. Seven of the 8 patients also received IVIG. Markers of inflammation, coagulopathy and cardiac injury normalized rapidly in all patients.

For tocilizumab use, there is risk of GI perforation, hepatotoxicity and infusion-related reactions.[32] In our experience while managing the case, tocilizumab was well tolerated. Tocilizumab is much cost effective than that of IVIG. Our reported case showed rapid drop in his later raised CRP and D-dimer, and lymphopenia as well as thrombocytosis soon corrected within 4 days following intravenous tocilizumab. We have seen, ferritin, ESR and later raised SGPT took time to normalize, which we are not considering markers for immediate treatment success. Nozawa et al[41], reported coronary-artery aneurysm in tocilizumab-treated children with kawasaki's disease. In our case, on further follow up upto 6 weeks, there was no significant adverse effects like worsening of coronary artery aneurysm or flare of infection associated with tocilizumab use. Rather, we have seen normalization of coronary arteries at 6 weeks follow up visit.

MIS-C patients who require treatment with steroids, irrespective of the dose, frequently require a gradual tapering over 2-3 weeks to avoid rebound inflammation.[26] For our patient, we continued oral steroid with gradual taper over 3 weeks after discharge, and we also did not experience any such rebound inflammation.

Conclusion

Though IVIG and steroid are so far widely used effective first line agents to treat severe MIS-C, failure to treatment can happen which may take about 72 hours to be evident. Predictors for treatment failure of MIS-C with IVIG need to be studied further. In this case report, tocilizumab, the IL-6 inhibitor, has been safely and successfully used in an adolescent as second line therapy. Considering this experience of safety, quick recovery response and relatively cheaper option, use of tocilizumab as a second line agent instead of repeat use of costly IVIG may be considered. If it is proved safe in larger study, it can be considered as even a first line therapeutic agent in treating MIS-C.

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