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Post COVID-19 multisystem inflammatory syndrome in children undergoing hematopoietic stem cell transplant

To the editor:

There is paucity of literature on outcomes of Post COVID-19 Multisystem inflammatory syndrome in Children (MIS-C) in pediatric hematopoietic stem cell transplant (HSCT) recipients. Here we report two cases of MIS-C in post HSCT.

Case 1. A 2-years old boy, case of Thalassemia major post-HSCT developed complaints of loose stools, fever, cough on day +155. He had rejection of donor cells on day +45 due to cytomegalovirus infection and had autologous recovery of counts. Child was off immunosuppression since last 5 months. He tested positive for SARS-CoV-2 infection by Reverse Transcriptase (RT) Polymerase Chain Reaction (PCR) on Day +135 post HSCT, prior to hospital admission for packed red cell transfusion. He stayed asymptomatic and tested negative for SARS-CoV-2 after 10 days by RT PCR. He was admitted with fever, loose stools and cough 20 days after diagnosis of COVID-19. Vitals were stable and chest examination revealed few crepitations bilaterally. Haemoglobin (Hb) 12.4g/dl, Total Leucocyte count (TLC) 2040/μL, Platelet Count (PC) 5000/μL, mild derangement in liver enzymes (SGOT 83U/L, SGPT 139U/L). He was started on intravenous (IV) fluids and antibiotics. After 6 hours, child again had an episode of fever. He also had bouts of cough and grunting. His oxygen saturation (SpO2) dropped to 80–85% on room air, BP 98/60 mmHg, respiratory rate of 48/minute and heart rate of 148/minute. A Chest X-ray (CXR) was done which showed bilateral middle zone haziness in lungs. Venous blood gas (VBG) was done which was suggestive of normal pH but lactate was slightly raised (3.7mmol/L). Child was started on supplemental oxygen by mask at 4 L/minute, with which SpO2 was 90%. His NT pro-BNP- 1860 pg/ml, D-Dimer-1117ng/ml were raised. In view of raised inflammatory markers and recent history of COVID-19, possibility of MIS-C was considered. IV methylprednisolone pulse at the dose of 20mg/kg body weight was started. Intravenous immunoglobulin (IVIG) at dose of 1 g/kg was also given. He received packed red blood cells and platelet support. Gradually his respiratory distress started settling from day 7 of this MIS-C illness and his laboratory parameters started showing improvement. His TLC declined from 2640/μL to lowest of 450/μL. His platelets stayed in the range of 4000 to 13,000/μL with supportive care. The lowest recorded S. Albumin was 2.45 gm/dl. CMV PCR was negative. His blood culture did not grow any organism. After giving Methylprednisolone at 20mg/kg for 4 days, steroids were tapered off to 3mg/kg for 2 days, followed by 3mg/kg for 2 days and then tapered off over next 10 days. Child was shifted to ward once off oxygen. Child was discharged in stable condition after 10 days of hospitalisation. Now he is one month post discharge and doing well.

Case 2. An 11-years old girl, case of acute lymphoblastic leukemia in complete remission-2 post matched sibling donor HSCT and chronic graft vs. host disease (GVHD) of skin presented on day +382 with complaints of cough, shortness of breath and tiredness for 2 days. She also had one episode of haemoptysis at home. For chronic GVHD, she was on oral Sirolimus (1mg/day), prednisolone (1mg/kg/day) and Ruxolitinib (5mg twice a day). At presentation to hospital, on examination, child had respiratory distress with SpO2- 70% on room air, tachycardia, tachypnoea, BP was 100/60 mm Hg and she was drowsy. In emergency department, she was started on supplemental oxygen by non-rebreathing mask, IV fluids, antibiotics. CXR showed diffuse bilateral infiltrates. RT PCR for SARS-CoV-2 was negative. Her respiratory distress worsened and she was shifted on BIPAP support. Investigations showed Hb 14.7 gm/dl, TLC 2940/μL, PC 40000/μL, S. Creatinine 0.6 mg/dl, electrolytes WNL, total bilirubin 2.2 mg/dl, serum albumin 3.5 gm/dl, SGOT-350U/L, SGPT 311U/L, GGT-3605U/L, CRP-574 mg/L, Ferritin-11200 ng/ml, NT pro BNP 41800 pg/ml, D-Dimer —2527ng/ml. Echocardiography showed Left Ventricular Ejection Fraction (LVEF) 40%, mild pulmonary regurgitation, moderate tricuspid regurgitation. Her Covid IgG antibody was positive (94.8Au/ml) and blood cultures were negative. In view of, raised inflammatory markers, multisystem involvement, negative culture and positive COVID IgG, diagnosis of Post COVID-19 MIS-C was considered. She received 24-hour oxygen support by High Flow Nasal cannula (HFNC) with flow rate of 20L/minute and FiO2 of 60%. Inflammatory markers were raised, Ferritin was 6370ng/ml, C-reactive protein (CRP) was 45.8mg/L. His NT pro-BNP- 1860 pg/ml, D-Dimer-1117ng/ml were raised. In view of raised inflammatory markers and recent history of COVID-19, possibility of MIS-C was considered. IV methylprednisolone pulse at the dose of 20mg/kg body weight was started. Intravenous immunoglobulin (IVIG) at dose of 1 g/kg was also given. He received packed red blood cells and platelet support. Gradually his respiratory distress started settling from day 7 of this MIS-C illness and his laboratory parameters started showing improvement. His TLC declined from 2640/μL to lowest of 450/μL. His platelets stayed in the range of 4000 to 13,000/μL with supportive care. The lowest recorded S. Albumin was 2.45 gm/dl. CMV PCR was negative. His blood culture did not grow any organism. After giving Methylprednisolone at 20mg/kg for 4 days, steroids were tapered off to 3mg/kg for 2 days, followed by 3mg/kg for 2 days and then tapered off over next 10 days. Child was shifted to ward once off oxygen. Child was discharged in stable condition after 10 days of hospitalisation. Now he is one month post discharge and doing well.
was started on IV methylprednisolone. Because of persistent severe respiratory distress and increasing BIPAP requirement, she was intubated and started on invasive ventilatory support. VBG showed severe respiratory and metabolic acidosis. Ventilatory requirement was very high, and she had persistent tachycardia despite appropriate fluid and inotrope support. She went into cardiac arrest and despite all resuscitative efforts, could not be salvaged. She died within 10 hours of presentation to hospital.

Post COVID-19, MIS-C is a severe complication with an incidence of 0.14% worldwide [1,2]. Also, post COVID-19 MIS-C can be fatal (mortality – 1.9%) [3]. Pathogenesis of MIS-C includes immune dysregulation, hyperinflammation, endothelial injury, multisystem involvement and both T-cell mediated as well as autoantibody mediated injury [4]. We could find only one prior case report of MIS-C post HSCT in a girl with severe immunodeficiency syndrome with T-cell disorder who required oxygen supplementation via nasal cannula only and recovered [5]. There are two reports of MIS-C post solid organ transplant [5,6]. A girl who had received kidney transplantation 12 years previously recovered after mechanical ventilation over 7 days [3]. A 3-year-old girl liver transplant recipient with a history of Caroli disease diagnosed with MIS-C complicated by portal vein thrombosis recovered by day 26.

Both children in our report fulfilled the CDC criteria to diagnose MIS-C [7]. Although Case 1 had autologous recovery after rejection post myeloablative conditioning HSCT but he was still immunosuppressed. He was only day +135 post HSCT when he got COVID19. So, we feel it is appropriate to include this case as MIS-C post HSCT. Although he was very sick but recovered fully with steroid and IVIG therapy. Our second patient with case with ALL and chronic GvHD was already on heavy immune suppression with Ruxolitnib, steroids and sirolimus and yet she could get MIS-C is difficult to explain. This highlights that post COVID-19, MIS-C can cause extremely high immune dysregulation despite patient being on immunosuppressive and immunomodulatory drugs. Also, steroids and Ruxolitinib may mask the symptoms like fever and may delay presentation to the hospital.

From our experience, we intend to convey that post COVID-19 MIS-C in post-HSCT children can be life-threatening. A very high index of suspicion for MIS-C and early institution of treatment would be the key to favourable outcomes in these children.

**Conflict of interest**

Nothing to declare.

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Nil.

**Patient’s Consent**

Patient consent has been received.

**References**

[1] Ahmed M, Advani S, Moreira A, Zoreic S, Martinez J, Chorath K, et al. Multisystem inflammatory syndrome in children: a systematic review. Sep E Clin Med 2020;26:100527. https://doi.org/10.1016/j.eclinm.2020.100527. Epub 2020 Sep 4. PMID: 32923392; PMCID: PMC7473262.

[2] Hoang A, Chorath K, Moreira A, Evans M, Burren-Morton F, Burren F, et al. COVID-19 in 7780 pediatric patients: a systematic review. E Clin Med 2020; Jun 26:24: 100433. doi:10.1016/j.eclinm.2020.100433 PMID: 32759562.

[3] Yasuhara J, Watanabe K, Takagi H, Sumitomo N, Kuno T. COVID-19 and multisystem inflammatory syndrome in children: a systematic review and meta-analysis. Pediatr Pulmonol 2021;56(5):837–48. https://doi.org/10.1002/ppul.25245.

[4] Consiglio CR, Cotugno N, Sardh F, Pou C, Amadio D, Rodriguez L, et al. The immunology of multisystem inflammatory syndrome in children with COVID-19. Nov 12 Cell 2020;183(4):968–81. https://doi.org/10.1016/j.cell.2020.09.016 e7, Epub 2020 Sep 6. PMID: 32966765; PMCID: PMC7474689.

[5] Remppis J, Ganzenmueller T, Kohns Vasconcelos M, Heinzel O, Handgretinger R, Renk H. A case series of children and young people admitted to a tertiary care hospital in Germany with COVID-19. BMC Infect Dis 2021;21(1):133. https://doi.org/10.1186/s12879-021-05791-8. Feb 1.

[6] Petters LM, Vogel TP, Munoz FM, Hernandez JA, Koohmaraie S, Nowicki MJ, Zumbro CE, Mysole KR. Multisystem inflammatory syndrome in children associated with SARS-CoV-2 in a solid organ transplant recipient. Am J Transplant 2021. https://doi.org/10.1111/ajt.16572. Mar 23, Epub ahead of print. PMID: 33754452.

[7] Abrams JY, Oster ME, Godfred-Cato SE, Bryant B, Datta SD, Campbell AP, et al. Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. May Lancet Child Adolesc Health 2021;5(5):323–31. https://doi.org/10.1016/S2352-4642(21)00050-X. Epub 2021 Mar 10.