

Strategies to mitigate inflammation in management of complex congenital heart disease complicated by “multisystem inflammatory syndrome in children”

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ABSTRACT

A 6-month-old boy, a case of Shone’s complex, presented in decompensated state was found to have severe mitral stenosis along with multisystem inflammatory syndrome in children (MISC) warranting urgent surgical intervention. Various modalities including cytokine-adsorbing hemofilter were used to target inflammation. Postoperatively, the child recovered from low cardiac output accompanied by decrease in the levels of inflammatory markers, inopressors, and ventilatory requirements. Open heart surgery in itself is a proinflammatory process and is best avoided during the active inflammatory phase of MISC. In the rare and unavoidable circumstance exemplified by this index case, multipronged strategy targeting inflammation as described can be successfully implemented.

Keywords: Cardiopulmonary bypass, congenital heart surgery, CytoSorb, multisystem inflammatory syndrome in children, Shone’s complex

INTRODUCTION

In the current COVID-19 pandemic, multisystem inflammatory syndrome in children (MISC) is a well-known post-COVID inflammatory condition. We present management strategies for patients undergoing complex congenital heart surgery concomitant with severe MISC.

CASE REPORT

A six month old, 6 kg, male presented with gasping respiration and history of acute febrile illness. Endotracheal intubation and inotropic support were employed during resuscitation. Chest X-ray revealed pulmonary venous congestion. Echocardiography (echo) showed severe mitral stenosis (MS) with severe pulmonary arterial hypertension (PAH). He was referred to our facility for urgent surgical intervention.

Past history

He was born to a primigravida mother who contracted COVID-19 infection 10 days before delivery. He was admitted on day 8 of life with pneumonia requiring mechanical ventilation for 2 days although COVID-19 panel was negative.

He was readmitted at 1 month for respiratory distress. Echo revealed Shone’s complex with severe coarctation of the aorta (CoA), parachute mitral valve causing moderate MS, severe left ventricular (LV) dysfunction, and PAH. Surgical correction of CoA was done, and the child was discharged with good LV function.

During the current admission, he demonstrated persistent high-grade fever (104°F), catecholamine-resistant shock

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with a vasoactive inotropic score (VIS) of 13, and Type 1 respiratory failure despite high ventilator settings. Preliminary investigations showed the presence of SARS-CoV-2 antibodies (level - 23.2, method - chemiluminescence immunoassay, positive >1), markedly elevated inflammatory markers (interleukin-6 [IL-6] and procalcitonin) [Figure 1a and b], elevated international normalized ratio (1.99), and elevated D-dimer (0.67 µg/ml, cutoff <0.25 µg/ml). Initial cultures (blood, blind bronchial aspirate, and urine) and respiratory BioFire panel for viruses and atypical organisms were negative confirming the diagnosis of severe MISC. Echo revealed critical MS with severe PAH, no re-CoA, and no coronary dilatation or myocardial dysfunction. Persistent pulmonary edema despite optimal supportive management necessitated urgent surgical correction.

The main challenge was to mitigate the preexisting cytokine storm which could potentially spiral out of control after subjecting the infant to the secondary insult of extracorporeal circulation mandatory for open heart surgery. Methylprednisolone (30 mg/kg) was administered 12 h before surgery as the first pulse dose, followed by a second dose given at induction. In addition to steroids, the use of hemofiltration (hemofilter UF 50F, Nipro Medical India Pvt. Ltd.) during and immediately after cardiopulmonary bypass (CPB) along with cytokine-adsorbing hemofilter (CAHF) (CytoSorb, 300 ml, CytoSorbents Corporation, NJ, USA) in the circuit was employed to reduce systemic inflammation [Figure 2]. Balanced ultrafiltration along with modified ultrafiltration (100 ml/kg of body weight) was performed during CPB run.

Surgery comprised of supra-mitral membrane excision and repair of parachute mitral valve. The aortic cross-clamp and bypass times were 63 and 116 min, respectively. Intraoperative transesophageal echo confirmed satisfactory repair. Weaning from CPB was facilitated with inotropes (adrenaline @ 0.05 µg/kg/min, milrinone @ 0.5 µg/kg/min) and vasopressors (vasopressin at 0.00015 IU/kg/min) accounting for VIS of 11.5. Postoperative low cardiac output was managed by escalation of vasoconstrictors to a VIS of 19.5 and 21 at 6 and 12 h, respectively. Targeting MISC, intravenous immunoglobulin (IVIG) (2 g/kg over 24 h), and methylprednisolone (2 mg/kg/day for 7 days followed by tapering over 3 weeks) were administered. In addition, peritoneal dialysis (PD) was initiated 48 h postoperative to target inflammation and manage fluid balance.

Postoperative trends of inflammatory markers and VIS score showed a decrescendo pattern as depicted in Figure 1a and b. As negative fluid balance was achieved, airway pressure and FiO₂ requirement gradually decreased [Figure 1c and d]. PD was discontinued on postoperative day (POD) 6. He was successfully extubated on POD 7 but showed persistently reduced right-sided air entry along with hypercarbia (PaCO₂ 80 mmHg), for which he required noninvasive ventilation. Computerized tomography of the chest showed right lower lobe collapse and contained pneumothorax which improved on conservative management. Fiber-optic bronchoscopy revealed right bronchial edema with bronchomalacia. With the use of inhaled steroids and bronchodilators, respiratory requirements decreased gradually and finally

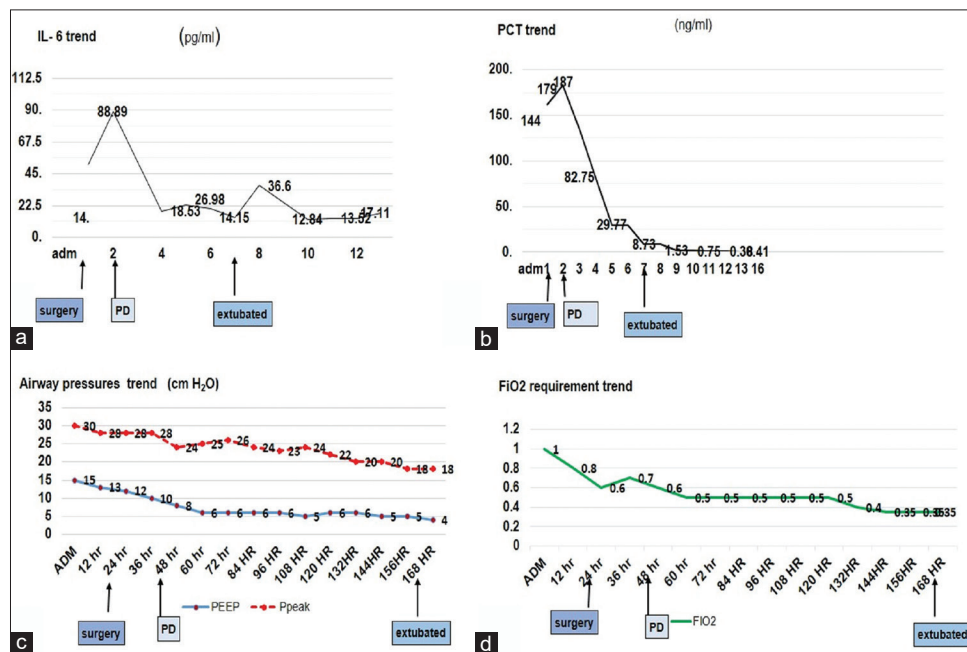


Figure 1: Trends of inflammatory parameters: (a) IL-6 (cutoff <6.4 pg/ml), (b) PCT (cutoff < 0.10 ng/ml) during first 2 weeks of stay. Trends of ventilator requirements: (c) airway pressures, (d) FiO₂ requirement during 1st week of stay. Boxes showing timing of surgery, initiation of PD, and day of tracheal extubation, PD – Peritoneal dialysis, IL-6 – Interleukin-6, PCT – Procalcitonin

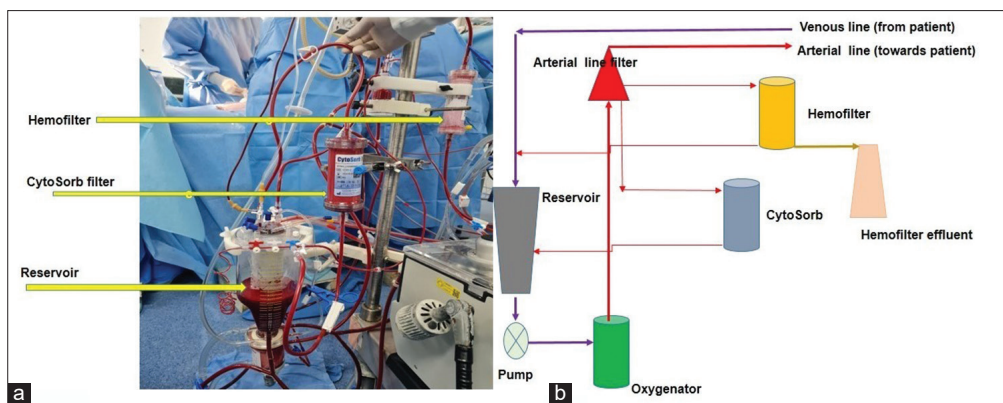


Figure 2: CPB circuit (a) and its schema (b) showing use of hemofilter and CAHf, CPB – Cardiopulmonary bypass, CAHf – Cytokine-adsorbing hemofilter

weaned to room air on POD 26. He was discharged on POD 32. On his last follow-up visit after 6 months, he was gaining weight (8 kg) and started achieving milestones and echo showed no MS with mild mitral regurgitation and good biventricular function.

CASE DISCUSSION

Shone's complex is a rare condition (0.6% of all congenital abnormalities) characterized by multi-level left-sided obstructive lesions.^[1] LV outflow obstructive lesions usually present early necessitating early intervention. Inflow obstructions of mild-to-moderate grade are approached conservatively, while reparative techniques are reserved for severe/symptomatic lesions.^[2]

In the index patient, CoA repair was performed at 1 month of age with regular follow-up advise for moderate asymptomatic MS. Up until 5 months of age, the mitral valve lesion was nonprogressive with insignificant PAH. During the current presentation, echo revealed a rapid increase in severity of MS with pulmonary edema and severe PAH. The possibility of hyperinflammatory state caused by MISC aggravating MS and PAH cannot be ruled out as reported by Raof.^[3] Elective surgical intervention in MISC is advised after 4–6 weeks of treatment; however, in view of deteriorating clinical status, urgent surgical intervention was performed with extracorporeal life support (ECLS) back up.

MISC, first described in April 2020, is a syndrome presenting in children after few weeks of COVID-19 infection resembling incomplete Kawasaki disease and toxic shock syndrome.^[4] Several studies suggest anti-spike (SARS-CoV-2 antigen) antibodies mediated triggering of inflammation.^[5] Diagnosis requires fever, SARS-CoV-2 antibody positivity, laboratory evidence of inflammation, and evidence of at least two-organ involvement. Depending upon the severity, treatment modalities other than supportive management include steroids, IVIG, antiplatelet drugs, anticoagulants, and less frequently biological agents.^[6]

Systemic inflammatory response syndrome (SIRS) also occurs after CPB exposure. Triggers for inflammation include blood contact with nonendothelial surfaces, surgical trauma, reperfusion injury, and endotoxins generated by splanchnic hypoperfusion.^[7] Traditionally, conventional pharmacological and nonpharmacological measures are utilized during surgery to obtund the SIRS.^[8]

To target SIRS-enhanced cytokine storm in this patient, preoperative pulse dose methylprednisolone was administered. This was augmented by using continuous ultrafiltration during the CPB run and modified ultrafiltration done after the termination of CPB. The goal of such hemofiltration strategies is to remove water soluble proinflammatory products. In addition, CAHf was also incorporated into the CPB circuit as a cytokine removal strategy [Figure 2]. CAHf is an hemadsorption cartridge for single use incorporated into extracorporeal circuits. It is filled with sorbent beads, which adsorb and capture cytokines as blood passes through it. Although the role of CAHf in decreasing inflammatory mediator levels (plasma-free hemoglobin, IL-6, IL-8, C3a, and C5a) and the need for vasopressors have been well demonstrated, it has not translated into improved survival.^[9] In children, it has been used in conjunction with ECLS and continuous renal replacement circuits to counter hyperinflammatory states including MISC.^[10]

Bokesch *et al.* suggested that peritoneal fluid may be a reservoir for the harmful proinflammatory cytokines after CPB and removal of peritoneal fluid could lower their serum concentrations.^[11] Some other studies also support the use of early PD in infants recovering postcardiac surgery by achieving greater net negative fluid balance, decreased inotrope requirements, and lower serum concentrations of inflammatory cytokines.^[12] In this case, after initiation of PD, we rapidly achieved negative fluid balance and consistent reduction in the serum inflammatory markers.

To the best of our knowledge, the use of CAHf during CPB in an infant with MISC has not yet been reported. Cytokine storm at the cellular level during MISC is mediated via multiple pathways. In this report, we monitored only levels of IL-6 and procalcitonin; therefore, it is quite difficult to adjudicate the role of any one modality to be solely responsible for the favorable outcome.

CONCLUSIONS

This report highlights the rare coexistence of a critical cardiac condition and MISC where exposure to CPB was unavoidable given the severity of MS. The preoperative, intraoperative, and postoperative management of life-threatening cytokine storm has been suggested. We propose that a multipronged strategy to mitigate this biochemical entity be undertaken which include steroids, IVIG, hemofiltration and CAHf during CPB, and early PD. We also realized that addition of CAHf in CPB circuit in infants is a safe and “possibly” effective strategy in the armamentarium of physicians involved in caring for such critically sick children.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Aslam S, Khairy P, Shohoudi A, Mercier LA, Dore A, Marcotte F, et al. Shone complex: An under-recognized congenital heart disease with substantial morbidity in adulthood. *Can J Cardiol* 2017;33:253-9.
2. St Louis JD, Bannan MM, Lutin WA, Wiles HB. Surgical strategies and outcomes in patients with Shone complex: A retrospective review. *Ann Thorac Surg* 2007;84:1357-62.
3. Raouf A. A case report of COVID-19 associated mitral stenosis: A causative association? *MAR Cardiol* 2021;2:6.
4. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med* 2020;383:334-46.
5. Carter MJ, Fish M, Jennings A, Doores KJ, Wellman P, Seow J, et al. Peripheral immune-phenotypes in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection. *Nat Med* 2020;26:1701-7.
6. Centers for Disease Control and Prevention Health Alert Network (HAN). Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). Available from: <https://emergency.cdc.gov/han/2020/han00432.asp>. [Last accessed on 2021 Sep 27].
7. Day JR, Taylor KM. The systemic inflammatory response syndrome and cardiopulmonary bypass. *Int J Surg* 2005;3:129-40.
8. Borisenko DV, Ivkin AA, Shukevich DL. Treatment of systemic inflammatory response syndrome following on-pump pediatric congenital heart surgery. *Complex Issues Cardiovasc Dis* 2021;10:113-24.
9. Garau I, Marz A, Seiner S, Reuter DA, Reichensperner H, Zöllner C, et al. Hemadsorption during cardiopulmonary bypass reduces interleukin 8 and tumor necrosis factor alpha serum levels in cardiac surgery: A randomized controlled trial. *Minerva Anestesiol* 2019;85:715-23.
10. Bottari G, Confalone V, Cotugno N, Guzzo I, Perdichizzi S, Manno EC, et al. Efficacy of CAHF in a pediatric case of severe multisystem inflammatory syndrome (MIS-C): A clinical case report. *Front Pediatr* 2021;9:676298.
11. Bokesch PM, Kapural MB, Mossad EB. Do peritoneal catheters remove pro-inflammatory cytokines after cardiopulmonary bypass in neonates? *Ann Thorac Surg Cardiovasc* 2000;70:639-43.
12. Sasser WC, Dabal RJ, Askenazi DJ, Borasino S, Moellinger AB, Kirklin JK, et al. Prophylactic peritoneal dialysis following cardiopulmonary bypass in children is associated with decreased inflammation and improved clinical outcomes. *Congenit Heart Dis* 2014;9:106-15.