Case Report

Systemic mastocytosis successfully managed using CytoSorb® during cardiopulmonary bypass for aortic valve replacement

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ABSTRACT

We describe the case of a 72-year-old male with a history of systemic mastocytosis scheduled for on-pump aortic valve replacement for severe aortic insufficiency. Anesthesia and peri-operative management included avoidance of histamine-releasing drugs, methylprednisolone and clemastin prophylaxis. Furthermore, a CytoSorb® cartridge has been added to the bypass circuit and hemoadsorption was performed throughout the entire cardiopulmonary bypass (CPB) duration. CytoSorb® is a hemoadsorption device designed to remove various cytokines and drugs from the blood. The use of CytoSorb® during CPB in our case was not associated with adverse events, and the patient did not present any allergic or anaphylactic reaction.

Keywords: Cardiopulmonary bypass, cytokines, CytoSorb®, hemoadsorption, systemic mastocytosis

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INTRODUCTION

Systemic mastocytosis (SM) is a rare hematologic disorder with an estimated incidence of 1:10,000 worldwide. SM results from a clonal proliferation of abnormal mast cells that accumulate in the bone marrow and/or in different other organs (skin, liver, etc.).[1] After various stimuli such as stress, medication, and hymenoptera stings, these cells can be activated and then release large amounts of mediators like histamine, leukotrienes, prostaglandins, and platelet activating factors, causing very severe anaphylactic reactions.[2,3]

Anesthesia is a potential trigger for mast cell degranulation[4] and can lead to profound hemodynamic instability and potentially fatal outcome.[5,6] Only limited data are available on peri-operative and anesthetic management of patients with SM, especially patients undergoing cardiac surgery with cardiopulmonary bypass (CPB).[7] Peri-operative management of patients with SM mainly consist of the avoidance of histamine-releasing drugs and other potential triggers of uncontrolled mast cell degranulation.[8] The induction of anesthesia is at high risk for developing severe hypotension and mast cell degranulation. The main drugs used in anesthesia daily practice and commonly involved in mast cell degranulation or histamine release include neuromuscular blocking agents (especially atracurium and mivacurium), opioids (morphine), non-steroidal anti-inflammatory drugs (NSAIDs), and antibiotics.[9] In contrast, some frequently used drugs like propofol, fentanyl, halogenated gases, and rocuronium can be safely used in patients with SM. Protamine administration is another significant trigger for anaphylactic reaction. In SM, adverse reactions to protamine could be mediated by the release of inflammatory mediators, including histamine.[10] However, the reversal of heparin with protamine remains the standard procedure in patients with SM as no other

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alternatives for on-pump cardiac surgery has been validated. Anesthetists must be prepared, and epinephrine, anti-histaminic, and corticosteroids should be immediately available. Moreover, on-pump cardiac surgery can induce a supplementary systemic inflammatory response through the contact of blood components with the surface of the CPB circuit, aortic cross-clamp, ischemia-reperfusion injury, and surgical trauma.[11,12] Furthermore, some surgical patients may develop a profound cardiovascular collapse following CPB in cardiac surgery, called vasoplegic syndrome.[13] The vasoplegic syndrome is multi-factorial, including surgical trauma, CPB circuit, ischemia-reperfusion, and systemic inflammatory response with release of pro-inflammatory cytokines (IL-1β, IL-6, IL-8, and TNF-α). Some studies described strategies and devices attempting to decrease the inflammatory response and subsequent vasoplegic syndrome in on-pump surgical patients.[14] In these cases, the hemoadsorption of pro-inflammatory cytokines (IL-6 and IL-8) is thought to be one of the main mechanisms involved. The hemoadsorption CytoSorb® cartridge system designed to remove cytokines from the blood appears safe and is easy to add in a bypass circuit. In our case, a CytoSorb® cartridge has been added into the CPB circuit with the hope to attenuate or abolish the possible inflammatory response and pro-inflammatory cytokine release, potentially avoiding a significant mast cell release and further hemodynamic instability. CytoSorb® (CytoSorbents Europe GmbH, Berlin, Germany) is a hemoadsorption device designed to remove cytokines from the blood.[15–17] It can easily be inserted into a cardiopulmonary bypass and has been shown to efficiently retrieve pro-inflammatory mediators and drugs from the circulation.[18] However, there are only limited data regarding the real efficacy of CytoSorb® during cardiac surgery.[17] As CytoSorb® is highly effective in adsorption of numerous inflammatory mediators,[19] we hypothesized that CytoSorb® might attenuate the pro-inflammatory cascade and therefore diminish the severity of a potential anaphylactic reaction by removing inflammatory cytokines and other mediators from the blood.

CASE PRESENTATION

AQ3 We report the case of a 72-year-old male (73 kg, 182 cm) with a history of SM complaining of increasing dyspnea NYHA III. The patient was diagnosed for SM 4 years ago after suffering from severe anaphylactic shock secondary to hymenoptera sting (basal tryptase level 59.9 mcg/L). The patient has no other medical history and no regular treatment. The pre-operative echocardiography revealed a severe aortic insufficiency (a regurgitation fraction of 54% determined by cardiac MRI) with severe left ventricle dilatation (an LV diastolic volume of 276 ml corresponding to 114 ml/m^2). Due to history of SM and the lack of risk factors for coronary disease, the pre-operative work-up consisted with a myocardial scintigraphy instead of the usual coronary angiography to avoid triggering any immunologic reaction. This exam showed a normal left ventricle function without a sign of coronary disease. The patient was admitted and scheduled for an elective surgical on-pump aortic valve replacement.

The induction of anesthesia was realized with propofol 1mg/kg, dexmedetomidine 0.5 mcg/kg over 10 minutes and then 0.5 mcg/kg/h, sufentanil 0.3 mcg/kg, and rocuronium 0.6 mg/kg. The patient also received 125 mg of methylprednisolone and 2 mg of clemastin at the induction of anesthesia. Antibiotic prophylaxis with cefuroxime 1.5 g was administered 30 minutes prior to skin incision. The anesthesia was maintained with sevoflurane (with MAC 0.7 to 1.0), and the patient received repeated boluses of rocuronium and sufentanil during the procedure. Norepinephrine infusion was used to maintain the blood pressure (with a maximum of 6 mcg/min) within the usual range. An activated clotting time (ACT) of 400 s was obtained after an intravenous injection of heparin (25,000 UI). A CytoSorb® cartridge was added into the CPB circuit, and hemoadsorption was performed throughout the entire CPB duration. Biological aortic valve replacement was performed successfully (Edwards® Resilia Inspiris 29 mm) with a CPB duration of 86 minutes and an aortic cross-clamp time of 66 minutes. The heparin was neutralized with slow administration of 40,000 IU of protamine chlorhydrate at the end of CPB. The procedure was uneventful; the patient was hemodynamically stable all along the procedure and could be extubated in the operating room at the end of the surgery without any complications. The post-operative course was uneventful, and the patient was treated for SM with oral levocetirizine during 7 days post-operative. Analgesia was adequately controlled with oral acetaminophen and intravenous fentanyl. The patient was then discharged from ICU on post-op day 2 and discharged from the hospital on post-op day 9.

RESULTS

The basal pre-operative tryptase was 59.6 mcg/L. Figure 1 illustrates peri-operative evolution of plasma tryptase level. There is a little decrease in blood tryptase level after induction of anesthesia and the beginning of the operation (from 59.6 mcg/L pre-operative to 48.8 mcg/L before initiation of CPB). This might be due to hemodilution with Ringer-lactate used during anesthesia. After 86 minutes of CPB, there is only a minor increase

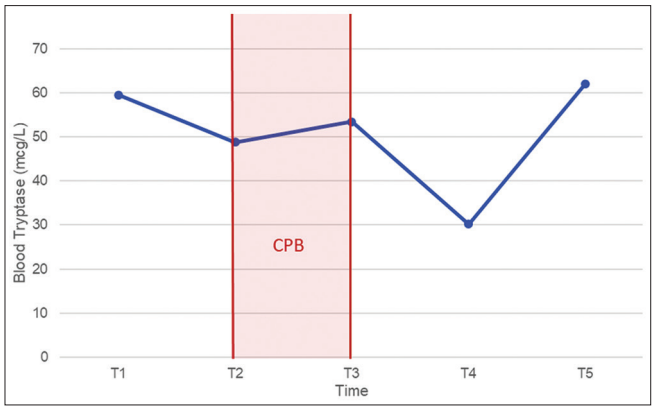

Figure 1: Evolution of blood tryptase levels. T1: day 1 before surgery; T2: CPB initiation; T3: CPB weaning; T4: day 3 post surgery; T5: 8 months post surgery

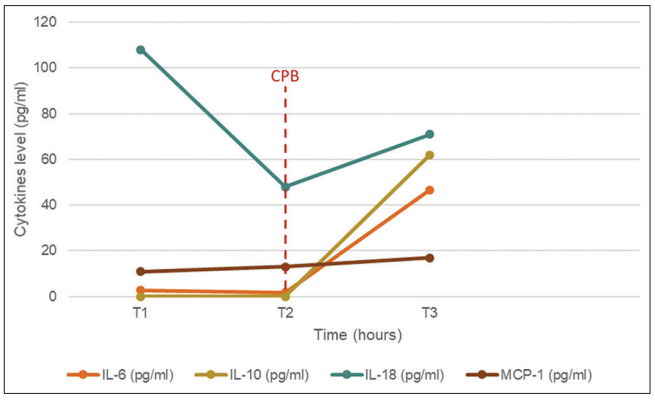

Figure 2: Evolution of cytokines blood levels following CPB. T1: Before induction of anaesthesia; T2: CPB initiation; T3: CPB weaning. IL-6, IL-18 and MCP-1 are pro-inflammatory cytokines. IL-10 is an anti-inflammatory cytokine

in blood tryptase level, from 48.8 mcg/L to 53.5 mcg/L, although CPB is a potential trigger for inflammatory and anaphylactic reaction in SM. We hypothesized that the use of CytoSorb® might have played a role in limiting the immunologic reaction and thus the increase in serum tryptase level following CPB. Moreover, small variations of tryptase levels might also be caused by fluid administration during anesthesia. The decrease in tryptase level on day 4 is not fully understood. It might be caused by the methylprednisolone and levocetirizine prophylactic administration. It might also be caused by the prolonged anti-inflammatory effect of IL-10 following hemoadsorption with CytoSorb®.[20]

The plasma cytokine level evolution is shown in Figure 2. As one could expect, there is a significant increase in pro-inflammatory cytokine blood levels following CPB, confirming that CPB generates a systemic inflammatory response. However, in our case, pro-inflammatory cytokines (both IL-6 and IL-18) and their respective increase are lower than the median values described in a previous study.[20] On the other hand, the increase of anti-inflammatory cytokine IL-10 is largely superior to previously described values. This large amount of IL-10 triggered by CPB might have attenuated the effects of other inflammatory mediators. Furthermore, in the study by Bernardi *et al.*,[20] the anti-inflammatory effect of IL-10 seems prolonged in the patients with hemoadsorption using CytoSorb® during CPB compared to patients under CPB alone. The clinical importance of this effect is yet not known.

In comparison with cytokine levels, there is no significant increase in blood tryptase levels, showing that the inflammatory response triggered by CPB did not result in a massive mast cells degranulation, even in the context of SM.

DISCUSSION

SM is a rare condition, and very limited data have been published regarding peri-operative and anesthetic management of SM. Several cases of patients with SM undergoing surgery, including cardiac surgery with CPB, have been described,[10] but to our knowledge, this is the first case describing the use of CytoSorb® during CPB in a patient with SM.

CytoSorb® is a non-invasive, relatively cheap device with no major side effects, although the clinical impact of removal of pro-inflammatory and anti-inflammatory cytokines is not well known. However, hemoadsorption with CytoSorb® result in a decrease in pro-inflammatory cytokine levels (such as IL-6, IL-18, and MCP-1) but also in anti-inflammatory cytokines (such as IL-10) and various drugs.[17] The net effect of unselective blood purification is not known. Because removal of pro-inflammatory cytokines could be beneficial, blood purification of anti-inflammatory cytokines and drugs could, on the other hand, be deleterious. In the case of a severe immunologic reaction due to SM and triggered by cardiac surgery, no matter the trigger is surgical or pharmacological, hemoadsorption could in theory attenuate the inflammatory reaction by removing cytokines from the circulation. Moreover, treatment of post-CPB vasoplegic syndrome with CytoSorb® is efficient and well established.[14] For this reason, CytoSorb® could reasonably be used in patients who are at risk of developing a severe reaction due to circulating cytokines, such as in SM. In conditions where a high level of pro-inflammatory cytokines is expected, one might suppose that the potential benefit of removing circulating cytokines, including anti-inflammatory cytokines, is probably higher than the risk.

CONCLUSIONS

The use of CytoSorb® during CPB for patients with SM appears to be safe and, in our case, was not associated with adverse events. However, whether CytoSorb® effectively prevented any potential cardiovascular collapse or mast cell degranulation is not known. The interest and efficacy of CytoSorb® to efficiently remove potential triggers in SM are not proven. Further studies are needed to evaluate the efficacy of CytoSorb® in the particular case of SM.

List of abbreviations

- ACT: Activated Clotting Time
- CPB: Cardiopulmonary Bypass
- IL: Interleukine
- MAC: Minimal Alveolar Concentration
- MRI: Magnetic Resonance Imaging
- SM: Systemic Mastocytosis.

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Conflicts of interest

There are no conflicts of interest.

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