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Case Report

Cardiopulmonary Bypass-Case Report

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ABSTRACT

Purpose: Cold agglutinins are autoantibodies that agglutinate Red Blood Cells (RBC) at low temperatures, creating hemagglutination and hemolysis. The normal coldagglutinin titer is below 1:32. Any titer more than 1:64 is considered positive with associated clinical significance. They are basically of no clinical gravity, though when people with cold agglutinins encounterheart surgery with hypothermia and cold cardioplegia, they can come up againstproblems. Thus, unique perioperative direction is needed for such patients.

Clinical Features: We set out a 52 years old woman with cold agglutinindisease (CAD) diagnosed and managed in a cardiac surgery during hypothermia on Cardiopulmonary Bypass (CPB). She had never suffered from any problems nor didshe have anyhematologicalmalady that emerged during routine preoperative evaluation. Since clots and clumps were revealed by accident on the CPB circuit, cannula and tubings, a certain scheme was used to manage the temperature of CPB and cardioplegia. She had normothermic heart surgery with warm cardioplegia.

Conclusion: An antegrade and retrograde warm cardioplegia with normothermic CPB is the best modus operandi to avoid disaster in these situations, and keep anappropriatesurgical field to complete the surgery and bail out.

Cold agglutinin disease is a rare autoimmune hemolyticanemia characterized by IgM antibodies against the patient's own RBC. These are typically activated between 28-31°C, but occasionally at body temperature . They can have myriad presentations like anemia, jaundice, hematuria, cold limbs, acrocyanosis, splenomegaly and livedo reticularis. Primary cold agglutinin disease is idiopathic. The reported incidence of cold agglutinins among screened cardiac surgical patients is low but not too rare (approximately 0.8%–4%), and different perioperative management is required for such patients.

Secondary cold agglutinin disease can be triggered by cold temperatures, viral/bacterial infections and cancers. Cold agglutinins are auto antibodies that agglutinate red blood cells at low temperatures, creating hemagglutination and hemolysis. They are basically of no clinical gravity, though when people with cold agglutinins encounter heart surgery with hypothermia and cold cardioplegia, they can come up against problems. Thus, unique perioperative direction is needed for such patients.

We report a rare case of cold agglutinin disease diagnosed intra-operatively in cardiac surgery during hypothermia on Cardiopulmonary Bypass (CPB), after having obtained written consent from the patient. Furthermore, we reflect on

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whether there should be a pre-pump routine of screening for cold agglutinin disease.

Keywords: Hypothermia; Hemolyticanemia; Cardiopulmonary Bypass (CPB);Hemodynamics; Autoagglutination; Cardioplegia

CASE DESCRIPTION

A 52 years old female, a known case of rheumatic heart disease, severe mitral stenosis and regurgitation and severe tricuspid regurgitation who had defaulted on cardiac medications for 3 months, presented with complaints of chest pain and palpitations, breathing difficulty for 2 days and cough for 2 days. She had undergone a Balloon Mitral Valvulotomy (BMV) 10 years prior [1]. No history of thrombotic or hemorrhagic complications was recorded. Pre-operative blood tests showed a Hemoglobin (Hb) concentration of 12.3 g/dL, hematocrit of 37%, Total Leucocyte Count (TLC) of 13,890/cu.mm, platelet count of 4.33 lakhs/cu.mm and a normal coagulogram. There was no evidence of abnormal clumping of RBCs on the routine Complete Blood Count (CBC). A repeat hemogram on the next day demonstrated a drop in Hb to 8.6 g/dL, an increase in TLC to 35,660/cu.mm and a decrease in platelet count to 1.82 lakhs/cu.mm. However, in view of worsening cardiopulmonary status and class IV New York Heart Association (NYHA), the patient was scheduled for emergency Mitral Valve Replacement (MVR)/Tricuspid Valve (TV) repair.

In the operating room, standard American Society of Anaesthesiologists (ASA) monitors were attached. Prior to induction wide bore peripheral intravenous (IV), central venous and arterial lines were secured.Induction was uneventful. A transesophageal echocardiography (TEE) probe was placed [2].

Baseline activated clotting time (act) was normal. Surgery proceeded with a median sternotomy:

Before aortic and bicaval cannulation, systemic heparinisation was done with 300 U/kg and ACT was 612 seconds. The patient was placed on CPB and cooling was initiated. When the patient was cooled to 28°C, as is customary in our cardiac unit, clots/clumps were noted in the CPB circuit, cannula and tubings (Figure 1).

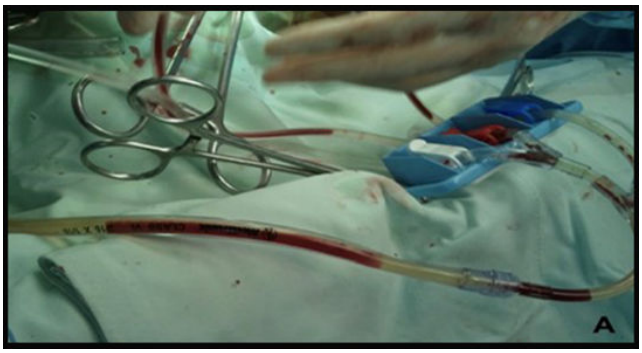

Figure1: Clots/clumps noted in CPB circuit, cannula and tubings.

The first dose of cardioplegia at a temperature of 4°C had already been administered by this time.

The ACT at this time was showing 999 seconds. Intra-operative immuno hematology workup revealed:

- EDTA sample suggestive of autoagglutination. Clotted sample showed haemolysis.
- Patient's blood group was O positive. Direct coomb's test and anti-complement antibody were positive.
- IgM antibodies characteristic of CAD were positive.
- Activated cold agglutinins present at 32°C.

A diagnosis of cold agglutinin disease triggered by hypothermia during CPB was made.

The CPB circuit was immediately flushed with warm priming solution and warm cardioplegia administered in anterograde and retrograde manner to wash out the clots and microemboli in circulation. Packed red cells and blood products were transfused after cross matching. Warming commenced immediately, and simultaneously MVR/TV repair was completed. The weaning off process was prolonged and involved high in otropy. Immediately after sternal closure, the patient developed hypotension and TEE showed severe RV dysfunction. The sternum was re-opened [3]. The patient was placed on normothermic CPB. After supporting on pump for about 50 minutes, the patient was weaned off CPB with high inotropic supports. He was then shifted to the cardiothoracic Intensive Care Unit (ICU). The laboratory analysis of intra operative blood samples revealed activated cold agglutinins present only at 4°C, they were absent at the tested thermal thresholds of 20, 26, 30 and 37°C. Furthermore, further laboratory testing reveled no evidence for perioperative hemolysis Micro embolization in coronary circulation was the probable reason for difficulty in weaning the patient off CPB. Subsequently, the patient's hemodynamics stabilized, she was extubated on the first post-operative day and was subsequently discharged uneventfully.

DISCUSSION

CAD discovered on CPB introduces a double dread of agglutination and hemolysis, which can cause multiorgan dysfunction and failure [4]. Clumps/clots on CPB during hypothermia in spite of adequate heparinization should rise suspicion of CAD [5]. Elimination of microemboli from the circulation should be a priority. Cooling should be suspended.

Warm cardioplegia given ante grade and retrograde is effective in removing emboli from coronary circulation. CAD is a primary or acquired autoimmune disease involving antibodies that lead to agglutination of RBCs at low temperature followed by complement fixation and hemolysis on rewarming.

CAD may be asymptomatic, be detected preoperatively or may present for the first time intraoperatively during hypothermic CPB. Intraoperative discovery of unanticipated CAD may prove

to be a challenge to the intraoperative team. Prevention is important and a normothermic cardiopulmonary bypass and warm myocardial protection are established means for preventing intravascular hemolysis in patients. If CAD presents for the first time during CPB, blood can be removed from the coronary circulation, avoiding further agglutination. The existing agglutinates endangering the microcirculation can be flushed back into the aortic root, where they can be suctioned by the aortic root vent. The retrograde as opposed to the antegrade route avoids agglutination and embolization in the coronary arterial tree with the blood returning through the non-coronary collaterals. Cardioplegia could be continued, providing myocardial protection and arrest.

Agglutinates that might have escaped into the systemic circulation may not cause any organ damage as rewarming would lead to de-aggregation of the cells. Anticoagulation or hemodilution do not help out in these situations. In such cases, speedy direction should entail taking up the core temperature to normothermia synchronous with warm retrograde myocardial flush. Any hemolysis or end-organ damage arising should then be tackled.

Laboratory assessment for CAD involves those correlated with haemolysis, and others correlated with the amount and activity of cold agglutinin antibodies [6]. There may beimprecision and consequential interobserver variance in bringing off antibody titers,as the end point of the reaction is instinctive [7]. Thermal activity (TA) harmonizes antibody activity to temperature and is outlined time and time again by quantifying the maximum temperature at which agglutination is declared *in vitro* . Climbing TA denotes auto antibody activity at warmer temperatures and thus aids complement fixation with good grace, with definite red blood cell hemolysis [6,7].

The question of whether there should be a pre-pump routine of screening for cold agglutinin disease remains unanswered. Quite a few case statements of perioperative problems due to cold agglutinins that are started up by induced hypothermia, involving RBC agglutination, hemolysis, and thrombosis are found in literature [6,8,9]. Large reports have remarked that such problems occur only scarcely [1], but how frequently, is a mystery, creating contradictions in execution of pre-pump assessment, result outlining, and operative direction of individuals encountering heart operations. Not surprising then, that most transfusion systems do not modify pre-pump assessment for these individuals, since the rarity of unlucky events verifies this outlook of assessment for heart surgery. Patient risk is best managed by preoperative clinical evaluation for potentially pathogenic cold agglutinins and intraoperative vigilance for agglutination.

Prior to surgery, checking for authentication of CAD is put forward as reasonable, involving review of a history of hemolysis or acrocyanosis and consideration of the cause of anemia if present. In our patient, although there was a decrease in the hemoglobin preoperatively, we could not fully investigate the patient given her worsening functional status that prompted us to consider emergency surgery. Similarly, the acute elevation of TLC was as cribed to the stress of progressive hemodynamic deterioration and although cultures were sent, we did not wait for the reports. In retrospect, her acute decrease in hemoglobin could have been due to acute hemolysis. Individuals with typical or definite cold agglutinin disease should be directed for an audience with the hematologist, and supplemental laboratory assessment to signal the antibody present, may be preferable. Operations should be lined up lacking hypothermia or, at least, at a temperature above TA of the cold agglutinins. Auxiliary proceedings for perioperative direction may be imperative if hypothermia is certain or with CPB conventions that avoid long durations of systemic hypothermia. Preoperative plasma pheresis may be a useful adjunct, especially in patients requiring operation under profound hypothermia and circulatory arrest. An in-line blood warmer should be considered to minimize cold agglutinin binding to transfused red cells.

During the operation, scrupulous surveillance of the patient and cardioplegia tubing course is warranted for RBC agglutination and hemolysis, lest cold agglutinins hither to undetected be present. If agglutination or hemolysis is noted, cold cardioplegia should be directly abandoned and the patient warmed as soon as possible. Agglutination in the cardioplegia tubing course can present as RBC disjunction, high pressure in the cardioplegia line, or difficulty in distribution of cardioplegia. Perfusionists should consistently pay attention to the heat exchanger and proximal cardioplegia line for agglutination before unlocking the line to distribute cardioplegia to the coronaries. We did not initially any early thrombus formation in the cardioplegia lines which might have alerted us to the possibility of cold agglutinin disease much earlier.

In cold agglutinin disease, the liver generally conducts withdrawal of Complement 3b (C3b) tagged red cells from circulation in a process known as extravascular hemolysis. If supplemental movement of the complement system occurs, the effect is the shaping of the C5 convertase enzyme (C4b2a3b), which then hews C5 to yield C5a and C5b. The C5b complement shard can then round up the complement membrane attack complex to create a pore in the RBC membrane with osmotic hemolysis as the end result. The occupancy of legions of complement regulatory proteins generally wards off this lethal attack on RBCs. This ravelled complement synchronization delineates thedeprivation of intravascular hemolysis in cases with cold agglutinin disease, such as the one under discussion [10-16].

To conclude, IgM autoantibodies agglutinating RBCs can cause microembolic complications during CPB. Clumps/clots in CPB during hypothermia in spite of adequate heparinisation should raise a suspicion of cold agglutinin disease (Figure 2).

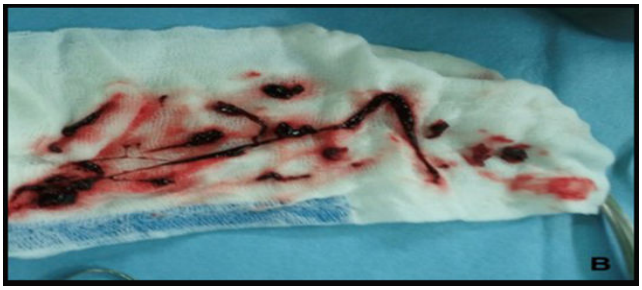

Figure 2: Clumps/clots taken out from the CPB circuit during hypothermia in spite of adequate heparinisation.

The premise that preoperative sorting of patients for cold agglutinins as part of usual practice would benefit patients, may not be correct [17]. With intraoperative recognition, the only options available are warm ante grade and retrograde cardioplegia and normothermic CPB. Options of off-pump cardiac surgeries should also be considered in CAD patients, especially coronary artery bypass graft surgeries, so that usage of hypothermic CPB and cold cardioplegia is precluded. A novel method of using intravascular catheter to maintain normothermia during surgery has also been devised. The Thermogard® XP system (zoll medical corporation) is approved by the U.S. Food and drug administration for use in cardiac surgery patients, to maintain normothermia during surgery. This was successfully used in CAD patients to prevent intraoperative clumping during cardiac surgeries. A multidisciplinary approach by team of anesthesiologist, surgeon, perfusionist and hematologist to decide on the perioperative care and management of the patients is imperative to decrease morbidity and mortality, thereby improving clinical outcomes.

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