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Case Report

Cold Agglutinin Disease and Cardiac Surgery: Pitfalls to Avoid

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Abstract

Cold agglutinin (CA) disease is an autoimmune disease characterized by the presence of high concentrations of circulating antibodies, usually IgM, directed against red blood cells, causing them to agglutinate and undergo lysis. It is a form of autoimmune haemolytic anaemia, specifically one in which antibodies bind red blood cells only at low body temperatures, typically 28 - 31°C. Patients with CA needing coronary artery bypass surgery (CABG) will need planning including multiple subspecialty involvement (Cardiology, Hematology), appropriate laboratory testing, keeping the theatre temperature at 27°C and transfusion to be done by blood warmer at 37°C for a successful outcome. We describe a case where a hybrid revascularization strategy was adopted with excellent outcomes.

Keywords: *Hemolysis; Cold Agglutinin Disease; Cold Cardioplegia; Off-pump Bypass*

Introduction

Cold agglutinin (CA) disease is an autoimmune disease characterized by the presence of high concentrations of circulating antibodies, usually IgM, directed against red blood cells, causing them to agglutinate and undergo lysis. It is a form of autoimmune haemolytic anaemia, specifically one in which antibodies bind red blood cells only at low body temperatures, typically 28 - 31°C [1]. These antibodies are present in most humans but are rarely of clinical significance because they do not react at temperatures that are normally seen by the blood [2].

Cold hemagglutinin disease (CHAD) is characterized by the formation of CA that is sufficiently active at temperatures achieved in the peripheral circulation, such as the distal extremities on exposure to cold, allowing haemolysis or agglutination to occur [3,4]. It is important to distinguish between CA and CHAD in that one represents a benign variant of normal and the other is a pathologic process. The benign and pathologic autoantibodies are directed toward the same common red blood cell antigens, most commonly IH, I, or i, but differ in that the benign autoantibodies are usually polyclonal, cause agglutination or complement fixation at < 25°C, and have titres < 64 at 4°C and less than 16 at 22°C [2]. The antibodies in CHAD are usually monoclonal, cause agglutination or complement fixation at 30°C to 37°C, and have titres > 512 at 4°C and > 128 at 22°C. CHAD is responsible for 16% to 32% of all autoimmune haemolytic anaemias in both children and adults, with an estimated prevalence of 10 to 16 cases per 1 million people [4-6]. With rare exception, CHAD almost exclusively involves immunoglobulin-M autoantibodies [4-7].

Cardioplegia is the deliberate paralysis of the heart during cardiac surgery, during which time cardiopulmonary bypass (CPB) on a heart-lung machine maintains the circulation. The rationale for cardioplegia is the initiation and/or maintenance of cardiac arrest during heart surgery, provision of a "bloodless" surgical field, reduction of the intraoperative metabolic demands of the heart, and protection against ischemia-reperfusion injury [8]. Myocardial protection via cardioplegia classically relies on diastolic arrest by means of a potassium-containing solution of blood ± crystalloid as well as cooling of the heart. Although "tepid" and "warm" cardioplegia have undergone considerable study in the past [9], most patients operated on today receive cold cardioplegia. In addition, patients generally undergo systemic cooling, either passive or active, to reduce both conductive rewarming of the heart and the oxygen requirements of the brain and other organs.

Case Report

69-year old woman was admitted to the coronary care unit (CCU) with symptoms of classical angina pectoris and a peak high-sensitivity troponin = 49 ng/L (normal = < 26 ng/L) on a background of diet-controlled diabetes mellitus, hypercholesterolemia, hypertension with multiple antibiotic allergies (penicillin and sulfa allergy manifesting as a rash). Her current medications include Aspirin 100 mg once daily, Telmisartan HCT (80/12.5) 1 tablet once daily, Rosuvastatin 20 mg once daily and Metoprolol 25 mg twice daily. The admission ECG showed sinus, normal axis with no localizing ischemic changes. Her admission laboratory testing showed normal renal and liver function tests but her hematology testing were deranges with Haemoglobin (Hb) = 82 g/dL (low) and Red Cell Count (RCC) = 2.47 x 10^12/L (low). Haptoglobin and blood film testing were requested. Haptoglobin = < 0.8 mg/dL (low) Haemolytic Anaemia (HA). The blood films showed agglutination when the sample was warmed to 37°C. CHAD was suspected and confirmed by a moderately positive Coombs test for C3D and identification of Auto2 Cold Antibodies. The planned inpatient invasive assessment was deferred and urgent hematology referral was made. The patient was treated with Rituximab and made a slow but steady recovery.

Two months post diagnosis and management, the patient was reviewed and an outpatient Bruce treadmill stress test was completed. The test was positive for reversible ischemia (poor effort capacity of 1.3 minutes with dyspnoea and inferolateral ST depression). She was re-referred for an invasive assessment. Invasive assessment via right trans-radial catheterization showed two-vessel coronary artery disease with a totally occluded left anterior descending coronary artery (LAD) in the proximal third, an eccentric and ectatic mid third 80% stenosis in the left circumflex coronary artery (LCX) and a dominant, diffusely diseased right coronary artery (RCA) with a mid-third eccentric and ectatic 30%. Left Ventricular (LV) angiography confirmed maintained LV systolic function at > 60%. The patient was referred for inpatient CABG with consultation with both Hematology and Cardiology. Given her complex medical background, the decision was made to adopt a modified Hybrid Coronary revascularization (HCR) strategy with an off-pump Left Internal Mammary Artery graft to the LAD (LIMA-LAD) and a staged percutaneous coronary intervention (PCI) to her mid LCX in two weeks to help reduce the operating time.

Surgical strategy

The patient was admitted a week prior to her planned LIMA-LAD. Baseline bloods including group and cross match and red cell phenotyping, cold agglutinin titre and establishment of thermal amplitude (temperature at which haemolysis occurs) were completed. The patient was transfused red cells (transfusion done by blood warmer at 37°C) with the aim for the pre-operative Hb ≥ 120 g/dL prior to surgery. In addition, strategies were made for the availability of red cells for transfusion by blood warmer at 37°C intraoperatively. On the day of the procedure, the theatre was warmed to 27°C (Warm Theatre) prior to commencement of the procedure. During the procedure, forced-air patient warming with 3M™ Bair Hugger™ System was done. The procedure was smooth and the LIMA harvested in conventional pedicle fashion and anastomosed to the mid LAD with a 7.0 Proline continuous suture. Heparin was reversed and the patient had an uneventful post-operative course. On day 5 post LIMA-LAD, the patient was loaded with Clopidogrel in anticipation of her PCI to her mid LCX.

PCI strategy

Repeat invasive assessment via left trans-radial catheterization confirmed a patent LIMA-LAD. The LCX was measured by quantitative coronary assessment (QCA) to be a 3.5 mm vessel. The mid LCX was "direct stented" with Bare Metal Stent (BMS) x 1 (Medtronic™ Integrity™ 3.5 mm x 15 mm). The stent was deployed at 16 atmospheres upsizing the 3.5 mm stent to 3.75 mm. It was a successful PCI with TIMI 3 flow, no residual dissections or perforations. The choice of deploying a BMS was made to avoid long duration of dual antiplatelet therapy (DAPT) given her background haematological issues (transfusion independent HA with active but well compensated haemolysis).

Discussion and Conclusion

Cold agglutinins are autoantibodies that agglutinate red blood cells at low temperatures, leading to haemagglutination and haemolysis. Though they are generally of no clinical significance, during cardiac operation with hypothermia and cold cardioplegia, agglutinins can produce systemic complications. The case discussed is uncommon as the prevalence of CA is 1 in 300,000 with various reports stating 7 - 25% of HA cases are due to CA [1]. However, on the occasion when a CA case needs CABG, it is prudent to have a multidisciplinary approach, making strong strategies to avoid complications. There are strategies proposed by several surgical units [10-13] but it is important to cater all strategies which suit the patient and the local surgical unit.

Although a hybrid approach is valid strategy, it is not the unique alternative to manage this rare situation. Off-pump surgery could also include total revascularization thereby avoiding staged PCI. Another alternative is to manage the temperature of cardiopulmonary bypass (CPB) and cardioplegia by using normothermic cardiac operation with warm cardioplegia. Continuous retrograde hyperkalemic infusion and intermittent antegrade infusion of warm cardioplegia with normothermic CPB is a recognized method to avoid hypothermia and excessive activity and metabolism of the heart, and to provide a suitable operative field, particularly for surgeons not used to working off-pump [14].

Certain patients undergoing off-pump coronary surgery can undergo spontaneous hypothermia. On-pump surgery in these instances is a valid alternative making it easier maintain a higher temperature during surgery. Normothermic on-pump heart-beating (OP-HB) approach which is CPB without aortic cross- clamping can be considered [15]. In the rare combination of aortic stenosis (AS) and cold agglutinins (CA), On-pump surgery may be the only surgical alternative [16]. With the emergence of Transcatheter Aortic Valve Implantation (TAVI), this could provide a good alternative in this small, unique and rare combination of AS and CA.

Problem-solving strategies for the incidental appearance of CA detected during cardiac surgery should be put in place [17]. We propose that red cell phenotyping, cold agglutinin titre and establishment of thermal amplitude (temperature at which haemolysis occurs) should be complete and made available pre CABG. In addition, though for our patient the advice was to aim for the pre-operative Hb ≥ 120 g/dL prior to surgery, the base principles of ensuring that the Hb level should be adequate to maintain tissue perfusion during and post CABG should be the goal. Ideally, the patient should be transfused red cells where the transfusion should be done by a blood warmer at 37°C. Furthermore, strategies should be made for the availability of red cells for transfusion by blood warmer at 37°C intraoperatively as well. On the day of the procedure, it might be worthy to warm the theatre 27°C (Warm Theatre) prior to commencement of the procedure and consider utilizing forced-air patient warming with 3M™ Bair Hugger™ System. Finally, if suitable and if local expertise is available, plan for a Hybrid Coronary Revascularization (HCR) strategy [18] given its obvious benefits.

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