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Cold Agglutinin Disease Coexisting with Left Main Coronary Artery Involvement and Ventricular Dysfunction- a challenging triad

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Abstract

Cold hemagglutinin disease (CHAD) is a rare autoimmune condition characterized by cold-reactive antibodies causing hemagglutination and complement-mediated hemolysis. This case report details the successful management of a 56-year-old male with CHAD, coronary artery disease, and left ventricular dysfunction. The patient underwent coronary artery bypass grafting (CABG) amid challenges, including a rapid drop in hemoglobin levels, limited compatible blood supply, and cardiac comorbidities. Treatment involved rituximab, bortezomib, and a meticulous perioperative protocol to prevent hypothermia. The multidisciplinary approach, including hematologists, anesthetists, and surgeons, played a crucial role. The patient achieved stable hemoglobin levels, and CABG was performed without intraoperative blood transfusion. Postoperatively, careful monitoring and interventions ensured a successful outcome, highlighting the importance of tailored management in CHAD cases. The case underscores the significance of close collaboration among medical specialties for accurate diagnosis and effective perioperative management of CHAD.

Keywords: NIL

Introduction

Cold hemagglutinin disease (CHAD) is an autoimmune condition resulting from cold-reactive antibodies, leading to hemagglutination and complement-mediated haemolysis when the body temperature drops. This poses considerable complications for patients undergoing cardiac surgery with hypothermia (1). Here, we present a case of successful treatment for CHAD coexisting with coronary artery disease and left ventricular dysfunction.

Case Report

A 56-year-old male, with no history of diabetes or hypertension, experienced fever followed by acute coronary syndrome. He was diagnosed to have non-ST-segment elevation myocardial infarction (NSTEMI). He underwent coronary angiography at another hospital and was referred to our hospital for further management, including coronary artery bypass grafting (CABG). Echocardiography revealed moderate left ventricular systolic dysfunction with

ejection fraction of 35%, stage II diastolic dysfunction and mild mitral regurgitation. As per documented information, the patient presented with a haemoglobin level of 9.1 gm/dL during the coronary angiography. Subsequent to the pre-surgical evaluation, there was a notable drop of 3 gm/dL in haemoglobin within 48 hours and there was no compatible blood available on cross match.

Patient was evaluated for haemolytic anaemia and haemolytic markers were positive (indirect bilirubin was 2.24 mg/dL, LDH (lactate dehydrogenase) was 506 IU/L, reticulocyte count was 9.1% and creatinine was 1.6 mg/dl). Polyspecific direct antiglobulin test (DAT) was positive, following which he was started on methylprednisolone 500 mg/day for 4 days and later on prednisolone at 1 mg/kg/day. A monospecific DAT was performed after 48 hours, showed positive for C3d and negative IgG, indicating the presence of cold hemagglutinin disease. Cold agglutinin (CA) titre was 1:256 with a thermal amplitude of 30ºC. However, there was no clinical evidence of a clonal disease (no lymphadenopathy or hepatosplenomegaly) except pallor and icterus.

A detailed investigation for assessing aetiology of CHAD was done. Contrast enhanced computerised tomography (CECT) chest and abdomen were unremarkable. Antinuclear antibody immunofluorescence test was negative. Paraprotein workup including serum protein electrophoresis, immunofixation and serum free light chain analysis showed no abnormalities. Bone marrow aspirate and biopsy revealed erythroid hyperplasia with no signs of any clonal disease (Figure 1).

Patient was started on rituximab 375 mg/m^2 weekly for 4 weeks. Meanwhile, the patient witnessed a drop in haemoglobin levels, reaching as low as 5.3 gm/dL. Plasmapheresis was discussed but considering the cardiac comorbidities and no compatible blood unit availability, the same was withheld. Intravenous immunoglobulin was also discussed as a rescue option. Bortezomib 2 mg once a week, was sandwiched between rituximab doses and four doses of the same were administered (Figure 2). Rapid taper of steroid was started considering limited role of the same in CHAD. Following the administration of the first dose of rituximab and bortezomib, there was a subsequent ascent in haemoglobin levels and by the completion of the four doses, the haemoglobin level of 12.1 gm/dL and CA titres of 1:32 were attained.

The patient was further scheduled for coronary artery bypass grafting (CABG), and a repeat echocardiogram demonstrated consistent findings with the previous examination. Blood investigations showed a haemoglobin level of 12.1 mg/dL, a haematocrit of 38.6%, a total leukocyte count of 8080/µl, platelet count of 176,000 /µl, lactate dehydrogenase level of 256 IU/L and a reticulocyte count of 9.2%.

He was continued on low tapering dose of prednisolone along with . He was planned on prophylactic gram positive and gram-negative antibiotics coverage in view of compromised state. Throughout the surgery, a strict protocol was followed to prevent hypothermia. The administration of blood products and intravenous fluids was conducted through a blood warmer, and the optimal temperature in the operating theatre was diligently maintained. Off pump CABG was done using left internal mammary artery to left anterior descending artery, radial artery to left sided target vessels and reverse saphenous vein to posterior descending artery. No intraoperative blood transfusion was required and he was shifted to surgical ICU in stable condition.

After shifting to the ICU, the patient's initial arterial blood gas analysis revealed a haemoglobin level of 7.8 mg/dL. Subsequent administration of one unit of leuco-reduced red blood cells via a blood warmer channel resulted in the recovery of haemoglobin levels to 13.3 mg/dL. The patient remained stable and was successfully extubated on same day. On postoperative day 1, his haemoglobin level was 10.8 mg/dl, bilirubin was measured at 2.28 mg/dl, reticulocyte count was 3.2% and LDH was 395 IU/L. On the second postoperative day, haemoglobin levels dropped to 7.5 mg/dl, prompting transfusion of two units of leuco-reduced red blood cells using similar approach. Concurrently, CA titres were assessed, revealing a titre of 1:8, reticulocyte count of 4%, LDH 343 IU/L and bilirubin was 0.85 mg/dL, indicating no haemolysis. Urine routine microscopy indicated a significant presence of red blood cells, possibly traumatic, explaining the blood loss. This was potentiated by dual antiplatelets and the patient was transitioned to a single antiplatelet regimen until

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the haematuria resolved. Given the ventricular dysfunction, the patient was maintained in a euvolemic state. By the fifth day, the haemoglobin level recovered to above 10 mg/dL and grossly clear urine, prompting a switch to dual antiplatelet regimen. The patient was discharged with cardiac medications. Steroid was completely tapered off within 8 weeks. Two months after initial diagnosis of CHAD and one-month post-surgery, patient is clinical stable with haemoglobin above 12 gm/dL.

Discussion

CHAD is a rare condition, and benign CA, although a variant of normal, rarely are detectable on routine screening. CHAD is responsible for 16% to 32% of all autoimmune hemolytic anaemias in both children and adults, with prevalence of 10 to 16 cases per 1 million people (2). CHAD may be a primary disorder or be secondary to malignancy (most commonly lymphoma), infection (infectious mononucleosis or Mycoplasma pneumonia infection), or autoimmune diseases (3).

The significance of CAs is contingent on two factors: the plasma concentration and the thermal range at which hemagglutination takes place. Healthy individuals typically exhibit low levels of CAs in their sera, approximately 1:16; nevertheless, elevated titres increase the likelihood of CA activation. (3) Careful temperature monitoring must be undertaken at all levels to avoid CA activation causing catastrophic hemagglutination and haemolysis.

Managing CHAD is challenging as steroid, one of the most important drugs to treat autoimmune haemolytic anaemia (AIHA) does not work well in cold agglutinins. It is a common practice to start steroid as soon as AIHA is suspected. In warm AIHA, the same is tapered off very slowly over several months. However, there is limited use of steroid in CHAD, and the same was rapidly tapered off in this case. The only reason of not totally stopping steroid was some lab evidence of reduction of blood incompatibility on cross match after the pulse steroid administration, even before the first dose of other therapy was administered. As CA is IgM, the same can be removed through plasmapheresis but this is challenging, particularly in the presence of low hemoglobin, ventricular dysfunction, and left main disease. There is no compatible blood available to prime the circuit and transfusion of least incompatible blood may always be at risk of a haemolytic crisis and antecedent renal shutdown. The same may become catastrophic is the background of cardiac comorbidities. Maintaining a warm environment is also a challenge. Efficacy of rescue therapy with intravenous immunoglobulin is not well characterised in CHAD (4).

Upstream complement inhibition by sutimlimab, a C1s inhibiting monoclonal antibody is an option but availability of the same is an issue (5). Rituximab, a anti CD20 monoclonal antibody is an important agent which help in reducing the antibody titre and help in controlling the haemolysis. In case a clonal disease is documented, the same can be combined with bendamustine or fludarabine, a form of chemotherapy (6). If a rituximab-based therapy is ineffective or contraindicated, bortezomib, a proteasome inhibitor or daratumumab, an anti-CD38 monoclonal antibody, may be used, although evidence for the same are available only in form of case reports (7,8).

Managing a CHAD case requires careful consideration of specific factors.

- **Anaesthetic considerations**

During general anaesthesia, heat is lost in a number of ways; predominantly by surface cooling through radiation and convection mechanisms, accounting for up to 40% and 30% of heat loss, respectively (9).

Simple measures like employing warming mattresses and ensuring the heating of inhalational anaesthetic gases to 37°C, intravenous fluids, and blood products should not be overlooked.

Similarly, the operating room temperature should be kept around 22 degrees.

- **Surgical considerations**

Irrespective of the technique employed, it is essential to limit systemic cooling during CPB if used so as to maintain the systemic perfusion temperature. Our case was done as off pump CABG.

Minimizing the surgical time is key to averting heat loss from the opened chest cavity.

- **General considerations**

The haematologists serve as part of the multidisciplinary team approach in patient's risk

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stratification, guiding and interpreting the preoperative testing, and assisting with preoperative reduction of CAs

Challenges encountered while the management of this case

On presentation, our patient had severe anaemia, and there was a lack of compatible blood for cross-matching. The concurrent presence of coronary artery disease involving the left main and triple vessels, along with ventricular dysfunction, in association with this state, may precipitate heart failure and cardiac deterioration. Rituximab and bortezomib were promptly initiated in combination, but they can only supress new antibody production. The preformed antibody persists and continues to hemolyse. Combination of both the agents was used, considering the cardiac comorbidities, and an urgency to reduce the antibody production at the earliest in order to prevent use of a rescue therapy, administration of which had multiple challenges as discussed previously.

Several factors were instrumental in effectively handling the case and attaining a favorable result:

1. Attaining the antibody titer below 1:64 prior to surgery with aggressive use of rituximab and bortezomib combination.
2. Employing off-pump CABG, eliminating the need for CPB and improving temperature control for better maintenance at normothermia.
3. Post operative administration of blood transfusions only when hemoglobin levels fall below 8 gm/dL and using a blood warmer for all necessary transfusions.
4. Identifying the postoperative decrease in hemoglobin as attributable to catheter-related trauma rather than haemolysis.

With a confirmed diagnosis of cold agglutinin disease, the plan of care can be focused on measures to maintain the patient's blood temperature at normothermia throughout their hospitalization including use of normothermic cardiopulmonary bypass (if required) with warm myocardial preservation techniques to prevent fatal complications.

Conclusion

Close monitoring for agglutination, aggressive management of haemolysis with rituximab, and judicious use of steroid/bortezomib may achieve rapid restoration of haemoglobin possibly avoiding risky transfusion and is essential to prevent life-threatening events. Maintaining a heightened sense of suspicion and actively involving the haematology team, implementing measures across perioperative stages, is essential for accurate diagnosis and effective management.

The multidisciplinary team approach is vital to deal with the disease during the perioperative period. Strict vigilance for agglutination, haemolysis, and end organ damage is required to avoid life-threatening events.

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Figure 1 shows the peripheral smear (A & B) and bone marrow (C & D) slides. (A) Red cell agglutination is seen in a background of normal WBC and platelet counts (100x, Leishman stain), (B) higher magnification showing agglutination (400x, Leishman stain); (C) bone marrow is cellular with presence of trilineage haematopoiesis (40x, Leishman stain); (D) erythroid hyperplasia is seen and no atypical cell in the smear (400x, Leishman stain)

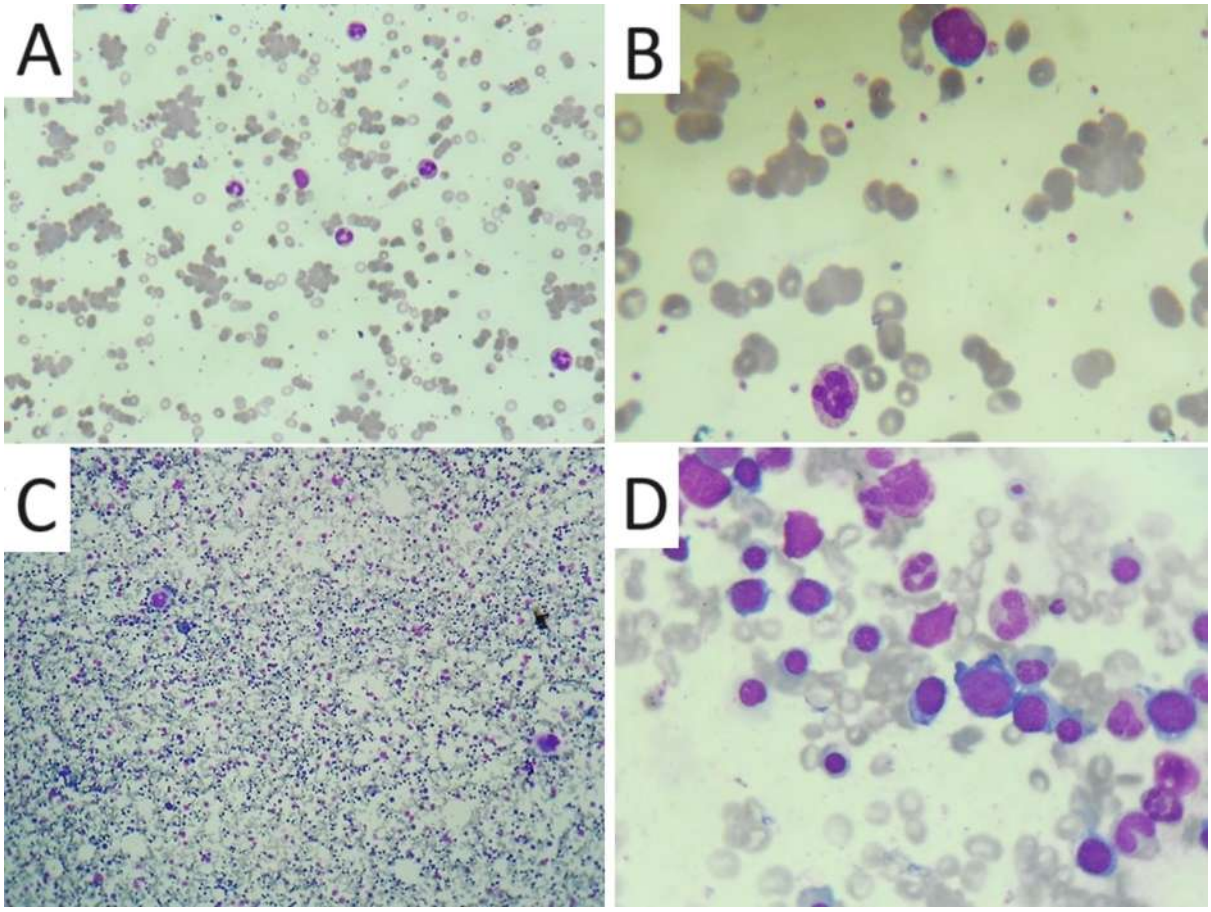

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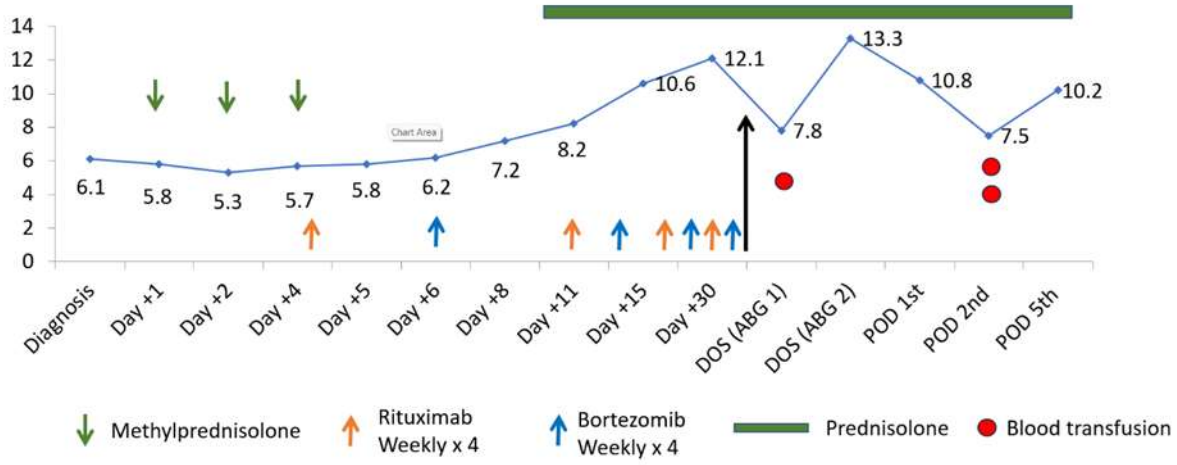
Figure 2 shows the trends in haemoglobin levels (blue line) and administration of methylprednisolone (green arrows), rituximab (orange arrows), bortezomib (blue arrows) during different phases of treatment. Red dots indicate the leuco-reduced blood transfusion in the post operative period.



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