Perioperative Challenges in Orthogeriatric Patients with Cold Agglutinin Haemolytic Anaemia: Case Report and Management Algorithm

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Abstract

Most published reports on cold agglutinin (CA) haemolytic anaemia (CAHA), a rare condition with significant perioperative management challenges, are from patients who have undergone cardiothoracic surgery with hypothermia. Here, we report a hip fracture patient with CAHA, and review the perioperative management. This is the second published case report regarding CAHA in an orthopaedic patient. An 86 year old female with a 4-year history of recurrent episodes of CAHA and multiple comorbidities (atrial fibrillation, hypertension, strokes, secondary epilepsy, vascular dementia, and type 2 diabetes mellitus complicated by diabetic retinopathy, osteoporosis, urinary incontinence, recurrent urinary tract infections, and multinodular goitre) was admitted because of a hip fracture. She was commenced on prednisolone a month prior the hip fracture. On admission, her haemoglobin was 69 g/L, lactate dehydrogenase 494 U/L, haptoglobin <0.1 g/L and the blood film showed red blood cell agglutination at room temperature, which dissociated at 37°C. She required transfusion of 5 units of packed red blood cells during her admission. Her management included intensive temperature monitoring, use of body thermal blanket, warming intravenous and irrigation fluids and medications before administration. Surgery was performed under general anesthesia on the 4th admission day. She received unfractionated heparin for venous thromboembolism prophylaxis, antibiotics for wound infection prophylaxis, continued prednisolone, and started anti-osteoporotic medications. The patient was discharged to another hospital for rehabilitation on the 7th postoperative day. Perioperative examination and treatment of orthogeriatric patients with CAHA is challenging. The pathophysiology of CAHA is shortly revied and a management algorithm is presented.

Keywords: Cold agglutinin; Haemolytic anaemia; Hip fracture; Orthogeriatric; Perioperative management

Abbreviations: AIHA: Autoimmune Haemolytic Anaemia; CA: Cold Agglutinin; CAHA: Cold Agglutinin Haemolytic Anaemia; CAD: Cold Agglutinin Disease; CAS: Cold Agglutinin Syndrome; CRP: C - reactive protein; Hb: Haemoglobin; HF: Hip Fracture; LDH: Lactate Dehydrogenase; PRBC: Packed Red Blood Cells; RBC: Red Blood Cell; TE: Thrombotic Event

Introduction

Hip fracture (HF), a substantial and growing global public health problem, is associated with multimorbidity. In geriatric patients undergoing HF surgery, preoperative anaemia is a common (about 45%) [1] and important factor for poor, including fatal, postoperative outcomes [2-5]. While anaemia in most patients is iron deficient, rare causes, such as haemolytic anaemia (HA), which can be life-threatening and/or complicated by thromboembolic [6]
An 86 year old Caucasian female with a 4-year history of recurrent episodes of CA-related haemolysis presented because of a HF. Her past medical history also included atrial fibrillation (anticoagulated with dabigatran), hypertension, and strokes with secondary epilepsy, vascular dementia, and type 2 diabetes mellitus complicated by diabetic retinopathy, osteoporotic vertebral fracture, urinary incontinence, recurrent urinary tract infections, and multinodular goitre with subclinical hyperthyroidism. The presence of CAs was identified in 2016 and confirmed thereafter several times; over the following years she developed CAHA. In 2019 she was admitted to hospital with a transient ischaemic attack complicated by community acquired pneumonia, her haemoglobin (Hb) dropped to 90 g/L (reference: >120g/L) during the admission. The following year, in early 2020, she was admitted with a urinary tract infection and evidence of acute haemolysis (Hb 71 g/L) requiring transfusion of 2 units of packed red blood cells (PRBC); the Hb stabilised in the mid 90s once the infection was treated. Several months later she presented with E.coli urosepsis once again accompanied with acute haemolysis (Hb of 71 g/L) and received 2 units of PRBC. She demonstrated a strongly positive direct Coombs test specific for complement component C3d, a very high cold agglutinin titre of \(>4096\) at \(4^\circ\)C, raised lactate dehydrogenase (LDH 398 U/L, reference range: 120-250 U/L) and decreased haptoglobin (<0.1 g/L, reference range: 0.3-2.0 g/L). Serum protein electrophoresis detected an extra band upon a polyclonal background which was identified as IgM kappa. Her Hb stabilised in the mid 80s once the infection was treated and she was commenced on prednisolone (110 mg twice daily), telmisartan (40 mg), spironolactone (25 mg), atorvastatin (40 mg), sodium valproate (200 mg twice daily), metformin modified release (1000 mg once daily), colecalciferol (1000 IU), calcium carbonate (600 mg), mirabegron modified release (25 mg), methenamine hippurate (1g twice daily), magnesium aspartate (1000 mg twice daily) and pantoprazole (40mg). A month later she experienced a left HF. On admission, her Hb was 69 g/L, mean corpuscular volume (MCV) 99 fl (reference range: 80-96 fl), absolute reticulocyte count 136.6 x10^6/L (reference range: 20-110 x10^6/L), LDH 494 U/L, haptoglobin <0.1 g/L, and the blood film showed RBC agglutination at room temperature, which dissociated at 37°C (Figure 1); her C-reactive protein (CRP) was 36.6 mg/L (reference: <6 mg/L) although no acute medical illnesses besides HF were detected on clinical examination and laboratory investigations. Serum ferritin was elevated (1756 ug/L, reference range: 30-370 ug/L) also indicating an acute phase reaction. Other haematinic and biochemical parameters including bilirubin, serum folate, vitamin B12, transferrin saturation, 25 hydroxy vitamin D and parathyroid hormone levels were in the normal range. Thyroid function blood tests confirmed subclinical hyperthyroidism with thyroid stimulating hormone (TSH) <0.03 mIU/L (reference range: 0.34-3.40 mIU/L), fT4 of 21.0 pmol/L (reference range:10.7-17.0 pmol/L), fT3 of 3.8 pmol/L (reference range:3.4-5.4 pmol/L) and TSH receptor antibodies <0.8 IU/L (reference: <1.8 IU/L). During this admission she required transfusion in total of 5 units of PRBC. Initially, she was transfused 2 units of PRBC in the emergency department, unfortunately, not warmed. Repeat blood test demonstrated Hb of 101 g/L which remained stable until surgery. Her management included intensive temperature monitoring, use of body thermal blankets, warming intravenous and irrigation fluids and all intravenous medications as well as meals and drinks before administration. Surgery was performed on the 4th admission day under general anaesthesia due to concerns over keeping the patient sufficiently warm under spinal anaesthesia. Intraoperatively 1 unit of warmed PRBC was transfused to compensate for estimated blood loss; on day 1 postoperatively her Hb was 99 g/L with no signs of haemolysis. However, on the 3rd postoperative day, despite thermal protection and temperature monitoring, a new episode of acute haemolysis occurred with Hb of 65 g/L, LDH of 501 U/L and haptoglobin <0.1 g/L; she received 2 units of warmed PRBC. No identifiable trigger for the haemolysis was identified, no episodes of hypothermia or fevers (body temperature was ranging between 36.3°C and 37.4°C postoperatively), as well as no signs of urinary, chest or skin infection recorded, but the CRP had peaked at 105.0 mg/L indicative of an inflammatory response; there was also a mild troponin I rise (31 ng/L, reference:<16 ng/L) on the 1st postoperative day. Postoperatively she received unfractionated heparin (5000 IU subcutaneously twice daily) for venous thromboembolism prophylaxis, an antibiotic (cefazolin sodium 2 g eight hourly on day 1, followed by oral cefalexin 500 mg six hourly) for wound infection prophylaxis, and continued prednisolone (62.5mg daily) per haematologist’s advice; antihypertensive medications were withheld for several days due to mild hypotension, dabigatran was withheld pre-operatively and
restarted when Hb was consistently >90g/L. The patient and her general practitioner were advised to commence adequate osteoporotic treatment with an antiresorptive drug. The patient was discharged to the rehabilitation hospital on the 7th postoperative day. Bone marrow biopsy was not organised due to patient’s preferences.

Figure 1: Blood films; demonstrating agglutination of red blood cells at room temperature (A), and dissociation of agglutination at 37°C (B)

Discussion

We report the second case of a patient with CAHA and HF, focusing on perioperative management challenges and created a diagnostic and treatment algorithm for the perioperative care of orthogeriatric patients. CAHA represents “the least uncommon” disorder among the heterogeneous group of autoimmune haemolytic anaemias (AIHAs), diseases characterised by RBC agglutination and premature destruction due to autoantibodies against surface erythrocyte’s antigens. This group of diseases encompasses cold agglutinin disease (CAD), cold agglutinin syndrome (CAS), warm AIHA, mixed AIHA, paroxysmal cold hemoglobinuria, drug-induced and atypical AIHA [10-14]. There are two main subtypes of CAHA [12,15] primary CA disease (CAD), which is defined as a low-grade clonal lymphoproliferative B-cell bone marrow disorder [16-18], characterised by a monospecific direct antiglobulin test (DAT) strongly positive for complement fragment C3d and a CA titre of 64 or higher at 4°C [12], and secondary CA syndrome (CAS) when presence of CA underlies other diseases and causes, such as systemic autoimmune disorders, aggressive lymphomas [8], infections (Mycoplasma pneumoniae, Epstein-Barr virus [19]), organ transplantation, solid tumours or drugs [20]. CAHA accounts for 25%-30% of all AIHAs [15]. CAD is rare, with an estimated prevalence of 13-16 cases per 1 million people [21-23]; the median age at diagnosis is ≥ 67 years [24]. Most published reports on CAHA describe patients who have undergone cardiac surgery [21,25] or organ transplantation [26,27] often with hypothermia during the procedure. In the orthopaedic literature we found only one case report of a patient with CAD and HF (not mentioned whether surgery performed) [28], one report on a patient who underwent lumbar laminectomy for lumbar canal stenosis [29] and one geriatric patient with polytrauma in whom CAS was induced by reactivation of cytomegalovirus infection [30]. The pathogenesis of AIHA including CAHA is complex, involving humoral, cellular and innate immunity and still not fully understood [15,31]. CAs are circulating autoantibodies, commonly of the IgM class, directed against polysaccharide antigens located on the erythrocyte surface. Presence of CA often does not affect daily living, patients may be unaware of the condition and CAHA may be discovered incidentally during surgery. The benign CAs cause haemagglutination and complement fixation at less than 25°C, therefore, only CAs with thermal amplitudes from 28°C-30°C (optimal temperature of reactivity with erythrocyte antigens) are of clinical significance [9,21,22,32]. Low temperature activates CAs and the classical complement cascade resulting in haemagglutination, lysis, increased blood viscosity, microvascular thrombosis and organ failure which can be fatal [22]. In both CAD and CAS, the IgM bound to antigens on the surface of RBCs causes complications involving two mechanisms [22,33]: (i) activation of the classical complement pathway (by binding of the C1 complex) and phagocytosis of erythrocytes opsonized with complement protein C3b results in predominantly extravascular RBC destruction and modest intravascular haemolysis, and (ii) agglutination of erythrocytes in acral body parts reduces microcirculation, causes vasospasm and acrocyanosis.

In individuals with mixed AIHA (warm and cold) a high titre of CAs coexist with DAT positive for IgG and C3 [12], while in patients with paroxysmal cold haemoglobinuria (mainly in children with a history of a viral “flu-like” infection) a temperature-dependent IgG autoantibody binds to the P antigen on RBCs in cold, detaches from RBCs when the temperature
≥ 37°C but the activated complement causes intravascular haemolysis [12]. In CAHA the haemolytic process is entirely complement dependent [22,34] and low levels of complement proteins limit the rate of RBC destruction [9]. Many patients with CAD are only mildly anaemic, blood transfusions are required by about half of them [15]. However, trauma, major surgery, febrile infections or inflammation triggers an acute phase reaction which may increase complement C3 activity by 100 to 1000-fold resulting in a significant exacerbation of haemolysis and anaemia [15,30,32,34]. The clinical presentation of CAHA is influenced by many factors including subtype of CAHA, thermal amplitude, rate and degree of haemolysis, underlying diseases, concomitant comorbidities, bone marrow status and its compensatory abilities. Not surprisingly, the outcomes are highly variable: asymptomatic, mild-moderate anaemia, acrocyanosis, fatigue, life-threatening haemolysis, infections, pulmonary embolism [7,14,15,19,22,35]. The severity of anaemia at onset correlates with the recurrence of relapses, refractoriness, and fatal outcome [27]. Our patient demonstrated recurrent episodes of severe CAHA (Hb<80g/L on multiple occasions) and fulfills the diagnostic criteria for CAD proposed by the First International Consensus Group for autoimmune haemolytic anaemias [12,15]: chronic (over 4 years) haemolysis, absence of any disorders known to precipitate CAS (no overt malignant or systemic autoimmune disease, or viral infections, or drugs associated with AIHA), DAT positive for C3d and CA titre ≥64 at 4°C. Our patient, however, did not have a bone marrow biopsy to confirm a CA-associated lymphoproliferative disorder (this is not required for diagnosis). A recent study demonstrated that in AIHA cases without features suggestive of a lymphoproliferative disorder the value of a routine bone marrow biopsy is low [36]. The haemolysis on the 3rd postoperative day when all precautions were taken to avoid cooling of the patient and to keep the administered meals and drugs warm, requires an explanation. There were no obvious signs of an infection or evidence of any other condition that might trigger haemolysis except a significant post-operative inflammatory response with increased CRP. A similar “paradoxical” haemolysis (at normal-elevated body temperature) associated with acute inflammation, febrile episodes and increased concentrations of CRP has been observed in the only one other reported in the literature patient with HF and CAD [9,28]. The authors hypothesised that the paradoxical haemolysis in CAD is mainly due to increased complement synthesis caused by acute phase responses. CAHA has also been reported in a patient during room temperature fluid resuscitation [37]. Of note, a substantial number of patients (30-70%) with CAD may experience an exacerbation of haemolysis during elevated body temperatures [22,28]; this is of practical importance and should be considered in the management of patients with CAHA. Furthermore, in about 25% of CAHA patients with increased CRP levels absence of any identifiable infection was observed [15].

Overall, our patient, who presented with acute CAHA and HF, required immediate surgery, had anaemia corrected preoperatively and during surgery, and then experienced a new haemolytic episode with significant drop in Hb on the 3rd postoperative day due to the acute phase reaction. The perioperative management challenges in our patient’s care included: 1) maintaining normal body temperature, 2) warming of intravenously administrated fluids and blood products, 3) rapidly correcting anaemia, 4) liaison with the operating theatres, anaesthetic, orthopaedic and haematology teams, 5) nursing staff education, 6) appropriate short-term (high risk of perioperative thromboembolism because of CAHA and immobility) and long-term (chronic underlying diseases requiring therapeutic anticoagulation, e.g., atrial fibrillation, advanced cerebrovascular disease) use of anticoagulants despite surgery-related blood loss and ongoing episodes of symptomatic haemolytic anaemia, 7) prevention of infectious complications, and 8) avoiding an exacerbation of comorbid disorders, including optimising postoperative pharmacotherapy by choosing drugs not associated with AIHA.

In the perioperative care of patients with CAD in addition to non-pharmacological management (thermal protection) specific considerations should be given to prevention and treatment of thromboembolism, infections and selection of appropriate drugs (avoidance of medications associated with AIHA). About 10-20% of AIHA patients experience a venous, arterial and cerebral thrombotic event (TE) [6,12,23]. In patients with CAD the risk of such complications is at least 2-fold higher compared to individuals without CAD [38]. At 1 year after CAD diagnosis TE occurred in 7.2% of patients vs. 1.9% of controls, at 3 years in 9.0% vs. 5.3%, respectively, at 5 years in 11.5% vs. 7.8%, respectively [23], and over a 10-year period in 29.6% vs. 17.6%, respectively [38]. Similar rates were observed in Japan (34.9% vs. 17.9%, odds ratio 2.8) [39]. Active haemolysis, greater severity of anaemia and higher LDH levels are associated with an increased risk of thrombosis [12]. Europeans with CAD demonstrated higher rates of venous thromboembolism [38,40], while in the Japanese patients the arterial TEs were particularly high [39]. The pathogenesis of hypercoagulability in AIHA involves activation of the complement system and haemolysis (release of extracellular haemoglobin and heme) both of which promote activation of neutrophils, induce inflammation and vascular damage [41,42]. In CAD, compliment-mediated haemolysis and thromboembolism risk persist year round [43]. It is possible that the stroke and TIs in our patient were, at least partially, CAD-related. Obviously, anticoagulation is important during episodes of acute haemolysis and also in all patients with common risk factors for TE (e.g., atrial fibrillation, reduced mobility, active cancer).

The relationships between CAHA and infections are bidirectional: infectious agents may cause AIHA onset and relapse,
and on the other hand, infectious complications can be triggered by AIHA as a result of viral and bacterial reactivations due to immune dysregulation, use of immunosuppressive treatments and effects of the underlying chronic disorders. Infections in AIHA occur in 6-14% of cases, and approximately in one of 4-5 patients result in a fatal outcome (hazard ratio of 4.8) [7].

Most orthogeriatric patients have multiple chronic conditions requiring complex pharmacotherapy. Awareness regarding drug-related CAHA and use of appropriate medications remains an underestimated issue in the peri- and postoperative care of patients with CAD. The development of warm AIHA has been associated with over 150 drugs [12]. Drug associated AIHAs may be caused by both drug-dependent antibodies that activate an immune response only while the drug is present and drug-independent non-specific antibodies which create an autoimmune response in the absence of the offending drug [11,12,44-48]. Drug-induced AIHA is associated with high mortality (up to 23%) [47]. The most common drugs associated with AIHA in the 1970s were methyldopa and penicillin, in the beginning of the 2000s were cefotetan, ceftriaxone [11,44] and piperacillin [49]. Current data indicates as drugs inducing AIHA antibiotics (cefotetan [50,51], ceftriaxone [52-55], penicillins [56], trimethoprim-sulfamethoxazole [57]), NSAIDs (diclofenac [47]), antineoplastic/chemotherapeutic drugs [11,12,46,58], cimetidine [59], and contrast media [60]. Our patient did not receive any of the medications known to be associated with drug-associated AIHA, and transfusions of PRBC were performed when anaemia became life-threatening.

The appropriate therapy of AIHA, including CAHA, is dependent on the correct diagnosis and its severity. The cold-induced IgM-mediated agglutination in some patients can be prevented by keeping the body temperature and circulating fluids at 37°C and avoiding substances associated with the disorder. Drug treatment is indicated in symptomatic individuals. Pharmacotherapy targets two main pathophysiological mechanisms: B-cell lymphoproliferation and activation of the classic complement pathway. In the perioperative period, blood transfusion is the most rapidly effective measure. Other options in patients with severe CAD include plasma exchange to remove IgM (highly effective but short-lived since IgM production persists), inhibition of autoantibody production by chemo-immune therapy (leads to long-term remission, but the response is delayed on average for 1.5 months plus side effects - infections, immunosuppression), and inhibition of the complement cascade activation. For decades the standard therapy of AIHA used corticosteroid administration (with or without azathioprine or cyclophosphamide) and even splenectomy (as the third line of treatment for warm AIHA in therapy-refractory patients). However, CAD responds poorly to steroids and alkylators, and according to some authors, corticosteroids should not be used to treat CAD [61]. Recently, new groups of drugs that inhibit immune responses at various levels have been developed. In most patients with CAD requiring treatment, B cell-directed approaches such as monotherapy with rituximab (an anti-CD20 antibody which depletes B cells) or combined with purine nucleoside analogues (e.g., bendamustine, fludarabine) are currently recommended as the first choice [18,61-64]. Prophylactically used eculizumab (anti-complement C5 monoclonal antibody) prevented exacerbation of haemolysis in a patient with chronic CAD who underwent aortic valve replacement with full cardiopulmonary bypass at normothermia [34]. The most recent studies reported a rapid and sustained effect in patients with chronic CAHA treated with sutimlimab, a selective complement C1s inhibitor [62,65-68]. In a patient with CAD, sutimlimab sufficiently blocked exacerbation of haemolysis during surgery and postoperatively [33]. The new drugs, unfortunately, are still expensive and not always available.

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Clinicians should consider CAHA in the differential diagnosis of anaemia, especially in geriatric orthopaedic patients admitted with a fracture and/or polytrauma. Individuals with CAHA undergoing surgery are at high risk of an exacerbation of haemolysis (due to significant increases in complement factors) and serious perioperative complications, especially thrombosis and infection. They require careful perioperative examination and prompt initiation of effective therapy to optimise outcomes. Based on literature data [11,12,15,62,70-72] and our case, we have created an algorithm for the perioperative diagnosis and management of patients with CAHA and fracture. In geriatric orthopaedic patients admitted with a fracture and/or polytrauma, anaemia is a common feature of multifactorial origin (chronic iron deficiency, blood loss, malnutrition and/or malabsorption, etc.); when after careful clinical examination and routine laboratory tests the aetiology of anaemia remains unclear /uncertain, AIHAs must be considered in the differential diagnosis. If the haemolytic screen is positive, further detailed analyses are required and CAHA, although rare but often severe and potentially fatal, should be suspected (particularly in patients affected by lymphoproliferative, autoimmune, and viral diseases and/or users of abovementioned drugs associated with AIHA), carefully investigated, antibody testing performed, and appropriate treatment started when the diagnosis confirmed; this stepwise approach is summarised in Table 1.
Table 1: Simplified algorithm for management of orthogeriatric patients with cold agglutinin haemolytic anaemia (CAHA).

**Preoperative**

(Fracture identified and surgical management planned)

**Diagnostic considerations:**

Is the patient anaemic? (Hb<120g/L in female, Hb<130g/L in male)

Anaemia of unknown origin present

Haemolysis suspected if:

- Medical and drug history positive,
- Reticulocyte count elevated,
- Blood smear: RBCs agglutination, polychromasia, spherocytosis,
- LDH elevated,
- Total bilirubin elevated,
- Haptoglobin low,
- Direct Coombs test positive.

CAHA identified if:

- Agglutination of RBCs on blood film,
- DAT positive only for compliment C3d,
- Cold agglutinin titre: ≥64 at 4°C (in CAD),
- DAT Ig negative.

**Management:**

- Comprehensive nursing,
- Monitoring patient’s temperature,
- Arrangement of warm environment (thermal blankets and warm air devices),
- Warm blood products, intravenous fluids, drinks and meals,
- Packed RBC transfusion
- Anaesthesiology and haematology consultations, close collaboration.

**Intraoperative**

- Raise operating room temperature,
- Continue warming,
- Correct anaemia,
- Administer all intravenous products and irrigation fluids warmed.

**Postoperative**

- Continue warming,
- Correct anaemia,
- Prewarming all intravenous blood products, irrigation fluids, drinks and meals,
- Adequate venous thromboembolism prophylaxis,
- Prevent and treat complications promptly (e.g. infections),
- Avoid drugs that can cause haemolysis (e.g. cefotetan, ceftriaxone, piperacillin, NSAIDs, methyldopa, chemotherapeutic drugs, contrast media, etc.),
Haematologist review (consider rituximab, eculizumab, sutimlimab, folic acid supplementation, specific treatment of the underlying lymphoproliferative disorder, Optimise pharmacotherapy for chronic comorbidities, 
Introduce adequate osteoporosis treatment.

**On discharge**

Education regarding avoidance of cold exposure (regardless of symptoms), cold showers, icy drinks, adequate clothing,
Continue medications chosen for chronic diseases,
Add systemic treatment if substantial anaemia occurs and/or disabling symptoms or signs (e.g., acrocyanosis, Raynaud phenomenon) present,
Follow-up by an orthopaedic surgeon, haematologist and geriatrician.

**Conclusions**

Based on the second case report of a patient with CAHA and HF and literature data we described perioperative management challenges in orthogeriatric patients and created a diagnostic and treatment algorithm for care of such patients. Although CAHA is rare, it presents diagnostic and therapeutic dilemmas, high risks of poor outcomes and warrants an increased awareness and screening for individuals suspected of carrying CAs antibodies.

**Consent for Publication:** Written informed consent for publication of this case report was obtained from the patient’s daughter (carer and power of attorney holder). A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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