Original Article

Access this article online
Quick Response Code:

Website: www.ajts.org
DOI: 10.4103/ajts.ajts_65_23

Clinical and laboratory characteristics of patients with cold agglutinin disease: A retrospective analysis at a tertiary medical center

Harshita Mehrotra[1], Zaher K. Otrock[1,2]

Abstract:

BACKGROUND: Cold agglutinin disease (CAD) is relatively rare and has primarily been reported as retrospective case series.

AIM: We reviewed our experience with CAD to shed light on this disease.

STUDY SETTINGS AND DESIGN: This was a retrospective review of all patients with CAD managed at our institution between 2007 and 2018.

MATERIALS AND METHODS: The study was approved by our institutional review board. We extracted patients' demographic, clinical, and laboratory data, blood transfusions, and outcomes from their electronic medical records.

STATISTICAL ANALYSIS USED: Statistical analysis was performed using SPSS version 17. The method of Kaplan–Meier was used to plot survival curves.

RESULTS: Forty-eight patients fulfilled the inclusion criteria for CAD. The median age of patients was 73.1 (range, 43–99) years; 36 (75%) were female. The majority ($n = 38$; 79.2%) of patients were Caucasians. Most patients ($n = 25$, 52.1%) presented with symptomatic anemia. Eight patients were asymptomatic. The median hemoglobin level was 8.6 g/dL (range, 3–12 g/dL); 7 (14.6%) patients had concurrent thrombocytopenia. Lactate dehydrogenase was elevated in 40/47 (85.1%) patients and haptoglobin was below normal in 35/46 (76.1%) patients. Coagulopathy was observed in 19 (52.8%) of 36 patients. Sixteen (33.3%) patients required blood transfusion during admission at the time of diagnosis with a median number of 3.5 red blood cell units. Twenty-five (52.1%) patients were alive after a median follow-up of 50.1 months. The 5-year and 10-year survival was estimated at 58.2% and 30.8%, respectively.

CONCLUSION: CAD poses considerable burden on patients and health-care systems. Patients vary widely in their disease severity and course.

Keywords:

Blood transfusion, characteristics, cold agglutinin disease, survival

[1]Department of Pathology and Laboratory Medicine, Henry Ford Hospital, [2]Department of Pathology, Wayne State University School of Medicine, Detroit, MI, USA

Address for correspondence:
Dr. Zaher K. Otrock, Wayne State University School of Medicine, Detroit, MI, USA. Department of Pathology and Laboratory Medicine, Henry Ford Hospital, K-6, 2799 W Grand Blvd, Detroit 48202, MI, USA. E-mail: zotrock1@hfhs.org, zaherotrock@hotmail.com

Submitted: 29-03-2023
Revised: 05-05-2023
Accepted: 21-05-2023
Published: 26-12-2023

Introduction

Autoimmune hemolytic anemias (AIHAs) are characterized by the production of autoantibodies against red blood cell (RBC) antigens, thus increasing RBCs destruction and decreasing their survival. AIHAs are classified as warm-, cold-, or mixed-autoantibody types depending on the temperature at which the autoantibodies bind RBC antigens.[1] Cold AIHA (cAIHA) accounts for 15%–25% of AIHA; the involved autoantibodies are usually of the IgM class, are potent activators of the classical complement pathway, and can bind to their RBC antigens RBCs at temperatures ≥3°C depending on their

How to cite this article: Mehrotra H, Otrock ZK. Clinical and laboratory characteristics of patients with cold agglutinin disease: A retrospective analysis at a tertiary medical center. Asian J Transfus Sci 2023;17:229-33.

thermal amplitude.[2,3] Hemolysis in cAIHA is mostly extravascular but can also be intravascular in severe cases and acute exacerbations.[4] cAIHA can further be subclassified based on etiology into primary (idiopathic; cold agglutinin disease [CAD]) and secondary to underlying diseases (cold agglutinin syndrome [CAS]) such as malignancies, lymphoproliferative diseases, autoimmune disorders, and infections.[1,5] CAD diagnosis is made with the findings of hemolytic anemia, elevated lactate dehydrogenase (LDH), low haptoglobin, reticulocytosis, positive direct antiglobulin test (DAT; Coombs) for anti-C3d (and negative or weakly positive for Immunoglobulin [Ig] G), and cold agglutinin titer of ≥64 at 4°C.[1]

CAD is relatively rare with a reported incidence of 1/1,000,000 people per year.[1,6] It mostly affects elderly patients with a median age of 76 (range, 51–96) years.[6] Given its low prevalence, CAD has primarily been reported as retrospective series in the United States.[1,7] It is difficult to conduct randomized controlled trials for these patients which has led to differing opinions on management of this disease.[8] To shed more light on this disease, we reviewed our institutional experience with CAD.

Materials and Methods

We conducted a retrospective review of all patients with CAD managed between January 2007 and December 2018. Patients were managed at our institution which comprised an 877-bed tertiary academic medical center in Detroit, Michigan, and 5 subsidiary hospitals, with a total of 2405 beds. Eligible patients fulfilled the following criteria: (1) age ≥16 years at diagnosis; (2) positive DAT with positive C3d pattern (and negative or weakly positive for IgG); (3) cold agglutinin titer of ≥64 at 4°C or evidence of cold autoantibodies on immunohematology workup; and (4) diagnosis of AIHA with features of hemolysis defined by elevated LDH, low haptoglobin, elevated bilirubin, or peripheral smear findings. Anemia was defined according to the World Health Organization (WHO) definition: mild anemia was defined as hemoglobin (Hgb) 11–11.9 g/dL in females and 11–12.9 g/dL in males, moderate anemia was defined as Hgb 8–10.9 g/dL in females and males, and severe anemia was defined as Hgb <8 g/dL in both females and males.[9] We extracted patients' demographic, clinical, and laboratory data, blood transfusions, and outcome from their electronic medical records. The underlying hematologic diagnoses were based on bone marrow aspirate and trephine biopsy histology, immunohistochemistry, flow cytometric analysis, and serum protein electrophoresis and immunofixation. The study was performed in accordance with the ethical standards of the Helsinki Declaration and was approved by our local institutional review board (IRB # 12884). Informed consent was waived due to the retrospective study design.

Statistical analysis

Statistical analysis of data was performed using SPSS (Statistical Package for the Social Sciences) version 17.0 software (SPSS Inc., Chicago, IL, USA). Results were expressed as median plus range or mean ± standard deviation for continuous variables and as numbers with percentages for categorical variables. Thirty-day mortality (early mortality) was defined as death from any cause within 30 days of admission. Overall survival was defined as the time from the first presentation to the date of death from any cause or the date of the last follow-up evaluation. The method of Kaplan–Meier was used to plot survival curves and estimate survival probabilities. Follow-up data were updated in January 2023.

Results

Patient characteristics

Forty-eight patients fulfilled the inclusion criteria and diagnosis of CAD. Figure 1 shows the flowchart of patients' inclusion. Patients' clinical characteristics are summarized in Table 1. The median age of patients was 73.1 (range, 43–99) years; 36 (75%) were female and 12 (25%) were male. The majority (n = 38; 79.2%) of patients were Caucasians, and 10 (20.8%) were African American. The most common clinical presentation was symptomatic anemia in 25 patients, jaundice in three, abdominal pain in two, exacerbation of known malignancy in three, sepsis in two, acute liver failure in two, and other symptoms in three patients. Eight patients were otherwise asymptomatic. Splenomegaly was documented radiologically in 14/45 (31.1%) patients. One patient had deep venous thrombosis (DVT) of the lower extremity on presentation.

Table 1: Initial characteristics of patients with cold agglutinin disease (n=48)

Characteristic	n/value
Gender (male/female)	12/36
Age (years), median (range)	73.1 (43–99)
Ethnicity (Caucasian/African American)	38/10
Splenomegaly (%)	14/45 (31.1)
Hgb (g/dL), median (range)	8.6 (3–12)
Reticulocyte count (×10^9/L), median (range)	163 (20–341)
Platelet count (×10^9/L), median (range)	221 (22–753)
LDH (IU/mL), median (range)	355 (150–16,555)
Haptoglobin (mg/dL), median (range)	30 (8–226)
Total bilirubin (mg/dL), median (range)	1.9 (0.4–13.7)
DAT (%)	
Positive C3d only	39 (81.2)
Positive C3d and weakly positive IgG	9 (18.8)

Hgb=Hemoglobin, LDH=Lactate dehydrogenase, DAT=Direct antiglobulin test, IgG=Immunoglobulin G

Laboratory characteristics

The median Hgb level on presentation was 8.6 g/dL (range, 3–12 g/dL), and 75% (33/44) of patients showed increased reticulocyte count (>120 × 10^9/L). Two patients (2 females) had mild anemia, 26 (19 females and 7 males) had moderate anemia, and 20 (15 females and 5 males) had severe anemia as defined by the WHO. On the first presentation, 7 (14.6%) patients had concurrent thrombocytopenia (<100 × 10^9/L). All cases had positive DAT for C3d by definition, and nine patients also had weakly positive DAT for IgG. LDH was elevated in 40/47 (85.1%) patients, haptoglobin was below normal in 35/46 (76.1%) patients, and bilirubin was increased in 30/44 (68.2%) patients. Coagulopathy, defined as prolonged prothrombin time and/or prolonged activated partial thromboplastin time, was observed in 19 (52.8%) of 36 patients. Not all patients were tested for cold agglutinins on presentation, and these were detected in 20/26 (76.9%) patients. Specificity testing for autoantibodies was not performed. Table 2 summarizes patients' underlying hematologic diagnoses.

Treatment

Treatment was not standardized and consisted of immunosuppressive therapy with rituximab alone in 16 patients (33.4%), rituximab with steroids in six patients (12.5%), steroids alone in four patients (8.3%), rituximab with bendamustine in five patients (10.4%), and malignancy specific chemotherapy regimens in six patients (12.5%). Eleven (22.9%) patients received supportive treatment only.

Table 2: Patient's underlying hematologic diagnoses (*n*=48)

Diagnosis	Number of patients (%)
MGUS	14 (29.2)
Non-Hodgkin's B-cell lymphoma	8 (16.6)
Lymphoproliferative neoplasm	7 (14.6)
Small lymphocytic B-cell lymphoma/CLL	6 (12.5)
Reactive lymphocytosis	6 (12.5)
Low grade B-cell lymphoma	4 (8.3)
Marginal zone lymphoma	2 (4.2)
Lymphoplasmacytic lymphoma	1 (2.1)

MGUS=Monoclonal gammopathy of undetermined significance, CLL=Chronic lymphocytic leukemia

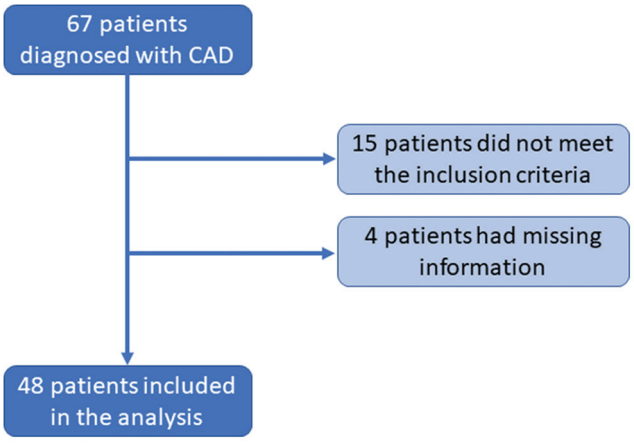

Figure 1: Flowchart of patients with CAD who met the inclusion criteria. CAD = Cold agglutinin disease

Blood transfusions

Sixteen (33.3%) patients required blood transfusion during admission at the time of diagnosis with a median number of 3.5 (range, 2–23) RBC units. Blood transfusions were received by 0%, 25%, and 75% of patients with mild, moderate, and severe anemia, respectively. At the last follow-up, 37 (77.1%) patients required blood transfusion during the entire course of their disease with a median of six units (range, 2–137 units) transfused over a median follow-up period of 50.1 months.

Follow-up and outcome

Four patients (8.3%) died within 30 days of initial diagnosis of CAD; the cause of death was acute liver failure in two patients, sepsis in one patient, and respiratory failure in one patient. Two patients experienced unilateral DVT, one of them on initial presentation. At the last follow-up, 25 (52.1%) patients were alive after a median follow-up of 50.1 months (range, 10 days to 160.6 months). The 5-year and 10-year survival was estimated at 58.2% and 30.8%, respectively [Figure 2].

Discussion

cAIHA accounts for up to 25% of cases of AIHA with an incidence of 1/1,000,000 people per year. Its prevalence is estimated to be 13–16 per million.[6,10] cAIHA is subclassified based on etiology into primary CAD and secondary to underlying diseases (CAS) such as malignancies, lymphoproliferative diseases,

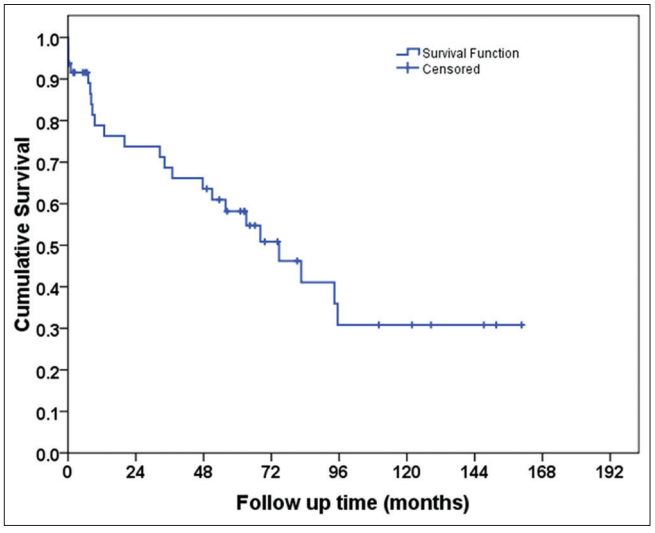

Figure 2: Kaplan–Meier survival curve of 48 patients with cold agglutinin disease

autoimmune disorders, and infections. CAD has recently been recognized as a distinct clonal B-cell lymphoproliferative disorder in the 2022 revision of the WHO classification of hematolymphoid neoplasms.[11,12] CAD poses a considerable burden on health-care systems with a considerable number of patients presenting with anemia, coagulopathy, and end organ failure requiring intensive management. Given the low incidence and prevalence of this disease, it is difficult to conduct large-scale studies. We conducted a retrospective review of all patients with CAD managed at our health system from 2007 to 2018. We presented the clinical and laboratory characteristics and outcome of CAD patients.

We identified 48 patients with CAD who fulfilled the inclusion criteria. CAD predominantly affects elderly patients. Our patients' median age was 73.1 years which is consistent with results from previous studies.[1,10,13] We had a female preponderance in our cohort (74.5%), which was also reported by other studies.[7,10,14,15] Our cohort was predominantly Caucasian (38 patients, 79.2%) with a higher rate of African American patients compared to other studies.[1] This might reflect a referral bias, given the population distribution in previous studies[1,7] and the diverse ethnicities covered by our health-care system.

In our cohort, patients presented with a wide range of symptoms, of which symptomatic anemia was the most common presentation (n = 25; 52.1%), followed by jaundice (6.2%) and abdominal pain (4.2%). Eight (16.7%) patients were asymptomatic at the time of CAD diagnosis. This is consistent with previous studies where anemia was the most common presenting symptom.[1,6,7,10] Although studies have described patients reporting cold-induced symptoms such as acrocyanosis,[1] this presentation was not documented in our cohort.

Anemia is common in patients with CAD and its severity varies over time with the disease course.[7] The median Hgb in our cohort was 8.6 g/dL (range, 3–12 g/dL). According to the WHO definition of anemia,[9] most of our patients (n = 46, 95.8%) presented with moderate-to-severe anemia. Mullins *et al*. reported comparable Hgb of 8.2 g/dL.[7] Other studies have reported higher median levels of Hgb (≥10 g/dL) and less percentages of patients with moderate-to-severe anemia.[1,13,16]

Patients with CAD have an increased risk of thrombotic events.[15,17] In a recent retrospective insurance-based registry study of 608 patients diagnosed with CAD, 30% of patients developed thrombosis versus 18% of controls over a 10-year follow-up period (adjusted hazard ratio 3.1; 95% confidence interval: 2.24–4.30).[15] The suggested mechanisms of thrombosis in CAD are multiple including complement activation, release of free heme which leads to nitric oxide scavenging and subsequent vasoconstriction and platelet aggregation, generation of reactive oxygen species that promote inflammation, cytokine excretion, and endothelial injury.[18-20] Among our patients, one patient had DVT on presentation and another had DVT during follow-up.

Supportive blood transfusion may be needed in CAD patients with symptomatic or severe anemia. Anemia in CAD can be induced by multiple factors including complement-mediated hemolysis, coagulopathy, and underlying triggers such as malignancies and autoimmune disease. The reported blood utilization in CAD ranged from 30% to 80% in the medical literature.[1,6,7,21] In our study, 16 (33.3%) patients required blood transfusion during admission at time of diagnosis.

We acknowledge some limitations in our study. First, this is a retrospective study and dependent on chart review and medical record documentation. Thus, we cannot exclude the possibility of inaccurate diagnoses or missing information. In addition, our study included 48 patients which could be considered a relatively small cohort compared with registries. In addition, the study spans a long period with evolving understanding and management of CAD; this can explain the nonstandard diagnostic approach and missing clinicopathological parameters for some cases.

Conclusion

CAD poses considerable burden on patients and health-care systems. Patients vary widely in their disease severity and course, and the majority require CAD-related therapy during the course of their disease. Most patients present with anemia and coagulopathy, and one-third of patients require blood transfusion on presentation.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Swiecicki PL, Hegerova LT, Gertz MA. Cold agglutinin disease. Blood 2013;122:1114-21.
2. Gertz MA. Cold agglutinin disease. Haematologica 2006;91:439-41.
3. Berentsen S, Röth A, Randen U, Jilma B, Tjønnfjord GE. Cold agglutinin disease: Current challenges and future prospects. J Blood Med 2019;10:93-103.
4. Gabbard AP, Booth GS. Cold agglutinin disease. Clin Hematol Int 2020;2:95-100.
5. Berentsen S, Tjønnfjord GE. Diagnosis and treatment of cold agglutinin mediated autoimmune hemolytic anemia. Blood Rev 2012;26:107-15.
6. Berentsen S, Ulvestad E, Langholm R, Beiske K, Hjorth-Hansen H,

Ghanima W, *et al.* Primary chronic cold agglutinin disease: A population based clinical study of 86 patients. Haematologica 2006;91:460-6.
7. Mullins M, Jiang X, Bylsma LC, Fryzek JP, Reichert H, Chen EC, *et al.* Cold agglutinin disease burden: A longitudinal analysis of anemia, medications, transfusions, and health care utilization. Blood Adv 2017;1:839-48.
8. Lechner K, Jäger U. How I treat autoimmune hemolytic anemias in adults. Blood 2010;116:1831-8.
9. World Health Organization (WHO). Haemoglobin Concentrations for the Diagnosis of Anaemia and Assessment of Severity, Vitamin and Mineral Nutrition Information System (WHO/NMH/NHD/MNM/11.1). Geneva, Switzerland: World Health Organization; 2011. p. 1-6. Available from: https://www.academia.edu/4215770/WHO_Haemoglobin_concentrations_for_the_diagnosis_of_anaemia_and_assessment_of_severity_Vitamin_and_Mineral_Nutrition_Information_System_Geneva_World_Health_Organization_2011_WHO_NMH_NHD_MNM_11_1_.
10. Bylsma LC, Gulbech Ording A, Rosenthal A, Öztürk B, Fryzek JP, Arias JM, *et al.* Occurrence, thromboembolic risk, and mortality in Danish patients with cold agglutinin disease. Blood Adv 2019;3:2980-5.
11. Jäger U, Barcellini W, Broome CM, Gertz MA, Hill A, Hill QA, *et al.* Diagnosis and treatment of autoimmune hemolytic anemia in adults: Recommendations from the first international consensus meeting. Blood Rev 2020;41:100648.
12. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IB, Berti E, *et al.* The 5th edition of the World Health Organization classification of haematolymphoid tumours: Lymphoid neoplasms. Leukemia 2022;36:1720-48.
13. Berentsen S, Barcellini W, D'Sa S, Randen U, Tvedt TH, Fattizzo B, *et al.* Cold agglutinin disease revisited: A multinational, observational study of 232 patients. Blood 2020;136:480-8.
14. Kamesaki T, Nishimura JI, Wada H, Yu E, Tsao E, Morales J, *et al.* Demographic characteristics, thromboembolism risk, and treatment patterns for patients with cold agglutinin disease in Japan. Int J Hematol 2020;112:307-15.
15. Broome CM, Cunningham JM, Mullins M, Jiang X, Bylsma LC, Fryzek JP, *et al.* Increased risk of thrombotic events in cold agglutinin disease: A 10-year retrospective analysis. Res Pract Thromb Haemost 2020;4:628-35.
16. Pham HP, Wilson A, Adeyemi A, Miles G, Kuang K, Carita P, *et al.* An observational analysis of disease burden in patients with cold agglutinin disease: Results from a large US electronic health record database. J Manag Care Spec Pharm 2022;28:1419-28.
17. Schär DT, Daskalakis M, Mansouri B, Rovo A, Zeerleder S. Thromboembolic complications in autoimmune hemolytic anemia: Retrospective study. Eur J Haematol 2022;108:45-51.
18. L'Acqua C, Hod E. New perspectives on the thrombotic complications of haemolysis. Br J Haematol 2015;168:175-85.
19. Rother RP, Bell L, Hillmen P, Gladwin MT. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: A novel mechanism of human disease. JAMA 2005;293:1653-62.
20. Zhong H, Yazdanbakhsh K. Hemolysis and immune regulation. Curr Opin Hematol 2018;25:177-82.
21. Prabhu R, Bhaskaran R, Shenoy V, Rema G, Sidharthan N. Clinical characteristics and treatment outcomes of primary autoimmune hemolytic anemia: A single center study from South India. Blood Res 2016;51:88-94.