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Successful Management of Refractory Autoimmune Hemolytic Anemia with Cold Agglutinin Disease with Splenectomy: A Case Report with Review of Literature

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Background: Cold agglutinin disease (CAD) is a rare autoimmune hemolytic anemia characterized by agglutination of red blood cells at temperatures below the normal core body temperature. In patients with CAD, splenectomy is not indicated because of its low therapeutic effect on hemolytic anemia induced by extravascular hemolysis. Herein, we report a case of refractory hemolytic anemia with CAD successfully managed with splenectomy.

Clinical Case: A 60-year-old man visited a municipal hospital with the chief complaint of fatigue. He was found to have hemolytic anemia and icterus with increased cold agglutination and was diagnosed with CAD. Malignant lymphoma was suspected as the underlying disease; however, no clear underlying disease was identified. Hemolytic anemia progressed during the subsequent winter seasons, and he was treated with temperature control, warming, and weekly blood transfusions. However, despite the blood transfusions, his hemoglobin level did not improve during the summer 2 years after diagnosis, and his previously observed splenomegaly had progressed. He was referred to our department, and a splenectomy was performed to diagnose any occult malignant lymphoma and improve the refractory hemolytic anemia. Because histopathological examination revealed no evidence of malignant lymphoma, a diagnosis of primary CAD was made. The hemolytic anemia improved, and no blood transfusion was required after splenectomy.

Conclusions: Splenectomy significantly improved the patient's refractory hemolytic anemia due to primary CAD. Thus, it may be an effective treatment option in such cases, although further cases and studies are required to evaluate the effects of splenectomy.

Cold agglutinin disease (CAD) is rare, with a prevalence of 16 cases per million people and accounts for approximately 15% of autoimmune hemolytic anemia (AIHA) cases [1]. Extravascular hemolysis causes acute hemolytic anemia in which agglutination of red blood cells occurs at temperatures below the normal core body temperature in CAD [2]. CAD is classified into primary and secondary. Secondary CAD is related to autoimmune disorders, viral infections, and hematologic malignancies including leukemia and malignant lymphoma. The common infectious causes associated with CAD are Epstein–Barr virus and *Mycoplasma pneumoniae*. Recently, CAD has been reported to be caused by COVID-19 [3]. CAD is a well-defined clinicopathological entity wherein a specific clonal lymphoproliferative B-cell bone marrow disorder causes AIHA [1]. Patients with symptomatic anemia or disabling circulatory symptoms should be treated [1]. In general, temperature control and warming are the first treatment choices for CAD. Rituximab or corticosteroids are effective in severe or intractable cases, although reports of cases in which splenectomy improved hemolytic anemia in CAD are few [1]. Herein, we report a rare case of refractory hemolytic anemia with CAD successfully managed with splenectomy.

CLINICAL CASE

A 60-year-old man consulted a local doctor with the chief complaint of fatigue. Blood tests revealed a hemoglobin (Hb) level of 7.8 g/dL and an indirect bilirubin level of 7.7 mg/dL. Additionally, cold agglutinin (CA) levels were elevated, and the direct Coombs test was positive for C3d and negative for IgG. Abdominal computed tomography revealed mild splenomegaly. In this case, the clinical findings of anemia and jaundice and the

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laboratory findings of decreased Hb levels and reticulocytosis met the diagnostic criteria for hemolytic anemia. Additionally, exacerbation of hemolysis due to cold exposure was observed. Therefore, the patient was diagnosed with CAD. A secondary type of CAD was suspected because bone marrow examination revealed a group of clonal cells. However, since other tests did not lead to a definitive diagnosis of malignant lymphoma, and no other underlying diseases were clearly identified, the patient was diagnosed with primary CAD. During the first winter after diagnosis, he was found to have severe anemia with a Hb level of approximately 5 g/dL; therefore, he was treated with warming and weekly blood transfusion. The Hb level recovered to 13 g/dL in the summer. In the second summer, 2 years after diagnosis, the anemia did not improve, and his splenomegaly had worsened; therefore, he was referred to our department for excluding malignant lymphoma and improving refractory hemolytic anemia. He had no prior medical history, although his aunt had a history of malignant lymphoma. His height was 172.9 cm, weight was 51 kg, and body mass index was 17 kg/m^2. He had a weight loss of 10 kg in three years. On abdominal examination, the spleen was palpable. The results of the laboratory investigation done preoperatively are presented in Table I.

Table I. Patient's laboratory data

Laboratory test	Value	Normal range
White blood cells	1900/μL	4000-8500/μL
Red blood cells	1.67 × 10^6/μL	4.15-5.50 × 10^6/μL
Hemoglobin	5.9 g/dL	13.5-17.5 g/dL
Platelets	11.8 × 10^4/μL	12-36 × 10^4/μL
Prothrombin time	89.5%	80-125%
Sodium	139 mEq/L	136-147 mEq/L
Potassium	4.3 mEq/L	3.5-5.0 mEq/L
Chloride	103 mEq/L	98-108 mEq/L
Total protein	5.8 g/dL	6.5-8.2 g/dL
Albumin	3.7 g/dL	3.8-5.3 g/dL
Total bilirubin	7.6 mg/dL	0.4-1.5 mg/dL
Indirect bilirubin	7.2 mg/dL	0.2-1.3 mg/dL
Aspartate aminotransferase	27 U/L	8-40 U/L
Alanine aminotransferase	9 U/L	5-45 U/L
Alkaline phosphatase	257 U/L	100-340 U/L
Gamma-glutamyl transpeptidase	11 U/L	0-75 U/L
Lactate dehydrogenase	934 U/L	115-245 U/L
Cholinesterase	119 U/l	239-485 U/l
Total cholesterol	92 mg/dL	130-219 mg/dL
Triglyceride	96 mg/dL	30-149 mg/dL
Blood urea nitrogen	11.6 mg/dL	8.0-23.0 mg/dL
Creatinine	0.69 mg/dL	0.61-1.08 mg/dL
C-reactive protein	1.03 mg/dL	0-0.30 mg/dL
Hemoglobin A1c	5.2%	<6.0%
Hepatatis B surface antigen	Negative	Negative
Hepatitis C virus antibody	Negative	Negative
Cold agglutination reaction	512	<64

They revealed mild jaundice with indirect hyperbilirubinemia associated with hemolytic anemia. Abdominal computed tomography revealed splenomegaly (26.5 × 8.5 × 17.0 cm) and 2091 mL on preoperative volumetry (Figure 1).

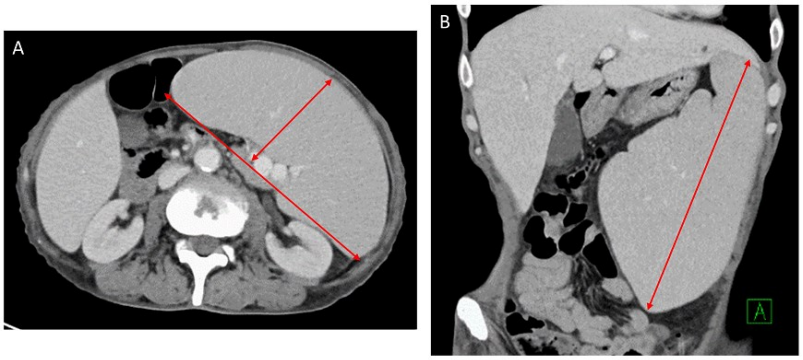

Figure 1. Preoperative computed tomography images
(A) Axial image
(B) Coronal image

The spleen was larger in size than at the initial examination. Consequently, a splenectomy was performed. Intraoperative findings are depicted in Figure 1. The operative time was 188 min, and blood loss was minimal. The intraoperative blood transfusion volume was 560 mL. The spleen weighed 2200 g. A gross pathological examination revealed no obvious mass lesions (Figure 2A). In the surface antigen analysis, a kappa-positive cell population was identified in approximately 5% of the total population. Histopathological examination revealed no evidence of malignant lymphoma (Figure 2B).

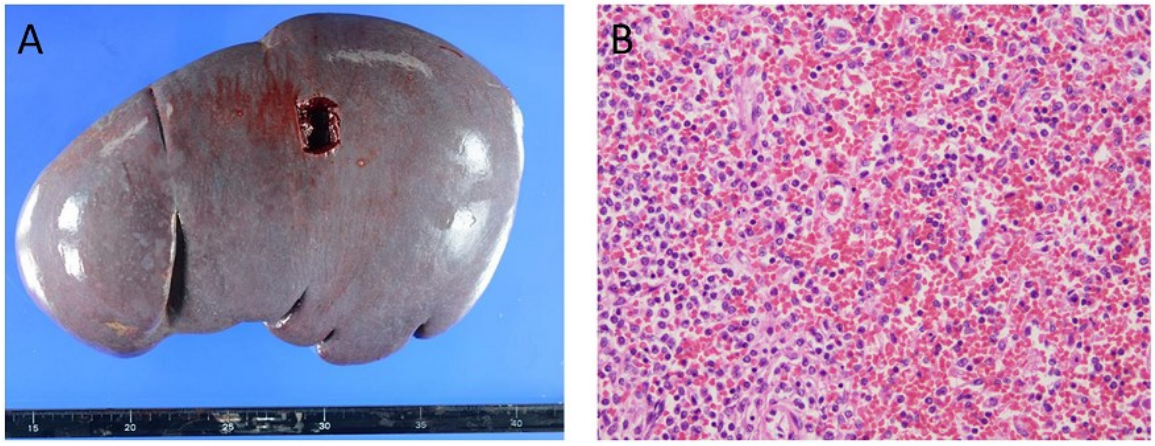

Figure 2. (A) The resected specimen.
A small block of the specimen was submitted for the surface antigen analysis.
(B) Pathological examination (hematoxylin–eosin stain, ×20)

As a result, he was diagnosed with primary CAD. Postoperatively, the patient developed transient paralytic ileus and pancreatic fistula, which improved with conservative therapy. The patient was discharged on postoperative day 17. At 18 months after the operation, the hemolytic anemia has gradually improved, and no blood transfusion was required postoperatively (Figure 3). The cold agglutinin level was still high between 128 and 512 after surgery. In addition, IgG turned positive during the treatment course, and he was diagnosed with mixed-type AIHA.

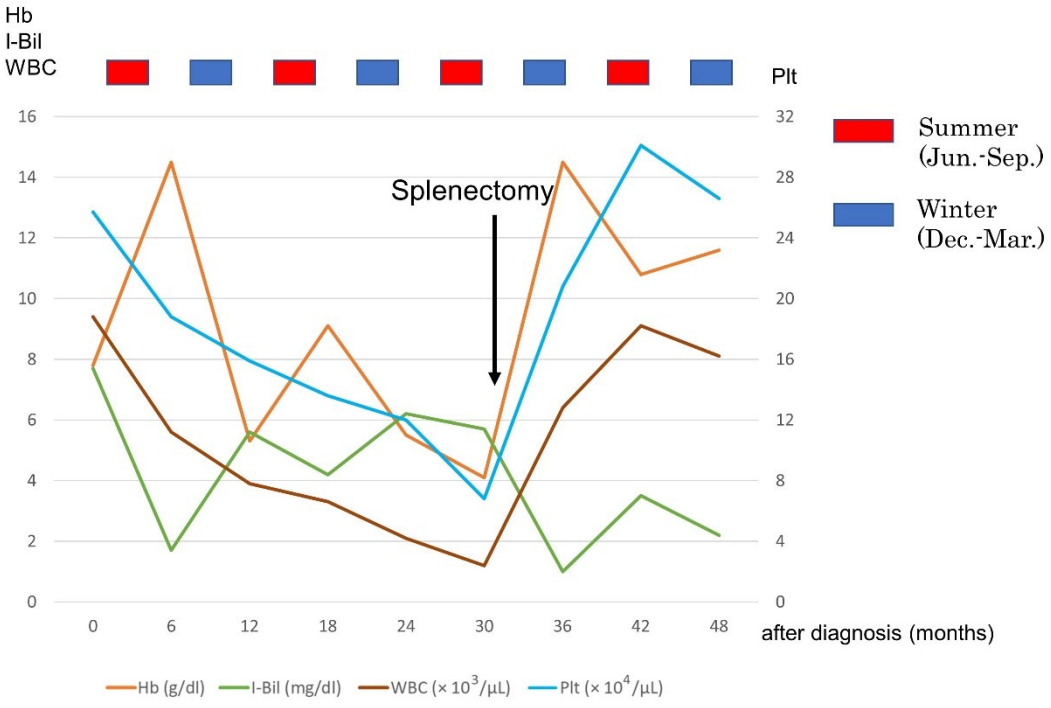

Figure 3. The transition of hemolytic anemia. Pancytopenia and hemolysis due to hyperfunction of the spleen are observed before surgery, that improved after the surgery.

DISCUSSION

AIHA is categorized into warm and cold reactive antibody types. CAD is one of the cold types and is further classified into two types: primary and secondary. The primary type was regarded as unrelated to underlying conditions. Secondary CAD is related to autoimmune disorders, viral infections, and hematological malignancies. Inflammation and infection can act as triggers and drivers of hemolysis, exemplified by exacerbation of CAD in situations with acute reactions [4]. In the present case, no causative infection was determined; however, malignant lymphoma was suspected because the bone marrow examination revealed a clonality cell group with B cells. However, histopathological results revealed no evidence of malignant lymphoma. Consequently, the patient was diagnosed with primary CAD.

The agglutination and subsequent destruction mechanisms of red blood cells are the cooling of the blood to approximately 4℃ during passage through the acral parts of the body allowing binding to red blood cells and precipitating agglutination [5]. The antigen-antibody complexes induce complement binding and activation via classical pathways. C1 esterase activates C2 and C4, generating C3 convertase. It leads to the formation of C3b. When the blood returns to the central parts of the body and is warmed to 37℃, CA separates from the cell surface, allowing aggregated red blood cells to separate from each other. However, C3b remains bound, and some C3b-coated erythrocytes are mainly destroyed by C3-receptor-bearing reticuloendothelial cells in the spleen and liver [6]. Thus, the spleen enlarges as hemolytic anemia progresses [1]. According to the mechanism, the diagnostic criteria of CAD are the presence of hemolytic anemia, the presence of complement in the indirect Coombs test, increased CA titer in the serum, and the presence of hemolysis due to cold exposure [7].

According to recent studies on CAD, the median age of patients with CAD is 76 years, and the median age at presentation is 67 years [6,8]. The main clinical symptoms of CAD are hemolytic anemia and various cold-induced circulatory symptoms, including mild acrocyanosis and disabling Raynaud's phenomenon. Previous studies have reported that the average Hb level in CAD is 9.0 g/dL [9]. Moreover, Hb levels have been reported to be as low as 4 g/dL [10], and approximately half of the untreated patients are considered short-term or long-term transfusion-dependent [6,8]. Here, the patient had a more severe hemolytic anemia than in typical CAD cases, although no other peripheral circulatory symptoms were observed.

The most effective treatments for CAD are temperature control and warming. Several studies have reported that moving to a warmer location improves hemolytic anemia [2]. Patients with CAD should avoid hypothermia and infusion of cold liquids. The patients and extremities selected for transfusion should be warmed, and an in-line blood warmer is recommended to be used [6]. In this case, we used an in-line blood warmer perioperatively to avoid hemolysis. In the case of secondary CAD, treating the primary disease is crucial. Corticosteroids or cytotoxic immunosuppressive drugs should be used as the second line of treatment, unless warming or treatment of primary disease fails to improve the hemolysis. Although corticosteroids are effective in 70%–85% of patients with warm AIHA, they are much less effective in patients with CAD (14%–35%). Even if they are effective, these patients require high doses of corticosteroids [11]. However, steroids are discouraged because the responses have never been supported by systematic studies [12,13]. In contrast, cytotoxic immunosuppressive drugs such as rituximab have therapeutic effects (30%) by inhibiting the classical complement pathway [14]. However, complement modulations have limitations in that they do not improve cold-induced symptoms and need continuous administration to maintain their effectiveness [11].

In general, splenectomy is not effective for CAD because its extravascular hemolysis occurs mainly in the liver by the action of IgM (immunoglobulin M) and Kupffer cells, while splenectomy is an effective treatment for warm-type AIHA because its extravascular hemolysis occurs mainly in the spleen by the action of IgG. However, cases of CAD with extravascular hemolysis in the spleen due to the action of IgG are rarely reported [15,16]. In this case, extravascular hemolysis may have occurred because of IgG rather than IgM, and massive splenomegaly was likely caused by hemolysis in the spleen. Therefore, predicting the effect of splenectomy preoperatively may have been possible by measuring the Ig class levels and the presence of massive splenomegaly in the case of CAD. In addition, in this case, there was hypersplenism associated with splenomegaly, and significant pancytopenia was observed before surgery. After the splenectomy, the pancytopenia was improved. Therefore, the presence of pancytopenia due to hypersplenism may also be a predictor of the therapeutic efficacy of splenectomy.

This case report had several limitations. First, the immunoglobulin class was not measured preoperatively. Second, this case was initially diagnosed with CAD and turned to mixed-type AIHA in treatment progress. However, there was a possibility that this case was AIHA of Coombs-negative at first.

Splenectomy is indicated for patients with refractory hemolytic anemia, as in this case. Since the treatment strategies for CAD remain unclear, further studies are required to establish the therapeutic effect of splenectomy in patients with refractory hemolytic anemia due to CAD.

CONCLUSIONS

Splenectomy may be an effective treatment option for CAD in patients with intractable hemolytic anemia. As reports of successful splenectomy in patients with CAD are few, further studies with more patients are required to evaluate the effect of splenectomy.

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