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# Cold Agglutinin-induced Hemolytic Anemia as the Primary Presentation in Systematic Lupus Erythematosus (SLE) in Pregnancy Triggered by Infection: A Case Report

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## ABSTRACT

Autoimmune hemolytic anemia (AIHA) may be the first manifestation of systematic lupus erythematosus (SLE). Antierythrocyte antibodies in SLE are mainly warm-type Immunoglobulin G (IgG), but mixed-type AIHA is also reported. Cold antibody-mediated hemolytic anemia is extremely rare in SLE. Only a few cases have been reported in the literature. A 37-year-old pregnant woman presented with features of hemolytic anemia and was later diagnosed as an SLE case. Although rare, a new case report highlights that cold-type autoimmune hemolytic anemia may be an early manifestation of SLE.

## Introduction

Cold agglutination disease (CAD) is a rare acquired form of autoimmune hemolytic anemia (AIHA) caused by cold-reacting autoantibodies. Autoantibodies that bind to the erythrocyte membrane lead to premature erythrocyte destruction (optimum temperature: 3-4°C). The vast majority of cold agglutinins are Immunoglobulin G (IgG) [1]. A peripheral blood smear may reveal clumps of red blood cells.

CAD, which commonly affects adults who are of middle age and older, may manifest as a primary disease, in

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which the underlying mechanism is not known, or as a secondary disease caused by other underlying medical issues such as bacterial infections, viral infections, parasitic infections, other autoimmune disorders such as systemic lupus erythematosus (SLE), and certain types of cancers (lymphoid malignancies).

In many cases, individuals with circulating cold agglutinins may be unaware of these antibodies' presence unless or until they are exposed to cold temperature that enhances antibody binding to red blood cells (RBCs) [2]. Typical findings are as follows: anemia (median hemoglobin, 9.5 g/dl, 90%), hemolytic markers [high lactate dehydrogenase (LDH), reticulocyte count, bilirubin, and low haptoglobin, 90% each], and cold-induced symptoms (mostly acrocyanosis, 52%). The severity can range from compensated hemolysis without anemia to severe hemolytic anemia requiring transfusion [1, 3].

Episodes of hemolysis may be intensified by exposure to colder ambient temperature, fever, and acute illnesses [4]. Delays in diagnosis are expected, with a delay of one or more years between symptom onset and diagnosis in many cases [3, 5]. Most cold agglutinins associated with infections or autoimmune disorders are likely to resolve spontaneously with a resolution of the infection or treatment of the autoimmune disease. This study describes a case of acute hemolytic anemia due to cold agglutinin antibodies based on SLE, which is probably triggered by an infection.

## Case Presentation

A 37-year-old Iranian woman, G3 L1 D1, with a history of two cesarean sections, with a gestational age of 26 weeks, was referred to our center due to dark urine and anemia. Her pregnancy was wanted and in spontaneous conception. She had a history of early-onset severe fetal growth restriction (FGR) and severe preeclampsia and eclampsia in her first pregnancy (13 years before this pregnancy), which terminated at 26 weeks of gestation. In her second pregnancy (5 years before this pregnancy), she had a successful term pregnancy (Neonatal weight: 2700 gram) on aspirin and low molecular weight heparin (LMWH). She did not have any medical disease and was on aspirin and LMWH during this pregnancy. In family history, her sister was a known case of SLE. She did not have any symptoms and signs of rheumatologic diseases, especially SLE. Due to her obstetric and family history, she was not evaluated with any rheumatologic or antiphospholipid antibody lab tests.

One week before admission, she had common cold symptoms and then presented with dark urine for two days. She did not have any medication usage, such as antibiotics. Her first-trimester fetal screening tests and anomaly scan were normal. Her Hgb was 11.5 g/dl one month before this admission. Her lab tests had hemoglobin (Hgb): 7.8 g/dl, AST: 56, ALT: 38, so-referred to our center for better evaluation. She did not have a history of high blood pressure and preeclampsia signs like headache, blurred vision, nausea, vomiting, and epigastric pain. Also, she did not have respiratory symptoms. In our center, on arrival, her reading was 15/15, as measured on the Glasgow Coma Scale, blood pressure: 110.70 mmHg, heart rate: 88 beats per minute, respiratory rate: 12 breaths per minute, temperature: 37°C.

On general examination, the following were recorded: fetal heart rate: 148 beats per minute, uterine height: 23 centimeters, uterine contractions: negative. Chest and heart examinations were normal, with no evidence of jaundice, lymphadenopathy, or leg edema. Skin and mucosa were intact in the examination. Our evaluation detected severe fetal growth restriction, hepatosplenomegaly, anemia, and positive cold agglutination antibodies. Her lab tests showed WBC: 9×10 9/L (75% PMN, 20% lymph), Hgb: 7.9 g/dl, MCV: 95, Platelet: 257,000, agglutination of RBCs in blood tube and on PBS in cold temperature. BUN: 8, Creatinine: 0.7, AST: 22, ALT: 24, ALP: 227, Total bilirubin: 0.8, Direct bilirubin: 0.2, LDH: 729, Corrected reticulocyte count: 2%, PT: 12.4, INR: 0.94, PTT: 28, Fibrinogen level: 497, BS: 77, Na: 142, K: 4.3, Ca: 9, Ph: 3,5, Mg: 2.4, CRP: 16, TSH: 5.32, Indirect and direct coombs tests: negative, Wright and 2ME: negative, RF: negative, Serum iron (SI): 85, TIBC: 416, Ferritin: 679, Urine analysis: normal without hemoglobin in urine, Vitamin B12 level: 392 (normal), Folate:8.9 (normal), 40 mg protein in urine 24 hours (normal range), C3.4: normal range, but high ANA, Anti-ds-DNA, high titers of anti-phospholipid antibodies were detected. Anti-Ro and La antibodies and TORCH studies were negative. Cold agglutinin titer was 1/1200.

We did not have facilities to check the Direct Coombs test for C3d on RBCs in our country. Also, COVID-19 PCR was negative. In the abdominal ultrasound, the spleen's size was 12.5×6 centimeter, and the size of the liver was 15.3 centimeter (mild hepatosplenomegaly). In echocardiography, ejection fraction (EF) was 55%. In fetal ultrasound, symmetric FGR (HC<2%, BPD: <2%, AC<2%, FL<2%, EFW: 598 gram <2%), oligohydramnios (AFI: 6 centimeters), absent umbilical artery Doppler was demonstrated and fetal echocardiography was normal. She

has followed with serial lab tests, and her hemolytic anemia was not progressive.

On her admission, ANA and antiphospholipid antibodies were not ready, so she was discharged with a diagnosis of cold agglutinin disease secondary to viral infections based on her history of infection lab tests in our country. Her fetus was followed with a serial Doppler assessment. After one week, she came to our center with the results of her lab tests (positive ANA, Anti-ds-DNA, and high titers of Antiphospholipid antibodies), and her Hgb was 8.5 gr/dl, and LDH was normal. She was admitted and visited by a rheumatologist, and with a diagnosis of cold agglutination disease secondary to SLE, oral low dose corticosteroid was started for her. Due to reverse umbilical artery Doppler and severe oligohydramnios (AFI: 2 cm), termination of pregnancy was offered, and cesarean section was done for her, and a male baby weighing 600 g was born after two days died due to prematurity.

After three days, the mother was discharged in good condition and Hgb: 8 gr/dl. We suspect the infection has triggered anemia based on SLE. The diagnosis was confirmed by repeated lab tests 12 weeks later. She had three diagnostic criteria of SLE (hemolytic anemia, positive ANA, and anti-ds-DNA). Now she is under the follow-up of a rheumatologist. In regular follow-up, she has a good response to corticosteroids without attacks of hemolytic anemia.

## Discussion

Cold agglutinin-induced hemolytic anemia as the primary presentation in SLE is extremely rare [6]. The typical diagnostic approach in any suspected hemolytic anemia generally starts with a complete blood count (CBC) and a review of the RBC indices on the PBS. It may be followed by testing for hemolysis, including LDH, indirect bilirubin, reticulocyte count, haptoglobin, and Direct Coombs Testing (DCT).

In our case, we had anemia and high LDH. Anemia may be absent if hemolysis is mild or reticulocytosis is sufficient to compensate. Usually, the reticulocyte count increases if there is ongoing (chronic) hemolysis. The reticulocyte count may be normal if hemolysis has occurred and there was insufficient time for reticulocytes to appear in the PBS. There is an underlying bone marrow disorder that interferes with compensatory erythropoiesis. In our case, due to acute hemolysis, she did not have reticulocytosis. The mean corpuscular volume (MCV) may be high due to RBCs agglutination. The WBC and platelet count are typically normal, like in our case. RBC agglutination may be apparent in a blood tube or on PBS. We detected RBC agglutination on PBS.

The DCT is positive for the complement C3b and generally negative for Ig [5, 7]. We did not have this method in our laboratory. Complement C3 and C4 are often reduced, reflecting a continuous consumption [7]. However, serum complement levels generally do not help evaluate CAD, as they are relatively nonspecific. In this case, we had normal complements level. Not all individuals with cold agglutination have clinical manifestations. For those who do, treatment is directed at minimizing cold-induced symptoms, maintaining an acceptable hemoglobin level, and addressing underlying disorders (infections, autoimmune disorders, lymphoproliferative disorders) [1, 8]. Compensated, mild, and stable hemolysis may not require aggressive treatment.

Transfusion can be given for individuals with severe or symptomatic anemia, and plasmapheresis may be used as a temporizing measure. In our case, anemia was not severe and was not progressive, so she did not transfuse with packed cells. If an underlying autoimmune disorder is identified, treatment should be directed at the underlying disorder. In cold AIHA, corticosteroids have less effect than in warm AIHA. Our patient responds well. In the first pregnancy, this patient had a history of early-onset severe preeclampsia, eclampsia, and FGR and a positive history of SLE in her sister without evaluation. According to history, our suspicion of SLE antiphospholipid syndrome (APS) was high.

Overall, while CAD-induced AIHA as the primary clinical presentation of SLE is extremely rare, the diagnosis may be missed easily. Our case had a history of respiratory infection before hemolysis, and without good history taking, the disease could be easily misdiagnosed with cold agglutinin-induced anemia secondary to infections. The infection may be the trigger for the onset of the disease. This case highlights awareness about SLE presenting as hemolytic anemia.

## Conclusion

In the cases of hemolytic anemia, the underlying causes must be considered. SLE is a secondary cause of hemolytic anemia, caused mainly by warm autoantibodies, and should be considered in young women. Cold agglutinin autoantibodies are less common than warm autoantibodies. A good history and physical examination are beneficial for diagnosis.

## Ethical Considerations

### Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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### Conflict of interest

The authors declared no conflict of interest.

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