

Case Report

Cold agglutinin disease related mismatch between hematocrit and hemoglobin values

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ABSTRACT

Autoimmune hemolytic anemia is a disease characterized by destruction of red blood cells (RBC) and anemia, caused by production of antibodies released against the body's own RBCs. While this condition is more commonly idiopathic, it may accompany autoimmune diseases as well. Cold agglutinin disease (CAD) is a rare subtype of acquired autoimmune hemolytic anemia, however, is an idiosyncratic clinical and pathological terminology, usually seen in older ages. This condition is caused by IgM antibodies called "cold agglutinins" formed against I antigens on RBC membranes which cause agglutination of RBCs at lower temperatures. In this case, a 56 year old male patient who was diagnosed with CAD secondary to Epstein-Barr virus (EBV) infection is being presented.

Keywords: Cold agglutinin disease, Hemoglobin-hematocrite mismatch, Epstein-Barr virus

INTRODUCTION

Cold agglutinin disease (CAD) is usually a chronic type of acquired hemolytic anemia. Cold agglutinins are detected in approximately 20% of patients with autoimmune hemolytic anemia. IgM-type autoantibodies that have specificity to I/i antigens in erythrocytes and act by binding to these antigens, are associated with cold agglutinin disease.¹ These autoantibodies become active at lower temperatures. Thus, cold agglutinin disease is usually present in areas with a cold climate or in the peripheral body parts, such as the nose, ears and fingers.² Most chronic CAD cases are idiopathic. In addition, it can be seen secondary to waldenström macroglobulinemia, lymphoma and chronic lymphocytic leukemia (CLL). The most common treatment for chronic CAD is the anti CD20 antibody rituximab. There are also ongoing studies for other treatment options. Splenectomy and prednisone have no place in the treatment. Acute CAD develops more frequently postinfectiously. This condition may develop after viral infections such as infectious mononucleosis,

cytomegalovirus (CMV) or bacterial infections such as mycoplasma pneumonia and heals spontaneously within 3-4 weeks. Other chronic diseases such as diabetes mellitus, thyroid dysfunction, chronic renal failure and gastrointestinal loss anemia which may lead to chronic anemia should also be excluded in the differential diagnosis.³⁻⁶ In this case, a male patient who was diagnosed with acute CAD secondary to Epstein-Barr virus (EBV) infection is being presented.

CASE REPORT

A 56 year old man with productive cough and shortness of breath presented at internal medicine outpatients department. The patient who described preceding flu-like symptoms, high fever, fatigue about a month ago also explained that he began expectorating green pus and coughing for the last 10 days. His past medical history included hypertension, benign prostatic hyperplasia (BPH), heart failure (HF). He had histories of urologic operation for nephrolithiasis and orthopedic operation for carpal tunnel syndrome. His family history also

included HF. His medications included nebivolol, losartan/hydrochlorothiazide, spironolactone. He stated 40 year/pack cigarette smoking, which he stopped a while ago as he claimed. He had no history of alcohol use. In his physical examination, his blood pressure was 120/80 mmHg, his temperature was 37.2 °C. His lung sounds were coarse and bibasilarly reduced. He had no other abnormal findings in his systemic examinations. The patient was admitted to internal medicine clinic with his existing findings. His complete blood count (CBC) results were as following: haemoglobin (Hb) was 12.8 g/dl, hematocrit (Hct) was 22.4%, mean corpuscular volume (MCV) was 103fl, mean corpuscular hemoglobin concentration (MCHC) was 53 g/dl, red blood cells (RBC) was $2.3 \times 10^6/\text{ul}$. His corrected reticulocyte count was 2.7. In his biochemistry results, it was measured that c-reactive protein (CRP) was 38 mg/l and procalcitonin was 0.67 ng/ml, while his total bilirubin was 3.27 mg/dl (indirect bilirubin: 1.92 mg/dl), lactate dehydrogenase (LDH) was 266 U/l. His iron, vitamin B12, and serum folate levels were normal. His direct antiglobulin (coombs) test was positive. Arterial blood gas (ABG) results revealed Hb was 13.2 g/dl, Hct was 39%. The existence of Hb-Hct mismatch in his CBC, positive coombs test result and high MCHC values suggested that the patient likely had CAD. Downey cells due to EBV infection were seen in patient's peripheral blood smear (Figure 1). Thereas on why Hb-Hct mismatch was not observed in ABG result was thought to be because of the fact that ABG samples are processed quicker than hemogram samples, without letting the sample cool down. The cold agglutinin titers were measured to be positive at a value of 1/128 when the sample temperature was brought down to +4 °C. Screening tests were arranged for the patient who got the diagnosis of CAD, in order to reveal underlying etiologies. Thorax-computed tomography (CT) scan showed multiple mediastinal lymphadenopathy (LAP)s, the largest one having a size of 3×15 cm. Other tests required for differential diagnosis of hematologic malignancies showed no significant positive results. His peripheral blood smear revealed no atypical cells. Positron emission tomography (PET)-CT did not show any uptake favoring malignancy in terms of existence of mediastinal LAPs that were seen in previous thorax-CT. Due to existence of high fever and fatigue in the patient's history in addition to his existing mediastinal LAPs, EBV infection as a differential diagnosis was also thought possible. Therefore, his serologic testing was sent, which resulted positive for EBV-Epstein-Barr nuclear antigen (EBNA) IgG, EBV viral capsid antigen antibody (VCA) IgM and EBV VCA IgG. When all these findings were evaluated together, the patient was thought to be primarily suffering from cold agglutinin disease secondary to EBV infection (infectious mononucleosis). In his follow-up testing, the patient's symptoms got resolved in three weeks and his Hb-Hct mismatch in his CBC vanished. The patient was advised to go to outpatients department check-ups at infectious diseases polyclinic department for his EBV infection and was discharged after being informed that he required regular follow-up visits at internal medicine polyclinic

department. His follow-up visits still continue at our internal medicine clinic.

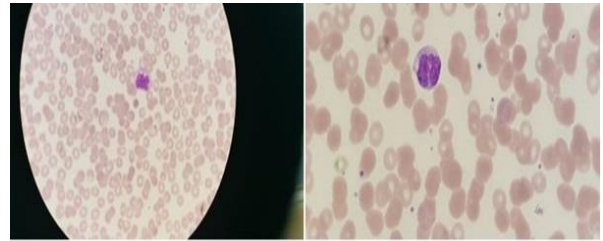


Figure 1. Peripheral blood smear revealed Downey cells due to EBV infection.

DISCUSSION

Cold agglutinin disease is a rare type of chronic autoimmune hemolytic anemias caused by cold agglutinins which are IgM autoantibodies formed against I antigens of RBC membranes.² While IgM antibodies typically react weakly with RBCs at a temperature of 37 °C, cooler temperatures such as 0-4 °C cause them to have a strong hemolytic effect against RBCs.⁷ Therefore the symptoms are more frequently seen at cooler climates or at winter season. Because the high temperature of circulating blood in human body rarely drops down below 20°C even at peripheral tissues, autoantibodies that are capable of being activated at higher temperatures usually cause clinical findings. These clinical findings can be usually observed at peripheral organs such as nose, fingers or ears. When the circulating blood reaches a higher temperature, however, IgM autoantibodies detach from the surface antigens of RBC membranes that they were previously bound to; this detachment results in reduction of symptoms. Extravascular hemolysis due to macrophage mediated RBC destruction within Kupffer cells of the liver secondary to complement (usually C3b) activation and rarely intravascular hemolysis due to the effect of membrane attack complex may be seen.^{8,9} Cases with CAD are usually idiopathic (also called primary cold agglutinin disease). CAD can also be seen in Waldenström macroglobulinemia, lymphoma, CLL, infectious mononucleosis, CMV infection and autoimmune diseases.^{11,12} CAD usually manifests itself with symptoms such as acrosyanosis, livedo reticularis, episodic back pain, dark urine. Reticulocytosis due to hemolysis, indirect hyperbilirubinemia, positive coombs test along with Hb-Hct mismatch and mild anemia that usually does not require transfusion may be detected.¹³ Treatment approach to CAD is usually symptomatic. Especially avoidance of cold exposure increases quality of life. Unlike other etiologies of autoimmune hemolytic anemia, splenectomy and prednisone are not helpful as treatment options. Blood transfusion is also unhelpful, since RBCs in donor blood also have I antigens. If the patient suffers from deep anemia requiring transfusion, transfusion must be done at warm temperatures. In case of patients not responding to symptomatic treatments or avoidance therapy, treatment option is Rituximab. Response rate to Rituximab is 60%.

Drug combinations such as Rituximab-bendamustin or Rituximab-fludarabin can also be used.¹⁴ In addition, studies with monoclonal antibodies that prevent complement activation proceed.

CONCLUSION

As seen from our patient, in patients who suffer from symptoms of hemolytic anemia after having an infection especially at cooler temperatures in addition to having Hb-Hct mismatch in their CBC results, cold agglutinin disease as differential diagnosis should be considered.

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REFERENCES

1. Swiecicki PL, Hegerova LT, Gertz MA. Cold agglutinin disease. *Blood*. 2013;122(7):11-4.
2. Berentsen S. How I manage patients with cold agglutinin disease. *Br J Haematol*. 2018;181(3):320.
3. Yenigün M, Türker T, Ataoğlu HE, Temiz LE, Ahabab S. From obesity to diabetes. *Haseki Tıp Bülteni*. 2005;43:1-12.
4. Saler T, Keşkek SO, Ahabab S, Cakir S, Ortoğlu G, Bankir M, et al. Frequency of Hashimoto's thyroiditis in women with vitamin D deficiency: A cross sectional study. *Am J Int Med*. 2014;2(3):44-8.
5. Atasoy A, Atay A, Ahabab S, Hanedar M, Yenigün M. Diyabetik nefropatiye genel bir bakış. *Haseki Tıp Bülteni*. 2015;53:16-9.
6. Saler T, Keşkek ŞÖ, Kırk S, Ahabab S, Ortoğlu G. H. pylori May Not Be Associated with Iron Deficiency Anemia in Patients with Normal Gastrointestinal Tract Endoscopy Results. *Adv Hematol*. 2014;375915:4.
7. 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(4):460.
8. Zilow G, Kirschfink M, Roelcke D. Red cell destruction in cold agglutinin disease. *Infusionsther. Transfusions Med*. 1994;21(6):410.
9. Baines AC, Brodsky RA. Complementopathies. *Blood Rev*. 2017;31(4):213.
10. Crisp D, Pruzanski W. B-cell neoplasms with homogeneous cold-reacting antibodies (cold agglutinins). *Am J Med*. 1982;72(6):915.
11. Horwitz CA, Moulds J, Henle W, Henle G, Polesky H, Balfour HH, et al. Cold agglutinins in infectious mononucleosis and heterophil-antibody-negative mononucleosis-like syndromes. *Blood*. 1977;50(2):195.
12. Oshima M, Maeda H, Morimoto K, Doi M, Kuwabara M. Low-titer cold agglutinin disease with systemic sclerosis. *Intern Med*. 2004;43(2):139.
13. Nikousefat Z, Javdani M, Hashemnia M, Haratyan A, Jalili A. Cold Agglutinin Disease; A Laboratory Challenge. *Iran Red Crescent Med J*. 2015;17(10):e18954.
14. Gertz MA. Management of cold haemolytic syndrome. *Br J Haematol*. 2007;138(4):422-9.

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