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UCTD – A RARE CAUSE OF SECONDARY WARM AUTOIMMUNE HEMOLYTIC ANEMIA

Medicine

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ABSTRACT

Anemia caused due to Red Blood Cell (RBC) destruction is called Hemolytic Anemia; which can be due to hemoglobinopathies, enzymopthies, autoantibodies, infections, drugs and toxic agents. Autoimmune Hemolytic Anemia (AIHA) is a type of hemolytic anemia caused by autoantobodies to RBC surface antigens causing extravascular hemolysis in most cases; but can cause intravascular hemolysis in severe cases. The antibodies are usually of warm type (IgG) but can also be of cold variant (IgM). Warm AIHA is the most common type of AIHA. It is usually of primary (idiopathic) type but it can be due to secondary causes (like viral infections, autoimmune diseases, lymphoproliferative disorders, immunodeficiency states or pregnancy). Here is a case of secondary AIHA induced by Undifferentiated Connective Tissue Disorder (UCTD) which was refractory to usual treatment modalities.

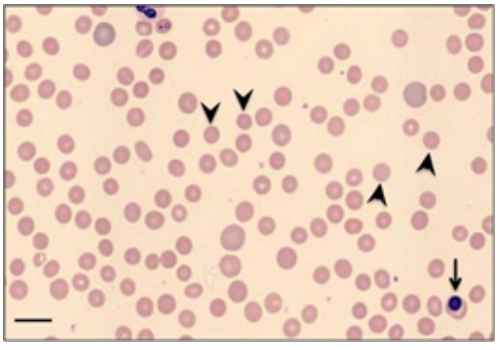
KEYWORDS

INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is caused by autoantibodies that react with self red blood cells (RBCs) and cause them to be destroyed. AIHA is most commonly caused by antibodies that react with red cell antigens optimally at 37ºC (warm antibody). About half of the AIHA cases are primary because of no specific etiology whereas the rest are secondary to other recognizable causes like viral infections (eg. EBV, HCV, HIV, HEV, SARSCov-2), autoimmune conditions (eg. SLE, RA, UC, scleroderma), lymphoproliferative disorders (eg. CLL, Lymphoma, MGUS, etc), immunodeficiency state (eg. Hematopoetic stem cell transplant, solid organ transplant, etc) and pregnancy. In warm AIHA the antibody is usually IgG type while in Cold Agglutinin disease (CAD) it is generally of IgM type. The typical laboratory abnormalities include –

- Reduced hemoglobin
- Raised Reticulocyte count (suggesting that bone marrow is responding)
- Elevated LDH levels (500-5000 units/L)
- Low/ absent Haptoglobin levels (typically less than 25 mg/dL)
- Blood smear showing spherocytes / microspherocytes
- A positive Direct Antiglobin Test (DAT) – the strength of the test correlates with the degree of hemolysis; DAT is negative in drug-induced AIHA

Fig 1 : Peripheral smear showing spherocytes in Warm Autoimmune Hemolytic Anemia



Warm AIHA is diagnosed when an individual has antibody-mediated (DAT [Coombs] positive) hemolytic anemia not due to any other cause such as a hemolytic transfusion reaction, Paroxysmal Nocturnal Hemoglobinuria (PNH), or Cold Agglutinin Disease (CAD).

CASE REPORT

A 25 year old male patient who is occasionally alcoholic presented with complain of generalized weakness, easy fatigability, fever and yellowish discoloration of sclera since 15-20 days with no similar complains previously, no history of acute bleeding from any site and no family history of any blood related disease. He did not have any rash, hair loss, oral ulcers or joint paint. On examination he was found to be pale along with icterus in sclera with mild splenomegaly. His laboratory investigations revealed severe anemia (Hb 5.10 gm/dL) with leucocytosis (WBC – 20100/ microlitre; 83% neutrophils and 12% lymphocytes), mild thrombocytopenia (PLT – 1.21L/ microlitre) and MCV-105; LFT – Total Bilirubin (11.34 mg/dL) and direct bilirubin (1.38 mg/dL) with normal liver enzymes; RFT was also normal; RBS on presenatation was 307 mg/dL. On further investigation, his Serum Vit B12, Serum Iron, Serum Ferritin level were normal; Stool for occult blood was negative; Initial retic count was 2.20%; Negative for all viral markers (HIV, HBsag, HCV, HAV, HEV); USG (Abdo), CXR (PA) and baseline ECG were also normal. HbA1c turned out to be 6.9% with normal Thyroid function tests. On doing Coombs' test, DCT was found to be grade 4 positive and ICT was grade 3 positive. DCT was positive for warm type of IgG with a titre of 1:64. ANA by ELISA was grade 4 positive (with speckled pattern) and on ANA profile was found to be positive for SSA/Ro60KD antibodies. Bone marrow biopsy showed hypercellular bone marrow with mild eosinophils, mild plasmacytosis, mild lymphocytosis and reactive marrow changes. Serial CBC revealed reducing Hb trend (with a nadir of 2.3 gm/dL).

Hence, a provisional diagnosis of Undifferentiated Connective Tissue Disease (UCTD) induced secondary Autoimmune Hemolytic Anemia (AIHA) was kept and patient was treated initially with methylprednisolone pulse, Rituximab (at a dose of 375 mg/m^2/week for 4 weeks) and Hydroxychloroquine with vitamin B-complex and Folic acid supplementation.

Due to no improvement in hemoglobin (Hb), later patient was given one dose of 500mg of Cyclophosphamide. Still the Hb did not improve beyond 3.5 gm/dL and so patient was started on Mycophenolate Momefatil (MMF). Still, due to ineffective response, patient was started on High-dose IV gamma globulin (2gm/kg over 5 days) along with Danazol. Patient's Hb started rising and the bone marrow started responding with a retic count of 40% and DCT grade reduced to 2 and ICT grade reduced to 1 after 4 days of starting IV gamma globulin. Patient was discharged on tapering steroids, hydroxychloroqiune and Danazaol and Metformin. On followup, patient is maintaining Hb more than 13 gm/dL with no other complains.

DISCUSSION/CONCLUSION

Autoimmune hemolytic anemia (AIHA) is a rare and heterogenous disease that affects 1-3/100,000 patients per year. The autoantibodies are almost always IgG, although IgA and warm-acting IgM have been reported. The subtype of IgG likely influences the rate of red blood cell (RBC) destruction, with IgG3 and IgG1most able to fix complement and thus more destructive than other subtypes. Most commonly, warm

autoantibodies are directed against the Rh or against glycophorin antigens. In warm AIHA, RBCs are mostly cleared extravascularly (in reticuloendothelial macrophages). Intravascular hemolysis may be seen in severe cases if the reticuloendothelial system becomes overwhelmed or if the complement membrane attack complex is deposited on the RBC surface. There is significant heterogeneity in symptoms, ranging from mild to fulminant. Patients usually present with anemia-related symptoms (dyspnea on exertion, fatigue, bounding pulse or palpitations), chest pain, jaundice or dark urine and splenomegaly, Evans syndrome (presence of AIHA in association with immune-mediated thrombocytopenia). The physical examination may show pallor and/or jaundice;moderate splenomegaly; may have signs and symptoms of cardiac decompensation (tachycardia, tachypnea, or signs of heart failure).Patients with warm AIHA have a high risk of thromboembolic complications (up to 30 percent of patients). Treatment of the underlying condition is generally appropriate (with rareexceptions); however, this may not always lead to resolution of hemolysis, or it may work more slowly than is needed. Initial responses are common,but many individuals experience a waxing and waning course and require retreatment periodically. The prognosis of secondary warm-AIHA largely depends on the course of underlying disease. The actual survival after 10 years is 73%.

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CONFLICT OF INTEREST
There are no conflicts of interest.

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