A rare case of Coombs negative autoimmune haemolytic anaemia in a young male

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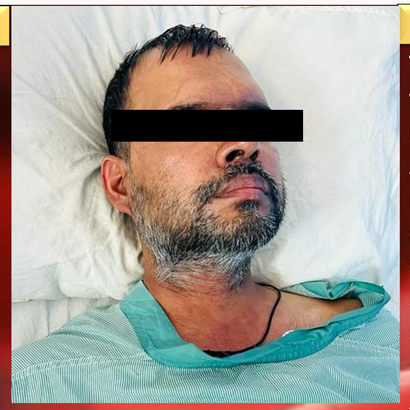
INTRODUCTION

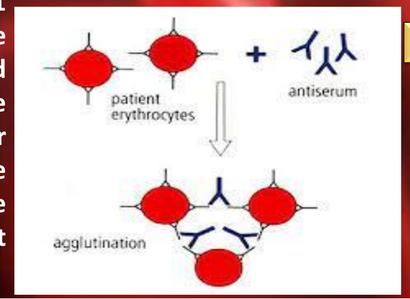
Autoimmune hemolytic anemia (AIHA) occurs when antibodies directed against the person's own red blood cells cause them to burst, leading to an insufficient number of oxygen-carrying red blood cells in the circulation. The lifetime of the RBCs is reduced from the normal 100–120 days to just a few days in serious cases. The antibodies are usually directed against high-incidence antigens, therefore they also commonly act on allogenic RBCs (RBCs originating from outside). Autoimmune Haemolytic Anaemia (AIHA) is an uncommon disorder with an estimated incidence of 0.8-3 per 100,000/year and a prevalence of 17:100,000 in the adult population. It can be of warm autoimmune type , cold autoimmune type or coombs negative. Coombs negative AIHA is characterized by laboratory evidence of hemolysis plus a negative Coombs test. We report a case of a young male who presented with acute hemolysis and was later diagnosed as coombs negative AIHA.

CASE

A 31 year old hypertensive male presented to MGH with c/o of fever, jaundice, reddish discoloration of urine and fatigue. On examination he had severe pallor and icterus. Baseline investigations were s/o severe anemia, LDH and reticulocyte count were high with indirect hyperbilirubinemia. Abdomen ultrasound showed splenomegaly (13 cm) and fatty liver (15 cm). Hemolytic anemia was suspected. DCT and ICT were done to know the type of anemia, both were negative. G6PD level was normal, PNH clone was absent, ANA tested negative, ceruloplasmin was normal. Hence, the diagnosis of Coombs negative AIHA was made. He was started on steroid pulse therapy with IV Solumedrol 1 g for 3 days, to which he did not respond and continued to have symptoms with haemoglobinuria and severe anemia, thereby requiring daily blood transfusions. On day 7 of admission, he had an episode of severe abdomen pain referred to the left shoulder, managed by IV analgesics. Due to poor steroid response patient was shifted to second line treatment with IVIg at 1 g/kg/day for 2 days along with steroid pulse 40 mg for 4 days, this led to slight symptomatic improvement and decline in frequency of transfusions . After steroid pulse was over patient was started on oral prednisolone in a dose of 1 mg/kg and Rituximab 375 mg/m2 weekly was initiated. After 2nd dose of Rituximab patient became transfusion independent, maintaining Hb> 8gm% for 1 week. For etiological work up, he was tested for HIV, Hep B, Hep C, CMV, EBV, all tests were negative except Anti-HbC ELISA came out positive, he was started on tenofovir as a prophylactic measure as he received rituximab therapy and is on higher risk of Hep B reactivation. A whole body PET CT was also done to rule out anything that could have been missed, it showed presence of splenomegaly with multifocal infarcts, this was believed to be secondary to massive intravascular hemolysis. He was started on Aspirin 75 mg for the same. Patient gradually improved and was discharged after 3rd dose of rituximab and is still in follow up.



Investigation	Result
Hb	6.1 g/dl
MCV	78 Fl
Retic count	4.9 %
LDH	780 U/L
Bilirubin(D/I)	8.1 mg/dl (2/6.1)
DCT	Negative
ICT	Negative
Urine for Hb	+
Haptoglobin	32 mg/dl
ANA	Negative
HbSAg/ Anti HCV/HIV/ EBV/ CMV	Negative
Anti HbC	Positive
Ceruloplasmin	35 mg/dl



DISCUSSION

The diagnosis of AIHA is based on low hemoglobin concentration, a positive coombs test and at least one feature of hemolysis i.e high reticulocyte count, raised LDH, raised indirect bilirubin or splenomegaly. A positive coombs suggests diagnosis of AIHA however coombs negative AIHA occurs in 5-10% of patients. AIHA with negative coombs is uncommon and requires investigations to exclude secondary causes and regular follow up as it is difficult to establish that hemolysis is due to autoimmune etiology. A negative coombs test may be due to presence of IgG autoantibodies in quantities lesser than detectable threshold, IgA or IgM autoantibodies and low affinity autoantibodies. The Natural killer cell mediated antibody independent cytotoxicity has also been postulated in the pathogenesis of AIHA which may also contribute to a negative coombs test. Despite the difference in pathologic mechanisms in coombs positive and negative AIHA, there is no difference in terms of effectiveness of steroid therapy, survival at one year and long term complications between these two conditions. However, patients with coombs negative AIHA clinically have a milder degree of hemolysis and require low doses of steroids for maintenance as compared to patients with coombs positive AIHA. Serological tests for Epstein-Barr virus, Cytomegalovirus, HIV, Hepatitis B, Hepatitis C were performed to exclude AIHA secondary to these infections, all negative. Antibody for Hepatitis core antigen was positive in our patient, but this was due to the presence of family history of positive hepatitis B surface antigen. Patient responded well to Rituximab therapy, thereby confirms autoimmune etiology of hemolysis.

CONCLUSION

High degree of clinical suspicion of autoimmune hemolytic anemia should be made in patients presenting with acute hemolysis and should be diagnosed after exclusion of secondary causes by appropriate investigations including Coombs test. Negative coombs does not rule out possibility of AIHA and in such cases compatible clinical course helps in diagnosis of AIHA.

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