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A RARE C ASE OF PRIMARY COLD AGGLUTININ DISEASE ASSOCIATED WITH MEGALOBLASTIC ANEMIA

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ABSTRACT

Introduction: Auto immune haemolytic anemias are caused by antibody production by the body against its own RBCs. They are characterised by a positive direct anti globulin test and divided into warm and cold types. Vitamin B12 deficiency associated with Auto immune hemolytic anemia leads to severe complications such as severe anemia, pancytopenia, and rarely hemolysis.

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Case presentation:A 37 year old male presented with c/o breathlessness, yellowish discolouration of eyes, oral ulcers, generalised fatigue, decreased appetite for 3 weeks. Clinical examination was unremarkable except for pallor, icterus and oral ulcers. Lab reports revealed severe anemia with peripheral smear Peripheral smear showed macrocytic normochromic anemia, hypersegmented neutrophils, cabot rings with hemolysis features. S.Folate and B12 levels were Low.Direct Coomb's test was positive. LFT revealed Indirect Hyper Bilirubinemia, Increased LDH. Patient treated with PRBC transfusion and Inj.Vitamin B12 intra venously .On follow up patient symptoms got improved .

Conclusion: Macrocytic anemia presented with Hemolysis is rare in occurence.The fact that patients anemia resolved after vitamin B12 treatment indicates a possibility of vitamin B12 Deficiency causing AIHA.

Key words: AIHA, CAD, B12 Deficiency

INTRODUCTION

Primary chronic cold agglutinin disease (CAD) is a well-defined clinicopathologic entity in which a specific, clonal lymphoproliferative B-cell bone marrow disorder results in autoimmune hemolytic anemia[1,2]

Auto immune hemolytic anemia (AIHA) is a collection of disorders characterized by the presence of autoantibodies that binds to the patients own erythrocytes leading to premature Red cell destruction. AIHA classified into 3 types [3,4]- 1.Warm type 2. Cold type and 3.Mixed type.Cold Auto immune hemolytic anemia consists of a) primary cold agglutinin disease (CAD) and b) secondary cold agglutinin syndrome (CAS) . Primary ColdAgglutininDisease accounts for 15% of Auto immune hemolytic anemia.

Warm-antibody AIHA (WA-AIHA) accounts for 75% of the cases. Warm antibodies show optimal binding at 37°C and are mostly IgG subtype. Red blood cells (RBCs) coated with IgG subtype removed via Fc-gamma receptor-mediated phagocytosis that occurs in spleen, whereas RBCs coated with activated C3b, are destroyed via complement-receptor mediated phagocytosis that happens in the liver.These leads to Extravascular hemolysis.

Cold-antibody AIHA (CA-AIHA), the antibodies optimally bind to RBCs at 0°C–4°C and are mostly IgM subtype C3b binds to the complement receptors on phagocytes leading to erythrocytes destruction in the liver. C3b is converted to C3d on the erythrocytes leading to a positive direct antiglobulin test (DAT) for C3d, significant of CA-AIHA[5,6] . In some cases, complement activation may progress beyond the C3b formation step, resulting in C5 activation, which leads to formation of the membrane attack complex and finally intravascular haemolysis. secondary CA-mediated hemolytic anemia may complicate with other specific diseases, such as *Mycoplasma pneumoniae* pneumonia, Epstein-Barr virus infection, or aggressive lymphoma.

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CASE DESCRIPTION

A 37 year old male patient came to Medicine opd with complaints of yellowish discolouration of eyes since 3 weeks. History of decreased appetite and generalized fatigue since 3 weeks.History of Nausea since 3 weeks. History of oral ulcers and Burning sensation in the tongue since 3 weeks.

There was no history of generalized itching all over the body, No history of vomitings, No history of pins and needle sensations in the palms and sole ,No history of muscle weakness or difficulty in walking, No history of blood in urine,stools or vomiting, No history of Malaena, No history of palpitations ,No history of Multiple joint pains or swelling, No history of fever, No history of shortness of breath, No history of similar complaints in the past.On examination Pallor was present, Icterus present. On local examination,oral ulcers present in the buccal mucosa. Bp and pulse were normal.Systemic examination was normal.

Blood count revealed pancytopenia. Hb- 4.5g/dl, RBC- 1.14 milli/cu mm,PCV - 14.8,% MCV - 129.8 fl,MCH -39.5 pg,MCHC- 30.4g/dl, TLC- 3,810 cells/cu mm. Platelet count - 95,000 lakhs/cumm. Peripheral smear showed macrocytic normochromic anemia, hypersegmented neutrophils, cabot rings with hemolysis features. USG abdomen showed mild speelnomegaly(15 cm). LFT revealed Indirect hyperbilirubinemia -3.3 mg/dl. Further, Reticulocyte count - 1.1%. Direct Coombs test - positive. LDH - 1687 U/L. Serum Haptoglobin - <40 mg/dL. Cold IgM antibodies- positive. Warm antibodies - negative negative. Both folate and vitamin B12 values were found to be decreased.Serum folate level -4.05.ng/mL vitamin B12 value <159 pg/mL.ANA Profile was negative.2D Echo was normal.UGI scopy was done and revealed normal study. Subsequent serum testing for the presence of anti-parietal cell antibodies, intrinsic factor antibodies were negative. CT abdomen, CT chest showed no significant abnormality. Blood culture showed no growth. Bone marrow aspirate showed hypercellularity, erythroid hyperplasia with megaloblastosis and megakaryocytic lineage.Patient was transfused PRBCs and was started on injection vitamin B12. Patient improved symptomatically and was discharged. Serial follow up of patient was done and his hematologic parameters and clinical condition improved.

DISCUSSION

Cold agglutinins were first described by Landsteiner in 1903. CAD is characterized by an auto-antibody which is able to agglutinate red blood cells (RBCs) at temperatures lower than that of the body, and activate the complement system responsible for lysis of RBCs.Cold agglutinins usually react at lower temperatures but pathological cold agglutinins may react up to 37°C

Cold antibodies may be monoclonal or polyclonal. Monoclonal antibodies are more commonly seen in idiopathic cases and CAD secondary to lymphoproliferative diseases[7,8,9] Polyclonal antibodies are generally determined after mycoplasma pneumonia, Epstein-Barr virus, or cytomegalovirus infections .

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Asim Haider et.al[4] done a similar case report of Idiopathic CAD in a 71 year female presented with generalised weakness and tiredness . These patients should avoid cold exposures until the underlying cause of CAD has resolved or been eliminated and CAD is a rare cause of Auto immune hemolytic anemia.

Nesibe Esra Yasar et.al presented a case of 55 year old woman presented with Joint pains and k/c/o Hyperthyroidism and found to have Cold agglutinins can cause interference in laboratory tests.

Shinsaku Imashuku et.al[5] reported 2 cases of primary CAD which are concurrent with our case that includes Megaloblastic anemia who presented with severe anemia and Jaundice and evaluated and diagnosed as Primary CAD and treated with B12 Supplementation.

Sariya Wongsaengsak et.al[2] presented a case report of 75-year-old woman with underlying hypertension, asthma and hypothyroidism came with shortness of breath and dyspnea on exertion for 2 weeks with no history of abnormal bleeding. During workup .Patient diagnosed as CAD with a rare presentation of Diffuse large B cell Lymphoma.

Our patient presented with yellowish discolouration of eyes and oral ulcers ,on investigating the patient,we had an incidental finding of Cold Agglutinin disease associated with B12 Deficiency.Patient improved with Vitamin B12 supplementation and Pulse therapy of Steroids.

CONCLUSION

AIHA is greatly heterogeneous disease due to the several immunologic mechanisms involved in its pathogenesis .Macrocytic anemia accounts for approximately 3.6 % of Anemias[10]. Megaloblastic anemia associated with Hemolysis is rare in occurrence. Patients presented with Anemia and Indirect hyperbilirubinemia should be evaluated for Auto immune hemolytic anemias. These patients should be treated for the cause of Hemolysis .Vitamin B12 supplementation in these patients resolves the patient's symptoms and helps in their recovery.

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