Case Series

Warm Autoimmune Haemolytic Anaemia due to IgA and IgG — A Rare Clinical Scenario

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Autoimmune Haemolytic Anaemia (AIHA) is a decompensated acquired haemolysis caused by the host immune system producing autoantibodies that bind to the antigens on the surface of circulating erythrocytes, leading to haemolysis and decreased red cell survival. It requires efficient and advanced immunohaematological and transfusion support. Despite advances in medical field, simple test like Direct Antiglobulin Test (DAT) still remains the diagnostic hallmark. The sensitive column gel technology further helps to characterise these antibodies according to class, subclass and titre of antibodies. It is very important to characterize these autoantibodies as there is a relation between strength of DAT and in vivo haemolysis. Serologically, cases are divided into warm (mainly due to IgG), cold (mainly due to IgM) or mixed depending upon the thermal amplitude of the antibody. IgA and IgG antibodies causing warm type of AIHA are rare as monospecific gel cards are not available in all centres. We here report rare case series of warm AIHA caused by dual antibodies IgA and IgG.

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Key words **: AIHA, Direct Antiglobulin Test, IgA Antibody.**

Autoimmune Haemolytic Anaemia (AIHA) is a fairly uncommon disorder with annual incidence of 1-3 cases per lakh population[1,2]. There is production of autoantibodies against RBCs which leads to RBC destruction via complement or Reticuloendothelial system. It may present as an idiopathic disorder or associated with some other medical conditions. It ranges from a spectrum of warm to cold to mixed AIHA.The diagnostic test ranges from simple blood tests like reticulocyte count, bilirubin, serum haptoglobin and LDH to specific tests like Direct Antiglobulin Test (DAT) (also known as Direct Coombs test- DCT) and sensitive gel based tests. These tests help in assessing the severity of disorder as well as identifying the antibody and complement which helps to classify AIHA into warm and cold type. Also detailed characterization of antibody is important as there is relation of antibody type and titre with in vivo haemolysis and clinical severity of AIHA.The antibodies involved are IgG in warm AIHA and IgM in cold AIHA. IgA mediated warm AIHA is rare and the incidence is 0.2 to 2.7 % cases[3] and the diagnosis is often missed if polyspecific antihuman globulin(AHG) (containing anti-IgG and anti-complement C3d) is used for DAT. We here report four cases of warm AIHA with IgG and IgA antibody.

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Editor's Comment :

- Autoimmune hemolytic anaemia is an uncommon immune disorder which often causes a diagnostic dilemma to the physicians. Delay in diagnosis might increase the morbidity and mortality.
- The autoantibody characterisation by mono specific gel card test which is not widely available aids in diagnosis as well as in planning the treatment.
- Warm AIHA caused by dual antibiodies (IgG and IgA) is a rare association which can be diagnosed by gel card. It may also helps to determine the prognosis and in guiding further treatment plan

Case 1 :

64 years old male patient presented with generalised weakness and yellowish discolouration of eyes and urine for two weeks. Physical examination revealed pallor, icterus, tachycardia and hepatomegaly. There was no lymphadenopathy, splenomegaly or rash. Blood examination showed Hb-4.4gm/dl, TLC-3200/cmm and platelet 168000/cmm. Peripheral blood smear showed anisopoikilocytosis, spherocytes and nucleated red cell. Serum bilirubin-8.2 mg/dl, direct bilirubin-1.3mg/dl, SGOT-56 IU/L, SGPT-28 IU/L, LDH-2799 mg/dl, Ferritin 104. Serum Vitamin B12 and Folic acid levels were normal. Epstein Barr virus DNA PCR and Mycoplasma IgM were negative. ANA was negative. Direct Coombs Test (DCT) was 4+. Extended DCT was IgG 4+, IgA 1+, IgM, complements C3d & C3 were negative. Indirect Coombs Test (ICT) was negative. A diagnosis of warm AIHA was made. Patient received 2 units of best matched Packed RBC (PRBC) and was started on Injection Methylprednisolone 1gm/day for 3 days. His symptoms started improving and Haemoglobin was stable at 9gm/dl. His jaundice improved. He was continued on oral prednisolone 1mg/kg for 3weeks followed by tapering

schedule. He is asymptomatic and now off any medication for AIHA.

Case 2 :

34 years old female presented with generalised weakness. On physical examination she had pallor, icterus, tachycardia and mild splenomegaly. There was no hepatomegaly or lymphadenopathy. Blood tests revealed Hb 6.3gm/dl, TLC 8900/cmm, platelet 136000/cmm. Bilirubin was 4.5 mg/dl, direct bilirubin 0.6 mg/dl. Her DCT was 4+. Extended DCT was- IgG 4+, IgA4+, IgM, C3d and C3 were negative. ICTwas also positive. She received 1unit of PRBC and was started on Prednisolone 1mg/kg for 3 weeks. She relapsed when steroid dose was tapered so she was started on weekly Rituximab 375mg/m2/week for 4 doses along with low dose steroids. Steroid was stopped and now she is in remission.

Case 3 :

61 years old male known case of Chronic Lymphocytic Leukaemia (CLL) on observation presented with weakness for 2 weeks and two episodes of dark coloured urine. Physical examination revealed pallor, icterus and left cervical 1.5cm lymphadenopathy. There was no hepatosplenomegaly. Blood examination revealed Hb 6.1gm/dl, TLC 3,61,500/cmm, platelet 1.47 lakh/cmm, Bilirubin-5.1 mg/dl, direct bil-0.7 mg/dl. His DCTwas 4+, Extended DCT was IgG4+, IgA 3+ but IgM, C3c and C3d were negative (Fig 1). ICT was positive. Urine examination showed haemoglobinuria. He was started on inj methylprednisolone 1 gm for 3days. He also received 4 units PRBC transfusion. As his lymphocyte doubling index was high so he was planned for starting CLL treatment. He was treated with cyclophosphamide and prednisolone. CLL fluorescence in situ hybridization (FISH) panel was negative. Rituximab was not given as TLC was very high so there was a chance of flare. Fludarabine and chlorambucil were avoided in view of their potential for aggravating AIHA. After 15 days he came to emergency with a haemoglobin of 5.7gm/dl, TLC-119,00/cmm, platelet-2.36 lakh/cmm and DCT was 4+. He received 3 units of PRBC transfusion uneventfully and was started on Bendamustine/Rituximab(BR) chemotherapy. His haemoglobin improved to 9gm/dl.

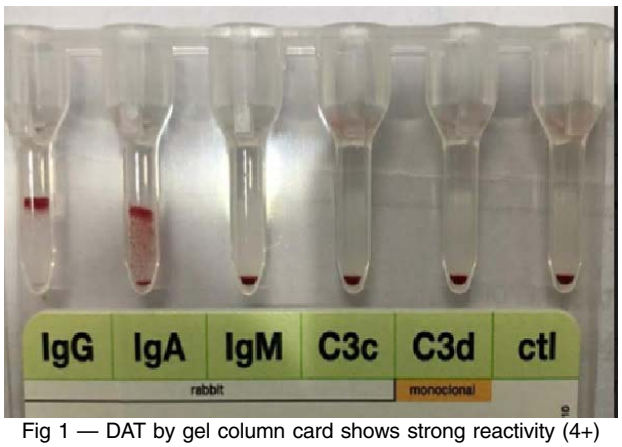

Fig 1 — DAT by gel column card shows strong reactivity (4+) in anti IgG, strong reactivity (3+) in anti IgA and no reactivities in anti IgM, anti C3c and anti C3d

Case 4 :

47 years old multigravida female presented with lethargy and breathlessness. On examination she had severe pallor, mild icterus and tachycardia. There was no hepatosplenomegaly or lymphadenopathy. Examination of cardiovascular & respiratory systems showed no abnormality. Her Hb was 4.6gm/dl, TLC 4300/cmm, platelet 1.62 lakh/cmm, bilirubin was 4mg/dl with direct bilirubin 0.6mg/dl and LDH 876 mg/dl. DCT was 4+. Extended DCT was 4+ for IgG and 2+ for IgA. She received 3 units of PRBC and was started on oral prednisolone with dose of 1mg/kg/day. She responded well and haemoglobin increased to 9gm/dl with normalisation of bilirubin and LDH but when steroid was tapered her haemoglobin started to reduce so she was started on Azathioprine with tapering dose of steroid but again she relapsed. She received 4 doses of Rituximab (375mg/m^2/week) along with low dose steroids to which she has responded well.

DAT and IgG & IgA antibody positivity pattern of all patients are shown in Table 1.

Table 1 — *Shows DAT and IgG & IgA antibody positivity pattern of all patients*

Age	Sex	DAT	IgG antibody	IgA antibody
64 years	Male	4+	4+	1+
34 years	Female	4+	4+	4+
61 years	Male	4+	4+	3+
47 years	Female	4+	4+	2+
69 years	Female	4+	4+	1+
60 years	Female	3+	3+	2+

Discussion

Autoimmune haemolytic anaemia is an important cause of acquired haemolytic anaemia. They result from the development of autoantibodies directed against antigens on the patient's own red cells. Anaemia is of variable severity and some patients present with pallor, icterus, hepatosplenomegaly and haemoglobinuria due to fulminant haemolysis[4]. Diagnosis of AIHA depends on clinical features of haemolytic anaemia, increased serum bilirubin mainly unconjugated hyperbilirubinemia, reticulocytosis and positive DAT. A positive DAT is predictive in 83% of suspected AIHA patients but not all AIHA cases are DAT positive[5]. 48-70% of AIHA cases are due to warm autoantibodies[6,7]. Some patients have cold AIHA due to IgM antibody. Some patients have mixed AIHA with both the antibodies. Here we have reported 4 cases of warm AIHA due to both IgG and IgA antibodies which are very rare in literature. The AIHA patients have severe worsening anaemia and they cause problem in cross matching as all the blood is mismatched due to the presence of autoantibodies. The problem in transfusing

these patients depends upon the type of AIHA and the titre of these antibodies.

We have collected data from our centre from January 2013 to January 2020. The total number of DCTs done during this period was 2821. The numbers of positive DATs were 592. The incidence of AIHA was 75. There were 49 warm type, 9 cold type and 17 mixed AIHA patients. There were only 6 cases with both IgA and IgG positivity. For two of these patients we had no clinical data as they were referred from other centres. Among the remaining four patients one had haematological malignancy CLL for which he was on wait and watch policy, rest of the patients were idiopathic. IgA alone coating the RBCs is very rare with an incidence of 0.2 to 2.7%[3]. The role of IgA autoantibodies in causing RBC destruction is complex; they can act on their own or synergistically with other immunoproteins. On their own, warm reacting IgA autoantibodies cause haemolysis through immune adherence or via specific Fc receptors for IgA and by monocyte-mediated phagocytosis and antibody-dependent cellular cytotoxicity of sensitized RBCs[8]. The clinical significance of these IgA antibodies in determining severity of haemolysis is yet to be determined.

Corticosteroid therapy is the mainstay of treatment in warm AIHA and is less effective in cold AIHA. The mechanism of action of steroids is multifactorial. It delays the clearance of antibody coated RBC by Reticuloendothelial system, it reduces the avidity of antibodies and also decrease antibody production[9]. Relapse occurs in approximately 40-50% patients and requires maintenance doses of prednisolone[9]. Free autoantibody in the serum may disappear but DAT remains positive[10]. Transfusion of red cells gives only transient benefit but may be initially required in case of severe anaemia. Transfusion in AIHA may be complicated due to the problems in cross matching and rapid in vivo destruction of transfused cells due to the presence of auto antibodies[11,12]. If least incompatible blood is transfused then there is usually no post transfusion haemolysis. Immunosuppressive agents including monoclonal anti-CD 20 antibody(Rituximab) may prove useful in cold AIHA and refractory cases of warm AIHA. Splenectomy is of benefit in refractory cases of warm AIHA but is not useful in cold AIHA[13,14]. Overall response rates are probably 60-75% but many patients relapse or remain on low dose of steroids[7,9]. The response to splenectomy may be more in idiopathic AIHA than in secondary AIHA[9]. Mixed type of AIHA patients respond dramatically to steroid therapy and usually require few or no transfusions[15].

Our case series describe rare variant of AIHA with two warm antibodies IgG & IgA. Though all of our patients had moderately severe AIHA but the role of the IgA autoantibody in causing severe disease is yet to be confirmed.

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