## Teaching Round

# Autoimmune Haemolytic Anemia with Thrombocytopenia

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***Abstract***

A 40 year old female presented with autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia. A diagnosis of Evans Syndrome was made. The typical clinical course is chronic and relapsing, and therapy is generally progressive and poor. Evans syndrome is an uncommon condition. The present case was steroid-unresponsive but fortunately responded to intravenous immunoglobulins.

***Key words:*** Autoimmune diseases; autoimmunity; anemia; intravenous immunoglobulins

A 40-year female presented to medical emergency with chief complaints of easy fatiguability, bluish skin rash and gum bleeding since last one and half months. Patient also reported a similar episode one and a half year back which was associated with heavy menstrual bleeding, for which hysterectomy was performed. There was no history of joint pains, photosensitivity, oral ulcers or jaundice in the past. Physical examination revealed pulse- 110/min, B.P.- 110/70 mm Hg, pallor, wet purpura on tongue, non-palpable purpura all over the body. Patient had a firm splenomegaly (3 cm below left costal margin). Chest and cardiac examinations were normal except for an ejection systolic murmur. Investigations revealed Hb-3.5g/dL, TLC- 5600/$mm^3$, platelets-4000/$mm^3$, reticulocyte count of 17% (corrected count 6.5%), mean corpuscular volume was 91.5 fL and peripheral smear for malarial parasite was negative. Serum iron profile was with in normal limits, but serum LDH was elevated (1353 units/L). ANA was negative, hepatitis viral markers and HIV were negative. Coomb's test was positive- direct as well as indirect. Bone marrow aspiration was normal. Serum TSH was with in normal limits and urine examination was normal. PNH card test was negative.

**What is the diagnosis?**

A diagnosis of autoimmune haemolytic anemia with thrombocytopenia (Evans syndrome) was entertained.

**What are the other causes of autoimmune haemolytic anemias?**

A number of conditions could possibly be associated with autoimmune haemolytic anemias viz. lymphoproliferative disorders- lymphomas, chronic lymphocytic leukemias; autoimmune disorders including systemic lupus erythematosus; infections-infectious mononucleosis and other viral infections, syphilis, Mycoplasma and HIV infections; malignancies like ovarian tumors; Drug-induced-methyldopa and idiopathic causes. Table 1 classifies immune haemolytic anemias [1].

**What is Evans syndrome?**

In 1951, Evans and colleagues described a group of patients whose clinical course was characterised by immune thrombocytopenia and autoimmune haemolytic anemia (AIHA) [2]. The anemia and thrombocytopenia varied in time of onset, course, and duration. Spontaneous remissions and exacerbations were common, and a few patients had neutropenia.

Evans syndrome is the coexistence of simultaneous or sequential direct Coombs-positive AIHA in conjunction with immune-mediated thrombocytopenia, with no known underlying aetiology. The typical clinical course is chronic and relapsing, and therapy is generally progressive and poor. Although Evans syndrome seems to be a disorder of immune regulation, the exact

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**Table 1- Classification of Immune Hemolytic Anemias**

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| ***Cold active antibodies*** |
| Cold agglutinin disease |
| Primary or idiopathic |
| Secondary |
| Lymphoproliferative diseases |
| Autoimmune disorders |
| Infections- Mycoplasma pneumoniae, Infectious mononucleosis, Other viruses |
| Paroxysmal cold hemoglobinuria |
| Syphilis; Measles, mumps, other viruses |
| ***Mixed cold and warm active antibodies*** |
| ***Warm active antibodies*** |
| Idiopathic autoimmune haemolytic anemia |
| Secondary autoimmune haemolytic anemia |
| Lymphoproliferative disorders |
| Autoimmune disorders |
| Other malignancies |
| Viral infections |
| Immune deficiency states |
| Drug-induced haemolytic anemia |
| Drug adsorption type (penicillin) |
| Neoantigen type (quinidine/stibophen) |
| Autoimmune type (alpha-methyldopa) |
| Non-immune type (first generation cephalosporin) |
| Transplant associated haemolytic anemia |
| Haematopoietic stem cell transplant |
| Minor or major ABO group mismatch |
| Solid organ transplant |
| Passenger lymphocyte syndrome |
| Passive antibody transfer |

pathophysiology is unknown. Autoantibodies targeted at different antigenic determinants on red cells and platelets are assumed to cause isolated episodes of haemolytic anemia and thrombocytopenia, respectively. Evans syndrome is an uncommon but not rare condition [3]; its exact frequency is unknown. Familial occurrence is rare.

Pirofsky estimated the minimal annual incidence of immune haemolytic anemia to be one case per 80,000 US residents (mostly adults). In a combined series of 1064 patients with childhood immune thrombocytopenia, only nine had autoimmune haemolytic anemia associated with immune thrombocytopenia; however, thrombocytopenia occurs relatively often in patients with autoimmune haemolytic anemia. Frequencies of 1.6-59.4% have been reported in adults [4].

**What is the treatment offered in such cases?**

Patient was started on steroid therapy and transfusional support. However, her blood counts did not improve. Despite giving her oral steroids at a dose of 1mg/kg body weight for 4 weeks, her blood counts did not improve. In view of steroid-refractoriness, patient was started on intravenous immunoglobulin as 100 gm/day for two days (2 gm/kg body weight). Her platelet counts dramatically improved reaching up to 80,000 within two days of starting therapy. Patient was discharged on maintenance oral steroids and is in remission for the last six months. Other therapies effective in small series include danazol, cyclosporine, azathioprine, cyclophosphamide, mycophenolate mofetil and vincristine.

Recently rituximab (a chimeric human/mouse monoclonal antibody which targets CD20 on B lymphocytes) has been used in the management of refractory patients. Splenectomy and alemtuzumab administration are also alternatives. Haematopoietic stem cell transplantation is presently reserved for very severe and refractory cases [3].

**Key Points**

- Immune-mediated haemolytic anemias can be associated with a number of conditions ranging from infections, malignancies, autoimmune diseases, drug-related and idiopathic. The idiopathic variant is labelled as Evans syndrome.
- Steroid therapy is the treatment of choice and intravenous immunoglobulins can be used as an adjunct or in steroid-unresponsive cases. The present patient was steroid-unresponsive but responded dramatically to intravenous immunoglobulins and could then be maintained in remission on oral maintenance prednisolone.
- Several alternative approaches have been outlined in recent years and include- danazol, cyclosporine, azathioprine, cyclophosphamide, mycophenolate mofetil,

vincristine, rituximab, alemtuzumab and splenectomy. Haematopoietic stem cell transplantation is reserved for severe and refractory cases.

- A regular follow up with complete blood counts is important. Any sudden decrease in counts warrants admission and emergent component transfusions and stepping up of steroids or re-initiation of immunosuppression.

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