

## Case Report:

# Evans' syndrome- haemolytic anaemia with thrombocytopenia - a rare autoimmune disorder

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### ABSTRACT

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Evans syndrome is an uncommon condition defined as the combination (either simultaneously or sequentially) of immune thrombocytopenia (ITP) and autoimmune haemolytic anaemia (AIHA) with a positive direct antiglobulin test (DAT) in the absence of known underlying aetiology. It poses great diagnostic dilemma due to its variable presentation. We present a case of a 56-year-old female who had similar difficulty as it was not diagnosed initially when she presented with anaemia and thrombocytopenia and was treated by packed cell transfusion and platelet concentrate transfusion respectively. However, the patient showed repeated thrombocytopenia and low haemoglobin and referred to us and diagnostic work-up confirmed Evans' syndrome. This case stresses on the diagnostic importance of peripheral blood picture, reticulocyte count and direct antiglobulin test in every patient presenting with anaemia and / or thrombocytopenia to rule out haemolytic anaemia and thrombocytopenia of autoimmune etiology and thus help in arriving at right diagnosis.

**Key Words:** Evans' syndrome, Autoimmune hemolytic anaemia, Thrombocytopenia

Momin M, Aluri A, Reddy S, Pasupala NK. Evans' Syndrome-Haemolytic Anemia with Thrombocytopenia- a rare autoimmune disorder. *J Clin Sci Res* 2017;6:237-40. DOI: <http://dx.doi.org/10.15380/2277-5706.JCSR.17.08.004>.

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### INTRODUCTION

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Evans' syndrome is an autoimmune disorder described by Robert Evans in 1951 specifying that a link exists between primary thrombocytopenic purpura and acquired haemolytic anaemia. It was characterized by simultaneous destruction of the body's own red blood cells, white blood cells, platelets, which causes autoimmune haemolytic anaemia (AIHA) and idiopathic thrombocytopenia purpura (ITP) or immune neutropenia in absence of any cause.<sup>1</sup> It is a rare disorder found in only 0.8% to 3.7% of patient population with either ITP or AIHA at onset. It occurs in all age group individuals. Despite different therapeutic interventions, the great majority of patients have a chronic and relapsing course, which is associated with significant morbidity and mortality.<sup>2</sup> It is

Received: August 30, 2017, Accepted: September 20, 2017.

basically a diagnosis of exclusion and confounding factors such as infections, malignancies and rheumatologic diseases should be ruled out.

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### CASE REPORT

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A 56-year-old lady presented with complaints of generalised weakness, anorexia for two months and shortness of breath for seven days. She visited a private nursing home where she was treated as having viral thrombocytopenia and anemia and was transfused with platelet concentrate(s) and a packed red cell transfusion. As there was no improvement, patient presented to our center with same complaints. On examination blood pressure was 140/80 mm Hg, pulse 90 beats/min respiration 16/min; she was afebrile. Pallor, icterus and mild splenomegaly were also evident.

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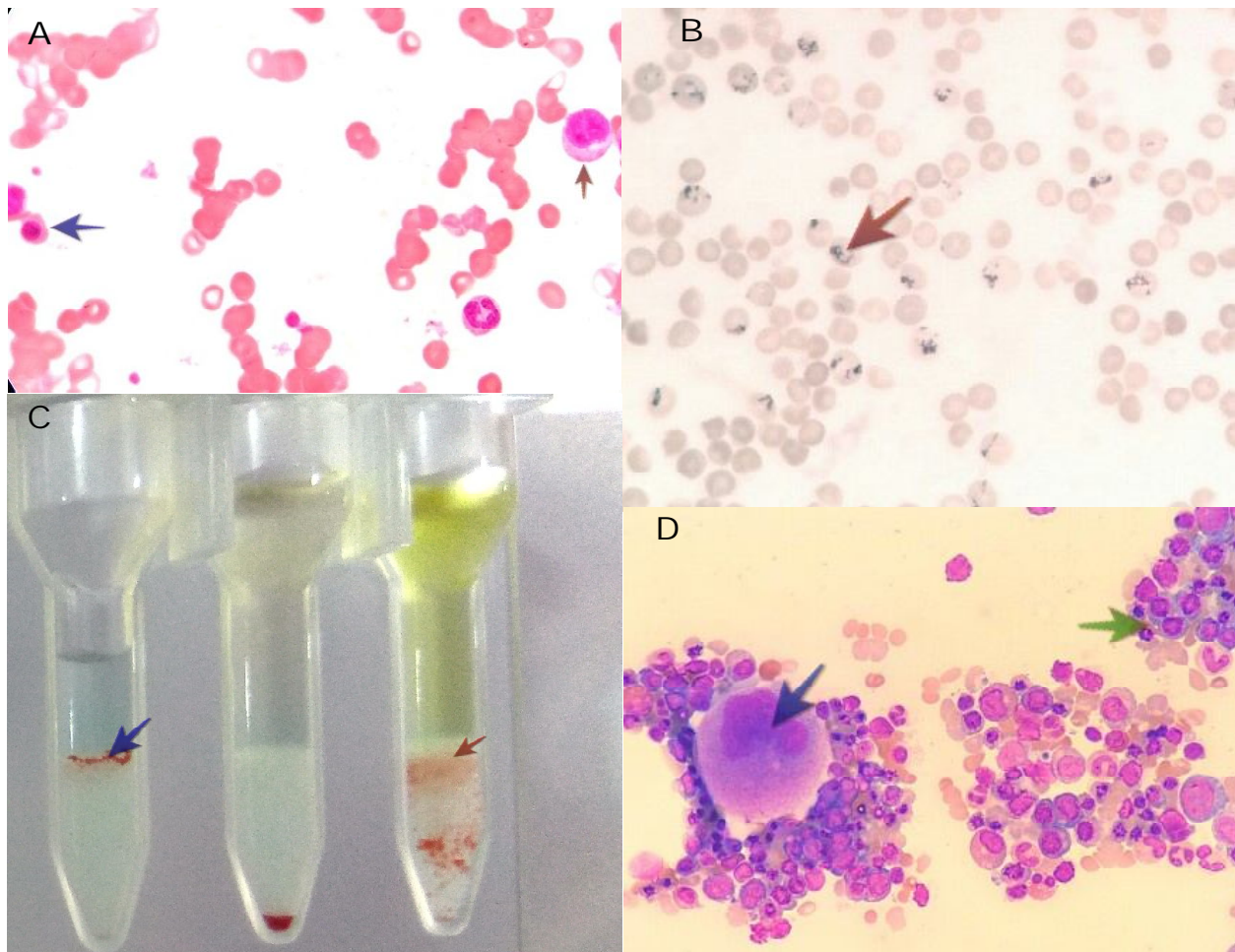
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DOI: <http://dx.doi.org/10.15380/2277-5706.JCSR.17.08.004>



**Figure 1;** Photomicrograph of peripheral blood smear showing leucoerythroblastic picture with nucleated RBCs and immature WBCs (arrows) (A); reticulocytosis (B); column glass bead method with positive direct and indirect Coomb's test (C); and bone marrow aspirate showing megakaryocytes and normoblastic erythropoiesis (D)

RBC = red blood cells; WBC = white blood cells

Laboratory examination results revealed haemoglobin 4.70 g/dL packed cell volume (PCV) - 14%, total leucocyte count 11400  $\text{mm}^3$  erythrocytes 1.56 millions/ $\text{mm}^3$ , platelet count 0.35 lakhs/ $\text{mm}^3$ , mean corpuscular volume - 91 FL, mean corpuscular haemoglobin 29 pg, mean corpuscular haemoglobin concentration 33%. Peripheral blood smear showed mild anisopoikilocytosis comprising normocytes and macrocytes, 2-3 nucleated RBCs/100 WBCs, few spherocytes and few immature myeloid precursors, thrombocytopenia suggestive of leucoerythroblastic picture (Figure 1A). Erythrocyte sedimentation rate (ESR) was 140 mm at the end of first hour. Reticulocyte count was 22% (Figure 1B). Direct and indirect Coomb's test were positive (Figure: 1C) (CAT

- using glass beads; Ortho Biovue® System, OCD - Johnson & Johnson Company, UK). Monospecific differential Coomb's test was positive for immuno globulin G (IgG) antibody implying Warm auto-immune haemolytic anaemia. Coagulation profile was normal. Kidney function tests were normal. Liver function tests showed increased total bilirubin (3.2 mg/dL), unconjugated 3 mg/dL, conjugated 0.2 mg/dL, aspartate aminotransferase 32 U/L, alanine aminotransferase 29 U/L, alkaline phosphatase 190U/L, total proteins 8.9gm/dl, albumin 4.6 g/dl & globulin 4.3 g/dl. Ultrasonography of abdomen show mild splenomegaly. Chest-X-ray and high resolution computed tomography of chest were normal.

Based on Coomb's positive haemolytic anemia and thrombocytopenia, the present case was diagnosed as Evans syndrome. Antinuclear antibody (ANA) [immunofluorescence (IF) method] tested positive. ANA profile was positive for SS-A antibody suggestive of underlying autoimmune disorder. Patient was treated with methyl prednisone 500 mg intravenously for 3 days and then was started on gradually tapering dose of oral prednisolone starting from 1 mg/kg/day. She responded dramatically and her platelets came to normal after four days, she was discharged and advised to follow-up. At discharge she was advised maintenance dose of 0.5 mg/kg/day of oral prednisolone. She was also told about the chronic nature of the condition, which included periods of remission and exacerbation.

### **DISCUSSION**

Evans' syndrome is listed as a "rare disease" by the Office of Rare Diseases (ORD) of the National Institutes of Health (NIH). There is no preferential distribution of Evans syndrome by age, gender, or ethnic group. Its chronic course is characterized by recurrent relapses and remissions. The etiology is unknown. However, suggested basic pathology is the role of non cross-reacting auto antibody against red cells and platelets.<sup>3</sup>

Clinical manifestations includes signs and symptoms of hemolysis (fever, pallor, jaundice, lethargy) and thrombocytopenia (petechiae, bruising and mucocutaneous bleeding). Physical examination may also reveal lymphadenopathy, hepatomegaly and / or splenomegaly.<sup>4</sup>

In 2005, the European Hematology Association's working group on thrombocytopenia set out to define the clinical spectrum of Evans' syndrome and described its clinical features. In their retrospective analysis of 68 cases of Evans' syndrome, half of the reviewed cases (n=34) were considered primary Evans

syndrome and half were associated with an underlying autoimmune, infectious, lymphoproliferative, or immunodeficiency related disorders. They also concluded ES, and its associated conditions, can be described as a state of profound immune dysregulation.<sup>5</sup>

The diagnosis of haemolytic anaemia requires direct agglutination test (DAT) positivity, although this investigation may be positive even in the absence of haemolytic anaemia. The indirect agglutination test (IAT) may also be positive in a small percentage of patients. Bone marrow examination is an essential investigation for the diagnosis of Evans syndrome. It is necessary to exclude infiltrative process in patients with pancytopenia, especially before starting corticosteroid therapy.

The bone marrow examination in this patient showed marked normoblastic erythroid hyperplasia and increased megakaryocytes with no infiltrative process indicating that the condition is probably due to circulating antibodies directed against antigens (non-specific) over red cells and platelets causing their destruction in peripheral circulation.<sup>6</sup>

In Evans' syndrome, the AIHA is largely warm-agglutinin type. This subtype represents 80% of all cases of AIHA and is characterized by autoimmune destruction of (RBCs). Antibodies, predominantly of the IgG subclass, affix themselves to RBC surface antigens forming an antigen (Ag) - antibody (Ab) complex. This complex directly interacts with the Fc receptors located on cytotoxic cell surfaces. For phagocytosis to ensue multiple Ag-Ab-Fc interactions must occur. The ideal location for these interactions to occur is located in the sinusoids of the spleen resulting in splenic sequestration and splenomegaly. The RBCs in which there is incomplete or partial phagocytosis develop an increased surface to volume ratio and become spherocytes.<sup>7,8</sup>

Review of peripheral smear for presence of spherocytes can provide valuable clues in

addition to laboratory findings of elevated lactate dehydrogenase (LDH), low haptoglobin, reticulocytoses and elevated indirect bilirubin. However, the gold standard for diagnosing remains the DAT. In this present case, leucoerythroblastic picture, spherocytes gives clue for underlying acute hemolytic picture with thrombocytopenia. Reticulocytosis, high ESR, positive DAT helped to confirm Evans' syndrome.

Other conditions that cause concurrent haemolytic anaemia and thrombocytopenia and may mimic Evans' syndrome include paroxysmal nocturnal haemoglobinuria (PNH), acquired thrombotic thrombocytopenic purpura, inherited ADAMTS-13 deficiency, haemolytic uraemic syndrome and Kasabach–Merritt syndrome.<sup>9</sup>

The management of Evans' syndrome remains a challenge. The syndrome is characterised by periods of remission and exacerbation and response to treatment varies even within the same individual. First line agents used for the treatment are corticosteroids like prednisolone at a dose of 1-2 mg/kg divided 2 or 3 times daily, intravenous immunoglobulin for acute episodes. Other immunological agents such as cyclosporine, azathioprine, cyclophosphamide, vincristine, rituximab and alemtuzumab can be used in Evans' syndrome.<sup>10</sup> Allogenic or autologous haematopoietic stem cell transplantation offers a hope for those relapse cases that do not respond to above drugs and which are difficult to treat.

The clinical course is complicated and associated with poor outcome in patients with Evans syndrome as compared to patients having isolated episodes of AIHA or AITP. Patients rarely do well with treatment and often disappointing. Evans' syndrome can be fatal occasionally.<sup>11</sup>Hence a strict constant follow-

up is very essential along with the education of the patient regarding the chronic nature of this condition.

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