

Case Report

A Female with Evans Syndrome Presented with Pancytopenia

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Abstract

Evans syndrome is an uncommon haematological disorder characterised by autoimmune haemolytic anaemia (AIHA), immune thrombocytopenia (ITP) and/or immune neutropenia. It may occur in all ethnic groups, all ages and has no sex predilection. The direct antiglobulin test (DAT) is almost invariably positive. This condition generally runs a chronic course and is characterised by frequent exacerbations and remissions. Corticosteroids and/or intravenous immunoglobulin (IVIG) are the most commonly used first line therapy. Here we report a case of a female who presented with severe shortness of breath, palpitation and low grade fever and on examination she was found severely pale and mildly icteric. Her CBC and PBF showed pancytopenia. Indirect bilirubin and LDH were raised and direct Coomb's test was positive. She was labeled as a case of Evans syndrome and responded to oral prednisolone. On subsequent follow-up her haematological profiles remained normal.

Key words: Evans syndrome; Pancytopenia; Direct antiglobulin test; Prednisolone

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Introduction

Evans syndrome is a rare disorder and was first described in 1951 by R. S. Evans and colleagues.¹ This haematological disorder is characterised by the sequential or simultaneous development of direct antiglobulin test (DAT) positive autoimmune haemolytic anemia (AIHA), immune thrombocytopenia (ITP) and/or immune neutropenia in the absence of known underlying aetiology.² Evans syndrome seems to be a disorder of immune regulation but the exact pathophysiology is unknown. It can be classified as primary (idiopathic) or secondary (associated with some diseases).³ The diagnosis is made by exclusion of other pathologies, including infectious, malignant and autoimmune diseases. 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. Here we report a case of a female who presented with pancytopenia and diagnosed as a case of Evans syndrome and responded well to steroid.

Case report

A 40-year-old housewife admitted in the Department of Pulmonology in January 2018 through emergency with severe shortness of breath, palpitation and low grade fever. She had no history of chest pain, menorrhagia, blood transfusion, joint pain, oral ulcer, photosensitivity or other systemic symptoms. She was normotensive, non-diabetic and non-asthmatic. She had three uneventful pregnancies. On examination

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she was severely pale, mildly icteric and afebrile. She had no organomegaly, lymphadenopathy, bony tenderness, purpura and ecchymosis. Her systemic examination revealed normal findings.

Her complete blood count showed haemoglobin (Hb) 3.30gm/dL, WBC 3500/cmm (neutrophil 34%, lymphocyte 63%) and platelet 100000/cmm. Pancytopenia was present in peripheral blood film. Reticulocyte count was 6% and LDH was 14580 U/L. Indirect bilirubin was raised and direct Coombs' test was positive. Bone marrow aspiration revealed erythroid hyperplasia with normal morphology (Fig 1). Blood group was O positive. Her prothrombin time, activated partial thromboplastin time (APTT), renal function, liver function, blood sugar, abdominal ultrasound and chest radiography were normal. Antinuclear antibodies (ANA), HbsAg and Anti-HCV were found negative.

Her clinical and laboratory findings went in favour of Evans syndrome (autoimmune haemolytic anaemia with immune thrombocytopenia). Tablet prednisolone 60 mg daily was started and one unit least incompatible O positive blood was transfused. On subsequent follow-up her haemoglobin was 10.20 gm/dL, and platelet 180000/cmm two weeks after treatment and haemoglobin 13.8 gm/dL and platelet 273000/cmm after four weeks. In next four weeks

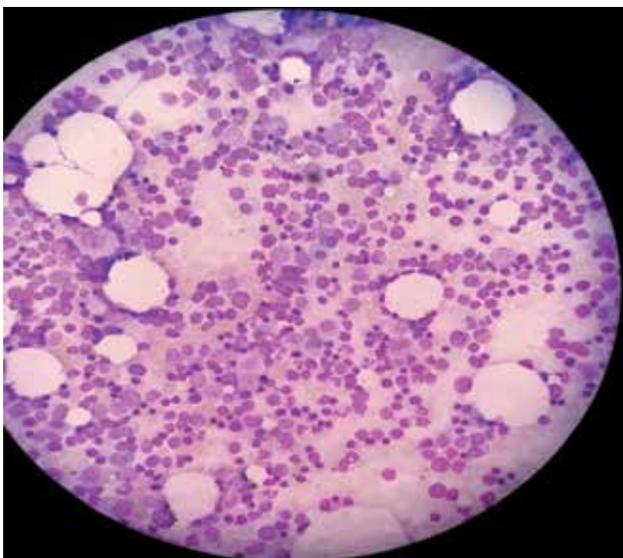


Fig 1. Bone marrow shows erythroid hyperplasia with normal morphology

steroid was gradually tapered and stopped. She was on regular follow up. She was clinically well and her complete blood count was within normal range.

Discussion

Evans syndrome is a rare haematologic disturbance comprised of immune thrombocytopenia, Coombs test positive immune hemolytic anemia, and/or immune neutropenia.¹ It is a rare disease and the exact frequency is unknown. No sex predilection is known and Evans syndrome has been described in all ethnic groups and at all ages.^{4,5} The exact pathophysiology is unknown. However, there is evidence to support abnormalities in both cellular and humoral immunity in Evans syndrome. The cytopenias that occur with Evans syndrome may be related to T cell abnormalities. Decrease in helper T cells, increase in suppressor T cells with increased constitutive production of interleukin 10 and interferon- γ cause activation of autoreactive, antibody-producing B cells.^{6,7} Evans syndrome can be grouped into primary or idiopathic where there is no associated other autoimmune disease and secondary where it is associated with another autoimmune diseases such as SLE, Sjögren syndrome, Hodgkin's disease, or chronic lymphocytic leukemia.⁵ In adults an underlying cause can be expected in 70% of the cases.³ Clinical presentation includes the features of haemolytic anaemia such as pallor, lethargy, jaundice, heart failure in severe cases and features of thrombocytopenia like petechiae, bruising and mucocutaneous bleeding. Examination may reveal lymphadenopathy, hepatomegaly and/or splenomegaly. The lymphadenopathy and organomegaly may be chronic or intermittent and in some cases may only be apparent during episodes of acute exacerbation.^{5,8,9} Our patient presented with shortness of breath, palpitation and low grade fever. On examination she was severely pale, mildly icteric and other general and systemic examination findings were normal. First line investigations are full blood count, blood film examination, unconjugated bilirubin, reticulocyte count and direct antiglobulin test. A full blood count will confirm the presence of cytopenias and blood film should be examined for features of AIHA (polychromasia, spherocytes) and to exclude other underlying diagnoses (malignancies,

microangiopathic haemolytic anaemia, congenital haemolytic and thrombocytopenic conditions). Features of haemolysis should be sought including a raised reticulocyte count, unconjugated hyperbilirubinaemia and decreased haptoglobins. The direct antiglobulin test (DAT) is almost invariably positive (although often weakly), even in the absence of haemolytic anaemia and may be positive for IgG and/or complement (C3).^{4,5,8,10,11} The indirect antiglobulin test may also be positive in 52–83% patients.^{4,10} Assays for antiplatelet and antigranulocyte antibodies have shown varied results.¹² Evans syndrome is the diagnosis of exclusion. So other causes of acquired immune cytopenias like SLE, IgA deficiency, Common variable immunodeficiency (CVID), HIV, APLAS, TTP–HUS, Kasabach–Merrit syndrome, Castelman's disease and inherited ADAMTS-13 deficiency should be excluded.^{9,13} Bone marrow aspiration is usually indicated for excluding aplastic anaemia or an infiltrative processes in patients who present with pancytopenia. Bone marrow examination is usually not indicated in classic cases when patients present with autoimmune haemolytic anemia (AIHA) or immune thrombocytopenia. Most of the laboratory parameters were consistent with the features of Evans syndrome in our patient.

Evans syndrome is characterised by frequent exacerbations and remissions and the response to treatment varies even within the same individual.¹⁴ Most patients require treatment although occasional spontaneous remissions have been reported.⁴ Indications for treatment have not been established by other evidence-based studies. However, it is reasonable and usual to treat symptomatic patients with low blood counts. All asymptomatic patients with low counts do not require treatment and the decision to treat or not should be considered according to each individual case.

Treatment depends on various factors, including the severity of the condition, presenting signs and symptoms and patient co-morbidities. Symptomatic management such as transfusion is required in those with low blood counts presenting with symptoms secondary to anaemia or thrombocytopenia. The most commonly used first-line therapy is corticosteroid

(prednisolone, methylprednisolone) and/or intravenous immunoglobulin (IVIG). It is our practice to use corticosteroids as the initial therapy and to add IVIG if patients fail to respond or are corticosteroid-dependent. Although most of the patients have been observed to respond to corticosteroids initially, the duration of response can vary and more than half relapse, making the use of additional or alternative treatment options imperative.² Rituximab or splenectomy may be considered in those refractory to the standard treatment or if steroid-dependent (≥ 15 mg prednisolone is required daily to prevent relapse). Danazol has frequently been used as a second-line treatment option especially with its corticosteroid-sparing effects.² Again, the responses can be variable. Immunosuppressive drugs can be used in those unresponsive to corticosteroids or rituximab. Various immunosuppressants have been tried, but cyclosporin A¹⁵ and mycophenolate mofetil¹⁶ are the preferred ones due to increased efficacy in autoimmune conditions. Others that have also been used include cyclophosphamide¹⁷, azathioprine⁴, and sirolimus.¹⁸ The choice of the immunosuppressant is dependent on patient factors, co-morbidities, and disease severity. Hematopoietic stem cell transplant has been used very rarely as a last resort in those unresponsive to all medical treatments. Both autologous and allogeneic stem cell transplantation were tried in a small number of patients with mixed results.⁴ Our patient responded to oral prednisolone. Now she is not on any drug and on regular follow-up with normal hematological profile.

Dietary restrictions are not usually required. Patients receiving steroid therapy should have some restrictions placed on their salt, sugar, and fluid intake to prevent excessive fluid retention. Activities may have to be restricted to some extent, depending on patient tolerance and the degree of anaemia and bruising.

The characteristic clinical course of Evans syndrome includes periods of remission and exacerbation. Patients rarely do well without treatment and responses to therapy are variable and often disappointing. Long-term survival data are limited. In patients followed for a median range of 3–8 years mortality ranged from 7–36%.⁴ The main causes of death were haemorrhage

and sepsis. None of these patients developed any malignancy.

Conclusion

Evans syndrome is an uncommon condition and generally runs a chronic course and is characterised by frequent exacerbations and remissions, but sometimes may present acutely. It is important to mention that primary Evans syndrome is a diagnosis of exclusion and causes of secondary Evans syndrome must be searched because treatment and responses considerably differ between primary and secondary Evans syndrome. A positive DAT test confirming ongoing immune haemolysis is expected. Instead of monotherapy with corticosteroids, combination of steroids with newer modalities like rituximab should be instituted early in order to prevent or delay life-threatening complications.

References

1. Evans RS, Takahashi K, Duane RT, Payne R, Liu C. Primary thrombocytopenic purpura and acquired hemolytic anemia; evidence for a common etiology. *Archives of Internal Medicine* 1951; 87(1): 48–65.
2. Michel M, Chanet V, Dechartres A, Morin AS, Piette JC, Cirasino L et al. The spectrum of Evan's Syndrome in adults; new insight into the disease based on the analysis of 68 cases. *Blood* 2009; 114(15): 3167–3172.
3. Kabir A, Banik J, Dasgupta R, Amin R, Faisal A, Islam A et al. Evan's Syndrome. *J Medicine* 2010; 11: 78–82.
4. Mathew P, Chen G, Wang W. Evan's syndrome: results of a national survey. *J Pediatr Hematol Oncol* 1997; 19(5): 433–437.
5. Savasan S, Warriar I, Ravindranath Y. The spectrum of Evans' syndrome. *Archives of Disease in Childhood* 1997; 77: 245–248.
6. Wang W, Herrod H, Pui C, Presbury G, Wilimas J. Immunoregulatory abnormalities in Evan's syndrome. *American Journal of Hematology* 1983; 15: 381–390.
7. Karakantza M, Moukaki A, Theodoropoulou M, Bussel JB, Maniatis A. Th 1 and Th 2 cytokines in a patient with Evans' syndrome and profound lymphopenia. *British Journal of Haematology* 2000; 110: 968–970.
8. Pui C, Wilimas J, Wang W. Evan's syndrome in childhood. *The Journal of Pediatrics* 1980; 97: 754–758.
9. Teachey DT, Manno CS, Axsom KM, Andrews T, Choi JK, Greenbaum BH et al. Unmasking Evan's syndrome: T-cell phenotype and apoptotic response reveal autoimmune lymphoproliferative syndrome (ALPS). *Blood* 2005; 105: 2443–2448.
10. Pegels JG, Helmerhorst FM, van Leeuwen EF, de Plasvan Dalen C, Engelfriet CP, von dem Borne AEGKR. The Evan's syndrome: characterisation of the responsible autoantibodies. *British Journal of Haematology* 1982; 51: 445–450.
11. Wang W. Evan's syndrome in childhood: pathophysiology, clinical course and treatment. *The American Journal of Pediatric Hematology/Oncology* 1988; 10: 330–338.
12. Fagiolo E. Platelet and leukocyte antibodies in autoimmune hemolytic anemia. *Acta Haematologica* 1976; 56: 97–106.
13. Schneppenheim R, Budde U, Hassenpflug W, Obser T. Severe ADAMTS-13 deficiency in childhood. *Seminars in Hematology* 2004; 41: 83–89.
14. Norton A, Roberts I. Management of Evan's syndrome. *Br J Haematol* 2006; 132(2): 125–137.
15. Bader-Meunier B, Aladjidi N, Bellmann F, Monpoux F, Nelken B, Robert A et al. Rituximab therapy for childhood Evan's syndrome. *Haematologica* 2007; 92: 1691–1694.
16. Emilia G, Messori C, Longo G, Bertesi M. Long-term salvage treatment cyclosporin in refractory autoimmune haematological disorders. *British Journal of Haematology* 1996; 93: 341–344.
17. Kotb R, Pinganaud C, Trichet C, Lambotte O, Dreyfus M, Delfraissy JF et al. Efficacy of mycophenolate mofetil in adult refractory autoimmune cytopenias: a single center preliminary study. *European Journal of Haematology* 2005; 75: 60–64.
18. Chang DK, Yoo DH, Kim TH, Jun JB, Lee IH, Bae SC et al. Induction of remission with intravenous immunoglobulin and cyclophosphamide in steroid-resistant Evans' syndrome associated with dermatomyositis. *Clinical rheumatology* 2001; 20(1): 63–66.