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Evan's Syndrome - A Case series

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Abstract: ***The Evans syndrome is a rare autoimmune disease and occurs when an individual's antibodies attack the blood and platelets in the body. It is characterized by the simultaneous or sequential development of Immune Thrombocytopenic Purpura (ITP) and Autoimmune Hemolytic Anemia (AIHA) with a positive Direct Antiglobulin Test (DAT). The type of antibody determines whether AIHA is cold, warm, or mixed. Approximately 80% of AIHA cases are warm AIHA. Warm AIHA is mostly caused by IgG antibody which reacts at 37C. Typically, warm AIHA occurs with Evans syndrome. Evans syndrome can be associated with leucocytosis in some variants. Three cases of Evans syndrome are presented here, which can be classified as 1. classical Evans syndrome, 2. Evans syndrome with leucocytosis and 3. Evans syndrome associated with neuropathic pain. In this case series, pathophysiology, workup done at blood centre and blood component transfusion support in patients with EVANS syndrome has been discussed.***

Keywords: Evans syndrome, Anemia, Autoimmune Hemolytic Anemia

1. Introduction

Evans syndrome (ES) is an uncommon condition characterised by the combination (either simultaneous or sequential) of direct antiglobulin test positive autoimmune haemolytic anaemia (AIHA), immune thrombocytopenia (ITP) and/or immune neutropenia in the absence of a known underlying etiology. The syndrome was first described by Robert Evans in 1951 when he demonstrated a relationship between primary immune thrombocytopenia and acquired haemolytic anemia. The combination of direct Coombs positive haemolytic anaemia and immune thrombocytopenia without any obvious underlying aetiology defines patients with ES [1].

ES is a very rare disorder and very little is known about its epidemiology. A study was conducted in Denmark where 242 patients were monitored for 40 years. Rarity of disorder was confirmed by incidence rate of1.8million/year. Mean age of ES is 58 years. Females are affected more in comparison to male [2].

ES is more common in the paediatric population than in adults and is often associated with underlying autoimmune disease, connective tissue disease, immune deficiency disorders, lymphoproliferative disorders, or malignancy of the immune system. ES is classified as either primary or secondary, depending on the presence of underlying autoimmune disease or connective tissue disease. Associated diseases include systemic lupus erythematosus (SLE), autoimmune lymphoproliferative syndrome (ALPS), and immune deficiency disorders such as common variable immunodeficiency (CVID), or lymphoid malignancy, including non - Hodgkin's lymphoma (NHL) and chronic lymphocytic leukemia (CLL) [3].

The current article discusses 3 cases, all presenting differently. Management can be started early if correct diagnosis is made.

2. Materials and Method

This study was conducted at Blood centre, tertiary care hospital, Ahmedabad and included three diagnosed cases of ES with the laboratory work done and blood transfusion support given to the patient and improvement of patient's laboratory profile.

Case 1

28 - year - old female arrived in emergency department with chief complains of general malaise, nasal bleeding, mucosal bleeding, decreased appetite, black coloured stool and easy fatigability since 10 days. On the day of admission, patient had low Hb and platelet count. Request for transfusion of 3 units of packed red blood cells and 6 units of platelet concentrate was received. Blood grouping, antibody screening and cross matching were done by blood centre. Direct and Indirect Antiglobulin Test was found positive while doing work up. Monospecific DAT was positive for both IgG (**Table1**). To find compatible blood unit for this patient, cross match was done with 20 PCV units out of which only 3 units got compatible. Out of them 2 units were transfused to the patient.

Table 1: Investigations and details of transfusion – Case 1

Investigations	On day of admission	Day 3	Day 5	Day 7	On day of discharge
Hb (gm/dl)	5.0	6.3	8.1	8.3	8.5
Platelet count	52 x10^3	58 x10^3	62x10^3	64x10^3	75 x10^3
DAT	Grade II positive	-	Grade II positive	-	-
IAT	Grade I positive	-	Negative	-	-
Monospecific (CAT)	IgGpositive (**Image1**)	-	-	-	-
Auto control	RT - Negative				

(CTT)	37° C - Positive (+2) 4° C – Negative				
ANA Profile	Presence of SM/RNA antibody (strong suggestive of ES)	-	-	-	-
Bone marrow biopsy		**RBC**: MICROCYTIC HYPOCHROMIC **PLATELETS**: Decreased **RETICULOCYTES:** INCREASED CELLULAR IMPRESSION suggestive of ITP			
Peripheral smear		**RBC**: MICROCYTIC HYPOCHROMIC **PLATELETS**: Thrombocytopenia **WBC:** normal range			
Blood component transfusion	PRC – 1 unit RDP – 3 unit	RDP – 3 unit	PRC – 1 unit	RDP – 2 unit	

DAT - Direct antiglobulin test
IAT - Indirect antiglobulin test
CAT - Column agglutination test
CTT - Conventional test tube method
ANA - Anti nuclear antibody
PRC - Packed red cells
RDP - Random donor platelet
ITP - Immune thrombocytopenic purpura

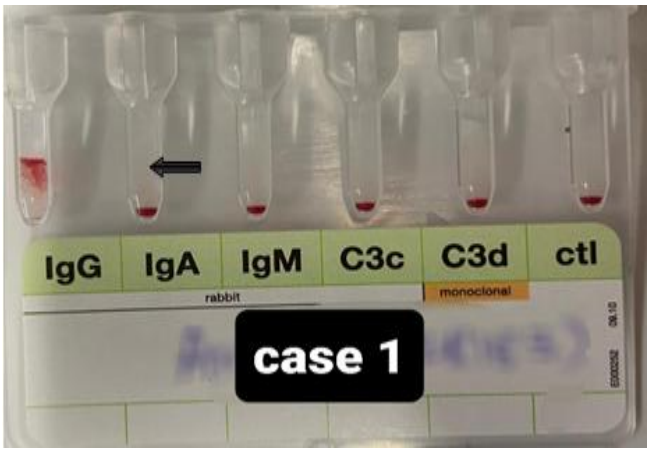

Image 1: Monospecific (column agglutination test) for CASE 1 – positive (IgG)

Results of bone marrow biopsy and ANA profile strongly suggestive of the diagnosis of classical ES. After blood component transfusion patient showed marked improvement in symptoms as well as laboratory parameters. Other treatment injectable corticosteroids for 5 days followed by oral MPS, tranexamic acid and Botox to control epistaxis and gum bleeding and other vitamins and mineral supplements was also going on along with blood transfusion.

Case 2

63 - year - old male arrived at emergency dept with sign and symptoms of giddiness, generalized weakness, low grade fever, cough, pedal edema, mild episodes of hematemesis and Malena. On the day of admission, patient had low Hb, platelet count and leucocytosis. Request for transfusion of 2 units of packed red blood cells and 10 units of platelet concentrate was received. Blood grouping, antibody screening and cross matching were done by blood centre. Direct Antiglobulin Test was positive while doing work up. In Monospecific DAT, IgG was positive (**Table 2**). To find compatible blood unit for this patient, crossmatch was done which came compatible and 2 compatible units of PCV were transfused to patient.

Table 2: Investigations and details of transfusion – Case 2

Investigations	On Day of Admission	Day 4	On Day of Discharge
Hb	7 gm/dl	7.2gm/dl	9.8 gm/dl
TLC	16.9x10^3	19x10^3	20x10^3
PLATELET COUNT	22□10^3	75x10^3	75x10^3
DAT	Grade II positive	-	-
IAT	Negative	-	-
Monospecific (CAT)	IgGpositive **(Image 2)**	-	-
Autocontrol (CTT)	RT - Negative 37°C - Negative 4°C – Negative		
Peripheral smear study	**RBC:** normocytic normochromic **PLATELETS:** Large **RETICULOCYTES:** Increased		
Bone marrow biopsy (done before 2 years)	Mild hypercellularity on all lineage of cells. Severe thrombocytopenia. **Lymphocytosis is seen but morphology is normal.**		

	Possibility of ES. S		
Blood component transfusion	PRC – 1 unit RDP – 4 unit	PRC – 1 unit RDP – 4 unit	

TLC - Total leukocyte count

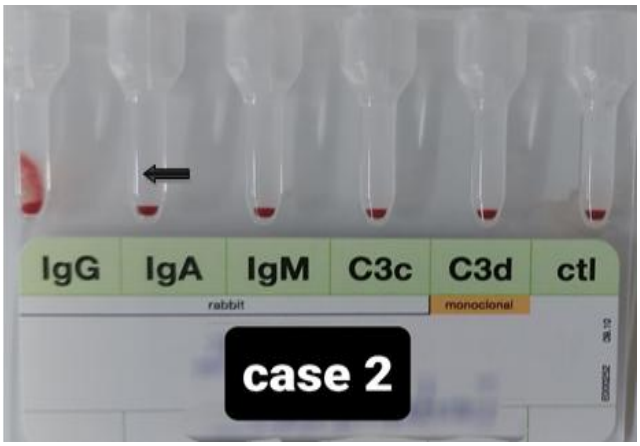

Image 2: Monospecific (column agglutination test) for CASE 2 – Positive (IgG)

Past History: Previously before 2 years, patient was treated for the similar symptoms at tertiary care cancer hospital.

From above described clinical presentation, investigations shows that the patient is diagnosed as warm AIHA with thrombocytopenia (ES) associated with leukocytosis. **Though possibility of lymphoma and chronic lymphocytic leukemia was ruled out by bone marrow biopsy.**

At present patient was admitted for the treatment of relapse episode of the disease. Along with transfusions patient was also kept on injectable corticosteroids followed by oral corticosteroids, immune suppressants like AZORAM and DANAZOL. After 7 days of hospital stay and appropriate treatment, patient got discharge on 7th day.

CASE: 3

A 38yr old woman admitted in emergency dept with complain of burning pain in both foot since 7 days, weakness, constipation, nausea and vomiting since1 month. Patient is known case of ESsince 5 years.

Past history: History of transfusion of 4 units of PCV at our institute 4 years back. At the same time patient was diagnosed as ES by Bone marrow biopsy finding at tertiary care cancer hospital.

Table 3: Investigation details – Case 3

Investigations	On day of admission	2nd day of admission	Onday of discharge
Hb	11.0gm/dL	12.9 gm/dl	12.6 gm/dl
Platelet count	15 ×10^3	22×10^3	39×10^3
DAT	-	Grade II positive	-
IAT	-	Grade II positive	-
Monospecific (CAT)	-	Presence of IgG and C3d (Image 3)	-

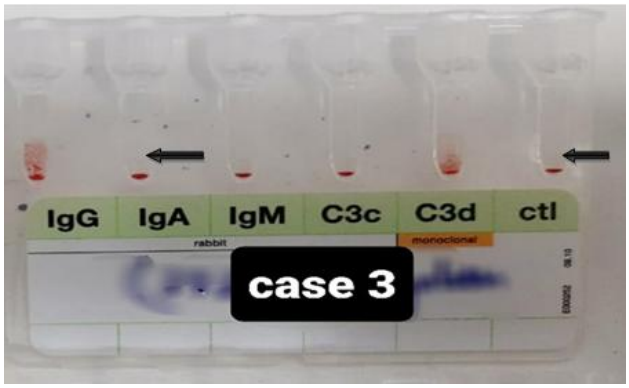

Image 3: Monospecific (Column agglutination test) for CASE 3– Positive (IgG and C3d)

As treatment with Immune suppressants like Azoram and Danazolwas going on, no need of transfusion was there for this patient of ES as hemoglobin and platelet count was almost near to normal range and patient was stable clinically.

3. Discussion

ES is uncommon disorder defined by Robert Evans in 1951 when he studied relationship between autoimmune haemolytic anemia (AIHA) and immune thrombocytopenic purpura (ITP) [1].

Evans described the diagnosis criteria of ES [1]:

- Presence of anemia
- Reticulocytosis
- Increased blood bilirubin and fecal urobilinogen
- No family history of hemolytic diseases,
- Evidence of antibodies against erythrocytes at 37°C,
- Hemolysis of transfused erythrocytes,
- Presence of purpura,
- Prolonged bleeding time,
- Bone marrow aspiration with normal or increased number of megakaryocytes and
- Absence of exogenous toxic agents or a baseline disease.

ES 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 noncross - reacting auto antibody against red cells and platelets. [4]

There is evidence to support abnormalities in both cellular and humoral immunity in Evans syndrome. Both CD4 and CD8 lymphocytes were reduced; increased constitutive production of interleukin - 10 and interferon - y caused activation of autoreactive, antibody - producing B cells.

Patients may present with AIHA or ITP either separately or concomitantly. Neutropenia occurs in up to 55% of patients at presentation, or pancytopenia (14%). The development of the second cytopenia may occur months to years after the first immune cytopenia and may delay diagnosis. Usual features of hemolyticanemia: pallor, lethargy, jaundice, heart failure in severe cases; and features of thrombocytopenia i. e: petechiae, bruising, mucocutaneous bleeding may be present. The lymphadenopathy and organomegaly (hepatomegaly and/or splenomegaly) may be chronic or intermittent and in some cases may only be apparent during episodes of acute exacerbation [5 - 8]

In our study clinical presentation among all 3 patients was different, patient with classical ES has anemia and thrombocytopenia, among other two patients with relapse of disease, one had anemia, thrombocytopenia with leukocytosis and another had neuropathic pain only.

Momin *et* al has shown a case of 56 year old female with ES and shown diagnostic importance of peripheral blood picture, reticulocyte count and direct antiglobulin test in every patient presenting with anemia and / or thrombocytopenia to rule out hemolyticanemia and thrombocytopenia of autoimmune etiology in his study [9].

Evidence has been there that antibodies found in the patients are reactive at 37°C. So, mainly AIHA is warm AIHA. Presence of purpura, mucosal bleeding, epistaxis and menorrhagia were related to ITP excluding other differential diagnosis. Mostly the antibodies are detected against RBCs only and those are IgG.

Michel *et* al has shown detection of antiplatelet antibodies (APA), 70% patients had positive circulating and/or fixed IgG APA, anti - IIb - IIIa (60% of the cases) were predominantly found antibodies in combination with anti - IbIX in 2 patients. In his study 43% patients had IgG positive and 53% had positive IgG + c3d on monospecific DAT result [10].

In our studymonospecific DAT result in one patient was IgG and c3d positive and in two patient it was IgG positive only.

Jordan *et* al has shown detection of Anti □□□ autoantibody was in patient of ES. Anti □□□ autoantibody reacts with high incidence antigens on glycophorin A (GPA), MN antigen carrying molecule. This antibody can cause haemolytic transfusion reaction [11].

Treatment modalities of ES include mainly blood product transfusions. According to the need packed red blood cells, Random donor platelets are transfused to patients and that have reported marked improvement in the patients' clinical condition, though relapse episodes are common in ES.

Therapeutic plasma exchange (TPE) is the third line of treatment for ES, but it can be considered in refractory conditions after trying all treatment modalities. There are evidences where TPE was done in ES and was found helpful [12].

Different drugs used for treatment of ES are corticosteroids, danazol, azoram, rituximab, IvIg along with the frequent blood products transfusion according to the need.

Scarce reports have documented the use of allogenic haematopoeticstem cell transplantation (HSCT) in ES. The main benefit of allogeneic HSCT is that it currently constitutes the only curative treatment option for ES by resetting the immune system [13] thus, this therapy could be a valuable alternative for patients with multiple relapses, with severe complications affecting their quality of life and/or if a lack of response to immunosuppressive drugs exists.

Oyama *et* al has shown a role of allogenic HSCT with aconditioning regimen of cyclophosphamide, 200 mg/kg plus anti - thymocyte globulin at 90 mg/kg in refractory EVANS syndrome in an adult patient treated with multiple interventions. Three months after transplant, antibodies against erythrocytes and platelets were negative with 100% chimerization. He maintained complete remission for the 30 months of follow - up [14]

4. Conclusion

Though it is very difficult as a transfusion medicine specialist to get compatible blood units for the patients with ES, proper work up and with the role of supportive treatment we can give compatible best match blood units to the patients and can improve patient's clinical condition. Relapse is very common in this disease so long term follow up is also essential for this chronic relapsing disease.

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