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EVANS Syndrome - A Rare Cause of AIHA with ITP: A Case Report

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Abstract: ***Background: Evan's syndrome is a rare autoimmune hematological condition, characterized by warm antibody AIHA with ITP with or without neutropenia. Secondary associations may include connective tissue disorders, infections and malignancies. Introduction: We present a case of a middle aged female patient who presented with anemia, bleeding manifestations refractory to repeated transfusions. Clinical features and laboratory and immunological workup was done and diagnosis was Evan's syndrome was made. Interventions: blood transfusion initially given to alleviate symptoms and corticosteroids were started. Outcome: with corticosteroids patient experienced dramatic improvement and patient is being followed up monthly and no remission is observed with the steroid doses being tapered. Conclusion: It can be concluded that considering Evan's syndrome in the differential diagnosis of AIHA and ITP can help to initiate early treatment with steroids, IVIG or immunemodulators and prevent the dreadful complications of massive bleeding.***

Keywords: AIHA, ITP, neutropenia, autoimmune disorder, corticosteroids, IVIG, Immunomodulators

1. Introduction

Evans syndrome was first described in 1951 by Dr. Robert Evans and associates[1]. Evans syndrome is a rare autoimmune disorder in which antibodies are directed against red blood cells (Coomb's positive autoimmune hemolytic anemia), platelets (idiopathic thrombocytopenic purpura) and white blood cells mainly neutrophils (idiopathic neutropenia). The cytopenias may occur simultaneously or may occur in succession, one following the other. The exact etiology remains unknown and mostly remains the diagnosis of exclusion. It may be primary or occur secondary to other autoimmune conditions like SLE, lymphoproliferative disease or primary immunodeficiencies. Signs and symptoms may include purpura, pallor, fatiguability, and light-headedness. Treatment varies from steroids, immunoglobulin therapy to splenectomy. Here we present a case of young female who presented with bleeding, jaundice and acute decompensated anemia. Although she was successfully treated with steroids, the exact etiology remains a mystery.

2. Case Report

A 35 years old female patient presented with complaints of
Dyspnoea on exertion
Hematuria
Easy fatiguability
Yellowish discolouration of skin and sclera.

Patient was a middle aged female. Initially patient observed shortness of breath on exertion which made her unable to do daily household activities since 15 to 20 days.

Then patient observed yellowish discolouration of skin and eyes and later she observed bleeding from gums and hematuria. She had consulted outside hospital where blood transfusion was given. Patient again started having similar complaints after 1 month and hence consulted out hospital. She was admitted for further investigations and treatment. On examination her pulse rate was 110 beats per minute, blood pressure was 120/80mm Hg, Respiratory rate was 18 cycles per minute. There was presence of pallor, icterus and mild splenomegaly. Bleeding from gums was present and collected urine samples showed evidence of hematuria. There was no significant family history. Patient has 2 offsprings and no history of similar episodes during antenatal or postnatal period.

Patient then underwent Laboratory Investigations whose results were as follows:

Investigations	Day 1	Day 2	Day 5	Day 7
Hb(g/dl))	2.8	5.4	6.8	10.1
HCT(%)	12.3	19.8	22.3	29.8
TLC(x10^3/ul)	12.3	10.2	8.9	7.6
RBC(x10^6/ul)	1.20	2.20	2.56	2.98
MCV(fl)	105.7	103.2	98.9	98.6
MCH(pg)	45.0	43.5	41.7	41.3
MCHC(g/dl)	43.9	41.8	41.9	40.3
Platelet count	7000	23000	32000	81000
Bilirubin(T)(mg/dl)	5.1	4.6	3.6	2.2
Bilirubin(ID)	4.7	4.3	3.2	1.8
Bilirubin(D)	0.4	0.3	0.4	0.4
AST(U/L)	72	65	49	39
ALT(U/L)	31	32	33	33
ALP(U/L)	97	98	104	98

Figure 1: leucoerythroblastic blood picture showing nucleated RBCs, tear drop cells, micro and macrocytosis and hypochromasia (right). Peripheral smear picture showing reticulocytois (left)

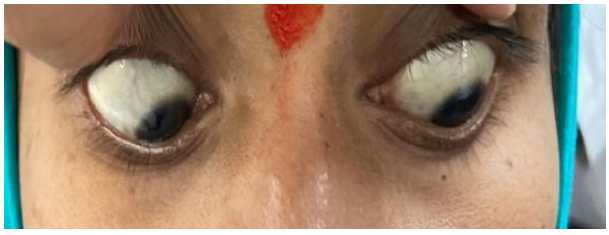
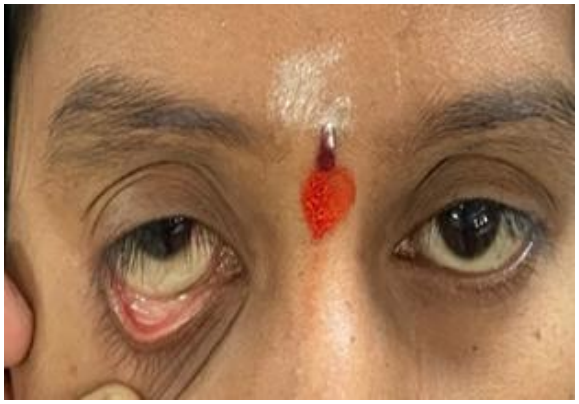


Figure 2: Icterus (right), pallor of nail beds (left)



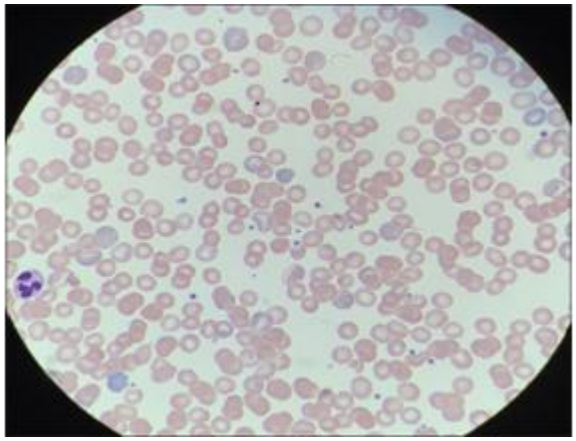


Figure 3: improvement after treatment (1st monthly follow up)-pallor (right), peripheral smear showing increased platelets and no normoblasts (left)

Peripheral blood smear showed reduced erythron, microcytosis, hypochromasia, moderate to severe anisopoikilocytosis, pencil cells; tear drop cells, scistocytes present, 20 nucleated RBCs per 100 WBCs present, suggestive of a leucoerythroblastic picture. Erythrocyte sedimentation rate (ESR) was 68 mm at the end of first hour. Immature platelet fraction was 5.4%. Reticulocyte count was 4.5%. Direct Coomb's test was positive. Direct Coomb's test was positive implying warm auto-immune haemolytic anaemia. Serum LDH was also raised (1317U/L). Unconjugated bilirubin was raised. Coagulation profile was normal. Kidney function tests were normal. 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. To find the secondary cause of Evan's syndrome, Antinuclear antibody (ANA) [immunoflourescence (IF) method] was tested and it was positive, however, other rheumatologic laboratory tests, including anti-SSA, anti-SSB, anti-double-stranded deoxyribonucleic acid (anti-dsDNA),

anti-ribonucleoprotein (anti-RNP), and anti-Smith, were negative. Bone marrow biopsy was not done considering the risk of bleeding and low platelet counts. Treatment was started 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 dramatically responded to steroids and her platelets came to normal after five days. On seventh day she was discharged and advised follow-up. At discharge she was advised maintenance dose of 0.5 mg/kg/day of oral prednisolone. She was explained about the chronic nature of the condition and also counselled about the exacerbations and remissions. Patient had come for follow up after 1 month when her Hb was 10.2 and Platelet count was 189000 and patient was clinically better.

The dose of corticosteroid was tapered and she was adviced to follow up monthly.

3. Discussion

Evans syndrome is defined as the association of AIHA with ITP and neutropenia (occurs less often; only in 15% cases[2]). Evans' syndrome is listed as a "rare disease" by the Office of Rare Diseases (ORD) of the National Institutes of Health (NIH) [3]. The type of AIHA that presents in Evans syndrome is warm AIHA, in which IgG antibodies react with red blood cell (RBC) surface antigens at body temperature, as opposed to cold AIHA. In ITP, the immune system is directed against GPIIb/IIIa on the platelets. Evan's Syndrome was considered as "primary" in half of the cases or is associated with an underlying disorder in remaining half of the cases, including mainly systemic lupus, lymphoproliferative disorders, and common variable immunodeficiency[2]. The use of drugs and vaccines has also documented in some cases as trigger for Evan's syndrome.

Exact etiology is not known and hence considered as idiopathic and few cases are thought to be familial referred to as 'Familial Evan's syndrome'. Some of these cases have been reported to co-occur with other disorders, such as heart defects, [4] or with inherited disorders such as hereditary spastic paraplegia[5] It is an autoimmune condition in which autoantibodies are produced by B cells which destroy own red cell, platelets and neutrophils.

It is a rare disease diagnosed in less than 5% patients of AIHA at onset and prevalence is more in females[2]. Patients present with shortness of breath on exertion, pallor, jaundice, fatigue, lightheadedness.

Work up includes complete blood counts (anemia, thrombocytopenia). To confirm hemolysis, investigations like Lactate Dehydrogenase, haptoglobulin, bilirubin and reticulocytosis is necessary. In our case Positive direct Coomb's test and spherocytes on peripheral smear further confirmed the diagnosis of warm AIHA and raised LDH, raised unconjugated bilirubin and reticulocytosis supported the diagnosis. Bone marrow biopsy and flow cytometry are helpful in the workup of Evans syndrome to assess for malignancies. For our patient, the workup for these possible secondary causes was only positive for ANA, which is nonspecific. As it is diagnosis of exclusion, it is important to rule out other possible diagnosis. Hence common etiologies such as cold agglutinin disease, thrombotic thrombocytopenic purpura (TTP) were ruled out through careful evaluation of the peripheral blood smear; infectious causes (such as HIV, Hepatitis C), other autoimmune conditions and malignancies were also ruled out through CXR, CT chest and abdomen. There are no specific guidelines for diagnosis and treatment hence and the evidence for treatment is based on case reports, case series, and retrospective studies. In an acute setting, blood transfusions and/or platelet transfusions may be required to alleviate symptoms, although their use should be minimized. In our patient 2 pint PCV and 4 pints of Platelets were transfused.

The Definitive management, first-line treatment is usually corticosteroids or intravenous immunoglobulin (IVIG). Steroids are given in the dose of 1-2mg/kg body weight in tapering doses over weeks. Most patients respond to steroids and some show relapses which may necessitate the use of alternative treatment. Rituximab or splenectomy may be considered in those refractory to the standard treatment or if steroid-dependent [5]. Again, the responses can be variable. Rituximab is usually preferred due to increased response and particularly when Evans syndrome is likely secondary to an underlying condition such as a malignancy or SLE[6], and also in those at increased risk of infections due to co-morbidities making it necessary to avoid splenectomy. Additional treatment modalities include intravenous immunoglobulin (IVIG), vincristine, cyclophosphosmide, azathioprine for the steroid-resistant or relapsing cases[6]. Danazol is effective for the treatment of refractory Evans' syndrome[7]. splenectomy has markedly reduced the sequestration and clearance of the IgG-coated erythrocytes but splenectomized patients were unable to maintain a steroid-free remission and the majority have become steroid dependent or refractory.[5]

Hence Evans syndrome carries grave prognosis in view of no specific diagnostic guidelines, ineffective treatment regimens and frequent remissions and relapses.

4. Conclusion

Evans syndrome is a very rare entity and a rare cause of AIHA with ITP.

Suspecting it as a differential diagnosis and initiating an early treatment can prevent the patient from dreadful complications from massive bleeding and also risk of thrombotic tendancies[8]. Workup for secondary causes like connective tissue disorders, hematological and other malignancies and infections can narrow down our spectrum.

An early diagnosis & prompt treatment can save the patient from life threatening condition of intense haemolysis.

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