Case Report

Evans Syndrome: A Case Report

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Abstract:

Evans syndrome, a combined clinical condition of autoimmune haemolytic anaemia (AHA) and idiopathic thrombocytopaenic purpura (ITP) and has non-specific pathogenesis. The clinical cases are extremely rare, since only 4% of AHA or ITP are incorporated with Evans. It is distinguished from differentials, such as lupus, IgA deficiency, and acquired immunodeficiency, by peripheral blood film, bone marrow, Coombs test, and coagulation profile. A case of adult female from Pabna, Bangladesh is documented in this report. She complained of high grade intermittent fever, exertional dyspnea, icteric skin and sclera. Other features included mild splenomegaly, dark urine, and profuse sweating after fever. Investigation reports were consistent with AHA and ITP, with normal coagulation and viral profile. However, the patient was treated with corticosteroids, platelet and blood transfusion. And in follow-up visits, there was a pattern of gradual decline in erythrocyte sedimentation rate (ESR) and reticulocyte count, with normalization of haemoglobin, red cell, and white cell count. No association with other diseases was found in this case.

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INTRODUCTION

Evans syndrome is an uncommon clinical condition defined by the combination of autoimmune hemolytic anemia (AHA) and idiopathic thrombocytopenic purpura (ITP).[1] It is a chronic immune- associated disease which has unknown pathophysiology. The true Evans syndrome is diagnosed when possibility of other confounding disorders is excluded. In 1951, Dr. Robert Evan discovered the spectrum like relationship between these two combined diseases after studying twenty-four cases.[1] Epidemiologically, the condition is extremely rare that only less than 4% of ITP or AHA are diagnosed as Evans syndrome.[2-5] There is evidence of both cellular and humoral immune-abnormalities in Evans syndrome.[6] Different scientists provided different types of hypothesis, but the exact disease mechanism is still unknown. However, clinic patients present more neutropenia than pancytopenia.[1,3,5] Secondary cytpoenia can occur later, which may delay the management.[5] There are presentations of anemia and thrombocytopenia, both combined with organomegaly and lymphadenopathy in chronic cases.[3,4,8] Blood count, peripheral blood film (PBF), bone marrow, Coombs test, BT,CT, PT and APTT are usual laboratory investigations for Evans syndrome. (6) To diagnose Evan syndrome finally, differentials like systemic lupus, IgA deficiency, and acquired immuno-deficiency should be excluded. Autoimmune lymphopro-liferative syndrome (ALPS) is another noteworthy differential of Evans syndrome.[8] In options of treatment, corticosteroids are considered as the first line therapy for the disease along with washed RBC and platelet transfusions.[3,5,7] Immunosuppressive agents (e.g. Ciclosporin), danazol, splenectomy, therapeutic antibodies (e.g. Rituximab), azathioprine etc. are used as the second line therapy.[6] As the third line therapy, which is usually not needed, cyclophosphamide or alemtuzumab can be prescribed. [7, 9-11] Even so, after the treatment, prognosis is not satisfactory. Relapse and remission of both ITP (more common) and AHA is seen in most of the cases. Follow-up showed limited data on long term survival. [6]

CASE REPORT

A 29-years-old normotensive non-diabetic married woman hailing from Chatmohor, Pabna was admitted in Bangabandhu Sheikh Mujib Medical University, Dhaka

on November 2, 2014. She had the complaints of fever for ten days with palpitation. She had generalized weakness and shortness of breath (SOB) for the same duration. Fever was high grade and intermittent, with a highest recorded temperature of 103°F. SOB was more marked during exertion and relieved by taking rest. Fever used to come with chills and rigor and subsided spontaneously with profuse sweating. She had also complaints of yellowish discoloration of skin, sclera, and passing of dark color urine for seven days. There was no history of contact with smear positive tubercular patient. There were absence of photosensitivity, oral ulcer, dysuria, chest pain, hematuria, and any bleeding manifestations. There was no significant recent history of travelling. On general examination, the patient was severely anemic and mildly icteric. There was no leukonychia, koilonychia, cyanosis, or clubbing. Lymphadenopathy, thyromegaly, and bony tenderness were absent. Systemic examination reveals only mild splenomegaly.

Table I shows the hematological changes in the investigation results of the patient. During that time, the patient was treated with corticosteroids therapy, platelet, and blood transfusions. White blood differential counts were variable in those time intervals. MCV (Mean Cell Volume), MCH (Mean Cell hemoglobin), MCHC (Mean Cell Hemoglobin Concentration) were mostly within the reference value in all reports. Reticulocyte counts were always high above normal, but came to normal after long term treatment. Peripheral blood film (PBF) was done both during diagnosis and followup. In PBF, Red cells were always dimorphic. Sometimes red cells were associated with anisocytosis, ovalocytosis, polychromatic cells, target cells, pencil cells, and elongated cells. White cells were mature during the treatment course with occasional myelocytes.

Bone marrow examination was done in 3rd and 10th visits. During the 3rd visit, the marrow was normocellular with normal myeloid/erythroid ratio. There were features of megakaryocytic hyperplasia (increased in number and some displastic change) only. There were active micronormoblastic erythropoiesis and active granulopoiesis. But in the 10th visit, after giving stimulant agents, there was hypercellularity and increased myeloid/erythroid ratio. Erythropoiesis was hyperactive and dimorphic. Granulopoiesis was hyperactive too. Megakaryocytes were same like the 3rd visit. So, there were both erythroid hyperplasia and megakaryocytic hyperplasia in the last report. Lymphocytes, plasma cells were normally seen and abnormal cells were absent. Direct coombs test was found positive on the 2nd visit. Systemic lupus erythematosus (SLE) and autoimmune diseases were excluded after negative results of anti-nuclear antibody (ANA) and thyroid function tests (TFTs). ANA was done again two months later to re-confirm the absence of SLE. Coagulation profile was done too.

BT, CT, PT and APTT were normal. Her HIV, HCV, VDRL, HBsAg, AND dengue titre were negative.

Liver function tests and an ultrasound of whole abdomen with hepatobilliary system were carried out in the first visit. In that time, total serum bilirubin was 66.4 pmol/l (reference value: 5-20 pmol/l), Lactate dehydrogenase (LDH) was 420 U/L (reference up to: 400 U/L), Creatinine 1.1 mg/dl (reference: 0.6 - 1.3 mg/dl),

Table I: Changes in hemogram during the course of treatment and revisit

	Date of investigations										
	1st visit 2 Nov, 2014	2nd visit 5 Nov, 2014	3 rd visit 8 Nov, 2014	4th visit 15 Nov, 2014	5th Visit 6 Dec, 2014	6th visit 30 Dec, 2014	7th visit 5 Jan, 2015	8th visit 8 Jan, 2015	9th visit 12 Jan, 2015	10th visit 14 Jan, 2015	11th visit 18 Jan, 2015
Hemoglobin (gm/dl)	2.5	6.5	9.4	10.8	8.4	6.0	3.3	8.3	9.1	10.2	10.4
ESR (Westergren)	160	115	20	10	65	135	135	70	25	10	15
RBC count ($x10^{12}$/L)	0.84	2.14	3.10	3.63	3.03	2.25	1.27	3.26	3.50	3.90	3.82
Platelet count ($x10^9$/L)	18	180	15	150	350	24	05	50	70	70	10
WBC ($x10^9$/L)	5.0	7.0	5.0	3.0	8.5	7.0	1.50	2.00	1.00	1.20	14.00

direct/conjugated bilirubin 6.7 pmol/l (reference: 0-4 pmol/l). There was no thyroid dysfunction and primary immune deficiency as per investigation. X-ray chest was normal. Ultrasound showed hepatosplenomegaly with homogenous and uniform pattern. There were no anatomical abnormalities in other organs. Random plasma glucose was found within normal limit, tested in the first and last visit. Blood electrolytes were explored during 8th visit and found normal.

In summary, patient had thrombocytopenia evidenced by reduced platelet count in blood, increased megakaryocytes, and absent neutropenia in bone marrow. It was idiopathic in nature because collagen disease, liver disease, acute or chronic infections, and other causing factors were absent. Splenic abnormality was unlikely as there was mild splenomegaly. Further, patient had anemia (low hemoglobin level showed in Table 1). Raised unconjugated bilirubin and LDH level reflected it as a hemolytic anemia.

So, combination or co-existence of autoimmune hemolytic anemia (AHA) and idiopathic thrombocytopenic purpura (ITP) diagnosed the cased as Evans syndrome.

DISCUSSION

It has been more than fifty years since Dr. Evan discovered the rare combination of AHA and ITP.[1] Though two diseases are merely idiopathic, their rare combination expects to have an underlying reason in 70% of the adult patients. (12) Graft versus host reaction or transplantation of blood progenitor cells is one of the causes of Evans syndrome. [13, 14] Sometimes Evan syndrome is associated with systemic lupus erythematosus (SLE), Sjogrens syndrome, immune deficiency, leukemia, and lymphoma. [4, 12] Even, metastatic small cell lung carcinoma was also reported in Evans syndrome. (15) However, we did not find any association of the conditions with our reported case.

Our Evans syndrome patient had fever, palpitation, SOB, chills rigor, weakness, sweating, yellowish skin- sclera, anemic pale color, and dark colored urine. The literature shows petechiae, bruising, and mucocutaneous bleeding can be present is Evans syndrome, which was absent in our case.[3,4,8] Examination may reveal hepatomegaly, splenomegaly, lymphadenopathy, and any other organomegaly in chronic or intermittent manner as per previous studies.[3,4,8] But, our patient only had hepatomegaly and mild splenomegaly.

Patient's full blood count and peripheral blood film were investigated routinely for several times. There were features of autoimmune hemolytic anemia. Underlying malignancies, microangiopathic hemolysis, hereditary hemolytic or thrombocytopenic conditions were excluded. Ongoing hemolysis was confirmed by increased reticulocytes, raised unconjugated bilirubin, and low haptoglobin levels. These are the confirmatory investigations, also done in previous reported cases. [3-5, 7, 16] It is claimed that thrombocytopenia in Evan syndrome may be followed by neutropenia, and pancytopenia.[5] However, our patient had pancytopenia at the first visit. After weeks, red and white cell count could be recovered by a course of treatment but thrombocytopenia was recurrent.

Septic shock, ischemic heart disease, cerebral ischemic attack, refractory anemia, and intracranial hemorrhage can be the fatal sequels of Evan syndrome.[10] Though our patient did not progress in any of the fatal outcomes, her condition was not satisfactory at all. It was relapsing and refractory. It is known that treatment for Evan syndrome is very challenging. As described before, there are first line, second line, and third line therapies. We treated the patient with blood transfusion, platelet infusion, corticosteroids (prednisolone) that made the patient better for a few days. But the condition was recurrent, signified by hemoglobin and platelet counts in Table 1.

CONCLUSIONS

Evan syndrome is a rare chronic disease and has non-specific pathogenesis. Patient under study was treated with blood transfusion, platelet infusion and corticosteroids, but the response was not satisfactory and it was assessed by follow-up haemoglobin and platelet count. The patient did not progress in any fatal condition. Large patient surveys, more drug control trials and correlation of international databases for fruitful management of Evans syndrome would be assured for the unique management.

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