Evan’s Syndrome Revisited

Priti Dave*, Kavita Krishna**, AG Diwan***

Abstract
A female aged 43 years presented with acute per vaginal bleeding since six days, severe thrombocytopenia and anaemia, she responded partially to platelets and blood transfusion initially. Four days later she started bleeding from nose, intravenous access sites, developed right sided hemiparesis and subsequently died. Her investigations were suggestive of Idiopathic Thrombocytopenia Purpura (ITP) and Autoimmune Haemolytic Anaemia (AIHA). So a diagnosis of Evan’s syndrome was made.

Introduction
Evan’s syndrome is an autoimmune disorder characterized by simultaneous or sequential development of Autoimmune Haemolytic Anaemia (AIHA) and Idiopathic Thrombocytopenia Purpura (ITP) and / or immune neutropenia in absence of any cause.1,3 Evan’s syndrome is a rare disorder because it is diagnosed in only 0.8% to 3.7% of all patients with either ITP or AIHA at onset.1 Most of the data available is from paediatric age group. Over all incidence in adults is not precisely known.

Case Report
A 43 years old female presented to gynaecology outpatient department with history of severe per vaginal bleeding since 6 days. Her last menstrual period was 15 days prior to this episode. Her menstrual cycles were fairly regular in duration in past but she complained of excessive flow and generalized weakness for last 6 months. There was no history of fever and rash. She had two uneventful pregnancies 18 and 15 years before. No obvious gynaecological cause for bleeding was found during examination and investigations. Her routine blood examination detected anaemia (Hb- 5.1 gm%) and low platelet count (17000 cells/cumm) for which she was referred to the physician.

On examination she was severely pale, afibrile, had mild hepatosplenomegaly with no lymphadenopathy. Two days later she developed ecchymotic patches on right forearm and abdomen. Her haemoglobin was 5.1 gm%, total leucocyte count 8800 cells / cu mm, reticulocyte count 3% and platelet count was 16000 cells/ cumm. Her peripheral smear showed microcytic hypochromic anaemia with polychromasia. Her serum iron level was 36 micro gm / dl (Normal (N) 41 - 141 micro gm / dl), serum ferritin 12 micro gm/dl (N- 10-150 micro gm/ dl) and serum iron binding capacity was mildly high. (450 micro gm / dl N= 251 - 406 micro gm/dl).

Her bone marrow revealed erythroid hyperplasia with crowding of megakaryocytes. No granulomas, malignant cells or parasites were seen in smear. Her unconjugated bilirubin was 2.8 mg/dl (N=2.9 mg/dl), BT, CT, PT and APTT were within normal range. Her VDRL, HBsAg, HIV, ANA, dSDNA, APLA (antiphospholipid antibody panel) and dengue titre were negative.

Haptoglobin was 26 mg/dl (N=30-200mg/dl) and serum lactate dehydrogenase LDH was elevated (patients - 323 U/L, N= 115-22/4/L). Haemoglobin electrophoresis found no abnormality. DAT (Direct anti globulin test) was positive. X-ray chest was normal and USG confirmed hepatosplenomegaly. There was no evidence of primary immune deficiency (IgG, IgA- Normal) and thyroid dysfunction.

She was given 2 units of blood and 8 units of platelets over the next 24 hours. On day three her platelet count was 46000 cells /cumm and Hb - 6gm%. The per vaginal bleeding reduced to spotting. She was started on prednisolone at dose of 1mg/ kg body weight (50mg). On fourth day she suddenly became irritable and developed right sided hemiparesis accompanied by generalized seizures. Her right plantar was extensor. She started bleeding from nose gums and intravenous access sites. Repeat platelet count dropped to 10000 cells/ cumm. Her repeat PT, APTT was normal. Fundus showed retinal haemorrhages. Her state of consciousness deteriorated and she subsequently died within an hour. CT brain showed left intra cerebral hemorrhage.

To summarize excluding any gynaecological aetiology for the per vaginal bleeding this patient had thrombocytopenia which was immune (Idiopathic) in nature. Her thrombocytopenia appeared to be idiopathic in nature as there was no evidence of collagenosis, infection and liver disease. Splenic sequestration was unlikely as there was only mild splenomegaly. Platelet production was not reduced as bone marrow revealed, crowding of mega karyocytes and absence of neutropenia. Her anaemia was haemolytic (unconjugated bilirubin and LDH raised, haptoglobins reduced) and iron deficiency type secondary to menstruation. With the coexistence of ITP and AIHA the patient was diagnosed to have Evan’s syndrome.

Discussion
Evan’s syndrome was first described in 19512 by Evan’s and associates. It has long been considered as a coincidental combination of ITP and AIHA and or immune neutropenia in the absence of any underlying cause. More recently the spectrum of the disease has broadened specially in children and there is increasing evidence to suggest that Evan’s reflects the state of profound immune disregulation as opposed to coincidental combination of immune cytopenias.

Evan’s Syndrome can be classified as primary (Idiopathic) or secondary (Associated with some disease). In adults an underlying cause can be expected in about 70% cases.2 There are case reports of Evan’s Syndrome with SlE, incomplete lupus,2 primary antiphospholipid syndrome, Sjogren’s syndrome,
common variable immuno deficiency, IgA deficiency, B and T cell non Hodgkins malignant lymphomas and chronic lymphocytic leukaemia. We could find no association of any disease in our patient.

In a latest study by Michael of sixty eight patients of Evan’s Syndrome death was seen in 23.5% cases. The causes being septic shock, associated cancers, stroke, acute myocardial infarction, refractory anaemia with excessive blast and lymphomas. Only one of two patients of stroke was suspected to have intracerebral haemorrhage like in our patient. The management of Evan’s Syndrome is challenging. Response to various modalities of treatment vary. Blood and platelets transfusion is the treatment given to alleviate symptoms and gain time but its use should be minimized. The first line of treatment is prednisolone, but relapses are frequent after weaning of steroids. Other treatment options are IVIG, immunosuppressants, danazol and even splenectomy.

Rituximab a chimeric monoclonal antibody against CD20 has been well tolerated by patients of refractory Evan’s Syndrome and other immune mediated haematological disease. More recently small number of patients have been treated by stem cell transplantation.

We have reported this case to highlight the need for awareness of this rare entity. This requires a high index of suspicion among primary care physicians as well as other specialities like gynaecology. Evan’s syndrome is a chronic and recurrent disease. Acute presentation and rapid deterioration as in our patient is not very common. Significance of Coomb’s test in patients with thrombocytopenia and anaemia needs to be reemphasized.

Newer modalities of treatment Rituximab along with steroids should be instituted early for more favourable outcome.

**Conclusion**

Evan’s Syndrome is a rare chronic, relapsing and refractory disease but sometimes may present acutely. In patients presenting as immune thrombocytopenia and anaemia with haemolytic component, DAT is mandatory. 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**