Evans syndrome complicated by chronic hypertension with superimposed pre-eclampsia with HELLP syndrome in pregnancy: A case report*

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ABSTRACT

The case of a pregnant woman initially presenting with low platelets and low haemoglobin and subsequently diagnosed as a case of Evans Syndrome is presented. Owing to its extremely low incidence, little research exists investigating pregnancies complicated by Evans Syndrome. Although diagnosis is simple and straightforward, management of a pregnancy of this nature has proven to be complex and challenging. Further complicating the case and its management is the concurrent diagnosis of Chronic Hypertension with Superimposed Pre-eclampsia, in complete HELLP Syndrome. Pre-eclampsia in the background of Evans Syndrome makes this case a truly interesting case. The individual effects of the two disease entities in a single patient are discussed in this report.

Keywords: Autoimmune hemolytic anemia, evans syndrome, HELLP syndrome, idiopathic thrombocytopenic purpura, pre-eclampsia

INTRODUCTION

Evans Syndrome is an extremely rare, chronic, relapsing and remitting hematologic condition characterized by the sequential or simultaneous diagnosis of Autoimmune Hemolytic Anemia (AIHA) and Immune Thrombocytopenic Purpura (ITP) in a patient. Evans Syndrome in the setting of pregnancy has not been well-documented and research largely involves the pediatric age group.

First described in 1951, Evans Syndrome has been largely considered as a diagnosis of exclusion, often clinched only when other more common clinical entities are ruled out. In terms of incidence, it is diagnosed in only 0.8% to 3.7% of all patients with either ITP or AIHA at onset.[1] Evans Syndrome is mostly diagnosed in the pediatric age group and Evans Syndrome among adults has not been well-documented.[2]

CASE REPORT

O. L. is a 37-year-old, G3P2 (2002) Catholic, married, housewife from Quezon City. Her two previous pregnancies were both uncomplicated, delivered vaginally at term. She was admitted at a tertiary hospital with an admitting diagnosis of G3P2 (2002) Pregnancy Uterine 30 weeks and 6 days AOG by LMP; Chronic Hypertension with Superimposed Pre-eclampsia, Evans Syndrome.

This patient was first admitted at 15 weeks and 3 days age of gestation for decreased hemoglobin and platelet count. Over the course of her 23-day stay, the patient was transfused with 38 units of platelet concentrate which raised her platelet count to 156,000. She was also transfused with 7 units of packed RBC to correct anemia with Hemoglobin of 76 g/L. Patient underwent a series of laboratory tests to investigate the possibility of a pre-existing autoimmune disorder or bleeding dyscrasia, which yielded the following results: peripheral blood smear showed mildly hypochromic, microcytic red blood cells with ovalocytes, there is rouleaux formation, leucopenia, no blast cells seen, platelets are inadequate; ANA Autoantigen Screen was equivocal at 0.8, PNH panel with FLAER negative for Paroxysmal Nocturnal Hemoglobinuria. On bone marrow aspiration and biopsy, findings were mildly hypercellular marrow with trilineage hematopoiesis, moderate to marked erythroid hyperplasia and mild to moderate megakaryocytic hyperplasia—morphologic findings consistent with Idiopathic Thrombocytopenic Purpura. Coombs Test done on the patient revealed positive Direct and Indirect Coombs results. Reticulocyte count was also found to be increased at 2.25, indicative of hemolytic anemia. Over her 3-week stay, patient developed blood pressure elevations as high as 170/100 mmHg. Diagnosis was G3P2 (2002) Pregnancy Uterine 18 weeks and 5 days AOG by LMP, Not in Labor, Chronic Hypertension, Evans Syndrome. Patient was started on Prednisone and Methyldopa 250 mg 2 tablets every 8 hours and was subsequently discharged.

Patient was readmitted at 30 weeks age of gestation

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for swelling of the right side of the face. Blood pressure was 160/110 mmHg, patient was noted to have swelling on the right side of the face, generalized petechiae on the abdomen and extremities (Figures 1, 2, 3). CBC showed normal hemoglobin and thrombocytopenia of 18,000. SGPT and SGOT were both significantly elevated. LDH was also significantly elevated. Renal function test was normal. Diagnosis was G3P2 (2002) Pregnancy Uterine 30 weeks AOG by LMP, Chronic Hypertension with Superimposed Pre-eclampsia, Evans Syndrome, Maxillary Cellulitis, Right.

Specialists in Hematology, OB-Infectious Diseases (OB-IDS), Perinatology and Otorhinolaryngology were involved in the management of this patient.

Biophysical profile and non-stress test were still reassuring. However, estimated fetal weight was 1122g, which falls below the 10th percentile. Doppler velocimetry study was contemplated. Antenatal corticosteroids were given for fetal lung maturity.

Methyldopa and Prednisone were continued. Despite increasing Prednisone dose to 60mg/day and transfusion of thirteen units of platelet concentrate, platelet count further decreased to 9,000, complete HELLP Syndrome was considered. Termination of pregnancy by vaginal delivery was decided. Cervical ripening agents were started. On Electronic Fetal Monitoring, fetal heart rate pattern showed a Category III trace (Figure 4), prompting

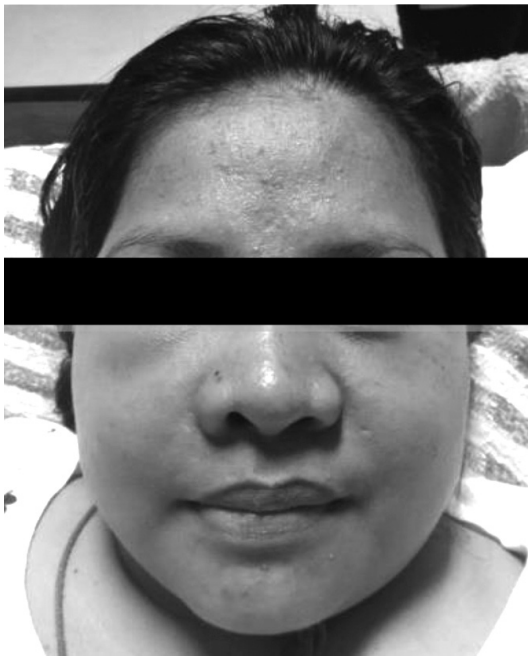


Figure 1. On admission, swelling of the face

Figure 2. Hematoma and petechiae on extremities

Figure 3. Multiple Petechiae on abdomen

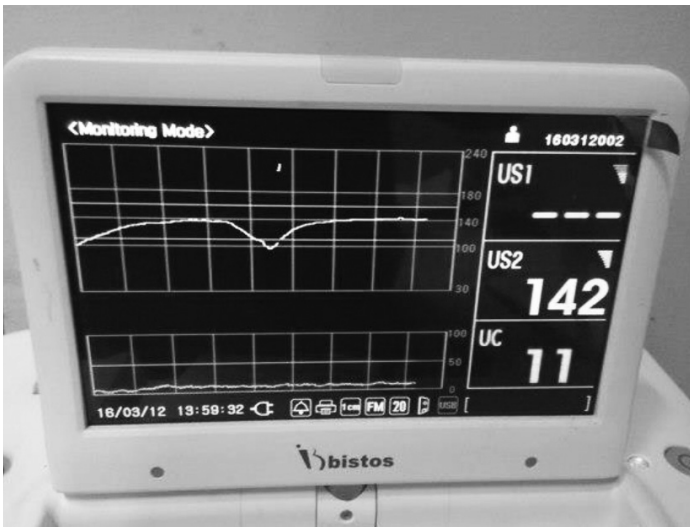


Figure 4. Multiple Petechiae on abdomen Category III Tracing—absent variability with spontaneous deceleration

an Emergency Cesarean Section under General Anesthesia. Intraoperatively, patient was transfused with 2 units of platelet concentrate and 2 units of Fresh Whole Blood. Estimated blood loss for the procedure was 1000mL. Patient delivered to a live preterm baby boy Apgar Score 8, 9 (Figure 5).

On the 2nd post-operative day, patient had uncontrolled blood pressure reaching up to 200/110 despite antihypertensive treatment. Patient went into a generalized tonic-clonic seizure and went into cardiac arrest.

The baby was admitted at the Neonatal Intensive Care Unit for observation. Hemoglobin and platelet count were normal. The baby demised on the third day of life due to prematurity.

CASE DISCUSSION

The clinical picture presented above is most compatible with the diagnosis of Evans Syndrome. Evans Syndrome is considered a rare hematologic condition that is diagnosed when a single patient presents with Immune Thrombocytopenic Purpura and Autoimmune Hemolytic Anemia simultaneously or in sequence.[3]

Idiopathic Thrombocytopenic Purpura or Primary Immune Thrombocytopenic Purpura is diagnosed when a patient presents with thrombocytopenia or low platelet count (less than 150,000) of unidentifiable etiology.[1] Thrombocytopenia in pregnancy must be throroughly investigated (Figure 6). Common causes of thrombocytopenia include infection, drug intake, blood dyscrasia, or it may be secondary to a disease. When none of these are identified, diagnosis of ITP is made.[1] In the patient's case, an extensive battery of laboratory tests effectively ruled out other possible causes of thrombocytopenia. In addition, the patient's blood picture consistently showed decreases platelet counts.

Autoimmune hemolytic anemia (AIHA) is diagnosed when a patient presents with decreased hemoglobin level (level) and evidence of Red Blood Cell hemolysis not attributable to other causes.[3] In AIHA, both the direct and indirect antiglobulin (Coombs) tests are positive. The positive result of the patient's Direct and Indirect Coombs test confirms AIHA. Along with this, the patient's history of low hemoglobin that required transfusion and the increased LDH support the diagnosis of AIHA in the patient.

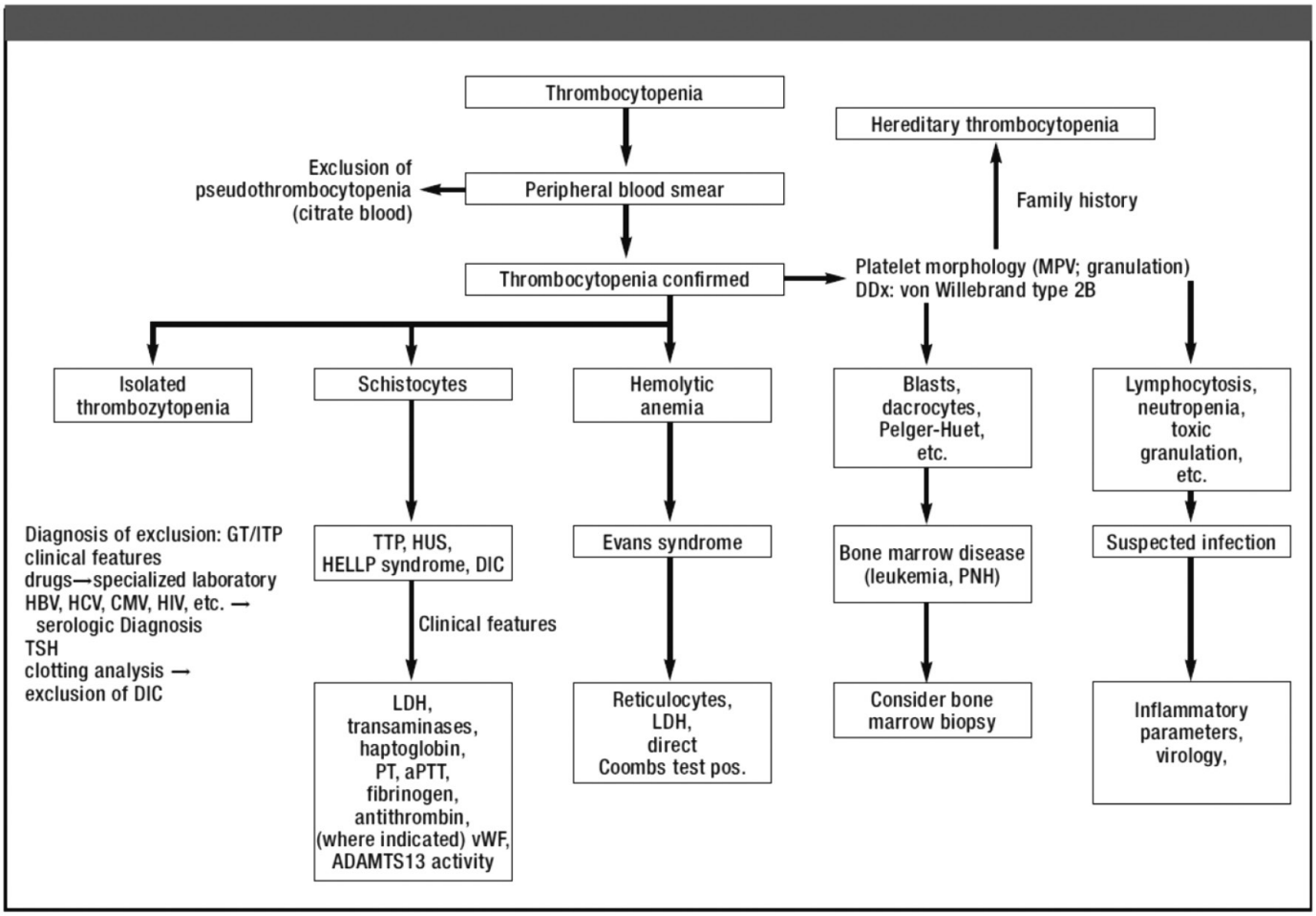
The pathophysiology of Evans syndrome is not clearly understood, but likely involves two major mechanisms[3]. The presence of autoantibodies directed against a base protein of Rh blood group leads to destruction of red blood cells (hemolysis) and a separate group of autoantibodies directed against platelet GPIIb/IIIa destroys platelets (thrombocytopenia)[4].

Figure 5. Baby delivered via "E" LTCS I

Clinical signs and symptoms for Evans Syndrome typically include the usual features of hemolytic anaemia: pallor, lethargy, jaundice, and in severe cases, heart failure. Clinical manifestations of thrombocytopenia include: petechiae, bruising, and mucocutaneous bleeding.[4] Its chronic course is characterized by recurrent relapses and remissions.[1] This is consistent with our patient who presented with generalized petechiae and bruising on the extremities and the abdomen.

With only seven reports documenting Evans Syndrome in Pregnancy based on an exhaustive search for available literature in PubMed, this disease in relation to pregnancy remains largely understudied. However, when taking into consideration ITP and AIHA, possible maternal and fetal complications may be identified. For the Immune thrombocytopenic purpura, possible consequences include maternal and fetal hemorrhage from thrombocytopenia.[4,5] For the Autoimmune hemolytic anemia, possible risks include life-threatening anemia, stillbirth or severe postpartum hemolytic anemia in infants.[5,6]

Possible complications during pregnancy include: spontaneous bleeding episodes[4], stroke and with the



Algorithm for the differential diagnosis of thrombocytopenia in pregnancy

CMV, cytomegalovirus; DDx, differential diagnosis; DIC, disseminated intravascular coagulation; GT, gestational thrombocytopenia; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HUS, hemolytic-uremic syndrome; ITP, autoimmune thrombocytopenia; LDH, lactate dehydrogenase; MPV, mean platelet volume; PNH, paroxysmal nocturnal hemoglobinuria; TSH, thyroid-stimulating hormone; TTP, thrombotic thrombocytopenic purpura; vWF, von Willebrand factor; modified from (4).

Figure 6. Algorithm for differential diagnosis of thrombocytopenia in pregnancy

Reference: Bergmann, F, Rath, W. "The Differential Diagnosis of Thrombocytopenia in Pregnancy", Deutsches Arzteblatt International, 2015.

patient's hypertension, one should always watch out for placental abruption. For the gravid patient with Evans Syndrome, goals of managing the Immune Thrombocytopenic Purpura are to minimize hemorrhage and to restore normal platelet count if possible.[7] During pregnancy, the goal is to maintain platelet count of at least 30,000. When approaching term, platelet count of at least 50,000 is recommended. Normal spontaneous delivery is still the preferred mode of delivery, but Cesarean section may still be considered if there is an identified obstetric indication. If the patient is to undergo Cesarean Section, achieving a platelet count of at least 80,000 is recommended.[7] In our patient, administration of steroids and transfusion of platelet concentrate were done in an attempt to improve the patient's platelet count prior to delivery. However, platelet count did not increase.

For Evans Syndrome in pregnancy, risks to the fetus include bleeding, intrauterine growth restriction because of the possible life-threatening anemia, fetal distress and ultimately, intrauterine fetal demise.[8] Neonatal thrombocytopenia may also develop as a complication of the patient's ITP, and this is observed in 9 to 15% of fetuses delivered to mothers with ITP regardless of the severity of the mother's thrombocytopenia. In the current case, the neonate underwent a complete blood count to check platelet count. This was done to investigate the possibility of neonatal thrombocytopenia, which is common among newborns of mothers with ITP. Another complication to watch out for is Intracranial Hemorrhage, observed in 1-3% of cases, which may lead to death or severe neurologic sequelae.[7]

When the diagnosis of Evans Syndrome is reached, first-line treatment given to the patient is corticosteroids, alone or in combination with intravenous immunoglobulin (IVIG).[8] Corticosteroids are considered the first-line

treatment option; it works to increase platelet production and decrease the production of platelet antibodies thereby decreasing platelet destruction.[8] If the patient is refractory to corticosteroids, IVIG may be given. Intravenous immunoglobulin helps to block the macrophages that work to destroy platelets prematurely, and improves platelet survival time. Second-line treatment options include rituximab and splenectomy.[7] In our patient, she was given Prednisone and received platelet concentrate transfusions. The latter may be done but this is only done as a temporizing measure. Owing to its extreme rarity, long-term survival data of patients with Evans Syndrome are limited, cited causes of death were mostly related to hemorrhage or sepsis. It is important to note that no clinical practice guidelines currently exist for Evans Syndrome, and that management is usually targeted on the patient's active problems—ITP and/or AIHA.

Along with the patient's diagnosis of Evans Syndrome, further complicating this case is the diagnosis of Chronic Hypertension with Superimposed Pre-Eclampsia with HELLP Syndrome. Initially diagnosed as a case of Chronic Hypertension at 15 weeks AOG, the patient developed Superimposed Pre-eclampsia later in pregnancy, which is a common finding among pregnant patients with autoimmune disorders. According to a study done by Lecarpentier, et al, pregnant women with Essential Chronic Hypertension have a 23.3% chance of eventually developing Superimposed Pre-eclampsia.[9] This is consistent with other previous studies that found the risk to be 17% to 34.9%.[8] Although no direct link between Evans Syndrome and development of Pre-eclampsia exists in literature, other autoimmune diseases have been shown to increase a woman's risk for developing pre-eclampsia. A study by Barnabe, Faris and Quan (2011) found that preeclampsia occurred in 18.4% of pregnancies of women with rheumatoid arthritis (7.3% for the control group) and 16.8% of pregnancies of women with lupus (9.3% for the control group).[10] For Evans Syndrome, its autoimmune nature gives cause to think that these patients may be at increased risk as well.

Once diagnosed with pre-eclampsia, termination of pregnancy is ideally done at 34 weeks age of gestation, unless emergency indications are identified.[11] HELLP Syndrome, when present, indicates poor maternal condition, prompting termination of pregnancy.[11]

When HELLP Syndrome was observed in our patient as a complication of the Pre-eclampsia, the thrombocytopenia could have been already present due to her Evans Syndrome, and only aggravated by the presence of HELLP Syndrome. However, because the patient is already being treated with steroids and platelet concentrate transfusions to correct the thrombocytopenia, the current thrombocytopenic state of the patient at this time may be more attributable to the HELLP Syndrome rather than the Evans Syndrome. In addition, the exacerbation of the thrombocytopenia, now refractory to both steroids and platelet concentrate transfusion, may be due to the combination of Evans Syndrome and HELLP Syndrome, but this is not supported by data.

When managing a patient with pre-eclampsia, the safety of both mother and fetus is of paramount importance.[11] Mother should be stabilized, length of gestation confirmed and fetal well-being must be assessed.[11] Possible fetal complications that should be watched out for in pre-eclampsia are perinatal death, placental abruption and development of non-reassuring fetal status. On the maternal side, HELLP Syndrome, pulmonary edema, eclampsia and acute renal failure are the commonly reported complications and patients must be watched out for the development of any of these. Of the complications, the development of HELLP syndrome is the most commonly documented complication, accounting for 4.1 to 27.1% of cases according to POGS.[11] This is applicable to our patient who developed complete HELLP Syndrome.

Fetal surveillance in this setting is highly recommended. Biophysical profile scoring is recommended every 3 days, daily non-stress test, regular monitoring of the fetal heart tones and perception of fetal movement.[11] All these were done in the current case to confirm viability and well-being of the fetus. Without an emergency indication, the management plan for the fetus is to deliver at term and to continue medical management as long as both patient and fetus remain stable.

The decision to terminate pregnancy at 31 weeks age of gestation proved to be a diagnostic dilemma. With the patient's thrombocytopenia not responding to Prednisone and platelet concentrate transfusions, spontaneous vaginal delivery was initially preferred to avoid blood loss, and Cesarean section was reserved only for obstetric indication. On one hand, the mother is noted to be deteriorating, having developed HELLP syndrome which should prompt immediate termination of delivery. On the other hand, terminating the pregnancy at this point would be disadvantageous to the baby, who, at 31 weeks age of gestation and with an estimated fetal weight of 1100 grams, has a poor prognosis in terms of outcome if delivered. However, upon hooking to electronic fetal monitoring, the baby was noted to have a Category III fetal tracing. With both mother and fetus in critical condition, the decision to proceed with an emergency cesarean section despite the severe thrombocytopenia was made. Preparations in the counselling and prognosticating the family regarding the conditions of the mother and the baby, as well as the securing of adequate blood products were done before proceeding with the operation. Ethical

issues may be discussed in this setting, primarily the principles of beneficence, non-maleficence and double effect. Ultimately, the decision to proceed with a cesarean section in this case became a necessity when both patients were noted to be deteriorating, and immediate action--termination of pregnancy—had to be taken to improve chances of a favourable outcome for both mother and baby despite the maternal thrombocytopenia and the fetal prematurity.

Because the baby was born to a mother with thrombocytopenia, it was imperative to obtain a blood picture of the baby to investigate the possibility of neonatal thrombocytopenia. Complete blood count, particularly the platelet count, was normal. However, on the third day of life, baby demised due to extreme prematurity. The possibility of an intracranial bleed may be considered given the maternal history, but a cranial ultrasound was not done to confirm this.

Despite aggressive management and close monitoring, patient demised 2nd post-operative day after developing elevated blood pressure readings now refractory to antihypertensive medications, and generalized tonic-clonic seizure. Cause of death was cardio-respiratory arrest secondary to Uncal Herniation probably secondary to Cerebrovascular Bleed.

SUMMARY

In this report, the case of a thirty-seven year old diagnosed with Evans Syndrome, Chronic Hypertension with Superimposed Pre-eclampsia in HELLP syndrome was presented. Diagnosis is simple but management remains complex and challenging, warranting future research.

Although it is an uncommon hematologic condition that is rarely diagnosed and not widely studied, Evans Syndrome must be considered by clinicians when confronted with a patient who has a Coombs positive anemia and thrombocytopenia on Complete Blood Count, especially since prognosis for Evans syndrome largely depends on its early recognition and timely management.

With the presence of Pre-eclampsia complicating the case, close monitoring particularly blood pressure and fetal heart tones, regular laboratory work-ups and fetal surveillance are warranted.

A multi-disciplinary approach involving specialists from Obstetrics, Pediatrics, and Internal Medicine, specifically Hematology, is recommended. Sufficient preparation for eventual delivery, close fetal and maternal surveillance and early management during pregnancy are imperative to increase the possibility of a favorable pregnancy outcome in these women. ■

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