

Thrombocytopenia in Pregnancy: Evans Syndrome an Unconventional Diagnosis, Evans Syndrome in Pregnancy: Case Report

Gebelik Trombositopenisi:
Nadir Bir Tanı Olan Evans Sendromu,
Gebelikte Evans Sendromu

Tuncay YÜCE,^a
Mehmet Murat SEVAL,^a
Dilek ACAR,^a
Cem ATABEKOĞLU^a

^aDepartment of Obstetrics and
Gynecology,
Ankara University Faculty of Medicine,
Ankara

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Yazışma Adresi/Correspondence:
Tuncay YÜCE
Ankara University Faculty of Medicine,
Department of Obstetrics and
Gynecology, Ankara,
TÜRKİYE/TURKEY
drtuncayyuce@gmail.com

ABSTRACT Evans syndrome, first described in 1951, is a rare hematological disorder characterized by episodes of autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura or neutropenia. It is an extremely rare event when it co-exist with pregnancy. To our knowledge there are 14 reported case co-exist with pregnancy. The diagnosis is made upon hemolytic anemia and idiopathic thrombocytopenic purpura, and also a positive direct Coombs test and an absence of any known underlying etiology. In this paper we report a woman with a prior diagnosis of Evans syndrome and had a flare-up during late trimester. This attack was unexpectedly and it was unlike previous attacks it revealed itself with pure thrombocytopenia as opposed to anemia and leukopenia in previous attacks. A healthy female fetus of 3370 gram was born. Fetal blood parameters were normal.

Key Words: Thrombocytopenia; anemia; pregnancy

ÖZET Evans sendromu ilk defa 1951 yılında otoimmün hemolitik anemi, idiyomatik trombositopenik purpura ya da nötropeni atakları ile karakterize bir hematolojik hastalık olarak tanımlanmıştır. Gebelikte birlikteliği çok nadirdir. Bildiğimiz kadarıyla literatürde gebelik ile birlikte olan 14 olgu bildirilmiştir. Tanı, alta yatan bir etyoloji bulunmadan görülen otoimmün hemolitik anemi ve idiyomatik trombositopenik purpura olması ve direkt Coombs testinin pozitif olması ile konur. Bu yazıda, önceki tanısı Evans sendromu olan bir kadın sunuyoruz. Geç trimesterde beklenmedik bir atağı oldu ve bu, öncekilerden farklı olarak anemi ve lökopeni olmadan ciddi trombositopeni şeklinde bulgu verdi. Sağlıklı 3370 gram kız fetus doğurtuldu. Fetal kan parametreleri normal olarak bulundu.

Anahtar Kelimeler: Trombositopeni; anemi; gebelik

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Evans syndrome, as first described by Robert Evans in 1951, is a haematological disorder characterized by episodes of autoimmune haemolytic anaemia (AIHA), idiopathic thrombocytopenic purpura or neutropenia caused by haemopoietic cell-specific autoantibodies.¹ Understanding the pathophysiology of the disease is elusive and still restricts knowledge about the identification of target antigens. Evans syndrome is a rare condition; estimated incidence of autoimmune haemolytic anaemia is 0,8-3 in 100 000 and incidence of immune thrombocytopenia (ITP) is approximately 6,6 in 100 000 in adult population. Real incidence of Evans syndrome is unknown but it is thought to be 1,8-10% of all patients diagnosed

with immune thrombocytopenia and with mild anaemia is actually Evans syndrome. ITP in pregnant women is quite rare (1-5 in 10 000) and by extension considering only a fraction of these patients are actually Evans syndromes; the disease stands out as an extremely rare event when it co-exist with pregnancy (25 in 1 000 000).² Therefore, it's difficult to illustrate the diagnosis, and induce over-diagnosis of this rare disease.

Evans syndrome is categorized into primary and secondary Evans syndrome regarding its cause. In adult patients 70% of cases have an underlying disease triggering the process. Secondary Evans syndrome due to systemic lupus erythematosus, primary antiphospholipid syndrome, Sjogren's syndrome, chronic lymphocytic leukaemia, non-Hodgkin's lymphoma was reported in the literature.²

In our case we treated a pregnant woman with a flare-up of Evans syndrome. This attack was unexpectedly occurred during third trimester and it was unlike previous attacks it revealed itself with pure thrombocytopenia as opposed to anaemia and leukopenia in previous attacks.

CASE REPORT

A 27 years old gravida 2 parity 1 pregnant woman presented with severe thrombocytopenia in Antenatal Care Clinic of Ankara University Medical Faculty in April 2014. She had a diagnosis of "Evans syndrome" 4 year after her first pregnancy in 2010. Her first attack in 2010 was characterised by complaint of malaise and her laboratory work-up revealed pancytopenia (Hemoglobin 6,3 mg/dL, Leukocyte count 1100/mm³, Neutrophil count 100/mm³, Platelet count 100 000/mm³). In the evaluation of peripheral blood smear, occasional nucleated red blood cells with rouleaux, schistocytes, spherocytes, polychromasia, macrocytosis and reduced platelet numbers were reported. Further laboratory evaluation revealed Total/Indirect Bilirubin ratio 14.11/10.77, lactate dehydrogenase 1141, absolute reticulocyte count 100 000/ml, decreased haptoglobin levels, 3 positive direct Coombs for IgG and negative for CD3, 1 positive indirect Coombs, normal protein elec-

trophoresis, normal and negative anti-dsDNA, ANA, ANCA, anti-Jo 1 and all subsets of ANA and lupus anticoagulants. Bone marrow aspiration and biopsy has been shown a hypercellular marrow (80-85%) with erythroid hyperplasia, no dysplastic changes and a sufficient number of mature megakaryocytes. Lymphoma was excluded with normal a total body computed tomography and no clonal lymphocyte increase or infiltrative processes was seen in bone marrow biopsy. After exclusion of other aetiologies a diagnosis of Evans syndrome was made. Treatment was initiated with 60mg of methylprednisolone and it was gradually increased to 120mg per day until therapy response was adequate. After 4 months of therapy response to steroids was deemed incomplete and therapy with intravenous immunoglobulin (IVIg) was initiated. During this period she developed febrile neutropenia. After she recovered disease was considered to be treatment refractory and a splenectomy was performed. After splenectomy her laboratory panel returned normal.

After remaining disease free for 2 years she presented in a local clinic with complaints of sores on her body. Laboratory work-up revealed anaemia with haemoglobin level of 7,9 g/dL, mild thrombocytopenia with a platelet count of 100 000/mm³ and leukopenia with a white blood cell count of 2000/mm³ (5% neutrophils). A bone marrow biopsy was performed again and reported as normal. Steroid treatment was initiated as previous attack and she recovered fully without additional complications.

Patient registered at our antenatal clinic for routine care of second pregnancy at 6 weeks of gestation, after two years disease free interval. Initial blood panel was obtained and complete blood count was completely normal at her first antenatal visit. She was followed-up with routine antenatal care and her blood panel remained normal until 28 weeks of gestational age. A blood panel obtain during that time revealed severe thrombocytopenia with a platelet count of 3000/mm³, normal haemoglobin levels with 2 positive Coombs test and normal white blood count. Reduced platelet number

was confirmed in the evaluation of peripheral blood smear.

Steroid treatment was initiated with an initial dose of 1 mg/kg/day methylprednisolone. Her platelet count responded well to steroid regimen and during her 38th week of gestation she underwent a caesarean section with an indication of prior caesarean section. Her preoperative complete blood count was; Haemoglobin 13.5 g/dL, platelet count 389 000/mm³, leukocyte 11 600/mm³

OUTCOME AND FOLLOW-UP

A healthy female foetus of 3370 gram was born. Fetal complete blood count and peripheral blood smear were normal. No any bleeding disorder was not recorded for the newborn foetus. Our patient responded dramatically to methylprednisolone and sustained that response over 3 months of tapering. The direct Coombs test remains positive but without active haemolysis and with normal platelet count. She is now asymptomatic and on regular follow up.

DISCUSSION

Evans syndrome is known as a disorder of immune regulation characterized by either concurrently or consecutively AIHA and ITP, sometimes together with immune neutropenia (<55% of the patient at the diagnosis). However Evans syndrome is thought to be a disorder of immune regulation, but the exact pathophysiology is not yet understood.

Evans syndrome is a rare disease, and diagnosis is made through the exclusion of other causes of acquired immune cytopenia. Direct Coombs is usually positive even in the absence of haemolytic anaemia and patients have the usual features of AIHA. Review of the peripheral blood smear is a critical step in the evaluation of Evans syndrome. Along with an assessment for pathognomonic red blood cell morphologies, such as fragmented RBC, spherocytes or schistocytes, examination of normal the white blood cells and reduced numbers of platelets for coexisting. In addition autoantibody testing for platelets and granulocytes may be positive but a negative result does not deny Evans syndrome and routine testing at the diagnosis has not

recommended yet. In our patient, the etiology of pancytopenia was widely investigated and Evans syndrome was diagnosed depending on the warm type haemolytic anaemia, splenomegaly and normal bone marrow. Unfortunately the platelet antibody level was not measured in this case.

The management of the Evans syndrome is challenge because of the limited large, prospective, randomized studies. Altogether these restrict results points toward, corticosteroids and/or IVIG is the first-line therapy and if patients fail to respond or steroid dependent, immunosuppressive agents, the monoclonal antibody rituximab and splenectomy may be considered a second-line treatment. Even in the acute setting, blood and/or platelet transfusions may also be needed to reduce the symptoms. Our patient also did not respond to steroid and splenectomy was performed by her physician's choice and she had stayed in remission for 4 years.

It's important to note that haemolytic anaemia, HELLP syndrome and other microangiopathic coagulopathies should be exclude carefully in pregnant women. To our knowledge there are 14 reported case of Evans syndrome presenting with a flare-up episode during pregnancy or getting diagnosed during pregnancy. Previous reports noted that patients might go through pregnancy without any significant change in blood panels. However anaemia, thrombocytopenia, leukopenia and preeclampsia can complicate the pregnancy in the natural course of disease during pregnancy.³

In our patient the initial diagnosis was made after and episode of pancytopenia. The first episode of disease was uncontrollable until a splenectomy, which was performed 7 months after initial diagnosis. And exacerbation of the disease was detected with pancytopenia again after 2 years of remission. But this time it was responded to steroid and in both of the episode febrile neutropenia requiring treatment was encountered. However severe thrombocytopenia didn't occur until the third episode of relapse, which happened during pregnancy. To our knowledge, many immunological disorders can be exacerbated by pregnancy and fu-

ture experiments are needed to explain these response mechanisms. It's known that our patient was in remission for two years until her period of pregnancy and this can explain her immune-mediated thrombocytopenia.

First case of Evans syndrome in pregnancy by Silverstein et al. was reported in 1966. In this report the patient had a prior diagnosis and was treated with splenectomy prior to pregnancy. Later the patient became pregnant and the disease relapsed with isolated thrombocytopenia during 8th week of gestational age, which responded to steroid treatment.⁴ In our case thrombocytopenia was encountered during 28th week of gestational age and entered remission with high dose steroid treatment. Obviously the role of splenectomy in the treatment of Evans syndrome is not clearly proven because the response rate is frequently low and transient. Even both women had normal blood counts for a while than relapse occurs post-splenectomy.

Relapse episodes in patients with a diagnosis prior to pregnancy are known to happen during 8-14 weeks of gestational age. Patients whose diagnosis made during pregnancy are more likely have symptoms late into gestational period.³ In our case;

even though our patient was diagnosed before she got pregnant, relapse episode happened during 28th week of gestational age and it's known that immune thrombocytopenia occurs rarely in the third trimester and in our patient all the other cause of thrombocytopenia was excluded. Even it should keep in mind, the patient had normal haemoglobin levels, and high positive direct Coombs test with mild haemolysis on peripheral blood smear was detected. These findings were directed us to confirm the diagnosis of Evans syndrome.

In summary; in this case we encountered a flare-up episode of Evans syndrome, which is exceedingly rare in pregnancy. Presenting with ITP like laboratory parameters, which was not seen in previous episodes, and occurring without neutropenia was the major differences. Our case is remarkable for third trimester flare-up of the disease, which can be mistaken for other aetiologies, as it's unexpected for both ITP and Evans Syndrome. Also it's noteworthy because thrombocytopenia was the only laboratory abnormality unlike previous attacks. This presentation confirms previous reports of Evans syndrome triggering thrombocytopenia unlike its traditional presentation.

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