Evans Syndrome, A Rare Presentation of Systemic Lupus Erythematosus: A Case Report*

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ABSTRACT

Evans Syndrome was first reported in 1951 by Evan and Duane, and is defined by the rare development of autoimmune hemolytic anemia and immune thrombocytopenia, whether simultaneous or sequential, with a positive Coombs test. In children, it is one of the rare presentations of autoimmune connective tissue disorders. Reported here is a case of a fifteen-year old girl with Evans Syndrome, which later evolved into Systemic Lupus Erythematosus. She had pale and sallow skin with multiple ecchymosis and petechial rashes on both upper and lower extremities accompanied by headache, lightheadedness, and generalized body weakness for 3 days. Initial investigation showed moderate normocytic hypochromic anemia with reticulocytosis and thrombocytopenia. Direct and indirect Coomb's test was positive. Other bleeding parameters were normal. The peripheral blood smear showed normocytic, hypochromic red blood cells with microcytic red cells, elliptocytes, ovalocytes, polychromatophilic cells, and occasional fragmented red cells, and markedly decreased platelets with occasional giant forms. Bone marrow aspiration was normal. Further investigation revealed a positive Anti-Nuclear Antibody. The patient was initially treated as Evans Syndrome with steroids which controlled the symptoms. She was then worked up for Systemic Lupus Erythematosus, and was treated accordingly.

Key words: Evans syndrome, Systemic lupus erythematosus

Evans Syndrome was first reported by Robert Evans and his colleagues in 1951 as an immune dysregulation characterized by Immune Thrombocytopenic Purpura and Autoimmune Hemolytic Anemia, sometimes with immune neutropenia, without any known underlying systemic disease. There has been no existing study at this time explaining the precise pathophysiology of the immune dysregulation. Most studies currently available are isolated case reports, and involve only small numbers of patients. In the last 3 decades, there has been roughly only 100 cases of Evans Syndrome published based on inconsistent definitions, and clinical data with long-term follow-up are still lacking. It has been estimated that between 0.8 to 4% of patients with immune thrombocytopenia or immune hemolytic anemia presents with this syndrome. There is no sex predilection known, and it generally has a sporadic condition that affects all ethnic groups and at any age group. A study involving one of the largest population of patients reported a tendency for the male gender in younger children, and female predominance in adolescents. The age of onset ranged between 5.5 to 7.7 years of age with an overall range of 0.2-26.6 years involving four case reports of Evans Syndrome. The clinical manifestations are typical features of hemolytic anemia (pallor, weakness, jaundice, heart failure in serious cases), thrombocytopenia (petechiae, ecchymoses, mucocutaneous bleeding, menorrhagia, hematuria, and gastric bleed), and neutropenia (recurrent infections).

In a study by Aladjidi et al (2015), it was reported that approximately 30% remained primary after a follow up period of 6.5 years, and was secondary in 10%. It can be secondary to other diseases, mainly infections, lymphoproliferative disorders, autoimmune diseases and immunodeficiencies. The prevalence of secondary Evans Syndrome in Systemic Lupus Erythematosus has been reported in 1.7-2.7% of cases. Of the 13/156 patients who developed

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SLE, 3 of which achieved the SLE clinical criteria concomitantly with the onset of ES, and 10 developed features of SLE within a 1-10-year period.

Evans Syndrome is a lifelong disorder characterized by multiple exacerbations and remissions, and patient usually become dependent on immunosuppressive therapy. It is a diagnosis of exclusion, and by definition, there should be absence of any underlying systemic diseases. Patients may present with Immune Thrombocytopenic Purpura, Autoimmune Hemolytic Anemia, and sometimes with immune neutropenia either concurrently or sequentially. The clinical presentation includes the characteristic features of hemolytic anemia, thrombocytopenia, and/or neutropenia. Physical examination may have splenomegaly, hepatomegaly, and lymphadenopathy. Laboratory examinations that will aid in the diagnosis include complete blood cell count, peripheral blood smear, reticulocyte count, bilirubin levels. There should be a strong consideration for Systemic Lupus Erythematosus and other autoimmune diseases, and should be screened, which includes the determination of antinuclear antibody, double-stranded deoxyribonucleic acid, and rheumatoid factor. Managing Evans syndrome remains a challenge. No evidence-based studies have definite treatment regimen, but for now, it is necessary to manage symptomatic cytopenias such as moderate to severe anemia, thrombocytopenia with bleeding, or severe neutropenia.

The objective of the report was to discuss a rare case of Systemic Lupus Erythematosus presenting initially as Evans Syndrome in an adolescent female.

THE CASE

This is a case of a 15-year old female who consulted in this institution due to multiple bruises on all extremities for 4 days after moderate physical activity from school. She also had occasional colds, with watery nasal discharge, and occasional dry non-distressing cough, usually at night. Two days prior to admission, the increasing size of the bruises on her extremities was accompanied by lightheadedness, generalized body weakness, and occasional generalized headache, pressing in character, with a pain scale of 5/10, relieved by rest. She was brought to a private physician with an unrecalled diagnosis, and given co-amoxiclav and ferrous sulfate. One day prior to admission, still with the above signs and symptoms, and increasing size of the bruises, there were flat reddish non-blanching pinpoint rashes on her extremities. Her complete blood count revealed moderate anemia (Hemoglobin: 94 g/L; Reference range: 125-160 g/L, Hematocrit: 0.29 L/L; Reference range: 0.37-0.47 L/L), and thrombocytopenia (Platelet count: 22 x 10^9/L; Reference range: 150-400 10^9/L). Pertinent physical examination at that time were sallow skin, pale palpebral conjunctiva, pale palms and soles, and multiple ecchymosis and petechial rashes on both upper and lower extremities. The initial impression was Immune Thrombocytopenic Purpura and Probable Iron Deficiency Anemia. Complete blood count showed normocytic hypochromic anemia and thrombocytopenia, with increased Mentzer's index (21.15) indicating iron deficiency anemia. Bleeding time, clotting time, prothrombin time, partial thromboplastin time, and bilirubin levels were all within normal limits. Peripheral blood smear showed normocytic, hypochromic red blood cells with microcytic red cells, elliptocytes, ovalocytes, polychromatophilic cells, occasional fragmented red cells, and markedly decreased platelets with occasional giant forms. Bone marrow aspiration revealed an M1 marrow with increased megakaryopoiesis The corrected reticulocyte count was elevated, and the indirect and direct Coomb's tests were positive. Antinuclear Antibody was also done. Intravenous Gammaglobulin and methylprednisone was not given due to financial constraints. She was initially started with hydrocortisone and later shifted to methylprednisolone and prednisone. Her symptoms gradually improved, and was discharged with the following medications: omeprazole, folic acid, vitamin E, multivitamins, prednisone, and isoniazid.

Upon follow-up 5 days after discharge, the Antinuclear Antibody yielded a positive result (ANA 1:10 = 3.5; Positive >1.0 Ratio), thus Lupus panel was done which revealed positive for Anti-nuclear antibody, moderate positive for Anti-SSA, and negative for Anti-double-stranded DNA, Anti-RNP, Anti-SM, and Anti-SSB. The patient also presented with alopecia, and petechial rashes on bilateral axillary areas, without any other findings such as the malar and discoid rash, oral or nasal ulcers, synovitis, serositis, renal, and neurologic manifestations. She was then admitted due to recurrence of thrombocytopenia (Platelet count: 11 x 10^9/L; Reference range: 150-400 10^9/L), and treated as a case of Systemic Lupus Erythematosus with hydrocortisone, azathioprine, hydroxychloroquine, calcium, and multivitamins to which provided resolution of her symptoms, and

improvement of complete blood count results. She was then discharged with prednisone, azathioprine, hydroxycholoroquine, calcium, and multivitamins. Lupus panel monitoring was done every 6 months.

DISCUSSION

Evans Syndrome is a rare disorder of simultaneous or subsequent development of immune thrombocytopenic purpura and autoimmune hemolytic anemia, sometimes with immune neutropenia. It is a lifelong autoimmune disease characterized by alternating periods of remission and exacerbation. Up to the present time, there has been no definite etiology identified and the pathophysiology remains unresolved, though several authors have proposed that Evans Syndrome could be a form of profound immune dysregulation with antibodies targeting erythrocytes, platelets and granulocytes. In most (60–70%) cases, auto-reactive IgG binds red blood cell antigens and causing the destruction, primarily in the extra-vascular compartment, by way of the antibody-dependent cellular cytotoxicity mechanism. Immune function of patients with Evans Syndrome compared with Chronic ITP patients were found to have decreased T4 or T-helper, increased T8 or T-suppressor, and a decreased ratio of T4:T8 cells. Immune-mediated thrombocytopenia is brought about by platelet opsonization by anti-platelet antibodies and/or immune-complexes leading to premature eradication by the reticuloendothelial system. Antibodies that recognize membrane antigens of neutrophils is primary to their peripheral destruction of, and are mostly located on IgG Fc receptor type 3b.

Patients may either present subsequently with AIHA or ITP after a median interval of 3 years (Aladjidi, et al, 2011), but more case reports involved simultaneous development of AIHA and ITP. Neutropenia occurred in 20-55% of patients either at presentation, during or after the diagnosis of Evans Syndrome. Warm AIHA is the type of AIHA present in Evans Syndrome wherein IgG antibodies are directed against red blood cells' membrane antigens at body temperature.

A thorough history, including the family history of any malignancies, hematologic and immunologic diseases, is important to determine any underlying diseases. It is also relevant to determine if there is recent administration of drugs or vaccination, which can bring about cytopenia. Clinical manifestations include the classic features of hemolytic anemia: pallor, weakness, jaundice; and thrombocytopenia: petechiae, easy bruising, mucocutaneous bleeding. Hepatomegaly, splenomegaly, and lymphadenopathy may be present on physical examination, and in some cases may only be evident during periods of relapse (Pui, et al. 1980; Savasan, et al. 1997; Teachey, et al. 2005). The patient came in with sallow skin, pallor, and multiple ecchymosis and petechial rashes on bilateral upper and lower extremities, accompanied by lightheadedness, generalized body weakness, and headache, which are typical signs of hemolytic anemia and thrombocytopenia. And the subsequent development of alopecia later on led the authors to the diagnosis of Systemic Lupus Erythematosus along with positive Antinuclear Antibody 1:10 = 3.5 (Positive >1.0 Ratio).

A complete blood count will identify the presence of cytopenias and a peripheral blood smear should be examined not only for features of autoimmune hemolytic anemia (polychromasia, spherocytes), but also to exclude other underlying diagnoses (myelodysplastic syndromes, microangiopathic hemolytic anemias, congenital hemolytic and thrombocytopenic conditions). The patient's peripheral blood smear showed elliptocytes or ovalocytes, which are seen in iron deficiency and thalassemia. The polychromatophilic cells are increased numbers of immature red blood cells as a result of being prematurely released from the bone marrow. The giant platelets are immature platelets, and is reflective of increased platelet turnover. The diagnosis of an immune-mediated hemolysis is based on a positive Coomb's test, reticulocytosis, indirect hyperbilirubinemia, increased lactate dehydrogenase (LDH) level and low serum haptoglobin. Antiplatelet and antineutrophil antibody assays can be requested to evaluate for cell-specific autoantibodies in the patient's serum, but these tests may be inaccurate and have a tendency to have false negative results. Bone marrow aspiration should be performed in order to exclude a proliferative disorder or myelodysplasia. The patient's bone marrow aspiration revealed an M1 marrow, indicating a normal bone marrow with only less than 5% involvement of lymphoblasts. Secondary Evans Syndrome must be investigated to exclude an underlying disease because management is different between primary and secondary Evans Syndrome. An SLE Panel was requested for the patient upon the diagnosis of Evans Syndrome to differentiate a possible secondary cause. Splenectomy was deemed

crucial for Primary Evans Syndrome with persistent thrombocytopenia, whereas this may not be needed for autoimmune diseases such as Systemic Lupus Erythematosus. Secondary Evans syndrome, as with the present case has been associated with various diseases including systemic lupus erythematosus, common variable immunodeficiency, and autoimmune lymphoproliferative syndrome in Non-Hodgkin's lymphoma, chronic lymphocytic leukemia, viral infections (such as Human Immunodeficiency Virus, and hepatitis C) and even following allogeneic hematopoietic cell transplantation. Screening for secondary causes includes the determination of antinuclear antibody, double-stranded deoxyribonucleic acid, and rheumatoid factor. Autoimmune lymphoproliferative syndrome can be ruled out by determination of elevated double-negative T cells by flow cytometry.

Managing Evans Syndrome remains to be a challenge. Its course is known to be erratic with periods of remission and exacerbation, and treatment response varies with different patients. To this date, there is no evidence-based treatment guidelines in treating Evans Syndrome, and current studies involve isolated case reports. At present, the choice of management will depend on the decision between the attending physician and the patient. The primary objective is to raise the platelet count to at least 20 x 10^9/L, and prevent development of any bleeding, most importantly intracranial hemorrhage though it is rare.

Corticosteroids with or without intravenous immunoglobulin (IVIG) is the most commonly used first line of therapy. Despite the lack of established evidence-based treatment, corticosteroids remain the mainstay of treatment to control cytopenias providing favorable initial results. The postulated mechanism for this is that steroids inhibit the ability of macrophages for clearing platelets and erythrocytes. The dose of prednisolone used ranged from 1-4 mg/kg daily; although some patients showed complete response in another scheme using megadose of methylprednisolone (30mg/kg daily for 3 days, then 20 mg/kg daily for 4 days, then tapering to dividing the dose into half every week) (Meytes, et al. 1985; Nanan, et al. 1995; Ozsoylu, 2004). Most pediatric cases respond well to prednisolone 1-2 mg/kg/day, but relapse during tapering off was reported to be common. Intravenous Immunoglobulin is also given especially for patients who are unresponsive to steroids or require very high doses to control signs and symptoms of cytopenias wherein steroid toxicity is possible. The potential effectiveness seems to be related to the saturation of FCγ receptors on the macrophages in the reticuloendothelial system by the concentrated IgG from human plasma donors. It could either be given simultaneously with steroids or after steroid failure. A dose of 0.8-1 mg/kg/day for 2 days appears to be sufficient for most cases. Increase in platelet count within 48 hours was reported in 95% of cases. Repeated courses may also be successful.

Besides first-line therapy with IVIg or steroids, almost 70% required a second-line treatment; 47% received multimodal second-line treatments (Aladjidi et al, 2015). Second-line drugs that have been used include immunosuppressants (ciclosporin, mycophenolate mofetil and danazol), rituximab (monoclonal antibody) and chemotherapeutic agents (vincristine). Splenectomy is also considered as a second-line treatment. The challenging issue particularly in patients who are at risk of serious long-term side effects of steroids is the very little data available on second and third-line approaches for the relapsing type. Although most of the currently available studies do not lead to a firm conclusion and are difficult to interpret, starting with a trial of ciclosporin, then mycophenolate mofetil, is usually the practice among the second-line modalities. One of the new approaches is the use of rituximab for patients who remain to be dependent on high-dose steroids, ciclosporin, or mycophenolate mofetil. Another alternative is to make use of combination drugs, which include vincristine and danazol, described by Scaradavou and Bussel (1995). When unresponsive to immunosuppressive agents, some studies have reported successful use of hematopoietic stem cell transplantation, although it is important to consider its potential life-threatening adverse effects.

The patient in the present case was given hydrocortisone 20 mg/kg daily for two days, and shifted to methylprednisolone 30 mg/kg daily for three days, then prednisone 50mg OD for 2 months. The initial plan was to start with Methylprednisolone and Intravenous Immunoglobulin, but was not fulfilled because the patient's family was not financially equipped at the time of admission. Thus, Hydrocortisone was initially started, and was shifted to Methylprednisolone when they finally were able to provide for it. The corticosteroids were able to control the cytopenias until after 2 months when she again developed signs and symptoms of anemia and thrombocytopenia (headache, and petechiae),

accompanied by alopecia, and on complete blood count revealed low platelet count (11 x 10^9/L). Her Lupus Panel revealed positive for Anti-nuclear antibody, moderate positive for Anti-SSA, and negative for Anti-double-stranded DNA, Anti-RNP, Anti-SM, and Anti-SSB. With the fulfillment of 4 out of the 17 criteria under the Systemic Lupus Collaborating Clinics, the patient was subsequently managed as a case of Systemic Lupus Erythematosus.

The relationship of SLE and Evans Syndrome has been reported in several studies. Prevalence of secondary Evans Syndrome in SLE was reported to be 1.7%–2.7% of cases. Steroids are usually the first line of therapy. In refractory cases, the use of rituximab at standard doses has been proven to be effective with a reduction in Platelet-associated IgG, DAT, lower antinuclear antibodies titer, and anti-CD19, -CD21, -B3, -TNF-α after 1-6 months of treatment. Interestingly, compared to the primary disease, secondary Evans Syndrome has a longer remission.

As for the prognosis, Evans Syndrome is known to be characterized by frequent episodes of relapse and remission. About 67% of patients are at risk of developing infections, most commonly respiratory, due to the prolonged use of immunosuppressive therapy. Most studies have described more cases of Immune Thrombocytopenic Purpura relapses than of Autoimmune Hemolytic Anemia, and was also harder to manage (Wang, 1988; Mathew, et al. 1997). Roughly 70% of children require a form of second-line therapy, and 10% expired by the age of 14.3 years old (Aladjidi, et al. 2015). In this prospective cohort study involving 156 pediatric cases of Evans Syndrome between 1981 and 2014, Evan Syndrome was secondary in 10% of cases, and remained primary, without any immune manifestations identified during the entire follow-up, in 30% of cases. 60% were revealed to have an association with other immune manifestations such as lymphoproliferation, other autoimmune diseases, and hypogammaglobulinemia. After a 5-year follow up period, Immune Thrombocytopenic relapse-free survival was 25%, and 61% for Autoimmune Hemolytic Anemia. 30 % of the mortalities were disease-related (cerebral or gastrointestinal hemorrhages), while 70% of the cause of deaths were all infectious in origin.

According to several studies, rarely do patients with SLE achieve long periods of drug free remission, and an active disease requiring chronic use of immunosuppressive treatment commonly persists. Unfortunately, younger patients with SLE have a more serious course of disease than of the adult-onset type. For over the 20 years, mortality rates have significantly decreased, with 10-15-year survival exceeding 85%. The most common causes of mortality are secondary to infection, end-stage renal disease, and cardiovascular disease. However, the longer the survival of the patients, the more likely it is to develop life-threatening co-morbidities including premature atherosclerosis, and myocardial infarction. There is also increased risk for malignancy in SLE, particularly lymphoma.

CONCLUSION

The authors have reviewed the clinical and laboratory characteristics of Evans syndrome and the possible pathophysiologies proposed. Evans Syndrome remains to be a diagnosis of exclusion, and a careful history will aid in the correct diagnosis of the cause of cytopenias. ES can be secondary in 10% of cases, and had been reported in SLE in 1.7-2.7% of cases, as with the present case. The authors have discussed the treatment regimens available; however, the lack of large patient evidences and the scarcity of randomized-controlled trials make it challenging to formulate evidence-based recommendations about the optimal management of these patients. Current data available suggests the role of corticosteroids with or without IVIG as first-line therapy. Second-line therapy, whether in the form of single modality or, for more aggressive cases, multiple immunosuppressive treatments will usually be required. Furthermore, alternative treatments should be selected on a case-by-case basis, taking into account the presence of underlying disorders and the previous treatment response.

Long-term outcome consists of several periods of relapse and remission requiring recurrent hospital admissions. SLE will definitely interfere with many aspects of the patient's daily life, with reportedly more than one third had a negative impact on the patient's education. Coping with the diagnosis of a lifelong, unpredictable, and aggressive course of disease in the adolescence is challenging for SLE patients, thus, awareness of their specific needs is key for optimal outcome.

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