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EVANS SYNDROME

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Abstract

Evans' syndrome is a rare autoimmune disorder in which the body makes antibodies that destroy the red blood cells, platelets and white blood cells. Patients are diagnosed with thrombocytopenia and Coombs' positive haemolytic anaemia and have no other known underlying aetiology. We report two cases of autoimmune haemolytic anaemia (AIHA) associated with immune thrombocytopenia which is known as Evans's syndrome. In these patient there were clinical evidence of haemolysis, serum bilirubin was elevated, blood film showed anaemia with trrombocytopenia but no spherocytosis. Immunosuppression was achieved with steroid. We would like to highlight that a negative Coomb's test is now often interpreted as absence of autoantibodies, but it is more or less preclusive for the diagnosis of AIHA.

Keyword: *Evan's Syndrome, autoimmune haemolytic anaemia*

Introduction

This combination of autoimmune haemolytic anaemia and idiopathic thrombocytopenic purpura is rare. It was first described by Evans and his associates (1951).[1] The patients may be affected by low levels of all three types of blood cells at one time, or may only have problems with one or two of them. The specific cause for Evans syndrome is unknown and it has been speculated that for every case the cause may be different.

There have been no genetic links identified. The course of Evans syndrome varies by case. The patient may be symptomatic of whatever blood levels are down. If the red blood cells are down, the problems complained of may be weakness, fatigue, shortness of breath and the usual things associated with anaemia. With low platelets, they are susceptible to bleeding and major bruising from minor bumps and cuts. With low white blood cells, the patient has increased susceptibility to infections and difficulty in fighting these infections. The patient may have problems with one, two or all three of these blood lines, at one time. The laboratory findings, including those on bone marrow aspirate and study, are compatible with haemolytic anaemia. Idiopathic thrombocytopenia with the presence of antiplatelet antibodies was also diagnosed. Serological evidence of autoimmune haemolytic anaemia (AIHA) is generally obtained by a direct Coomb's test (DCT). With few exceptions, a positive DCT is indicative for the presence of autoantibodies, however, DCT-negative AIHA is suspected to constitute up to 5% of all AIHAs.[2] Immune mediated haemolysis can be confirmed by fluorescent activated cell sorter (FACS) analysis using anti-human IgG or IgM immuno-globulin.[3]

Case Report

Case 1

A 40 years old, previously healthy female, presented to us with progressive pallor, passage of mustard oil coloured urine and generalized weakness. She had a history of fever of 5 days duration, one month back, associated with severe pallor and generalized weakness. At that time 7 units of blood was transfused and her fever subsided by antipyretic medication. But, she again developed generalized weakness with severe pallor and passage of mustard

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coloured urine; not associated with fever this time and she got admitted into our institution. On examination, she was severely anaemic, mildly icteric. She was hemodynamically stable and there was no bony tenderness, no skin rash, lymphadenopathy & any other positive clinical findings. Per abdominal examination revealed no organomegaly.

Sequential investigation on several occasions showed that her haemoglobin was persistently low ranging from 3.6 gm/dl to 6.1 gm/dl. Complete blood count revealed raised WBC count ranging from 16000/mm^3 to 60000/mm^3 with predominant neutrophils and there was no atypical cell. Platelet count was reduced, 20000 to 120000/mm^3. Her reticulocyte count was increased upto 15% and ESR was persistently raised upto 160 mm in 1st hour. On several occasions her PBF showed, mild to moderate anisochromia, anisocytosis with few elliptocyte, macrocyte and occasional normoblasts; WBC are mature and Platelets are grossly reduced in number. Bone marrow study revealed, hypercellular marrow, with reduced Myeloid/Erythroid ratio. Erythropoiesis was hyperactive & mild megaloblastic change, Granulopoiesis was active & mature to segmented form, Megakaryocytes were prominent & mature. USG of whole abdomen showed mild hepatosplenomegaly. Chest X-Ray was normal. ICT for malaria was negative. Urine examination revealed no abnormality. Her serum creatinine was 1.0 mg/dl, serum bilirubin was raised – 2.3 mg/dl. Both direct & indirect Coomb's test was negative. Anti Nuclear Antibody (ANA) was also negative.

Case 2

A 19 year old female presented with the complaints of progressively increasing yellowish coloration of skin, sclera and mucous membrane and passage of high colored urine for last 5 month associated with loss of appetite and weight loss. For the last 2 months she had developed generalized weakness, gradually increasing pallor and low-grade fever frequently occurring at night. She denied any history of abdominal pain, exertional breathlessness from childhood, bleeding from any site, rash or joint pain. There was also no history of cough or alternation of bowel habit but she gave history of contact with tuberculosis patient. She was a normally menstruating woman. She received 7 units of blood transfusion prior to admission in our hospital. There was no history of consanguinity between her parents.

Physical examination revealed she was severely anemic, mildly icteric and she had generalized lymphadenopathy, hepatosplenomegaly. Her complete blood count showed hemoglobin 2.8 gm/dL, ESR 150 mm in 1st hour, total platelet count 1,20,000/mm^3. Peripheral blood film showed bicytopemia (anemia with thrombocytopenia) and reticulocyte count 30%. Bone marrow study revealed erythroid hyperplasia with megakaryopoiesis. Direct Coomb's test was positive. Other biochemical parameters were within normal limit except serum bilirubin level which was 2.0 mg/dL. Antinuclear antibody (ANA) was negative. Her Mantoux test also returned negative. Chest X-ray was normal while ultrasonogram of whole abdomen revealed hepatosplenomegaly.

Discussion

Evans and associates (1951), considered a common aetiology of the two diseases, Autoimmune haemolytic anemia (AHA) and Idiopathic thrombocytopenic purpura (ITP) based on an immune mechanism because of similarity of behavior with or without splenectomy. The criteria for a diagnosis of Evans syndrome, according to Pui (1980) have been (1) hemolytic anemia with a positive direct Coombs test, (2) thrombocytopenia occurring either simultaneously or in succession, and (3) the absence of any known underlying aetiology.[1] In this case, the direct Coombs test was negative, the total bilirubin was increased and the other laboratory findings, including those on bone marrow aspirate, were compatible with hemolytic anemia and there was also thrombocytopenia. There was no evidence of underlying disease which might be appearing as acquired hemolytic anemia and thrombocytopenic purpura.

The main differentials of this syndrome in which AHA and ITP are found combined, includes the conditions where it may occur secondarily to an underlying disease: most frequently leukaemia and other lymphoproliferative disorders, SLE, scleroderma, mixed connective tissue disease, Hashimoto thyroiditis, haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura, cirrhosis of the liver, sarcoidosis, and amyloidosis. In adults, an underlying cause can be expected in about 70% of the cases of this syndrome. In our cases, the blood film excludes the leukaemias. SLE,

scleroderma and mixed connective tissue disease were excluded clinically and by negative ANA test. There were no history and clinical features suggestive of haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura. There were no features of cirrhosis of the liver, sarcoidosis, and amyloidosis. AHA and thrombocytopenia were found combined at the time in these cases, but the two diseases are not always present simultaneously. Development of thrombocytopenic purpura after the development of AHA were described in most of the studies but the reverse relation, had also been reported.[1]

In AHA the erythrocyte damage are mediated by the two major classes of antibody (IgG and IgM). Another mechanism is destruction of IgM-complement coated erythrocytes by cells of the reticuloendothelial system. In AHA, the hemolysis usually occurs extravascularly and this depends upon antibody concentration. Intravascular hemolysis is more likely to occur at high concentrations of the sensitizing antibody. Lysis usually results from phagocytosis of RBC by the reticuloendothelial cells of the liver and spleen. The liver functions as a 'coarse filter' for the removal of IgM-complement-coated erythrocytes and the spleen functions as a 'fine filter" and removes IgG-coated erythrocytes.[1]

The pathophysiology of thrombocytopenia has not as yet been established. In many cases of idiopathic thrombocytopenia IgG antiplatelet antibody was demonstrated on circulating platelets as well as in the serum and two distinct antibodies, one directed against platelets and the other against red cells were also reported.[4]

The etiology of Evans syndrome remains unknown. Many patients have associated disorders eg, systemic lupus erythematosus (SLE) and other autoimmune diseases, chronic lymphadenopathy, hypogammaglobulinemia, sex-linked agammaglobulinemia, common variable immunodeficiency, and IgA deficiency. One prior report of autoimmune hemolytic anemia and immune thrombocytopenia has been described in DiGeorge syndrome indicating there may be association between the 22q11.2 deletion spectrum and Evans syndrome.[5] Rarely it follows the use of certain drugs, such as D-penicillamine.[6]

Evans syndrome is a diagnosis of exclusion. Confounding disorders, such as infections, rheumatologic diseases, and malignancies can present with autoimmune cytopenias, and must be ruled out. Patient may present with signs of thrombocytopenia including purpura, petechiae, and ecchymoses and signs of anemia include pallor, fatigue, and light-headedness. Jaundice may indicate hemolysis.[1]

Laboratory studies show increased reticulocyte count along with anemia, thrombocytopenia, neutropenia, or combined cytopenias. Features of hemolysis include a raised reticulocyte count, increase in unconjugated bilirubin, and decreased haptoglobins. Bone marrow studies may reveal erythroid hyperplasia and, occasionally, hypoplasia if AIHA is the predominant finding. Normal levels or increased numbers of megakaryocytes confirm that thrombocytopenia is caused by increased destruction in the blood. Evans syndrome patients had decreased T4 (T-helper), increased T8 (T suppressor), and a decreased ratio of T4:T8 cells. Serum IgG, IgM, and IgA levels were decreased in most Evans syndrome patients.[7]

In Evans syndrome, the direct Coombs test result is almost invariably positive (often weakly) and may be positive for IgG, complement, or both. Indirect antiglobulin test findings may also be positive in some of the patients. However, DAT-negative AIHA should be suspected in all AIHAs with features of hemolysis. Several possible mechanisms can explain it, which includes sensitisation by a small amount of IgG that falls below the detection threshold and both IgA and IgM antibodies remain undetected by polyspeciûc antiglobulin reagents A highly sensitive gel technique can be introduced to overcome these problems.[2]

Direct Coombs-negative AIHA is characterized by negative Coomb's test performed by conventional tube technique (CTT) along with laboratory evidence of in vivo hemolysis, in clinically suspected AIHA patients. The immunoradiometric assay (IRMA) for red blood-cell-bound immunoglobulin G (RBC-IgG) can be used to diagnose these patients in whom CTT does not detect low levels of red cell autoantibodies.[8] Various antibodies directed against RBCs and platelets (eg, antierythrocyte, antineutrophil, antiplatelet antibodies) occur in association with Evans syndrome.[9]

The management of Evans syndrome is challenging. Although almost all patients require therapy at some

time during the course of the disease, the search for a consistent, effective, and nontoxic therapy continues. Medical therapy continues to be the mainstay. Response to therapy varies even within the same individual, and the disease is characterized by periods of remission and exacerbation. No randomized trials have been conducted in patients with Evans syndrome, and the evidence for treatment is based on case reports, case series, and retrospective studies. In an acute setting, blood transfusions and/or platelet transfusions may be required to alleviate symptoms, although their use should be minimized.

The most commonly used first-line therapy is steroid (prednisolone), for Evans syndrome but relapses may be frequent when patients are weaned off prednisone.[1] Additional treatment modalities include intravenous immunoglobulin (IVIG), vincristine, cyclophosphsmide, azathioprine for the steroid-resistant or relapsing cases.[10] Danazol is effective for the treatment of refractory Evans' syndrome.[11] However, these treatment options may be associated with serious side effects and are often unsuccessful.

Rituximab a chimeric monoclonal antibody against CD20 that depletes B cells in the circulation and in lymphoid tissues, has shown efficacy and was approved for the treatment of B-cell lymphomas. This drug has emerged as a promising treatment for idiopathic thrombocytopenic purpura and autoimmune hemolytic anemia (AIHA), including Evans syndrome. Rituximab should be used early in the treatment of Evans as a reasonable treatment option, if the syndrome is refractory to steroid treatment.[10]

Additional therapies include splenectomy. The splenectomy has markedly reduced the sequestration and clearance of the IgG-coated erythrocytes but splenectomized patients were unable to maintain a steroid-free remission and the majority have become steroid dependent or refractory. '6-Mercaptopurine' ('6-MP') can be used among patients who failed to respond adequately to corticosteroid therapy, after splenectomy.[1] Treatment with cyclosporine A can provide an effective therapeutic choice for refractory Evans syndrome.[12] The regimen of alternate-day cyclosporine and prednisone may prove to be useful in the treatment of other patients with refractory Evans syndrome.[13] In case of frequent relapse after splenectomy, treatment with combination agents (IVIG, steroids, vinca alkaloids, androgens and possibly cyclosporin) may provide a useful therapeutic approach to patients with Evans syndrome.[14] In our cases immunosupression was achived with prednisolone.

Evans' syndrome is a heterogeneous disorder which has significant morbidity and mortality and there is high incidence of quantitative serum immunoglobulin abnormalities, lymphoid hyperplasia, and associated systemic manifestations indicating that Evans' syndrome may represent a stage of a more broad spectrum, generalised immune dysregulation.[15] The prognosis in Evans syndrome is grave, because of ineffective treatment and frequent relapse rates.[1]

Conclusion

In conclusion, Evans syndrome is a chronic and recurrent condition which is often refractory to corticosteroids, IVIG and splenectomy. Responses to other agents have been anecdotal and inconclusive. For the early diagnosis of the disease the direct Coomb's test must be interpreted in conjunction with clinical and other laboratory data to avoid erroneous conclusions; as it can be false-negative. Elution of RBC antibodies is a valid additional procedure to clarify whether autoantibodies are present in Coomb's-negative patients. Besides the detection of autoantibodies, alloantibodies because of RBC transfusions may be detectable in the early stages of immunization. An early diagnosis & prompt treatment can save the patient from life threatening condition of intense haemolysis.

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