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A Case of Evans Syndrome, Successfully Treated with 6-Mercaptopurine

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A pediatric patient with combined primary thrombocytopenic purpura and acquired hemolytic anemia (Evans syndrome), whose condition did not respond to treatment with prednisolone, has enjoyed long-term remission following a period of treatment with 6-Mercaptopurine.

Key Words: Evans syndrome, 6-Mercaptopurine

This combination of autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura is rare in childhood, and treatment has been generally unsatisfactory. It was first described as it was seen in 8 adult patients by Evans and his associates (1951), and since then many other cases seen in adults have been reported, the illness of these patients having progressed gradually as terminal illness. The first were treated with splenectomies and blood transfusions, but not very successfully. Later, corticosteroids were added to these treatment methods in use, with good results, and yet later, when it was demonstrated that immunosuppressive agents could be helpful in treating this syndrome, they were added as another method of treatment.

A CASE REPORT

A 6-year-old boy was admitted to the hospital in November 1984 with a five-day history of increasing weakness, lassitude, fever, and palpitation. Immediately before admission he had developed vomiting and diarrhea. There was no relevant past or family history, and no history of blood transfusion or exposure to drugs or poisons.

On physical examination the patient was alert. The temperature was 36.7°C, the pulse 110, and respirations 44. The body weight was 23 Kg (97 percentile) and height 114 cm (90 percentile). The skin was pale, there was neither abnormal rash nor were there any petechiae. The conjunctiva was pale, and scleral icterus was noted. There were multiple petechiae on the hard palate. No abnormal enlarged lymph node was palpable on the neck. The lungs were clear, and the heart was normal. The abdomen was not distended, and the liver was palpable to 1 cm below the right costal margin. The spleen was not palpable.

The hemoglobin was 5.7 gm/dl; hematocrit, 16.8%; MCV, 86.8 μm^3; MCH, 29.5 pg; MCHC, 34.1 gm/dl, white cell count, 11,500, differential, normal; and the RDW (red cell distribution width), 29.5 (markedly increased). There was no gross hematuria, but 3-5/HPF RBC were detected. The total bilirubin was 3.4 mg/dl (the direct bilirubin, 0.5 mg/dl). The prothrombin time was 12.0 sec (100%), and the partial thromboplastin time, 25.9 sec (normal range: 20-30 sec). The direct Coombs test was negative, but the antibody screening test for the RBC was positive. The antiplatelet antibody level was positive.

On peripheral blood smear, there was markedly aniso-poikilocytosis with fragment cells. The reticulocytes were increased (corrected, 12%). The platelet count was 20,000 (Fig. 1).

Bone marrow examination showed a hypercellular marrow with erythroid hyperplasia (the myeloid/erythroid ratio was 1:1.1). The number of megakaryocytes were increased. The iron particles were adequate, and no leukemic cell was observed (Fig. 2).

Autoimmune hemolytic anemia with idiopathic thrombocytopenia (Evans syndrome) was diagnosed, and treatment with prednisolone (50 mg/day) was started, within two weeks of which time the peripheral

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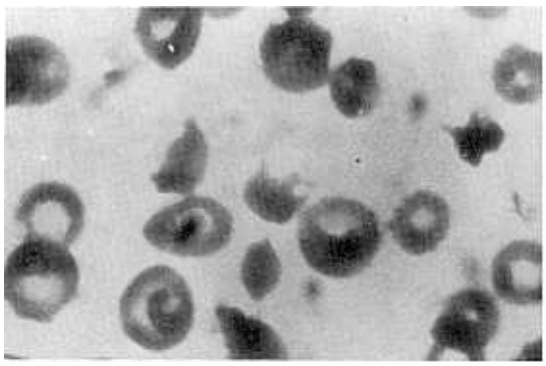

Fig. 1. Peripheral blood smear on admission shows marked aniso-poikilocytosis with fragment cells. Also shows decrease in number of platelets (Wright-Giemsa × 1,000)

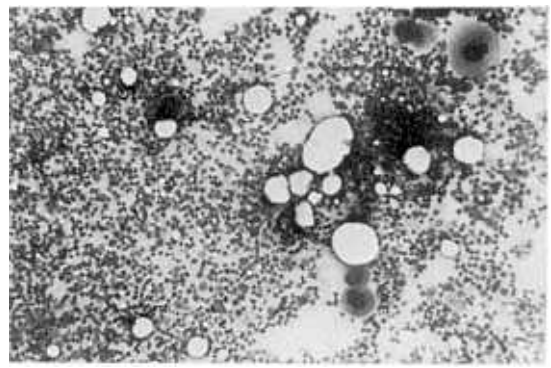

Fig. 2. Bone marrow aspirate smear on admission reveals hypercellularity with erythroid hyperplasia. There are an increased number of megakaryocytes (Wright-Giemsa × 100).

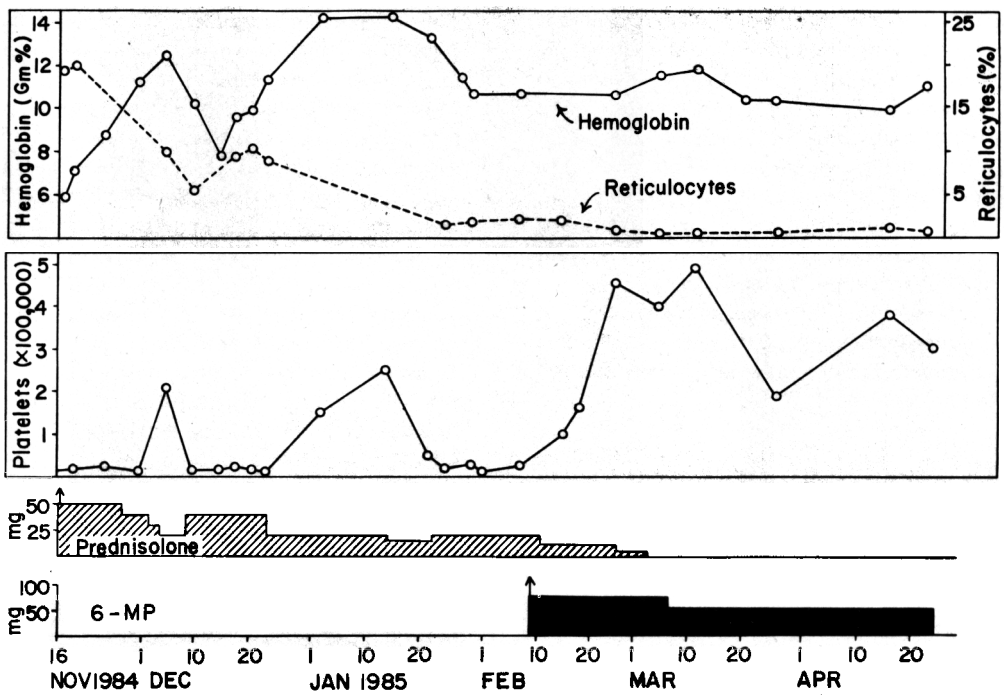

Fig. 3. Failure to respond to prednisolone with subsequent excellent remission on 6-Mercaptopurine.

blood picture returned to normal (Fig. 3).

However, when an attempt was made to reduce the steroid dosage, there was a severe excerbation of the thrombocytopenia, the number of platelets dropping to 18,000. When the effective dosage of prednisolone was re-instituted, the peripheral blood picture returned to normal. This took place repeatedly; each attempt to reduce the dosage of the steroid failed.

In February 1985, treatment with 6-Mercaptopurine

(75 mg/day) was started, and during the next three weeks the dosage of prednisolone was gradually reduced until it was discontinued. The peripheral blood picture remained normal. The dosage of 6-Mercaptopurine was successfully reduced (to 50 mg/day) and long term remission was achieved.

DISCUSSION

Evans and associates (1951) considered the two diseases, in all of the cases, to have a common etiology based on an immune mechanism because of similarity of behavior with or without splenectomy.

Several of a large number of cases of idiopathic thrombocytopenic purpura (ITP) in childhood have been reported, involving a combined total of 1,064 patients (Walker 1961; McClure 1975; Cohn 1976; Simons 1975). Only nine of these had autoimmune hemolytic anemia (AHA) associated with the ITP (0.85%). On the other hand, in adult patients, thrombocytopenia and AHA occur relatively frequently in combination. In adult series frequencies of 1.6 to 59.4% have been reported (Dausset 1959; Fagiolo 1976; Allgood 1967).

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 etiology. In this case, the direct Coombs test was negative, but the antibody screening test was positive, and the total bilirubin was increased. The laboratory findings, including those on bone marrow aspirate, were compatible with hemolytic anemia. Idiopathic thrombocytopenia with the presence of antiplatelet antibodies was also diagnosed. There was no evidence of underlying disease which might be appearing as acquired hemolytic anemia and thrombocytopenic purpura.

This syndrome in which AHA and ITP are found combined may occur secondarily to an underlying disease: most frequently leukemia, SLE, scleroderma, mixed connective tissue disease, Hashimoto thyroiditis, thrombotic thrombocytopenic purpura, cirrhosis of the liver, lymphoma, sarcoidosis, and amyloidosis. In adults, an underlying cause can be expected in about 70% of the cases of this syndrome (Silverstein 1966). In one report among 11 pediatric patients with AHA with ITP, three had SLE, and one had aplastic anemia (36% of the cases had an underlying etiology [Pui 1980]).

In this case, AHA and thrombocytopenia were found combined at the time of the initial diagnosis, but the two diseases are not always present simultaneously. Most studies describe thrombocytopenic purpura as occurring after the development of AHA. The reverse relation, that is, hemolytic anemia occurring in patients after ITP, has also been reported (Silverstein 1966).

The pathophysiology of erythrocyte damage in AHA, the two major classes of antibody (IgG and IgM) were mediated. IgG-coated erythrocytes or $C_{\overline{3b}}$. Another mechanism is one in which IgM-complement-coated erythrocytes were destroyed by cells of the reticuloendothelial system (Frank 1977). In AHA, the hemolysis usually occurs extravascularly rather than intravascularly. This, in part, depends upon antibody concentration; however, at high concentrations of the sensitizing antibody, intravascular hemolysis is more likely to occur. More commonly, lysis results from phagocytosis by the reticuloendothelial cells of the liver and spleen. The reticuloendothelial system of the liver functions as a 'coarse filter' for the removal of IgM-complement-coated erythrocytes. The spleen seems to function as a 'fine filter', removing IgG-coated erythrocytes (Frank 1977).

In this case, the antibody screening test for the RBC was positive. Because of pan-agglutination, the specific type of antibody (IgG or IgM) was not determined.

The pathophysiology of thrombocytopenia has not as yet been established. In many cases of idiopathic thrombocytopenia, not all, an increase in the number of antiplatelet antibodies can be detected (Nel 1983).

The treatment of Evans syndrome includes splenectomy and the use of steroids and immunosuppressive agents, but the result is unsatisfactory.

Although chronic ITP and chronic AHA, respectively, have 70% and 50% sustained remission rates following splenectomy, this procedure seldom results in prolonged, complete remission in patients with Evans syndrome. Pui and his colleagues (1980) have described the clinical course before and after splenectomy. According to their report, there was a beneficial effect from the procedure; however, none of splenectomized patients was able to maintain a steroid-free remission.

The response to treatment with steroids after splenectomy in AHA patients has been poor. Although steroid therapy has resulted in a transient remission in most patients who have failed to respond to splenectomy, the majority have become steroid-dependent or refractory (Allgood 1967). The splenectomy has markedly reduced the sequestration and clearance of the IgG-coated erythrocytes. However, as the antibody concentration has increased, splenec-

tomy has become less effective. The splenectomy, also, has not affected the clearance of IgM-coated cells because IgM-complement-coated erythrocytes are normally removed by the liver (Frank 1977). Steroids have decreased the production of anti-erythrocyte antibodies and inhibited the clearance of antibody-coated erythrocytes by fixed macrophages in the spleen or liver.

Schwartz (1962) treated fourteen patients with AHA with either '6-Mercaptopurine' ('6-MP') or thioguanine. Among nine patients who failed to respond adequately to corticosteroid therapy, four had a good effect from antimetabolite therapy. They could reduce the dosage of steroids and diminish the side effects of steroids. Bouroncle (1966) achieved good results in the treatment of ITP with azathioprine (Imuran). Richmond *et al.* (1963) reported a case in which a fulminating hemolytic anemia and thrombocytopenia developed some time after splenectomy for ITP. Large doses of steroids were ineffective and thymic irradiation produced only transitory improvement. The thrombocytopenia and anemia were finally controlled by Imuran and actinomycin D. Tattersall (1967) reported a case of Evans syndrome treated with a maintenance dosage of 6-MP and prednisone.

There are two kinds of immunosuppressive agents which can be used for the treatment of Evans syndrome, as antimetabolites and alkylating agents. They prevent antibody formatioon in response to primary antigenic stimulation (Frank 1977). Azathioprine (Imuran) has a less toxic and highly immunosuppressive effect than 6-MP. Since determining the dosage of 6-MP is difficult, because of possible side effects in the gastrointestinal tract or hematologic system, Bouroncle (1966) have recommended the use of Azathioprine (Imuran) rather than 6-MP.

In this case, high dose of a corticosteroid temporarily controlled the thrombocytopenia but a relapse of thrombocytopenia was occurred. Thereafter, he was treated with the dosage of 6-MP and long term remission was achieved with practically no toxic effects resulting.

The prognosis in AHA is, in general, good: only about 10% of the patients die in childhood and death is never caused by the anemia (Zupanska 1976), the prognosis in Evans syndrome is grave, because of ineffective treatment and frequent relapse rates. In a study carried out by Matthews (1965) among the patients with AHA, 71% with thrombocytopenia died, compared to 31% of patients without thrombocytopenia.

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