CASE REPORT

PROLONGED REMISSION AFTER SPLENECTOMY FOR REFRACTORY EVANS SYNDROME – A CASE REPORT AND LITERATURE REVIEW

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Abstract. We describe a patient with Evans syndrome (autoimmune hemolytic anemia and autoimmune thrombocytopenia) who was refractory to steroids and intravenous immunoglobulin. She responded to splenectomy and has remained in clinical remission for 3 years. In the majority of cases, splenectomy rarely induces a durable remission but it may be beneficial in a small group of patients, hence should be considered as alternative therapy in the management of these patients.

INTRODUCTION

Evans syndrome is a rare entity in children. It is defined by the presence of combined autoimmune thrombocytopenia and direct Coombs' positive hemolytic anemia in the absence of a known underlying etiology (Wang, 1988). The time of onset, course, duration and severity of anemia and thrombocytopenia are variable amongst patients. The first series of children with Evans syndrome was described previously (Pui *et al*, 1980). Evans syndrome usually has a chronic, relapsing course with episodes of thrombocytopenia and hemolysis that are refractory to multiple modes of treatments (Pui *et al*, 1980; Wang, 1988). The role of splenectomy in Evans syndrome has never been clearly established. The duration of response to splenectomy is transient, and almost all relapse after splenectomy (Scaradarou and Bussel, 1995). Here, we report a patient with Evans syndrome who underwent splenectomy after treatment failure with corticosteroids and intravenous immunoglobulin (IVIG). She has remained in clinical remission 3 years post-splenectomy.

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CASE REPORT

A 15-year-old girl first presented with Coombs' positive hemolytic anemia in September 1998 at age 10 years. The initial investigations revealed a white cell count of 7.0 x 10^9/l, hemoglobin of 5.1 g/dl, platelets of 147 x 10^9/l and reticulocyte count of 20%. The G6PD status was normal and connective tissue disease screening was negative. She received several red blood cell (RBC) transfusions and was started on prednisone 3 months later after recurrence of autoimmune hemolytic anemia (AIHA) and showed a good response. However, she had another recurrence of AIHA in February 1999, 1 month after stopping the drug. In March 1999, she developed another episode of AIHA while on a low dose of prednisone (0.25 mg/kg/day) in which thrombocytopenia was also present. This time with a platelet count of 79 x 10^9/l; a bone marrow examination showed increased megakaryocytes indicating peripheral destruction of platelets. A diagnosis of Evans syndrome was made. She required prednisone and occasional RBC transfusions between March 1999 and May 2000. Episodes of acute hemolysis occured whenever she was on a low dose of

prednisone. She developed marked steroid toxicity with Cushingoid features and hypertension in May 2000. IVIG, 2 g/kg was given in June 2000, after which the hemoglobin level normalized, but the platelet count rose marginally. She was restarted on prednisone 2 mg/kg/day 1 week post IVIG infusion. The platelet count rose to normal levels for 1 month. She then remained prednisone-dependent. In September 2000, the platelet count dropped to 5,000 when she was on low dose prednisone. She received another dose of 2 g/kg IVIG to no avail. No immunosuppresive agent was given as the parents refused. A splenectomy was adviced as she had developed steroid toxicity and a poor response to IVIG. Splenectomy was performed in October 2001. The platelet count has remained normal since then. She had no episodes of infection while being on prolonged steroids and after splenectomy.

DISCUSSION

Patients with Evans syndrome often show poor responses to several treatment modalities. This is in contrast to patients with either idiopathic thrombocytopenia (ITP) or AIHA, which respond well to standard therapy, such as steroids, IVIG or splenectomy (Beardley, 1993; Schreiber *et al*, 1993). Autoantibodies directed against antigens specific to red cells and platelets have been reported in the pathogenesis, however they do not cross-react (Pegels *et al*, 1982). Decreased synthesis of IgG and/or IgM *in vitro* and decreased serum IgG, IgM and IgA levels in Evans syndrome have been reported. T-cell abnormalities may be involved in the pathophysiology, but this is yet to be fully explored. Neutropenia has also been observed in some patients (Pui *et al*, 1980). Evans syndrome can also occur in association with lymphoproliferative disorders (*eg* chronic lymphocytic leukemia), autoimmune disease (*eg* systemic lupus erythematosus) or medication (Shvidel *et al*, 1997).

There is no established optimal treatment for Evans syndrome. Standard treatment consists of transfusions, corticosteroids, splenectomy, IVIG, anabolic steroids, vincristine, alkylating agents, or cyclosporine. The majority of children with Evans syndrome require combination treatment to control their disease (Mathew *et al*, 1997). Recently, treatment with allogenic stem cell transplantation using matched sibling bone marrow (Oyama *et al*, 2001), matched sibling umbilical cord blood (Raetz *et al*, 1997), or matched unrelated bone marrow (De Stefano *et al*, 1999) may also give encouraging results, although follow-up has been limited. Most centers use corticosteroids as initial therapy, although effect of corticosteroids has not been established in controlled trials. Corticosteroid treatment results in a transient remission in most patients, but the majority of them became steroid dependent or refractory (Allgood and Chaplin, 1967). Our patient had a good response to steroids but later became steroid-dependent and developed steroid toxicity.

IVIG lacks substantial proof in the treatment of Evans syndrome. Few anecdotal reports describe the beneficial use of high dose IVIG in patients who have not responded to corticosteroids or splenectomy (Oda *et al*, 1985; Nuss and Wang, 1987). Our patient had no rapid improvement in the platelet count with IVIG, but the level normalized after prednisone was resumed 1 week post-IVIG. We believe she responded to the prednisone rather than the IVIG.

Splenectomy has been shown to be beneficial in some patients who fail steroid therapy. However, prolonged complete remission after splenectomy is seldom achieved in Evans syndrome. Five patients have been described to have beneficial effects from the procedure (Pui *et al,* 1980). However, remissions lasted only 1 to 2 months without corticostreroids support in 4 patients, and 1 patient relapsed while tapering off the steroid after 5 months of remission post-splenectomy. Other reports give varying durations of response (increase in hemoglobin and/or platelets) to splenectomy, from 1 week to 5 years, with a median of 1 month in 15 patients who underwent splenectomy (Mathew *et al*, 1997). The indications for splenectomy were thrombocytopenia in 6 patients, hemolytic anemia in 5, and both conditions in 4. Seven patients had increased platelet counts, but only 2 patients had normalized platelet counts. One patient had no response. Only 1 patient had a normal hemoglobin level among 6 patients who

had increased hemoglobin levels. Another report describes two patients with short-lived responses (<1 month) after splenectomy performed for ITP and AIHA, respectively (Scaradarou and Bussel, 1995). They required other forms of treatment. A 4-month-old girl was reported to have a satisfactory response to corticosteroids and RBC transfusions but became steroid-dependent and failed to respond to IVIG, thymectomy and cyclophosphamide. Splenectomy was perfomed at the age of 2 years 3 months, and a complete response without steroids or transfusions was achieved for 7 years. In another report, a 5-year-old boy with severe Evans snydrome who underwent splenectomy at the age of 9 months only had a transient rise in his platelet count to greater than 100 x 10^9/l before rapidly falling to below 20 x 10^9/l (Raetz *et al*, 1997). A partial response in 2 out of 3 patients after splenectomy was performed has also been reported. Recently, 2 patients were reported to have normal platelet counts at mean follow-up of 18 months after laparoscopic splenectomy without any medical therapy (Duperier *et al*, 2003).

In summary, although complete resolution may be achieved in some patients, splenectomy appears to have limited value in the treatment of some patients with Evans syndrome and the procedure should be undertaken cautiously in view of the added risk of post-splenectomy sepsis in association with neutropenia and/or hypogamaglobulinemia. This case which did respond illustrats a sustained remission post-splenectomy.

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