Splenectomy for refractory Evans’ syndrome associated with antiphospholipid antibodies: report of two cases

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Abstract

The antiphospholipid syndrome (APS) is characterised by arterial/venous thrombosis, recurrent pregnancy loss, or thrombocytopenia in the presence of antiphospholipid antibodies (aPL). These antibodies are identified as lupus anticoagulant, which prolongs phospholipid dependent coagulation tests, or as anticardiolipin antibodies (aCL) detected by immunoassays. This entity, first described by Hughes in 1983 in patients with systemic lupus erythematosus (SLE), may appear in patients with no underlying disease—the “primary” APS.

There are well documented associations between aPL and abnormalities of specific cellular components of the blood, such as thrombocytopenia, haemolytic anaemia, and, less commonly, leucopenia. Thrombocytopenia is usually mild or benign (70–120×10^9/l), rarely associated with bleeding complications, and, generally, does not require treatment. Moreover, some authors have shown that haemolytic anaemia and Coombs positivity is also associated with aPL, and in some patients with primary APS, both thrombocytopenia and haemolytic anaemia may occur together.

We describe two patients with severe aPL associated cytopenias (haemolytic anaemia and thrombocytopenia) who required splenectomy after being refractory to steroids, immunosuppressive agents, and other treatments (intravenous gammaglobulin, danazol), and previously reported cases are reviewed.

CASE 1

The patient, a 32 year old woman, was admitted to our hospital because of haemolytic anaemia and thrombocytopenia that could not be controlled with drugs. When she was 30 the patient had presented polyarthralgias and spontaneous smooth bleeding. The laboratory variables showed leucopenia (2×10^9/l), normochromic anaemia (haemoglobin 90 g/l) with a positive Coombs test and a platelet count of 30×10^9/l. An immunological profile showed negative antinuclear antibodies. A bone marrow biopsy showed normal cellularity with an increased megakaryocyte count. The patient was diagnosed as having Evans’ syndrome, and treatment with prednisone (1 mg/kg/d) was started with an initial increase in the haematological values. In May 1992 the patient presented an acute respiratory infection, and the platelet count fell to below 50×10^9/l and the haemoglobin value under 80 g/l. High positive (+++) aCL of the IgM isotype were detected, and lupus anticoagulant was absent. Subsequently, the patient required several readmissions, most due to gastrointestinal or respiratory infections, with a coincidental severe decrease of the haemoglobin value and platelet count, and IgM aCL remained positive at high titre (+++). During this time the patient received different treatments with high doses of steroids, immunosuppressive treatments (oral cyclophosphamide 50 mg/d, azathioprine 100 mg/d), and danazol, without response. In April 1995 the first dose of intravenous gammaglobulin was given. A total of five doses were given until June 1997, without response. Finally, splenectomy was performed in January 1998, with previous prophylactic antibiotics and vaccination, without postoperative complications. After splenectomy, the haemoglobin stabilised above 120 g/l and the platelet count above 500×10^9/l and the haemoglobin value under 80 g/l. The patient received diuretics and immunosuppressive treatment with prednisone (1 mg/kg/d) was started with an initial increase in the haematological values. In May 1992 the patient presented an acute respiratory infection, and the platelet count fell to below 50×10^9/l and the haemoglobin value under 80 g/l. High positive (+++) aCL of the IgM isotype were detected, and lupus anticoagulant was absent. Subsequently, the patient required several readmissions, most due to gastrointestinal or respiratory infections, with a coincidental severe decrease of the haemoglobin value and platelet count, and IgM aCL remained positive at high titre (+++). During this time the patient received different treatments with high doses of steroids, immunosuppressive treatments (oral cyclophosphamide 50 mg/d, azathioprine 100 mg/d), and danazol, without response. In April 1995 the first dose of intravenous gammaglobulin was given. A total of five doses were given until June 1997, without response. Finally, splenectomy was performed in January 1998, with previous prophylactic antibiotics and vaccination, without postoperative complications. After splenectomy, the haemoglobin stabilised above 120 g/l and the platelet count above 500×10^9/l. Two years later, the patient is doing well without haemorrhagic manifestations and with a normal haemoglobin value and platelet count (fig 1).

CASE 2

The patient, a 49 year old woman, was admitted to our hospital because of haemolytic anaemia and thrombocytopenia that could not be controlled with drugs. When she was 30 the patient had presented polyarthralgias and spontaneous smooth bleeding. The laboratory variables showed leucopenia (2×10^9/l), normochromic anaemia (haemoglobin 90 g/l) with a positive Coombs test and a platelet count of 30×10^9/l. An immunological profile showed negative antinuclear antibodies. A bone marrow biopsy showed normal cellularity with an increased megakaryocyte count. The patient was diagnosed as having Evans’ syndrome, and treatment with prednisone (1 mg/kg/d) was started with an initial increase in the haematological values. In May 1992 the patient presented an acute respiratory infection, and the platelet count fell to below 50×10^9/l and the haemoglobin value under 80 g/l. High positive (+++) aCL of the IgM isotype were detected, and lupus anticoagulant was absent. Subsequently, the patient required several readmissions, most due to gastrointestinal or respiratory infections, with a coincidental severe decrease of the haemoglobin value and platelet count, and IgM aCL remained positive at high titre (+++). During this time the patient received different treatments with high doses of steroids, immunosuppressive treatments (oral cyclophosphamide 50 mg/d, azathioprine 100 mg/d), and danazol, without response. In April 1995 the first dose of intravenous gammaglobulin was given. A total of five doses were given until June 1997, without response. Finally, splenectomy was performed in January 1998, with previous prophylactic antibiotics and vaccination, without postoperative complications. After splenectomy, the haemoglobin stabilised above 120 g/l and the platelet count above 500×10^9/l. Two years later, the patient is doing well without haemorrhagic manifestations and with a normal haemoglobin value and platelet count (fig 1).

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lupus-like syndrome, and treatment with prednisone (1 mg/kg/d) was started, with an initial increase in the haematological values. Subsequently, she developed several complications related to corticosteroid treatment—namely, diabetes mellitus, Cushing’s syndrome, and osteoporosis—and the haematological values began to fall. Treatment with immunosuppressive drugs (oral cyclophosphamide and azathioprine), danazol, and intravenous gammaglobulin was also added, without response. Finally, splenectomy was performed in December 1998 and, one year later the patient has a normal haemoglobin value and platelet count without treatment.

Discussion
The main haematological manifestations seen in patients with aPL are thrombocytopenia and haemolytic anaemia. The co-occurrence of...
both immune mediated cytopenias was originally described by Evans in 1949. This strong association of thrombocytopenia and haemolytic anaemia suggests the possibility of a common mechanism of increased cellular destruction. Antibodies are thought to bind to the surface of the platelets and erythrocytes and fix complement, and the resulting cellular immune complex is destroyed by the fixed macrophages of the reticuloendothelial system. There has been increasing interest in recent years in the precise nature of the antigenic targets to which aPL bind platelets or erythrocytes, or both.4,5

Thrombocytopenia appears in about one third of the patients with aPL. Cuadrado et al reported a prevalence of 23% in a series of 171 patients with APS, being severe (<50 x 10^9/l) only in six of them (18%).4 Rarely, this disorder requires treatment and, owing to shared characteristics with idiopathic thrombocytopenic purpura, similar treatment could be followed—that is, high dose corticosteroids, immunosuppressive or immunomodulating agents, and intravenous immunoglobulin treatment. When steroids or immunosuppressive agents are unsuccessful, splenectomy is usually performed to remove the major site of platelet destruction and antibody production. There is improvement in 70-90% of patients after splenectomy, and platelets are permanently restored to normal levels in at least two thirds of patients.10 Unfortunately, there are no clinical or analytical variables that adequately predict the response to splenectomy. Only the intensity of bleeding, age, and the immediate postoperative peak platelet count are weak predictors of outcome.11

Some authors have analysed the relation between the isotype of aCL and haemocytopenia and found a significant association between IgM aCL and haemolytic anaemia.13,14 Furthermore, a prospective study showed that the presence of IgM aCL is associated with the development of haemolytic anaemia in patients with SLE.15 Recommendations for the management of immune mediated haemolytic anaemia associated with high titre aPL are similar to those for immune mediated thrombocytopenia.4

Previous experience of the value of splenectomy in the treatment of aPL associated cytopenias is limited (table 1).16-21 In 1995 Bal-lerini et al described the first case, a patient with primary APS and severe thrombocytopenia treated unsuccessfully with steroids, who was finally treated with splenectomy, with a sustained and complete remission.20 More recently, two studies have focused on the response to splenectomy in patients with APS and refractory thrombocytopenia. Hakim et al reviewed the outcome of splenectomy in 12 patients with severe thrombocytopenia, three of them with primary APS.19 After splenectomy, complete remission of the thrombocytopenia occurred. There were no complications from the splenectomy, and the patients who received this treatment within one year of diagnosis of thrombocytopenia seemed to respond well. In another recent study Galindo et al analysed 55 patients with APS with thrombocytopenia (<100 x 10^9/l) and reported that splenectomy was required in 11 (20%) patients, nine with an APS associated with SLE and the other two with a primary APS.20 Postoperative complications were not reported in any patient, and all but two were responsive to splenectomy. The results obtained in the patients published, including our patients, support the usefulness of splenectomy in the treatment of refractory cytopenias associated with aPL, with a high rate of response after the follow up and no postoperative complications.

In conclusion, patients with aPL related haemocytopenias (thrombocytopenia or haemolytic anaemia, or both) often gain long term remission of refractory cytopenias after splenectomy, without exacerbation of their primary disease. Modern surgical techniques and the use of prophylactic antibiotics and vaccin-
tion have made splenectomy a safer option in patients who do not respond to classic treatments, such as corticosteroids.


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