Refractory Thrombocytopenia in Antiphospholipid Syndrome

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Abstract

Thrombocytopenia is the second most common manifestation of antiphospholipid syndrome (APS). It is found in ~22% of the patients with this disease. Often it is not severe, platelet counts usually range between 50 x 10⁹/L and 150 x 10⁹/L without bleeding problems. Yet, it does not protect patients against thrombotic events. It rarely requires treatment and, due to similarities to idiopathic thrombocytopenic purpura (ITP), similar treatment rules usually apply. In this report two patients with APS are described who presented with severe thrombocytopenia that did not respond to standard treatment regimen namely glucocorticoids (GC) followed by intravenous immunoglobulin therapy (IVIG). Splenectomy had to be resorted to relieve the condition.

INTRODUCTION

The antiphospholipid syndrome (APS) is characterized by arterial/venous thrombosis, recurrent pregnancy loss, or thrombocytopenia in the presence of antiphospholipid antibodies (aPL)1-2. These antibodies are identified as lupus anticoagulant, which prolongs phospholipid dependent coagulation tests, or as anticardiolipin antibodies (aCL) detected by immunoassays. This entity was first described in 1983 by Hughes in patients with systemic lupus erythematosus (SLE)2. Subsequently, the same syndrome was also seen in patients who did not have SLE or any other underlying connective tissue disease. The later category was labelled “primary APS” in contradistinction to that seen in SLE or other connective tissue diseases, which were then identified as “secondary APS”.

Haematological manifestations of APS are thrombocytopenia, haemolytic anaemia, Evans Syndrome and, less commonly, leucopenia1-2. Thrombocytopenia is the second most common manifestation of antiphospholipid syndrome (APS). It is found in ~22% of the patients with this disease. Often it is not severe, platelet counts usually range between 50 x 10⁹/L and 150 x 10⁹/L without bleeding problems. Yet, it does not protect patients against thrombotic events. It rarely requires treatment and, due to similarities to idiopathic thrombocytopenic purpura (ITP), similar treatment rules usually apply. In this report two patients with APS are described who presented with severe thrombocytopenia that did not respond to standard treatment regimen namely glucocorticoids (GC) and intravenous immunoglobulin therapy (IVIG). Splenectomy had to be resorted to relieve the condition.

CASE REPORT

Case 1

45-year-old male anaesthesiologist, non-smoker who did not consume alcohol, presented in August 2002 with purpuric spots on the legs associated with gum bleeding of 2-month duration. He denied any arthralgias, myalgias, oral ulcers, red eyes, glandular swellings in neck, axillae or groin, weight loss, cough, chest pain, pain in abdomen, migraine or constitutional features. There was no previous history of thrombotic events. His past and family history was non-contributory. Physical examination revealed pallor and non-palpable purpura over trunk and both lower limbs. Laboratory investigations showed platelet count of 10×10⁹/l, normochromic anaemia (haemoglobin 80 g/l), positive direct Coombs’ test and a raised reticulocyte count (corrected RC 6), erythrocyte sedimentation rate (ESR) 45 mm for the first hour, total leukocyte count (TLC) 6.5 x 10⁹/l granulocytes 74%, lymphocytes 26%, normal liver and kidney function tests, normal x-ray chest (PA view) and normal high resolution CT of the chest and abdomen. Anti-nuclear antibodies were negative. IgG isotype of aCL antibodies were positive in low titre (32 GPL). A bone marrow biopsy showed normal cellularity with increased megakaryocytes. Diagnosis of Evans’ syndrome with sub-clinical APS was made. He was
administered intravenous infusion of 1 gm-bolus dose of methyl-prednisolone daily for 3 days. This was followed by daily oral prednisolone (1 mg/kg/d) treatment. He was readmitted after one week with Platelet counts of 8 x 10^9/l, he was given Intravenous Immunoglobulins (400 mg/kg/d-5 days) with an initial increase in the platelet counts and haemoglobin for 2 weeks, then decline in platelets to 10 x 10^9/l. Splenectomy was carried out in first week of October 2002 after which his platelets counts and haemoglobin became normal. He was given penicillin prophylaxis in the follow-up and remained asymptomatic for next two months. He developed hypertension, polyarthralgias and severe pain and impending gangrene of 2nd and 3rd toes of both feet in first week of January 2003. Investigations showed high titre IgG ACL (100 GPL), IgM ACL (74 MPL), negative lupus anticoagulants, negative antinuclear antibodies, normal blood counts, normal liver and renal functions; and normal Doppler studies of both the lower limbs. Diagnosis of primary antiphospholipid antibody syndrome (PAPS) was made. He was anticoagulated in standard manner (heparin in the beginning followed by oral anticoagulants with target INR of 3-3.5). He also required antihypertensive medications. He showed dramatic response to this treatment and became asymptomatic within weeks. He has continued to be in remission till last visit (10th April 04). He continues to be on oral anticoagulants with INR that is being kept between 3-3.5.

Case 2

A 16 years young girl presented with 15 days history of non-palpable purpura over legs. The platelet counts were 10 x 10^9/l. On further questioning she gave history of migraine-type severe headaches for the last 6 months, inflammatory polyarthralgias for 1 month and oral ulcers for 15 days. She denied any history of photosensitivity, hair loss, serositis, fever, constitutional features, myalgias, symptomatic anaemia, bone pains, glandular swellings in neck, axillae or groin, cough, Raynaud’s phenomenon or swelling in the extremities. The past and family history was non-contributory. Physical examination showed non-palpable purpura over legs and livedo reticularis over right thigh. The past and family history was non-contributory. Physical examination showed non-palpable purpura over legs and livedo reticularis over right thigh. Investigations revealed severe thrombocytopenia (platelet counts 8 x 10^9/L) and high titre IgG antiphospholipid antibody (>100 GPL). The other investigations showed an ESR of 24 mm at one hr, Hb 130 gm/l, leukocyte count 4.5 x 10^9/l with granulocytes 74%, lymphocytes 26%, normal LDH, normal liver and renal function tests. Chest radiograph and CT head were normal, antinuclear antibody test was negative, bone marrow examination showed hypercellular marrow with increased megakaryocytes, no evidence of granuloma. Diagnosis of APS was made and she was given intravenous infusions of methyl prednisolone-bolus at the dose of 1.0 gm/d for first three days followed by oral prednisolone. The platelets counts increased up to 80 x 10^9/l but it fell again 10 x 10^9/l after 3 weeks while she was taking 1 mg/kg prednisolone daily. She was given IVIG for 5 days (400 mg/kg/d for 5 days). The platelet counts increased to 200 x 10^9/l and livedo reticularis disappeared. She was readmitted after 2 weeks with a platelet count of 12 x 10^9/l. She was given Pneumococcal and influenza vaccines followed by splenectomy. The platelet counts rapidly increased to 600 x 10^9/l. Low-dose aspirin (150 mg daily) was initiated for headache. She was asymptomatic for last one year with platelet counts varying between 400-450 x 10^9/l with markedly reduced frequency and severity of headaches.

**DISCUSSION**

Thrombocytopenia appears in about one fourth of the patients with APS. Cuadrado et al. reported a prevalence of 23% in a series of 171 patients with APS; severe disease (<50×10^9/l) was, however, observed only in 6 of them (18%). Autoimmune haemolytic anaemia is seen in ~14-23% patients of APL. The co-occurrence of both immune mediated cytopoenias was originally described by Evans in 1949. There are few reports that describe co-occurrence of thrombocytopenia and autoimmune haemolytic anaemia as a presenting feature in APS. 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. Some authors have analysed the relation between the isotype of aCL and cytopoenias and found a significant association between IgM aCL and haemolytic anaemia.

Rarely, this disorder requires treatment and, owing to shared characteristics with idiopathic thrombocytopenic purpura, similar treatment is usually recommended namely, high dose glucocorticoids, immunosuppressive or immunomodulating agents, and intravenous immunoglobulin. When GC or immunosuppressive agents are unsuccessful, splenectomy is usually performed to remove the major site of platelet destruction and antibody production. There are several studies that confirm role of splenectomy in the treatment of APS associated cytopenias. 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.

Both the patients presented in this report presented with severe thrombocytopenia with a positive a CL. Initially both the patients were treated with GC and IVIG but the response was unsatisfactory. Therefore, splenectomy had to be resorted to which, both the patients responded dramatically and the response was
sustained.

In conclusion, thrombocytopenia in APS is usually mild, does not require any treatment in the majority of the patients. However, when it is severe and refractory to GC and IVIG treatment, splenectomy may have to be resorted for effective treatment. It gives long-term remission in the majority of the patients.

REFERENCES

Announcement

ITP Study Group

At the recently held First National Conference on Idiopathic Thrombocytopenic Purpura, it was decided to form ITP Study Group with a view to study the natural history of the disease in India and also to see the commonly prevailing practice in treating this disease. Based on the information collected in such study, recommendations can be made about the management of ITP in India including a possible role of alternative forms of therapy.

Those who are interested in joining the study group should contact: Dr B C Mehta at (labmed@ghrck-bk.org). It is necessary that those who wish to join the group have easy access to internet. All communications of the study group will be through e-mail and web. Members will have access to the data/information on web.