Case Report

Primary Antiphospholipid Antibody Syndrome and Autoimmune Haemolytic Anaemia — a rare combination

Saera Suhail,[1] Muhammad Shakil Baig,[2] Syed Mujahid Humail,[3] Amir Riaz[4]

Rheumatology Department, Baqai Medical University, Nazimabad,[1,2,4] Orthopaedic Surgery, Dow University of Health Sciences,[3] Karachi, Pakistan.

Abstract

Primary Antiphospholipid Antibody Syndrome (PAPS) and Autoimmune haemolytic anemia(AIHA) is a very rare combination. Antiphospholipid Antibody Syndrome (APS) with underlying SLE, however, has a well documented association with Coomb's positive Auoimmune Haemolytic Anaemia.[1,2] We describe a young girl with PAPS presenting with deep venous thrombosis, livedo reticularis and features of AIHA. The patient was refractory to treatment for 5 years however, her condition improved dramatically with anticoagulants, corticosteroid therapy and the addition of hydroxychloroquine and azathioprin. We have also discussed hydroxychloroquine therapy in PAPS which is not yet fully established and the probability of this patient developing other autoimmune disorders in future.

Introduction

Antiphospholipid Syndrome (APS) is a multisystemic disease with recurrent thrombosis in the presence of Antiphospholipid (aPL) antibodies, which may include cardiac, neurological, gastrointestinal, haematologic or cutaneous manifestations.[1] Primary Antiphospholipid Syndrome (PAPS) is defined as aPL antibody associated with vaso occlusive events without any underlying disease process. The presence of aPL antibodies and a vasooclusive event superimposed on an underlying disease such as SLE or malignancy, is a secondary Antiphospholipid syndrome. Patients with autoimmune haemolytic anaemia (AIHA) are sometimes associated with a distinct category of connective tissue diseases which includes anticardiolipin antibodies, thrombosis, thrombocytopenia and renal disease, often in the context of secondary Antiphospholipid syndrome.[2] Presence of autoimmune haemolytic anaemia in PAPS is a rare combination. Here, we report a case of 15-year-old girl with deep vein thrombosis (DVT), livedo reticularis and AIHA who turned out to be case of primary Antiphospholipid antibody syndrome.

Case Report

A 15-year-old girl presented to the outpatient department of the Baqai Rheumatology Unit of Baqai Medical University in Nov 2006 with a 5 year history of a rash and swelling of left leg. The rash was initially maculopapular but become confluent later over the years. It was raised and like bluish patches over the left shin. The swelling was painful and increased on walking and standing. It started from the ankles but then involved the whole thigh. She also had recurrent episodes of jaundice , right hypochondriac pain and easy fatigability on mild exertion over the last couple of years. There was no history of trauma, fever, oral ulcers, photosensitivity, chest pain, dyspnoea or joint pain. In the past she was prescribed high dose prednisolone for an undiagnosed tender swelling on the left lower shin in 2000. In 2001 she was anticoagulated by a physician for left leg DVT. In 2002 she developed jaundice and right upper abdominal pain when she was diagnosed by a haematologist as a case of Autoimmune Haemolytic Anaemia (AIHA). She was restarted on oral prednisolone 10mg daily with warfarin for a possible DVT but without strict INR monitoring and for determining the underlying reason for such a prolonged course of the DVT. Despite this treatment her leg swelling and rash gradually increased. Her jaundice had settled for some months. She was at that point referred to us for further evaluation.

At presentation, her vitals were normal. Examination of left leg revealed a hard nodular calf (due to oedema) with mosaic like reticular pattern over the skin of the shin which were suggestive of livedo reticularis. Tense oedema was present up to the left thigh. All pulses were palpable but a Homan's sign was positive. A provisional diagnosis of deep venous thrombosis was made which was confirmed by Doppler ultrasound showing left external iliac and left femoral vein obstruction. Further investigation showed normochromic normocytic anaemia with a Hb of 10.6 gm/dl and a thrombocytopenia of $90x10^9$. Total Leucocytes count was $7.5x10^9$ with a neutrophil of $4.5x10^9$ (60%) and lymphocyte $2.7x10^9$ (37%). ESR was 115mm in the first hour. Coagulation profile showed a PT of (15/12) and markedly raised APPT of (71/31). Liver function tests showed a haemolytic picture with a markedly raised indirect bilirubin of 11 mg/dl and total bilirubin 13.9 mg/dl. The rest of the liver enzymes were normal. Autoimmune serology was negative for ANA and Anti Ds DNA. Anti ENA profile was also negative except for anti Ro antibodies which were positive.

Anticardiolipin lgG was 40 GPL/ml (moderately elevated) and IgM was 13.GPL/ml(mildly elevated).

Lupus anticoagulant test was also positive twice which was done 12 weeks apart. Investigation for thrombophilias i.e. Factor V leidin, Homocystine, protein C and S and antithrombin III were also done but were within normal limits. Direct Coomb's test was positive. Although the reticulocyte count was not elevated, in the presence of coomb's positive haemolytic anaemia we used indirect bilirubin as a marker for haemolysis. Haptoglobulin was not done.

Anticoagulation was started with warfarin to keep the INR range 2.5-3.5. Her prednisolone was gradually tapered down whilst titrating against the markers of haemolysis to a maintenance dose of 5 mg once a day. She was kept on azathioprin 50mg (2 mg /kg) twice a day as a steroid sparing agent and hydroxychloroquin 200mg twice a day. Her condition started improving gradually the oedema decreased and mosaic pattern over the shins reduced to a few hyper pigmented patches. Her recent Doppler of left leg showed partial recanalization of external iliac and femoral veins. She has been repeatedly assessed for clinical and immunological markers for SLE and to date has only developed anti Ro antibodies.

Discussion

The association of AIHA and PAPS has not been well established.[1] Uptill now very few cases of APS with AIHA have been reported but all of them had an association with autoimmune disorder like SLE i.e. they were secondary APL syndrome.[3-5]

Our patient fulfills the criteria of APS on the basis of positive IgG titres of ACL antibodies, positive Lupus Anticoagulants, thrombocytopenia and the evidence of DVT. There is no evidence for the presence of systemic lupus erythematosis at any stage although Anti Ro Ab's are positive in this case. This patient has been taking high dose steroids for about 6 years from the initial symptoms and therefore it may be possible that her disease was 'modified' thereby altering its original course. The presence of Anti Ro antibodies in this patient, which are also present in about 50% of SLE patients may support this postulation.[6]

This patient is on regular follow up and should be investigated at regular intervals for the evidence of any other autoimmune disease in future.

Our patient on presentation was taking high dose steroids but was refractory to this treatment. Corticosteroids and splenectomy are standard treatment for AIHA. Recent reports suggest that Rituximab (anti CD chimeric monoclonal Abs) and mycophenolate mofetil, could be alternative options for treating AIHA in PAPS or AIHA with SLE.[7,8] Hydroxychloroquin is used as a disease modifying therapy usually in APS with SLE which has an additive effect of decreasing the risk of venous thromboembolism.[9] The patients' condition improved dramatically with the use of this drug, further trial of this drug in PAPS should be therefore considered.

We suggest that patients with PAPS should always be evaluated for AIHA as the combination is rare but not impossible. Furthermore, hydroxychloroquine could be a useful adjunctive treatment in patients with PAPS, further trials are needed to help our management of APS in future.

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