Catastrophic Antiphospholipid Syndrome in Immune Thrombocytopenic Purpura – Beyond Tenuous Concomitance!

Abstract

Significance of antiphospholipid antibodies in immune thrombocytopenic purpura is debatable and pose a diagnostic and therapeutic dilemma. Catastrophic antiphospholipid syndrome is a rare life-threatening entity, occurring in patients with antiphospholipid syndrome, usually after a triggering event. We describe an adult lady of chronic immune thrombocytopenic purpura (in remission) with antiphospholipid antibodies, who presented with rapidly progressive renal failure and had primary antiphospholipid syndrome nephropathy. The index manuscript titled exemplifies the fact that although the presence of APLA in ITP is known, however, management in the absence of clinical event remains debatable and may carry a future risk of thrombotic event/s mandating close monitoring with a high index of suspicion.

Keywords: *Antiphospholipid syndrome nephropathy, autoimmune disorder, immune thrombocytopenic purpura, treatment*

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Introduction

Antiphospholipid syndrome (APS) is the most common form of acquired thrombophilia leading to recurrent thrombotic events and/or obstetric complications.[1] It is an autoimmune condition occurring due to the presence of antibodies that recognize phospholipid-binding proteins.[2] Primary APS occurs in the absence of any autoimmune disease. Antibodies against beta 2-glycoprotein-1 (anti-β2GP1) and cardiolipin (aCL), together with lupus anticoagulant (LA), are considered in the revised criteria for the diagnosis of APS.[3] By international consensus, the diagnosis of APS requires fulfilment of at least one clinical criterion (vascular thrombosis or pregnancy morbidity) and one positive laboratory test, confirmed at least 12 weeks apart.[3] However, the clinical spectrum of APS extends beyond these classification criteria; for instance, large renal vessel thrombosis is classified as APS criteria, while "non-criteria APS manifestation" includes APS nephropathy (APSN).[4]

Case Report

A 38-year-old lady presented with gum bleeding of 3 days duration, two years back. On evaluation, she had isolated thrombocytopenia (platelet count-8000 cells/μL). In view of large platelets with normal morphology on peripheral smear, the patient was diagnosed as immune thrombocytopenic purpura (ITP) and managed with intravenous methylprednisolone (1000 mg daily for three days) followed by oral prednisolone (1 mg/kg) as maintenance therapy. She initially responded to therapy (platelet count increased to 50 × 10^9/L), however, developed severe thrombocytopenia upon gradual tapering of prednisolone (platelet count 9 × 10^9/L) requiring intravenous immunoglobulin (1 gm/kg; single dose), and hiking up of oral prednisolone (1 mg/kg).

One month later, she relapsed again following steroid taper and was initiated on eltrombopag (50 mg once daily) and thereafter attained partial remission with platelet count ranging from 30–50 × 10^9/L. One year later, she had unprovoked distal deep vein thrombosis (DVT) of the right lower limb. In background of thrombocytopenia, possibility of systemic lupus erythematosus was considered, however, her repeat ANA, anti-ds DNA were negative, complement levels (C3/C4) were within normal limit, but she

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had detectable aCL [IgM-negative, IgG-28 GPL (<15)] and anti-β2GP1 [IgM-negative, IgG-38 SGU (<20)] antibodies while LA was negative. In absence of obstetrical morbidity and low titres of antiphospholipid antibodies (aPLs), the patient was managed with an oral anticoagulant (OAC) with advice for close follow-up- However, she discontinued OAC after 6 months and was lost to follow-up.

She now presented with complaints of breathlessness and reduced urine output of five days duration. She denied a history of fever, cough with expectoration, hemoptysis, orthopnea, paroxysmal dyspnea, palpitations, chest pain, gravelluria, haematuria, frothuria, intake of alternative medications, loose frequent stools, and bloody diarrhoea. Clinically, she had pallor, hypertension (BP-170/100 mmHg) and bilateral infra-scapular crepitations on chest auscultation. Investigations revealed hemoglobin - 8.3 gm/dL, leukocyte count - 8000 cells/mm^3, and platelet count- 21000 cells/microL, blood urea - 131 mg/dL, creatinine - 9.7 mg/dL, with evidence of micro-angiopathic hemolysis on peripheral blood smear. Her urine examination showed dysmorphic erythrocytes without proteinuria. Troponin T was negative, 2D-echocardiography was normal, chest X-Ray suggested pulmonary edema. Ultrasonography showed bilateral normal-sized kidneys with the normal flow in renal vessels on renal doppler. Her repeat ANA, anti-ds DNA were again negative and complement levels (C3/C4) were within normal limits, however, this time she had triple positivity for aPLs with significant titers [aCL: IgM-Negative, IgG-119 GPL, anti-β2GP1: IgM-Negative, IgG-163 SGU, LA: Positive] making a provisional diagnosis of primary APS. To ascertain the etiology of rapidly progressive renal failure, she underwent renal biopsy (after correction of thrombocytopenia with platelet transfusions) which showed 16 glomeruli, out of which 4 were morphologically normal, 8 glomeruli showed endothelial swelling while remaining 4 glomeruli had extensive subendothelial widening and thrombotic occlusion of capillary lumen, with mild interstitial inflammation and edema [Figure 1]. Two arteries had extensive endothelial swelling with near obliteration of the lumen and fragmented erythrocytes in the intimal layer suggesting florid glomerular and vascular thrombotic microangiopathy (TMA) confirming APSN. Direct immunofluorescence was negative for immunoglobulins and complements. She was managed with plasmapheresis (40 ml/kg-5 sessions), intravenous methylprednisolone (1000 mg daily for 3 days) followed by oral prednisolone (1 mg/kg), unfractionated heparin and alternate day HD. She became nonoliguric, however, had worsening dyspnea on day 7 of admission. Pulmonary CT angiography revealed subsegmental pulmonary thromboembolism which was managed conservatively. The further hospital stay was complicated by refractory septic shock requiring empirical antibiotics, inotropes, and ventilatory support. however, She succumbed to her illness on day 11 of admission.

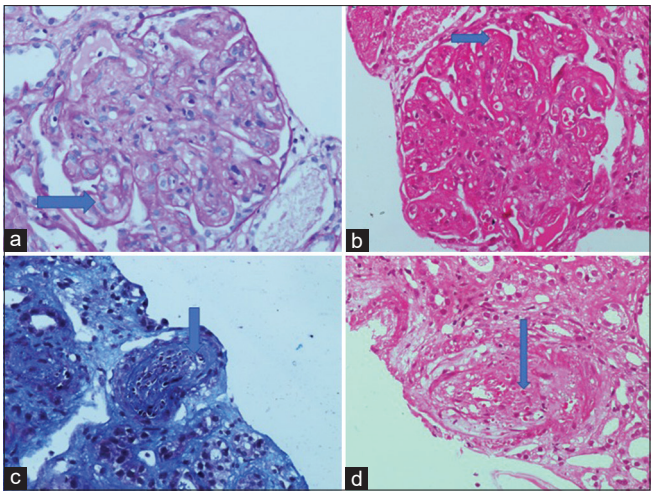

Figure 1: (a) Glomerulus showing severe endothelial swelling with an accumulation of subendothelial fluffy material (PAS × 40). (b) A glomerulus with subendothelial widening and the presence of RBC fragments in the subendothelium (H and E × 40). (c) Arteriole showing intraluminal fibrin thrombus (H and E × 40). (d) Arteriole showing extensive intimal swelling with the presence of fragmented RBCs in the intimal tissue (H and E × 40)

Discussion

Although the reported incidence of APLA in ITP varies considerably, ranging from 30% to 73%,[5] nevertheless, primary APS presenting with APSN with probable catastrophic antiphospholipid syndrome, complicating ITP has never been described and hence is being reported for its novelty.

The clinical significance of APLA in ITP is rather debatable and correlates poorly with thrombotic complications.[6] However, the persistence of APLA in patients with ITP subsequently increases the risk of APS[7] as evident in the index case.

Thrombocytopenia may occur in 20–40% of patients with APS[4] and is usually moderate (>50 × 10^9/L) without clinical manifestation and usually does not require intervention.[8] The index case had APSN complicating ITP, which added fuel to the fire and indeed posed a therapeutic challenge in managing a fine balance between the risk of bleeding and thrombosis.

Renal involvement in primary APS is typically caused by thrombosis occurring at any location within the renal vasculature, leading to diverse effects, depending on size, type and site of the vessel involved; consequent manifestations include renal artery stenosis, renovascular hypertension, renal vein thrombosis, renal infarction, APSN and allograft vascular thrombosis. The estimated prevalence of APSN in primary APS range from 2.7%[4] to 9%,[9] however, true incidence is probably underestimated. Firstly because of frequent occurrence of thrombocytopenia and hypertension discouraging renal biopsy; secondly, due to the increased risk of hemorrhage after renal biopsy owing to arterial vasculopathy and lastly withholding anticoagulation

to permit renal biopsy can itself be complicated by a thrombotic event. APSN is characterized by hypertension, proteinuria (mild to nephrotic syndrome), microscopic hematuria and renal insufficiency which is usually mild.[10] Absence of proteinuria, dialysis requiring renal dysfunction and eltrombopag[11] use necessitated renal biopsy in the index case. Hallmark for diagnosis of APSN on renal biopsy is thrombotic microangiopathy in the acute stage (as evident in the index case) with interlobular fibrous intimal hyperplasia, arterial and arteriolar recanalizing thrombi, fibrous arterial occlusion, and focal cortical atrophy.[12]

Therapy for primary APS has not been standardized. In a literature review of 46 patients,[13] steroid was the most common treatment (69%), followed by plasma exchange (62%), anticoagulant (48%), immunosuppressive agents (29%), and immunoglobulins (12%). We managed our patient with alternate day hemodialysis, plasmapheresis, platelet transfusions, steroids, anticoagulation, and IV Ig. Even rituximab was contemplated as a last resort, however, was deferred in view of fulminant sepsis complicating the hospital stay. Mortality from CAPS is estimated to be over 70%, and is predicted by age over 36 years, several organs involved and need for hemodialysis.[14] For reasons unknown, an incongruous interaction between ITP and APS remains underreported till date. We, therefore, suggest that patients with ITP with aPL antibodies need to be preemptively managed appropriately of this although an infrequent, yet the devastating entity

Conclusion

Our case exemplifies the fact that although the presence of APLA in ITP is known, yet management in the absence of clinical event remains debatable and may carry a future risk of thrombotic event/s mandating close monitoring with a high index of suspicion.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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