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Internal Medicine

A DIFFICULT CASE OF SERONEGATIVE ANTIPHOSPHOLIPID ANTIBODY SYNDROME

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ABSTRACT Antiphospholipid Antibody Syndrome is a multi-system autoimmune disorder characterized by arterial or venous thrombosis and recurrent pregnancy loss with persistently positive aPL. Seronegative APS is a condition where the clinical manifestations are highly suggestive of APS with persistently negative antibodies. Here we present a similar case with recurrent venous thrombosis.

KEYWORDS :

INTRODUCTION

Antiphospholipid Antibody Syndrome is a systemic autoimmune disease characterized by arterial or venous thrombosis and pregnancy morbidity associated with circulating antiphospholipid antibodies (1). According to 2006 Sidney Classification criteria, Anti Cardiolipin Antibodies or Anti-Beta 2 Glycoprotein antibodies estimated by ELISA or Lupus Anticoagulant detected by clotting assays are the recommended tests for detection of APS which should be present in two or more occasions 12 weeks apart.

Seronegative APS (SN-APS) is a variant, associated with thrombosis occurring in the setting of absent cardiovascular risk factors or an identifiable cause (2). Its clinical presentation is similar to APS , in the absence of antibodies in atleast 2 occasions 12 weeks apart. There are various other antibodies being studied extensively to have been associated with recurrent thrombosis including antibodies against Phosphatidylethanolamine, Phosphatidic acid, Phosphatidylserine, Phosphatidylinositol . However there is a lack of standardised assays to measure the levels of these antibodies in routine clinical practice.

Case Report

25 year old female, presented to the ED with complaints of high grade fever associated with dry cough and generalised weakness for past 2 weeks. History of hemoptysis, 2-3 episodes in the past 5 days, minimal in amount. Complaints of loss of appetite over the past 1 month. No past history of surgeries/ prolonged immobilisation.

On arrival in Emergency, Vitals were stable. Wells score was 1. Baseline investigations, Blood and urine cultures were sent and patient was shifted to ward for further management. After few hours, patient developed tachycardia, tachypnoea and hypotension and was shifted to MDCCU for further management.

Patient was started on HFNC and inotropes. ECG was done which showed S1Q3T3 pattern (FIGURE 1). 2D ECHO revealed dilated RA and RV with mild RV dysfunction, moderate PAH, Large Thrombus in RV Free wall, mild pericardial effusion with normal LV Function.

CTPE was done which showed massive pulmonary thromboembolism in right and left branches of pulmonary artery with thrombus seen extending into its segmental and subsegmental branches, with a left lower lobe pulmonary infarction (FIGURE 2). Thrombus was also seen involving renal veins on both sides, with extension into IVC.

On probing, attenders gave history of previous Cortical Venous Sinus thrombosis few years back, for which patient was started on Dabigatran 150mg BD, which she discontinued 2 months back, due to socio-cultural reasons. Patient was evaluated for Antiphospholipid Antibody syndrome back then, which was negative.

Patient was started here on Unfractionated Heparin . Bilateral Lower limb Venous Doppler was done which was normal. Baseline investigations revealed severe thrombocytopenia, elevated NTProBNP levels. Tropical Screening for infections turned out to be negative.

Patient was considered to fall under intermediate- high risk PE , but in view of severe thrombocytopenia, thrombolysis was deferred due to risk of bleeding and decision was taken to continue UFH and observe. Patient was switched over to LMWH in a day as therapaeutic APTT was not achieved and Heparin resistance was taken into consideration. Inotrope supports were slowly reduced and patient maintained saturation with nasal prongs.

Patient was extensively evaluated in view of unprovoked recurrent thrombosis. Vasculitis panel, Anti Cardiolipin Antibody, Anti-Beta 2 Glycoprotein Antibody, Anti Phosphatidylserine Ab and Lupus Anticoagulant were negative. ADAM TS 13 Antigen and activity were normal. PNH by Flow Cytometry and Thrombophilia screen were negative. Therefore a diagnosis of Seronegative APS was made.

Thrombocytopenia continued to persist. Therefore Bone Marrow Aspiration was done which was suggestive of ITP. Patient was treated with IvIg for the same. Platelet counts showed an increasing trend post treatment.

Condition of the patient improved symptomatically and was discharged on oral anticoagulants. MPN Panel and PET CT was adviced during follow up to evaluate for Myeloproliferative disorders and Malignancy as a cause for recurrent thrombosis which also turned out to be negative.

DISCUSSION

Antiphospholipid Antibody syndrome is a systemic autoimmune disorder characterized by arterial/ venous thrombosis and/or pregnancy morbidity in patients with persistently high levels of antiphospholipid antibodies. APS may be classified as primary or secondary, the latter being present in 30-40% of patients with SLE. Revised Sapporo criteria is used for the diagnosis of APS.

Individuals who present with clinical features highly suggestive of APS, in the absence of laboratory criteria are referred to as Seronegative APS. It is a diagnosis of exclusion with persistently negative APL antibodies tested on atleast 2 occasions and other causes of thrombosis should have been excluded such as Factor 2 and Factor 5 Leiden mutation, Protein C, Protein S and Antithrombin 3 deficiency, malignancy and prolonged immobilisation. It was first described by Hughes and Khamasta in 2003 as clinical manifestations highly suggestive of APS in the absence of laboratory criteria such as LAC, aCL, Anti Beta 2 Glycoprotein antibodies. (3) It could due to other antibodies that are reported to have been associated with thrombosis but are not routinely tested, which include antibodies against Phosphatidylethanolamine, associated with blocking of protein C pathyway (4) (5), phosphatidic acid, phosphatidylserine, phosphatidylinositol etc. Moreover around 30 different non-criteria autoantibodies directed against glycoproteins, phospholipids and

coagulation factors have been reported and potentially linked to thrombotic risk in APS.

Thrombocytopenia can be observed in these patients. The frequency of thrombocytopenia is higher in SLE associated APS than in primary APS.

The therapaeutic intervention in Seronegative APS is similar to seropositive APS. Patient is started on UFH or LMWH in hospital setting and is switched over to oral anticoagulants at discharge. Warfarin is preferred over Direct oral anticoagulant (DOAC). Although DOAC may reasonably be used in selected individuals. In our case, DOAC was preffered as patient was not compliant with medications previously and would be difficult to follow up.

DECLARATION-
Funding- None

Conflict Of Interest- None

Ethical Approval- Not Required

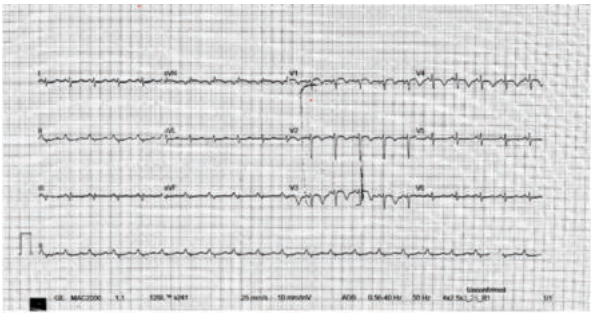

Figure 1-ECG- S1Q3T3 pattern with sinus tachycardia

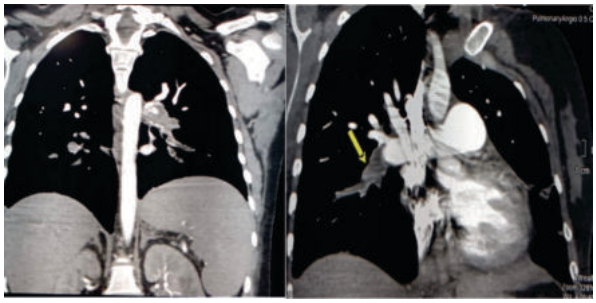

Figure 2- Pulmonary thrombus in left and right main pulmonary artery

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