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Case Report
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ANTIPHOSPHOLIPID ANTIBODY SYNDROME WITH AUTOIMMUNE HEMOPHILIA A & B IN FEMALE - A CASE REPORT

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ABSTRACT
Acquired Hemophilia A and B are very rare conditions which causes severe bleeding complications whereas APLA syndrome is an autoimmune disorder of thrombosis. We report a case of acquired hemophila A and B with APLA syndrome presented as recurrent stroke, deep vein thrombosis and obstetric complications, a very rare entity.

Introduction

Antiphopholipid Antibody syndrome (APLA) is an autoimmune disorder of thrombosis, occurring in those patients who have anti phospholipid antibodies in their serum. Its manifestations can be as severe as Catastrophic APLA causing thrombosis in multiple organs, or can occur as recurrent early abortions.[1] Acquired hemophilia is just the opposite side of the coin, a severe disorder of hemostasis mostly in elderlies. Autoantibodies formed against factor VIII and IX inhibits their coagulant activity, leading to hemorrhage. Association of Lupus anticoagulant and Acquired hemophilia is rare. [2] Our case is a very rare case of APLA syndrome along with Acquired hemophilia A and B in a young female.

Case Report

A 25 year old married Hindu female, resident of Rajasthan, presented with complaints of sudden onset left hemiplegia with slurred speech for one day. She had a significant past history of left lower limb deep vein thrombosis 10 years ago. She also had two similar episode of ischemic stroke 5 years back. Obstetrics history reveals that she had 12 abortions earlier, all were of less than 10 weeks of gestation. There was no history suggestive of any other chronic diseases, bleeding manifestations, or prolonged drug intake. There was no significant family history.

On examination, the patient was conscious, oriented to time, place and person. Vitals were stable.Neurological examination revealed left hemiplegia with left UMN facial palsy suggestive of cerebrovascular accident (CVA). There were few petechial patches over limbs. Rest of the systemic examinations were normal. MRI Brain was done which showed recent left Middle Cerebral Artery (MCA) territory infarct along with old ischemic changes.

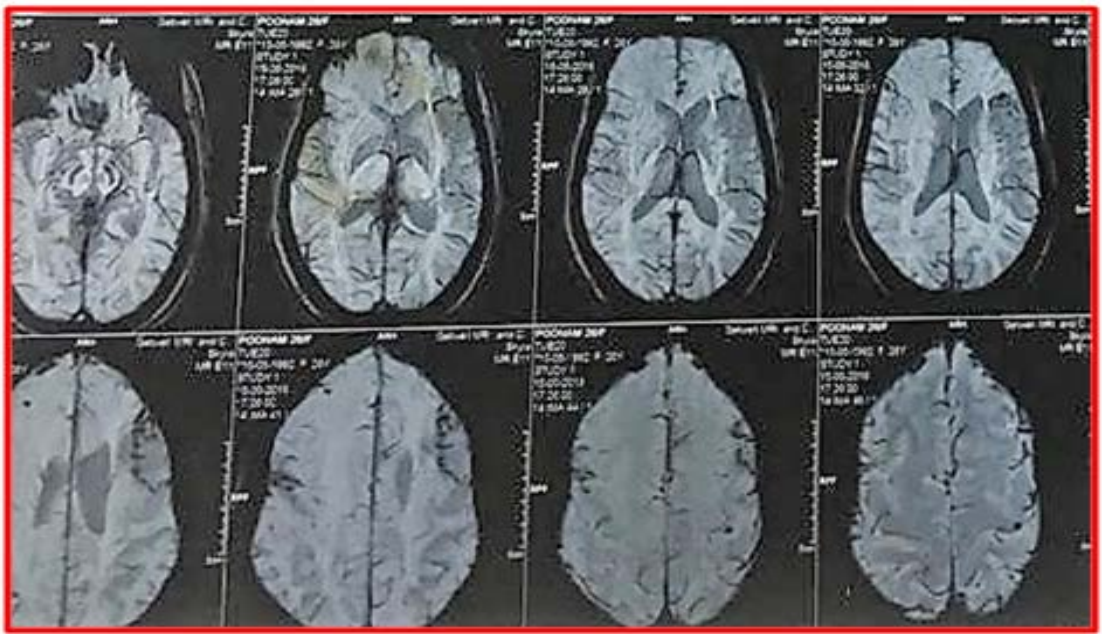

Figure 1: MRI Brain showing ischemic changes

Hemogram shows mild anemia with thrombocytopenia. (Hb – 10.0 g/dl, TLC – 7.7x 10^3/mm^3 Platelets - 95000/ml). In view of multiple thrombotic manifestations as well as recurrent early miscarriages, APLA syndrome was suspected. Activated partial thromboplastin time (aPTT) was elevated to 54.8 sec. Prothrombin time (PT) was low i.e. 5 sec. As aPTT is raised, it could be due to APLA syndrome or Hemophilia, so complete coagulation profile was done. Anti Nuclear Antibody test done by IF was positive with titre of 1:320(Cytoplasmic, Speckled Pattern).Anti-phospholipid IgG, IgM and Anti Cardiolipin IgG, IgM were negative. B 2 Glycoprotein-1 IgG was positive 40.73 RU/ml (<20) and β 2 Glycoprotein-1IgM was also positive 139.93 RU/ml (<20). As per the diagnostic criteria for APLA syndrome, Beta 2 Gylcoprotein IgM was repeated, which was also positive making it as APLA syndrome. To evaluate whether it's primary or secondary, complete ANA profile was sent which came out to be normal.

Table 1: Coagulation Profile

TEST	RESULTS	REFERENCE
PT	5 s	(10-12)
aPTT	**54.8 s**	(24-36)
Anti Phospholipid IgG & IgM	Negative	(<18)
Anti Cardiolipin Ab IgG & IgM	Negative	(<12)
Beta-2-Glycoprotein I-IgG	**Positive(40.73 RU/ml**	(<20)
Beta-2-Glycoprotein I-IgM	**Positive(139.93 RU/ml**	(<20)

Table 2: Antibody levels after 12 weeks.

Beta-2-Glycoprotein I-IgG	**Positive(51.93 RU/ml**	(<20)
Beta-2-Glycoprotein I-IgM	**Positive(122.28 RU/ml**	(<20)

Evaluating further for raised aPTT, coagulation factor activity were evaluated. Test showed there was significantly low activity of factor VIII and IX. Suspecting it as acquired hemophilia, mixing studies were done that came out to be positive.

Table 3: Coagulation Factors

Investigation	Result	Reference
PT	**5 sec**	**(10-12)**
aPTT	**54.8 sec**	**(24-36)**
FactorVIII	**40%**	**(60-150)**
FactorIX	**18%**	**(60-150)**
vWF(Von Willi Brand)	**96%**	**(50-160)**
Factor V	**93%**	**(65-150)**
Protein c	**79%**	**(70-130)**
Protein S	**35%**	**(55-140)**
Anti Thrombin III	**104%**	**(80-120)**

Table 4: Mixing Study

Test	aPTT
Sample	49.1 sec
Normal pool + Spot Sample (1:1)	46.5 sec
2 hr Incubation at 37° C	47.0 sec

Thus we reached to a final diagnosis of APLA syndrome with acquired hemophilia A and B.Low molecular weight heparins were given ,overlapped by warfarin 2mg after achieving target INR of 2-3.Tab Hydroxychloroquine 200 mg twice daily started. For elimination of inhibitors, oral steroids (prednisone 30 mg daily).Tablet Azathioprine 50 mg/daily was started. No adverse reactions were encountered. The patient was discharged. Limb Physiotherapy was advised. After one month she was re-evaluated. No haemorrhagic or thrombotic complications were reported. There was significant improvement in power in both limbs.

Discussion

Anti Phospholipid Antibody Syndrome is a term which explains the relation of antiphospholipid antibodies with its thrombotic complications, termed as disorder of hypercoagulability. It is an autoimmune disorder which primarily occurs alone but can be seen in association with other disorders like SLE.Specifically it consists of three types of autoantibodies, i.e. lupus anticoagulant, anti cardiolipin antibody, and anti-beta-2-glycoprotein 1 antibodies. Lupus anticoagulant manifests as thromboembolic events in contrary to its name.[3]

In Acquired Hemophilia, bleeding disorder occurs due to the formation of autoantibodies, also called as inhibitors, against coagulation factors. Commonly these are seen against factor VIII but very rarely, can form against factor IX also. In alteration to congenital hemophila which usually manifests as hemarthrosis, or hematomas, acquired hemophilia presents as mucosal bleed. The prevalence is 1 to 5 per 1 million people each year and equal in both sex. More than 50 % of the cases are seen to be idiopathic but its common association is seen with diabetes, pregnancy, malignancies and some other autoimmune disorder.[4]

In our case there was simultaneous presence of APLA syndrome as well as acquired hemophilia A and B.Its an exceeding rare condition. First case report of its type was reported in 1993 in which lupus anticoagulant were present with acquired hemophilia.[5] Usually bleeding manifestation predominates in it, but in our case thrombotic complications were more pronounced. Both the disorders leads to prolongation of activated partial thromboplastin time, the major differentiation factor is their mechanism of action.[6]

As discussed earlier, the diagnostic criteria for APLA is mainly dependent on both clinical events as well as antiphospholipid antibodies. Antiphospholipid antibodies were first seen in a syphilis patient in 1906.The antibodies acts against protein, phospholipids in cell membranes and many other factors involved in coagulation. As these antibodies can be seen positive in intercurrent illness or infections, it's mandatory

to repeat the test after 12 weeks for confirmation of APLA syndrome.[7] Diagnosis of acquired hemophilia is based on the history as well as coagulation test. There should be no earlier history of bleeding in himself as well as in family. Failure in correction of activated partial thromboplastin time after mixing study proves presence of inhibitors. Reduced factor levels can also be identified although its facility is in few laboratories only[8]

Recent EULAR 2019 guidelines for management of APLA have been developed. It's formulated that high risk antiphospholipid antibody profile leads to greater risk of obstetric as well as thrombotic complications. Patients who are asymptomatic but with antiphospholipid antibody positive, patient with systemic lupus erythematous without history of obstetric and thrombotic complication and also in non-pregnant women with history of obstetric complication-Low dose aspirin is strongly recommended. Patient having venous or arterial thrombosis requires treatment with vitamin k antagonists with a target INR of 2-3.Those with recurrent thrombotic events, low dose aspirin along with increase in target INR to 3-4 can be done. Low molecular weight heparins are safest to be used in pregnanacy. The goal for treating acquired hemophilia is to eliminate the inhibitors. It can be done by immunosuppressant's like prednisolone, azathioprine etc. Intravenous Immunoglobulin's (IVIG) and In Rituximab has also shown significant results.

In conclusion, simultaneous occurrence of Primary APLA syndrome with acquired hemophilia is a rare phenomenon. Our case was interesting as it has both antiphospholipid antibodies as well as FVIII and FIX inhibitors which manifested with predominantly thrombotic and obstetric complications.

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