CASE REPORT

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A Rare Case of Sjögren's Syndrome with Lupus Anticoagulant and Factor VIII Inhibitor Antibodies Presenting as Thrombocytopenic Purpura

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Abstract

A 27-year-old lady presented with complaints of menorraghia for 28 days and purpuric rashes on both upper and lower limbs. On evaluation, initial investigations showed thrombocytopenia and prolonged activated partial thromboplastin time (aPTT). Other routine investigations were normal. She was further evaluated for thrombocytopenia and prolonged aPTT; her ANA profile and factor inhibitor test were sent, and the patient was diagnosed with Sjögren's syndrome along with the presence of concomitant Lupus anticoagulant and factor VIII inhibitor antibodies. She was started on steroids, and became better with rising platelet numbers and no further bleeding.

Key words: Antinuclear antibody, factor VIII inhibitor, lupus anticoagulant, activated partial thromboplastin time, antiphospholipid syndrome.

Introduction

Antinuclear antibody (ANA) is a distinct characteristic of connective tissue diseases (CTD's), and a positive ANA has a high sensitivity for CTD's. Autoimmunity involves the adaptive immune system. The T- and B-cell-mediated effects play a central role in the complex pathophysiology of CTDs. These diseases can present with arthralgia, malaise, myalgia, low-grade fever, or any specific organ system manifestation. They may also present as thrombocytopenia, often due to antibody-mediated platelet destruction. Some common CTDs are SLE, Sjögren's, and Scleroderma, Sjögren's syndrome (SS) is an autoimmune disease evidenced by broad organ-specific and systemic manifestations, the most prevalent being decreased lacrimal and salivary gland function, xerostomia, keratoconjunctivitis sicca, and parotid gland enlargement[1]. It has also been recognised that patients with thrombocytopenia[2] might have lupus anticoagulant positivity[3,4]. Antiphospholipid syndrome (APS) may be associated with autoimmune diseases, rarely with Sjögrens syndrome, and can also present as isolated primary APS[5]. Patients presenting with thrombocytopenia along with Lupus anticoagulant positivity can present with prolonged activated partial thromboplastin time (aPTT). Another cause of prolonged aPTT is the presence of factor-VIII inhibitor antibodies.

Case report

A 27-year-old lady presented with complaints of menorrhagia for one month and purpuric rashes on both upper and lower limbs. There was no recent history of any fever or infection. There was no history of any drug intake and any prior medical comorbidity. Her complete blood count (CBC) report revealed total leucocyte counts of 5,500/mm^3, thrombocytopenia with platelet counts of 9,000/mm^3 and Hb of 10 g/dL. Peripheral blood film showed normocytic normochromic anaemia with no evidence of schistocytes or tear drop cells. Reticulocyte counts and lactate dehydrogenase (LDH) were within normal limits. The direct and indirect Coombs tests were negative. Ultrasound did not show splenomegaly or hepatomegaly. Serum iron studies were within normal range.

Her coagulation profile revealed a prolonged activated partial thromboplastin time (aPTT) of 72 seconds (normal: <27 seconds). The patient was further evaluated for prolonged aPTT, and a mixing study was done, which came out to be 52 seconds (normal: <27 seconds), hence still prolonged. Evaluating prolonged aPTT in a stepwise approach, her Lupus anticoagulant and factor inhibitor were sent; her Lupus anticoagulant was positive, and factor inhibitor screening was also positive, suggesting a high-risk of connective tissue disorder. Anticardiolipin IgM, IgG,

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and anti-Beta2 glycoprotein IgM, IgG were not elevated. The patient had no prior history of any thrombotic events. In light of the mixing study and her clinical history, the presence of a factor VIII inhibitor was suspected. To confirm that, a Bethesda assay was done and the result was 85.2 Bethesda units (normal <50.4), thus confirming factor VIII inhibitor antibody.

Table I: Relevant investigations.

Lab tests	Values
Haemogram (Hb/TLC)	10 g/dl, 5500/mm^3
Platelet Count	Day 1: 9,000/mm^3 Day 3: 70,000/mm^3 (after SDP transfusion) Day 5: 30,000/mm^3 Day 9: 1,25,000/mm^3 (After starting on steroids)
PT/INR/aPTT	14/1.3/ 72.6 (Normal reference range: <27 sec)
aPTT with mixing study	56.5 sec (Normal ref. range: <27)
Vitamin B12	450 pg/mL (Normal ref. range: 240 - 930)
ESR	23 mm 1st hour
Serum Electrolytes (Na+/K+/Cl)	140/4.1/109 meq/L
Fibrinogen	339 mg/dL (Normal ref. range: 220-496)
Reticulocyte Count	1.7% (Normal ref. range: 0.5 - 2.5)
LDH (Lactate Dehydrogenase)	208 u/L (Normal ref. range: 120 - 246)
ANA by IFA	Positive 1:80 Speckled
PBF	Normocytic Normochromic anaemia
Viral Markers (HBsAG, HIV1 and 2, HCV)	Negative
TSH, LFT, URINE R/E, RFT (Renal Functions)	Within normal limits (WNL)
ANA Profile	SS-A/RO60 KD +++SS-A/RO52 KD +++
Lupus Anticoagulant DRVV Screen (Test)	Detected 106.9 (Normal ref. range: 35 - 39 sec)

TLC: Total leucocyte count, PT/INR: Prothrombin time, international normalised ratio, aPTT: Activated partial thromboplastin time, LFT: Liver functon test, RFT: Renal function test, ANA: Antinuclear antibody.

Anti-Nuclear Antibody (ANA) by Indirect Immunofluorescence Assay (IFA) was positive, and it was (2++) of speckled appearance. ANA immunoblot revealed SS-A/Ro60/52 strong positive (3+++). The patient had no history of any joint pain, arthralgia, dry mouth, or any other sicca symptoms. The patient was further evaluated for Sjögren's syndrome. The ophthalmologist's opinion was taken, and Schirmer's test was done, which was conclusive in favour of dry eye disease. Her left eye showed no signs of tears (a severe form of dry eye), and her right eye revealed moderate dry eye (<6 mm). Her tear film break-up test (TFBT) revealed dryness in both eyes. In view of active bleeding and thrombocytopenia, 1 unit of SDP was transfused. The patient was started on tablet Hydroxychloroquine (HCQ) 200 mg twice a day and oral steroids at 1 mg/kg, and eventually her platelets increased, with no further active bleed, and she was discharged on oral steroids and tablet HCQ. On follow-up after 1 week, her platelets were 4,00,000/mm^3, and she was asymptomatic. The patient is on regular follow-up, with regular CBC profile monitoring. After 3 months of follow-up, her CBC revealed platelet count of 3,50,000/mm^3 and she is asymptomatic, on a tapering dose of steroids.

Discussion

Connective tissue disorders (CTDs), such as SLE, Sjögren's syndrome, antiphospholipid syndrome (APS), and undifferentiated connective tissue diseases (UCTD), are characterised by positive ANA tests and can sometimes present as thrombocytopenia.

One study showed[7] that the ANA-positive group's platelet count at diagnosis was lower than the ANA-negative group. The two primary autoantibodies detected in the study responsible for causing thrombocytopenia were anti-SSA and anti-Ro52, which is similar to our case but with no other presenting history of any sicca symptoms or arthralgias made this a bit unusual and also the presence of persistently raised aPTT was not explained by this syndrome; hence, further evaluation of prolonged aPTT was needed.

The unusual combination of the presence of an FVIII inhibitor and a Lupus anticoagulant (LA) in a patient who presented with bleeding manifestations with no prior thrombotic event poses difficulty in determining the cause of a prolonged aPTT[8] as aPTT can be prolonged by both FVIII inhibitors and a Lupus anticoagulant. Even though these autoantibodies are rare, it is possible to identify the underlying autoantibodies through a stepwise approach and manner. It is quite uncommon for a lupus anticoagulant and an acquired FVIII inhibitor to coexist together, and very few cases have been reported worldwide[8]. Along with that, the presence of an underlying autoimmune disease like Sjögren's syndrome makes this case ever rarer.

An acquired clotting factor inhibitor is a possibility when large ecchymoses or bleeding manifestations suddenly appear in a person without major trauma or a known bleeding condition, along with a prolonged aPTT. Antiphospholipid syndrome (APS) patients also exhibit prolonged aPTT, although their symptoms are thrombotic rather than bleeding most of the time. Disseminated intravascular coagulation (DIC) is also a differential for prolonged aPTT, but our patient did not fit this because she had a normal Prothrombin (PT) time as well as no sepsis, trauma, malignancy, or obstetric complications.

Normal liver function tests and a normal prothrombin time excluded liver disease as a possibility for her clinical picture.

The most common auto-antibody that affects clotting-factor activity is an antibody against factor VIII, leading to a bleeding disorder. A prolonged aPTT is the hallmark feature of acquired FVIII deficiency. The Bethesda assay measures the inhibitor titre and confirms the diagnosis. The Bethesda assay measures the quantity of factor VIII that the patient's plasma inactivates when it is mixed with normal plasma under specific circumstances[9]. One Bethesda unit (BU) is equal to the quantity of antibody that will neutralise 50% of factor VIII in a 1:1 mixture of the patient's plasma and normal plasma after a 2-hour incubation at 37° C. Our patient had an assay of 85.2 Bethesda unit (normal range <50 units).

Both FVIII inhibitors and LA prolong the aPTT, and each autoantibody interferes with the methods designed to detect the presence of the other. LA can interfere with PTT-based factor activity assays, resulting in a falsely decreased FVIII activity level and an erroneous diagnosis of congenital or acquired haemophilia A. Antiphospholipid antibody syndrome may be misdiagnosed due to presence of FVIII inhibitor-associated false positive results for LAs, especially when the silica clotting time (SCT) test is used. The diluted Rusell viper venom time test (dRVVT), which is unaffected by the presence of the other autoantibody, is useful for differentiating between the two[13] which was also the case in our patient, hence LA was tested by dRVVT method.

Lupus anticoagulants are a heterogeneous class of immunoglobulins that bind to glycoprotein I and, more rarely, prothrombin or other proteins in complex with negatively charged phospholipids. Lupus anticoagulants prolong phospholipid-dependent coagulation tests, including the aPTT[10]. The presence of lupus anticoagulants can be incidental or associated with an increased risk of thrombosis. Rarely, the presence of lupus anticoagulants is associated with an increased risk of bleeding.

A high-risk antiphospholipid antibody testing profile is defined by the presence of a positive lupus anticoagulant test[11], whereas the definitive diagnostic criteria include triple positivity for antiphospholipid antibodies (lupus anticoagulants, anticardiolipin IgM and IgG, and beta-2-glycoprotein IgM and IgG antibodies)[12].

In our patient with Sjögren's syndrome with thrombocytopenia and prolonged aPTT, on doing a mixing study to determine the factor inhibitor or factor deficiency, aPTT failed to normalise with the mixing study, and our patient was detected to have a concomitant Lupus anticoagluant and factor VIII inhibitor antibody with the presence of an underlying autoimmune aetiology, hence making this case a rare entity. The patient was started on steroids, and her platelets increased. She became symptomatically better, was then discharged, and is on regular follow-up.

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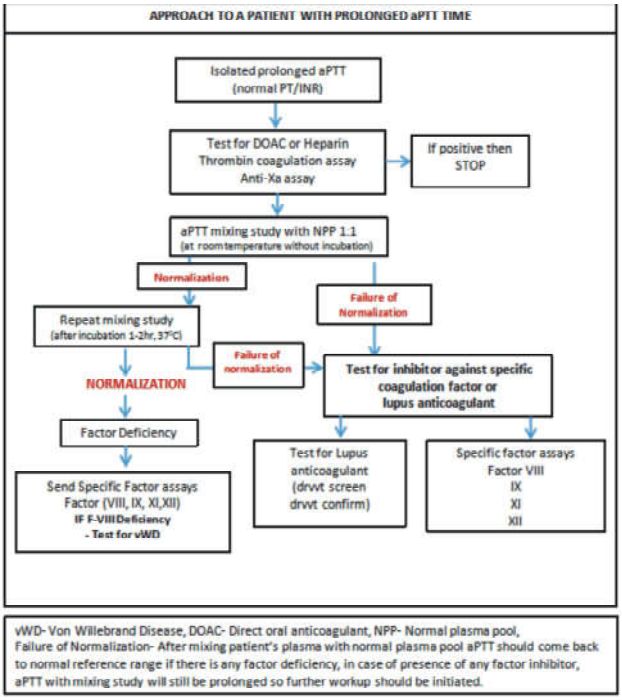

Fig. 1: *Approach to a patient with prolonged aPTT*[14].

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ANNOUNCEMENT

Invitation for Papers (Platform/Poster) for IACMCON-2024, Udaipur, Rajasthan

Scientific papers are invited for Platform Presentation and Poster Presentation during IACMCON-2024 being held from 27th – 29th September, 2024

at Bamboo Saa and SPA, Udaipur, Rajasthan

The Poster Size should be 3 feet x 4 feet (approx.)

Prizes will be given for Best Platform Presentation and Best Poster Presentation.

The abstract of the paper should be mailed to:

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The hard copy of the Abstract should be sent to:

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Last date for receiving the Abstracts is 15th July, 2024.