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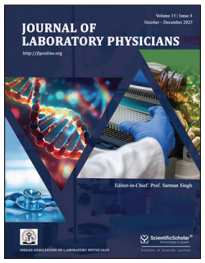

Case Series

Lupus anticoagulant-hypoprothrombinemia syndrome presenting as bleeding diathesis – A study of two cases

Paruvathavarthini Thambiraj[1], Narasimhapriyan Kannan[1], Rakhee Kar[1], Prabhu Manivannan[1]

[1]Department of Pathology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India.

***Corresponding author:**
Prabhu Manivannan,
Department of Pathology,
Jawaharlal Institute of
Postgraduate Medical
Education and Research,
Puducherry, India.

drprabhumanivannan@gmail.com

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ABSTRACT

Lupus anticoagulant (LA)-hypoprothrombinemia syndrome is a combination of acquired factor II (FII) deficiency and LA. Herein, we report two young females presenting with a clinical history of menorrhagia, epistaxis, and gum bleeding with prolonged prothrombin time and activated partial thromboplastin time. The inhibitor screen suggested the presence of an immediate-acting inhibitor; tests for the presence of LA were positive. Factor assays performed showed low FII levels. Early diagnosis of this entity is crucial as it results in fatal complications due to bleeding.

Keywords: Bleeding, Factor II, Inhibitor and hypoprothrombinemia, Lupus anticoagulant

INTRODUCTION

Clotting factor II (FII) or prothrombin is a Vitamin K-dependent coagulation cofactor that is cleaved by factor Xa to form thrombin. Inherited FII deficiency is uncommon, and acquired deficiency is commonly seen in severe liver disease and Vitamin K deficiency/antagonist treatment. In rare cases, acquired FII (prothrombin) deficiency has been associated with lupus anticoagulant (LA). Less than 100 cases have been reported in the literature till now.[1-12] This acquired deficiency is due to the presence of acquired antibodies against FII.[1-3] In general, cases showing LA positivity manifest with thrombosis; however, if they present with hemorrhagic manifestations due to low FII levels, such entity is known as LA-hypoprothrombinemia syndrome (LAHS). The diagnostic challenges in such cases are the prolongation of clot-based end-point tests such as silica clotting time (SCT) and dilute Russell viper venom test (DRVVT) due to inhibitors and concomitant factor deficiencies.[1-5] In this study, we would like to describe two cases of LAHS along with our suggestion to work up of such cases.

CASE SERIES

Case 1

A 21-year-old female presented with a history of menorrhagia for 1 year which required packed red blood cells (RBC) transfusion and hormonal therapy. The patient had a history of two spontaneous abortions before 20 weeks of gestation. There was no history suggestive of cardiac disease, rodenticide poisoning, or any history of anticoagulant therapy or significant

family history. There was no evidence of other bleeding manifestations. The local causes of uterine bleeding and arterio-venous malformation were ruled out by examination and imaging findings. The International Society of Thrombosis and Hemostasis Bleeding Assessment Tool (ISTH-BAT) score[13] was six, indicating significant bleeding.

The results of initial basic investigations and screening coagulation tests are highlighted in Table 1. The inhibitor screen was performed with a fresh and incubated mix of the patient plasma and normal pooled plasma at 0 h, 1 h, and 2 h that showed the presence of immediate-acting inhibitor. Hence, a screening test by DRVVT and SCT was done, which showed positivity for LA, and in view of bleeding, individual factor assays were performed after three levels of careful dilution, and results are described in Table 2, showing reduced FII levels; therefore, the diagnosis of LAHS was made.

It was advised to investigate further for autoimmune serology which showed positivity for antinuclear antibody (ANA) of 1+ and subsequently found to have positivity for anti-beta2-glycoprotein I (β2-GPI) antibody and anticardiolipin (ACL) by enzyme-linked immunosorbent assay (ELISA), thereby further adding the strength to the diagnosis. She was started on steroids and hydroxychloroquine, got symptomatically better, and discharged. She was followed up and showed persistence of positivity for DRVVT and SCT after 12 weeks, thereby confirming our diagnosis.

Case 2

A 19-year-old female presented with epistaxis, menorrhagia, and gum bleeding for 9 months and received three packed RBCs transfusions. Local causes for bleeding were ruled out, and there was no significant drug exposure/rodenticide poisoning or family history of bleeding. The ISTH-BAT score[13] was six (significant).

Table 1: Basic investigations and initial screening coagulation tests in case 1 and 2.

S. No	Tests	Case 1	Case 2	Control sample value	Reference range in our laboratory
1	Hb (g/L)	50	74	NA	126–152 (Females)
2	Total WBC count ($\times10^9$/L)	5.2	7.6	NA	4–11
3	Platelet count ($\times10^9$/L)	100	247	NA	150–450
4	Peripheral smear	Microcytic hypochromic RBCs, no atypical cells/ schistocytes	Microcytic hypochromic RBCs, no atypical cells/ schistocytes	NA	NA
5	Liver function tests	AST: 32 IU/L ALT: 30 IU/L Total bilirubin: 0.47 mg/dL)	AST: 21 IU/L ALT: 33 IU/L Total bilirubin: 0.53 mg/dL)	NA	AST: 20–40 IU/L ALT: 20–40 IU/L Total bilirubin: 0.2–1 mg/dL)
6	Blood and urine culture	Sterile	Sterile	NA	NA
7	Erythrocyte sedimentation rate at the end of 1 h	15	12	NA	4–10
8	C-reactive protein (mg/dL)	0.15	0.1	NA	0.1–0.3
9	Procalcitonin (ng/mL)	0.05	0.08	NA	0.01–0.2
10	D-dimer (Qualitative)	Negative	Negative	NA	NA
11	PT (s)	34.3”	34.0”	10.9”	9.4”–12.79”
12	APTT (s)	66.6”	82.4	31.1”	24.54–34.17”
13	TT (s)	17.6”	16.8”	14.3”	14.26–17.38”
14	Fibrinogen (mg/dL)	299	432	347	217–432 mg/dL
15	Mixing studies: APTT based (½ patient: ½ control)	46.5” (not corrected)	90.0” (not corrected)	NA	NA
16	Mixing studies: PT based (½ patient: ½ control)	12.8” (corrected)	16.2” (corrected)	NA	NA

Mixing studies done with normal pooled plasma (NPP) (from 20 healthy subjects) in 1: 1 ratio, “ indicates test values in seconds. Hb: Hemoglobin, NA: Not applicable, RBC: Red blood cells, WBC: White blood cells, AST: Aspartate transaminase, ALT: Alanine transaminase, APTT: Activated partial thromboplastin time, TT: Thrombin time, PT: Prothrombin time

Table 2: Screening tests for lupus anticoagulants and individual factor assays for case 1 and 2.

S. No	Name of the test	Test values of case 1	Test values of case 2	Control (C)	Reference range in our laboratory
1	DRVVT screen test/ratio	88.2”/2.86	169.0”/5.48	30.8”	25.88”–39.70”
2	DRVVT confirm test/ratio	61.7”/2.29	84.1”/3.12	26.9”	25.68”–32.41”
3	DRVVT normalized ratio	1.24*	1.75*	0.87	<1.2
5	DRVVT (½ patient: ½ control) mix - screen	96.6”	198.2”	30.8”	NA
6	DRVVT (½ patient: ½ control mix - confirm	40.5”	49.4”	26.9”	NA
7	SCT screen test/ratio	88.0”/2.29	138.1”/3.60	38.3”	30.12”-41.40”
8	SCT confirm test/ratio	105.1”/3.10	95.6”/2.82	33.8”	25.66–38.15”
9	SCT normalized ratio	0.73	1.27*	0.88	<1.16
10	Factor II assay	2.3%	3.2%	117.9% (C1), 109.4% (C2)	50–150%
11	Factor V assay	92.5%	71.7%	114.9% (C1), 114.9% (C2)	50–150%
12	Factor VII assay	42.2%	70.5%	87.7% (C1), 87.7% (C2)	50–150%
13	Factor VIII assay	127.1%	23.8%	108.8% (C1), 112.8% (C2)	50–150%
14	Factor IX assay	71.0%	2.0%	87.7% (C1), 108.8% (C2)	50–150%

NA: Not applicable, DRVVT: Dilute Russell viper venom test, SCT: Silica clotting time, “ Indicates test values in seconds, * Indicates repeat testing was positive in both the cases after 12 weeks, SLE: Systemic lupus erythematosus

Results of initial basic investigations and screening coagulation tests are tabulated in Table 1. The inhibitor screen showed the presence of an immediate-acting inhibitor, and subsequently screening test for LA by DRVVT and SCT was found to be positive. In view of bleeding, individual factor assays were performed after three levels of careful dilution, and results are described in Table 2. Interestingly, in addition to reduced FII levels, we also found reduced factor VIII and IX and could occur in the diagnosis of LAHS.

Further, she was found to have systemic lupus erythematosus (SLE) with positivity for ANA (4+), anti-dsDNA, and anti-histone protein. She showed positivity for anti-β2-GPI antibody and ACL by ELISA and persistence of positivity for DRVTT and SCT after 12 weeks on follow-up. She got symptomatically better and discharged with advice to take steroids and hydroxychloroquine.

DISCUSSION

LA is an antiphospholipid antibody that inhibits phospholipid-dependent clotting without affecting the activity of individual coagulation factors, leading to severe thrombotic disorders and obstetric complications.[1] These autoantibodies bind to phospholipid-binding proteins, and the target antigen is β2-GPI. Conventionally, these autoantibodies are assayed using phospholipid-dependent tests and are classified as LA and ACL based on their methods of detection.[1,2] Classically, these *in vitro* tests cause the prolongation of coagulation tests in the laboratory and are therefore called as “lupus anticoagulant;” however, this is a misnomer, and it actually causes “*in vivo*” thrombosis. The diagnosis of LA is based on Modified Sapporo criteria (Sydney revision 2006) and further updated in 2020.[2,3]

LAHS is a rare entity associated with hemorrhagic manifestations, more commonly seen in the pediatric age group (median age - 13 years) and young women with an overall female: male ratio of 1.5: 1, which was similar to our cases.[1-3] It is commonly associated with autoimmune conditions such as SLE or can occur secondary to viral infections especially in the pediatric age group, who usually have spontaneous resolution compared to adults.[4-12]

In most cases, the initial symptom is bleeding, such as epistaxis, ecchymosis, and petechiae, to severe hemorrhagic symptoms, such as macroscopic hematuria, intracranial bleed, and gynecologic bleeding.[4-12] Both of our cases presented with menorrhagia.

The hypoprothrombinemia was evident on the prothrombin time (PT)--based one-stage FII assay, which showed low FII levels and normal levels of other factors such as FV, FVII, and FX. The presence of LA interferes with phospholipid-dependent *in vitro* coagulation studies, causing prolongation of activated partial thromboplastin time (APTT) but does not cause much prolongation of PT as PT reagent contains more phospholipids, which saturates the LA inhibitor.[1-4] LAHS should be suspected when APTT is uncorrected, and PT gets corrected on mixing studies with an initial positive screening test for inhibitor.[1-3]

LA usually presents with thrombotic manifestation, and LAHS should be suspected if presented with bleeding and normal platelet count without evidence of sepsis, deranged liver parameters, and disseminated intravascular

coagulation. The presence of concomitant acute acquired hypoprothrombinemia and LA is known as LAHS, and hence, the final diagnosis was made in these cases.

Previous studies reported severe hemorrhagic complications in LAHS patients when FII activity is <10% of normal.[5-12] The FII activity of 2.3% (case 1) and 3.2% (case 2) resulted in severe bleeding manifestations. Some LAHS patients can occasionally show reduced factor VIII and IX, similar to our case 2, had low factor VIII (23.8%) and low factor IX (2.0%), which can be rectified by increasing dilution of sample testing, which attenuates the influence of LA *in vitro* studies.[7]

Corticosteroids should be considered the first-line treatment, followed by immunosuppressive treatment. It is also difficult to reach an optimal balance between bleeding and thrombosis in LAHS patients who receive either of this treatment option.[5-12]

CONCLUSIONS

The learning points are LAHS needs to be suspected strongly and FII assay is warranted when hemorrhagic complications occur in LA cases in the absence of severe thrombocytopenia.

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