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SEVERE BLEEEDING DUE TO ACQUIRED HYPOPROTHROMBINEMIA-LUPUS ANTICOAGULANT SYNDROME. CASE REPORT AND REVIEW OF LITERATURE

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ABSTRACT

A 17-year-old girl was admitted to our department with a hemorrhagic syndrome due to a serious coagulopathy; prothrombin time (PT) INR was 2.46 and the activated partial thromboplastin time (aPTT) ratio 3.46. Coagulation tests with pooled normal fresh plasma did not correct aPTT because of a coagulation inhibitor, and only partially corrected PT. Factor II activity reached only 5%. Diluted Russell viper venom test (dRVVT) and kaolin clotting time (KCT) of patient plasma (PP) and of a mixture of PP/normal plasma (NP) detected the lupus anticoagulant (LA). The level of factor II antigen was 10%. We diagnosed systemic lupus erythematosus (SLE) with a rare acquired hypoprothrombinemia-LA syndrome (HLAS). The patient was treated with corticosteroids and high-dose Ig and a normal PT value was re-established.

Key words: lupus anticoagulant, acquired hypoprothrombinemia

Lupus anticoagulant (LA) belongs to a heterogeneous group of antibodies directed against negatively charged phospholipids. These phospholipids are involved in reactions of the blood coagulation cascade, including prothrombin activation by activated factor X.[1,2] LA, paradoxically, predisposes more to thrombosis than to hemorrhage.[3-7]

Sometimes LA coagulopathy may initiate with a hemorrhagic syndrome when an evident thrombocytopenia, or an acquired thrombocytopathy, or an acquired inhibitor of factor VIII is present.[4,8,9] Rarely, in adults or in children with or without systemic lupus erythematosus (SLE), LA has been associated with a hemorrhagic diathesis caused by factor II (FII) deficiency.[10-24]

We report the clinical case of a girl whose SLE onset was a hemorrhagic syndrome caused by a serious coagulopathy with prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT) due to a hypoprothrombinemia-LA syndrome (HLAS).

Case report

A 17-year-old girl was admitted to our hospital in January 1996 with a 2-month history of almost daily bilateral epistaxis that was not stopped by cauterization, a 3-month history of cutaneous hematomas, persistent metrorrhagia in the last month and intermittent temperature for 10 days. She took only one aspirin a week before hospitalization. The girl had no past history of congenital coagulopathy or other important illness.

Clinical examination showed a cutaneous hematoma on the left arm and some small hematomas on the legs, hard palate oral mucosa petechias, pathological lymph nodes of 2-3 cm in the left supraclavicular, bilateral laterocervical and bilateral axillary regions.

Clinical lab values were the following: ESR 121, hemoglobin (Hb) 8.1 g/dL, red blood cells (RBC) 2.83×10^{12}/L, MCV 85 fL, white blood cells (WBC) 2.9×10^{9}/L with N 1.37×10^{9}/L, Lym 1.06×10^{9}/L and LUC cells 8.6%, platelets (Plt) 119×10^{9}/L. PT INR was 2.46, the aPTT ratio 3.64, antithrombin III 103%, fibrinogen 637 mg/dL and XDP between 200 and 500 ng/mL. A peripheral blood smear was normal, lactate dehydrogenase (LAD) was 471 U/L, haptoglobin 0.68 g/L, reticulocytes 0.5%. Total proteinemia was 7.2 g/dL with a polyclonal hypergammaglobulinemia, C3 0.35 g/L (normal value 0.9-1.8 g/L) and C4 less than 0.03 g/L (normal value 0.1-0.4 g/L); no cryoglobulins were present in the serum. Renal and hepatic function were normal. There was an albuminuria of 1360 mg/24h. Tests for anti-nucleoprotein antibodies (ANA) were positive 1:2560, anti-DNA 1:160 positive, anti-RNP and even anti-SM were positive. Direct Coombs' test IgG and C3d was positive.

The patient coagulation data on the 2nd day were following: PT INR 2.01, PT ratio of a 1:1 mixture of patient's plasma (PP) and normal plasma (NP) was 1.32. The aPTT ratio was 2.99, aPTT mix PP/NP ratio 2.72, diluted Russell viper venom test (dRVVT) more than 160 seconds, dRVVT mix more than 160 seconds (Table 1). There were a serious PT prolongation and a correction albeit partial of PT in the PP/NP mixture. Factor II activity was 5% (n.v. 70-

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Table 1. Patient coagulation data during hospitalization and follow-up.

Day	1st	1st fresh frozen plasma	2nd	5th	15th	60th
			HDIg x 5 days + PDN 1 mg/kg/day			
PT ratio	2.46	1.85	2.01	1.78	1.74	1.12
PT mix ratio			1.32	1.20	1.19	
aPTT ratio	3.64	3.04	2.99	2.63	1.60	1.28
aPTT mix ratio			2.72	2.17	1.21	
dRVVT ratio			> 160 sec	4.43	1.75	
dRVVT mix ratio			> 160 sec	5.22	3.84	
KCT ratio					1.72	
KCT mix ratio					3.97	
Ab aCL IgG			50			neg
Ab aCL IgM			60			neg
Factor II coagulant			5%			
Factor II antigen			10%			

mix=mixture of patient's plasma and normal plasma at a ratio of 1:1. dRVVT= dilute Russell's viper venom time. KCT= kaolin clotting time. Ab aCL= anticardiolipin antibodies IU/mL. HDIg=Ig 400 mg/kg/day. PDN=prednisolone.

130) and its immunological level was 10%. The values for the others factors influencing PT were not remarkably reduced (factor V 51%, factor VII 59% e factor X 58%). There were also low levels of factor VIIIc (4%), factor IX (1%), factor XI (35%) and factor XII (3%); this pattern is typical of LA and reflects nonspecific interference by the anticoagulant in the assay system. In the end a diagnosis of HLAS in SLE was formulated.

For the serious coagulopathy condition the patient was treated on the first day of hospitalization with 1 unit of fresh plasma from apheresis. After that the PT INR was found to be 1.85 and the aPTT ratio 3.04. Next we started treatment with prednisolone 1 mg/kg/day and Ig 400 mg/kg/day for 5 days (HDIg). At that time coagulation tests were as follows: PT INR 1.78 and PT mix PP/NP ratio 1.20, aPTT ratio 2.63 and aPTT mix PP/NP ratio 2.17, dRVVT ratio 4.43 and dRVVT mix PP/NP ratio 5.22. Coagulation tests after 15 days of corticosteroid treatment showed these values: PT INR 1.74 and PT mix ratio 1.19, aPTT ratio 1.60 and aPTT mix ratio 1.21, dRVVT ratio 1.75 and dRVVT mix ratio 3.84, kaolin clotting time (KCT) 1.72 and KCT mix ratio 3.97 (Table 1). The patient was discharged on corticosteroid treatment at a dosage of 1 mg/kg/day.

After 2 months the patient had a regular mestrual period and no hemorrhagic events. Clinical lab values were then: PT INR 1.12, aPTT ratio 1.28, positive LA; a search for anticardiolipin antibodies (aCL) was negative (Table 1). ESR was 39, Hb 10.3 g/dL, WBC 4.21×10^9/L with N 1.6×10^9/L and Lym 2.1×10^9/L, Plt 245×10^9/L, C3 0.44 g/L and C4 0.04 g/L, direct Coombs' test positive for IgG and C3d, proteinuria absent, ANA still positive (1:2560) and anti-DNA negative.

Discussion

LA is an acquired coagulation inhibitor which acts on the phospholipid-dependent coagulation tests.[1,2] It causes a prolongation of the times of many of these tests, such as aPTT, KCT and dRVVT,[25] as well

Table 2. Literature survey of patients affected by HLAS.

N.	Age/sex	Hemorrhagic syndrome	Factor II activity	Factor II antigen	SLE	Other diseases	Therapy	References
1	12F	yes	< 1%	nd	yes		1	10
1	17F	yes	2%	nd	yes		1	11
1	12M	yes	< 1%	5%	yes		1 + 2	12
1	39M	no	20%	19%	no	lymphoma	1 + 2	13
2	4 F	yes	< 1%	absent	no	viral	—	14
	12F	no	6%	6%	yes		1 + 2	
2	40F	—	19%	9%	yes			15
	38F	—	45%	22%	yes		—	
1	66M	no	32%	nd	no	ns	1 + 3	16
3	ns	yes	10%	< 5%	ns	ns	—	18
	ns	yes	9%	< 5%	ns	ns	—	
	ns	yes	4%	< 5%	ns	ns	—	
1	24M	yes	2%	absent	yes		1	19
4	3 M	no	16%	<12%	no	viral	—	20
	4 F	no	10%	<12%	no	viral	—	
	7 F	no	22%	<12%	no	viral	—	
	5 F	no	11%	<12%	no	viral	—	
1	3 F	yes	< 1%	absent	yes		1	21
1	5 F	yes	15%	nd	no	viral	—	22
3	15F	yes	5%	nd	yes		1	23
	10F	yes	12%	nd	yes		1	
	11F	yes	4%	nd	yes		1	
1	38M	yes	13%	nd	no	ns	1	24

1 = steroid; 2 = azathioprine; 3 = cyclophosphamide; nd = not determined; ns = not specified.

as venous and/or arterial thrombotic events in 30-40% of the carrier subjects.[3-7]

Our patient started with a hemorrhagic syndrome caused by a complex coagulopathy characterized by a marked prolongation of PT and aPTT. The failure of the aPTT, dRVVT and KCT coagulation times to normalize, even when normal plasma was added, demostrated the presence of a LA-type inhibitor.[25] The serious deficit of aPTT-dependent factors was typical of LA.[25] The factor II deficiency (5%) explained by marked PT prolongation. Should we therefore suspect the presence of another coagulation factor inhibitor? No, there was not because the prothrombin antigen level was found to be very low (10%). This confirmed that our patient was affected by HLAS.

HLAS is a rare disease (we found only 23 cases in literature).[10-24] It appears mostly in young females, even infants[10,14,20-23] (Table 2). It presents as a complication of SLE[10,12,14,15,19,21,23] or transitory viral infections[14,20,22] (Table 2). HLAS may from laboratory reports as prolonged PT and aPTT prolongation, or from clinical signs such as cutaneous purpura and epistaxis.[10-12,14,18,19,21-23] In only one case was a brain hemorrhage described.[24] Hemorrhage occurs when the factor II deficiency is very low, usually under 10%[10-14,19,21,23] (Table 2). HLAS is characterized by a very strong LA and polyspecific antibodies. They bind the epitopes of the anionic phospholipids and of prothrombin, but they do not neutralize prothrombin.[14,15,17,18] Therefore FII activity deficit is not due to an inhibitor, as suspected, but to an evident factor decrease owing to the higher clearance of the prothrombin-antibody complex in the reticuloendothelial system.[14,15,19,21,24]

Corticosteroid therapy is the treatment of choice for HLAS associated with SLE; it normalizes the PT time[10-14,19,21,23] (Table 2). In cases associated with viral infection, HLAS reverses spontaneously with the resolution of the infection. Steroid therapy is therefore not necessary[14,20,22] (Table 2).

Given the complex coagulopathy of our patient, caused by an acquired inhibitor, and the risk of serious major hemorrhage, we started steroid therapy and added HDIg. HDIg are known to be useful in the treatment of circulating inhibitor coagulopathies.[26] We obtained progressive improvement of PT and aPTT times until complete PT normalization of the former and contemporary resolution of the hemorrhaging. Finallly, as the other authors we show that LA not always produces aPTT prolongation, but may also produce a more complex coagulopathy with PT prolongation-HLAS type. HLAS onset could be hemorrhage related with an added FII deficit and marked inhibitor effects of aPTT-dependent factors. In our patient HLAS was the first and the most important clinical sign of the onset of the systemic illness. Our patient's HLAS was successfully treated with steroids, confirming that these compounds represent the leading therapy for this coagulopathy. We also associated HDIg but it is not possible to say whether they are useful in normalizing PT in this case.

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