A CIRCULATING HEPARIN-LIKE ANTICOAGULANT WITH NO BLEEDING COMPLICATIONS: CASE REPORT

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INTRODUCTION

To date, only few case reports in the literature describe the acquisition of heparin-like anticoagulant, with bleeding severity ranging from severe to nearly asymptomatic. Cirrculating heparin-like anticoagulant has been associated with different disorders like hematological malignancies, solid tumors, hepatic failure, chronic renal disease and acquired immunodeficiency syndrome. However, the source and the mechanism of release of endogenousn heparin-like anticoagulants are poorly understood.

PATIENT HISTORY

70-year-old man referred to our hospital due to an unexplained proingation of thrombin time found as the only pathological result of screening assays on several occasions during his preoperative laboratory workup. The patient has no prior bleeding history or spontaneous bleeding manifestations, although he underwent several operations.

MATERIALS AND METHODS

REAGENTS

- **PROTHROMBIN TIME (PT) – Innovin/BCS XP (Siemens Medical Solutions Diagnostics, Germany)**
- **ACTIVATED PARTIAL THROMBOPLASTIN TIME (aPTT) – Actin FS/BCS XP (Siemens Medical Solutions Diagnostics, Germany)**
- **THROMBIN TIME (TT):**
  - **Bovine thrombin - BC Thrombin/BCS XP (Siemens Medical Solutions Diagnostics, Germany)**
  - **Human thrombin – STA Thrombin/BCS XP (Diagnostica Stago, France)**
- **FIBRINOGEN – Multifibren U/BCS XP (Siemens Medical Solutions Diagnostics, Germany)**
- **FIBRINOGEN ANTIGEN – N Fibrinogen/BN II (Siemens Medical Solutions Diagnostics, Germany)**
- **REPTILASE TIME – Bathroxobin/BCS XP (Siemens Medical Solutions Diagnostics, Germany)**
- **ANTITHROMBIN ACTIVITY (AT) – Berichrom Antithrombin III (A)/ BCS XP (Siemens Medical Solutions Diagnostics, Germany)**
- **FIBRINOGEN/FIBRIN DEGRADATION PRODUCTS (FDP) – FDP Plasma (Diagnostica Stago, France)**
- **D-DIMER – VIDAS D-Dimer Exclusion/mini VIDAS (bioMérieux, France)**
- **LUPUS ANTICOAGULANT SCREENING TESTS/BCS XP: (according to the guidelines proposed by the SSC Subcommittee on Lupus Anticoagulant and Phospholipid-Dependent Antibodies of the ISTH)**
  - **dPT – Innovin (Siemens Medical Solutions Diagnostics, Germany)**
  - **dAPTT and aPTT – Dapttin (Technoclone GmbH, Austria)**
  - **dRVVT – LA1 (Siemens Medical Solutions Diagnostics, Germany)**
- **LUPUS ANTICOAGULANT CONFIRMATORY TESTS:**
  - **dRVVT – LA2/BCS XP (Siemens Medical Solutions Diagnostics Germany)**
  - **LUPUS ANTICOAGULANT TEST Reagent Kit/(Technoclone GmbH, Austria); LCA index >15 means lupus anticoagulant positive**

ADDITIONAL REAGENTS:

- **HEPARINASE I – Hepzyme (Siemens Medical Solutions Diagnostics, Germany)**
- **PROTAMIN HYDROCHLORIDE (1000 IE/1mL) – Protami Valeant 1000 (Valeant Pharmaceuticals, Switzerland**

RESULTS

Table 1. Result of the initial and repeated coagulation studies in tested patient plasma samples

Coagulation assay	1st visit May 2009	2nd visit October 2009	3rd visit December 2010	4th visit November 2011	Reference interval
PT	1.05	1.03	1.04	1.04	>0.70
aPTT (sec)	30.3	36.2	34.5	35.7	24-33
TT (sec)	98.9	139.0	98.2	103.9	16.0-21.0
Fibrinogen (g/L)	2.2	3.1	3.5	3.1	1.8-4.1
Fibrinogen antigen (g/L)	2.5	4.0	n.d.	n.d.	1.8-3.5
Reptilase time (sec)	17.1	17.1	15.1	n.d.	16.0-22.0
Antithrombin activity (%)	106.4	n.d.	n.d.	n.d.	75.0-125.0
FDP (mg/L)	<5	n.d.	n.d.	n.d.	<5
D-dimer (mg/L FEU)	n.d.	0.32	n.d.	n.d.	<0.5
Lupus anticoagulant	negative	positive	n.d.	positive	negative

n.d.-not determined

Table 2. Thrombin time results obtained in native patient plasma samples and after mixing study

Tested plasma sample	Thrombin time (sec)	
	1st visit May 2009	2nd visit October 2009
Patient (native sample)	98.9	139.0
Patient + Heparinase I (Hepzyme)	88.3	132.8
Control	18.2	16.7
Patient + control (1:1)	38.1	78.3
Patient + control (1:4)	23.1	34.0
Patient + control (1:9)	n.d.	22.6

n.d.-not determined

Table 3. Thrombin time results obtained by using bovine and human thrombin

Tested plasma sample (October 2009)	Thrombin time (sec)*	
	Bovine thrombin	Human thrombin
Patient (native sample)	139.0	111.1
Control	16.7	13.9
Patient + control (1:1)	67.5	70.5
Patient (inactivated 10 min at 56 °C) + control (1:1)	23.1	34.0

*reference interval: bovine thrombin 16-21 sec; human thrombin < 21 sec

Table 4. Thrombin time results obtained after *In vitro* addition of protamine

Protamine concentration U/mL	Thrombin time (sec)*
0.0	119.5
0.1	52.5
0.2	30.2
0.3	21.7
0.4	16.0

*reference interval:16-21 sec

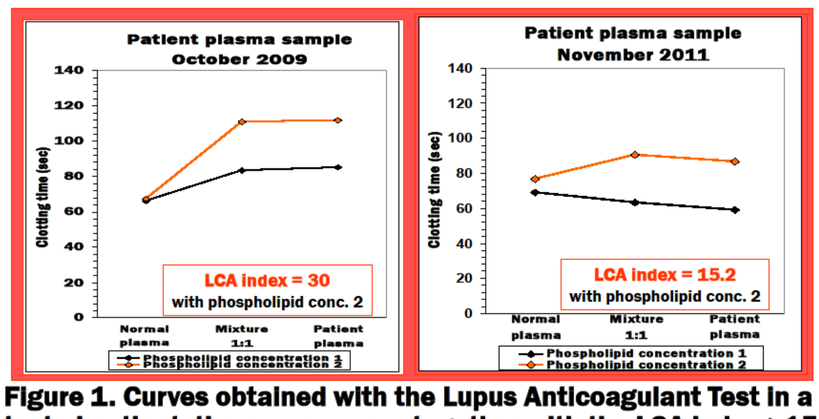

Figure 1. Curves obtained with the Lupus Anticoagulant Test in a tested patient; the convex curve together with the LCA index >15 obtained with phospholipid concentration 2 means an additional confirmation of the presence of lupus anticoagulant

CONCLUSIONS

The correction of the thrombin time after the *in vitro* addition of protamine hydrochloride suggested that the cause of prolonged thrombin time was the presence of a cirrculating heparin-like anticoagulant. The patient was followed for three years without bleeding complications, but he became and remained lupus anticoagulant positive. However, the uderlying mechanism responsible for the production and release of heparin-like anticoagulant is not clear yet.

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