Human antithrombin inhibitor associated with lupus anticoagulant in a patient undergoing aortic valve replacement: a case report

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Summary

Our case report describes the perioperative management of an 84-year-old patient hospitalized one day before aortic valve replacement, in which we discovered the presence of a human antithrombin inhibitor associated to a lupus anticoagulant.

Introduction

Literature overflows with reports on acquired inhibitors of thrombin or acquired coagulation factor inhibitors (2). We here report the unique case of a patient scheduled for heart surgery, who developed a lupus anticoagulant associated with an acquired inhibitor of human thrombin. This pathology did not appeared to be linked to any precipitant factor. Such acquired disorders can manifest in variable ways (4), including thrombotic, hemorrhagic, or asymptomatic clinical pictures. Guidelines for treatment of such cases remain vague (5).

Patient information:

An 84-year-old man was admitted to the cardiac surgery department for an elective aortic valve replacement. His past medical history consisted in chronic high blood pressure that was treated with beta-blockers and calcium antagonists, and atrial tachycardia that had been treated by cordarone in 2012. His past surgical history encompassed cholecystectomy, colon cancer surgery, and parotidectomy. He had never received any blood products before, and had a negative hemorrhagic diathesis questioning.

The clinical preoperative evaluation revealed asthenia and normal clinical parameters. Preoperative assessment was performed outside our hospital, and revealed severe aortic stenosis, as well as normal coronarography, normal electrocardiography, and normal respiratory function. He had had preoperative blood analyses one day before surgery that showed a hemoglobin concentration...
of 15.2 g/dL, a platelet account of 248 $10^3$/mm$^3$, and normal renal and hepatic functions. Lactate dehydrogenase concentration was 662 UI/L (normal range: 313-618 UI/L).

**Hemostasis evaluation**

The first hemostasis evaluation took place in 2012. During the pre-operative evaluation for a parotidectomy, the discovery of a thrombin time > 120 seconds, not corrected by protamine and with d-dimers and fibrinogen in the normal range, prompted the institution where those analyses were made to transfer blood samples of the patient to our lab. For further investigations, our lab tested the thrombin time with two different reagents: STA®-Thrombin (Diagnostica Stago) containing human thrombin and Thrombin Time (Werfen) containing bovine thrombin. The thrombin time was normal (20.7 sec; normal range: 19-26 sec) when tested with the bovine thrombin on the ACL-TOP coagulometer (Werfen), but significantly prolonged when tested with the human thrombin on the STA-R coagulometer (> 120 sec; normal range: 19-26 seconds). The reptilase time was also tested, and was in the normal range (19.9 seconds, normal range: < 20 sec). This allowed excluding heparin use. A generation thrombin test was also carried out … (Jon). The conclusions of those testing were that the patient had an inhibitor directed against human thrombin.

In parallel, basic coagulation testing revealed a PT of 100 %, with prolonged synthasil-activated APTT (59.7 sec; normal range: 26-38 sec). This APTT remained prolonged after a 50/50 mix with NPP, which indicates the presence of an inhibitor and not a factor deficit. In addition to this, factors II, V, VII, X, VIII, IX, and XI were measured, and were in the normal range. When measured with CK-prest, a cephalin less sensitive to lupus anticoagulant, the APTT almost completely corrected. One of the reasons of this slight prolongation of APTT might be the presence of anti-human thrombin. Presence of lupus anticoagulant was also confirmed. The anticardiolipine (IgM, IgG) and the anti B2 GP1 (IgM, IgG) antibodies were absent.

A summary of those results is presented in Table 1.

The patient was admitted to our Institution in January 2015, in order to beneficiate from an aortic valve replacement. His hemo-static abnormal assessment came to our knowledge on the day before surgery. Based on this, thrombin time was again directly tested using the two reagents, namely human and bovine thrombin. PT, TCA (APTT with synthasil), and TCK (APTT with CK-prest) were also reassessed. The results are shown in Table 2, and are consistent with the previous findings.

**Clinical impact**

At this moment, two problems emerged for the perioperative management of this patient. First, the presence of a lupus anticoagulant may affect the results of activated clotting time (ACT) measured with the Hemochron® Signature Elite. Indeed, this coagulation assay is used in the operating room to
assess heparin anticoagulation level during cardiac surgery (7)(8). To overcome this problem, we measured the basal ACT before surgery with a coagulometer of our laboratory (KC10), and compared the results with the Hemochron®. Results were similar, exempting us from adapting a reference range for different heparin anticoagulation levels (ref à ajouter). The results of these ACTs are shown in Table 3.

Second, insofar as antithrombin inhibitors can have variable clinical manifestations, either severe bleeding, thrombosis, or be asymptomatic, we wondered how managing eventual severe bleeding, particularly for this patient scheduled to undergo high bleeding risk surgery. The question was to prepare for administering either fresh frozen plasma, factors concentrate (PPSB), fibrinogen, factor VII, or a combination of them (1). A clear answer to this question could not be found in the literature. The only reassuring element was the existence of several uneventful previous surgeries in this patient.

**Therapeutic intervention**

On the day of surgery, the patient was equipped with two peripheral venous lines and an arterial line. He received sufentanil, midazolam, ketamine, propofol and rocuronium for induction of anesthesia, before endotracheal intubation. An ultrasound-guided venous central line was placed in the internal jugular vein. Sevoflurane and sufentanil infusion were used for maintenance of anesthesia. The patient received a bolus of 1 g of tranexamic acid before incision, followed by a continuous infusion of 1 mg/kg/h.

The aortic valve replacement (bioprosthesis) was performed through a mini-sternotomy incision. Before starting bypass, the patient received 30000 UI of heparin, which elevated the ACT to 408 s. Cardiopulmonary bypass lasted 60 minutes, and aortic clamping 35 minutes. Five thousand supplementary units of heparin were need to maintain a correct ACT during that time. Heparin was antagonized after leaving bypass using 30000 UI of protamine.

No complications occurred. The patient showed a clinically normal hemostasis and received only cristalloids (normal saline, 1650 mL), gelofusine (1500 mL), and autologous blood transfusion (cell-saver marque – 374 cc) during surgery.

He was transferred to the intensive care unit when stable. This transfer occurred under sedation, and with a noradrenaline infusion of 5 µg/min. He developed an acute renal failure at day 2, which responded to crystalloid filling well and normalized at day 7. He also developed a post-operative high blood pressure episodes, which were treated using an angiotensin-converting enzyme inhibitor. An ectopic atrial rhythm appeared at day 2, which turned into atrial fibrillation at day 3 and required therapeutic low molecular weight heparin anticoagulation. This treatment switched to vitamin K antagonist on day 10.
TCA, PT and TT (human thrombin and bovine thrombin were alternatively used) were followed during the postoperative period. Upon arrival in the intensive care unit, hemoglobin level was 10g/dL, and platelet account was $10^3\times10^3$/mm$^3$. Prolonged PT appearing at the end of hospital stay can be explained by the introduction of the vitamin K antagonist. Regarding TT and TCA disturbance during the postoperative period, a possible explanation resides in a direct effect of bypass or/and hemodilution on those parameters.

Finally, no events related to bleeding or thrombosis were to be reported, and the patient could leave the cardiac surgery department at day 16.

**Discussion:**

Although acquired inhibitors of coagulation factors are quite common, acquired inhibitors of human thrombin are more or less rare inside the human population. An acquired inhibitor of human thrombin associated with a lupus anticoagulant is rare. Our patient didn’t have any personal or familial history of hemostatic issues. We were incidentally aware of this problem, and measured the TT with two different reagents directly. We also confirmed our diagnosis with specific explorations.

The ACT to monitor heparin anticoagulation during bypass was also a problem; the laboratory did help us to make sure that the Hemochron® Signature Elite used in the operating room would not be affected by the patient’s auto immune system (référence tableau).

Literature asserts that most inhibitor of thrombin or coagulation factors cases concern people with either exposure to topical preparations of bovine thrombin (3) or with a predisposing illness (6). Among those reports, one describes the case of a patient who developed rectal bleeding from an arteriovenous malformation after endoscopic injection of fibrin glue containing human thrombin into a gastric ulcer. It triggered the release of an inhibitor against factor V, and a severe coagulopathy (3). Another case concerned a previously healthy elderly woman without any personal or familial history of bleeding. She presented to the emergency department with an acute hemorrhage, ending to her death. This fatal bleeding diathesis was caused by a spontaneously acquired human thrombin. Her thrombin time was 118 sec (normal range 16-27 sec) with a human reagent, and lupus anticoagulant was negative. Therapy begun only one week after presentation, and the patient finally had a massive fatal hemorrhage. After autopsy, no systemic disease was found (6). The first reported pediatric case was a 12-year-old girl, who presented with intractable menorrhagia several days after an acute infectious episode. Her laboratory tests were disturbed, and showed an antibody directed against human thrombin. She was unresponsive to standard treatments, but intra venous recombinant factor VIIa (Novoseven®) resulted in a successful outcome (1). An acquired inhibitor of thrombin was also described in a patient with a lupus-like syndrome triggered by a procainamide therapy (9). Four other reports described acquired inhibitors: one had evidence of underlying autoimmune disease (10), the
second had a lupus inhibitor in addition to an acquired inhibitor of factor II (11), the third had just
gone under major surgery, and was therefore at risk of having been exposed to topical bovine thrombin
(12), and the fourth had recurrent history of thrombosis (13).

Bio part...

From the above, it appears the effects of an acquired human thrombin can result in variable clinical
pictures: hemorrhage (1)(6), thrombosis, or be asymptomatic. The asymptomatic ones can be assumed
to be either not diagnosed or not being reported. The underlying health status of patients is of
importance. Indeed, our patient had a lupus inhibitor, got his thrombin time normalized, and altered
again thereafter. No particular trigger could be find. The choice of coagulation factors to treat those
patients can be uneasy (3)(1): fresh frozen plasma, factors concentrate (PPSB), fibrinogen, or
recombinant factor VII can all be options that may reveal efficient or not. There is still a lot of work to
refine management principles in those patients.

Our patient may have not suffered from any hemostatic issues, or needed any kind of specific
treatment. However, he underwent major, and we had to be able to treat or prevent any coagulation
disorder. Shouldn’t we have had discovered the prolonged thrombin time, we wouldn’t have had any
clue to treat an hemorrhagic or thrombotic event (4)(5)(6). Normal coagulation on one day does not
mean normal coagulation forever.

Informed consent:

We received the patient approval for using his data for a case report.

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