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### Case Report

## Acquired deficiency of coagulation factor VII



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### Introduction

Factor VII (FVII) is found in small amounts in plasma and has a very short half-life in circulation.

FVII is vitamin K-dependently synthesized in the liver. As such, hepatopathies, vitamin K deficiency, or use of vitamin K antagonists is the cause of acquired deficiency. Other types of acquired FVII deficiencies are rare.<sup>1</sup> Here we describe a case of acquired factor VII deficiency associated to the presence of lupus anticoagulant.

### Case report

A 36-year-old black male patient was hospitalized in March 2013 after a four-day period of low back pain, bruised hips, macroscopic hematuria, and gingival bleeding. At admission, he was conscious, oriented, pale, and tachycardic (108 beats per minute), with a blood pressure of 120/90 mmHg, mild edema, and varicose veins of the lower limbs. In addition, chronic malleolar ulcers were observed, with signs of bleeding and bruising in the pelvic region. The patient denied any personal or family history of bleeding diathesis. Renal and

urological diseases were also ruled out. Additional examinations revealed a hemoglobin level of 4.8 g/dL, platelet count of  $270 \times 10^9/L$ , and incoagulable blood based on the prothrombin time (PT) and activated partial thromboplastin time (APTT). The patient received a transfusion of red blood cells, cryoprecipitate and fresh frozen plasma. He was then transferred to the intensive care unit. Two days later, the patient still presented with hematuria, ecchymosis, and incoagulable blood according to PT, with patient-to-control APTT ratio of 1.79. Thus, transfusion support was continued. The patient had positive results for lupus anticoagulant antibodies and negative results for anticardiolipin immunoglobulin (IgM, IgG and IgA antibodies, as well as antinuclear and rheumatoid factors. The activity levels of the coagulation factors were 3%, 130%, 150%, >200%, 47%, and 75.8% for factors VII, II, V, VIII, IX and X, respectively. We chose to start intravenous pulse therapy with methylprednisolone and administer a prothrombin complex concentrate for persistent bleeding. The patient recovered well, with no bleeding after the administration of the prothrombin complex concentrate and corticotherapy. Corticotherapy was maintained with the oral administration of 1 mg/kg/day prednisone. The patient was discharged after 17 days of hospitalization and referred for follow-up in an outpatient clinic. The corticoid dose was reduced after monitoring

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**Table 1 – Evolution of tests over eight months.**

	Initial	After 8 months
PT (%) (RV: 70–100)	Incoagulable	83.2
APTT (P/C ratio) (RV: 0.9–1.25)	Incoagulable	1.05
Fibrinogen (mg/dL) (RV: 200–400)	396	248.7
Factor II (%) (RV: 70–120)	130	130
Factor V (%) (RV: 70–120)	180	180
Factor VII (%) (RV: 60–140)	3	60.6
Factor VIII (%) (RV: 50–150)	>200	>200
Factor IX (%) (RV: 50–150)	47	47
Factor X (%) (RV: 70–150)	75.8	75.8
Lupus anticoagulant	Positive	Negative

PT: prothrombin time; APTT: activated partial thromboplastin time; RV: reference value; P/C ratio: patient/control ratio.

in the clinic, and consecutive PT test results showed a progressive tendency toward normality. The patient's condition stabilized, without new hemorrhagic episodes. The corticoid treatment was suspended six months after the initial administration. Two months after, the PT was 83.2%, patient-to-control APTT ratio was 1.05, fibrinogen level was 248.7 mg/dL and FVII activity level was 60.6%.

Table 1 shows the evolution of the main tests from hospitalization to two months after the discontinuation of corticosteroids.

## Discussion

Hereditary coagulation factor deficiencies, except hemophilia, are autosomal recessive hereditary diseases, with incidences ranging from one case in 500,000 to one case in two million people.<sup>2</sup> Thus, they are considered rare coagulopathies. The suspected diagnosis is confirmed using prolonged PT and/or APTT, thereby suggesting the need for further evaluations. Among the rare congenital factor deficiencies, FVII deficiency is the most common.<sup>2</sup> The clinical manifestations of this condition range from asymptomatic to severe hemorrhagic disorders, although the most common bleeding sites are the skin and mucosae.<sup>3</sup>

Acquired FVII deficiency, which is not associated with vitamin K deficiency, antagonists or hepatopathies, though rare, is correlated with the presence of different tumors,<sup>1,4</sup> the occurrence of sepsis,<sup>5</sup> antiphospholipid antibodies,<sup>6</sup> aplastic anemia<sup>7</sup> and hematopoietic stem cell transplantation.<sup>8</sup>

Coagulation inhibitors are abnormal endogenous compounds that inhibit blood coagulation. Most of these inhibitors are antibodies that partially or completely neutralize the activation or function of a specific coagulation factor, but they can also interfere with interactions between several factors.

In most cases, these antibodies lead to deficiency of a specific factor due to increased peripheral clearance.<sup>6</sup>

The presence of lupus anticoagulant was originally identified in association with systemic lupus erythematosus but is currently described as associated with other inflammatory and benign diseases, as well as in healthy individuals without any apparent underlying disease.<sup>9</sup> *In vitro*, lupus anticoagulant is associated with prolonged APTT and rarely to prolonged PT. *In vivo*, the situation is different and it is strongly associated with arterial and venous thromboses and rarely with bleeding.

However, the presence of lupus anticoagulant may also be associated with antibodies against FVII, resulting in severe hemorrhagic diathesis. In a study of 33 patients presenting with antiphospholipid syndrome, Bidot et al.<sup>10</sup> reported that 67% of the patients had low FVII levels.

There are reports of acquired FVII deficiency associated with different clinical conditions. Granger and Gidvani<sup>1</sup> described a case of FVII deficiency in association with Wilms' tumor in a 2-year-old child, and Fatimi et al.<sup>4</sup> reported a 64-year-old patient with isolated prolonged PT, severe reductions in FVII activity, and a giant right atrial myxoma. After the surgical removal of the myxoma, the PT normalized and the FVII activity level increased within the first 24 h after surgery. Bidot et al.<sup>5</sup> described a 24-year-old patient with intra-abdominal septic focus who developed FVII deficiency, without evidence of inhibitors; the deficiency partially recovered only with the intravenous administration of vitamin K. With the resolution of sepsis, the patient's PT and FVII activity normalized. Lim et al.<sup>6</sup> reported a 71-year-old patient with an expanding hematoma of the thoracic and abdominal walls, and prolonged APTT and PT. Additional examinations revealed a potent lupus anticoagulant and reduced levels of multiple coagulation factors.

It is noteworthy that, in the current case, the prolonged PT may be related to the factor VII deficiency and the prolonged APTT to the presence of lupus anticoagulant, but it is possible that high levels of lupus anticoagulant can affect both PT and APTT<sup>6,11</sup> and, although rare, the titers may be reduced or even normalized with immunosuppressive therapy.<sup>11</sup> However, the paradoxical effect of thrombotic tendency should be remembered in the presence of lupus anticoagulant *in vivo* as there are reports of thrombotic complications due to the treatment of secondary bleeding using prothrombin complex concentrates and recombinant activated FVII in the presence of lupus anticoagulants.<sup>12,13</sup>

This patient did not present thrombotic complications secondary to the treatment instituted and, although he had a history of venous insufficiency and chronic malleolar ulcers, there is no evidence of current or previous venous thromboembolism. So the diagnostic criteria for antiphospholipid syndrome should not be closed because, despite having positive lupus anticoagulant test results, there are no clinical criteria, namely: (1) arterial, venous or small vessel thrombosis occurring in any tissue or (2) miscarriages in women.<sup>14</sup>

Isolated acquired FVII deficiency is rare, and its physiopathological mechanism is sometimes difficult to elucidate. No consensus has been reached regarding the treatment of secondary bleeding in such conditions. Antifibrinolytic agents, fresh frozen plasma, and prothrombin complex, as well as recombinant activated FVII (rFVIIa) concentrates, have been

used depending on the severity of bleeding and their availability in each institution. Some reports describe the use of immunomodulatory therapies, with varying success depending on individual patients. Noteworthy was the successful use of rFVIIa to control acquired and congenital FVII deficiency-induced bleeding, which was administered in repeated doses until the risk of hemorrhage was eliminated.<sup>12,13,15</sup>

Although the presence of a lupus anticoagulant is often related to thrombotic events, in this study, we describe a patient with an associated bleeding disorder. During treatment, the patient did not present other symptoms that justified FVII deficiency. As we have observed, lupus anticoagulant may also develop in normal individuals. This case study was based on the administration and subsequent discontinuation of high doses of corticoids, and the administration of prothrombin complex concentrates to control acute bleeding. The clinical course of the patient was satisfactory.

### Conflicts of interest

The authors declare no conflicts of interest.

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