

LETTER TO THE EDITOR

Prophylactic preparation and surgical extirpation of a very large abdominal blood cyst in a severe haemophilia A patient with inhibitors managed by rFVIIa

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Dear Editor,

The development of destructive haemophilic cysts (pseudotumours) occurs in approximately 1% of patients with severe haemophilia [1]. The recurrent bleeding can cause an encapsulated haematoma, most commonly in the pelvic bones, femur, tibia, small bones of the hand and soft tissues. Destructive haemophilic cysts are typically slow growing and asymptomatic; however, in some cases, surgical intervention is necessary to prevent progressive enlargement and potential complications. For example, bone fractures, massive haemorrhage, infection and compression, and eroding of adjacent structures [2].

Surgery in patients with haemophilia is challenging, and for those who develop inhibitors to replacement factors, successful surgical intervention is even harder to achieve. The development of bypassing agents, such as recombinant activated factor VII (rFVIIa) has greatly improved the treatment options available to inhibitor patients; for example, allowing patients to undergo elective orthopaedic surgery despite the risks of bleeding or thromboembolic events [3]. Since 1998, the Institute of Hematology and Blood Transfusion has gained wide experience with rFVIIa in the treatment of on-demand bleeding and minor surgery in patients with haemophilia and inhibitors.

We report here the removal of an abdominal blood cyst in a patient with severe haemophilia A and inhibitors. Haemostatic control was effectively maintained both before and during surgery with rFVIIa.

A 51-year-old haemophilia A patient was diagnosed with haemophilia A at 3 months of age (FVIII

levels below 1%, nonsense mutation in exon 24) when massive bleeding occurred following herniectionomy. After this initial bleeding episode, the patient was repeatedly hospitalized for bleeding into his joints (knees and elbows), haematuria, and for bleeding into the tonsils during tonsillitis. During this period, the patient was treated with cryoprotein followed by plasma-derived FVIII concentrates, including the period prior to detection of FVIII inhibitors.

Inhibitors to FVIII were first detected in 1983 when the patient was aged 28 years. Despite immunosuppressive therapy with corticosteroids and cyclophosphamide the inhibitors remained, with titres oscillating between 1 and 54 BU mL⁻¹. The patient came to the centre for treatment sporadically, and only in cases of severe bleeding. Most bleeding episodes into the joints were untreated.

In 1989, an ultrasound scan of the abdomen revealed an extensive, hypoechogenic, mostly homogenous infiltrate (at least 9 cm in size) below the left kidney, most probably a haematoma of the soft tissues. A calcification in an older haematoma was revealed below this site, and was later (1990) verified by computerized tomography (CT) when the patient was hospitalized for spontaneous haemo-peritoneum and acute bleeding into the right iliopsoas muscle. Therapy with by-passing agents was recommended and non-surgical treatment was indicated. This led to a slight regression of the infiltrate. At this time, the patient had no serious complaints.

In July 2006, there was rapid progression of the infiltrate and the blood cyst almost entirely filled the left side of the abdominal cavity, resulting in bulging of the abdominal wall to the umbilical line. Expansion of the blood cyst was associated with compression and displacement of abdominal cavity organs

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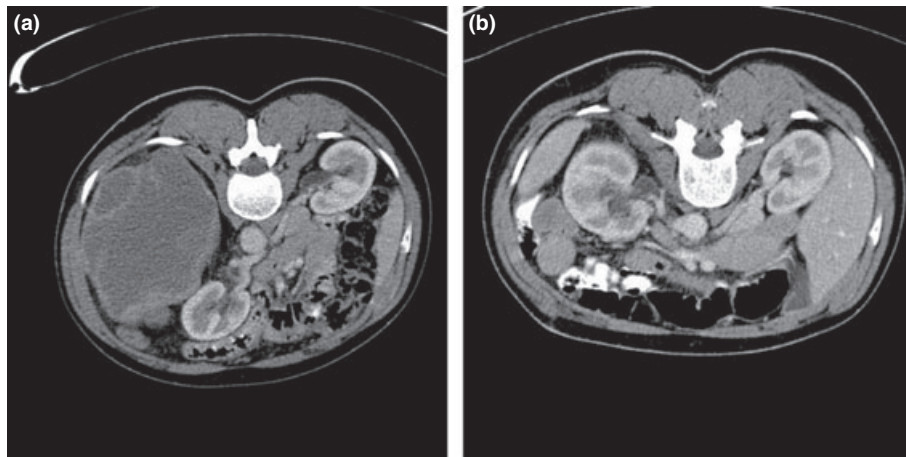


Fig. 1. CT of the abdominal cavity (a) with the extensive blood cyst and (b) after extirpation of the blood cyst.

and compression of the gastrointestinal tract. A CT confirmed the presence of a multi-lobular tumour with calcifications, which was pressing on the anterior abdominal wall, dislocating organs in the left side of the abdominal cavity, cranially compressing the stomach and spleen, and caudally extending down to the left inguinal region (Fig. 1a).

As a result, the patient's state of health deteriorated and he experienced repeated bouts of pain in the left half of the abdomen and dyspepsia. The situation was deemed life threatening because of the risk of perforation and subsequent haemorrhage into the abdominal cavity and progression of the blood cyst with compression of the intra-abdominal organs and ileus. Extirpation of the blood cyst was therefore strongly recommended.

Because of the rapid progression of the tumour and the need to avoid aggravating the situation, the patient was stabilized prior to surgery with rFVIIa prophylaxis. Treatment was started at a dose of rFVIIa $120 \mu\text{g kg}^{-1}$ administered twice weekly (starting in July 2006). After 2 months of rFVIIa prophylaxis, the subjective symptoms (abdominal pain and dyspepsia) receded and the patient stabilized without any spontaneous bleeding during the prophylactic period. There was also a slight palpating regression of the blood cyst.

The patient underwent major abdominal surgery which took place on 22 September 2006. At surgery, the blood cyst extended from the diaphragm and, displacing the left kidney, continued below the inguinal ligament to the ventral side of the thigh. The tumour weighed 6.8 kg and was fully removed from the abdomen after 8 h of surgery (Fig. 1b).

During surgery, the patient received 800 mL of his own blood via the red cell salvage auto-transfusion

system. A further 2 U of packed red blood cells and 11 U of fresh frozen plasma were administered. No other blood products were required postoperatively. After extirpation of the tumour, the surface of the wound was covered with a local haemostatic agent (Nu-knit[®], Ethicon, Johnson & Johnson, Somerville, NJ, USA).

During the procedure and postoperatively, haemostasis was maintained with rFVIIa without additional antifibrinolytic therapy. rFVIIa was preferred in order to achieve efficient haemostasis because the patient was a high-responder, and because rFVIIa is a recombinant agent with a favourable side-effect profile. We also selected rFVIIa because of its rapid effect in case the patient experienced unexpected bleeding complications during the surgery, and also because, contrary to activated prothrombin complex concentrate, the daily dose of rFVIIa can be increased if required. In order to prevent thromboembolic complications, the patient received anticoagulation therapy with the low molecular weight heparin, nadroparine (3800 IU day^{-1} as a continuous infusion) from the day of surgery until he was fully mobile (18 days). Haemostasis during surgery was monitored with routine coagulation tests (activated partial thromboplastin time, prothrombin time, fibrinogen, D-Dimer and inhibitor levels) and rFVIIa treatment was monitored with thrombelastography (ROTEM[®], Pentapharm, Basel, Switzerland). rFVIIa dosing in the peri- and postoperative period was as follows: a single bolus dose of rFVIIa $200 \mu\text{g kg}^{-1}$ was administered 1 h prior to surgery; this was followed by a fixed dose of $120 \mu\text{g kg}^{-1}$ given every 2 h for a period of 48 h. As there was no bleeding, dose intervals were gradually extended (2 days every 3 h, 2 days every 4 h, 3 days every 6 h, 3 days every

8 h, 5 days every 12 h, 5 days every 24 h and 10 days twice weekly). As there was no postoperative bleeding, rFVIIa therapy was discontinued 1 month after surgery. The patient's inhibitor titre increased from 1.8 BU mL⁻¹ before surgery to 270 BU mL⁻¹ after surgery.

The results of the case report described above suggest that rFVIIa may provide safe and effective haemostatic cover during major abdominal surgery in patients with FVIII inhibitors. It should be noted that the patient detailed above underwent 2 months of rFVIIa prophylaxis (twice weekly infusion of rFVIIa 120 µg kg⁻¹) with the aim of avoiding the development of complications and producing greater haemostatic stability prior to surgery. In comparison, no prophylactic treatment was given to haemophilia patients with destructive haemophilic cysts described previously by Takedani *et al.* [4] and O'Connell *et al.* [5]. We also used a different scheme of rFVIIa administration, except for a single bolus dose of 200 µg kg⁻¹ administered 1 h prior to surgery. During the peri- and postoperative periods, the dose of rFVIIa (120 µg kg⁻¹) remained unchanged, but the dosing intervals were gradually extended over a 30-day period. It is our opinion that the use of rFVIIa prophylaxis pre- and postoperatively was likely responsible for the lack of postoperative bleeding and infection in this patient. Although the inhibitor titre increased after surgery (1.8–270 BU mL⁻¹), this can likely be attributed to the administration of packed red blood cells and fresh frozen plasma. We therefore recommend further investigation into the use of rFVIIa prophylaxis in this challenging patient population.

Importantly, there was no postoperative requirement for blood products, and no thromboembolic events or complications because of infection were

observed in this patient. In addition, no antifibrinolytic therapy was required.

In summary, the outcome of this patient supports the use of rFVIIa for the treatment and management of bleeding in inhibitor patients undergoing surgery.

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Disclosures

Peter Salaj has acted as a paid speaker for Novo Nordisk s.r.o. Czech Republic in some company-organised scientific events.

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