Case Report

Splenectomy in an uraemic patient with acquired factor X deficiency due to AL amyloidosis

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Introduction

The clinical signs of amyloidosis are dependent on the organ systems involved [1]. A common finding is renal involvement which manifests as nephrotic syndrome. Cardiac involvement may result in congestive cardiomyopathy with conduction defects and arrhythmias. Amyloid deposits especially in the spleen may bind clotting factors, which can lead to coagulation abnormalities. Factor X deficiency is an unusual complication of the amyloid light-chain type (AL) of the disease [2]. We report a case of a patient in whom splenectomy was initially successful. The case illustrates the fluctuations of factor X levels before and after splenectomy.

Case report

A 53-year-old Caucasian man (height: 182 cm; weight 101 kg) presented with nephrotic syndrome. His blood pressure was normal at 125/80 mmHg, and electrocardiogram revealed a normal sinus rhythm at 72 beats per minute. Echocardiographic studies showed a good left ventricular function, a small pericardial effusion, and concentric hypertrophy of the left ventricle; no outflow obstruction could be demonstrated. An ultrasound study revealed moderate hepatomegaly; the spleen was of normal size. The patient’s blood values were normal except for an increased prothrombin time (20 s), an increased activity of gamma-glutamyl transferase, and increased concentrations of serum creatinine and blood urea nitrogen. The creatinine clearance was 27.3 ml/min. Urinalysis showed Bence–Jones proteinuria. A renal biopsy was performed which resulted in the diagnosis of Aλ amyloidosis as revealed by polarization microscopy after Congo red staining and immunohistochemistry using a panel of anti-amyloid antibodies including antibodies directed against the amyloid classes AA, Aλ, Aκ, ATTR and Aβ2m [3].

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Fig. 1. Course of the prothrombin time, factor X level, and creatinine clearance in the 7 months before splenectomy.

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The patient was treated with a 4-day course of chemotherapy, which consisted of daily administration of melphalan 12.5 mg and prednisolone 100 mg.

Three months later renal failure had progressed, and the creatinine clearance was determined at 8 ml/min (Figure 1). An arteriovenous fistula was established on the left forearm to allow for intermittent haemodialysis. Prothrombin time was measured to be 23 s. The determination of the coagulation factors revealed normal values for all factors except factor X, which was decreased to 15% of normal. Laboratory studies excluded the presence of a factor X inhibiting antibody and lupus anticoagulants. The platelet count was in the normal range, and aggregometry studies revealed normal values.

Four months later, the prothrombin time had increased to 41 s. Subsequently, the factor X concentration was determined again and measured to be 2% of normal. Additional kinetic studies revealed a factor X half-life of only 6 min (normal: 24–48 h). In the meantime, a bleeding diathesis appeared which led to several episodes of diffuse bleeding from the gingiva and the gastrointestinal tract. Each bleeding episode could be successfully treated by the administration of commercially available prothrombin complex concentrates. It was hypothesized that factor X would bind to splenic amyloid, thus leading to the short in vitro half-life of factor X.

Following the reports of Greipp et al. [4] and Rosenstein et al. [5], splenectomy was considered as a therapeutic means in order to increase factor X levels and to increase the life expectancy of the patient.

Fig. 2. Immunofluorescence microscopy. (a) Splenic tissue reacted with a polyclonal antibody specific for immunoglobulin λ-chains and (b) monoclonal anti-human factor X.
Disease-specific risk factors for anaesthesia and surgery were cardiac amyloid deposits, renal failure, and the bleeding tendency associated with factor X deficiency. The patient was then scheduled for surgery. Prior to surgical incision, factor X was supplemented intravenously via administration of a commercially available prothrombin complex concentrate (Prothromplex, Immuno, Heidelberg, Germany) which was given at an initial bolus dose of 4000 IU. The antithrombin III levels were kept >100% of normal throughout the procedure by infusion of antithrombin III concentrates (AT III, Immuno, Heidelberg, Germany). Before ligation of the splenic artery, an additional 12,000 IU of the prothrombin complex concentrate had to be administered to keep the prothrombin time <17 s. The removed spleen was found to be enlarged 4-fold. In order to avoid post-operative bleeding complications, the prothrombin time was kept <20 s for 4 days, which necessitated additional administration of a total of 8000 IU of prothrombin complex concentrate. In the immediate post-operative phase, no bleeding problems or thrombotic complications occurred.

Histologic evaluation of the spleen using light and polarization microscopy (not shown), as well as immunohistochemistry confirmed the diagnosis of amyloidosis of the AA type (Figure 2a). When the spleen was stained with an anti-factor X antibody (Figure 2b), a staining pattern was observed which was congruent with the anti AA-staining pattern. The patient’s spleen was analysed for its factor X content using Western blot analysis. It contained much more factor X than the spleen of a control patient (Figure 3).

Following splenectomy, the prothrombin time increased again to values of 40 s. Factor X concentrations increased 3-fold immediately after surgery, but decreased again to 4% of normal in the ensuing 12 weeks. Three months later, intractable intra-abdominal bleeding occurred which resulted in abdominal dehiscence. The patient refused any further treatment and died 2 days later.

**Discussion**

Factor X deficiency associated with AL amyloidosis [2,6] has only been reported in patients with immunoglobulin-derived amyloidosis, but not in patients with acquired amyloidosis secondary to chronic infectious or neoplastic diseases. The primary disease is characterized by the deposition of light-chain derived amyloid, and thus, only this AL type may result in factor X-related haemostatic abnormalities. The underlying mechanism does not involve an increase in the turnover of factor X [7], but consists of direct binding of factor X to amyloid deposits [8]. Thus, the amount of amyloid available for binding of factor X correlates with the decrease in half-life of factor X. Consistent with this diagnosis, the lambda light chain-specific antibody and the factor X recognizing antibody disclosed similar if not identical staining patterns in splenic tissue.

There is data suggesting that a prednisone/melphalan regimen may prolong life; this however, did not prove to be effective in our patient. Newer, but more toxic treatment approaches such as the anthracycline idodeoxydoxorubicin [9] were not used in our case. Because splenic amyloid deposits are generally responsible for factor X binding, splenectomy was considered a therapeutic modality [4,5,10]. In our patient, splenectomy was associated with an improvement in the haemostatic abnormality. However, this partial amelioration lasted only several weeks suggesting that increasing amounts of extrasplenic deposits took over a significant part of the factor X binding capacity. Continuously increasing AL-amyloid deposition after splenectomy may have resulted in an amyloid load sufficient to reduce the factor X half-life to pre-splenectomy levels. With respect to this observation and the published survival of other patients with factor X deficiency due to AL amyloidosis, we would suggest that splenectomy should only be performed in those individuals in whom progression of the disease is slow, because otherwise extrasplenic amyloid deposits will take over and bind factor X.

The perioperative handling of haemostasis is delicate due to the risk of intra- and post-operative bleeding. In our patient, peri-operative bleeding problems were apparently avoided by administration of prothrombin complex concentrates, therefore increasing the factor X concentration to an acceptable level. These concen-
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trates contain the coagulation factors II, VII, IX, and X in addition to protein C and S. Large quantities of prothrombin complex concentrates were required to offset the short half-life of factor X. This poses the risk of procoagulatory complications [11] and necessitates careful titration. To avoid dangerous activation of the coagulation cascade when such high doses of these concentrates are administered, we kept the plasma antithrombin III level at 100% of normal. Using this strategy a total of more than 20 000 IU of this concentrate were administered in a short time period without causing any thromboembolic problems. These observations illustrate the safety of the commercial preparation used in our case.

We conclude from our experience that (i) splenectomy can be safely performed in patients with acquired factor X deficiency associated with factor X binding to splenic amyloid deposits, (ii) substitution of prothrombin complex concentrates helps to avoid perioperative bleeding, and (iii) the benefit of splenectomy may be transient if the factor X binding capacity of extrasplenic amyloid deposits is further increasing.

References


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