

CASE REPORT

Successful treatment of a noninhibitory antibody-mediated acquired factor X deficiency in a patient with marginal-zone lymphoma

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Introduction

Factor X, also known as Stuart–Prower factor, is a vitamin K-dependent serine protease produced in the liver. It is a key component of both intrinsic and extrinsic clotting pathways. Activated factor X cleaves prothrombin to thrombin, which facilitates the conversion of fibrinogen to fibrin which ultimately leads to the formation of a fibrin clot [1]. Acquired factor X deficiency is commonly caused by the use of coumarin derivatives or due to liver disease. Both causes result in a depletion of all vitamin K-dependent coagulation factors. Liver disease additionally shows a decrease in some vitamin K-independent coagulation factors. Isolated factor X deficiency is a rare disorder and was first described in the early 1950s [2, 3]. Genetic factor X deficiencies are inherited in an autosomal recessive manner. Only a few families have been described, probably

Key Clinical Message

Prolonged clotting times were observed in a patient with spontaneous hemorrhage. Analysis showed severe factor X deficiency due to clearance by a noninhibitory antibody. Lymphadenopathy identified on imaging led to diagnosis of marginal B-cell lymphoma. Treatment of lymphoma with rituximab and chlorambucil resulted in complete disappearance of the bleeding disorder.

Keywords

acquired coagulation disorders, clotting factor related research, non-Hodgkin lymphoma.

due to factor X's essential role in the hemostasis [4, 5]. Symptoms vary from mild hemorrhage, such as bruising and mucocutaneous bleeding, to more severe bleeding, for example, gastrointestinal bleeding and muscle bleeding. Bleeding severity depends on the plasma concentration of factor X. Values between 1 and 10% are associated with minor bleeding or more serious bleeding provoked by surgical procedures or trauma, while spontaneous and severe bleeding is described with values below 1% [1, 6].

Acquired isolated factor X deficiency is mostly associated with amyloid light-chain (AL)-amyloidosis [7–13]. In amyloidosis, factor X binds permanently to amyloid fibrils within the vasculature, liver and spleen and is thereby scavenged from blood circulation [14]. There are also a few reports of factor X deficiency concomitant with respiratory disease, antibiotic treatment, leprosy, burns or malignancy such as acute myeloid leukemia [15–28]. In some cases an

inhibitor was found [18, 20, 22–24]. Rao et al. (1994), proposed that in the context of post-infectious disease, similar epitopes may be found on viral antigens leading to generation of an anti-factor X inhibitor [24]. In several other cases the etiology of the acquired factor X deficiency remains unclear [17, 19, 21, 23, 27, 28]

In addition to earlier reports, we describe an 81-year-old patient without a bleeding history who presented with moderate to serious spontaneous bleeding symptoms due to clearance of factor X by a noninhibitory antibody. This antibody was related with an indolent malignant lymphoma. His bleeding disorder completely disappeared upon treatment of the underlying disease.

Methods

Overall standard laboratory methods were used. Coagulation assays were performed with patient plasma collected in 3.2% sodium citrate. Plasma for further testing was stored at -80°C . The prothrombin time was measured using Innovin reagent (Siemens Healthcare, Erlangen Germany) and the aPTT using Actin FSL reagent (Siemens Healthcare).

Mixing studies were done by mixing equal volumes of patients plasma and normal plasma pools (control N, Siemens Healthcare and in-house prepared pool). The aPTT was measured immediately and after 2 h of incubation at 37°C to detect a time dependent inhibitor. Heparin was neutralized in 1 mL of plasma by addition of heparinase I using Dade Hepzyme (Siemens Healthcare) according to manufacturer's instructions. All factor assays were performed using one stage assay and factor X antigen level was determined using enzyme linked immunoassay (ELISA). For lupus anticoagulant testing a diluted Russell's Viper Venom Time (La screen/mixing reagent, Gradiopore Hawthorne NY) and a lupus sensitive aPTT (BioMerieux, Marcy l'Etoile France) were used.

Anti-factor X Bethesda assay

The Bethesda inhibitor assay for detecting inhibitory antibodies directed toward factor X was done according to the Classical Bethesda Assay described for factor VIII [29]. In-house prepared pooled plasma was used as normal plasma source (a pool of more than 32 adult donors). Factor X activity was measured using the previously mentioned one stage assay.

Anti-factor X radioimmunoassay

Radioimmunoassay (RIA) for detecting factor X antibody was performed according to Wolbink et al. [30]. In short, 1 mg Sepharose-immobilized protein A beads (GE Healthcare, Little Chalfont, Buckinghamshire, UK) were

incubated overnight with 50 μL prediluted in phosphate-buffered saline (PBS)/0.3% bovine serum albumin (BSA; EMD Millipore, Billerica, MA) plasma of the patient, polyclonal rabbit antihuman factor X antibody or plasma from a healthy control in a total volume of 800 μL PBS-AT (PBS containing 0.3% BSA, 0.2% Tween-20 (Merck, Darmstadt, Germany) and 0.01 mol/L ethylenediamine tetraacetic acid (EDTA), thereby coupling all antibodies to the Sepharose beads. The beads were subsequently washed two times with PBS-T (PBS containing 0.005% Tween-20) and four times with tris-buffered saline (TBS)-CT (10 mmol/L Tris, 5 mmol/L CaCl_2 , 140 mmol/L NaCl, pH7.4 with 0.05% Tween-20). Beads were resuspended in 0.5 mL TBS-C-AT (TBS-C containing NaN_3 , BSA and 0.2% Tween-20). Thereafter beads were resuspended in 0.5 mL TBS-C-AT and 2 ng of biotin labeled factor X (provided kindly by M. Boon-Spijker, dept. Plasma Protein, Sanquin Research, Amsterdam) was added to the samples followed by overnight incubation and rotation using a rotor. Thereafter the beads were washed five times with TBS-CT and incubated overnight with 50 μL radioactive ^{125}I labeled streptavidin dialyzed in TBS-CA and diluted in 500 μL TBS-C-AT. Unbound ^{125}I was removed by washing five times with TBS-CT and samples were counted using a Wallac 1260 Multigamma II counter. Results were expressed as percentage binding of the labeled factor X.

Case history and results

An 81-year-old previously healthy Caucasian man presented on the emergency ward with a spontaneous hematoma of the skin and soft tissue in his left abdominal flank and around his left shoulder. Two weeks prior to admission, he had received a red blood cell concentrate transfusion after an episode of acute anemia caused by bleeding due to a minor trauma. Previous to this presentation, there was no history of an abnormal bleeding tendency. Complaints consisting of tiredness and slight weight loss in the past month were reported upon admission. He used hydrochlorothiazide, atenolol and lercanidipine to control hypertension. He did not use any antiplatelet drugs or anticoagulants, which was confirmed by toxicology screening.

At presentation, his vital signs were normal. Examination of the oral cavity did not show any mucosal bleeding or gingival abnormalities. The results of cardiovascular, pulmonary and neurological examinations were normal. On the left side of his abdomen there was a painful hematoma of approximately 12×8 inches. A painless swelling of about 8×8 inches was present on his left shoulder region. Computed tomography (CT) of thorax and abdomen showed intramuscular hematoma of the

latissimus dorsi on the left side and enlarged inguinal, intra-abdominal and intrathoracic lymph nodes. Hepatosplenomegaly was not present.

Initial laboratory evaluation revealed anemia with a hemoglobin level of 7.1 g/dL (12.9–16.9 g/dL), with normal red blood cell indices. His white blood cell and platelet counts were normal. Plasma electrolytes and liver enzymes were within the normal ranges. However, lactate dehydrogenase (LD) was slightly elevated: 325 U/l (<248 U/l). Further analysis showed neither serum M-protein by electrophoresis nor elevation of serum-free light chains. Urine analysis was normal, including absence of Bence-Jones proteins.

Both, prothrombin time (PT) and activated partial thromboplastin time (aPTT) were prolonged 23.3 sec (PT normal range 9–12 sec) and 51 sec (aPTT normal range 24–34 sec), respectively. Fibrinogen levels were normal.

Pre-analytical contamination of the sample with heparin was ruled out using Hepzyme treatment. The *in vitro* addition of normal plasma to the patients plasma resulted in complete correction of PT and aPTT times, immediately after mixing as well as after 2 h of incubation at 37°C. This result is suggestive of a factor deficiency rather than an antibody neutralizing procoagulant function.

In the acute clinical situation the cause of the bleeding tendency was unknown. The patient initially received

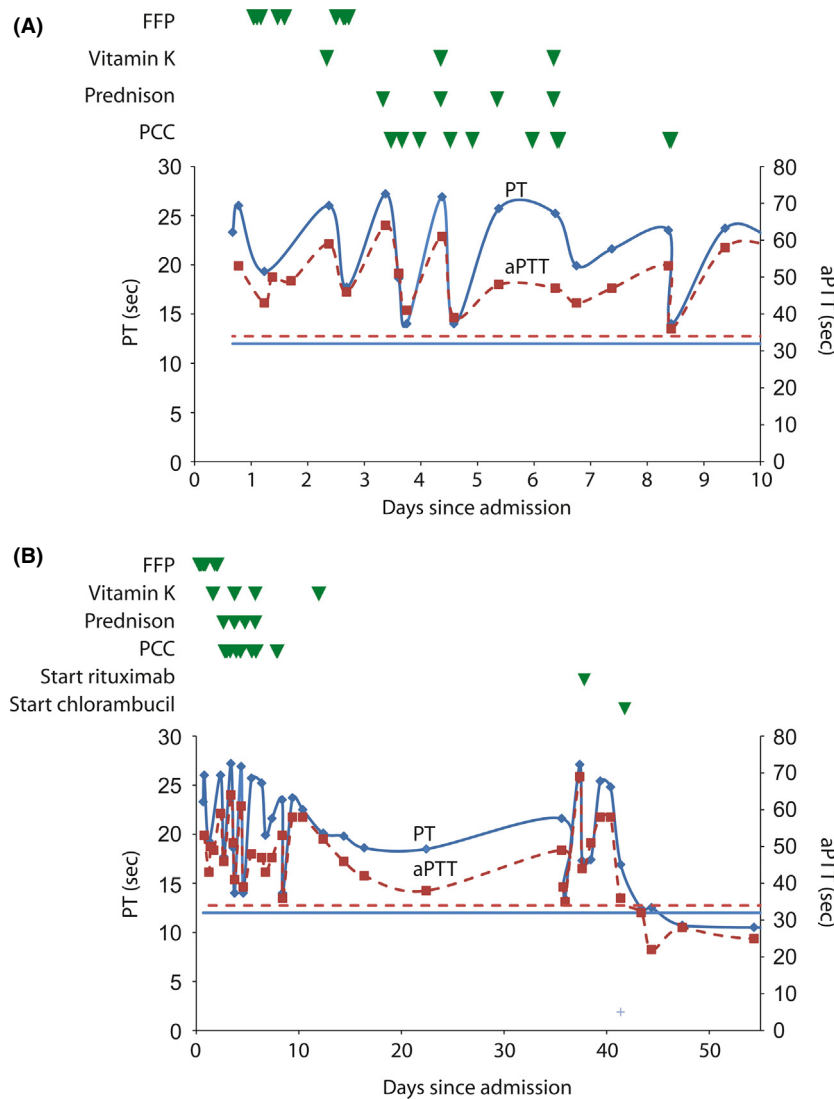


Figure 1. Clotting times in patient plasma in relation to treatment. (A) Effect on activated partial thromboplastin time (aPTT, dashed lines) and prothrombin time (PT, solid lines) in response to fresh frozen plasma (FFP), vitamin K and prothrombin complex concentrate (PCC) in first 10 days of hospitalization of acute setting. (B) Response during rituximab and chlorambucil treatment. Each green triangle represents one unit of FFP, 5 mg of vitamin K, 80 mg prednisone or 500 U PCC. Horizontal lines represent the upper limit of normal.

three red blood cell concentrates resulting in an increase of his hemoglobin level to 9.3 g/dL. Treatment with vitamin K, prednisone, fresh frozen plasma (FFP) and prothrombin complex concentrate (PCC) was started, which resulted in a temporary and partial response on the clotting times (Fig. 1A). More detailed analysis of blood coagulation factor levels showed slightly reduced activity of factor II (54%), VII (52%), IX (56%) and XII (64%) and extremely low activity of factor X (3–4%) (Table 1). The factor X activity was measured both via the intrinsic and extrinsic pathway. Additionally, a markedly reduced factor X concentration was found with the antigen assay correlating with the functional deficiency.

The factor X deficiency in our patient was considered to be acquired, given the absence of a bleeding history. In an attempt to clarify the cause of the acquired factor X deficiency, the patient underwent a biopsy of an enlarged inguinal lymph node. The results revealed the diagnosis, a marginal-zone B-cell lymphoma. There were no amyloid fibrils seen in the biopsy of the lymph node. Furthermore, neither bone marrow biopsy examination nor the aspirate from the abdominal fat showed signs of amyloidosis.

Presence of a factor X antibody was suspected based on the lack of response to FFP and PCC. We were not able to detect an inhibitor in the mixing studies or using a Bethesda assay against functional antibodies inhibiting factor X activity. Despite the fact that there was no inhib-

itory antibody detectable, the probability of the presence of a noninhibitory antibody was considered and consequently the patient was first treated with prednisone as first-line treatment for an auto-immune antibody-mediated disease. Because of a new abdominal soft tissue bleeding, more rigorous treatment was initiated in an attempt to firmly tackle the marginal-zone lymphoma, considering a relation between the factor X deficiency and the lymphoma.

Treatment consisted of chemo- and immunotherapy, chlorambucil and rituximab, resulting in normalization of PT, aPTT levels (10.7 and 28 sec, respectively, Fig. 1B), LDH level of 210 U/l and a factor X activity of 106% within three weeks time.

The normalization of the factor X activity after treatment of the patient strongly suggested that a noninhibitory antibody against factor X was present. Such an antibody would bind factor X without inhibiting the function but facilitating fast clearance from the circulation. Laboratory evaluation of vitamin K dependent procoagulant factor activities just before and after rituximab and chlorambucil treatment are shown in Table 2. A RIA assay detecting factor X antibody binding capacity was used to demonstrate the presence of a possible factor X antibody in the patient plasma before treatment and after normalization. Indeed, the presence of a noninhibitory antibody was ultimately demonstrated in the before treatment sample of our patient and not in the sample after treatment (Table 3). As a positive control rabbit antihuman factor X was taken which showed a good

Table 1. Blood coagulation parameters at initial laboratory screening and before treatment.

Parameter	Value	Normal range
PT	23.3	9–12 sec
aPTT	51	24–34 sec
PT mixing (1:1 normal plasma)	11.8	
PT mixing after 2 h incubation at 37°C	11.8	
aPTT mixing (1:1 normal plasma)	29.6	
aPTT mixing after 2 h incubation at 37°C	30.4	
Fibrinogen	2.5	1.8–3.6 g/L
Factor II	54	80–120%
Factor V	94	70–140%
Factor VII	52	65–150%
Factor VIII	200	70–140%
Factor IX	56	70–140%
Factor X (extrinsic)	4	80–120%
Factor X (intrinsic)	3	80–120%
Factor X antigen	7	80–120%
Factor XI	95	80–120%
Factor XII	64	80–120%
Factor X inhibitor	<0.4	<0.4 BU
Lupus anticoagulants	not detected	
D-dimer	1042	<500 µg/L

PT, prothrombin time; aPTT, activated partial thromboplastin time.

Table 2. Vitamin K dependent procoagulant clotting factor activities before and after rituximab and chlorambucil treatment.

Parameter	BT	AT	Normal range (%)
Factor II	63	86	80–120
Factor VII	54	106	65–150
Factor IX	53	102	70–140
Factor X (extrinsic)	8	106	80–120

BT, before treatment; AT, after treatment.

Table 3. Results RIA assay before and after rituximab and chlorambucil treatment.

Sample	% Binding factor X-biotin
Blank 0.3% BSA	7.0
Healthy control 1:50	6.7
Patient BT 1:50	12.2
Patient BT 1:250	8.1
Patient AT 1:50	6.6
Patient AT 1:250	5.3

BT, before treatment; AT, after treatment.

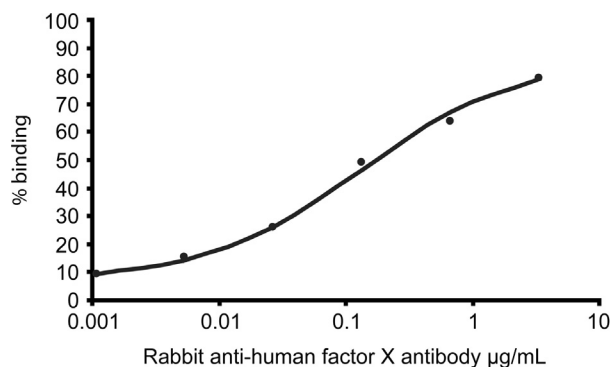


Figure 2. Dose response curve of rabbit anti-human factor X using radioactive immunoassay. Serial dilution of positive control rabbit anti-human factor X antibody was made and incubated overnight with Sepharose A beads to capture them. After washing, biotin labeled factor X was added and incubated with the beads overnight. Streptavidin labeled with radioactive iodine was added overnight after washing the beads again. The amount of ^{125}I -streptavidin bound was measured after washing and calculated back to the percentage of biotin binding to the antibody.

dose-response (Fig. 2). The patient samples were measured in a 1:50 and 1:250 dilution, both in duplicate. The 1:50 dilution was within the dose-response curve of our positive control, showing a low but detectable amount of factor X binding. Plasma from a healthy person and patient plasma after treatment were used as negative controls, in this experiment. In both samples no signal above the blank was observed. In addition, the antibody found in the patient appeared to be calcium dependent. No binding of the antibody to biotinylated factor X in the absence of calcium was observed (data not shown).

Factor II, VII and IX were also slightly reduced in our patient, although to a much lesser extent than factor X. No binding antibody could be detected for factor II and IX using the same RIA experiment using biotinylated factor II and IX as antigen, suggesting a specific antibody against factor X only.

One year after the diagnosis, the patient remains asymptomatic with normal factor X levels. A CT-scan to evaluate effect of chlorambucil and rituximab treatment showed complete remission of the non-Hodgkin lymphoma.

Discussion

We described a previously healthy 81-year-old man with an extensive and spontaneous cutaneous- and soft tissue hematoma as well as muscle bleeding associated with a nodal marginal-zone lymphoma. The factor X activity and antigen levels were shown to be very low. Since our patient did not have a bleeding tendency in the past, we concluded that this patient suffered from an acquired factor X deficiency.

Acquired factor X deficiencies are most frequently described in relation to amyloidosis, factor X inhibitors or vitamin K deficiency [7, 16]. At the first instance, because all measured vitamin K-dependent clotting factors were reduced, it was thought that the patient had a mild vitamin K deficiency. However, it is rather unlikely that vitamin K deficiency was the main cause of the grossly reduced factor X activity and therefore the cause of the bleeding complication. Moreover, this assumption is in agreement with the nonresponsiveness observed after vitamin K supplementation. Also the liver function tests were normal.

Biopsy of an inguinal lymph node demonstrated a marginal-zone lymphoma. This is an indolent disease and treatment is initiated only in the presence of symptoms. Considering the physiology of the marginal zone in lymph nodes, where mature B cells can rapidly proliferate and differentiate into antibody secreting plasma cells, it was hypothesized that an antibody related factor X deficiency was present. Mixing studies and factor X Bethesda assays could not demonstrate an inhibitory antibody. Initial treatment with FFP or PCC demonstrated a temporary response in the factor X levels. The period of response did not correlate with the half-life of factor X, which is around 48–72 h [31]. This result suggested the presence of an antibody causing enhanced clearance of factor X from the blood circulation. A few reports described noninhibitory autoantibody related with a factor deficiency [27, 32, 33].

One study describes a noninhibitory antibody in a patient with cutaneous lymphoma. The patient had combined deficiency of factor II and X. A cross-reactive antibody was found to bind to factor II, IX and X via the common metal-ion-dependent conformational epitope found on the vitamin K-dependent γ -carboxyglutamic acid (Gla) domain [27]. Also, in a patient with a low grade follicular center cell non-Hodgkin lymphoma, the presence of a noninhibitory autoantibody binding via a calcium-dependent epitope of factor II was found, which accelerated its clearance [32]. In another patient also a calcium-dependent noninhibitory antibody to factor II was found, which had low affinity for factor II [33].

The presence of a noninhibitory antibody against factor X was found in our patient, which was calcium dependent. This suggests that our antibody is directed against a factor X epitope that is metal dependent, maybe also the common metal-ion-dependent conformational epitope found on the Gla domain. In the RIA assay using biotinylated factor II and IX, we could not detect binding to these clotting factors.

Due to the severity and recurrence of bleeding we had promptly started treatment with rituximab and chlorambucil according to the guidelines for treatment of nodular

marginal-zone lymphoma [34]. Treatment resulted in complete remission of the lymphadenopathy and normalization of factor X levels, proving that factor X deficiency was related with the non-Hodgkin lymphoma.

Acquired coagulopathies related to marginal-zone lymphomas have previously been described. Tefferi et al., reported a patient with an acquired Von Willebrand disease related to a marginal-zone lymphoma [35]. The authors suggest that the von Willebrand factor (VWF) protein was absorbed by tumor cells, showing an aberrant tumor-cell expression of the platelet VWF receptor (GpIb). Another case report in which a patient was diagnosed with splenic marginal-zone lymphoma without bleeding problems, showed reduced factor activities of factor II, V, VII, VIII, IX, X, XI and XII. The authors found a specific inhibitor against factor IX and assumed presence of a non-factor specific inhibitory antibody [36].

Our case is another example of an acquired factor X deficiency associated with the presence of a lymphoproliferative disease.

This is the first patient to our knowledge diagnosed with an acquired factor X deficiency caused by a noninhibitory antibody related to nodal marginal-zone lymphoma. We advise to start treatment of the underlying disease as soon as possible when there are symptoms of hemorrhage or if there is a high risk of hemorrhage due to low-factor X levels.

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Conflict of Interest

None declared.

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