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Spontaneous Bleeding in a Patient with Malignant Lymphoma: A Case of Acquired Hemophilia

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Summary
Background: Acquired hemophilia is a rare condition which can be associated with lymphoproliferative disease. ***Case Report:*** Eleven years after the diagnosis of immunocytoma had been made, a 72-year-old man developed a high-titer factor VIII inhibitor. At this time, the lymphoma was without significant progress and there was no paraprotein in the serum. Partial thromboplastin time (PTT) was 83 s, factor-VIII clotting activity was <1%, and inhibitor level was 50.4 Bethesda units. The patient presented with spontaneous hematomas in the skin and musculature of the extremities. Following combination chemotherapy with cyclophosphamide, vincristine and prednisolone (COP), there was a prompt disappearance of the inhibitor and normalization of coagulation; however, the patient developed serious infectious complications. When the inhibitor recurred he was treated with low-dose cyclophosphamide and prednisolone. This time there was a more delayed response, but the inhibitor disappeared again completely. Two months after cessation of therapy, there was again relapse. ***Conclusion:*** Causal relationship between lymphoma and acquired hemophilia remains speculative. At least in some cases of factor VIII inhibitors associated with malignant disease, immunosuppressive therapy may be sufficient to suppress the inhibitor.

Zusammenfassung
Hintergrund: Die erworbene Hämophilie ist selten und kann mit lymphoproliferativen Erkrankungen assoziiert sein. ***Kasuistik:*** Elf Jahre nach Diagnosestellung eines Immunozytoms entwickelte ein 72jähriger Mann einen hochtitrigen Faktor-VIII-Inhibitor. Zu dieser Zeit zeigte das Lymphom keinen eindeutigen Progreß und im Serum war kein Paraprotein nachweisbar. Die partielle Thromboplastinzeit (PTT) betrug 83 s, Faktor VIII: C war <1% und der Inhibitor-Titer lag bei 50,4 Bethesda-Einheiten. Der Patient entwickelte spontane Hämatome an Haut und Muskulatur der Extremitäten. Nach Polychemotherapie mit Cyclophosphamid, Vincristin und Prednisolon (COP) kam es zu einem raschen Verschwinden des Inhibitors und zu einer Normalisierung der Gerinnung, der Patient entwickelte jedoch schwere Infektkomplikationen. Ein Rezidiv wurde mit niedrig dosiertem Cyclophosphamid und Prednisolon behandelt. Das Ansprechen schien protrahiert, aber der Inhibitor verschwand wieder vollständig. Zwei Monate nach Therapiebeendigung zeichnete sich ein neues Rezidiv ab. ***Schlußfolgerung:*** Ob ein Kausalzusammenhang zwischen dem Lymphom und der erworbenen Hämophilie besteht, kann nur spekuliert werden. Zumindest in einigen Fällen von Faktor-VIII-Antikörpern, die mit malignen Erkrankungen assoziiert sind, kann eine immunsuppressive Therapie ausreichen, um den Inhibitor zu unterdrücken.

Introduction

Acquired hemophilia due to factor VIII inhibitor is a rare clinical condition. The incidence is reported as about one per million annually [1, 2]. But it represents the most common type of spontaneously acquired inhibitors against a clotting factor [3]. Both sexes are affected equally [1, 4]. The incidence increases with age, the majority of patients being over 50 years of age. There is a second small peak of incidence in the 3rd decade, accounted for by women affected around parturition [4].

A wide range of associated conditions has been described in the literature. In a large survey [4] of 215 patients with factor

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VIII inhibitors, 18% had concomitant autoimmune disorders like rheumatoid arthritis and systemic lupus erythematosus, 7% were postpartum women, 7% had malignancies, 5% had been trated with drugs (penicillin, phenytoin), 5% had skin disorders like psoriasis and pemphigus, and 12% had various conditions like asthma, multiple transfusions, diabetes or hepatitis. In 46%, no associated disease could be identified. Beside this case series, both various solid tumors [5, 6] and hematologic malignancies [3, 7–14] like plasma cell dyscrasias and lymphoproliferative disease are reported frequently in the literature in conjunction with factor VIII inhibitors. Whereas in autoimmune disorders and hematologic malignancies a causal relation between autoantibody formation and associated disease seems possible, as there is both a plausible pathogenesis and clinical evidence [3, 15], the nature of this correlation is less clear for most of the other conditions. And the fact that most of them tend to occur in the elderly may indicate a coincidental relationship [1].

Case Report

A 72-year-old man was admitted to the hospital because of spontaneous hematomas of the upper and lower extremities. Eleven years before admission, the diagnosis of a low-grade non-Hodgkin's lymphoma, specified as nonsecretory immunocytoma stage IV A (Binet stage A) with enlargement of axillary, supraclavicular, mediastinal and paraaortal lymph nodes and infiltration of bone marrow, had been made. The patient had no treatment, and during regular follow-up no progression of the lymphoma was observed. He had developed anteroseptal myocardial infarction 21 years before admission and since then suffered from stable angina pectoris, which was controlled by bisoprolol and isosorbide dinitrate. In addition he took acetylsalicylic acid 100 mg daily. He had a history of psoriasis, which was without any activity at admission. He had scmoked until 11 years before admission.

Three weeks before admission he consecutively developed hematomas of the left elbow, right upper arm, left thigh, right gluteal region and left forearm, which had led to tension of the musculature with imminent compartment syndrome. All hematomas developed overnight without adequate trauma. The patient's general practitioner found a prolonged partial thromboplastin time (PTT), which until then had been normal in all routine controls. Intravenous injection of vitamin K 2 days before admission had been without effect on PTT. On admission, the patient was well except for a mild exertional dyspnea. The musculature of the left forearm was tense and tender, but radial pulses were palpable on either side. No petechial bleeding could be found. There was no past or family history of bleeding tendency. The temperature was 37 °C, the pulse was 76/min, and blood pressure was 120/70 mm Hg. On auscultation, lung and heart sounds were clear. The abdomen was soft without evidence of ascites or organomegaly. Small lymph nodes could be palpated in both axillae and the right supraclavicular region. The bleeding time, measured with the standardized Surgicutt device, was normal (4 min). The urine was positive (+++) for blood. Laboratory tests were performed (table 1). The electrocardiogram was without pathologic finding. A chest radiograph showed slight left ventricular enlargement and pleural adhesions at the base of the right lung, which was known from previous films.

Two units of fresh frozen plasma were given on the 1st hospital day and were without effect on the PTT. Oral antibiotic treatment with cefaclor was initiated to prevent superinfection of hematomas. The left forearm was cooled with ice to prevent further swelling and compartment syndrome. While microscopical examination of a blood smear was normal, immunophenotyping of the peripheral blood by flow cytometry showed elevation of CD19+ B cells (69% of mononuclear cells CD19+; 21% CD3+) and light-chain restriction in CD19+ B cells (47% c_κ/CD19+; 1% c_λ/CD19+), consistent with the presence of a malignant clone of B cells in the peripheral blood. An abdominal ultrasound scan showed multiple concrements in the gallbladder. A CT scan of the abdomen showed multiple paraaortic and paracaval lymph nodes enlarged slightly above 1 cm. A CT scan of the thorax showed multiple mediastinal lymph nodes also at the size of 1 cm.

On the 6th hospital day, factor VIII clotting activity (factor VIII:C) was lower than 1% (normal range 70–150%) and could not be raised substantially immediately and 2 h after mixing of patient and normal plasma, indicating the presence of a factor VIII inhibitor in the patient plasma. The inhibitor level was determined with 50.4 Bethesda units. PTT and factor VIII:C did not change substantially 2, 4, and 10 h after intravenous infusion of desmopressin acetate (36 μg in 30 min). The von Willebrand factor activity was 152%. The diagnosis of acquired hemophilia caused by factor VIII inhibitor possibly related to low-grade non-Hodgkin's lymphoma (immunocytoma) was made.

On the 8th hospital day, immunosuppressive therapy with steroids (prednisolone 100 mg/day) was initiated and chlorambucil (20 mg on day 8 and 15 mg on day 9) was given to treat the underlying malignant disease. To prevent further and probably life-threatening bleeding, 3,000 IU of activated prothrombin complex concentrate with factor VIII inhibitor bypassing activity (FEIBA S-TIM 4 Immuno®, Baxter, Vienna, Austria) were given intravenously as a bolus on days 10–14. As only a slight decrease of PTT could be achieved by these measures, the need for a more intensive antineoplastic therapy was seen. On the 12th hospital day, polychemotherapy was initiated according to the COP regimen (cyclophosphamide 400 mg/m^2 i.v., days 1–5; vincristine 2 mg i.v., day 1; prednisolone 100 mg

Table 1. Laboratory values on first admission

	Patient value	Normal value
White cell count/nl	12.1	4.0–10.0
Differential count		
Neutrophils, %	42	50–70
Lymphocytes, %	47	25–40
Monocytes, %	5	2–10
Eosinophils, %	2	0–5
Basophils, %	1	0–1
Hemoglobin, g/dl	11.7	14.0–18.0
Platelet count/nl	168	150–400
INR	0.9	
PTT, s	83	26–36
Creatine, mg/dl	1.2	0.7–1.2
Sodium, mmol/l	142	135–145
Potassium, mmol/l	3.9	3.5–5.0
Total protein, g/dl	6.9	6.1–8.2
Serum electrophoresis		
Albumin, %	66.1	55.0–69.0
α1-Globulin, %	4.1	1.6–5.8
α2-Globulin, %	7.8	5.9–11.1
β-Globulin, %	13.0	8.0–12.0
γ-Globulin, %	9.0[a]	11.0–20.0
C-reactive protein, mg/dl	0.7	0.0–0.8
β2-Microglobulin, mg/l	1.8	0.8–2.5
Immunoglobulin		
G, mg/l	507	700–1,600
A, mg/l	60	70–400
M, mg/l	90	40–230
Thyroid-stimulating hormone, mE/l	1.6	0.2–3.5
Cardiolipin antibodies, GPL-U/ml	2	0–12

[a] Without monoclonal component.

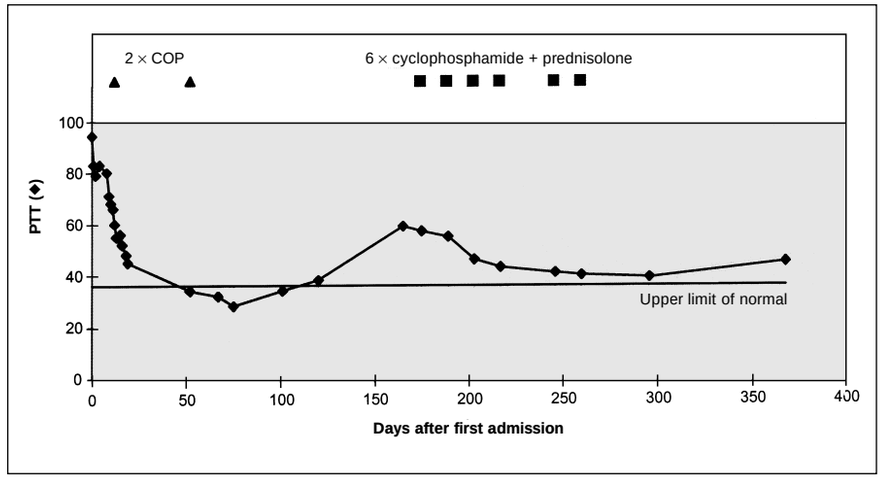

Fig. 1. PTT and chemotherapy.

per os days 1–5). Consecutively, PTT dropped to 45 s on the 20th hospital day without clinical signs of further bleeding, and the patient could be discharged. Steroid therapy was continued with prednisolone 100 mg/day.

On day 52 after first admission, the patient presented without any further bleeding and with a normal PTT. Prednisolone was reduced to 50 mg/day. The second course of COP chemotherapy was given in an outpatient setting in our hematologic clinic. On day 67, the patient was admitted to the hispital with bilateral atypical pneumonia and exanthema of the right inguinal region and scrotum which was suspicious for herpes simplex. White blood count was 1.1/nl. Prednisolone was tapered, 30 g immunoglobulins and broad-spectrum antimicrobial therapy were given intravenously. Neutropenia resolved on the 2nd day, but the clinical condition improved slowly. On day 101, factor VIII:C was 57.0%, consistent with low-titer factor VIII inhibitor. On bone marrow aspiration, a focal infiltration by lymphocytes (5%) showing morphologic characteristics of immunocytes was found. Immunophenotyping of bone marrow blood confirmed light-chain restriction in CD19+ lymphocytes (15% c_κ/CD19+; <1% c_λ/CD19+), consistent with infiltration of the bone marrow by the malignant B-cell clone. As there was no further bleeding, a decision for a wait-and-see strategy was made.

Consecutively, PTT slowly increased and exceeded the upper limit of normal on day 120, but factor VIII:C was 85% and the patient was well without bleeding.

On day 165, PTT was 59 s, factor VIII:C had decreased to 2% and factor VIII inhibitor level was 1.6 Bethesda units. Although there was no bleeding, the need for therapy was seen. Regarding the severe infectious complications of polychemotherapy and the lack of significant lymphoma progression, a decision was made for a mild nonmyelotoxic immunosuppressive therapy with cyclophosphamide 100 mg per os, days 1–4, and prednisolone 100 mg per os, days 1–4, q15 days. Six courses of this therapy were given starting on days 175, 189, 203, 217, 246, and 260. During this period, PTT slowly decreased without reaching normal range, factor VIII:C rose to 65% on day 246 with undetectable factor VIII inhibitor, and no bleeding, neutropenia, or infectious complications developed. On reevaluation on day 368, the PTT showed a tendency to increase (45 s), indicating recurrence of factor VIII inhibitor (fig. 1).

Discussion

Factor VIII inhibitors bind to functional epitopes or antigeneic sites of the factor VIII molecule, preventing interaction with other clotting factors or increasing neutralization [17]. The development of a factor VIII inhibitor has serious consequences. In a large survey [4], major bleeding occurred in 87% of patients, and 22% died either directly or indirectly as a consequence of having the inhibitor. The most common presentation is bleeding into the skin, soft tissue and muscles, which can lead to compartment syndrome. There can be mucosal bleeding like epistaxis, gastrointestinal bleeding or hematuria. In elderly patients with concomitant cardiac disease the resulting anemia may lead to angina pectoris or signs of heart failure. There may be iatrogenic bleeding after invasive diagnostic procedures, intravenous catheter placement and surgery [1]. Retroperitoneal and intraperitoneal hemorrhage is often fatal [4, 16]. For unknown reasons, joint bleeding seems to be rare in contrast to congenital hemophilia [2].

The hallmark of laboratory diagnosis of factor VIII inhibitors is prolongation of the PTT, whereas the prothrombin time is normal. Factor VIII:C is measured in a mixing assay using factor VIII-deficient plasma. Mixing of normal and patient plasma can distinguish between primary factor deficiency (like in congenital hemophilia and von Willebrand's disease) and secondary deficiency due to an inhibitor. While addition of normal plasma to factor-deficient plasma normalizes the PTT, mixing of normal plasma with plasma containing an inhibitor fails to correct PTT. A widely accepted method for quantifying the inhibitor is the Bethesda assay [17, 18]. Dilutions of patient plasma are incubated with normal pooled plasma for 2 h at 37 °C, and residual F VIII:C is measured and expressed as percentage of a control assay. Results are converted to antibody units using a conversion graph and multiplying according to the dilutions used. One Bethesda unit (BU) represents the amount of antibody that yields 50% residual activity in the test system. Quantification of the inhibitor may be an important prerequisite for treatment decisions [1].

Management of patients with factor VIII inhibitors has two objectives: (1) therapy and prevention of acute bleeding, and (2) reduction and elimination of the autoantibody [1].

The therapy of acute bleeding requires a variety of expensive blood products dependent on the titer of inhibitor (table 2). In patients with a low-titer inhibitor, elevation of factor VIII level with desmopressin (DDAVP) or substitution of human factor VIII may be sufficient. In patients with higher titers the substi-

Table 2. Treatment of acute bleeding

Titer, BU	Bleeding	Treatment
< 5	not limb- or life-threatening	a) DDAVP, 0.3 μg/kg i.v. over 20 min. If no response, give b) Recombinant human F VIII, 100 U/kg, then 10 U/kg/h, or c) Porcine F VIII, 0–100 U/kg, then 4 U/kg/h
5–30	serious	a) Porcine F VIII, 50–100 U/kg, then 4 U/kg/h, or b) Recombinant human F VIIa, 90 μg/kg every 2–3 h, or c) Activated prothrombin complex concentrate, 50–75 U/kg every 8–12 h
> 30	serious	a) Porcine F VIII, 100–200 U/kg, then 10 U/kg/h, or b) Recombinant human F VIIa, 90 μg/kg every 2–3 h, or c) Activated prothrombin complex concentrate, 50–100 U/kg every 8–12 h

tution of porcine factor VIII, which interacts less strongly with autoantibodies and thus leads to higher levels of circulating, F VIII:C [19, 20], may be indicated. Alternatives are the use of recombinant factor VIIa [21], which activates factor X when complexed with tissue factor at the site of injury, thus bypassing deficient factor VIII and resulting in local thrombin formation; or of activated prothrombin complex preparation, which likewise bypass factor VIII. Factor substitution can be preceded by plasmapheresis or immunoadsorption if available. Another method to decrease the inhibitor level in the phase of acute bleeding is the intravenous infusion of high-dose immunoglobulins (e.g., 1 g/kg daily for 2 days), as these preparations contain anti-idiotypic antibodies, which are directed against the patient's autoantibody [22].

It is still under debate whether the factor VIII inhibitor can be reduced and possibly eliminated by immunosuppressive therapy with steroids and/or cytotoxic drugs. Approximately on third of patients who receive supportive therapy only (transfusion of blood and factor concentrates) show spontaneous remission. These are mostly patients in pregnancy and postpartum or without underlying disease and low-titer inhibitors, who rarely develop life-threatening bleeding [2, 4]. Following this observation, some authors tend to regard acquired hemophilia as a rather benign condition not warranting, some authors tend to regard acquired hemophilia as a rather benign condition not warranting the use of potent immunosuppressive and possibly oncogenic drugs. However, spontaneous loss of the antibody is unpredictable, may take months or years during which the patient is at risk for serious hemorrhage, and supportive therapy with blood products is expensive. Therefore, efforts to reduce or eliminate the antibody are justified. A large survey [4] showed that 56% of patients had benefit from drug therapy (either steroids or cytotoxic drugs or both), suggesting that immunosuppressive therapy accelerates inhibitor disappearance compared with supportive therapy alone. There is much anecdotal evidence for the efficacy of immunosuppressive therapy [3, 5, 8–10, 23]. A prospective randomized trial [16, 24] showed the efficacy of prednisone and cyclophosphamide both alone and in combination. In this trial, responders to drug therapy had lower mean factor VIII antibody titers and higher mean factor VIII levels compared to non responders.

Based on this evidence, it is recommended [1] to administer steroids as a 1st-line treatment (prednisolone 1 mg/kg for 3 weeks, then taper). If the inhibitor persists, cytotoxic drugs like cyclophosphamide (2 mg/kg orally for 3–6 weeks) or azathioprine (2 mg/kg/day orally) should be given as 2nd-line treatment either alone, in combination with steroids, or in combination chemotherapy like the COP regimen. Should antibodies persist, cyclosporine is another option of proven efficacy for the 3rd-line therapy (up to 5 mg/kg/day yielding plasma levels of 150–350 ng/ml). Therapy should be continued until complete normalization of coagulation, and retreatment may be needed if inhibitors recur [23].

In our case there are two disorders, which are regarded as possibly connected to factor VIII antibody formation: (1) psoriasis, which was without significant activity at the point of antibody appearance and during all follow-ups, and (2) low-grade B-cell lymphoma, which had been diagnosed 11 years prior to the appearance of factor VIII antibodies and had been without significant progress apart from the development of an immunoglobulin deficiency. Furthermore, there was no monoclonal gammopathy, to which the activity against factor VIII could have been ascribed. Antibodies against factor VIII are known to be predominantly composed of immunoglobulin G [18]. In a case of Waldenström's disease, factor VIII antibodies have been shown to be polyclonal IgG molecules and thus not to be part of the IgM paraprotein [14].

In our case, it can only be speculated about the nature of the relationship between factor VIII antibodies and lymphoma. Autoantibodies can arise from malignant B cells or from a normal polyclonal lymphatic population. Autoantibody formation in normal lymphocytes can be triggered by the presence of a malignant cell clone. Alternatively, both disorders only coincidentally coexist in one individual.

With the intention to treat 'underlying' disease the patient received two courses of COP polychemotherapy with prompt normalization of coagulation parameters but with serious infectious complications. At recurrence of the inhibitors he received immunosuppressive therapy with prednisolone and cyclophosphamide with a more delayed response. Both therapies were effective but neither completely eradicated the inhibitor. Under either therapy the lymphoma showed no significant

change. We conclude that, at least in some cases of factor VIII inhibitors associated with malignancy, immunosuppressive therapy may be sufficient to suppress the inhibitor, and antineoplastic chemotherapy is not warranted unless indicated by the course of malignant disease itself.

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