Acquired hemophilia: a case report

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Abstract: Acquired hemophilia is a severe bleeding diathesis that affects both males and females. It is caused by suddenly appearing autoantibodies that interfere with coagulation factor VIII activity. This disorder is characterized by spontaneous and post-traumatic subcutaneous bleeds and massive mucosal hemorrhages. We report in the current article a case of acute renal failure and bleeding from the urinary tract caused by idiopathic acquired hemophilia in a 54-year-old woman. Hemostatic tests indicated prolonged activated partial thromboplastin time (APTT) to 107.8 sec (norm 26–36 sec), normal value of the prothrombin index which was 82% (norm 70–130%), increased fibrinogen concentration to 583 mg/dl (normal value 200–400 mg/dl), the bleeding time was 5 min and 20 s (norm <10 min) and the platelet count was 366×10^9/l (norm $130–400 \times 10^9$/l). The autoantibody against factor VIII in a titer of 121 Bethesda Units/ml (BU/ml) and decreased factor VIII activity to 2% (norm 50–150%) with normal plasma concentration of factor IX. Activated (FEIBA, Baxter) and nonactivated prothrombin complex concentrates (factor IX concentrate) have been used in the treatment of bleeding episode. Immunosuppressive treatment with the combination of oral prednisone 60 mg/24h and cyclophosphamide 150 mg/24h was administered in order to remove the factor VIII inhibitor. Reduction of the factor VIII inhibitor titer to 38 BU/ml and increase of factor VIII activity to 4% was initially achieved. This treatment has been continued for two years and led to normalization of hemostatic parameters (APTT 26 sec, factor VIII activity 108%) which means a total removal of factor VIII inhibitor.

Key words: acute renal failure, factor VIII inhibitor, hematuria, prolonged activated partial thromboplastin time

INTRODUCTION

Acquired hemophilia (AH) a severe bleeding diathesis caused by autoantibodies which impair the function of the coagulation factor VIII [1]. These antibodies are defined as the circulating anticoagulant, or factor VIII inhibitor. Acquired hemophilia is common in both males and females. In both classic and acquired hemophilia, the cause of bleeding tendency is the same – a decrease in factor VIII activity in the patient plasma. However, the clinical manifestation of both diseases is not identical. Spontaneous bleedings into joints are typical in classic hemophilia, whereas in AH, massive subcutaneous blood extravasations and mucosal hemorrhages are usually observed. The etiology of AH remains unknown. Some diseases (autoimmune disorders, cancer) and clinical conditions (puerperium) seem to induce the AH occurrence; however, in over 50% of cases, factor VIII autoantibodies are of idiopathic origin. In a patient with AH with normal prothrombin, thrombin and bleeding time values, normal platelet count and fibrinogen concentration, a 2- or 3-fold prolongation of the activated partial thromboplastin time (APTT) is usually observed. The first manifestation of AH is often a massive hemorrhage. In such situation, only quick diagnosis and the immediate administration of appropriate treatment can save the patient's life [2].

CASE REPORT

A 54-year-old woman, who had so far not been treated for any chronic diseases, was admitted from a regional hospital to the Department of Nephrology, Hypertension and Internal Diseases in Bydgoszcz for anuria, increased serum creatinine levels to 424.32 μmol/l (4.8 mg/dl), symptoms of impaired urine flow from the the pyelocalyceal system of the right kidney, diagnosed on ultrasound examination, and symptoms of hemorrhagic diathesis in the form of extensive extravasations. In the anamnesis, the patient reported that 4 months earlier, a severe bleeding followed about 2 hours after a tooth extraction, and required hospitalization and a transfusion of red cell concentrate. The coagulation system was

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not examined at that time. Earlier extractions as well as 2 spontaneous labors were not complicated by bleedings. Two months after the alveolar bleeding, the patient suffered from acute urinary retention with strong urgency and colicky pains in the left lumbar region. Several hours later macroscopic hematuria occurred with the presence of numerous clots, and was followed by polyuria. The symptoms lasted one day and resolved spontaneously. Despite these symptoms, the patient did not consult a doctor and did not take any medication.

A few days later, deep-vein thrombosis was suspected in the lower limbs and therefore, without the examination of the coagulation system, 12–8–4–2 mg daily doses of acenocoumarol were administered in ambulatory conditions. After about a week of such a treatment, a bleeding occurred from the urinary, genital and gastrointestinal tracts. The patient was hospitalized in the surgical department, where after additional examinations she was diagnosed with normocytic anemia. The hemoglobin level was 90 g/l (normal value for women 120–160 g/l), hematocrit 0.28 (normal value for women 0.37–0.48). Moreover, the white blood cell count (WBC) increased to 14.7×10^9/l (normal value $4.3–10.8 \times 10^9$/l) with normal platelet count 200×10^9/l (normal range $130–400 \times 10^9$/l). Coagulogram test was not performed. In urinanalysis, microscopic hematuria (isomorphic erythrocytes in test field) and albuminuria (40 mg/dl) were observed. Due to the symptoms of gastrointestinal bleeding, gastroscopy was performed which showed stomach mucous membrane covered with clots as well as erosion within the duodenal cap. On the 5th day of hospitalization, anuria occurred, and additional examinations showed creatinine levels increased to 521.56 μmol/l (5.9 mg/dl) (normal value <133 μmol/l, <1.3 mg/dl) and blood urea nitrogen (BUN) increased to 20.31 mmol/l (56.9 mg/dl) (normal value 3.6–7.1 mmol/l, 10–20 mg/dl). Due to an acute renal failure, the patient was transferred to the internal ward, where she was hospitalized for 5 days. An ultrasound examination of the urinary system showed features of the bilateral nephrectasis of the pyelocalyceal system (the size of the kidneys: right 127×70 mm, left 131×60 mm). Urine was not collected daily during the hospitalization period. However, the patient reported another one-day macroscopic hematuria episode followed by anuria. The examination of the coagulation system, performed for the first time, showed prolongation of the APTT to 97 sec (normal range 26–36 sec), international normalized ratio was 2.57 (normal range 0.9–1.2) with normal bleeding time 5 min 20 sec (normal value <10 min, Ivy method).

The patient had never smoked. She menstruated regularly and had given 2 spontaneous uncomplicated births. She had worked as an accountant and benefited from an early pension for the last year. The family history indicated that the father suffered from Alzheimer's disease, whereas the mother died of colorectal cancer. There had been no records of hematologic or systemic diseases.

On admission to the nephrological outpatient clinic, the patient underwent physical examination revealing obesity (body weight 107 kg, height 170 cm, body mass index 37 kg/m^2). ecchymoses on the lower limbs, and crural varices.

Laboratory tests showed normocytic/normochromic anemia (hemoglobin 96 g/l, mean corpuscular volume 85 fl [normal range 86–98 fl], mean corpuscular hemoglobin concentration 325 g/l [normal range 320–360 g/l], and mean corpuscular hemoglobin 27.6 pg [normal range 28–33 pg]). Leukocytosis was also diagnosed; the WBC count was 23.3×10^9/l. Platelet count was normal, 366×10^9/l. The coagulation system examination showed prolongation of the APTT to 107.8 sec (normal range 26–36 sec) with normal results of the prothrombin index 82% (normal range 70–130%) and increased fibrinogen concentration to 583 mg/dl (normal range 200–400 mg/dl). Creatinine levels increased to 380.12 μmol/l (4.3 mg/dl), and BUN increased to 19.63 mmol/l (55 mg/dl). General urine analysis showed isomorphic erythrocytes (25–40 hpf) and leukocyturia (10–15 hpf). Serum electrolyte levels were normal, i.e., Na^+ 137 mmol/l (normal range 136–145), K^+ 3.7 mmol/l (normal range 3.5–5), Ca^{2+} 2.44 mmol/l (normal range 2.2–2.6). Disproteinemia was diagnosed with mild hypoalbuminemia 34 g/l (normal range 35–55 g/l), α_1-globulin level increased to 3.9 g/l (normal range 2–4 g/l) and β-globulin increased to 17.6 g/l (normal range 6–11 g/l). The presence of anti-nuclear antibodies was not observed in serum. Repeated ultrasound examination showed symptoms of urinary retention in the pyelocalyceal system of the right kidney, the liver enlarged to 175 mm in the mid-clavicular line and hypoechogenic area of heterogeneous echostructure, size 73×70 mm, in the view of the body and the fundus of the uterus. On the basis of the plain X-ray of the abdomen, the presence of calcic shadows was excluded in the view of the urinary system. The X-rays examination of the knee joints showed initial degenerative lesions. Because of symptoms of acute infrarenal failure, the patient required urological consultation. Urography showed impaired urinary outflow from the right kidney as well as a tumor shaping the upper wall of the urinary bladder. During the patient's stay at the nephrological outpatient clinic, as a result of conservative treatment of acute renal failure, diuresis increased to the maximum rate of 5100 ml/24h and creatinine level decreased to 61.8 μmol/l (0.7 mg/dl).

Persistent bleeding from the genital tract and abnormal results og the imaging tests, a gynecological consultation was necessary; the patient was diagnosed with uterine fibroids. As symptoms of urinary tract infection and symptomatic bacteriuria (*Enterococcus foecalis* 10^6 cells/μl, *Pseudomonas fluorescens* 10^5 cells/μl) were observed, ciprofloxacin was administered according to the antibiogram.

The symptoms of bleeding diathesis in the form of extensive subcutaneous extravasations persisted especially in the region of the lower limbs, accompanied by microscopic hematuria, bleeding from the genital tract and prolongation of the APTT. Therefore, fresh frozen plasma was administered which did not, however, result in either the normalization of the blood coagulation parameters, or the resolution of the genital tract bleeding. on the eleventh day of hospitalization occurred

a severe painful condition and weakened muscle power in the right lower limb accompanied by decreased hemoglobin levels from 92 to 79 g/l. Flaccid right lower limb paresis was diagnosed, and the magnetic resonance imaging showed a massive hematoma of the right iliopsoas muscle.

On the basis of the clinical manifestation progressing with a clinically significant bleeding diathesis showed by the presence of the massive hematoma of the right iliopsoas muscle, the late bleeding after a tooth extraction in the anamnesis, and a significant prolongation of the APTT which did not shorten after administation of fresh frozen plasma, with normal values for the bleeding time, the prothrombin index and the platelet count, suspicion of idiopathic acquired hemophilia was made. The patient was moved to the Institute of Hematology in Warszawa for further diagnostic evaluation and treatment. During the patient's stay at the Institute of Hematology, in the additional examinations, a significant prolongation of the APTT to 85.5 sec was observed (normal range 25–33 sec) as well as normal values of the prothrombin index 81.6% (normal range 80–120%) and the thrombin time 15 sec (normal value 15 sec). The factor VIII activity decreased to 2% of the norm (normal range 50–150%) with clinically insignificant, slightly decreased activity of the factor VII (66%, normal range 70–120%) and factor X (68%, normal range 70–120%), normal level of the factor IX (71%, normal range 50–150%) and also a clinically insignificant increase of the factor V level (180%, normal range 70–120%). A fibrinogen concentration increased to 720 mg/dl (normal range 200–500 mg/dl). The presence of the circulating anticoagulant was confirmed in a correction test (prolongation of the APTT in the mixture of equal parts of the patient plasma and normal plasma). Using the Bethesda method, the presence of anti-human factor VIII antibodies was indicated in the patient plasma in a titer of 121 Bethesda Units/ml (BU/ml). The hepatitis B virus antigen, anti-hepatitis C virus antibodies, and anti-human immunodeficiency virus antibodies were not observed. The result of the syphilis examination using the enzymatic method (Trepanostika) was negative.

Due to the active bleeding diathesis, treatment was administered with activated (FEIBA, Baxter) and nonactivated prothrombin complex concentrates (factor IX concentrate) in doses of 50–100 units of FEIBA or factor IX *i.v.* every 8–12 hours. After cessation of bleeding, immunosuppressive treatment was administered in order to remove the factor VIII inhibitor. At first, 60 mg of prednisone per day was used, and then it was combined with 150 mg of oral cyclophosphamide daily. Only a slight reduction of the factor VIII inhibitor titer to 38 BU/ml was achieved and an increase of factor VIII activity to 4%. After 24 days of the therapy, the patient was discharged from hospital. Continuation of immunosuppressive treatment in the same form was recommended. After two years of this treatment, the inhibitor was removed, which was confirmed by the normalization of APTT to 26 sec (normal range 25–33 sec) and restoring normal factor VIII activity to 108% (normal range 50–150%). For the next 3 years, the patient has remained untreated and has shown no clinical manifestations of the disease.

DISCUSSION

This case report shows that analysis of the blood coagulation system is important in solving diagnostic problems in everyday medical practice. An atypical symptom like a prolonged bleeding after a tooth extraction, followed by an acute posthemorrhagic anemia should encourage to perform hemostatic tests to exclude hemostasis disorders.

Congenital hemophilia affects mainly men, while women are usually carriers of the disease and their factor VIII activity is close to the lower limit of reference values. Classic hemophilia very rarely occurs in women and is caused by X chromosome disorders (among others, in Turner syndrome with abnormal inactivation of the X chromosome inherited from one of the patient's parents) or occurs as a result of inheriting the genes of hemophilia from each of the parents (father suffers from hemophilia, mother is a carrier). In the present case, hematologic diseases were not reported in the family history, and the patient did not show phenotypic features of Turner syndrome. Lack of the history of nose bleeds or gum bleeds, prolonged menstrual bleedings and bleedings into joint cavities or muscles, as well as a normal course of delivery made it impossible to diagnose the congenital bleeding diathesis, including hemophilia.

Among the clinical situations which include the prolongation of the APTT with normal prothrombin time, the following must be distinguished:

1) treatment with low-molecular-weight heparin (at high doses of heparin, prothrombin time may also be prolonged)
2) the presence of lupus anticoagulant (with very rarely prolonged prothrombin time)
3) deficiencies of factor VIII, factor IX, factor XI and factor XII, prekalikrein or high-molecular-weight kininogen
4) the presence of factor VIII inhibitor in plasma; factor IX, factor XI and factor XII inhibitors present much less frequently.

In the treatment of this patient, heparin was not administered, which excluded the drug-induced APTT prolongation. The presence of lupus anticoagulant might be indicated by the history of deep-venous thrombosis in lower limbs with the prolongation of the APTT [3]. During the current hospitalization, the patient has not been tested for lupus anticoagulant. This syndrome may be excluded with high probability because the prolonged APTT was accompanied by hemorrhagic, not thrombotic, events [4,5].

Because deep vein thrombosis in the lower limbs was diagnosed in the past solely on the basis of clinical examination, the duplex ultrasound of the lower limb veins was performed during hospitalization. Thrombotic lesions were excluded in the test. The symptoms which suggested a previous deep vein thrombosis might have resulted from impaired venous blood

outflow caused by venous compression exerted by the hematoma of the thigh muscle [6]. Treatment of venous thrombosis with antivitamin K when it has not been confirmed in examinations may pose a life threat due to possible treatment-related hemorrhagic complications and masking the presence of inhibitors of the plasma coagulation factors [7]. Acute renal failure observed in the current case probably resulted from the obstruction of the urinary tract by blood clots. in the clinical manifestation of obstructive nephropathy, urinary disorders are typical. Diuresis may be normal, increased or decreased up to anuria. If urethral obstruction is only partial, oliguria and polyuria may occur alternatingly. If the urinary outflow is impaired, tenesmus, pollakiuria, or paradoxical ischuria may occur. After automatic or mechanical removal of the obstacle, polyuria occurs. Among the reasons for hematuria, one must above all include nephrolithiasis, but in its course microscopic hematuria occurs more often than macroscopic hematuria and it seldom occurs in the form of anuria. Ureterolithiasis may be easily excluded by widely available ultrasound examination. In case deposits or fragments of renal papillae are present, urography and anamnesis may be decisive. Urography performed in the current case did not show any obstacle of the urine outflow.

Acquired hemophilia should be suspected in a patient who had never shown bleeding tendencies and suddenly shows symptoms of severe bleeding diathesis. The diagnosis of acquired hemophilia may be confirmed by laboratory tests of factor VIII inhibitor. Unfortunately, these tests are available only in specialized hematology laboratories and therefore, the time necessary to make a diagnosis is often alarmingly prolonged, consequently delaying the administration of proper antihemorrhagic treatment which often determines the patient's survival. If the clinical manifestation is typical for AH, an initial diagnosis of AH may be established only on the basis of hemostatic screening examination and proper antihemorrhagic treatment may be administered.

Therapeutic management of patients with AH includes two major aims: short-term, which is treatment and prophylaxis of bleedings, and long-term, which is inhibitor removal [1]. It must always be remembered that there is a possibility of coexistence of different diseases which are conducive to acquired hemophilia and their diagnosis and proper treatment may play a significant role in the patient's future.

In prophylaxis and treatment of bleedings in patients with AH, transfusions of fresh frozen plasma and cryoprecipitate are usually ineffective because they contain little factor VIII so antibodies neutralize them very fast. Administering high doses of human factor VIII concentrate may prove efficient only in a small number of patients with low inhibitor titer, whereas higher inhibitor titers require administration of porcine factor VIII [8]. However, the drugs of choice for stopping bleedings in patients with AH are activated prothrombin complex concentrates (FEIBA and Autoplex) and recombinant activated factor VII [9]. These concentrates activate blood coagulation skipping the stage which depends on the presence of factor VIII. Clinical tests have proven their efficiency in the treatment of bleedings in AH. The removal of the factor VIII inhibitor may be performed either by extracorporeal adsorption onto columns coated with protein A of *Staphylococcus* (Therasorb®) which selectively binds a fragment of the Fc of human immunoglobulin G, or by the plasmapheresis method [10]. However, the result of such treatment is brief, technically difficult, and available only in highly specialized centers. Therefore, immunosuppressive drugs play the most important role in the removal of the inhibitor. It is believed that immunosuppressive treatment should be administered as soon as possible after AH is diagnosed, although possible contraindications for this form of therapy must be always taken into consideration. In the immunosuppressive treatment of acquired hemophilia A, prednisone and cyclophosphamide (CTX) are first-line therapy. The combination of these two agents has remained a basic method of treatment for many years and increased the percentage of positive responses [11]. In cases where the inhibitor has not been removed during 6–8 weeks after administering such treatment, so-called second-line drugs may be administered, like rituximab, cyclosporine A and other immunosuppressive and immunomodulatory drugs [1]. A combination of 2 or more medicines is usually administered (e.g. vincristine, CTX and prednisone in 4-week cycles) [12]. Reports of high effectiveness of rituximab administered in monotherapy or in combination with corticosteroids or cyclophosphamide are very promising [13]. Some researchers claim that simultaneously administration of immunosuppressive treatment and intravenous injections of high doses of factor VIII shortens the time necessary to remove the inhibitor [14].

Applied diagnostic methods

Blood cell count was determined using the hematology analyzer Sysmex XE 2100.

Hemostatic parameters (prothrombin time, APTT, thrombin time) were determined with coagulation method using Dade Behring reagents on the BCT analyzer [15]. The activity of the coagulation factors VIII, IX, XI, and XII was determined by a one-stage clotting assay based on APTT modification [15]. The activity of the coagulation factors V, VII, and X was determined with a one-stage clotting assay based on prothrombin time modification [15]. The APTT corrective test in the mixture of equal parts of the patient's plasma and normal plasma was performed after 60 minutes of incubation at 37°C [15]. The factor VIII inhibitor was detected with the Bethesda method [16]. Fibrinogen concentration was determined with the Clauss thrombin time method [15]. Bleeding time was measured with the Ivy method [15].

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