Clinical heterogeneity of acquired hemophilia A: a description of 4 cases

Acquired hemophilia A is a rare but severe autoimmune bleeding disorder characterized by the presence of autoantibodies directed against clotting factor VIII. Acquired hemophilia A may be idiopathic or associated with several conditions, such as postpartum, autoimmune diseases, malignancies or drugs. The treatment modalities of bleeding episodes and eradication of the factor VIII autoantibody depend on the titer of anti-factor VIII:C and may include desmopressin (DDAVP), prednisolone, prednisolone-cyclophosphamide, high dose intravenous gammaglobulin, FVIII-VWF concentrate and/or recombinant FVIIa (rFVIIa). In this study we report four cases of autoimmune factor VIII inhibitors (2 associated with autoimmune disorders, 2 idiopathic) demonstrating the heterogeneity of this disease from pathogenic, clinical, therapeutic and prognostic points of view.

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Acquired hemophilia A is an uncommon but potentially life-threatening hemorrhagic disorder caused by the development of autoantibodies directed against coagulation factor VIII (F VIII) in adults or elderly male or female patients, who do not have a personal or family history of bleeding episodes.[1-5] The clinical picture of acquired hemophilia A differs from that of *classical* hereditary hemophilia A. In fact, more than 80% of patients with factor VIII autoantibodies present with hemorrhage into the skin, muscles or soft tissues and mucous membranes (e.g. epistaxis, skin hematomas, ecchymoses, gastrointestinal and urological bleeds, retroperitoneal hematomas), whereas hemarthroses, typical of congenital factor VIII deficiency, are unusual. Not rarely the hemorrhages in patients with autoimmune factor VIII inhibitors are serious or life-threatening, such as in the case of rapidly progressive retroperitoneal hematomas or compartment syndrome due to intramuscular bleeds.[3] Other manifestations include prolonged postpartum bleeding and excessive bleeding following trauma or surgery or even serious or fatal cerebral hemorrhage.[2]

The diagnosis of acquired hemophilia A is easy to make, but frequently delayed because of unfamiliarity with the typical laboratory features of this rare bleeding disorder in internal medicine. The combination of a normal bleeding time, platelet count and prothrombin time (PT) with prolonged activated partial thromboplastin time (APTT) that is not corrected in a mixture of patient and normal plasma is highly suspicious for acquired hemophilia.

Acquired hemophilia A may be associated with the postpartum condition,[6-11] autoimmune diseases,[12-15] as well as various types of neoplasia and drugs,[16,17] but in nearly half of the cases it occurs spontaneously in elderly people.[18,19] The therapeutic strategy has two aims: long-term suppression of the autoantibody and control of any hemorrhages.[20-28] The treatment for eradicating the antibody is immunosuppressive drugs, such as prednisone and cyclophosphamide, and/or immunomodulators, such as immunoglobulins at high doses. More recently, serotherapy with anti-CD20 monoclonal antibody (rituximab) has been reported to reduce antibody titers within a short time in single cases.29 The treatment of bleeding episodes depends on the titer of the factor VIII inhibitor: patients with a low inhibitor titer (< 5 Bethesda Units [BU/mL]) can be treated with high doses of human factor VIII concentrates, intravenous high dose IgG and/or desmopressin, whereas patients with a high inhibitor titer (> 10 BU/mL) are generally treated with porcine factor VIII or activated prothrombin complex concentrates or activated recombinant factor VII (rFVIIa). In patients with a high titer of inhibitor and severe hemorrhage, extracorporeal removal of the autoantibody by therapeutic plasmapheresis, or immunoadsorption of immunoglobulins to staphylococcal protein A or to polyclonal sheep antibodies against human immunoglobulins, can be used prior to factor concentrate treatment.[30,31]

In this study we describe four cases of acquired hemophilia A which testify to the broad heterogeneity of the pathogenic, clinical, therapeutic and prognostic aspects of this condition.

Patients and Methods

The prothrombin times was measured on a Behring Coagulation System (BCS, Dade Behring, Marburg, Germany), employing human thromboplastin Thromborel, ISI 1.07 (Dade Behring) and results were converted into an International Normalized Ratio (INR). The activated partial thromboplastin time was measured in duplicate on a Behring Coagulation Timer (BCT, Dade Behring) employing Pathromptin SL (micronized silica + calcium chloride solution, Dade Behring). The activity of clotting factor VIII was measured on BCT using a modification of the one-stage APTT test (Behring Diagnostic GmbH, Marburg, Germany). Von Willebrand factor antigen (VWF:Ag) was measured by a commercial automated enzyme-linked immunosorbent assay on a mini Vidas analyzer (bioMerieux, Marcy-l'Etoile, France); von Willebrand ristocetin cofactor activity (VWF:RCo) was assessed on a Behring Coagulation Timer (BCT, Dade Behring) by a platelet agglutination method. For mixing studies, the patient's plasma was mixed with an equal volume of normal plasma (termed 1:1) and incubated for 1 hour at 37°C; the test was repeated noting the degree of correction. Correction of the abnormality indicates that the added plasma contains the factor deficient from the test sample, whereas a persisting abnormality might signify the presence of inhibitors or lupus anticoagulant. Inhibitor assays were performed using the Bethesda method, according to the Nijmegen modification.[32] In brief, serial dilutions using factor VIII assay buffer of the patient's plasma were prepared. A standardized amount of factor VIII in the form of a normal plasma pool was added to each dilution of test plasma. In the factor VIII assay, carried out after 2 hours of incubation, the control mix of normal plasma and buffer was used as the standard reference and the factor VIII concentration of other mixtures calculated against this. According to the Nijmegen modification, the normal plasma was buffered either by the addition of 0.1 M imidazole pH 7.4 or by using buffered pooled normal plasma. At the end of the incubation period, the residual factor VIII level was measured by coagulant factor VIII activity assay and the inhibitor calculated from a graph of residual factor VIII vs. inhibitor units.

Results

Figure 1 (A-D) reports the factor VIII activity and inhibitor levels at diagnosis and during treatment for all 4 consecutive patients with acquired hemophilia A (2 males and 2 females, median age 64.5 years) seen at our hemophilia center between 1998 and 2003.

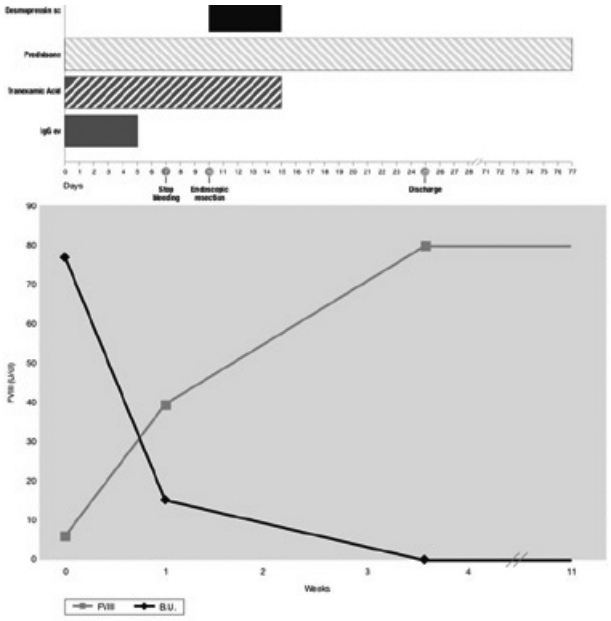

Figure 1. A-D. Acquired hemophilia A: case descriptions.

Case 1

A 75-year old woman was admitted to our city hospital in November 1998 because of rectal bleeding and extensive hematomas on the left thigh and right upper arm. There was no family or personal history of a congenital bleeding diathesis. Laboratory tests revealed anemia (hemoglobin 9 g/dL), a prolonged APTT of 64 sec., which was not corrected by normal plasma, decreased factor VIII activity (6 U/dL) and the presence of a high-titer factor VIII inhibitor (30 BU/mL). Investigations for conditions most frequently associated with the formation of inhibitors (e.g. autoimmune disorders, malignancies, dermatological disorders, reaction to drugs) were negative. A rectosigmoidoscopy revealed the presence of 3 bleeding rectal polyps. Given the patient's age and the severe but not life-threatening clinical presentation, we started therapy with intravenous tranexamic acid 1g thrice daily for 15 days, oral prednisone 1 mg/kg/day for 3 weeks which was gradually reduced by 5 mg/week and intravenous immunoglobulins (Ig Vena, Kedrion, Castelvecchio Pascoli, Italy) 400 mg/kg/day for 5 days. Two days after the end of the infusions of intravenous immunoglobulins, rectal bleeding had stopped and the hematomas were fading. Laboratory test results had also improved: APTT and factor VIII inhibitor titer had fallen to 38 sec. and 6 BU/ml, respectively, while factor VIII activity had increased to 40 U/dl. Three days later the patient underwent endoscopic resection of the rectal polyps: subcutaneous desmopressin (Emosint, Kedrion, Castelvecchio Pascoli, Italy) 0.3 μg/kg (started 60 minutes before the operation) was added for 5 days to the ongoing therapy (oral prednisone and tranexamic acid). Blood tests 60 minutes after desmopressin injection showed normalization of APTT and factor VIII activity. The patient was discharged 15 days later: the hematomas had disappeared and hemostatic parameters remained within normal ranges. No factor VIII inhibitor was detected in the patient's serum. She continued with her steroid therapy which was tapered off over the next two months in order to reduce the risk of side effects, which are particularly common in the elderly. A recent check-up (February 2004) confirmed the absence of factor VIII inhibitor.

Case 2

A 74-year old woman was admitted to our hematology emergency unit in June 2000 with headache, nausea, vomiting, a significant superficial face hematoma and massive muscle hematomas on the right arm and left thigh. Blood tests showed severe anemia (hemoglobin 6.5 g/dl) and a markedly prolonged APTT (108 sec.); PT, fibrinogen and platelet count were within the normal ranges. Neurological examination and CT scans of the skull excluded a cerebral bleeding problem. The absence of a family and personal bleeding history, together with the fact that the APTT was not corrected by addition of normal plasma, was highly suspicious for a coagulation inhibitor. Considering the emergency of the initial clinical picture, we decided to start transfusion therapy immediately with red blood cell concentrates and anti-hemorrhagic treatment with rFVIIa (Novoseven, Novo Nordisk, Rome, Italy) in a 120 μg/kg intravenous bolus followed by 90 μg/kg after 2 hours, the same dose then being administered every 3 hours. We also gave the patient 1 g tranexamic acid intravenously every 8 hours. The laboratory tests showed an extremely low value of F VIII (F VIII <1 U/dL) and of a high titer inhibitor directed against human factor VIII (220 BU/mL). This inhibitor cross-reacted with porcine F VIII (55 BU/mL). The high levels of anti-nuclear antibodies (ANA, titer 1:5000) demonstrated an underlying auto-immune disease. Concomitant immunosuppressive therapy was started with 1 mg/kg prednisone per day and 100 mg cyclophosphamide per day orally. The anti-hemorrhagic therapy with rFVIIa quickly brought the bleeding under control; as a result, hemoglobin levels stabilized, the need for blood transfusions decreased and the hematomas stopped progressing. From the third day in hospital the rFVIIa was decreased to 90 μg/kg every 4 hours, the same dose being administered every 6 hours from the sixth day onwards. Over this period the patient's dependence on transfusions ceased, her hemoglobin concentration stabilized around 11 g/dL and a slow but progressive resorption of hematomas was observed. From the twelfth day the rFVIIa was further decreased to 90 μg/kg every 8 hours, and on the sixteenth day it was discontinued, because the hematomas had almost completely disappeared. Since high titers of factor VIII inhibitor and low factor VIII values persisted despite the protracted immunosuppressive therapy, administration of intravenous immunoglobulins was started on 25th hospital day at a dosage of 400 mg/kg per day for 5 days. On the 27th day the clinical picture was complicated by a biliary colic with jaundice (bilirubin, mainly direct, up to 15 mg/dL) and high serum amylase concentrations due to a stone blocking the common bile duct. Emergency papillosphincterectomy (ERCP) was performed after the patient had resumed therapy with 120 μg/kg rFVIIa, followed 2 hours later by 90 μg/kg, the same dose then being administered every 3 hours. The post-operative recovery was regular and free from bleeding complications. From the 4th day after surgery the rFVIIa was decreased to 90 Ìg/kg every 4 hours until it was discontinued 8 days post-operatively (35th hospital day). From day 30 the patient had shown a progressive improvement of coagulation parameters (Figure 1-B). On day 32 the oral cyclophosphamide therapy was discontinued (total dose administered 3.2 g) because of the onset of leukothrombocytopenia. From the day 35, after documented full remission of the disease (the APTT was back to normal and the inhibitor had disappeared [Figure 1-B]), the steroid was gradually reduced by 5 mg per week. On day 45, the acquired hemophilia recurred as documented by

laboratory tests (Figure 1-B), the steroid therapy was brought back to full dosage (prednisone 1 mg/kg per day per os) and the treatment with cyclophosphamide (500 mg bolus intravenously) and with intravenous immunoglobulins (400 mg/kg per day, for a scheduled 5-day course) was resumed. Tests for antinuclear antibodies remained positive (titer 1:2000). On day 47 after admission the patient died of severe, sudden onset bleeding, characterized by melena, spontaneous superficial and muscle hematomas and hemorrhage in the left temporo-occipital area of the brain (the post-mortem confirmed the CT scan findings).

Case 3

A 45-year-old male was hospitalized in July 2003 for recurrent hemarthroses of the left knee and spontaneous ecchymoses on the forearms. Rheumatologic screening revealed a weakly positive test for antibodies to nuclear antigens (titer 1:80), whereas coagulation tests showed a normal PT and a prolonged APTT (55 sec). The concentration of factor VIII was 4 U/dl and a low titer inhibitor to FVIII (1 BU/mL) was found. The patient had undergone surgery without bleeding complications 4 years previously for a post-traumatic femoral fracture. His family history was negative for blood coagulation disorders. An X-ray of the left knee showed early stage arthropathy. Due to the low titer inhibitor, a DDAVP test was tried. The patient's response to subcutaneous desmopressin (see Table 1) at the standard dose of 0.3 μg/kg was successful. Desmopressin therapy (0.3 μg/kg s.c. once daily for 3 days) and immobilization of the left leg led to rapid resolution of the hemarthrosis. The patient refused therapy to eradicate the autoantibody. In December 2003 the patient was seen again at our hemophilia center for a hematoma of the cheek which faded away after DDAVP therapy (0.3 μg/kg s.c. once daily for 3 days). A laboratory check performed on admission confirmed the presence of a low titer inhibitor to coagulation factor VIII (titer 4.5 BU/mL) with a F VIII of 3.6 U/dL. Antinuclear antibodies were confirmed to be weakly positive (titer 1:80). Since the patient accepted eradication treatment, oral prednisone was started at a dose of 1 mg/kg per day for 3 weeks and gradually tapered off over the next two months, but the low titer factor VIII inhibitor persisted after discontinuation of prednisone (see Figure 1-C). Two months later (February 2004) coagulation tests showed F VIII in the normal range and no inhibitor could be detected.

Case 4

A 64-year old man was admitted to our hospital in July 2003 because of the appearance of massive hematomas on his trunk and arms. Blood chemistry tests performed on admission revealed severe anemia (hemoglobin 8.2 g/dL). A rheumatologic screening was negative, whereas thyroid laboratory tests (increased anti-thyroglobulin antibodies) were compatible with his thyroid disease (the patient had been receiving replacement treatment with l-thyroxine for 5 years because of autoimmune hypothyroidism). The patient's personal and family history were negative for hemorrhagic disorders. Coagulation tests revealed an APTT of 160 s which was not corrected by adding normal plasma. A diagnosis of inhibitor to F VIII was made; the F VIII level was 2.6 U/dl and the inhibitor titer was 20 BU/mL. Transfusion of packed red blood cells was necessary (during the hospital stay 11 units of RBC were transfused). Therapy with intravenous rFVIIa was immediately started at a dose of 90 μg/kg every 4 hours for 4 consecutive days. At the same time, therapy was started with intravenous immunoglobulins (400 mg/kg per day for 5 consecutive days), steroids (methylprednisolone 1 g i.v. once daily for 3 consecutive days followed by oral prednisone 1.5 mg/kg per day) and cyclophosphamide (1g i.v. followed by 100 mg per day per os). From the fourth day, the interval between administering rFVIIa was lengthened to every 6 hours. On day 11, treatment with rFVIIa was suspended. There was a slow but progressive improvement of the clinical picture (reduction of hematomas and blood requirement) and a laboratory coagulation check performed 15 days after the beginning of immunosuppressive treatment showed an increase of F VIII up to 14 U/dl and a reduction of inhibitor titer to 3 BU/mL. Steroid therapy was gradually tapered down and the patient was discharged (on day 26 of therapy) while receiving 1 mg/kg per day of prednisone and 100 mg/day of cyclophosphamide, both given orally. At discharge the APTT was 76 sec, whereas F VIII and inhibitor titer were 15 U/dl and 3 BU/ml, respectively. Seven days later the patient was readmitted with a large hematoma of the right thigh and severe anemia (hemoglobin 6.9 g/dL) which required transfusion of 5 units of RBC and treatment with rFVII (90 μg/kg i.v. every 4 hours for 4 days). On re-admission the APTT was 54 sec, F VIII was 16 U/dl and the inhibitor titer was 2 BU/mL. Immunosuppressive treatment was maintained unchanged. During the hospital stay the patient's clinical conditions and coagulation tests improved progressively. A mild conjunctival hemorrhage developed on the seventh day after admission, for which the patient was successfully treated with s.c. desmopressin (a DDAVP test showed APTT and F VIII normalization 1 hour after a test injection) at a dose of 0.3 μg/kg per day for 2 consecutive days. At discharge (14 days after admission), the APTT was 41 sec, F VIII was 35 U/dL and the inhibitor titer was 0.9 BU/mL. Since October 2003, monthly follow-ups (last control February 2004) repeatedly confirmed the absence of hemorrhages, the normalization of APTT and F VIII and the disappearance of the inhibitor. In October 2003, oral cyclophosphamide was suspended and oral prednisone was gradually tapered down to 0.25 mg/kg per day.

Table 1. Case 3: results of the desmopressin test.

Time	*APTT* (seconds)	*F VIII* (U/mL)	*VWF:Ag* (U/ml)	*VWF:RCo* (U/ml)
Basal	55	4	98	66
60 minutes*	43	38	175	160
120 minutes*	41	44	210	190

*Normal range: APTT, 26-34 seconds; F VIII, 50-150 U/dl; VWF:Ag (von Willebrand factor antigen), 60-150 U/dl; VWF:RCo (von Willebrand factor: ristocetin cofactor), 40-145 U/dl. *After s.c. injection of desmopressin at a dose of 0.3 μg/kg.*

Discussion

The description of our cases shows again that acquired hemophilia A is a heterogeneous condition from pathogenic, clinical and therapeutic points of view. Delgado and colleagues,33 in a recent meta-analysis of 20 retrospective and prospective surveys including 234 patients with acquired hemophilia, identified three prognostic factors independently associated with a decreased overall survival: related conditions (malignancy vs. others vs. postpartum), age (> 65 years vs. < 65 years) and achievement of complete remission (no vs. yes). Our case reports are in line with this evidence: in fact all the three patients who achieved a complete remission (cases 1, 3 and 4) were long-term survivors. Two out of our four cases were asso-

ciated with autoimmune disorders (cases 2 and 4). Case number two bears witness to the importance of treating the underlying disorder: in fact, this patient, who died of a severe hemorrhage, was affected by a not well identified autoimmune disorder which was not eradicated by immunosuppressive treatment, as documented by the persistence of positive antinuclear antibodies. In patient number 4, acquired hemophilia A was associated with a pre-existent autoimmune hypothyroidism: this is the second case reported in the literature.14 The border-line positive test for antinuclear antibodies in patient number 3 was not conclusive for an underlying autoimmune disorder; however, it is well known that the appearance of an inhibitor to coagulation factor may precede the onset of an autoimmune disease by several years and this could be the case in our patient. The clinical presentation of acquired hemophilia in this last patient was also atypical: in fact joint bleeding is an unusual clinical manifestation of acquired hemophilia, which is preferentially manifested by bleeding into the skin, muscles or gastrointestinal and urinary tracts. However, the pre-existing early stage arthropathy in this patient may have created a preferential bleeding site. Our cases documented the efficacy and safety of rFVIIa, given intravenously at boluses of 90-120 µg/kg every 4-6 hours, in treating the most severe bleeding episodes in patients with FVIII inhibitors. Furthermore, cases 1, 3 and 4 showed the efficacy of desmopressin in treating non-life-threatening hemorrhages both in low-titer inhibitor patients (case 3) and in patients with a previous high-titer inhibitor who respond to immunosuppressive therapy (cases 1 and 4). These last 2 cases testify the efficacy of the combination therapy steroid/cyclophosphamide as first line inhibitor eradication treatment. Prospective multicenter studies are needed in order to identify the proper treatment options for the control of bleedings and eradication of the factor VIII inhibitor for each individual with acquired hemophilia A.

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