

Acquired hemophilia A: three different presentations of the same disease

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Acquired hemophilia A is a rare disorder characterized by the presence of an autoantibody (mainly immunoglobulin G) to the clotting factor VIII with a clinical resemblance to hemophilia A. This autoantibody may arise because of dysregulation of the immune system. It is associated with various autoimmune or dermatologic diseases, pregnancy, or drug ingestion, but in almost 50% patients, the cause is unknown. In the present study, we have reported three different clinical presentations of acquired hemophilia. In two cases, the underlying disorder was the probable respiratory chronic disease (asthma), and in the other, it was idiopathic. We reviewed the response to a given treatment. The severity of the clinical presentation was different in all the cases, and was taken into account when we decided on the best course of treatment. The present report presents two patients successfully treated with a tapering course of

steroids, and one with the anti-CD20 monoclonal antibody not given as first line treatment. *Blood Coagul Fibrinolysis* 21:188–191 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Acquired hemophilia A is an unusual bleeding disorder, and is usually caused by the development of autoantibodies (inhibitor), mainly immunoglobulin G (IgG), against the clotting factor VIII.

It is most common in the elderly, and is associated with various conditions (autoimmune or dermatologic diseases, pregnancy, cancer, or drug ingestion), but up to 50% of the reported cases are idiopathic.

There are a few studies on the presentation and clinical courses, and prospective studies are needed to determine the efficiency of the treatment [1]. Acquired hemophilia A could potentially be a life-threatening hemorrhagic disorder, and has a low incidence of 1–1.5 cases/million people per year [2,3].

The diagnosis of this disease is often difficult. Very often, patients exhibit no personal or familial history of bleeding episodes. Clinical presentation differs from congenital hemophilia. More than 80% patients demonstrate bleeding in skin, muscles, or soft tissues and mucous membranes. Hemarthroses, typical in congenital hemophilia, is unusual.

Treatment of acquired hemophilia A is complex, and response to the treatment that we administer in most of the cases is not predictable. The treatment is focused on

two aspects, to stop the bleeding and to control the autoantibody.

The treatment options include factor VIII replacement therapy or activated prothrombin complex concentrates, and more recently, recombinant activated coagulation factor VII (rFVIIa), which can circumvent the actions of inhibitory antibodies present in acquired hemophilia patients [4]. On the contrary, antibodies suppression could be possible by some immunosuppressive therapy, including steroids, cyclophosphamide, cyclosporine, and rituximab [5]. Some combinations have also been described. A course of steroids and one or more additional agents is a usual treatment strategy. These treatments are related to several adverse effects with bad tolerability, which is higher in older patients. New agents such as Mabthera (F. Hoffmann-La Roche Ltd, Basel, Switzerland), an anti-CD20 monoclonal antibody, have been used to eliminate the autoantibody production by targeting B cells [6]. Furthermore, there are few cases reported to have been treated with rituximab. In this study, we have reviewed three new diagnostic cases, from 2003 to 2006 in our hospital.

Case one, a 51-year-old athletic man with lichenoides toxicoderma, anxious depressive syndrome, and who is allergic to sulfonamides, came to the emergency department because of a big hematoma on his left arm due to a trauma as a result of an accidental fall. Physical examination

revealed indurate hematoma on the left forearm with hypoesthesia in fingers, and presence of hematomas in other localization (right arm, left leg).

He was attended by a traumatologist, who decided that a fasciotomy should be done because of compartment syndrome.

Four hours after surgery, the patient started bleeding and developed hemorrhagic shock, requiring treatment in the intensive care unit. Complete blood count was normal, but laboratory examination showed a prolonged activated partial thromboplastin time (APTT) of 68 s and a ratio of 2.1 international normalized ratio (INR) 1.0.

Normal APTT failed to restore with the administration of normal plasma, and an inhibitor was suspected. A factor-clotting dosing revealed 1% of factor VIII and the inhibitor of factor VIII of 9 Bethesda Units/ml (BU/ml).

The patient was treated with rFVIIa in a bolus every 2 or 3 h after surgery to stop the bleeding, and antifibrinolytic therapy, 1 g tranexamic acid every 6 h, and prednisone at a dosage of 1 mg/kg per day to treat the inhibitor. Two days later, he was treated with polyvalent immunoglobulin of 1 g/kg per day for 2 days.

After 7 days of diagnosis, the level of factor VIII continued to be 3%, and the ratio of APTT still prolonged. Consequently, the patient received Mabthera (anti-CD20 monoclonal antibody) of 375 mg/m² on a weekly dosage, four times.

Prophylactic rFVIIa was administered before other surgical procedures, and because of significant bleeding, the patient required retreatment with rFVIIa after local surgery, every 2 h.

Even at 11 days after the disorder started, the patient was continued with the rFVIIa treatment.

In the whole period, the patient received a transfusion of 41 red cell concentrates, 21 frozen fresh plasma, and almost 40 000 KU of rFVIIa.

Subsequently, the patient recovered and was discharged with the prescription of a tapering course of steroids. After 24 days, the level of factor VIII was still low (5%) with the antibody level of 6.5 BU/ml, and the APTT was 39 s. The control at 3 and 14 months for factor VIII was 64 and 91%, respectively.

Currently, the patient is alive without any side effects, with normal level of factor VIII. No underlying disorder was found.

Case two, a 68-year-old woman with several medical histories came to our hospital. She had asthma, atrial fibrillation, was under anticoagulant treatment, and had severe valvulopathy. She was diagnosed with simple refractory anemia, and a gastric surgery was done 9 years previously.

She was admitted to the surgery department due to asthenia, hemoptoic expectoration, and fever; she also reported weight loss in the past few months. She took anticoagulant treatment (warfarina), digoxina, diuretics, and nitroglycerine patch. Blood test showed anemia (Hb of 8 g/dl), prothrombin time (PT) of 37%, INR of 1.76, APTT of 56.8 s, and ratio of 1.80, but normal fibrinogen level.

Twenty-four hours after the patient arrived, hematomas were observed in both the legs. As the blood test showed a long cephaline coagulation time, a test for the diagnosis of the inhibitor was carried out, which showed a factor VIII level of 8%. The coagulation test result did not show correlation with the normal plasma. The Bethesda inhibitor was 1.6 BU/ml.

The patient was treated with corticoids, and required blood cells and plasma transfusion. She needed bronchodilator treatment due to asthma symptoms. She received antifibrinolytic treatment (tranexamic acid) for bleeding and she responded well. Oral anticoagulant treatment was stopped until the bleeding episode was resolved. The patient was discharged from the hospital after 25 days with normal level of factor VIII (65%) without evidence of bleeding.

She was asked to continue the corticoid treatment in decreasing dosage for the subsequent 4 weeks.

After 9 months, the patient died due to respiratory and cardiac insufficiency, and no records of acquired hemophilia were present at that moment.

Case three, a 66-year-old man was referred to the external consultant for examination. He complained of asthenia and weight loss and almost unspecific bone pain.

A complete blood test was carried out, showing long cephaline coagulation time, with no other alterations.

The patient had a history of asthma, often requiring steroids, with no other medical diseases or bleeding. Some months earlier, the patient had spontaneous hematomas in the legs, but were not relevant and very small.

An acquired hemophilia A was suspected based on the findings of the blood test, the level of factor VIII of 7% and Bethesda inhibitor of 14.4 BU/ml.

The patient was administered corticoid treatment (1 mg/kg per day) and the level of factor VIII quickly returned to normal level, and the inhibitor disappeared. Later, corticoid therapy was tapered until it stopped. Furthermore, there was no bleeding at any time.

After 2 years without treatment, the patient has been continuing to have a normal factor VIII level. An underlying neoplastic disturbance was looked for, but until now, there has not been any evidence of any other medical conditions, and his respiratory situation has been stable.

Discussion

Acquired hemophilia A has a significant mortality percentage. In 87% of the cases, clinical bleeding is observed, and it was cause of death in 8–22% dependent on different series [7,8]. This wide range is influenced by the different therapeutic options employed, and sometimes, the delay in diagnosis.

In this hematological disorder, the most common cause of death due to bleeding develops in the first week of diagnosis, and hence, it is advised to start treatment as soon as possible.

A meta-analysis carried out with 249 patients demonstrated the most relevant prognostic factors related to survival, which include condition or related disease, complete remission of the inhibitor, and the age of the patient [8]. To achieve better prognosis, eradication of the inhibitor and maintenance of normal level of clotting factor VIII are considered to be important.

About one-third of the patients do not exhibit significant bleeding at diagnosis [7]. On the contrary, some patients could resolve inhibitor in a few weeks, with or without immunosuppressant therapy, but in other cases, it could be present some years later. There are some reported cases associated with fatal bleeding after 5 months due to the appearance of the inhibitor [7].

Because of low incidence and low specificity of the diagnostic test, the disease cannot be identified. Early diagnosis and preventive measures could influence the development of the disease. We consider that in our first case reported, the rapid identification of the disease and early treatment influenced the course of the disease, and prevented it from being a life-threatening case.

Choosing the type of the hemostatic treatment may depend not only on the severity of the symptoms, but on the location as well as level of the inhibitor titer. Furthermore, the pattern of bleeding differs between acquired and congenital hemophilia. It is known that in acquired hemophilia, factor VIII inhibitor presents type-2 kinetics, and hence, it is difficult to saturate

(different from congenital hemophilia that exhibits type-1 kinetics). In these cases, there may be no linear relation between the titer level and the severity of bleeding.

Nowadays, we have two types of treatment for bleeding control, one of them is to elevate the level of clotting factor VIII (DDVA, porcine FVIII, and human FVIII) and other agents known as the pass agents (CCPA, activated FVII).

In severe situations, sometimes, it is necessary to administer more than one type of treatment to control bleeding, as in our first case reported. However, in situations with low inhibitor titer and light bleeding, it could be useful to employ the inhalator or endovenous desmopresin, DDVA [9]. In almost all the situations, antifibrinolytic therapy is recommended.

In this study, we reported three cases in which we had used different types of treatment, because they showed different clinical manifestations.

Not all patients require immunosuppression to eradicate the autoantibody, but it is recommended for all the patients with acquired hemophilia A to reduce the length of time at risk of severe bleeding [7], although the inhibitor is cleared naturally in up to one-third of the patients [10]. The best results have been obtained with corticotherapy (prednisone 1–2 mg/kg per day), which could eradicate the inhibitor in 30% cases. In addition, if we administer cyclophosphamide, then this level could be increased up to 60–100% [11,12]. Previously, the median response time for the patients on steroids was reported to be only 49 days, and if steroids were combined with cytotoxins, it was 39 days [7]. Two of our three cases achieved remission with steroids alone, but the other required additional immunosuppressive therapy.

The rate of relapse was observed to be about 20–23%, with 78–90% patients prone to a second remission [7,13]. However, none of our reported cases showed recurrence.

Furthermore, there are some other immunosuppressant agents used for treating this disease. In the past years, Mabthera, the anti-CD20 monoclonal antibody, has been used, which produced good results. A review of 10 cases of acquired hemophilia A demonstrated that most of the patients responded to Mabthera (80% cases) at first, whereas the remaining 20% patients responded after the addition of cyclophosphamide [14].

Another retrospective analysis that compared 42 cases after treatment with Mabthera, with 44 cases treated with cyclophosphamide and prednisone, demonstrated no significance between both the groups, with 80% response rate [15].

Thus, it can be concluded that the low incidence and heterogeneity of clinical manifestation make it difficult to establish controlled trials to analyze the optimal therapy schedule for eradicating the inhibitor in acquired hemophilia A. In general, the therapy for eradication of the inhibitor should be started as soon as a patient is diagnosed with acquired hemophilia A.

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