

Acquired Hemophilia A: A Concise Review

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Acquired hemophilia A is a rare but severe autoimmune bleeding disorder. It is more frequent in the elderly and results from the presence of autoantibodies directed against clotting factor VIII. In this review, we briefly report on the present state of knowledge regarding acquired hemophilia A, analyzing its epidemiology, pathogenesis, diagnostic, and clinical features. We also describe the main characteristics of this disorder according to its association with different conditions and the most important advances in the treatment of bleeding episodes and the eradication of the autoantibody. *Am. J. Hematol.* 80:55–63, 2005. © 2005 Wiley-Liss, Inc.

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INTRODUCTION

Acquired hemophilia A (AHA) is an uncommon but potentially life-threatening hemorrhagic disorder caused by the development of autoantibodies directed against the coagulation factor VIII (FVIII) [1–12]. The severity of the clinical presentation of this disorder, compounded by its rarity, challenges the clinician's skills [5].

The diagnosis of acquired hemophilia A is often difficult because the patient does not have a personal or family history of bleeding episodes. Thus, the patient may be seen by several specialists, and may be subjected to dangerous invasive investigations and interventions before the correct diagnosis is made. To complicate the diagnosis further, the clinical picture of AHA differs from that of "classical" hereditary hemophilia A. In fact, more than 80% of patients with FVIII autoantibodies hemorrhage into the skin, muscles, or soft tissues and mucous membranes (e.g., epistaxis, gastrointestinal and urological bleeds, retroperitoneal hematomas), whereas hemarthroses, typical of congenital factor VIII deficiency, are unusual. The hemorrhages in AHA are often serious or life threatening, such as in the case of rapidly progressive retroperitoneal hematomas or the compartment syndrome due to intramuscular bleeds [1]. Other manifestations include prolonged postpartum bleeding and excessive bleeding following trauma or surgery and sometimes cerebral hemorrhage [2].

Thus, it is clear that the diagnosis and management of acquired hemophilia A is complex. Moreover, it is difficult to draw any firm conclusions about the epidemiology, clinical aspects, and therapy of this disease from the literature, because most of the reports are anecdotal and include only a few cases.

In this review, we report briefly on the present state of knowledge in acquired hemophilia A, with particular attention to the epidemiology and treatment of this disease.

LABORATORY INVESTIGATIONS

The diagnosis of acquired hemophilia A is based on the demonstration of an isolated prolongation of the activated partial thromboplastin time (APTT), not corrected by incubating the patient's plasma with equal volumes of normal plasma (mixing study), associated with reduced factor VIII levels, and evidence of

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a factor VIII inhibitor in a patient with no previous personal or family history of bleeding [1].

Autoantibodies occurring in patients with acquired hemophilia A differ in many aspects from alloantibodies developing in patients with congenital hemophilia A after replacement therapy. Like the alloantibodies occurring in severe hemophilia A, factor VIII inhibitors have been characterized as being predominantly polyclonal, belonging to an IgG4 subclass [1]. However, in contrast to the situation in congenital hemophilia, monoclonal IgA or IgM antibodies have also been described in patients with acquired hemophilia A associated with hematologic malignancies [7]. Another difference between FVIII autoantibodies and alloantibodies lies in their method of inhibition. The differences are, however, subtle, as autoantibody inhibitors are mainly directed against single epitopes on the factor VIII molecule (A2 domain, A3 domain, and, more frequently, C2 domain), whereas alloantibodies are usually directed against both the A2 and C2 domains and sometimes against the A3 domain [13]. Figure 1 illustrates the

major functional binding sites and epitopes of inhibitory autoantibodies within the FVIII molecule. As shown in the figure, inhibitor antibodies may exert their effect by interfering with thrombin cleavage of FVIII or with the interaction of FVIII with FIXa, FX, or phospholipid and von Willebrand factor (VWF). The inactivation of FVIII resulting from this interaction is, however, very different between autoantibodies and alloantibodies. In fact, whereas alloantibodies usually inactivate FVIII activity completely (type I kinetics), autoantibodies often inactivate FVIII activity incompletely (type II kinetics), and some residual FVIII can be assayed in the patient's plasma [8,14]. Thus, the Bethesda assay, which quantifies the in-vitro inhibitor titer, may underestimate the in-vivo inhibitor potency due to the complex, nonlinear reaction kinetics and complicate therapeutic choices and monitoring.

Nearly 15% of otherwise normal healthy individuals have low titers of anti-FVIII antibodies with no evidence of associated diseases or coagulopathy. These autoantibodies, predominantly of IgG1 and

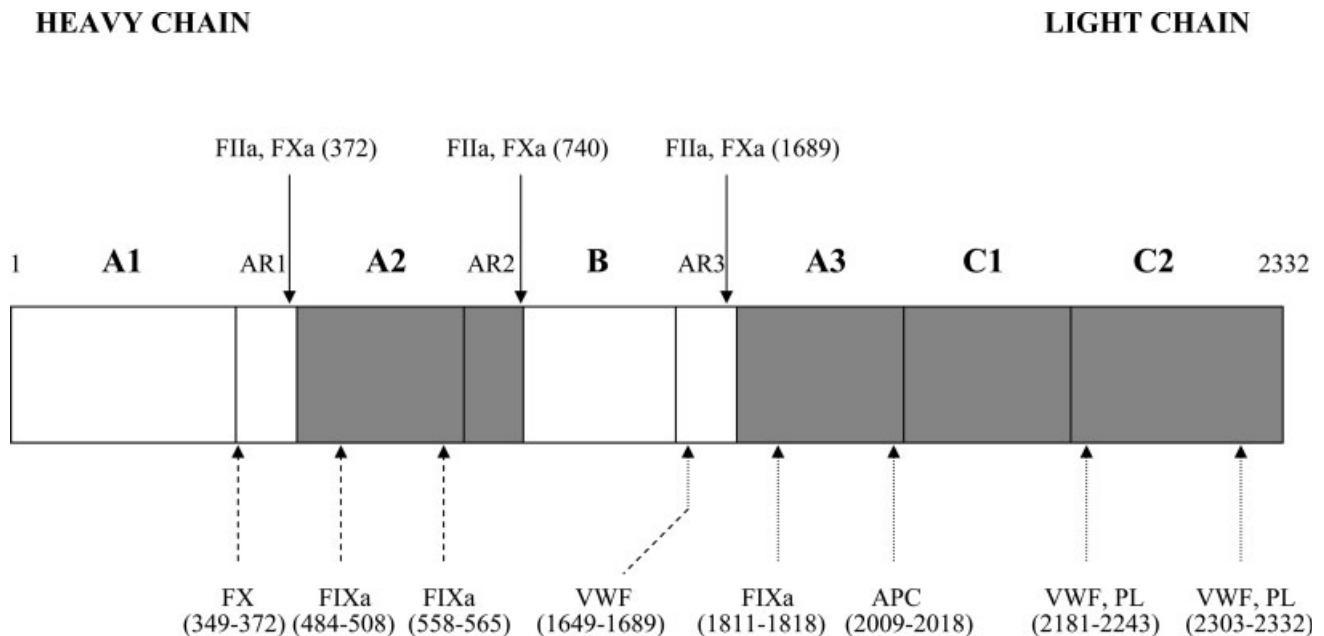


Fig. 1. Structure–function relationship of the circulating factor VIII molecule and main epitopes of inhibitory autoantibodies. The circulating FVIII molecule (~300 kDa, 2,332 amino acid residues) is a heterodimer consisting of a heavy chain (domains A1, A2, and B) and a light chain (domains A3, C1, and C2). In plasma, FVIII is non-covalently bound to von Willebrand factor (VWF) which protects it from inactivation by activated protein C (APC). The regions involved in binding to VWF are within the light chain (residues 1649–1689 of the acidic region 3 [AR3] preceding the A3 domain, residues 2181–2243 and 2303–2332 of the C2 domain). APC interacts with the FVIII molecule at residues 2009–2018 of the A3 domain. The acidic regions 1 and 2 (AR1 and AR2) and the binding sites for the intrinsic Xase complex (FX, FIXa, phospholipid [PL] membrane) are also shown. Factor VIII is activated by thrombin and FXa, which cleave the FVIII molecule at residues 372 and 740 within the heavy chain and at residue 1689 of the light chain. Inhibitors interfere with FVIII activity by preventing the thrombin cleavage or the interaction with FIXa, FX, PL, and VWF (the ligand-binding sites that are targets for inhibitory antibodies are shown in gray).

IgG2 classes, are mostly directed against the C2 domain of the factor VIII protein, and, in in-vitro mixing studies with normal plasma, display inhibitory activity against FVIII [15,16]. Some authors have postulated that this in-vitro activity does not correspond fully to the real in-vivo situation because these healthy subjects produce anti-idiotypic antibodies that neutralize circulating autoantibodies to factor VIII [14].

EPIDEMIOLOGY OF ACQUIRED HEMOPHILIA A

The incidence of AHA has been estimated to be 0.2–1.0 case per 1 million persons per year, but this figure may be an underestimate given the difficulty in making the diagnosis. Moreover, many of the low-titer inhibitors may be unrecognized unless patients undergo surgery or trauma. The mortality rate has been estimated to be in the range of 7.9% to 22% [17–24], with most hemorrhagic deaths occurring within the first few weeks after presentation. The reduction in the mortality rate observed in the most recent studies may reflect therapeutic improvements in the management of acute bleeding during the last few years (first porcine factor VIII and prothrombin complex concentrates [PCC], and then recombinant activated factor VII [rFVIIa]). Nevertheless, the morbidity and mortality rates may be underestimated due to the high median age at the time of diagnosis (60–70 years old) [17–24].

The age distribution of autoantibodies is typically biphasic with a small peak between 20 and 30 years (postpartum inhibitors) and a major peak in patients of age 68–80 years [1,25]. Overall, factor VIII inhibitors affect both sexes equally, although females predominate in the younger age group because of the association with pregnancy, while males constitute the majority of patients over the age of 60 [1,2].

In approximately 50% of cases, FVIII autoantibodies occur in patients lacking relevant concomitant diseases (spontaneous antibodies) [5,11], and in nearly 10% of cases autoantibodies to FVIII appear during the postpartum period, usually in primiparous women within 3 months of delivery [26,31]. Table I lists several conditions and diseases associated with the development of factor VIII inhibitors.

TREATMENT OF ACQUIRED HEMOPHILIA A

Appropriate treatment of patients with acquired inhibitors to factor VIII essentially depends on the natural history of any concomitant pathology and the clinical presentation of the coagulopathy [5]. Some patients, for instance those with post-partum or drug-induced inhibitors, may require nothing other

TABLE I. Conditions Associated With Acquired Hemophilia A

Condition	Condition
Idiopathic	Diabetes
Pregnancy	Acute hepatitis B and C infection
Autoimmune disorders	Malignancies
Systemic lupus erythematosus	(a) Solid tumors
Rheumatoid arthritis	Prostate
Multiple sclerosis	Lung
Temporal arteritis	Colon
Sjögren syndrome	Pancreas
Autoimmune hemolytic anemia	Stomach
Goodpasture syndrome	Bile duct
Myasthenia gravis	Head
Graves disease	Neck
Autoimmune hypothyroidism	Cervix
Inflammatory bowel disease	Breast
Ulcerative colitis	elanoma
Dermatologic disorders	Kidney
Psoriasis	(b) Hematologic malignancies
Pemphigus	Chronic lymphocytic leukemia
Respiratory diseases	Non-Hodgkin lymphoma
Asthma	Multiple myeloma
Chronic obstructive pulmonary disease	Waldenström macroglobulinemia
Allergic drug reactions	Myelodysplastic syndrome
Penicillin and its derivatives	Myelofibrosis
Sulfamides	Erythroleukemia
Phenytoin	
Chloramphenicol	
Methyldopa	
Depot thioxanthene	
Interferon-alpha	
Fludarabine	
BCG vaccination	

than close observation, as these inhibitors tend to disappear spontaneously within a few months after delivery or the discontinuation of drug therapy [2,3,17]. In the remaining cases treatment and, whenever possible, cure of the associated disease often leads to the disappearance of the inhibitor [32,33]. When this is not the case, the therapeutic strategy in patients with acquired hemophilia A is symptomatic, and involves the treatment of the bleeding episodes and eradication of the autoantibody (Table II) [1–3,34–42].

The treatment of bleeding episodes depends on the titer of the inhibitor. Patients with a low titer of inhibitor (<5 Bethesda units [BU]/mL) can be treated with concentrates of human FVIII, administered in large enough doses to overwhelm the inhibitor so that hemostatic levels of factor VIII can be achieved [7,39]. Desmopressin, alone or in association with FVIII concentrates, may also be effective in patients with low titers of inhibitor and minor bleeding episodes [41,42]. When the titer is high (>5 BU/mL), heterologous porcine factor VIII, which has reduced cross-reactivity with anti-human factor VIII

TABLE II. Therapy of Acquired Hemophilia A

Treatment of the bleeding episode
Patients with a low titer of inhibitor (<5 BU/mL)
-Human factor VIII concentrates
-Desmopressin
Patients with a high titer of inhibitor (>5 BU/mL)
-Porcine factor VIII concentrates
-Activated prothrombin complex concentrates (APCC)
-Recombinant activated factor VII (rFVIIa)
Temporary reduction of inhibitor titer
Extracorporeal removal of the autoantibody
-Therapeutic plasmapheresis
-Immunoabsorption of immunoglobulins to staphylococcal protein A
-Immunoabsorption of immunoglobulins to polyclonal sheep antibodies against human immunoglobulins
Eradication of the autoantibody
Immunosuppressive agents
-Corticosteroids
-Cyclophosphamide
-Azathioprine
-6-Mercaptopurine
-Vincristine
Second-line therapy
-High-dose immunoglobulins
-Cyclosporin
Other treatments
-Interferon-alpha
-Rituximab
-Immune tolerance induction (ITI)

antibodies [43–45], or bypassing agents, which circumvent the site of activity of inhibitors, must be employed. Prothrombin complex concentrates derived from plasma and containing activated vitamin K-dependent coagulation factors (factors VIIa, IXa, and Xa and thrombin) are able to promote hemostasis in the absence of factor VIII [46–51]. A major step toward the control of bleeding in acquired hemophilia has been achieved with a new hemostatic agent, recombinant activated factor VII (rFVIIa), which has been shown to be clinically safe and effective as both first- and second-line treatments for acute bleeding episodes [52–61]. A high response rate (88% after 8 hr and 92% after 24 hr) was observed by Hay and colleagues in a multicenter study [54].

In patients with high titers of inhibitor and severe hemorrhages, extracorporeal removal of the autoantibody by therapeutic plasmapheresis, or immunoabsorption of immunoglobulins to staphylococcal protein A or to polyclonal sheep antibodies against human immunoglobulins, can be used prior to factor concentrate treatment [62–66].

Not all patients require immunosuppression in order to eradicate the autoantibody. In fact, the inhibitor is cleared naturally in up to one third of patients. Spontaneous resolution is often observed in patients with low titer inhibitors (<5 BU/mL). As discussed

previously, drug-induced or pregnancy-associated autoantibodies frequently resolve spontaneously, whereas those associated with underlying autoimmune diseases rarely do. Immunosuppressive agents utilized for eradication of inhibitors include corticosteroids and cytotoxic drugs such as cyclophosphamide, azathioprine, 6-mercaptopurine, and vincristine [1,5,67–77]. The best results have been obtained with prednisone, given alone at doses of 1–2 mg/kg/day for 3 weeks, or in association with oral cyclophosphamide (1–2 mg/kg/day) [69]. High-dose immunoglobulin therapy (0.4 g/kg/day for 5 consecutive days) [73] and cyclosporin (200–300 mg/day), alone or in combination with prednisone [74–76], have also been shown to be effective in acquired hemophilia and can be given to patients who do not respond to standard immunosuppressive regimens. Interferon-alpha, a biological response modifier, also has been used successfully [77]. More recently, therapy with rituximab, an anti-CD20 monoclonal antibody, has been shown to be effective in immune disorders caused by autoantibodies, including acquired hemophilia A [78,79]. Finally, immune tolerance induction (ITI) protocols, similar to those used for the treatment of alloantibody inhibitors against factor VIII or IX in patients with congenital hemophilia A or B, have been recommended for the eradication of autoantibodies against coagulation factors [80–82]. A protocol consisting of a combination of human factor VIII, cyclophosphamide, and methylprednisolone was shown to be highly effective in eradicating FVIII autoantibodies in patients presenting with severe bleeding [82].

Clinical Associations

Idiopathic. Idiopathic acquired hemophilia A occurs most frequently in older adults and often presents acutely with life-threatening hemorrhages. However, in some cases, idiopathic autoantibodies, especially those at low titer, may resolve spontaneously [32]. The advanced age of patients and the presence of comorbid conditions sometimes limit the therapeutic options, precluding the most aggressive treatments (e.g., plasmapheresis) and necessitating dose reductions of drugs (e.g., steroids in diabetes), which lead to a lower response rate and thus a decreased survival rate. The most frequent clinical features at presentation are cutaneous and intramuscular bleeds. Spontaneous and rapidly progressive retroperitoneal hematomas and gastrointestinal and urological bleeds are not rare, and excessive bleeding following trauma and surgery has been reported. In a recent meta-analysis focused on therapy and prognostic factors in acquired hemophilia, Delgado and colleagues [83] observed that successful eradication of the inhibitor, the age of the patient, and other

patient-related conditions had independent influences on overall survival. For instance, the higher mortality observed in elderly patients was due to the lower complete remission (CR) rate, which was directly related to the patient's inability to tolerate aggressive, long-lasting immunosuppressive treatment. Furthermore, the authors found a high percentage of deaths related to neutropenia-associated infections in elderly patients receiving cyclophosphamide alone or in association with steroids. Thus, drug-related side effects should be considered when making decisions about the choice of treatments.

Pregnancy. The postpartum development of an inhibitor against factor VIII is a rare but severe complication of pregnancy. It occurs most frequently (in up to 80% of the cases) after the first delivery. Most autoantibody inhibitors (over 60%) disappear spontaneously after a median period of 30 months and usually do not recur with subsequent pregnancies [31]. However, in a few cases, the autoantibody may persist and cause life-threatening hemorrhages in a subsequent fetus because of transplacental transfer of the IgG antibodies [84]. The most serious clinical presentation is severe uterine bleeding during labor or delivery, although more frequently bleeding occurs during the postpartum period, between 3 and 150 days after delivery [27]. A severe hemorrhage often requires hysterectomy [85]. Low-titer inhibitors (<5 BU/mL) tend to disappear spontaneously within a few months, whereas high-titer inhibitors (>5 BU/mL) may persist for years despite immunosuppressive treatment (e.g., corticosteroids, intravenous immunoglobulins, cytotoxic agents) and may precede the development of an overt autoimmune disorder. It is, therefore, advisable to evaluate these patients for autoimmune disorders because the discovery of an underlying autoimmune disease would require a change in the therapeutic approach. In 1995, Hauser and colleagues [29] analyzed the 51 cases of postpartum inhibitors published thus far in the literature and highlighted the considerable heterogeneity in the interval between delivery and onset of symptoms (most being within the first 3 months), the titer of inhibitors (between 5 and 200 BU/mL), and the severity of hemorrhages. Although there were 3 deaths, in 76.5% of cases the autoantibody disappeared. Soly-moss [26] also reported heterogeneity in the clinical severity associated with postpartum anti-factor VIII autoantibodies among 14 patients. No fatal episodes were reported over a total of 80 bleeding episodes, although five of these were life or limb threatening. Steroids alone or in combination with cyclophosphamide led to eradication of autoantibody in 86% of cases. Baudo et al. [86], in a recent description of the results of the Italian registry of acquired factor VIII

inhibitors, reported a median time of 60 days between delivery and the onset of significant bleeding due to an identified inhibitor. The authors observed a high rate of complete remission: in fact the autoantibody was eradicated from 14 out of the 18 patients (78%) treated with steroids alone or in association with other agents (cyclophosphamide, azathioprine, or high-dose immunoglobulins). The response to therapy was independent of the baseline inhibitor titer, which also did not correlate with the severity of bleeding at diagnosis. However, the median inhibitor titer at presentation was rather low (8.5 BU/mL) in this series. In contrast with previous observations [29], Baudo et al. recorded a high percentage of relapses (42%), but all women were rescued by additional combination therapy (steroids plus cyclophosphamide or azathioprine). The studies reported above confirmed the good prognosis of pregnancy-associated AHA found by Delgado and colleagues [83] in their meta-analysis of data from 20 retrospective and prospective surveys of patients with acquired inhibitors against factor VIII. In fact, these authors recorded only 1 death in the 34 cases of postpartum inhibitors collected. In the majority of the reported cases, the potency of the inhibitors was low, and this accounted for the high percentage of spontaneous remissions and, thus, the good outcome of the postpartum inhibitor syndrome.

Autoimmune diseases. The most common diseases associated with acquired hemophilia A are collagen vascular disorders, including systemic lupus erythematosus [87,88], rheumatoid arthritis [89,90], multiple sclerosis [91], temporal arteritis [17], Sjögren syndrome [92,93], autoimmune hemolytic anemia [94], Goodpasture syndrome [95], myasthenia gravis [17], Graves disease [96], and autoimmune hypothyroidism [94]. Other disease states believed to be autoimmune disorders, such as inflammatory bowel diseases (ulcerative colitis) [17] and graft-versus-host disease after allogeneic bone marrow transplantation [97], have been anecdotally associated with clinically significant acquired hemophilia A. In some cases, severe bleeding due to a high-titer inhibitor is the presenting symptom of an autoimmune disorder [98]. In fact, unlike women with postpartum inhibitors, patients with AHA associated with autoimmune disorders usually have high-titer inhibitors that rarely resolve spontaneously or with steroids alone. The addition of a cytotoxic agent (e.g., cyclophosphamide) increases the chance of success. However, the prognosis depends on the response of the primary disease to immunosuppression [84].

Malignant neoplasms. Nearly 10% of patients with AHA have an underlying malignancy, either solid or hematologic. In their meta-analysis, Delgado and

colleagues [83] found that patients with malignancy-associated AHA had lower inhibitor titers at presentation than did other patients. However, this was not a favorable finding because the presence of an underlying malignancy was associated with a poorer prognosis. A relationship between the appearance of a factor VIII inhibitor and an altered immune status is suggested by the fact that lymphoproliferative disorders (chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, Waldenström macroglobulinemia) are the most frequent hematologic malignancies associated with the development of inhibitors [99,100]. Other hematologic diseases that have been linked to AHA include myelodysplastic syndromes, myelofibrosis, and erythroleukemia [99]. Although inhibitors to FVIII are usually of the IgG variety, IgA and IgM monoclonal antibodies have also been described in lymphoproliferative malignancies, particularly multiple myeloma and chronic lymphocytic leukemia.

Sallah and colleagues [99] recently described eight patients with an acquired hemophilia syndrome associated with hematologic malignancies, reporting that patients in whom complete resolution of the circulating anticoagulant was achieved, had lower mean inhibitor titers and a higher overall survival than those who had a persistently high titer of inhibitor.

Antibodies to factor VIII may arise among patients with a variety of solid tumors [101–109] and may be considered para-neoplastic phenomena. The solid tumors most frequently involved are prostate and lung cancer, although a wide variety of cancers have been described (colon, pancreas, stomach, bile duct, head and neck, cervix, breast, melanoma, kidney) [107,108]. Population surveys [17] have indicated that cancer is the second most frequent risk factor (after collagen vascular and other autoimmune disorders) for the development of anti-FVIII autoantibodies. In fact, a solid tumor was detected in 12% of individuals with acquired hemophilia A, and this association was found mainly in elderly males (median age at presentation, 69 years) [102]. In spite of this association, the authors [102] did not find any specific feature associated with the development of inhibitors, such as dissemination of disease (localized or metastatic) or histological type. There is a 50–70% success rate in eliminating the inhibitor, although often the inhibitor does not disappear despite successful eradication of the tumor by chemotherapy and/or radiotherapy. Conversely, the reappearance of the inhibitor may not predict the recurrence of the neoplasm. Sallah et al. [103] reviewed 41 cases of patients with cancer-associated FVIII inhibitors reported in the literature, including patients with solid and hematologic malignancies, and found a 70% complete

responses rate to treatment. Low-titer inhibitors associated with early-stage tumors were more likely to disappear after treatment than high-titer inhibitors, and the eradication of autoantibody was associated with a higher overall survival. The same authors also observed that 22% of responders achieved complete remission after treatment of the cancer. On the basis of this high response rate, the authors concluded that the treatment of the primary malignancy in patients with cancer-associated FVIII inhibitors is of great importance and facilitates the eradication of the antibody. The presence of an underlying cancer is not a contraindication to the use of immunosuppressive therapy aimed at eradicating the autoantibody if the primary antitumor therapy has not eliminated the inhibitor. These patients should be treated in the same manner as other patients with AHA. However, the decision to use immunosuppressants in patients with cancer and inhibitors against coagulation FVIII should be highly individualized on the basis of the patient's age, the titer of the inhibitor, the severity of the hemorrhage and the type of tumor.

Other conditions. Allergic reactions to medications (penicillin and its derivatives [33], sulfamides, phenytoin [110], chloramphenicol, methyl dopa, depot thioxanthene [11], BCG vaccination [112]) have been associated with the development of autoimmune FVIII inhibitors. The prognosis in these cases is favorable because the inhibitor usually disappears shortly after withdrawing the offending agent. Acquired hemophilia A has also been seen after treatment with drugs that interfere with the immune system, such as interferon-alpha and fludarabine [113–116]. Many other conditions associated with acquired hemophilia A are characterized by immune dysregulation, such as dermatologic disorders (psoriasis, pemphigus) [17], respiratory diseases (asthma, chronic obstructive pulmonary disease) [17,33], neurologic diseases (myasthenia gravis) [17], diabetes [14], and acute hepatitis B and C infections [117]. However, these reports are anecdotal and do not permit a clear definition of the laboratory and clinical patterns associated with particular disease states.

CONCLUSIONS

Acquired hemophilia A due to autoantibodies against FVIII is a rare and incompletely understood disease. The recent advances in the understanding of the pathophysiology of this syndrome have clarified the mechanism by which these autoantibodies neutralize FVIII activity.

Acquired hemophilia A is a heterogeneous condition although several subtypes of this syndrome, with

different laboratory, clinical, and prognostic features, can be identified. The availability of bypassing agents, such as activated prothrombin complex concentrates and rVIIa, has significantly reduced mortality during the acute phase of the disease in patients with high titer inhibitors. New therapeutic strategies have improved the prognosis of AHA, success depending in part on the underlying disorder.

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