Acquired Hemophilia A: A Current Review of Autoantibody Disease

Douglas W. Sborov, MD, and George M. Rodgers, MD, PhD

Abstract: Acquired hemophilia A (AHA) is a rare, potentially life-threatening hemorrhagic disorder that presents a complex clinical challenge. The immune-mediated production of autoantibodies, known as factor VIII inhibitors, often results in clinically significant soft tissue or post-procedural bleeding episodes in patients without a previous diagnosis of a bleeding disorder. Acquired antibodies against factor VIII are associated with an extensive list of conditions, including pregnancy, autoimmune disease, and malignancy. There is great potential for morbidity and mortality resulting from autoantibody development. Death is more frequent within the first few weeks after symptomatic manifestation, making prompt recognition and treatment vitally important. Treatment focuses on stabilization of initial bleeding and long-term eradication of the acquired inhibitor. As no randomized clinical trials have been conducted regarding treatment in this patient population, clinical expertise and experience continue to guide treatment recommendations. This report provides an algorithm for the diagnosis of AHA and outlines potential treatment recommendations, most notably concomitant use of recombinant factor VIIa (rFVIIa) and factor VIII inhibitor bypassing agent to control bleeding in patients not responsive to single-agent therapy, and use of rituximab and prednisone for inhibitor eradication therapy.

Case

A 69-year-old man with a medical history of ulcerative colitis (UC) and prostate cancer was admitted for development of a right neck hematoma following placement of an inferior vena cava (IVC) filter. The patient had presented to an outside institution with symptomatic anemia likely secondary to occult gastrointestinal bleeding in the setting of UC. Upon presentation, unilateral lower extremity swelling was noted and deep vein thrombosis was suspected. As the patient was considered high risk for anticoagulation therapy and worsening gastrointestinal bleeding, an IVC filter was thought to be optimal therapy. In retrospect, the patient likely had a subcutaneous lower...
extremity hematoma. However, IVC filter placement was completed, and the patient was discharged the day of the procedure without apparent postoperative complications. The patient awoke the following morning with continued oozing from the right internal jugular vein intervention site, prompting presentation to our institution.

Careful examination of the patient’s medical history and review of systems revealed numerous abnormal bleeding events spanning several years. These included knee hemarthrosis and psoas hematoma formation following minor trauma, prolonged bleeding after a minor dental procedure, and 2 years of easy bruising. He also reported a 2-year history of persistent and progressively worsening fatigue likely related to iron-deficiency anemia in the setting of occult gastrointestinal bleed and uncontrolled UC. Of note, results of prior coagulation studies were not available.

At presentation, initial coagulation results were significant for an activated partial thromboplastin time (aPTT) of 76 seconds (normal range, 24–35 seconds) and a normal prothrombin time. A thrombin time assay was normal, indicating the absence of heparin. Failure of correction on a PTT mixing study prompted further evaluation of individual clotting factors. There was a profound decrease in factor VIII activity (<1%). A Bethesda titer for factor VIII antibody was completed and found to be significantly elevated (180 Bethesda Units [BU]).

The diagnosis of AHA was made.

The patient was initially treated with recombinant activated factor VII (rF7a) at 90 µg/kg every 2 hours for treatment of acute bleeding (5 doses). This dose was unsuccessful in controlling the bleed, so the rF7a dosage was increased to 120 µg/kg given every 2 hours (11 doses). As bleeding continued, rF7a was stopped and a prothrombin complex concentrate, factor VIII inhibitor bypassing agent (FEIBA), was started (75 IU/kg every 12 hours). Hemostasis was not achieved with the use of either bypassing agent alone. On day 4 of hospitalization, rF7a was added (90 µg/kg every 12 hours) to an increased FEIBA dose (90 IU/kg every 12 hours). These agents were given in alternating fashion so that the patient received bypassing therapy every 6 hours. Immunosuppressive therapy was also initiated at presentation with a high-dose corticosteroid (methylprednisolone 125 mg every 12 hours) and rituximab (Rituxan, Genentech; 375 mg/m² weekly for 4 weeks). During hospitalization, due to persistent bleeding from his neck venipuncture site, transfusion of 14 units of packed red blood cells and 10 units of fresh frozen plasma were necessary for maintenance of adequate perfusion and hemostasis.

The combination of rF7a and FEIBA was instrumental in controlling the patient’s bleeding by hospital day 4. Bethesda titers were monitored throughout hospitalization and remained elevated despite clinical improvement. All medications were continued at discharge, though prednisone 60 mg daily was substituted for methylprednisolone. Combination therapy was continued for a total of 19 days. rF7a was discontinued 2 weeks post-hospitalization with evidence of a decreasing Bethesda titer (38 BU), and FEIBA was continued for an additional 2 weeks thereafter (titer of 20 BU at discontinuation). Four weekly cycles of rituximab were completed, and the patient self-tapered prednisone after a total of 5 weeks. Bethesda titers did not fully normalize (1 BU) until the fourth month after hospitalization, but this treatment regimen prevented further bleeding events. We believe that the patient’s flare of UC may have been associated with acquisition of his factor VIII antibody.

**Clinical Characteristics**

Acquired factor VIII autoantibodies in non-hemophiliacs is a rare but clinically significant entity. The incidence of AHA increases with age, and ranges between 1.3 and 1.5 per million per year (0.3/million/year in 16–64 year olds, 9.0/million/year in 64–85 year olds, and 15.0/million/year in persons over age 85).1,3 There is a biphasic age distribution with a small peak between 20–40 years of age and a larger peak in patients aged 68–80 years (mean age, 77 years). The incidence of disease is similar between men and women in the latter peak, but higher in women in the former (primarily due to higher rates found in the postpartum period).2,6

Autoantibody development results in a wide range of clinical presentations, from minimal or no bleeding, to spontaneous, life-threatening hemorrhage. Whereas bleeding episodes in congenital hemophilia are primarily defined by trauma-related muscle bleeds and hemarthroses, these are rare in AHA.7,8 Soft tissue bleeds are most commonly seen (approximately 80%), but mucocutaneous, gastrointestinal, and urogenital bleeds also occur.2 Often, bleeding episodes correspond with iatrogenic interventions that fail to respond to routine treatment. The European Acquired Haemophilia Registry (EACH2) reported that 6% of patients present with no clinically significant bleeding.6 Severe bleeds occur in up to 90% of patients, and mortality rates range from 3–33% with a progressive decrease in mortality rates since the 1980s, likely resulting from greater awareness of the disease and improved efficacy of therapeutic interventions.1,4,6 Early hemorrhagic death (within the first week) is commonly associated with gastrointestinal or pulmonary bleeding, and late deaths more likely result from intracranial or retroperitoneal bleeds.1,9

In approximately 50% of AHA cases, especially in the elderly, the development of autoantibodies against factor
VIII is idiopathic.\textsuperscript{3,8} In all other cases, monospecific antibodies to factor VIII can arise spontaneously, associated with a wide range of clinical states (Table 1). Common associations include pregnancy, autoimmune disorders, underlying malignancy, and certain medications.\textsuperscript{1,4,6,8,10}

The association between pregnancy and AHA is well established and accounts for approximately 10% of all cases. Development of factor VIII autoantibodies is most closely associated with a first pregnancy (80%) and may result in severe uterine bleeding.\textsuperscript{4} Reemergence of autoantibodies in subsequent pregnancies is rare. Though most commonly arising between 1–4 months after delivery, cases have been reported to occur over a year after parturition.\textsuperscript{4,7} In the majority, the potency of the inhibitor is low.\textsuperscript{7} This likely accounts for the spontaneous disappearance of inhibitor in a mean period of approximately 30 months (>60%) and the relatively low mortality rates (0–6%).\textsuperscript{4,7} In patients with higher titer inhibitors, there is a risk for inhibitor persistence despite aggressive treatment regimens. An inability to eradicate inhibitors in these patients is an indication for evaluation of other commonly associated disorders (autoimmune disease and malignancy). Importantly, transplacental transfer of immunoglobulin G (IgG) antibodies (inhibitors) is possible and increases the risk for potentially fatal fetal hemorrhage.\textsuperscript{6,11}

Unlike pregnancy, autoimmune disorders are associated with development of high-titer factor VIII autoantibodies that less commonly resolve spontaneously. An autoimmune association has been noted to represent 17–18% of cases.\textsuperscript{6} Specific associations include systemic lupus erythematosus (SLE), rheumatoid arthritis, multiple sclerosis, dermatologic conditions such as psoriasis and pemphigus vulgaris, temporal arteritis, Sjögren syndrome, autoimmune hemolytic anemia, Goodpasture syndrome, inflammatory bowel disease, and graft-versus-host disease.\textsuperscript{4,7} These patients often require a higher acuity of treatment for inhibitor eradication, including both bypass and immunosuppressive therapy.

Underlying malignancy (solid organ or hematologic) accounts for approximately 10% of patients with AHA.\textsuperscript{4,7} The most common hematologic malignancies include those associated with altered immune status, such as chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, and Waldenström macroglobulinemia.\textsuperscript{4} Elderly patients usually have solid tumors associated with factor VIII inhibitors. Debate exists as to whether autoantibody development is related to the tumor itself or to other underlying comorbidities. The most commonly associated tumors are prostate and lung cancer.\textsuperscript{4} Interestingly, there is no association with specific histologic type or extent of metastasis. Treatment of the underlying malignancy and direct therapy against factor VIII inhibitor may be necessary for complete antibody eradication. In a 2001 review of 41 cases, Sallah and Wan concluded that inhibitor eradication is much easier after treatment of the underlying malignancy, and that the presence of an underlying malignancy is not a contraindication to the use of immunosuppressive therapy to further suppress autoantibody production, even if the primary tumor has not been eliminated.\textsuperscript{12}

Other associated conditions include use of certain medications. Cases have been reported in both pediatric and adult populations of autoantibody development and use of penicillins and sulfa antibiotics. Other medication associations include phenytoin, chloramphenicol, methyldopa, Bacillus Calmette-Guérin vaccination, interferon alpha, fludarabine. Acute hepatitis B and C infection.

<table>
<thead>
<tr>
<th>Table 1. Classification of Thrombotic Microangiopathies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alloantibody development</strong></td>
</tr>
<tr>
<td>Congenital hemophilia A and use of factor replacement therapy</td>
</tr>
<tr>
<td><strong>Autoantibody development</strong></td>
</tr>
<tr>
<td>Idiopathic</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Autoimmune diseases</td>
</tr>
<tr>
<td>• Systemic lupus erythematosus</td>
</tr>
<tr>
<td>• Rheumatoid arthritis</td>
</tr>
<tr>
<td>• Multiple sclerosis</td>
</tr>
<tr>
<td>• Dermatologic conditions: Psoriasis, pemphigus vulgaris</td>
</tr>
<tr>
<td>• Temporal arteritis</td>
</tr>
<tr>
<td>• Sjögren syndrome</td>
</tr>
<tr>
<td>• Inflammatory bowel disease</td>
</tr>
<tr>
<td>• Goodpasture syndrome</td>
</tr>
<tr>
<td>• Graft-versus-host disease</td>
</tr>
<tr>
<td>• Myasthenia gravis</td>
</tr>
<tr>
<td>• Graves disease</td>
</tr>
<tr>
<td>• Autoimmune hemolytic anemia</td>
</tr>
<tr>
<td><strong>Underlying Malignancy</strong></td>
</tr>
<tr>
<td>• Hematologic malignancy: Chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, Waldenström macroglobulinemia</td>
</tr>
<tr>
<td>• Solid organ tumors</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
</tr>
<tr>
<td>• Antibiotics: Penicillin, sulfonamides</td>
</tr>
<tr>
<td>• Others: Phenytoin, chloramphenicol, methyldopa, Bacillus Calmette-Guérin vaccination, interferon alpha, fludarabine</td>
</tr>
</tbody>
</table>

Acute hepatitis B and C infection.
Laboratory Analysis

A clinical suspicion for AHA in a bleeding patient with an isolated prolonged aPTT should prompt further evaluation (Figure 1). An isolated prolonged aPTT may be seen in either isolated factor VIII deficiency or in the presence of an inhibitor. To differentiate between these, a 1:1 mixing study with normal plasma should be performed. A mixing study that corrects is indicative of a specific factor deficiency. If the mixing study fails to correct, an inhibitor is likely present, most commonly against factor VIII.1,2,6 Although most inhibitors have an immediate onset of action, factor VIII inhibitors function in a time-dependent manner, so mixing studies should include analysis at time 0 and 2 hours.1,2,6 Once the presence of a factor VIII inhibitor is confirmed, the Bethesda assay (Nijmegen modification) is used to assess the strength of the inhibitor.

The International Guidelines for the diagnosis of AHA put forth by Huth-Kuhne and colleagues in 2009 recommend ruling out lupus anticoagulants (LA) with specific testing (dilute Russell’s viper venom time), as LA may lead to artificially low factor VIII levels and therefore may mimic AHA.1 Of note, LA testing will be normal in the presence of factor VIII inhibitors. If LA is present, the Bethesda and Nijmegen assays are deferred, and the enzyme-linked immunosorbent assay (ELISA) is recommended for direct quantification of factor VIII inhibitor.1,6,11,14,15 LA must be ruled out in recently hospitalized patients, who must also have a heparin effect excluded with the thrombin time assay.6

Treatment

The treatment goals for AHA include immediate control of bleeding, inhibitor eradication with immunosuppressive agents, and treatment of any underlying disease. No randomized controlled studies exist to direct treatment. Thus far, selection of appropriate treatments has been based primarily upon expert opinion and clinical experience. Recently, however, several groups have proposed treatment guidelines.1,2,10

Inhibitor development represents a broad range of clinical presentations, and a complex choice of treatment modalities must be considered. At initial presentation and evaluation, it is necessary to obtain basic clinical information pertaining to the setting of inhibitor development. Other initial considerations should include severity of bleeding, inhibitor titer and persistence, previous history of inhibitor development and treatment response, need for acute surgical interventions, and specific triggering events. When possible, a hematologist should be consulted for the initiation of appropriate therapy and monitoring response to treatment.

Traditionally, inhibitor titers had been used to guide therapy against autoantibody inhibitors. Recent guidelines suggest that in autoantibody-mediated AHA, factor VIII levels and inhibitors do not correspond with clinical phenotype and are of limited value in guiding treatment during acute hemorrhagic events.1,2,8,10 Instead, it has been proposed that severity of bleeding should be used as the lone determining factor for choice of initial therapy. That being said, inhibitor titers should be obtained at the time of diagnosis as no randomized studies have definitively excluded their usefulness in all subsets of patients to monitor initial treatment success and guide inhibitor eradication therapy. In our patient, clinical improvement did correlate with a decrease in inhibitor titer while he received eradication therapy.

aPTT Prolongation Without Bleeding

It is possible that patients with low-titer inhibitors may not have a clinically relevant presentation and that the presence of inhibitors is a transient event. Spontaneous remission has been reported in approximately 25% of patients and is commonly seen in the postpartum period or in the setting of antibiotic therapy.6,10 In these cases, treatment may represent unnecessary consumption of substantial resources. In other instances of inhibitor development, treatment of the underlying disorder may be sufficient to eradicate the presence of inhibitors. Though absolute disappearance of inhibitor may occur in these settings, patients may be at increased risk of severe bleeding episodes until the inhibitor has been fully eradicated.3,10 This finding prompted a recommendation that all AHA patients undergo eradication therapy to reduce the length of time the patient is at risk for severe bleeds.9

Minor Bleeding Episodes

Inhibitor titer levels may be helpful in patients with evidence of minimal bleeding.6,11 In patients with low-titer inhibitors (<5 BU) presenting with minimal bleeding and who do not require surgery, it may be appropriate to observe and monitor abnormal laboratory findings.

If treatment is necessary, initial intervention should include routine hemostatic techniques, avoidance of invasive procedures, and possible discontinuation of any antiplatelet or anticoagulation agents after assessment of comorbidities (coronary stent and replacement of mitral or aortic valve). In the case of mucosal hemorrhage, additional therapy with an anti-fibrinolytic agent and topical fibrin glue may be useful.3

If bleeding persists, factor VIII concentrates and/or desmopressin (DDAVP) should be used as first-line therapeutic agents.6,8,11,16 An “overcome strategy” is employed with the goal of achieving a sufficient increase in the factor VIII level to control bleeding. This strategy incorporates giving a loading bolus of human-plasma-derived or recombinant factor VIII concentrates that act to neutral-
A C q u I r e d  H e m O p H I l I A

ize the inhibitor in order to achieve a hemostatic level of factor VIII. Subsequent boluses or continuous infusion are then employed to maintain an appropriate response. When using human factor VIII concentrates, an approximate initial bolus is calculated as 20 IU/kg for each 1 BU of inhibitor plus 40 additional IU. The plasma factor VIII level should be determined 10–15 minutes after the initial bolus and if there is not an appropriate response, a second bolus should be given. In those patients with minor bleeding and factor VIII level over 5% of normal or BU less than 3, DDAVP should also be considered (0.3 mg/kg, up to 24 g maximal dose) either alone or as adjunctive treatment with factor VIII concentrates. In a healthy person, desmopressin initiates the release of endogenous factor VIII.

Figure 1. An approach to diagnosis of AHA. It is recommended that patients be evaluated for both LA and factor VIII antibodies since the presence of an LA may mimic AHA. Patients identified as having a factor VIII antibody should have Bethesda titers performed to quantitate potency of the antibody. AHA=acquired hemophilia A; aPTT=activated partial thromboplastin time; FIX=factor IX; FVIII=factor VIII; FXI=factor XI; LA=lupus anticoagulant.
VIII and von Willebrand factor and increases blood levels two- to threefold. This action accounts for the possibility of overcoming the inhibitor and subsequent achievement of hemostatic stability.

**Major Bleeding Episodes**

Recent guidelines propose that bypass agents be used as initial therapy for all non-hemophiliacs with autoantibody inhibitors and evidence of significant bleeding (Figure 2). The “bypass strategy” incorporates the use of activated prothrombin complex concentrates (aPCC) and activated recombinant factor VII (rF7a) to obtain effective hemostasis by activating the coagulation cascade independent of factor VIII. The most widely used aPCC is FEIBA. Sallah reported in 2004 that use of FEIBA in AHA patients was associated with 100% hemostatic efficacy for moderate bleeds and 76% efficacy for severe bleeds, with an overall response rate of 86%. Recommended doses for FEIBA are 50–100 IU/kg every 8–12 hours (not to exceed 200 IU/kg/day). Risk for adverse events has limited its use in certain patient populations, but FEIBA has been found to have a low incidence of thrombosis (equivalent to rF7a) and anamnesis, and has shown to be well-tolerated overall, despite published associations with myocardial infarction and disseminated intravascular coagulation.

---

**Figure 2.** A strategy for treatment of bleeding episodes in patients with acquired hemophilia A. The Bethesda titer may be useful in defining the best approach for controlling bleeding (“overcome” vs “bypass”). Patients for whom the “overcome” strategy is not successful should receive bypass therapy. All patients should be considered for antibody eradication therapy to prevent future bleeding episodes (unless they have transient antibodies, eg, associated with pregnancy or drugs). DDAVP=desmopressin; FEIBA=factor eight inhibitor bypassing agent.
Recombinant F7a functions by initiating the formation of a complex between tissue factor and factor VIIa resulting in the downstream formation of thrombin. As with aPCCs, rF7a has been primarily studied in hemophiliacs with inhibitors, but the drug has also been successfully used in non-hemophiliacs. In 1997, Hay and associates reported on the treatment of 74 bleeding episodes with rF7a in patients with inhibitors. The response rate was 100% when rF7a was used as first-line therapy, and 75% and 17% showed good or partial responses, respectively, when it was used as second-line or salvage therapy. Importantly, those patients that did not respond within 24 hours were unlikely to respond to rF7a treatment. Similarly, Sumner and coauthors collected data on 204 bleeding episodes in 139 AHA patients, and showed an overall success rate of 88%, a 95% success rate when used as first-line treatment, and 80% effectiveness when used as second-line or salvage therapy. Most recently, the EACH2 registry showed a 91% first-line efficacy in 170 reported bleeds. Optimal doses of rF7a have not been defined, but the current recommended dose is 90 g/kg given every 2–3 hours until hemostasis is achieved. Of note, rF7a is generally well tolerated with few side effects.

The FENOC (FEIBA Novo Seven Comparative) study was a crossover trial published in 2007 that compared FEIBA and rF7a in the treatment of acute bleeding episodes in hemophiliacs with inhibitors. Though the study failed to reach an equivalency goal, both agents showed a high success rate (FEIBA 80% and rF7a 78%). The findings of this study suggest that either agent may be chosen as first-line treatment, and that after 12 hours, if one agent does not sufficiently control bleeding, then the other drug should be used. As reported by Collins in 2011, the EACH2 registry confirms this finding, further supporting that the 2 agents have indistinguishable hemostatic efficacy.

In approximately 10% of patients, treatment with single bypass agents is ineffective in controlling bleeding episodes. Alternative strategies may be employed, and include use of single agents alone or in combination to reduce inhibitor load and allow for effective replacement therapy with factor concentrates. One option is combination bypass therapy, as was done in the case described above and another reported by Miranda and Rodgers in 2009. Other strategies include removal of the inhibitor with plasmapheresis and immunoadsorption of the inhibitor to staphylococcal protein A or polyclonal sheep antibodies. Importantly, high-dose intravenous immunoglobulin (IVIG) has not been shown to be effective in AHA patients.

**Eradication Therapy**

Control of acute bleeding may be a life-saving intervention, but eradication of acquired inhibitors to factor VIII must be considered as a long-term goal to decrease the possibility of recurrent bleeding. Consensus recommendations put forth by Collins and coworkers in 2010 state that all AHA patients should receive immunosuppressive therapy at the time of diagnosis. Though the optimal therapeutic regimen is unknown, the mainstay of eradication treatment includes immunosuppression with steroids and cytotoxic agents, alone or in combination. The primary focus of research in this area is the use of prednisone and cyclophosphamide. In the United Kingdom Hemophilia Center Doctors’ Organization (UKHCDO), there was no significant difference in response rates between patients treated with prednisone alone or in combination with cyclophosphamide (60–70% vs 70–80%). The EACH2 registry observed a lower response rate with steroids alone (58%), but a similar response rate for combination therapy (80%). Though data are limited, there is some evidence for the superiority of combination therapy and that use of both agents is warranted. Prednisone (1 mg/kg/day) and cyclophosphamide (1.5–2 mg/kg/day) for a maximum of 6 weeks is an effective starting point for eradication of autoantibodies. Importantly, when considering eradication therapies with immunosuppression, patient comorbidities must be taken into account, considering a greater risk of morbidity and mortality (especially in the elderly population) when these medications are used.

In addition to these classic therapies for acquired factor VIII inhibitors, rituximab (monoclonal chimeric antibody to the B-cell CD20 antigen) has shown promise as an effective eradication agent. Although no randomized trials of rituximab have been conducted, case reports and series present positive results with its use as a single agent and in combination with other immunosuppressive agents. In a small, open-label trial with 10 patients, 8 patients with an inhibitor titer of less than 100 BU attained a complete response when rituximab was used alone at a dose of 375 mg/m² once weekly for 4 consecutive weeks. Three patients that relapsed were treated with a second regimen of the same dosage and achieved a sustained response. Additionally, 2 patients with high-titer antibodies (>100 BU) showed only a partial and decreased titer level in response to rituximab, but after addition of pulse-dosed intravenous cyclophosphamide, a complete and sustained response was attained. Further, Franchini and Lippi compiled data on a total of 65 patients with AHA treated with rituximab. They note that a complete or partial response was reached in over 90% of cases, but that high inhibitor titer (>100 BU) was a negative prognostic factor for therapeutic responsiveness. These reports support that single-agent rituximab may be effective in patients with initial inhibitor titers of less than 100 BU, and the addition of combination therapy with cyclophosphamide or corticosteroid may be indicated in patients with initial titers of more than 100 BU.
Discussion

Development of autoantibodies against factor VIII is a rare, potentially life-threatening immune-related disorder. It represents a disease with a wide range of potential underlying etiologies. Activation of an immune response, most commonly with IgG4 antibodies, causes abnormalities of the coagulation cascade and subsequent bleeding diathesis. Common disease manifestations include soft tissue bleeding, with potential for severe hemorrhagic events. Early clinical suspicion for a bleeding diathesis, thorough diagnostic workup, and initiation of appropriate treatment can be life-saving measures in an individual that develops autoantibodies to factor VIII. Incorporation of a hematologic specialist for immediate and follow-up care is vitally important and highly recommended.

Diagnostic and treatment guidelines of AHA should be continually reevaluated based on clinical evidence of successful management and treatment. The case presented above highlights several important diagnostic and treatment options that may assist in future clinical management of patients that develop factor VIII autoantibodies.

AHA must be considered in any patient presenting with bleeding diathesis, especially those with a soft tissue bleed or bleeding following an invasive procedure. As was done with our patient, a historically useful diagnostic algorithm inclusive of coagulation and mixing studies, a thrombin time assay to confirm absence of heparin, and a Bethesda assay for specific detection of factor VIII antibody should be incorporated for appropriate diagnosis. Though the usefulness of Bethesda titers in making treatment decisions has been questioned, we believe that antibody titer levels provide an important laboratory measure of therapeutic success. For this reason, we propose that titer levels be obtained for every patient at the time of diagnosis and throughout the course of treatment.

That being said, we do agree that bleeding severity alone (and not Bethesda titers) should dictate initial treatment decisions. As in the case of our patient, single agent bypassing therapy should be initiated in patients presenting with significant bleeding. Either bypassing agent (rF7a or FEIBA) may be attempted as first-line therapy, but if initial treatment is unsuccessful, the other must be used. In cases when neither agent alone is effective in controlling blood loss, we propose that combination therapy may be an effective approach. In our patient, combination therapy (NovoSeven and FEIBA) on day 4 of hospitalization led to significant clinical improvement and cessation of acute bleeding. This clinical decision was made based upon previously documented therapeutic success at our institution. Our success with this regimen for the second time emphasizes the importance of attempting the use of rF7a and FEIBA together when bleeding is not controlled with a single agent.

In concordance with the 2-pronged approach (bleeding control and inhibitor eradication) for treatment of AHA, inhibitor eradication was started at initial presentation. Considering the patient’s high inhibitor titer level, combination therapy with rituximab and corticosteroid was started. The decision to use rituximab was based upon its potential for clinical effectiveness as highlighted in previous case studies and its ease of use (once weekly dosing regimen without necessary lab monitoring). Though complete inhibitor eradication did not occur for approximately 4 months post-hospitalization, this case provides an additional example of therapeutic success with use of rituximab and corticosteroids in a patient with high-titer disease.

Lastly, this case provides an additional example of AHA occurring in a patient with underlying UC. We identified 2 possible underlying disease states that could have led to autoantibody development in our patient: UC and prostate cancer. As an acute flare of UC coincided with the development of bleeding diathesis in our patient, this seemed to be the most likely cause. Prostate cancer was deemed less likely, as he had no evidence of disease recurrence following brachytherapy. The pathophysiologic mechanism accounting for development of auto-antibodies specifically against factor VIII in UC patients is not yet known, but it may be related to a dysregulated immune response to endogenous bacteria in the gastrointestinal tract. It is postulated that in our patient, immunosuppressive therapy with rituximab and corticosteroids allowed for adequate control of his acute UC flare while eliminating aberrant B-cell activity.

Several important observations were made from this case. Firstly, not all patients will respond to single-agent bypass therapy, and these patients may respond to salvage combination therapy. Second, the combination of rituximab and a corticosteroid is effective eradication therapy in a patient with factor VIII antibodies resulting from UC. Lastly, monitoring antibody levels during eradication therapy may correlate with resolution of factor VIII inhibitor.

Acknowledgment: The University of Utah Institutional Review Board did not require approval for the presentation of this single case report.

References


