Acquired hemophilia A

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ABSTRACT

Acquired inhibitors of coagulation are a group of rare but potentially life-threatening blood disorders characterized by the presence of autoantibodies directed against clotting factor. Autoantibody against factor VIII is the most common form of clotting factor inhibitor, a condition also known as acquired hemophilia A. We present a clinical series of nine patients diagnosed and treated for acquired hemophilia A at our institution. Among these nine patients, there were five men and four women with a median age of 64 years. All patients presented with bleeding diathesis. Factor eight inhibitor bypassing agent and/or recombinant factor VIIa were predominantly used for control of active bleeding. For elimination of autoantibodies, either steroids alone or the combination of steroids with rituximab or oral cyclophosphamide was used. Despite aggressive measures, two of the patients had a poor outcome; seven of the nine patients (77%) had a good clinical outcome. Acquired hemophilia A should be strongly suspected in any patient presenting with bleeding and a prolonged activated partial thromboplastin time. Early initiation of factor bypassing agents such as activated prothrombin complex concentrates or recombinant factor VIIa, along with the use of immunosuppressive agents, can be lifesaving.

KEYWORDS Acquired hemophilia A; acquired inhibitors of coagulation; activated prothrombin complex concentrates; recombinant factor VIIa

Acquired inhibitors of coagulation are a group of rare but potentially life-threatening blood disorders characterized by the presence of autoantibodies directed against clotting factors.¹ Autoantibody against factor VIII (FVIII) is the most common form of clotting factor inhibitor, a condition also known as acquired hemophilia A (AHA) that presents with bleeding which can be life-threatening. We present nine patients diagnosed and treated for AHA at our institution.

PATIENT DESCRIPTION

Among the nine patients with AHA, there were five men and four women with a median age of 64 years (range 47–89 years). All patients presented with bleeding diathesis that included mucosal bleeding, gastrointestinal bleeding, persistent surgical site bleeding, intramuscular bleeding, intracranial bleeding, and bleeding from site of intravenous access, as listed in [Table 1](#). Patients had a prolonged activated partial thromboplastin time (aPTT) with a normal or slightly elevated prothrombin time. The cause of prolonged aPTT was investigated with a mixing study, and failure to correct the aPTT indicated the presence of an inhibitor of coagulation. Our patients universally

had very high titers, with a median of 35 Bethesda units (BU) (range 15 to >860 BU). One patient (#9) also had associated factor IX inhibitor (activity of 15% with titer of 32 BU) and factor X inhibitor (activity of <10% with titer of 20.6 BU) apart from FVIII inhibitor. We could identify an associated underlying cause in only two patients: patient 3 had rheumatoid arthritis, and patient 9 had non-Hodgkin lymphoma.

Factor eight inhibitor bypassing agent (FEIBA) and/or recombinant factor VIIa (rFVIIa) were predominantly used for control of active bleeding. Four patients received FEIBA only and demonstrated good response, and one of the patients responded appropriately with rFVIIa alone. Three patients received rFVIIa in addition to FEIBA due to poor response to FEIBA alone. In one of the patients (#9), bleeding stopped spontaneously without the need for FEIBA or rFVIIa. Patient 2 also received two doses of 3000 U of recombinant FVIII due to continued oozing of blood from a surgical wound. For elimination of autoantibodies, either steroids alone or a combination of steroids with rituximab or oral cyclophosphamide was used, as shown in [Table 1](#). Two patients received all three agents: steroid, rituximab, and cyclophosphamide. Despite aggressive measures including

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Table 1. Characteristics of nine patients diagnosed with acquired hemophilia A

Variables (baseline)	Patient								
	1	2	3	4	5	6	7	8	9
Sex	F	M	F	F	M	F	M	M	M
Age (y)	73	47	71	89	56	55	69	66	62
Hemoglobin (g/dL)	13.7	7.9	4.8	8.5	9	6.6	8.4	6.7	9.8
Platelet count (k/uL)	186	88	256	250	180	215	219	343	242
PT (ref 10.2–10.9 sec)	14.2	15	17.2	12	12	8.3	12	12	21
aPTT (ref 25.1–36.5)	53	57.5	71.7	53.1	105	102	73	89	57.1
Factor 8 activity (ref 50%–150%)	8	6	<1	7	<1	<1	1	<1	<1
Inhibitor titer (BU)	35	Not available	30.2	15	30	>860	31	55	36
Bleeding manifestation	Intracranial hemorrhage	Persistent surgical site bleeding	Soft tissue hematoma	Nontraumatic muscle hematoma	Nontraumatic muscle hematoma	Persistent surgical site bleeding	Bleeding from intravenous access	Soft tissue hematoma	Gastrointestinal bleeding
Treatment for acute bleeding control	FEIBA	FEIBA, FVIII replacement	FEIBA, rFVIIa	FEIBA	FEIBA	FEIBA, rFVIIa	FEIBA, rFVIIa	rFVIIa	Bleeding stopped without intervention
Treatment for eliminating inhibitors	Steroids, rituximab	Steroids alone	Steroids, rituximab, cyclophosphamide	Steroids, rituximab	Steroids, rituximab	Steroids, rituximab, extracorporeal plasmapheresis	Steroids, rituximab	Steroids, rituximab, cyclophosphamide	Steroids, rituximab
Outcome	Remission	Remission	Death	Remission	Remission	Death	Remission	Remission	Remission

aPTT indicates activated partial thromboplastin time; BU, Bethesda unit; FEIBA, factor eight inhibitor bypassing agent; FVIII, autoantibody against factor VIII; PT, prothrombin time; rFVIIa, recombinant factor VIIa.

FEIBA, rFVIIa, rituximab, steroids, and blood transfusions, two of the patients (#3 and #6) continued to have bleeding. In one of these patients (#6), extracorporeal plasmapheresis was performed without success. Understanding the poor prognosis, both patients pursued comfort care and passed away shortly afterwards. Seven of the nine patients (77%) had a good clinical outcome with cessation of bleeding during their inpatient stay and normalization of aPTT and FVIII activity 3 to 4 weeks after diagnosis.

DISCUSSION

Acquired inhibitors of clotting factors occur due to the presence of autoantibodies that either inhibit the activity or accelerate the clearance of the clotting factors. Autoantibodies targeted against FVIII are the most common form of acquired inhibitors of clotting factors. Antibodies targeting other clotting factors are extremely rare. AHA is a type of bleeding disorder that stems from autoantibodies interfering with the activity of FVIII.² A study conducted in the United Kingdom showed that the incidence of AHA was 1.34 to 1.48 patients per million population per year.^{3,4} In a meta-analysis involving 249 patients with AHA, the median age of the patients was 64 years, and 55% of the patients were women.⁵ The most

common underlying risk factors associated with AHA include pregnancy, postpartum period, rheumatoid arthritis, systemic lupus erythematosus, malignancy, and drug reaction, but in up to 50% of patients, the underlying cause is not identified.⁵

The most common initial clinical presentation is bleeding, which can occur spontaneously or after surgery.⁶ Bleeding is often severe and life threatening with a high mortality rate.⁷ AHA should be suspected in any bleeding patient with elevated aPTT and a normal prothrombin time. The first step in a suspected case after excluding the use or presence of heparin is to perform a mixing study⁸ (Figure 1). Failure to correct the aPTT is suggestive of the presence of coagulation inhibitor and warrants checking for FVIII activity along with FVIII inhibitor titer (Bethesda assay), which is performed by serial dilution of the patient's plasma incubated with pooled plasma to calculate the BU. A higher BU signifies stronger inhibition of anticoagulation. Patients should be evaluated for underlying autoimmune disease and malignancy as a cause of AHA as indicated.

Management of AHA involves two fundamental steps: controlling the acute hemorrhage and long-term eradication of autoantibodies by using immunosuppressive agents^{9,10} (Figure 2). Two strategies are available for the treatment of

Figure 1. An algorithm for an initial approach in a patient with suspected acquired hemophilia A. *The patient's medication list should be reviewed for the presence of heparin and heparin-like products. If the presence of heparin is suspected in the blood sample, blood should be redrawn from an uncontaminated peripheral vein. The presence of heparin can be confirmed by performing thrombin time and relapsing test. Direct thrombin inhibitors (argatroban, dabigatran) can prolong both activated partial thromboplastin time (aPTT) and prothrombin time (PT) but at low levels may not prolong PT. Direct factor Xa inhibitors can variably prolong PT and aPTT. †Presence of antiphospholipid antibody should be excluded by adding the source of phospholipid. Correcting of mixing study signifies the presence of lupus anticoagulant, which is more likely to be associated with thrombosis than bleeding. HMW indicates high molecular weight.

acute hemorrhage: using bypassing agents or raising the level of circulating FVIII. This further depends on the severity of bleeding and inhibitor titer (BU).^{10,11} For bleeding with low inhibitor titers (generally <5 BU), human FVIII products at higher doses can be used to overcome the inhibitors.¹² For life-threatening bleeding with a high inhibitor titer, factor bypassing agents such as activated prothrombin complex concentrates (aPCC; e.g., FEIBA) and recombinant activated human factor VIIa (rFVIIa) are currently the treatments of choice.^{13–16} Although no studies have compared aPCC and rFVIIa for treatment of acute hemorrhage in AHA, both are considered equally effective, and the choice depends on local experience and availability.¹⁷ Among our nine patients, four received FEIBA alone and one received rFVIIa alone. Three patients received rFVIIa in addition to FEIBA due to poor response to FEIBA alone; two of these patients still had poor control of bleeding culminating in fatality.

Various immunosuppressive agents and their combinations are used for the elimination of FVIII autoantibodies. Glucocorticoids alone or glucocorticoids with either cyclophosphamide or rituximab are primarily used in this regard. Other treatment options, including high-dose intravenous immunoglobulins and exchange plasmapheresis, have been used along with immunosuppressive agents on refractory patients.^{18,19} Based on our positive experience and various studies with promising results, the combination of steroids and rituximab was our first choice in most patients.^{20,21} The treatment of the underlying cause is also important, as it will often lead to the disappearance of the inhibitors.²² Response to treatment is assessed by monitoring the cessation of bleeding, stability/improvement of hemoglobin, and ultimately a decrease in inhibitor titer. It is recommended to check aPTT only every 2 to 3 weeks, as inhibitor titers drop slowly. The relapse rate after the first successful remission is about 20%, and 70% of those who relapse usually achieve a second complete remission.⁴

Figure 2. Algorithm for the management of acquired hemophilia A (AHA). *In a patient with suspected AHA with major bleeding, the factor bypassing agents activated prothrombin complex concentrates (aPCC) or recombinant factor VIIa (rFVIIa) should be administered while awaiting the inhibitor titer. *Use of factor bypassing agent is always recommended if available or if the patient continues to bleed. ^Both factor eight inhibitor bypassing agent (FEIBA) and rFVIIa are considered equally effective. The choice depends on availability and local experience. +Listed is the commonly used regimen. BU indicates Bethesda unit.

In conclusion, AHA should be strongly suspected in any patient presenting with bleeding and a prolonged aPTT. Early initiation of factor-bypassing agents aPCC or rFVIIa, along with the use of immunosuppressive agents, can be lifesaving.

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