Clinical challenge of managing patients with multiple myeloma and acquired hemophilia A with risk of both thrombosis and bleeding: a narrative review

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Clinical challenge of managing patients with multiple myeloma and acquired hemophilia A with risk of both thrombosis and bleeding: a narrative review

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Abstract
Acquired hemophilia A (AHA) is a rare bleeding disorder, caused by the development of autoantibodies (inhibitor) against endogenous clotting factor VIII (FVIII). A common clinical manifestation is subcutaneous bleeding, but soft tissue hematomas and excessive post-operative hemorrhages may also occur.
A diagnosis of AHA is made in patients presenting with an isolated prolonged activated partial thromboplastin time without correction in a mixed plasma study, and decreased FVIII activity.
Multiple myeloma (MM) is a hematological malignancy of terminally differentiated plasma cells producing monoclonal protein (M protein). Although malignancy is found as an underlying disorder in 6–18% of AHA cases, MM seems to be a very rare cause of AHA. MM is associated with an increased risk of thrombotic complications, while AHA leads to bleeding in up to 95% of cases (although one third of patients do not require hemostatic treatment) and therefore management of patients with concomitant AHA and MM is a clinical challenge. For bleeding control and therapy of AHA, the by-passing agents activated prothrombin complex concentrate and recombinant activated factor VII, as well as porcine recombinant factor VIII, are efficient. However, for inhibitor eradication, immunosuppressive treatment can be insufficient, and therefore intensive myeloma-aimed treatment is required. Disease- and
therapy-related coagulation alterations in MM patients carry the risk of both thrombosis and bleeding, complicating the treatment of AHA in this group of patients.

Key words: acquired hemophilia A, multiple myeloma, thromboembolic events, bleeding management

Introduction

Acquired hemophilia A (AHA) is a rare bleeding diathesis with an annual prevalence of up to 1.3–1.5 cases per million [1–3]. Despite this low prevalence, management of AHA is a significant clinical challenge, burdened with life-threatening bleeding events and their expensive treatment. The clinical manifestation of AHA is characterized by the acute onset of bleeding in a person without any previous individual or family history of hemophilia, regardless of gender. AHA is commonly manifested with subcutaneous bleeding and intramuscular hematomas, gastrointestinal bleeding with hematemesis or melena, retroperitoneal hemorrhage and, rarely but often fatal, intracranial bleeding [1]. It is caused by an autoimmune reaction resulting in the production of the inhibitor against clotting factor VIII (FVIII) [4]. In 50% of cases, we can find underlying conditions promoting inhibitor formation such as autoimmune disorders, drugs, pregnancy and the postpartum period and both solid tumors and hematological malignancies, especially plasma cell dyscrasias as well as multiple myeloma (MM) and monoclonal gammopathy of undetermined significance (MGUS) [1]. According to the European Acquired Hemophilia Registry (EACH2), hematological malignancies and MGUS are responsible for, respectively, 3.8% and 2.6% of all AHA cases [1]. The coincidence between MM and AHA was first described in 1965 in a patient with de novo IgG lambda MM who developed subcutaneous hematomas and prolonged bleeding after minor surgical intervention [5].

In most cases, both MM and AHA are diseases of the elderly. MM is a hematological malignancy of terminally differentiated plasma cells in which clonal plasma cells infiltrate the bone marrow leading to anemia, bone destruction and the production of monoclonal proteins detectable in the serum and/or urine [6, 7]. It is diagnosed according to the Internal Myeloma Working Group (IMWG) criteria [8] and the median onset age is 74 years [9]. Similarly, the median age at diagnosis of AHA is 73.9 years [10]. In both diseases there is a slight male preponderance, except for the age group 20–40, when AHA is often related to pregnancy and the postpartum period [2]. Despite its extremely low prevalence, the management of a
coincidence of AHA and MM is challenging and requires a careful approach at every stage of treatment, from diagnosis through to bleeding management and inhibitor eradication.

The aim of this review was to provide current knowledge of the topic and to identify areas of further ongoing research.

To realize this goal, we performed extensive literature searches including all available studies, case reports and guidelines/recommendations, irrespective of the original language, year or publication status: the studies were included in our analysis if there was sufficient evidence and if they were related to the topic. Our review was limited to studies related to FVIII inhibitor formation, bleeding management, and immunosuppressive treatment in patients with plasma cell dyscrasias. We obtained our information from the National Library of Medicine, with the use of PubMed/Medline, with the following strategy: firstly we conducted a search using Medical Subject Headings (MeSH), and then others based on text word searches performed by 1 October 2021. In order to focus in even closer, more related articles were evaluated. We also reviewed and assessed bibliographic studies to obtain supplementary information. Furthermore, the recommendations of international societies were investigated. The bibliographic references of all the retrieved studies and reviews were assessed for additional reports of studies.

Because of a lack of data based on randomized or quasi-randomized studies in this field, published before the end date of our search process, we present the results of this research in the form of recommendations for the management of acquired hemophilia A in myeloma patients as a narrative review, according to the Cochrane Methodology Review Groups.

Pathophysiology

In general, AHA is an immune system disorder caused by the production of autoantibodies which specifically bind FVIII leading to the inhibition of its function in the clotting cascade or increasing its serum clearance [10]. Inhibition of FVIII activity in serum leads to a decrease in thrombin generation and a lack of fibrin clot formation [11, 12]. The autoantibodies in AHA are usually IgG1 or IgG4 subclass which typically bind to FVIII epitopes: binding to C2 domains causes a blockage of the FVIII-phospholipid interaction, while binding to A2 domains prevents intrinsic tenase complex formation [11, 12]. Occasionally, the AHA autoantibodies affect the interaction between FVIII and von Willebrand factor (vWF), although they have not been proven to bind complement or trigger allergic reactions [11, 12].
The occurrence of IgA-antibodies, observed in 46% of AHA patients, has been associated with a lower CR ratio and longer time-to-response than in an IgA-negative group [13]. In contrast to the alloantibodies against FVIII produced in congenital hemophilia, the autoantibodies in AHA are characterized by nonlinear kinetics in their interaction with FVIII [11, 12]. Therefore, even in high inhibitor plasma titer, we can detect residual FVIII activity. However, this does not prevent spontaneous bleedings [12].

Immune system dysregulation plays a key role, not only in autoimmune disorders such as AHA, but also in carcinogenesis [14]. Recent studies have shown that chronic inflammation is an important factor in the development of lymphoproliferative disorders [15]. Moreover, chronic antigen stimulation by inducing rapid cell divisions may lead to pro-oncogenic mutations and, as a result, in the development of plasma cell dyscrasias [16]. In the literature, a number of reports and case studies have suggested an association between plasma cell dyscrasias and autoimmune disorders such as autoimmune cytopenia, autoimmune hemolytic anemia, autoimmune neutropenia, and immune thrombocytopenia, rheumatological disorders such as rheumatoid arthritis, systemic lupus erythematosus, dermato- and polymyositis, Sjögren’s syndrome or vasculitis, as well as neurological immune disorders such as myasthenia gravis and multiple sclerosis [17]. Moreover, myeloma patients can develop acquired inhibitors to other clotting factors such as von Willebrand factor, or factor V, factor X and vWF [18].

Although, in most cases, AHA is caused by polyclonal autoreactive antibodies [11], the M protein produced in plasma cell dyscrasias can act as a specific FVIII inhibitor resulting in the typical laboratory and clinical features of acquired FVIII inhibitor [19]. In 2009, Decaux et al. presented the case report of a 44-year-old female with an IgA kappa smoldering myeloma who developed AHA. They investigated, *in vitro*, the role of the IgA kappa M protein in AHA development, employing polyclonal antibodies specific for IgA kappa and IgA lambda. In the patient's plasma mixed with anti IgA kappa antibodies, the anti-FVIII inhibitor activity was completely suppressed, whereas in the control study with anti-IgA lambda antibodies, the FVIII inhibitor titer was unchanged [19]. These results suggest that the IgA monoclonal protein is responsible for the factor VIII inhibitor activity.

Another indirect indication that the M protein is a part of FVIII inhibitor activity was delivered by Brás et al. They presented a patient with *de novo* diagnosed multiple myeloma (MM) and concomitant AHA. The described subject achieved simultaneous remission of both disorders after chemotherapy and, experiencing a protein M increase even without myeloma symptoms, he developed an immediate AHA relapse [20]. In the literature, various types of M
protein have been described in myeloma patients with AHA [5, 19–35]. The most common M protein type is IgG kappa (31%), though some patients have been diagnosed with IgA and light chain disease (LCD), both kappa and lambda (Table I).

Table I. Acquired hemophilia A (AHA) reported cases

Interestingly, AHA can develop simultaneously with MM diagnosis in 65% of cases. Moreover, in some cases, extensive diagnostics in AHA patients lead to the discovery of underlying plasma cell dyscrasia. On the other hand, in 29% of patients, AHA symptoms occurred during myeloma relapse (Table I). This may suggest the contribution of other mechanisms in AHA development in MM patients besides that of the direct impact of M protein.

Clinical features

Clinically, AHA differs from congenital hemophilia. Common manifestations include: subcutaneous and intramuscular hematomas, gastrointestinal bleeding with hematemesis or melena, prolonged post-partum or post-operative bleeding, and iatrogenic hemorrhages as a result of central vein or bladder catheterization. Retroperitoneal hemorrhage and intracranial bleeds are rare, but often fatal. Intraarticular hematomas, typical for CHA, are rare [2]. The bleeding patterns in the course of AHA are believed to be distinctly more severe and anatomically varied when compared to congenital hemophilia A. Nevertheless, the reason for such bleeding patterns remains unclear. Severe or life-threatening hemorrhages affect more than 80% of cases, and 20% result in the patient’s death. The highest risk of an unfavorable outcome is during the first few weeks after diagnosis [4]. Some patients are diagnosed in the presymptomatic phase of the disease by the incidental discovery of a prolonged activated partial thromboplastin time (aPTT) [1, 36]. According to the literature, the bleeding pattern in AHA with MM coincidence does not differ from other AHA cases (Table I). The most common manifestations of AHA are soft tissue hematomas (63%) and mucosal bleeding (21%) with gastrointestinal or uterine hemorrhage. Some patients develop hemarthroses [31, 34] and others present post-operative bleeding [22, 33]. One patient developed cardiac
tamponade as a result of pericardial hemorrhage [31]. Two cases were completely asymptomatic and were diagnosed by isolated prolongation of aPTT [24, 29].

**Diagnostic workup**

A typical laboratory finding is isolated prolonged aPTT, usually up to 2-3 times longer, detectable when the FVIII activity is decreased below 45% of the mean normal level [36]. The prothrombin time (PT), thrombin time (TT), closure time in platelet function analyzer (PFA-100), platelets number and fibrinogen activity are within normal limits [37]. Furthermore, aPTT does not normalize in mixing studies of patient plasma with normal plasma, and the FVIII activity remains decreased [37]. In some cases, with weak autoantibodies, aPTT may be within normal limits in the standard diagnostic procedure, but when the mixture is incubated for at least 1 or 2 h at 37°C degrees, prolonged aPTT may be found [38]. It is noteworthy that in AHA patients with high titer inhibitor, similarly as in lupus anticoagulant presence, the activity of other clotting factors (XII, XI, and IX) may be falsely decreased. However, during repeated dilutions of the patient’s plasma, the activity of these factors increases up to normal values while the FVIII activity remains low [39]. The diagnostic algorithm in AHA is presented in Figure 1.

The next step after confirmation of the AHA diagnosis should be inhibitor quantification. The most commonly used method is the Bethesda assay with the Nijmegen modification [10]. This method relies on the measurement of residual FVIII activity during the dilution of normal and patient’s plasma with FVIII-deficient plasma [40]. One Bethesda unit (BU) is defined as the amount of inhibitor resulting in 50% residual FVIII:C activity of a defined test mixture [40]. The threshold between low and high inhibitor titer is established as 5 BU/mL [41]. However, there is no correlation between the level of inhibitor titer and the frequency or severity of bleeding episodes [2]. According to the data, the majority of myeloma patients with AHA (93%) develop high inhibitor titer. The mean inhibitor titer was 18.7 BU/ml (4.9–108) with a mean residual factor VIII activity of 2% (Table I).
Figure 1. Diagnostic algorithm in acquired hemophilia A; aPTT — activated partial thromboplastin time; PT — prothrombin time; TT — thrombin time; VKA — vitamin K antagonist; DOAC — direct oral anticoagulant; DIC — disseminated intravascular coagulation; F — factor; vWF — von Willebrand factor; AHA — acquired hemophilia A; LA — lupus anticoagulant
Management

The management of AHA associated with MM consists of the following goals: immediate bleeding control, long-term eradication of the autoantibody inhibitor, and treatment of the underlying disease (MM) [42] (Table II).

Table II. Bleeding and inhibitor eradication management in patients with acquired hemophilia A (AHA) and multiple myeloma coexistence

<table>
<thead>
<tr>
<th>Bleeding management</th>
<th>Inhibitor eradication</th>
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</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td><strong>Dosing</strong></td>
</tr>
<tr>
<td><strong>Replacement therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Recombinant porcine FVIII</td>
<td>50–100 IU/kg initially</td>
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<tr>
<td></td>
<td>Further dosing depends on response and FVIII activity</td>
</tr>
<tr>
<td>By-passing agents</td>
<td></td>
</tr>
<tr>
<td>aPCC</td>
<td>50–100 IU/kg every 8–12 h Maximum daily dose</td>
</tr>
<tr>
<td>Drug</td>
<td>Dosage</td>
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<tr>
<td>------</td>
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<tr>
<td><strong>rVIIa</strong></td>
<td>200 IU/kg</td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Emicizumab</strong></td>
<td>Loading dose 3 mg/kg subcutaneously, weekly for 2 to 3 doses, followed by maintaining dosage with 1.5 mg/kg every 3 weeks</td>
</tr>
</tbody>
</table>
RVd, VCd

| Cyclophosphamide | 500 mg weekly | In combination with glucocorticosteroids and:
|------------------|---------------|---------------------------------
|                  |               | - bortezomib (CyBorD or VCD)
|                  |               | - IMIDs

FVIII — factor VIII; IU — international unit; pFVIII — recombinant porcine factor VIII; aPCC — activated prothrombin complex concentrate; rVIIa — recombinant activated factor VII; IMIDs — immunomodulatory drugs; VMP — bortezomib + melphalan + prednisone; VTd — bortezomib + thalidomide + dexamethasone; RVd — lenalidomide + bortezomib + dexamethasone; VCD — bortezomib + cyclophosphamide + dexamethasone; CyBorD — cyclophosphamide + bortezomib + dexamethasone

**Bleeding control**

Ideally, invasive procedures should be avoided, but if they are urgently needed, hemostatic therapy is required during the procedures [10]. In general, the choice of first-line hemostatic agents is based on the severity of the bleeding, the clinical setting, and the presence of low or high titer inhibitors [42].

The treatment options consist of by-passing agents (BPA), FVIII replacement therapy, drugs mimicking FVIII activity in the patient’s plasma, and antifibrinolytic agents [10, 43, 44]. In the general population of AHA patients, the most frequent method of immediate bleeding control is the use of BPA which trigger thrombin generation even in the presence of FVIII inhibitors: recombinant activated factor VII (rVIIa) [43, 45] or activated prothrombin complex concentrate aPCC [33, 43, 46].

aPCC is a plasma-derived concentrate containing zymogenic and enzymatic forms of prothrombin complex coagulation factors and natural anticoagulant factors [46]. rVIIa is a recombinant zymogen of FVII. Its short half-life of about 2.7 hours necessitates frequent
administration to sustain hemostatic balance [47]. According to the EACH2, an international Web-based registry supported by an unrestricted grant from Novo Nordisk Region Europe A/S, they have similar efficacy in bleeding control in 80–90% of AHA cases [4, 43]. The main disadvantage of these therapies is the lack of accessible laboratory methods to monitor their effectiveness [48]. Their efficacy can only be assessed in specialized hemostasis laboratories with access to global coagulation process tests such as thrombin generation assay (TGA) and thromboelastometry (TEM) [48].

Another option in bleeding control in patients with auto- and alloantibodies against FVIII may be porcine FVIII (pFVIII) supplementation [10]. Susoctocog alfa is a recombinant, B-domain deleted porcine FVIII approved for the treatment of bleeding episodes in patients with acquired hemophilia [49]. Porcine and human FVIII (hFVIII) have the same activity in the clotting cascade, linking the interaction between activated factor IX (aFIX) and factor X (FX) on the intrinsic coagulation pathway [50, 51]. pFVIII has been used for bleeding management in AHA patients due to the low cross-reactivity of anti-human FVIII antibodies towards porcine FVIII [50]. The most commonly targeted autoantibodies, FVIII A2 and C2 domains in the pFVIII and hFVIII molecules, are homologous, only 84% and 76% respectively [51]. The great advantage of this drug is the ability to measure and monitor FVIII activity levels with the one-stage clotting assay. Susoctocog alfa is efficient in bleeding control in 93% of AHA patients when used as first-line treatment, and in 73% of patients previously treated with other hemostatic agents [49]. Due to the immunogenicity of porcine protein, the use of pFVIII is a burden carrying the risk of the formation of alloantibodies which neutralize its activity and may cause allergic reactions [49, 52].

The use of 1-deamino-cys-8-D-arginine-vasopressin (DDAVP) is no longer recommended in patients with AHA [10].

A promising new therapeutic option in the general population of AHA patients is emicizumab [44]. This bispecific antibody binds to activated factor IX and factor X, mimics FVIII activity, and enables intrinsic pathway clotting cascade propagation even in the presence of a FVIII inhibitor [53]. Emicizumab, used nowadays widely in patients with congenital hemophilia A with a FVIII inhibitor, has been successfully used in AHA patients [44]. In the study by Knoebl et al. [44], the safety and efficacy of emicizumab in AHA was investigated in a group of 12 AHA patients. Emicizumab was started with a standard dose of 3 mg/kg subcutaneously, weekly for 2–3 doses, followed by maintaining dosage with 1.5 mg/kg every three weeks for keeping the lowest effective FVIII levels. A clinically impressive improvement of bleeding was observed within three days, with no breakthrough bleeding.
events. Emicizumab was stopped as the FVIII levels exceeded 30%. No deaths or thrombotic events were observed [44]. Emicizumab seems to be an effective hemostatic therapy for AHA, with good hemostatic efficacy and the possibility of early discharge due to subcutaneous administration, but its usage in patients with myeloma patients with AHA can be controversial. Its efficacy and, more importantly, safety, in this group of patients has not been investigated so far. Any thrombotic risk associated with myeloma [18] and emicizumab itself [53] seem to be an option reserved for patients with life-threatening bleedings refractory to other hemostatic agents.

The typical dosing of the most commonly used drugs in AHA-related bleeds are set out in Table II.

In AHA patients with MM, the most common form of bleeding control remains BPA usage. The available data suggests their efficacy and safety in this group of patients. In 37% and 24% of patients, aPCC and rVIIa respectively were used, and in all cases they succeeded in controlling bleeding. Another therapeutic option used in MM patients with AHA in previous studies was human factor VIII. As in the general population of AHA patients, the usage of such treatment proved ineffective. In other studies, fractionated porcine FVIII was used, confirming its effectiveness (Table 1). Although no thromboembolic events have been described in myeloma patients with AHA, the myeloma-dependent high thrombotic risk seems to incline care-givers towards careful administration of hemostatic agents and monitoring for detection of any early symptoms of thromboembolic events, especially in patients with FVIII activity recovery >50 IU/mL.

**Inhibitor eradication**

The major long-term goal in the management of AHA is inhibitor eradication, which enables the restoration of normal hemostasis [10, 43]. Partial remission (PR) is defined as no active bleeding and an FVIII activity increase above 50 IU/dL, while complete remission (CR) is defined as PR plus FVIII inhibitor below detection level –0.6 BU/ml [1]. Due to the autoimmune background of AHA, inhibitor eradication is usually obtained by immunosuppressive treatment (IST) [10]. However, in patients with a known AHA underlying disorder, the eradication therapy must include treatment of the underlying disease [10]. This is especially important in patients with AHA in malignancy when anti-cancer treatment may induce eradication of factor VIII inhibitor [32]. This approach cannot be overestimated in plasma cell dyscrasias patients, especially in cases where the M protein is acting as a factor
VIII inhibitor [19]. In these patients, the eradication of myeloma clones through the use of anti-myeloma drugs may be crucial for the elimination of the inhibitor, and AHA remission [20]. Fortunately, the drug used in IST treatment overlaps with multidrug MM chemotherapy protocols. In a typical AHA patient, first line inhibitor eradication treatment comprises glucocorticosteroids (GCS) in monotherapy or in combination with cyclophosphamide [10, 36]. According to the majority of guidelines, prednisone or prednisolone should be used at a daily dose of 1 mg per kilogram of body weight [10, 36, 42]. The majority of MM chemotherapy regimens including GCS have been confirmed to be highly active against neoplastic plasma cells [54]. Inhibitor-eliminating protocols recommend cyclophosphamide (CPA) in AHA is used at a dose of 1–2 mg/kg/day [10, 36, 42]. As an alkylating agent, it causes dose-dependent lymphodepletion: at standard low ISS dosage, its cytotoxicity acts selectively on the B lymphocytes responsible for producing autoreactive antibodies in AHA, with the preservation of the T helper lymphocyte function [55]. CPA in MM therapy is used in multidrug combination [56].

Bortezomib may be of more interest among the various therapeutic options in patients with AHA in the course of MM. Bortezomib has a directly cytotoxic effect on neoplastic plasma cells through the inhibition of the proteasome/nuclear factor-kappa B (NF-κB) axis which is essential for interaction with the myeloma environment [57, 58]. Furthermore, bortezomib has been described as an ISS drug efficient in SLE [59] and myasthenia gravis [60]. Bortezomib affects both cellular and humoral immune responses. It affects B cell activation and impairs activated B cell proliferation. On the other hand, it decreases the CD4 activated T cells population and reduces Th1 cytokines via NF-κB pathway inhibition [57]. Effective first-line therapy based on a regimen with bortezomib has been described in a few cases of AHA in the course of MM [22–24, 30]. It is also effective in refractory AHA in myeloma patients [20]. Bras et al. described the case of a 90-year-old patient with MM-associated AHA refractory to a combination of CPA and dexamethasone despite partial remission of MM. After four cycles of bortezomib-based treatment, the patient achieved CR of AHA [20]. Bortezomib has also been successfully used in idiopathic AHA refractory to rituximab. After four cycles of bortezomib at a dose of 1.3 mg/m² on days 1, 4, 8 and 11 of a 21-day cycle, the patient achieved durable complete remission of AHA [61].

Therapeutic options in the absence of remission after six weeks of first-line AHA therapy include rituximab, bortezomib and lenalidomide (Table II). Therapy with rituximab (RTX), a chimeric anti CD-20 monoclonal antibody widely used in other autoimmune
disorders and which causes depletion of B-lymphocytes expressing CD-20 molecules, i.e. all maturation stages from the pre-B to mature B-lymphocyte [62], is recommended as a standard second-line treatment of AHA without multiple myeloma [10].

The efficacy of RTX in AHA in the course of MM is unclear: plasma cells, both normal and neoplastic, do not express CD20 [63], therefore it may be inefficient to eliminate neoplastic clones producing M proteins with FVIII inhibitor activity. There is only one literature case of an MM patient in complete remission after a VTD regimen who developed AHA with cardiac tamponade and soft tissue hematomas, and was successfully treated with RTX (4 doses of 750 mg/m$^2$ once a week) and intravenous immunoglobulins (IvIg; 1 mg/kg/d, eight cycles) [31].

Lenalidomide, another drug widely used in MM therapy, has an ambiguous role in AHA. In multidrug combination, lenalidomide is highly active against myeloma clones [64] and can induce AHA remission [65]. On the other hand, it can be responsible for drug-induced FVIII inhibitor development. Saburi et al. described the case of a myeloma patient developing AHA on lenalidomide-based treatment. The patient achieved CR after drug discontinuation and standard immunosuppressive treatment with steroids and CPA usage, although FVIII inhibitor occurred immediately after the reintroduction of lenalidomide [29].

According to the available data, in MM patients with AHA, almost all patients (95%) have received inhibitor eradication treatment, 82% including steroids, and 58% CPA. In 47%, bortezomib was used. One patient achieved CR of AHA on treatment with rituximab combined with IvIg but was in CR of MM after a VMP regimen [31]. Both attempts at inhibitor elimination through plasma exchange were unsuccessful [21, 32].

Therapies focused solely on eradication of the inhibitor based on CPA with or without GCS have usually been ineffective and burdened with life-threatening complications [5, 21, 26, 28, 33]. Among the whole group, 63% of patients achieved CR, 16% of patients achieved PR, and 16% did not respond to the therapy; and all of these died of hemorrhagic complications. One patient developed a relapse of AHA with concomitant subclinical MM relapse seven months after achieving CR: both were treated successfully with bortezomib [20]. One patient required only topical treatment to control the bleeding, and data on the therapy of MM and inhibitor eradication was not provided [19].

**Thrombotic risk in myeloma patients with AHA**
The thrombotic risk management in MM patients with AHA is challenging because of various myeloma-associated coagulation abnormalities comprising thrombotic risks, and the excessive bleeding tendency due to myeloma-induced bleeding tendency and AHA itself [18].

**Thromboembolism risk in AHA patients**

Although AHA is a severe bleeding disorder, it carries some risk of thrombotic complications as well. In the literature, some venous thromboembolic episodes (TEs) in AHA patient have been described [66]. Most cases involve the development of TEs as a result of bleeding management in AHA [66]. By-passing agents, both aPCC and rVIIa, are associated with a thromboembolic risk. In AHA patients treated with rVIIa, thromboembolic events were observed in 0–5% of cases [45, 67–70] comprising arterial and venous thrombosis as well as disseminated intravascular coagulation (DIC) [68, 69]. The TE incidence rate was two times higher in patients with the addition of tranexamic acid to rVIIa [45]. Arterial or venous TEs have been observed in 4.8% of cases treated with aPCC [43]. A systematic review of the use of aPCC in congenital and acquired hemophilia patients, including 39 studies, reported an incidence rate of TE at 2.87 per 10,000 infusions. It is noteworthy that the incidence rate of TE was significantly higher in patients with acquired hemophilia: 288 per 10,000 infusions compared to the congenital form which had a prevalence of below 0.01 per 10,000 infusions [71]. Although in the case of uncontrolled bleeding from one type of BPA in patients with FVIII inhibitor, the guidelines recommend consideration of the parallel (concomitant or subsequential) use of rVIIa and APCC, this approach seems to be burdened with a high risk of thrombotic complications, up to 55% with a high mortality rate [67]. Tranexamic acid employment is also restricted by the risk of thrombotic complications, especially with concomitant usage of BPA. In the GTH study, two fatal thromboembolic events were observed in patients receiving tranexamic acid in combination with rFVIIa [45]. International recommendations therefore suggest caution when combining tranexamic acid with bypassing agents. Moreover, some AHA patients can develop TEs in the recovery phase of FVIII inhibitor, especially in the presence of other TE risks such as advanced age, comorbidities, high-dose glucocorticoid therapy, and high levels of vWF activity [72]. Thus, careful monitoring of the coagulation parameters is required.
Thromboembolic risk in AHA can be increased in the rare situation of the simultaneous presence of lupus anticoagulant (LA). Brings et al. [73] described an upper extremity deep vein thrombosis followed by thigh muscle hematoma in a patient with concomitant LA and AHA. Moreover, in a review of such a coincidence by Saxena et al., one patient developed simultaneous thrombosis and bleeding [74]. To the best of our knowledge, there has been no described simultaneous occurrence of AHA and LA in myeloma patients, but there are two cases of MGUS-associated AHA cases with LA coexistence [75, 76]. In both cases, thrombotic episodes were not observed, but Belfeki et al., because of concern about the thrombotic risk to their patient, decided to introduce thromboprophylaxis therapy with acetylsalicylic acid after FVIII recovery [75].

Thromboembolic risk in MM

Myeloma patients with AHA seem to be especially at risk of TE development. Firstly, patients with cancer have a 4–7 times higher thrombotic risk compared to healthy coevals [77] and, among all cancer types, multiple myeloma has one of the highest risks of thrombosis [78]. The etiology of this hypercoagulable state in myeloma patients is complex and depends on patient-, disease- and treatment-related factors [77].

Patient-related factors are similar to the general population i.e. previous thrombosis history or known thrombophilia, obesity, older age, immobility, surgery, central venous catheter or pacemaker placement, smoking, and comorbidities, especially cardiovascular disorder, hypertension and/or acute infection [77]. The biology of the disease is also important: advanced stage, multiple bone fractures leading to immobility, and high tumor burden can significantly increase the thrombotic risk in myeloma patients [77, 79]. Interestingly, the type M protein also has also an impact on the thrombotic risk: IgM monoclonal proteins increase thrombotic risk even in patients with a pre-myeloma condition i.e. monoclonal gammopathy with undetermined significance [80]. In myeloma patients, we observe the hypercoagulable state through increased FVIII, vWF activity and acquired protein C resistance [77, 81]. Previous observations have shown that the risk of thrombotic events is the highest during the first few weeks of myeloma treatment, so the impact of anti-myeloma drugs on thrombosis risk seems to be obvious [81].

It has been proved that immunomodulatory drugs like thalidomide [79, 81], lenalidomide [79] and pomalidomide [82] are associated with an increased thrombosis risk, especially when used with high doses of glucocorticosteroids [81]. On the other hand, the
proteasome inhibitor bortezomib seems to decrease the thrombotic risk through its anti-
platelet activity [83, 84].

All these observations have resulted in the recommendation of thrombosis prophylaxis. The scheme depends on the individual thrombotic risk: both the International Myeloma Working Group (IMWG) [79] and the National Comprehensive Cancer Network [85] recommend the use of 100–375 mg of acetylsalicylic acid in low risk thrombosis patients. When there is a high risk of thrombosis, a more intense treatment is preferred with low-molecular-weight heparin (LMWH), vitamin K antagonists (VKA), and direct oral anticoagulants (DOACs) [79, 85]. In AHA patients with multiple myeloma, antithrombotic prophylaxis is obviously contraindicated due to their bleeding tendency, although AHA does not rule out the possibility of thrombosis, especially when by-passing agents are used in bleeding management [67–71].

In line with the general guidelines for AHA, the initiation of antithrombotic prophylaxis should be considered in patients with a high risk of thrombosis events in the course of MM and concomitant AHA who, as a result of inhibitor eradication and/or anti-myeloma treatment, have achieved FVIII activity restoration above 100 IU/dl with a subsequent reduction of immunosuppression therapy [86].

Conclusions

Based on the current literature, MM and AHA coincidence is extremely rare, but the clinical management of this situation is very challenging. The mechanism of AHA development in myeloma patients is complicated. It includes not only a neoplasm-induced autoimmune reaction resulting in the production of anti FVIII antibodies, but also, in some cases, the M protein itself can act as a selective FVIII inhibitor. Due to the different mechanisms triggering AFI development, AHA in this population can be refractory to standard ISS treatment and requires MM clone eradication-focused management with the use of novel anti-myeloma drugs. Bortezomib, with its immunosuppressive and antitymoma activity, seems to be a very potent drug, both in newly-diagnosed and refractory MM.

Bleeding control in myeloma patients with AHA must take into account complex hemostasis aberrations including both thrombosis and bleeding diathesis combined with the disease and myeloma treatment. APCC or rFVIIa seem to be equally efficient in bleeding control, and remain the first line AHA treatment in MM patients.
Authors’ contributions
AH conceived idea for this study. JR-M and LG contributed to design of research. All authors were involved in data collection. AH and JR-M analyzed data. All authors edited and approved final version of manuscript.

Conflict of interest
None.

Financial support
None.

Ethics
The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; uniform requirements for manuscripts submitted to biomedical journals.

References


<table>
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<th>No</th>
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<th>Bleeding symptoms</th>
<th>FVIII activity (%)</th>
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**MM relapse**

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**MM remission**

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**MM status unknown**

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