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Review Article

Acquired Hemophilia: A Review And Case Series.

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Abstract

Inhibitory autoantibodies against factor VIII (FVIII) are a hallmark of acquired hemophilia A (AHA), a rare and potentially fatal autoimmune disease that causes bleeding either spontaneously or as a result of trauma. In order to assess patient characteristics, therapies, and results, this study examines a single-center cohort. Methods: From 2012 to 2024, we looked back at the medical records of 22 adult patients who had been diagnosed with AHA.Demographics, clinical presentation, lab results, therapies, and results were all included in the data. Gender comparisons, treatment approaches, and remission results were assessed using statistical analysis. Results: The cohort's average age was 62 years old, with a gender distribution of equal numbers (22–102 years). Pregnancy accounted for 27% of the suspected reasons, followed by cancer (23%), autoimmune disorders (5%), and idiopathic causes (45%).In 82% of cases, spontaneous cutaneous hematoma was the most frequent manifestation. Nine percent of cases involved severe bleeding that required hemostatic treatment. Forty-five percent of patients who had corticosteroid-based initial immunosuppressive therapy (IST) experienced remission; others needed subsequent Rituximab or Cyclophosphamide treatment. An individual with severe refractory bleeding was successfully treated with emicizumab, a new FVIIImimetic. Within a median of three months, 64% of patients experienced remission, whereas 14% experienced recurrence. Although corticosteroid adverse effects, including one hip fracture, were reported, no thrombotic events were observed. Conclusions: Although adverse effects call for customized management, IST continues to be the mainstay of AHA treatment. Emicizumab exhibits potential, especially in fragile populations and refractory patients..

Keywords : *Emicizumab, Rituximab, acquired hemophilia, pregnancy-induced acquired hemophilia, and acquired bleeding disease.*

INTRODUCTION

An uncommon autoimmune condition known as acquired hemophilia A (AHA) causes inhibitory autoantibodies to form against clotting factor VIII (FVIII). This leads to either trauma-induced bleeding or potentially fatal spontaneous bleeding [1,2]. Although AHA can afflict people of any age, it is more common among the elderly, with a median starting age of 70–76 years. It is equally prevalent in both sexes and frequently associated with comorbidities and age-related immunological impairment [2,3].

According to estimates, there are between 0.65 and 1.5 instances of AHA for every million persons annually. The remaining cases are idiopathic, meaning they have no known cause, while the other half are linked to autoimmune disorders, cancers, infections, or pregnancy [1,2].

Malignancy is responsible for about 10% of AHA cases [4]. Hematological malignancies are among them, with chronic lymphocytic leukemia (CLL) accounting for up to 30% of all cases. Approximately 50% of solid tumors that cause AHA are thought to have an underlying lung or prostate cancer [4]. Although it can be detected up to a year after delivery, obstetric-associated AHA is more prevalent in the postpartum phase and often manifests up to three months after delivery. Large soft-tissue hematomas at several locations or inexplicable, continuous vaginal bleeding should raise suspicions of this disorder [5].

It is believed that primigravid poses a risk for postpartum AHA [5]. It is also crucial to remember that maternal IgG antibodies may cross the placenta in cases of AHA during pregnancy and, in rare instances, result in bleeding symptoms in the fetus or the infant [6,7].

AHA has also been linked to autoimmune diseases, including rheumatoid arthritis, Sjogren's syndrome, dermatomyositis, and systemic lupus erythematosus (SLE) [1].

There have been several documented instances of AHA that were characterized as drug-induced [8].

One of the most common clinical signs of AHA is bleeding into soft tissues, primarily subcutaneous and intramuscular bleeds, which frequently occur on their own.Intracerebral hemorrhage, genitourinary system bleeding, and gastrointestinal bleeding are examples of more severe bleeding presentations that may also happen at presentation [1]. The hereditary type of hemophilia, which is typified by excessive bleeding following trauma, injury, or invasive procedures, and spontaneous bleeding into joints, differs

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from these clinical presentations.

Because AHA is uncommon, its symptoms are vague, and medical practitioners are unaware of it, diagnosis is frequently postponed. The hallmark diagnostic clue is atypical bleeding symptoms, a prolonged activated partial thromboplastin time (aPTT) that does not improve with a mixing study, decreased FVIII activity, and the presence of inhibitors, all of which are verified by a Bethesda assay [3].

The two main objectives of treatment are to stop the bleeding and get rid of the inhibitor. Hemostatic care usually entails avoiding drugs like activated prothrombin complex concentrate (aPCC) and recombinant activated factor VII (rFVIIa), occasionally with the help of tranexamic acid [1,3]. Recombinant FVIII (rFVIII) is another method for controlling bleeding. Autoantibody production is suppressed by immunosuppressive therapy (IST), which includes corticosteroids, cyclophosphamide, or rituximab [1,3]. IVIg treatment was once thought to be optional, however current recommendations oppose this practice [3].Emicizumab, a bispecific monoclonal antibody that mimics the function of FVIII, has become a novel off-label therapy option for treating AHA in recent years. It is approved for congenital hemophilia A with and without FVIII inhibitors [9,10]. By bridging active factor IX and factor X, emicizumab mimics the actions of FVIII and so avoids the requirement for FVIII. Although more study is required to thoroughly evaluate Emicizumab's long-term efficacy and safety in AHA patients, preliminary studies and case reports indicate that it can effectively prevent bleeding episodes and minimize them [9–11].

METHODS

All adult patients (over the age of 18) who received an AHA diagnosis at the Sheba Medical Center between 2012 and 2024 were the subject of our retrospective analysis.

The following were the requirements for inclusion: (1) age greater than 18; (2) a positive FVIII antibody level (>0.5 BU); and (3) ongoing ambulatory follow-up at our coagulation clinic.Patients with concurrent congenital coagulopathis (congenital hemophilia A or other uncommon bleeding diseases) and those diagnosed while in the hospital but never followed up with in our ambulatory coagulation clinic were excluded.The MDClone platform, a secure system created to generate data from the hospital's digital health records while protecting individual privacy and guaranteeing compliance, was used to obtain retrospective patient data that had been prospectively acquired during hospitalization and follow-up.

Notably, our specialized coagulation laboratory was used for all laboratory assays. One-stage tests and conventional methods were used to determine FVIII, Bethesda units (BUs) were used to assay FVIII inhibitors, and chromogenic assays utilizing bovine reagents were carried out as needed for patients receiving emicizumab [11].

The following data was manually extracted from eligible patient records:

Demographics: sex, age, and other pertinent information.

Medical History: comorbidities and previous illnesses.

AHA appearance: first appearance and clinical symptoms.

APTT, FVIII activity levels, and FVIII inhibitor levels are among the laboratory results.Clinical outcomes include mortality and bleeding episode recurrence.

Data analysis included comparisons of means and distributions across different subgroups, including sex and treatments. The IBM SPSS Statistics 26 software was used to conduct the statistical analysis. Scale variables were compared using the Independent Sample t-test, while nominal variables were compared using the Chi square test and Fisher's exact test, when applicable.Only short-term outcomes were evaluated because of the small sample size and inconsistent follow-up times among patients.This study was approved by the Sheba Medical Center's Ethics Committee and was given a waiver for informed consent because it used de-identified data.

RESULTS

Of the 22 AHA patients in our group, half were female. With a median age of 71 and an interquartile range (IQR) of 33.75–83.00, the age range at presentation was 22–102. Table 1 displays all of our patients' demographic information.

Six individuals (27.2%) had pregnancy as the likely cause of AHA, five patients (22.7%) had cancer, and one patient with bullous pemphigus (0.045%) had an autoimmune illness. The etiology was idiopathic in the ten patients that remained.

Every patient received their diagnosis in a medical facility. During the AHA investigation, three individuals in our group received a cancer diagnosis. One patient was diagnosed with renal cell carcinoma (RCC), while two patients were diagnosed with hematological malignancies (splenic lymphoma and CLL). The range of FVIII levels at presentation was less than 1% to 7%. At presentation, inhibitor levels ranged from 1.1 BU to 343 BU, with a median of 18.5 BU (IQR 5.5–29.75).

Just two patients (9%) needed hemostatic therapy; one of them had a subdural hematoma, and the other had severe PPH.rFVII (NovoSeven® RT, Novo Nordisk, Bagsvaerd, Denmark) was administered to both patients.

One patient was given human recombinant FVIII, and the dosage was adjusted based on repeated assessments of FVIII activity. It began at 70–80 IU/kg and was repeated three times a day. Later, it was tapered off in response to inhibitor decrease and a slow rise in FVIII levels.Immunosuppressive treatment (IST) was administered to the majority of patients after diagnosis.Ten patients (45%) needed no additional IST after nearly all patients (20/22) had corticosteroid treatment initially. One of the two patients who were not

on immunosuppressive therapy denied treatment, and the other was lost to follow-up. Five patients (75%) experienced postpartum AHA, and eight patients (36%) received further Rituximab treatment. One patient (0.045%) had Emicizumab treatment, whereas four patients (13.6%) received Cytoxan.

Additionally, two patients (0.09%) who were gathered from the cohort's early years received intravenous immunoglobulins (IVIg).The 26-year-old female patient who needed Emicizumab treatment was diagnosed with AHA at another clinic six months after giving birth and presenting with lower limb hematomas.

She was treated with prednisone, azathioprine, and FFP at first, but she needed to be transferred to our clinic after developing an infected internal iliac muscle hematoma and seeing her hemoglobin levels drop from 12 g/dL to 7.3 g/dL. Her FVIII level was less than 1%, her aPTT was greater than 150 s, and her FVIII inhibitor level was 13.6 BU at admission.

After receiving antibiotics, rFVII for hemostasis, and Rituximab for IST as part of the initial therapy, the patient was discharged with an FVIII level of 8%. It resolved the hematoma. She required readmission after developing a fresh intramuscular bleed in her right calf despite continued IST. Her hemoglobin level decreased from 12.38 mg/dL to 9.2 mg/dL, her FVIII level decreased to less than 1%, and her inhibitor level rose to 2.7 BU during the second stay.

After a median of three months, 14 out of 22 patients had no more FVIII inhibitor. Three patients (13.6%) had FVIII levels of roughly 20% and were unable to attain complete remission. Five patients could not be reached for follow-up. Figure 1 (panels A, B, and C, respectively) displays the dynamics of laboratory assays, including PTT, FVIII, and FVIII inhibitor values.Table S1 in the Supplementary Materials contains more details on the test results, treatment plans, and outcomes for specific cohort patients.The time to AHA remission in our population is shown in Figure 2. The majority of patients (10/14) who experienced remission did so within six months of their diagnosis. Despite receiving IST treatment, one patient experienced remission after a lengthier 14-month time.

DISCUSSION

The demographic distribution of patients and etiologies observed in this single-center case series is comparable to that reported in earlier research [1]. Aside from the evident peripartum AHA etiology in women, we did not identify any statistically significant differences between baseline features in males and females.As advised by the literature, corticosteroid medication was used as the first immunosuppressive treatment.The development of corticosteroid side effects (n = 2), an inadequate increase in FVIII levels (n = 6), or an inadequate decrease in FVIII inhibitor levels (n = 4) were the reasons given for the decision to add another immunosuppressive agent to this cohort, despite the fact that current guidelines recommend adding an additional IST, such as Rituximab or Cytoxan, depending on the inhibitor level. Perhaps because Rituximab had fewer cytotoxic side effects than Cytoxan, it was used more frequently in women with pregnancy-related AHA. Rituximab treatment was more prevalent in younger patients, according to a prior statewide investigation of the prevalence, management, and results of AHA in patients carried out in Finland [12]. A different case series comparing IST with Cyclophosphamide against Rituximab revealed comparable safety and efficacy; however, Cyclophosphamide appears to be better for patients with a poor prognosis because it was associated with a much higher number of remissions [13].

One patient in our sample had cancer-associated AHA; she was a very old woman, 102 years old at the time of diagnosis. Two months after starting steroid medication, her AHA went into remission, and she declined to receive any treatment for her original ailment. Despite steroid reduction and cession, no relapse was observed in the year that followed. The spontaneous remission in AHA is called into question by this case. A postpartum woman in our group went into spontaneous remission after refusing therapy. AHA patients have been demonstrated to be capable of spontaneous remission, but some may experience fatal bleeding [14]. In the case of postpartum AHA patients, it has previously been argued that immunosuppressive treatment has no bearing on the natural course of acquired hemophilia postpartum.

Although thrombosis may be a frequent side effect of AHA and is linked to patient comorbidities and hypercoagulable states after the administration of bypass agents [16], our sample did not experience any thrombosis. The fact that only two patients got rFVIIa therapy for comparatively brief durations (one to two days only) to manage bleeding signs may be the cause of this.IST, which is effective but can have serious adverse effects such infections and a loss of bone density, is the mainstay of current therapy guidelines for AHA [17]. One older woman in our group experienced a hip fracture while receiving steroid treatment, as previously mentioned. Our cohort also reported hypertension and sleeplessness as additional steroid-associated side effects, all of which were manageable and reversible after IST was stopped.However, as IST is not benign, any successful "IST sparing" treatments could potentially improve AHA results and patient safety. Emicizumab treatment could revolutionize the way AHA is managed in this susceptible group [18]. Emicizumab has been demonstrated in numerous studies to be effective in reducing bleeding while also reducing the adverse effects of IST and bypassing medications. According to the results of a phase 2 trial recently published by Tiede et al., giving Emicizumab to patients with AHA can stop bleeding without giving IST

concurrently, which lowers the risk of thromboembolic events, serious infections, and deaths [19]. In another study, Shima et al. reported the findings of a prospective, multicenter, open-label phase III study that is currently underway to assess the pharmacokinetics, safety, and effectiveness of emicizumab.

IST is not benign, though, therefore any effective "IST sparing" therapies may enhance patient safety and AHA outcomes. Treatment with emicizumab has the potential to completely change how AHA is treated in this vulnerable population [18]. In addition to lowering the negative effects of IST and avoiding the need for medication, emicizumab has been shown in multiple studies to be helpful in minimizing bleeding. providing Emicizumab to patients with AHA can stop bleeding without providing IST simultaneously, which reduces the risk of thromboembolic events, major infections, and mortality, according to the findings of a phase 2 trial recently published by Tiede et al. [19]. The results of a prospective, multicenter, open-label phase III research that is presently being conducted to evaluate the pharmacokinetics, safety, Depending on the patient's clinical symptoms and bleeding diathesis, emicizumab is recommended as either first- or second-line treatment for AHA in the most recent consensus recommendations [21].

After her first pregnancy, a young woman with post-partum AHA had IST with steroids. Rituximab was then administered because of a gradual increase in FVIII levels. She had no further spontaneous hematomas and was able to reach FVIII levels of roughly 20%. After reviewing the material, she inquired about when to get pregnant again and was told to keep on birth control until her FVIII levels returned to normal. The literature review did not find any prior reports of pregnancy in a woman who did not attain remission. There are serious repercussions from the possibility of antibody transmission to the fetus.

During the AHA etiology inquiry, three patients in this group received a cancer diagnosis. Although AHA is typically identified after cancer is diagnosed, a 2012 analysis of 58 literature on the topic found seven case reports where the diagnosis of AHA was made two to seven months before the cancer diagnosis [4]. This highlights how crucial cancer screening is for people who have idiopathic AHA.According to the literature [12], recurrence rates were comparable for men and women. An invasive operation in one instance and an increase in the disease burden in another were the causes of recurrence.

There are various restrictions on this study. Seven out of twenty-two patients in this retrospective cohort were lost to follow-up following their initial admission.Owing to AHA's rarity, treatment approaches varied over time and were not consistent. Future research with a longer follow-up time and more patients, in our opinion, can assist address the shortcomings of this study and offer more precise data on appropriate treatment approaches for this patient group. However, our cohort supports the established risk factors for AHA occurrence in young women and older men, emphasizing the value of IST-sparing treatment, such as hemostatic non-replacement therapies like Emicizumab, and the significance of cancer screening because AHA presentation may occur before cancer diagnosis. Future research is necessary to more accurately determine the likelihood of recurrence in particular populations, such as women of reproductive age who become pregnant again after experiencing full or partial remission.

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