Acquired Hemophilia A in a Female: A Case Report

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Acquired Hemophilia A in a Female: A Case Report

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Abstract

INTRODUCTION: Coagulation factor deficit is a very uncommon hemostatic condition in which a single component or numerous factors are lacking. Hereditary coagulation factor defects are autosomal recessive, meaning that they can affect both men and women. However, hemophilia A, caused by lack of clotting factor VIII (FVIII), is an X-linked condition. Acquired hemophilia A (AHA) is a bleeding disorder caused by autoantibodies to FVIII. It should be distinguished from congenital hemophilia, an inherited disorder caused by a mutation in the FVIII gene. Here, we report the first known case in Indonesia, a 24-year-old female diagnosed with AHA.

CASE PRESENTATION: A 24-year-old woman was referred to our facility for prolonged epistaxis. She had no previous history of extended menstrual flow or frequent epistaxis episodes, and there was no history of epistaxis or prolonged bleeding in her family. Bleeding time and prothrombin time were both normal, but time to activate partial thromboplastin was longer. The patient was diagnosed with AHA after von Willebrand disease (VWD) was ruled out.

DISCUSSION: In some rare situations, females can be affected by X-linked illnesses such as hemophilia A and B. This may be due to a carrier mother or affected father, skewed X chromosome inactivation, Turner syndrome, inhibitory antibodies (acquired hemophilia), or a random mutation on the active X chromosome. In such instances, treatment is challenging. The usual treatment of choice is recombinant coagulation factors.

CONCLUSION: Although VWD is the most frequent hereditary bleeding problem in females, other rare disorders such as AHA may be implicated. Clinicians should be aware of this when faced with patients that lack a history of bleeding disorders. Furthermore, AHA should be considered as a differential diagnosis in every female patient suffering from hemorrhage. Therefore, a comprehensive diagnostic approach is needed.

Introduction

Hemophilia is an inherited (sex-linked recessive) hematological disorder, manifesting in a deficiency of blood clotting factors [1]. Between 1940 and 1950, experts identified FVIII and factor IX deficiencies as hemophilia types A and B, respectively. Deficiency occurs as the result of mutations in the clotting factor genes [1], [2], [3]. In 2017, the World Federation of Hemophilia (WFH) estimated there to be around 241,535 people living with hemophilia worldwide [3]. Hemophilia types A and B represent 80–85% and 10–15%, respectively, of total hemophilia cases regardless of race, geography, or socioeconomic status. A report from the WFH Annual Global Survey 2020 showed that as many as 2334 hemophilia A patients and 353 hemophilia B patients resided in Indonesia [4]. Hemophilia is an X-linked chromosomal disorder mainly affecting males, whereas females are generally carriers. The ratio of females to males with hemophilia from the Universal Data Collection project data is 1:32 (0.031 females for each male with hemophilia) [5].

A family history of bleeding occurs in approximately two-thirds of all patients, while in a third of patients, the disease is caused by spontaneous mutations, and there is no previous family history [1], [2]. Although patients with hemophilia A, the most prevalent X-linked inherited bleeding illness, are almost exclusively male, their female relatives may be carriers of disease-causing genes and may, therefore, transmit the trait to their male children. Therefore, it is crucial to carry out genetic testing on potential carriers and offer genetic counseling to the affected families. There is a strong inheritance pattern within families, with more than half of patients having a brother or other male relative with the same condition. However, in families with a single hemophilia A patient – about 30% of all cases – the disease is considered sporadic [6], [7]. Hemophilia A presents significant difficulties for genetic diagnosis of carriers and risk assessment in genetic counseling. The mother of the index patient may not be a carrier, or she may have a *de novo* mutation or carry a mutation acquired from her parents [6].

AHA is a bleeding disorder caused by autoantibodies to FVIII. It should be distinguished from congenital hemophilia, an inherited disorder caused by a mutation in the FVIII gene, which generally appears at a young age [8]. Here, we report the first known case in Indonesia, a 24-year-old female diagnosed with AHA.

Case Presentation

A 24-year-old female visited our institution after being referred from Jayapura Hospital, Papua Province, Indonesia, to our emergency department with suspected hemophilia. Her chief complaint was repeated bleeding occurring from the nose and bruises in the flexural area of the extremities (thigh and calves). The patient did not have a previous history of prolonged bleeding, malignancy, bleeding in joints or muscles, prolonged history of menstruation, or a history of malarial infection.

The patient was hospitalized at Bhayangkara Hospital, Jayapura, Indonesia, in March 2021 after complaining of dizziness accompanied by continuous nasal bleeding for 2 consecutive days before admission. Laboratory results showed that her Hb level was 4.2 g/dL. The patient was transfused with three bags of packed red cells and given a tranexamic acid injection. Treatment lasted for 1 week. As the internist then suspected a potential blood disorder, the patient was referred to our institution. There were no reports of coughing, shortness of breath, chest pain, or history of chest pain. Furthermore, there was no history of COVID-19, chills, headache, fever, or previous history of fever. The patient was the eldest of four siblings, and the three younger brothers were in good health. Both parents had a history of consanguineous marriage (cousin) and were in good health, without any history of bleeding.

On physical examination, the patient was conscious but looked unwell. However, her nutritional status was well-nourished (body mass index of 24.6 kg/m^2 [normoweight]) and her vital signs were within the normal limits. The head-to-toe assessment showed that all parameters were within the normal limit apart from the presence of two hematomas in the right femur region, with diameters of approximately 6 cm and 3 cm.

On laboratory examination, we observed the following parameters: Hemoglobin at 7 g/dl (normal value: 4–10 × 10^3/µl), thrombocytes at 488 × 10^3/dl (normal value: 150–400 × 103/dl), and leukocytes at 7.0 × 10^3/µl (normal value: 4–10 × 10^3/µl). Bleeding time and prothrombin time were normal. However, as there was a marked prolongation of activated partial thromboplastin time (aPTT; 56 s), further tests were carried out. While the lupus anticoagulant (LA) test was negative, and Coombs test was normal, screening for FVIII showed a very low value of 7% (referral value 60%–150%).

The patient was diagnosed with AHA based on history, chief complaint, and laboratory results (prolongation of aPTT, normal prothrombin time, negative LA test, and very low level of FVIII). After treatment with 1000 mg human FVIII (administered intravenously once a day for 3 days), the patient's condition improved and she returned to normal activities.

Discussion

AHA differs from classical hereditary hemophilia A in several ways. Classical hereditary hemophilia A is a recessive and sex-linked inherited disease, mostly affecting males from birth, while in contrast, AHA arises at adult or mature ages and affects both males and females. The acquired condition results from the development of autoantibodies against FVIII and decreased coagulation factor levels and is associated with significant bleeding diathesis [9], [10].

The European Acquired Hemophilia (EACH2) registry was established to collect a large-scale prospective pan-European database of demographics, diagnosis, comorbidities, bleeding manifestations, treatments, and outcomes of AHA patients. Results were obtained from 501 patients (266 males and 235 females) from 117 centers and 13 European countries, registered between 2003 and 2008. In 467 cases, AHA diagnoses and investigations were prompted by bleeding as the main clinical manifestation. The mean age of the patients was 73.9 years on diagnosis. Idiopathic AHA contributed to 51.9% of cases, while malignancy or disease autoimmunity was linked with 11.8% and 11.6% cases, respectively. Overall, 57% of cases that were not related to pregnancy were found to be in males [8], [11], [12]. A strong correlation between pregnancy and AHA has been reported, accounting for 10% of all cases. The development of autoantibodies against FVIII is mostly related to a first pregnancy (80%) and may cause severe uterine bleeding [8], [12].

The production of autoantibodies against FVIII in AHA is rare but clinically significant. The incidence of AHA increases with age, ranging between 1.3 and 1.5 per million per year (0.3/million/year at age 16–64 years, 9.0/million/year at age 64–85 years, and 15.0/million/year above age 85). Biphasic age distribution has been shown, with a small peak among 20 to 40 years old and a larger peak between the ages of 68 and 80 years (mean age of 77 years). Disease incidence is relatively similar among males and females, but a higher occurrence has been reported in women during the postpartum period [12].

Immunity disorders associated with a high titer of FVIII autoantibodies rarely resolve spontaneously. Autoimmunity is implicated in 17%–18% of cases. Specific correlations include systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, dermatological conditions such as psoriasis and pemphigus vulgaris, temporal arteritis, Sjögren syndrome, autoimmune hemolytic anemia, Goodpasture's syndrome, and intestinal inflammatory disorders [8], [12]. In our case, we examined antinuclear antibody (ANA) by indirect immunofluorescence to look for the possibility of LA but obtained a negative result.

Patients with underlying malignancies (solid organ or hematologic) make up around 10% of AHA

cases. The most common hematologic malignancies include chronic lymphocytic leukemia, non-Hodgkin's lymphoma, multiple myeloma, and Waldenstrom macroglobulinemia. Solid tumors are associated with FVIII inhibitors in some elderly patients [8], [12]. In our patients, malignancy is assessed through history and physical examination, rather than conducting further specific examinations.

Diagnosis of AHA is challenging if there is no family or personal history of bleeding incidents in a patient. This condition can only be recognized after consulting specialists, requiring invasive examinations before confirmation of diagnosis [9], [10]. Furthermore, meticulous history-taking and physical examination should be conducted to uncover the familial history and bleeding manifestations, as well as to look for underlying diseases.

The clinical picture of AHA differs from that of classic hemophilia A (Table 1). In fact, in more than 80% of patients with FVIII autoantibodies, bleeding occurs in the skin, muscle, or soft tissues and mucous membranes (epistaxis, gastrointestinal, and urological bleeding and retroperitoneal hematoma), whereas hemarthrosis is typical of congenital FVIII deficiency [9], [10].

Table 1: Differences between hereditary hemophilia and acquired hemophilia (acquired hemophilia A) [16]

Hereditary hemophilia	Acquired hemophilia
Hereditary, sex-linked recessive	Acquired, autoimmune disease
Occur in males, females as carriers	Occur in both males and females
In 30% cases, alloantibody was found as inhibitor	Caused by autoantibodies
Manifests on first 2 years of life and later	Most cases manifests in age 60–80 years, smaller occurrence in age 20–40 years
Polyclonal antibody to IgG4 (most often)	Antibody to IgG1, IgG2, IgA, and IgM
Hemarthrosis, muscle hematoma due to trauma and other causes	Most of bleeding (80%) cases occur subcutaneously and within mucosal lining. Hemarthrosis rarely occurs

In a survey of 24 cases admitted to a single care center over a 28-year period, purpura and soft tissue hemorrhage were the most common symptoms, while bleeding into the soft tissues could worsen rapidly into compartment syndrome. Other presentations included hematuria (four cases), gastrointestinal bleeding (two cases), and prolonged postpartum hemorrhage (four cases) [9]. Bleeding in AHA is often serious or life-threatening, as in the case of rapidly progressive retroperitoneal hematoma or compartment syndrome due to intramuscular hemorrhage. Other manifestations reported elsewhere include bleeding after trauma or surgery and occasionally cerebral hemorrhage [10], [13], [14].

Diagnostic measures for AHA (recommended by Collins *et al.* [15]).Isolated prolonged aPTT is the typical laboratory result supporting AHA. Prolongation of aPTT may occur due to deficiency of a coagulant factor (FVIII, FIX, FXI, or FXII), or the presence of an inhibitor (against FVIII or FIX) or LA, as shown in Figure 1 [14], [15]. A mixing test is performed to distinguish these possibilities. This involves mixing patient plasma with normal plasma (1:1) at 37°C and measuring aPTT immediately or after 2 h of incubation.

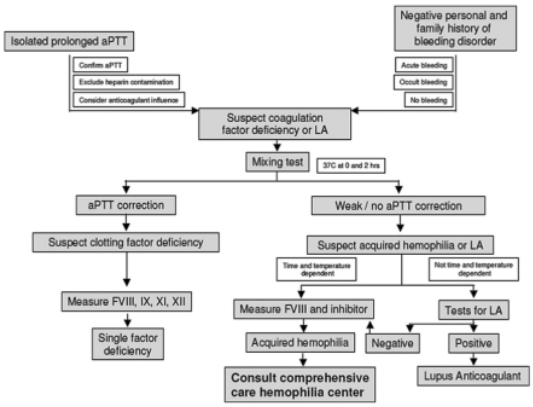

Figure 1: Algorithm for treating patients with suspected AHA [14]. AH: Acquired hemophilia; LA: Lupus anticoagulant; F: Coagulation factors; aPTT: Activated partial thromboplastin time

In patients with clotting factor deficiency (including intrinsic pathway factor deficiency, i.e., deficiency of factors XII, XI, IX, VIII, or von Willebrand factor), aPTT returns to the normal range after the mixing test.

However, if an autoantibody or LA is present, or if an inhibitor of one of these clotting factors is present in the patient plasma, aPTT remains prolonged or improves by <50%. The diagnosis of AHA is then confirmed (decreased FVIII levels and evidence of FVIII inhibitors) by examination of the Bethesda test [14], [15]. The aPTT, prothrombin time, and complete blood count (CBC) are all used as screening tests for VWD. The CBC may be normal, but it may also reveal microcytic anemia (if the person is iron deficient) or thrombocytopenia, particularly in type 2B VWD. The aPTT is typically normal, however, it can become prolonged in severe cases of type 1 VWD, type 2N VWD, or type 3 VWD when the FVIII level falls to below 30–40 IU/dL (the normal range is about 50–150 IU/dL) [16]. In our case, the patient had recurrent bleeding with a prolonged aPTT and a low FVIII activity level; whereas vWD usually has bleeding manifestations without aPTT prolongation. Therefore, we did not test for ristocetin levels in our case.

In congenital hemophilia A, alloantibodies often completely inactivate FVIII in a linear way (type 1 or first-order kinetics) that is reliant on both concentration and time. In contrast, autoantibodies in AHA exhibit a rapid initial inactivation phase followed by a later equilibrium phase (type 2 kinetics), while some residual FVIII activity can be found *in vitro* even in the presence of high-titer inhibitors. Therefore, because of the intricate nonlinear pharmacokinetics of autoantibodies, the Bethesda assay may underestimate inhibitor potency in AHA when used *in vivo*. Thus, it is impossible to determine which patients with AHA are more likely to experience fatal bleeding episodes or to forecast the severity of bleeding events using FVIII activity or inhibitor titer [13].

As AHA development has been reported as a serious adverse reaction to certain drugs, recent

drug use should be carefully reviewed. Drugs that have been reported in published cases include antibiotics (such as penicillin, sulfonamides, and ciprofloxacin), immune-modifying drugs (interferon and fludarabine), psychotropic drugs (phenytoin, flupentixol, and zuclopenthixol), and the antiplatelet agent clopidogrel [9].

Regarding hemophilia treatment, the main priority is to control acute bleeding with bypassing agents. Activated recombinant factor VII and activated prothrombin complex concentrate [aPCC] are considered first-line treatment options for bleeding episodes in AHA patients. Both types of bypassing agents have been shown to be effective, although their relative efficacy has not been compared in trials [9], [13].

Only one aPCC product is currently offered in the United States – a freeze-dried sterile human plasma fraction with factor eight (VIII) inhibitor bypassing activity (FEIBA). Both FEIBA NF (anti-inhibitor coagulant complex, nano-filtered) and FEIBA VH are brand names for the product (anti-inhibitor coagulant complex, vapor heated) [17]. For FEIBA (aPCC), the dosage guidelines for drug administration are in the range of 50–100 units every 8–12 h through intravenous infusion; dosage should not exceed 200 units/kg in a 24 h period as this is associated with a higher risk of venous thromboembolism. Tranexamic acid should not be given concurrently with this agent. The efficacy of APCC plasma-derived products (FEIBA, Baxalta, Bannockburn, IL, USA) in AHA has been documented by various reports in the literature as well as a retrospective review of 34 patients. Overall efficacy of 86% was demonstrated when the treatment was used as a first-line option at a typical dose of 75 U/kg every 8–12 h [9].

The International AHA Recommendation (2009) advocates the use of human FVIII concentrate or desmopressin only if treatment with a bypassing agent is unavailable [13]. In our patient, we treated with human FVIII at a dose of 1000 mg (intravenously) due to the unavailability of bypassing agents at our institution (Dr. Wahidin Sudirohusodo Hospital).

In EACH2, the efficacy of treatment for the first bleeding episode was assessed in 288 patients, of whom 219 (76%) received bypassing agents and 69 (24%) received human FVIII or desmopressin. Patients given human FVIII concentrate or desmopressin had higher baseline FVIII levels, lower inhibitor titers, less bleeding, and received tranexamic acid more frequently. When comparing group matched score trends (n = 60 per group), significantly lower efficacy rates were observed for treatment with FVIII or desmopressin (68%), compared with bypassing agents (93%) [13].

While hemostatic agents are given to control bleeding episodes, some form of immunosuppressive treatment is also needed to suppress the production of the underlying inhibitory antibody. It is recommended that immunosuppressive therapy (IST) be initiated as soon as the diagnosis of AHA is established [9]. The usual treatment is prednisolone (prednisone) at a dose of 1 mg/kg, combined with cyclophosphamide at 50–100 mg/day, orally. Azathioprine is an alternative immunosuppressive agent. Treatment should be continued for up to 2 months, with routine control [9], [13].

The 2009 International AHA Guidelines also recommend IST in all AHA patients soon after diagnosis. This recommendation is based primarily on the high bleeding related mortality rate in the previous studies and the observation that early bleeding tendencies do not predict major or even fatal bleeding in later life. Initial treatment with corticosteroids alone or in combination with cyclophosphamide is recommended for up to 6 weeks, whereas second-line therapy with rituximab is recommended if first-line IST fails or is contraindicated [18], [19].

The Gesellschaft für Thromboseund Hämostaseforschung (GTH)-AH 01/2010 study protocol was designed as a variant of this recommendation and was the first IST protocol to be investigated prospectively. Patients were enrolled 7 days after starting IST, and follow-up data were collected weekly until complete remission was achieved [18].

Conclusion

Although VWD is the most frequent hereditary bleeding problem in females, other rare disorders such as AHA may be implicated. Clinicians should be aware of this when faced with patients that lack a history of bleeding disorders. Furthermore, AHA should be considered as a differential diagnosis in every female patient suffering from hemorrhage. Therefore, a comprehensive diagnostic approach is needed.

Ethical Approval

The study is exempt from ethical approval in our institution.

Consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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References

1. Shoukat HM, Ghous G, Tarar ZI, Shoukat MM, Ajmal N. Skewed inactivation of X chromosome: A cause of hemophilia manifestation in carrier females. Cureus. 2020;12(10):e11216. https://doi.org/10.7759/cureus.11216.
2. Stonebraker JS, Bolton-Maggs PH, Brooker M, Evatt B, Iorio A, Makris M, *et al*. The world federation of hemophilia annual global survey 1999-2018. Haemophilia. 2020;26:591-600. https://doi.org/10.1111/hae.14012.
3. World Federation of Hemophilia. Report on the Annual Global Survey 2017. Vol. 6. World Federation of Hemophilia; 2018. p. 3-74. Available from: https://www.wfh.org [Last accessed on 2021 Dec 29].
4. World Federation of Hemophilia, Report on the Annual Global Survey 2020, World Federation of Hemophilia; 2021. p. 3-17. https://www.wfh.org [Last accessed on 2021 Dec 29].
5. Siddiqi AA, Ebrahim SH, Soucie JM, Parker CS, Atrash HK. Burden of disease resulting from hemophilia in the US. Am J Prev Med. 2010;38(Suppl 4):S482-8. https://doi.org/10.1016/j.amepre.2009.12.016
   PMid:20331947
6. Lu Y, Xin Y, Dai J, Wu X, You G, Ding Q, *et al*. Spectrum and origin of mutations in sporadic cases of haemophilia A in China. Haemophilia. 2018;24(2):291-8. https://doi.org/10.1111/hae.13402
   PMid:29381227
7. Miller CH. The clinical genetics of hemophilia B (factor IX deficiency). Appl Clin Genet. 2021;14:445-54. https://doi.org/10.2147/TACG.S288256
   PMid:34848993
8. Sborov DW, Rodgers GM. How I manage patients with acquired haemophilia A. Br J Haematol. 2013;161(2):157-65. https://doi.org/10.1111/bjh.12228
   PMid:23373521
9. Giangrande P. Treatment of Hemophilia: Acquired Hemophilia. Montreal, Canada: World Federation of Hemophilia; 2012. p. 1-7.
10. Franchini M, Gandini G, Di Paolantonio T, Mariani G. Acquired hemophilia A: A concise review. Am J Hematol. 2005;80(1):55-63. https://doi.org/10.1002/ajh.20390
    PMid:16138334
11. Knoebl P, Marco P, Baudo F, Collins P, Huth-Kühne A, Nemes L, *et al*. Demographic and clinical data in acquired hemophilia A: Results from the European acquired haemophilia registry (EACH2). J Thromb Haemost. 2012;10:622-31. https://doi.org/10.1111/j.1538-7836.2012.04654.x
12. Sborov DW, Rodgers GM. Acquired hemophilia a: A current review of autoantibody disease. Clin Adv Hematol Oncol. 2012;10:19-27.
    PMid:22398803
13. Kessler CM, Knöbl P. Acquired haemophilia: An overview for clinical practice. Eur J Haematol. 2015;95(Suppl 81):36-44. https://doi.org/10.1111/ejh.12689
    PMid:26679396
14. Bakta IM. Acquired Hemophilia A: An Overview of Diagnosis and Management. WMJ. 2018;2:44. https://doi.org/10.22225/wmj.2.2.230.44-51
15. Collins P, Baudo F, Huth-Kühne A, Ingerslev J, Kessler CM, Castellano ME, *et al*. Consensus recommendations for the diagnosis and treatment of acquired hemophilia A. BMC Res Notes. 2010;3:161. https://doi.org/10.1186/1756-0500-3-161
    PMid:20529258
16. James PD, Goodeve AC. von Willebrand disease. Genet Med. 2011;13(5):365-376. https://doi.org/10.1097/GIM.0b013e3182035931
17. Awad NI, Cocchio C. Activated prothrombin complex concentrates for the reversal of anticoagulant-associated coagulopathy. P T. 2013;38:696-701.
    PMid:24391389
18. Tiede A, Collins P, Knoebl P, Teitel J, Kessler C, Shima M, *et al*. Giangrande, International recommendations on the diagnosis and treatment of acquired hemophilia A. Haematologica. 2020;105():1791-1801. https://doi.org/10.3324/haematol.2019.230771
    PMid:32381574
19. Huth-Kuhne A, Baudo F, Collins P, Ingerslev J, Kessler CM, Levesque H, *et al*. International recommendations on the diagnosis and treatment of patients with acquired hemophilia A. Haematologica. 2009;94(4):566-575. https://doi.org/10.3324/haematol.2008.001743
    PMid:19336751

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