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CASE REPORT

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Acquired Hemophilia A and urothelial carcinoma

Fadi Taza [a], Nawar Suleman [a], Robert Paz [b] and Christopher Haas [a,c]

[a]Department of Medicine, MedStar Health Internal Medicine Residency Program, Baltimore, MD, USA; [b]Department of Medicine, MedStar Health Hospitalist Program, Baltimore, MD, USA; [c]Georgetown University Medical Center, Washington, DC, USA

ABSTRACT

Acquired Hemophilia A (AHA) is a rare entity, resulting from the production of autoantibodies against Factor VIII of the coagulation cascade. These autoantibodies may develop in response to autoimmune conditions, drugs, neoplastic diseases, and pregnancy. Diagnosis involves clinical presentation, mucocutaneous or intramuscular bleeding, and laboratory findings, such as prolonged activated partial thromboplastin time, decreased levels of Factor VIII, and the presence of Factor VIII autoantibodies. The etiology is diverse, with a variety of underlying culprits. Malignancy-associated AHA has been associated with approximately 15% of cases. Urothelial malignancy-mediated AHA is exceedingly rare, with only two previously published reports. The management of AHA includes stabilization and control of bleeding via the use of hemostatic agents, and elimination of the inhibitor with immunosuppressive therapy. Here, we report a case of AHA secondary to urothelial malignancy and review the pathobiology and pathogenesis of Hemophilia A and AHA.

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1. Introduction

Hemophilia A is a well-recognized, albeit rare potentially life-threatening bleeding disorder classically characterized by spontaneous joint and muscle hemorrhage, ecchymoses, gastrointestinal bleeding, hematuria, and intracerebral hemorrhage. Of these, bleeding into the muscles and joints are pathognomonic of the disease. While the overwhelming majority of Hemophilia A cases are inherited in an X-linked recessive fashion with varying mutations in Factor VIII, there exists a rare Hemophilia A subset – Acquired Hemophilia A (AHA) – that is clinically indistinguishable from the classic, inherited form of Hemophilia A – that is characterized by the presence of inhibitory autoantibodies to Factor VIII [1]. AHA itself is more rare with an incidence of 1.3 to 1.5 cases per million per year [2]. While the etiology for AHA is diverse with a variety of underlying culprits – idiopathic, autoimmune disease, pregnancy, recurrent transfusion, malignancy [3] – malignancy-associated AHA has been associated with approximately 15% of cases [4,5]. Urothelial malignancy-mediated AHA is exceedingly rare, with only two previously published reports [6,7]. In this case report, we present a patient with AHA secondary to urothelial malignancy and review the pathobiology and pathogenesis of Hemophilia A and AHA.

2. Case presentation

A 76-year-old man with a history notable for hypertension, hyperlipidemia, and chronic obstructive pulmonary initially presented in to an outside facility with a chief complaint of hematuria. At that time, he remained hemodynamically stable and laboratory diagnostics were significant for a preserved hemoglobin and unremarkable metabolic panel. Urinalysis demonstrated marked hematuria. Coagulation studies were within normal limits; prothrombin time (PT) of 14 seconds (s) (reference value RV 11.8–14.6s), activated partial thromboplastin time (aPTT) of 36 s (RV 23.4–36.2s), and international normalized ratio of 1.3 (RV 0.8–1.4). Diagnostic workup included a Computerized Tomography cystogram which demonstrated the presence of a bladder mass, which was confirmed on cystoscopy, and he underwent Transurethral Resection of Bladder Tumor (TUBRT). On pathology, microscopic examination revealed non-invasive high grade papillary urothelial carcinoma with rare foci of invasion. His postoperative course was complicated by urosepsis secondary to Enterobacter cloacae managed with vancomycin and cefepime.

Five months later, the patient was admitted to our hospital non-traumatic ecchymosis. He reported usual health until approximately one week prior to presentation at which time he noted the spontaneous development of multiple discrete areas of bruising localized to his hands and upper extremities that

CONTACT Fadi Taza fadi.taza@medstar.net Department of Internal Medicine, MedStar Health Internal Medicine Residency Program, Baltimore, MD 21237, USA

appeared in a successive fashion over the course of the week and demonstrated various stages of ecchymosis-related changes. He noted no new exposures, trauma, nor medications, and denied a history of prior bruising. He denied bleeding from his gums, bright red blood per rectum, and melena. Physical examination demonstrated a hemodynamically stable elderly Caucasian male in no acute distress with multiple discrete areas of bruising along the abdomen, entire left forearm with varying degrees of healing as well as the left hand and a lesion along the right elbow. Laboratory diagnostics demonstrated a microcytic anemia (hemoglobin 6.3 g/dL (RV 12.-5–16.5 g/dL)), MCV 76 (RV 81–100)), elevated RDW (21.2 (RV 11.5–15.5)), reticulocyte hypoproliferation (reticulocyte index 0.89), and a hematocrit of 22.1%, for which he was transfused a single unit of packed red blood cells. His platelet count remained preserved (245 k/uL) and peripheral smear demonstrated an absence of schistocytes. The metabolic panel was unremarkable except for an elevated total bilirubin of 2.2 mg/dl (RV 0.2–1.3) and direct bilirubin of 0.61 mg/dl (RV 0–0.30), likely reflecting hematoma resorption. Coagulation studies revealed a mildly prolonged PT of 17.4 s, a markedly prolonged aPTT of 117s, INR of 1.4 and a preserved fibrinogen level of 416 mg/dL (RV 213–536 mg/dL). Mixing studies revealed an elevated PTT (89.4s) with failure to correct to the normal range upon 1:1 mixing of patient to normal pooled plasma (PTT 65s), suggesting the presence of an inhibitor. To determine whether the etiology was secondary to an autoimmune or viral etiology an extensive diagnostic workup was sent and resulted negative (Table 1). The coronavirus-19 Polymerase chain reaction was negative. Given the patients clinical presentation and abnormal mixing studies, the presence of a coagulation factor inhibitor was suspected. While Factor V, IX, and vWF levels were 60% (RV 70–140), 76% (RV 60–150), and 484% (RV 50–130) respectively, Factor VIII levels were found to be 1% (RV 55–175%). The Bethesda assay confirmed the diagnosis, demonstrating the presence of a Factor VIII inhibitor at 57 Bethesda Units (BU)/mL (RV < 0.5 BU). The patient was diagnosed with Acquired Hemophilia A.

Table 1. Autoimmune and viral workup results.

The direct antiglobulin test IgG	Negative
The direct antiglobulin test C3	Negative
Cardiolipin Antibodies (IgA)	Negative
The anti-double stranded DNA	Negative
Anti-smith antibody	Negative
Hepatitis A virus IgM	Negative
Hepatitis B virus Core IgM antibodies	Negative
Hepatitis B surface Antigen	Negative
Hepatitis C virus Antibodies	Negative
HIV-1/2 Antigen and Antibodies	Negative
Mononuclear Heterophile Test	Negative

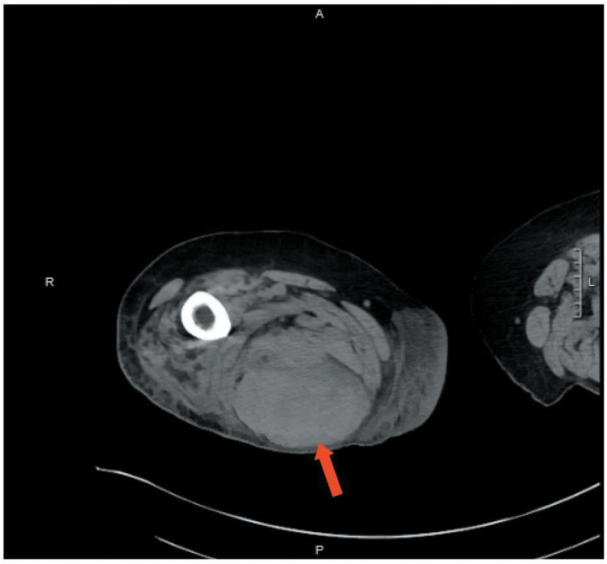

Figure 1. Computed Tomography of the lower extremities demonstrates a large intramuscular hematoma in the posterior right thigh.

Immunosuppressive treatment with prednisone 1 mg/kg daily was initiated and resulted in improvement in his aPTT to 73s from a peak of 133s and the patient was subsequently discharged. Unfortunately, four days post-discharge, the patient developed severe right thigh pain with an associated ecchymosis. Physical examination confirmed hematoma formation in the posterior right thigh and laboratory diagnostics were notable for worsening anemia with a hemoglobin drop from 8.3 g/dl to 6.8 g/dl. CT scan of lower extremities showed large partly intramuscular hematoma in the posterior right thigh measuring up to 10 × 8 x 27 cm (Figure 1). He was started on tranexamic acid 1300 mg three times/day and cyclophosphamide 1 mg/kg daily in addition to 100 mg daily prednisone. He was also treated with factor eight inhibitor bypassing activity (FEIBA) 100 mg/kg twice daily for 2 days. After two weeks his Factor VIII level remained persistently low <1%, and as a result cyclophosphamide was discontinued and he was initiated on intravenous Rituximab 375 mg/m2 weekly for 4 weeks. Following initiation of rituximab his Factor VIII level was noted to increase (59%) with an associated decline in his inhibitor to 4 BU and normalization of aPTT (34.9). His course was complicated by Escherichia coli bacteremia, which was treated with meropenem.

3. Discussion

Acquired Hemophilia A (AHA) is a rare bleeding disorder that is clinically indistinguishable from inherited hemophilia A, as both disorders are characterized by multiple sites of spontaneous, severe, and recurrent bleeding – muscles, joints, gastrointestinal,

and cerebral. Of these multiple sites, bleeding into the muscles and joints are pathognomonic. Of note, in contrast to hereditary Factor VIII deficiency, spontaneous hemarthroses are unusual in those with the acquired disease [3]. While the majority of Hemophilia A cases are inherited in an X-linked recessive fashion with variable degrees of penetrance dependent upon the underlying mutation, AHA in contrast, is typified by inhibitory autoantibodies against Factor VIII [8] While the mechanism of Factor VIII inhibitory autoantibody production remains unknown, a variety of predisposing factors – autoimmune disease, pregnancy, medications, and malignancy – have been idenfied [9], with solid organ malignancy-mediated AHA a rare etiology [4,5]. Indeed only a limited number of reports regarding malignancy-associated AHA have been published. When considering the types of malignancy associated with AHA, prostate and lung cancer were the most commonly associated solid tumors, while lymphoproliferative disorders were the most predominant hematologic malignancies [10]. To date, only two previously published reports on urothelial malignancy-associated AHA [6,7].

While there exist a variety of potential etiologies of new onset bleeding in individuals with underlying malignancy, including de novo thrombocytopenia and disseminated intravascular coagulation, clinical presentation and laboratory diagnostics assist in determining the underlying etiology. In cases of AHA, clinical evaluation demonstrates spontaneous bleeding with laboratory diagnostics demonstrating an isolated prolongation of the aPTT, secondary to diminished levels or activity of Factor VIII, with a normal PT and platelet count. While the etiology of isolated aPTT is diverse – deficits of the intrinsic clotting cascade (Factor VIII, IX, XI, or XII deficiency or inhibitors), von Willebrand Factor deficiency, or heparin product use – the use of mixing studies as well as detection of specific inhibitors confirms the diagnosis. In patients with factor deficiency or von Willebrand disease, the mixing of patient plasma to pooled normal plasma results in aPTT correction, whereas persistent prolongation of the aPTT indicates the presence of an inhibitor. To further establish the diagnosis, in this case of an acquired Factor VIII inhibitor, the Bethesda assay confirms the diagnosis. Indeed, the patient presented here demonstrated the presence of spontaneous bleeding with an associated aPTT prolongation without concomitant abnormalities in PT, INR, platelet count, or fibrinogen, and was found to have mixing studies suggestive of inhibitor presence and was ultimately found to have AHA based upon the Bethesda assay.

AHA is an autoimmune disease caused by the production of neutralizing Immunoglobin G (predominantly IgG1 and IgG4) autoantibodies targeting A2, A3, or C2 domains of the endogenous Factor VIII, blocking its interactions with active Factor IX, phospholipids, and von Willebrand Factor [11]. It is associated with various autoimmune diseases, pregnancy, cancer or drug ingestion; however, in 50% of patients, no underlying disorder is found [3]. Data from multiple studies emphasizes the association of certain genetic polymorphisms (e.g. HLA, CTLA4), as well as the importance of autoreactive CD4 + T lymphocytes in the generation of the Factor VIII inhibitors [12,13]. The causal relationship and underlying mechanism by which cancer induces neutralizing autoantibodies to Factor VIII have not yet been elucidated due to the rarity of the disease and the paucity of data regarding malignancy antigen-associated immunological cross-reactivity with Factor VIII. It has been hypothesized that the tumor microenvironment triggers local micro-inflammation and an altered antigen presentation process that activates an adaptive immune response [14].

In this case report, the patient developed a Factor VIII inhibitor following the diagnosis of an underlying papillary urothelial carcinoma. Multiple prior studies have demonstrated an association between AHA and an underlying malignancy in approximately 15% of cases [5]. In a review of 105 patients with AHA and associated solid tumors, prostate (25.3%), lung (15.8%), and colon cancers (9.5%) had the highest associated rates, whereas urothelial malignancy was exceedingly rare (2%) [15]. Of note, however, multiple other associations have also been noted in the literature, including sepsis-mediated [7,16,17] and idiopathic-mediated [18] Factor VIII inhibitor formation, and in the setting of the patients diagnosis of urosepsis shortly following his TURBT as well as his age, these alternative etiologies could not be completely ruled out. Nevertheless, the temporal relationship between the discovery of his papillary urothelial papillary carcinoma and his presentation suggest at least a causal association.

The management of AHA consists of a two-tiered strategic approach targeting initial patient stabilization and control of bleeding, with the use of hemostatic agents, and elimination of the inhibitor, with the use of immunosuppressive therapy. The determination of which agents to use is based upon clinical and laboratory assessment, specifically the severity and site of bleeding at presentation, responsiveness to the initial treatment, and Factor VIII inhibitors levels. Intriguingly, while Human Factor VIII replacement is not considered effective in patients with high titers of Factor VIII inhibitors (>5 BU/ml) [19], however the use of porcine Factor VIII replacement was found to be effective in achieving therapeutic Factor VIII levels and hemostasis even in the presence of high inhibitor titers [20]. Activated prothrombin complex concentrates (aPCC e.g., factor

eight inhibitor bypassing activity [FEIBA]), and recombinant human Factor VIIa (rFVIIa) can also be used to achieve hemostatsis [21]. Desmopressin (DDVAP) is of limited utility in AHA and should be reserved for minor bleeding in patients with low inhibitor titers (<2 BU/ml) [22]. Tranexamic acid in combination with either aPCC or rFVIIa has been shown to normalize clotting ability with no adverse events observed [23]. The second objective, elimination of the Factor VIII inhibitor, is targeted by the use of immunosuppressive therapy. First line recommended treatment includes corticosteroids, alone or in combination with cyclophosphamide or rituximab. In a large retrospective analysis, the outcomes of various immunosuppression regimens in 331 subjects enrolled in the European Acquired Hemophilia Registry, complete remissions (ie, undetectable inhibitor levels, factor VIII levels >70 International units/mL, and cessation of immunosuppression) were noted in 48, 70, and 59% of those treated with glucocorticoids alone, glucocorticoids plus cyclophosphamide, and glucocorticoids plus rituximab, respectively [24]. A meta-analysis of 249 patients concluded that cyclophosphamide, with or without corticosteroids, was more effective in achieving complete remissions comparing to corticosteroids alone [25]. Multiple case reports and retrospective studies have described patients with acquired hemophilia refractory to first-line immunosuppressive treatments who subsequently responded to rituximab [26]. In cases of malignancy-associated AHA, a retrospective analysis demonstrated that successful treatment of the underlying malignancy with chemotherapy or surgery was associated with eradication of the acquired Factor VIII inhibitor [27].

4. Conclusion

In conclusion, while Hemophilia A is a well-recognized X-linked recessive disorder of coagulation of variable penetrance that impairs the intrinsic coagulation cascade and leads to classic findings such as hemarthrosis, Acquired Hemophilia A is a pathological mimic, characterized by the presence of a specific inhibitor. While the underlying etiologies of AHA are diverse and the pathophysiology is poorly understood, it is hypothesized that the autoantibody production in patients with malignancies results from a complex interplay of host genetic predisposition and activation of both cell-mediated and humoral immune systems by tumor cells. Despite the poorly understood physiology, laboratory diagnostics in both Hemophilia A and AHA demonstrate a prolonged aPTT with normal platelets, but differ in their response to plasma mixing studies, with failure of AHA to correct with normal plasma, due to the presence of an inhibitor. Thus, management of these two similar, albeit drastically different disease entities, consists of patient stabilization and provision of factors. For AHA, however, the use of immunosuppression is required to limit autoantibody production. In this report, we present the case of presumed papillary urothelial cell carcinoma-mediated AHA and highlight the presumed pathophysiological mechanisms of the disease and its management.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Fadi Taza http://orcid.org/0000-0002-6478-8170
Nawar Suleman http://orcid.org/0000-0001-6537-7472

References

[1] Green D, Lechner K. A survey of 215 non-hemophilic patients with inhibitors to factor VIII. Thromb Haemost. 1981;45(3):200–203.
[2] Collins PW, Hirsch S, Baglin TP, et al. Acquired hemophilia A in the UK: a 2-year national surveillance study by the UK Haemophilia centre doctors' organisation. Blood. 2007;109(5):1870–1877.
[3] Knoebl P, Marco P, Baudo F, et al. Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). J Thromb Haemost. 2012;10(4):622–631..
[4] Reeves BN, Key NS. Acquired hemophilia in malignancy. Thromb Res. 2012;129(Suppl):S66–8.
[5] Cohen AJ, Kessler CM. Acquired inhibitors. Baillieres Clin Haematol. 1996;9(2):331–354.
[6] Onitilo AA, Skorupa A, Lal A, et al. Rituximab in the treatment of acquired factor VIII inhibitors. Thromb Haemost. 2006;96(1):84–87..
[7] Kreuter M, Retzlaff S, Enser-Weis U, et al. Acquired haemophilia in a patient with gram-negative urosepsis and bladder cancer. Haemophilia. 2005;11(2):181–185.
[8] Ma AD, Carrizosa D. Acquired factor VIII inhibitors: pathophysiology and treatment. Hematol Am Soc Hematol Educ Program. 2006;432–437. DOI:10.1182/asheducation-2006.1.432
[9] Kruse-Jarres R, Kempton CL, Baudo F, et al. Acquired hemophilia A: updated review of evidence and treatment guidance. Am J Hematol. 2017;92(7):695–705..
[10] Sallah S, Wan JY. Inhibitors against factor VIII in patients with cancer. Analysis of 41 patients. Cancer. 2001;91(6):1067–1074.
[11] Franchini M, Lippi G. Acquired hemophilia A. Adv Clin Chem. 2011;54:71–80.
[12] Oldenburg J, Zeitler H, Pavlova A. Genetic markers in acquired haemophilia. Haemophilia. 2010;16(Suppl 3):41–45.
[13] Pavlova A, Zeitler H, Scharrer I, et al. HLA genotype in patients with acquired haemophilia A. Haemophilia. 2010;16(102):107–112.

[14] Sakurai Y, Takeda T. Acquired hemophilia A: a frequently overlooked autoimmune hemorrhagic disorder. J Immunol Res. 2014;2014:320674.
[15] Napolitano M, Siragusa S, Mancuso S, et al. Acquired haemophilia in cancer: A systematic and critical literature review. Haemophilia. 2018;24(1):43–56.
[16] Yamamoto K, Niiya K, Shigematu T, et al. Transient factor VIII inhibitor in a hemophilia patient after staphylococcal septic shock syndrome. Int J Hematol. 2000;72(4):517–519.
[17] Laporte F, Cestac P, Favre V, et al. Treatment of a septic patient with acquired haemophilia. La Rev Med Interne. 2003;24(10):692–695.
[18] Borg JY, Guillet B, Le Cam-Duchez V, et al. Outcome of acquired haemophilia in France: the prospective SACHA (Surveillance des Auto antiCorps au cours de l'Hémophilie Acquise) registry. Haemophilia. 2013;19(4):564–570..
[19] Nemes L, Pitlik E. New protocol for immune tolerance induction in acquired hemophilia. Haematologica. 2000;85(10 Suppl):64–68.
[20] Kruse-Jarres R, St-Louis J, Greist A, et al. Efficacy and safety of OBI-1, an antihaemophilic factor VIII (recombinant), porcine sequence, in subjects with acquired haemophilia A. Haemophilia. 2015;21(2):162–170.
[21] Baudo F, Collins P, Huth-Kühne A, et al. Management of bleeding in acquired hemophilia A: results from the European Acquired Haemophilia (EACH2) registry. Blood. 2012;120(1):39–46.
[22] Franchini M, Lippi G. The use of desmopressin in acquired haemophilia A: a systematic review. Blood Transfus. 2011;9(4):377–382.
[23] Tran HTT, Sørensen B, Rea CJ, et al. Tranexamic acid as adjunct therapy to bypassing agents in haemophilia A patients with inhibitors. Haemophilia. 2014;20 (3):369–375..
[24] Collins P, Baudo F, Knoebl P, et al. Immunosuppression for acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). Blood. 2012;120(1):47–55..
[25] Delgado J, Jimenez-Yuste V, Hernandez-Navarro F, et al. Acquired haemophilia: review and meta-analysis focused on therapy and prognostic factors. Br J Haematol. 2003;121(1):21–35.
[26] Franchini M, Lippi G. Acquired factor VIII inhibitors. Blood. 2008;112(2):250–255.
[27] White KT, Aggarwal A, Napolitano M, et al. Autoantibody inhibitor eradication in acquired hemophilia associated with cancer: a retrospective analysis. Blood. 2010;116(21):1418.