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## Case Report

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### Spontaneous Bleeds: Acquired Hemophilia a in Malignancy

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#### Abstract

Acquired haemophilia A due to factor VIII antibodies development is a rare entity seen in association with malignancy. It usually presents as spontaneous bleeding in subcutaneous tissue resulting in the limb or threatening conditions. We described one such case with emphasis on early diagnosis, the diagnostic challenge that clinicians can face, factors affecting the outcome and review of the treatment options.

**Keywords:** Autoimmune hemolytic anemia; Breast cancer; Etiology; Spontaneous Bleeds

#### Abbreviations

AHA	:	Autoimmune hemolytic anemia
Aptt	:	Activated partial thromboplastin time
Hgb	:	Hemoglobin
FEIBA	:	Factor Eight Inhibitor Bypassing Activity
UA	:	Urinalysis

#### Introduction

Acquired hemophilia A due to factor VIII antibodies development is a rare entity seen in association with malignancy. It usually presents as spontaneous bleeding in subcutaneous tissue resulting in the limb or life threatening conditions. We described one such case with emphasis on early diagnosis, the diagnostic challenge that clinicians can face, factors affecting the outcome and review of the treatment options.

#### Case Discussion

A 71-year-old female with a past medical history of breast cancer (in remission), diabetes, hyper lipidemia, presented with acute onset left hip pain for 2 days. Two weeks prior she noticed

easy bruising of her arms. No history of any trauma, use of blood thinner and bleeding disorder was reported. Right-sided mastectomy was done for breast cancer treatment. No history of bleeding disorder was present in the family.

She was scheduled to get a hysterectomy for her uterine lesions by a surgical oncologist in a few months.

Initial labs were notable for leukocytosis, stable hemoglobin (Hgb), thrombocytosis and positive urinalysis (UA), mildly elevated activated partial thromboplastin time (Aptt), elevated CA 19-9 levels. Imaging of left lower extremity did not reveal any acute fracture or dislocation. CT scan of the abdomen/ pelvis revealed large left retroperitoneal hematoma, extending from the inguinal region to spleen, approx. 11 cm inferior to the spleen and 7 cm in AP and transverse diameter. Uterus revealed irregular contour and cystic and solid abnormalities suggesting malignant changes. CT chest detected new multiple pulmonary nodules bilaterally suggesting the metastatic process.

Due to urinary retention and positive UA, treatment for urinary tract infection (UTI) was started with ceftriaxone which was later changed to cefepime. The next day, 4 units drop in Hb was noted without any evidence of visible bleed. Prolonged Aptt was noted. Blood and fresh frozen plasma were transfused. CT abdomen/pelvis showed worsening retroperitoneal hematoma. RBC tag study was negative for any gastrointestinal bleed. IR was

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consulted however no intervention was done given the idea that retroperitoneal bleeds resolved on its own and risk of contrast-induced nephropathy. Meanwhile, Aptt continued to get worse. The mixing study failed to correct Aptt. Blood workup revealed the presence of factor VIII inhibitor presence, low factor VIII activity (2%) with high Bethesda unit (1.8).

Treatment was started with steroids and recombinant factor VII (Novo 7). Repeat CT scan showed a decrease in hematoma size. A total of 12 blood transfusions, 1 fresh frozen plasma, and 1 cryoprecipitate were used over 2-week period to keep Hgb stable.

Surgery and lung biopsy was held due to high bleeding risk. The patient was transferred to a higher level of care to rule out concurrent coagulation factor inhibitors and for further workup of uterine malignancy and pulmonary nodules.

## Discussion

Acquired hemophilia is defined as hemorrhagic coagulopathy that develops as a result of neutralizing antibodies or inhibitors against factor VIII. Acquired factor VIII has an annual incidence of 1-4 per million people per year, with a mortality rate of 41%.

Its association with malignancies is described in 10-15% of cases. Other etiologies include autoimmune disorders e.g SLE, Sjogren's, rheumatoid arthritis (14%), pregnancy (9%), postpartum, drugs, respiratory diseases (asthma, COPD). In 50% of cases, no underlying etiology is found. In 80% of cases, patients are >60 years old.

10% of cases have been associated with solid tumours while the rest of the reports are associated with hematologic malignancies. In the majority of patients, the onset of bleeding is sudden, spontaneous, however, in 25% cases, the onset is seen after trauma or invasive procedure. Majority of patients present after a major bleeding event (65%) [1].

The development of these inhibitors likely represents an autoimmune response to tumor antigens that resemble FVIII. These inhibitors good respond to the autoimmune treatments further strengthen the autoimmune pathophysiology. The development of FVIII autoantibodies may be an epiphenomenon, given the predominance of acquired FVIII inhibitors in the elderly, among whom cancer is also relatively common [2].

Theories explaining immune dysfunction have been well defined in hematologic malignancies. It is thought that immune dysfunctions result from either an abnormal T - cell response to an unknown antigen or an abnormal interaction between T and B cells lead to the development of autoantibodies to FVIII. For example, the leukemic clone of neoplastic B cells in chronic lymphocytic leukemia and lowgrade lymphoma, respectively, may mediate the generation of an abnormal FVIII molecule or another similar antigen by unknown mechanisms, eliciting an antibody response against normal FVIII. In the setting of malignancy, abnormal regulation of T lymphocytes, particularly the CD4<sup>+</sup> subset, may impact the normal processes of recognizing foreign antigens and monitoring antibody production from B lymphocytes, ultimately leading to the production of antibodies that target FVIII. In the case of plasma cell malignancies, such as multiple myeloma, associated paraproteins may affect the activity of coagulation

factors, including FVIII, although this is the result of abnormal monoclonal immunoglobulin M (IgM) proteins forming a complex with the coagulation factor, not an inhibitor. Because acquired FVIII inhibitors are polyclonal IgG antibodies, the antibody structure may be used to determine whether decreased FVIII activity in such malignancies is the result of associated paraproteinemia or the development of an acquired inhibitor.

The presence of cancer portends a poor prognosis in patients with AHA. The most common solid cancer associated with AHA is prostate cancer followed by lung cancer. Other cancers describe in the literature associated are gastric cancer, hepatocellular carcinoma. In most cases, the diagnosis of cancer predates or is concurrent with the bleeding disorder [3].

More than 80% of patients diagnosed with an anti - FVIII autoantibody present with bleeds involving the skin, muscles, or other soft tissues, or mucosal surfaces of the nasal, gastrointestinal, or genitourinary tracts. Retroperitoneal bleeding occurs in 20% of cases. Retropharyngeal, retroperitoneal, or intracranial hemorrhages are largely responsible for the relatively high morbidity Reason being the blood loss itself or complications of bleeding in those anatomic sites (e.g airway obstruction resulting from retropharyngeal bleeding).

Lab workup for acquired FVIII inhibitors usually reveal isolated prolongation of activated partial thromboplastin time (aPTT), with a normal prothrombin time (PT), thrombin time, and platelet count Such lab profile eliminates other clinically relevant thrombocytopenia, platelet dysfunction, DIC, and advanced liver diseases.

Other causes of an isolated prolonged aPTT include heparin effect, which can generally be ruled out based on a history of any exposure to heparin and/or an appraisal of sampling techniques, and lupus anticoagulant which usually manifest in the form of thromboembolic complications rather than bleeding. A mixing study combining the patient's plasma with a similar volume of normal plasma indicates whether the prolonged aPTT is the result of an intrinsic factor deficiency or an inhibitor. Of note, FVIII inhibitors are time (and temperature) dependent so the aPTT may initially decrease or, rarely, normalize when mixing normal plasma with that from a patient with a FVIII inhibitor.

Therefore, incubation for at least 2 hours is recommended when testing for an FVIII inhibitor. If the aPTT remains prolonged or increases after 1 hour of incubation, an inhibitor is the most likely cause. Lupus anticoagulant is also checked to rule out false prolongation by the presence of the antiphospholipid syndrome. The inhibitor titer is expressed in Bethesda units. One Bethesda unit is defined as the amount of inhibitor that will inactivate 50% of normal FVIII activity in a mixture of normal plasma and patient plasma after incubation at 37°C for 1 to 2 hours. However, the inhibitor titer may not reliably predict bleeding risk or response to treatment, particularly FVIII replacement, in patients with acquired FVIII inhibitors due to in-vivo inhibition of circulating factor VIII by antibodies which is in contrast to patients with congenital hemophilia A and inhibitors [2].

Our patient had isolated prolong aPTT along with lupus anticoagulant positive. But mixing studies and measurement of the factor VIII confirmed the acquired hemophilia A.

Numerous studies conducted on a cancer patient with acquired hemophilia revealed that higher eradication of the antibodies was achieved once the underlying cancer is treated by chemotherapy or surgery or hormonal therapy with disappearance in 22% cases. Also, recurrent antibodies indicate a relapse of underlying malignancy [4,5].

Due to the rarity of the condition, diagnosis is often delayed resulting in poor outcomes in a population who are already at risk due to advanced age, are friable and are suffering from cancer.

The management of AHA involves the control of active bleeding and specific therapies to eliminate the FVIII-inhibitor. The bleeding management can be done with homeostatic agents such as the FVIIa bypassing agents, namely, Factor Eight Inhibitor Bypassing Activity (FEIBA®, Baxter Healthcare Corporation, USA) or recombinant human (rh) FVIIa (Novo Seven; Novo Nordisk A/S, Bagsvaerd, Denmark). The activated prothrombin complex concentrate (aPCC), vasopressin (DDAVP), and FVIII concentrate. In most cases, rFVIIa and aPCC have greater efficacy than human FVIII or DDAVP in achieving hemostasis and are considered the treatment of choice [3].

Recombinant factor VII agent achieves hemostasis by generating thrombin in the absence of FVIII at the site of bleeding. While FEIBA has a longer half-life of 4-7 hours, the half-life for rhFVIIa is approximately 2 hours. Neither of these agents has a reliable biomarker that correlates with clinical efficacy, and bleed containment cannot be achieved in all patients. In addition, both agents are associated with the risk of thromboembolic events, especially in patients with AHA who are frequently older and have comorbidities.

RpFVIII was approved by the Food and Drug Administration in 2014 for rescue treatment of severe bleeding in AHA patients. It allows functional clotting FVIII while preventing inactivation by circulating human anti-FVIII antibodies. Therapeutic FVIII activity levels are generally achieved with goal FVIII levels >25% and maintained with intermittent rpFVIII administration until bleeding resolves. The advantages of this new therapy included no related serious adverse events, thrombotic events, allergic reactions, or thrombocytopenia in the registration study. In addition, the level of FVIII can be directly monitored to evaluate its efficacy. The major limitation is the cost and the fact that its efficacy is shown in a small study of 28 patients with little real-world experience available [6].

Steroids are the first-line treatment with the addition of cytotoxic medications if the need arises. Few studies reported a high remission rate of 70% with combine use of steroids and cytotoxic (cyclophosphamide) medications but at the expense of the high rate of sepsis 33% reported. Rituximab is the new drug that has been associated with a remission rate of 80% in studies [7].

Other novel therapeutic approaches include utilizing small inhibitory RNAs to disrupt the liver's generation of antithrombin III by disrupting the intrinsic pathway of coagulation or by utilizing an antibody (Concizumab) that binds tissue factor pathway inhibitor, which inhibits factor Xa. Recently, a Japanese trial is

testing Emicizumab (ACE910), a bispecific antibody and FVIII mimetic that acts by bringing activated factor IX and factor X together, mediating the activation of factor X and thus essentially mimicking the function of FVIII.

Immunoadsorption is another technique that has been used with good results in some small trials and individual cases. The advantage of immunoadsorption over plasmapheresis is the specific removal of the inhibitor without the removal of other clotting factors. Spontaneous remission is achieved in 11 patients out of 31 patients, who received no therapy other than supportive transfusions and factor VIII concentrate on an average of 14 months [8].

Our case is the first case of AHA in the setting of a gynecologic malignancy, that presents with a life threatening retroperitoneal hematoma and it was managed with Factor VII and steroids.

## Conclusion

The presence of diagnosed or undiagnosed malignancy is a risk factor to develop acquired deficiencies. It should be considered in a patient who presents with spontaneous hematoma and bruising and has of failure of Aptt correction with the mixing studies.

Given high mortality, prompt recognition and treatment are of crucial importance.

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