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CASE REPORT

Life-threatening hemorrhage from acquired hemophilia A as a presenting manifestation of prostate cancer

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Acquired factor VIII deficiency (acquired hemophilia A) is a rare condition characterized by the acquisition of autoantibodies that affect the clotting activity of factor VIII (fVIII). The most common manifestation in affected patients is a hemorrhagic diathesis. This disorder is associated with autoimmune diseases, pregnancy, postpartum period, drugs, and malignancy. Management of this condition begins with attempts to arrest an acute bleed based on the site and severity of bleeding and inhibitor titer. The next priority is eradication of the fVIII antibodies using immunosuppressive therapies. We report the case of a 66-year-old male who presented with spontaneous right thigh hematoma with prolonged activated partial prothrombin time and normal prothrombin time. Mixing studies confirmed the presence of an inhibitor. Further investigation for the underlying etiology of acquired hemophilia A leads to diagnosis of prostate cancer. Treatment consisted of bypassing agents including activated factor VII and activated prothrombin plasma concentrate to arrest the bleeding. Steroids and cyclophosphamide were added to suppress the fVIII inhibitors. Concomitant treatment of locally advanced prostate cancer with chemotherapy confirmed the eradication of the inhibitors. To our knowledge, this is the first reported case of prostate cancer diagnosed and treated simultaneously with acquired hemophilia A resulting in favorable patient outcome.

Keywords: *acquired hemophilia A*; *prostate cancer*; *activated factor VII*; *activated prothrombin plasma concentrate*

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Acquired hemophilia A (AHA) is a rare immune-mediated disease, which can affect any clotting factor, with factor VIII (fVIII) being the most common target of antibody formation. The annual incidence is 1–4 per million populations with a mortality rate of 8–22% in affected patients when left untreated (1–3). About 50% of these cases are idiopathic, while the rest are associated with autoimmune diseases, malignancies, pregnancy, medications, or dermatologic disease (1–6). Among cancer patients, AHA has been associated with solid tumors or hematologic malignancies (7).

The diagnosis is often made in the presence of prolonged activated partial thromboplastin time (aPTT) with normal prothrombin time (PT). Mixing studies confirm the presence of an inhibitor. Management of this condition begins with attempts to arrest an acute bleed based on the site and severity of bleeding and inhibitor titer (8). The next priority is eradication of the fVIII antibodies. Prednisone in combination with cytotoxic therapy such as cyclophosphamide has been recommended for the eradication of fVIII antibodies (9, 10). In this report, we present a rare case of locally advanced prostate cancer associated with AHA.

Case report

The patient was a 66-year-old male with a medical history of schizophrenia, who presented with a 1 month history of inability to ambulate secondary to right thigh pain and swelling that progressively worsened over 2 weeks. There was no history of trauma to the leg or intravenous drug abuse. The patient denied taking any prescribed or over-the-counter medications. There was no personal or family history of bleeding disorders. Physical examination was remarkable for hard and swollen right mid-thigh area. Computed tomography (CT) scan of right lower extremity showed heterogeneous enlargement of the musculature of the anterior compartment of the right thigh (Fig. 1) and an enlarged prostate (Fig. 2). Concern for compartment syndrome led to immediate surgical intervention and a large hematoma was evacuated from the right thigh. Tissue biopsy confirmed the diagnosis of hematoma. Postoperatively, the patient started bleeding profusely from the incision site, requiring multiple units of packed red blood cell transfusions and fresh frozen plasma for hemostasis as an emergency measure. Laboratory analysis revealed that aPTT was prolonged at 65 s (reference range 25–38 s) with normal PT 12.8 (reference range 11.7–13.9 s)

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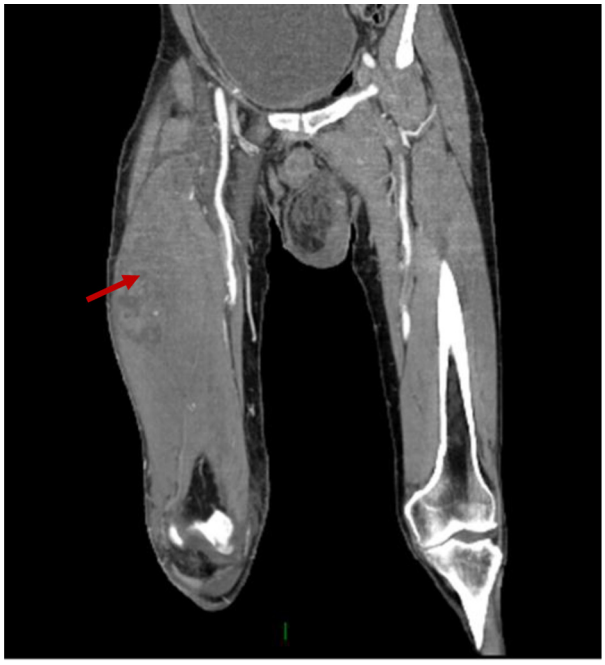

Fig. 1. Heterogeneous enlargement of the musculature of the anterior compartment of the right thigh consistent with hematoma (shown by red arrow).

and International normalized ratio (INR) 1.0 (reference range 0.9–1.1). Further investigation with mixing studies revealed time-dependent inhibitor of fVIII. fVIII inhibitor level was elevated at 140.9 Bethesda units (reference range $\leq$ 0.4) and fVIII activity was $<$1% of normal (reference range 50–180%), thus establishing a diagnosis of acquired fVIII deficiency. After confirmation of the diagnosis, hemostatic fVIII inhibitor bypassing agent recombinant activated factor VIIa (rfVIIa) was infused, however; the patient experienced recurrent bleeding requiring activated prothrombin complex concentrate (aPCC) to stabilize the bleed. Prednisone 1 mg/kg/day and cyclophosphamide 2 mg/kg/day were initiated in addition to supportive care to suppress the production of inhibitor.

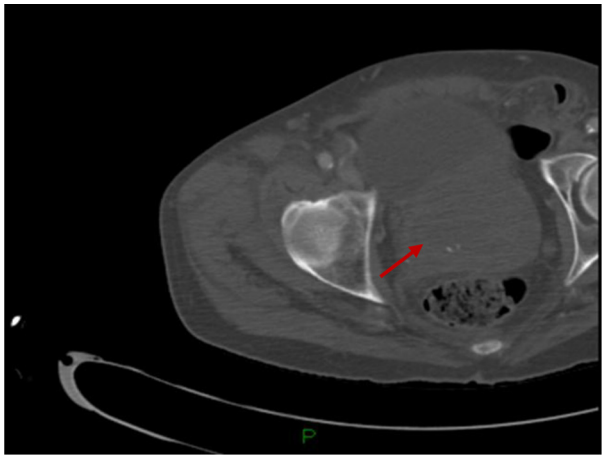

Fig. 2. CT finding of an enlarged prostate measuring 7.0 cm $\times$ 7.6 cm (shown by red arrow).

Further workup to diagnose the underlying etiology revealed significantly elevated prostate-specific antigen (PSA) level at 131 ng/ml (reference range 0.05–4 ng/ml), and a diagnosis of prostate cancer was made (11, 12). Serum human immunodeficiency virus, hepatitis panel, erythrocyte sedimentation rate, and antinuclear antibody were negative. In addition to normal alkaline phosphatase, CT scan of chest, abdomen, and pelvis with intravenous contrast did not show any evidence of bony metastasis or lymph node involvement. In light of high bleeding risk and patient's overall critical condition, decision was made to treat locally advanced prostate cancer with hormonal therapy alone. The patient was started on luteinizing hormone-releasing hormone analogue leuprolide and antiandrogen therapy with bicalutamide. The patient had a prolonged hospital course complicated by hemorrhagic shock, acute upper gastrointestinal bleeding secondary to severe erosive esophagitis, and small bowel obstruction. The patient continued to improve and was eventually discharged to a skilled nursing facility after 35 days of hospitalization.

Three weeks after the discharge, the patient was readmitted due to minor bleeding from the surgical wound, requiring one dose of aPCC and local application of aminocaproic acid. The patient was discharged in stable condition after 2 days of inpatient stay. The patient had a follow-up positron emission tomography–computed tomography (PET-CT) scan with F-18 fludeoxyglucose (FDG), which confirmed an irregularly enlarged prostate gland 5.5 cm $\times$ 5 cm (compared to 7.6 cm $\times$ 7.0 cm, 7 months ago) extending into inferior portion of urinary bladder, suggesting prostate cancer. There were not any hypermetabolic abnormalities elsewhere suggesting evidence of metastasis.

At 3 months follow-up, no further hemorrhagic episodes were noted. The patient's aPTT was 30.6 s and the PSA level (1.3 ng/ml) had normalized. FVIII inhibitor was non-detectable and fVIII activity level had increased to 170% (Table 1). The patient continues to remain asymptomatic with regular follow up in our outpatient hematology and oncology clinic.

Discussion

AHA is an extremely rare condition with age distribution of inhibitors being typically biphasic with a small peak between ages 20 and 30 years (due to postpartum inhibitors) and a major peak in patients of ages 68–80 years. The diagnosis of AHA is based on clinical history and laboratory investigations. It is distinct from classical inherited hemophilia, which is caused by deficiency of fVIII or factor IX that usually presents with hemarthrosis, whereas patients with AHA often present with soft tissue,

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Table 1. Time course of hemostasis parameters and serum PSA

Labs	Reference range	On admission	One month follow-up	Three months follow-up
FVIII activity	50–180%	<1%	50%	170%
FVIII inhibitor level	≤0.4	141	34	Non-detectable
aPTT	25–38 s	65	32	31
PSA	0.05–4.00	131	3.8	1.3

FVIII, factor VIII; aPTT, activated prothrombin thromboplastin time; PSA, prostate-specific antigen.

skin, muscle, or mucus membrane bleeds (1, 5, 7). Our patient presented with right thigh intramuscular hematoma that occurred spontaneously. Prolonged aPTT in the setting of skin or soft tissue bleeding should alert clinicians about the presence of an inhibitor to fVIII. Mixing studies, including Bethesda assay, confirm and quantify the presence of fVIII inhibitor, enabling the clinician to start immediate treatment.

Even though more than half of the cases are idiopathic, workup should target possible underlying etiologies such as malignancies, infections, and autoimmune disorders, as well as offending medications. AHA is associated with malignancies in 7–15% of cases, with the majority related to solid tumors. Our patient had significantly elevated PSA level (131 ng/ml) consistent with diagnosis of prostate cancer (11, 12). Treatment generally consists of achieving hemostasis, suppression of fVIII inhibitors, and treatment targeted at the underlying etiology, such as malignancy in our case. The cure of the associated disease sometimes leads to the eradication of the factor inhibitor (13).

The three-step approach for the management of patients with AHA and bleeding diathesis is presented in the following.

Hemostasis can be achieved by two approaches: the use of bypassing agents or raising fVIII level depending on the site and severity of bleeding. Two bypassing agents, rfVIIa and aPCC, have been used as first-line treatment.

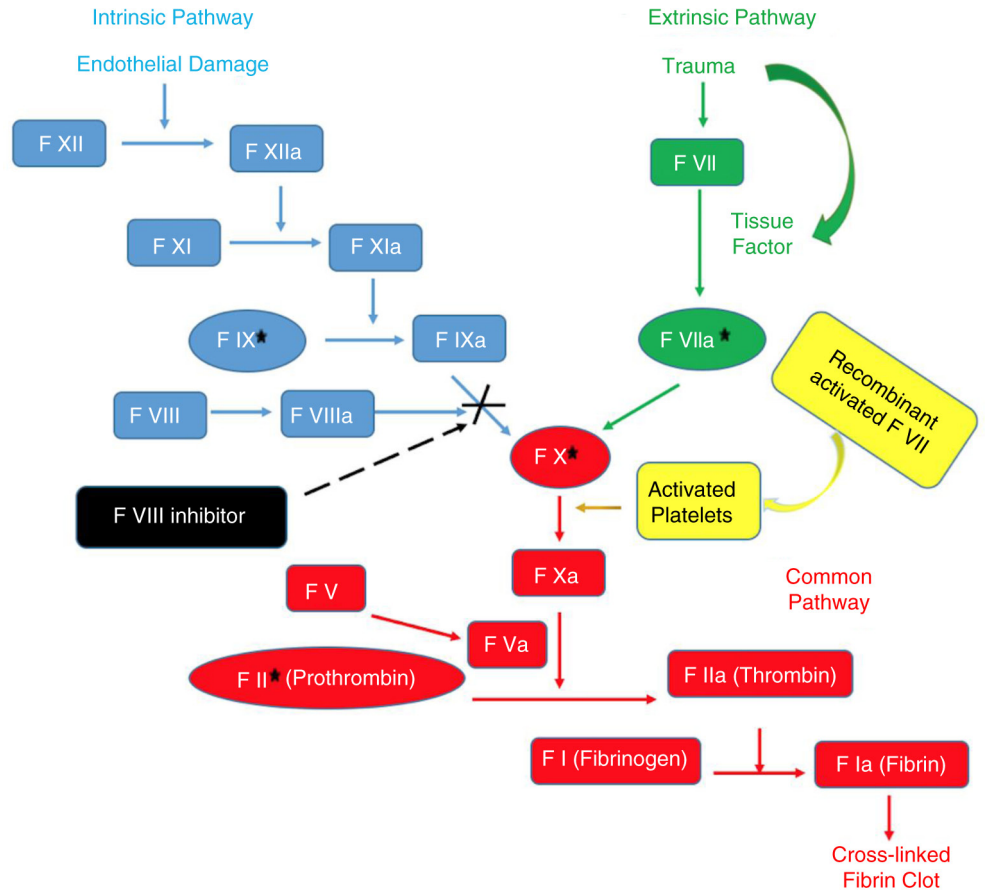

Fig. 3. Coagulation cascade. Factor VIII inhibitor blocking intrinsic pathway (shown by black box); mechanism of action of recombinant activated factor VII (shown by yellow blocks), which binds with activated platelets to activate factor X and generate factor Xa; activated prothrombin complex concentrate contains activated factor VII and inactivated factors II, IX, and X (shown by the symbol ★).

rfVIIa binds directly with activated platelets to activate factor X to produce factor Xa, activating common pathway, while aPCC contains four different coagulation factors, mostly activated factor VII and inactivated factors II, IX, and X (14, 15). Both products bypass the need for fVIII and activate common pathway to generate clot formation (Fig. 3). Retrospective studies have shown the overall efficacy rate for rfVIIa at 88% and for aPCC around 86% (16, 17). Patients with life-threatening bleeding and a very high titer level should be managed by rfVIIa or aPCC. In our patient, we were unable to achieve adequate hemostasis with rfVIIa; therefore, aPCC was used successfully to attain complete hemostasis (16–19).

Minor bleeding episodes with low titer level can be controlled by human or porcine fVIII concentrate or desmopressin, either alone or in combination. Fresh frozen plasma is often ineffective because of a very low level of fVIII concentration.

Suppression and eradication of fVIII inhibiting antibodies is achieved through immunosuppressive therapy as well as targeted therapy at underlying etiology. Immunosuppressive therapy includes steroids, cytotoxic drugs (e.g., cyclophosphamide, azathioprine, and rituximab), high-dose intravenous immunoglobulin, and immunoadsorption (9, 10, 20–22). Prednisone plus cyclophosphamide is considered a first-line treatment of AHA. The majority of evidence comes from case reports or retrospective studies. In the EACH2 study, stable complete remission was achieved with steroids plus cyclophosphamide in 70% of patients, compared to steroids alone (48%) or rituximab-based regimens (59%) (23). Only one randomized prospective trial on this patient population as well as few case series showed that oral steroid in combination with oral cyclophosphamide for 5 weeks was successful in achieving a complete remission (10). In our case, we used a combination of prednisone 1 mg/kg/day and cyclophosphamide 2 mg/kg/day for 5 weeks. Once the fVIII level was normalized and inhibitors were undetectable, cyclophosphamide was stopped and prednisone was tapered off. Concomitant treatment of locally advanced prostate cancer with hormonal therapy also improved the patient's survival.

In conclusion, this case demonstrates the importance of history taking, for instance, sudden onset of bleeding especially into the skin, soft tissues, mucus membranes, or muscles with no prior personal or family history of bleeding episodes (24) and quick analysis of coagulation panel with isolated prolonged aPTT and normal PT, as a delay in diagnosis and treatment can lead to life-threatening bleeding. As illustrated by our patient, concomitant treatment of underlying etiology, in our case prostate cancer, along with immunosuppressive therapy resulted in a favorable outcome.

Conflict of interest and funding

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