

Acquired factor VIII deficiency in prostate adenocarcinoma presenting as multiple hematomas and hemarthrosis

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Abstract

Acquired hemophilia A or acquired factor VIII deficiency is a rare bleeding disorder due to the presence of autoantibodies to factor VIII. It has been associated with autoimmune conditions, certain medications, and malignancy. It has a high morbidity and mortality, and early diagnosis and treatment is critically important. Acquired hemophilia A usually manifests with soft tissue bleeding, such as epistaxis, genitourinary, or gastrointestinal bleeding and rarely with hemarthrosis. In this case report, we present the management of an uncommon case of acquired hemophilia A in a patient with metastatic prostate adenocarcinoma who presented with both hemarthrosis and soft tissue bleeding. Bleeding was controlled with recombinant factor VIIa, factor VIII bypassing agent, and immunosuppressive therapy with prednisone and rituximab. Chemotherapy with docetaxel was also promptly initiated to address the underlying condition and achieve long-term remission, which is currently ongoing for 10 months.

Keywords

Biochemistry, hematology, internal medicine, oncology

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Introduction

Factor VIII deficiency, also known as hemophilia A, is an inherited lifelong bleeding disorder caused by an X-linked deficiency of factor VIII (FVIII). An acquired form of factor VIII deficiency or acquired hemophilia A (AHA) usually appears later in life due to the production of autoantibodies that either increase its clearance or decrease its activity. AHA is associated with autoimmune disease, medications and malignancy, occurring in 10%–15% of patients with solid tumors.^{1,2} There is high morbidity and mortality associated with AHA due to severe bleeding, most commonly in the skin, soft tissues, muscles, genitourinary or the gastrointestinal tract. Unlike congenital factor VIII deficiency, hemarthroses are rare in AHA.^{3,4} Bleeding is often a medical emergency and management is based on clinical findings as well as laboratory data.⁴ The cornerstone of therapy in AHA is to control the bleeding, reduce the autoantibody titers with immunosuppressive therapy, and initiate appropriate long-term therapy for the underlying condition, such as chemotherapy in malignancy. This case describes the diagnosis and management of AHA in a patient with metastatic castrate-resistant prostate cancer who

presented with spontaneous hemarthrosis and hematomas in the retroperitoneum and left thigh.

Case presentation

The patient is a 78-year-old Haitian man with a medical history of chronic kidney disease and metastatic castrate-resistant prostate adenocarcinoma. His stage IV prostate cancer was initially diagnosed in 2010 with metastasis to bones and retroperitoneal lymph nodes. He was managed with anti-androgen therapy and palliative external beam radiation therapy (EBRT) to the prostate due to obstructive uropathy until 2015 when he developed castrate-resistant disease.

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Figure 1. Rolled lateral X-ray view of the left knee showing suprapatellar joint effusion.

At that time he was treated with abiraterone which he received intermittently for 2 years, and later switched to enzalutamide in December 2017 due to progression of disease. He also received palliative radiation therapy to the right femur for bony metastasis at that time. Most recent scans in May 2018 showed further progression in the bones and lymph nodes, prompting discontinuation of enzalutamide with plans to start chemotherapy. When the patient was seen in the oncology clinic, he complained of knee pain and thigh swelling; he denied any trauma or history of previous knee pathology. Due to two recent hospitalizations, one for right forearm hematoma and a second for left thigh hematoma, and a recent elevated activated partial thromboplastin time (aPTT) (60s, normal range 22–29s), a coagulopathy was suspected and the patient was sent to the emergency department for management. Of note, the patient's hematomas during the previous episodes had resolved with supportive management. The patient's factor VIII activity level was found to be low at 8% (50–100) indicating acquired factor VIII deficiency. Factor VIII inhibitor level was subsequently obtained and found to be elevated at 34 Bethesda units (nL 0.0–0.5 BU).

On admission, the patient was hemodynamically stable and physical exam revealed a swollen, warm, and tender left knee with some tenderness in the distal inner thigh. Complete blood count (CBC) revealed a hemoglobin (Hb) of 7.5 g/dL (14–18 g/dL) and a platelet count (PLT) of 537/nL (130–400/nL). Prothrombin time (PT) was 10.1 s (10.4–12 s) and aPTT was 57.4 s (22–29 s). Left Knee X-ray revealed moderate suprapatellar joint effusion without bony destruction (Figure 1). Left lower extremity ultrasound showed 1.9 cm of fluid in the suprapatellar bursa with a 1.5 × 0.7 cm quadriceps muscle intramuscular hematoma (Figure 2(a) and (b)). Six hours after admission, the patient's Hb dropped to

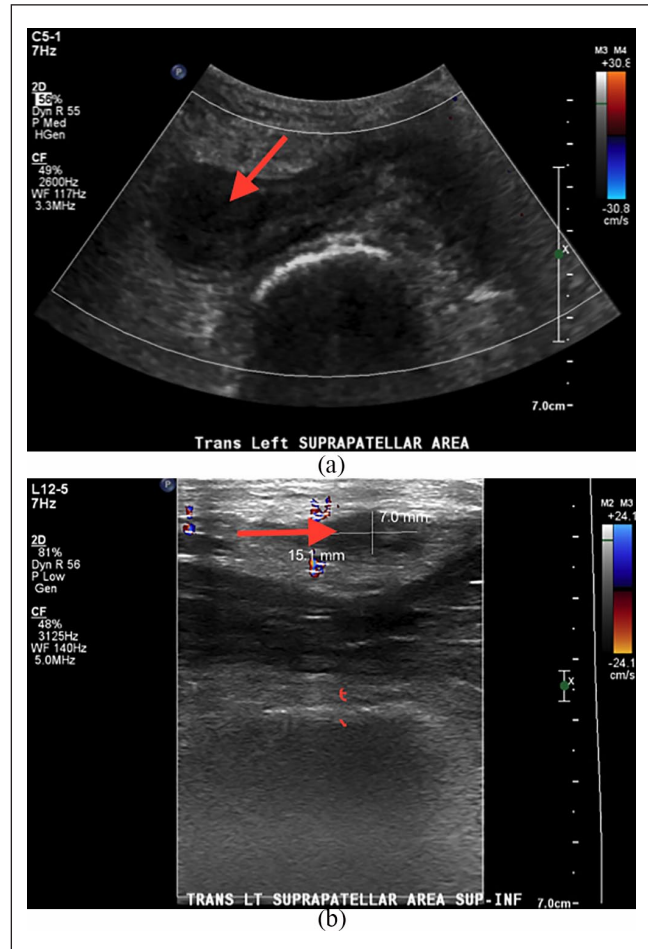


Figure 2. (a) Ultrasound of the left lower extremity showing fluid in the suprapatellar bursa; (b) ultrasound of an intramuscular hematoma in the quadriceps muscle.

6.5 g/dL and he received 2 Units (U) of packed red blood cells (PRBCs) and 1U of Prothrombin complex concentrate (PCC). At this time, immunosuppressive therapy with prednisone 1 mg/kg was initiated with a plan to continue for 6 weeks. Computed tomography (CT) of abdomen and pelvis showed resolving retroperitoneal hematoma measuring 2.4 × 2.9 cm (Figure 3) and magnetic resonance imaging (MRI) of the left lower extremity showed a 16-cm intramuscular hematoma of the inferior thigh and large suprapatellar hemarthrosis (Figure 4(a) and (b)). No surgical intervention was recommended. Twelve hours after the PRBC transfusion, the patient's Hb inadequately increased indicating ongoing bleeding, with another unit administered without any response. He was then started on standing recombinant factor VIIa (NovoSeven®), 90 µg/kg, every 3 h which was continued for 7 days (admission day (AD) 1–7) then switched (due to shortage) to factor eight inhibitor bypass activity (FEIBA), 50 units/kg, every 6 h (AD 7–9) when the half life of recombinant factor VIIa was completed, with taper to every 12 h (AD 9–12) until bleeding was adequately controlled.

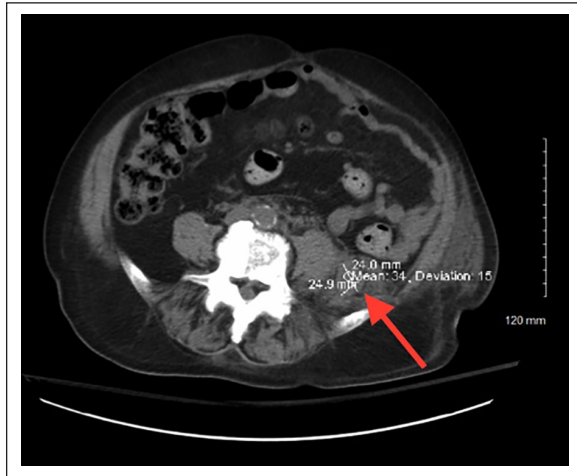


Figure 3. Non-contrast CT abdomen and pelvis showing 2.4 mm \times 2.9 mm left-sided retroperitoneal hematoma.

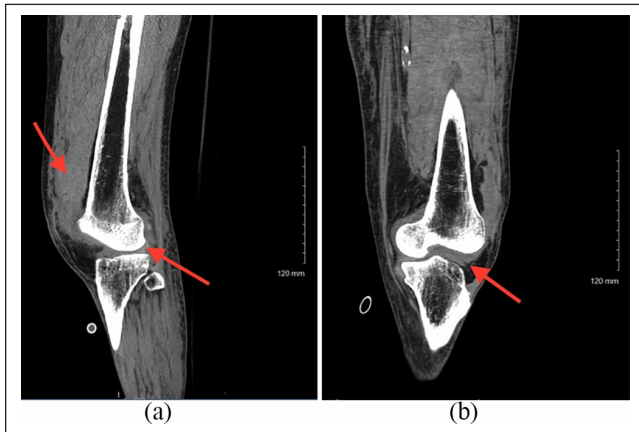


Figure 4. (a) Sagittal T1 weighted image visualizing left thigh hematoma and hemarthrosis; (b) coronal T1 weighted image visualizing left hemarthrosis.

While on FEIBA, he was also started on rituximab (AD 8). Over the course of his hospital stay, he remained hemodynamically stable and received a total of 7U of PRBCs (Table 1). His Hb stabilized between 8.5 and 9.5 g/dL, and factor VIII inhibitor level decreased to 12BU (AD 12) and subsequently to 0.9BU (AD 29). The patient was discharged after 13 days of hospitalization and completed 4 weekly cycles of rituximab. His PTT and Hb normalized by 41 days from admission (Figure 5) and he has remained in clinical remission for 9 months with no further episodes of recurrent bleeding. He continues to be on chemotherapy with docetaxel for his prostate cancer.

Discussion

AHA is a rare disease caused by factor VIII autoantibodies, most commonly associated with autoimmune conditions,

pregnancy, certain medications, dermatologic conditions, and malignancy, with an incidence rate of 0.2–1.48 per 1,000,000 population per year.^{5–7} Acquired factor VIII inhibitor has been previously reported in prostate cancer, often presenting as a life-threatening bleed.^{1–5,8} Remarkably, acquired factor VIII deficiency usually presents as soft tissue bleeding in contrast to the classic presentation of hemarthrosis in congenital hemophilia A.^{8–10} Given this patient had no other medical history other than chronic kidney disease, it is likely his AHA was associated with his malignancy. No etiology is known for the difference in bleeding between acquired and congenital hemophilia, and no demonstrable platelet impairment has been found.¹¹ Acquired factor VIII deficiency from prostate cancer has been associated more often with genitourinary hemorrhages compared with acquired factor VIII deficiency from other solid tumors or non-malignant diseases.¹² Often the sites of bleeding are related to iatrogenic causes, such as surgery, intravenous or intramuscular injections.^{13,14}

The diagnosis of AHA, or acquired factor VIII deficiency, is suspected based on the isolated prolongation of partial prothrombin time (PTT) that is not corrected by a mixing study (i.e. PTT remains elevated after adding normal plasma). The diagnosis is then confirmed with reduced Factor VIII activity and evidence of increased FVIII inhibitor level.⁵ The general principles for treatment involve eradicating the autoantibody and maintaining hemostasis.

Treatment of the underlying malignancy is advocated as a possible curative measure since the autoantibodies are present in the setting of uncontrolled or untreated cancer. However, immunosuppressive therapy is recommended for those patients who fail treatment of the primary tumor, or for those who present acutely with bleeding or are unable to receive chemotherapy.¹ The EACH2 study established standards in eradicating factor VIII autoantibodies, with first-line treatment of prednisone and cyclophosphamide (70% complete remission), and second-line treatment of rituximab (59% complete remission).¹² However, complete responses to rituximab alone have been noted in patients with high titer inhibitors in several small trials and case reports.¹⁵ In addition, a literature review of 65 patients with AHA treated with rituximab monotherapy at a dose of 375 mg/m²/weekly for 4 weeks showed a clinical response in 90% of the cases.¹⁶ In this patient, there was concern that cyclophosphamide could exacerbate bone marrow suppression and prevent scheduled administration of docetaxel in the future. Once his bleeding was under control, he received a dose of Docetaxel inpatient and continues to receive it on the outpatient setting.

While patients with congenital hemophilia A can be treated with Factor VIII concentrates, this is not recommended in acquired hemophilia A. For patients with high titer inhibitors, hemostasis can be established through bypassing the intrinsic coagulation cascade using the extrinsic pathway through agents like rVIIa or activated prothrombin complex concentrate (Factor VIIa, II, IX, X), factor eight

Table 1. Showing hemoglobin response after blood transfusions.

Dates	AM Hb	Units PRBC given	BP range	HR range
29 May 2018	7.9	0	99–126/64–71	68–73
30 May 2018	7.5	2	91–103/51–88	70–91
31 May 2018	6.9	2	91–107/49–51	83–91
01 June 2018	6.7	3	95–104/47–51	76–95
02 June 2018	8.6	0	99–128/52–58	66–80
03 June 2018	8.8	0	118–154/61–77	67–80
04 June 2018	8.9	0	122–130/62–68	68–71
05 June 2018	9.2	0	114–127/58–72	66–72
06 June 2018	9.1	0	106–120/57–64	71–85
07 June 2018	8.8	0	114–134/53–74	67–81

Hb: hemoglobin; PRBC: packed red blood cells; BP: blood pressure; HR: heart rate.

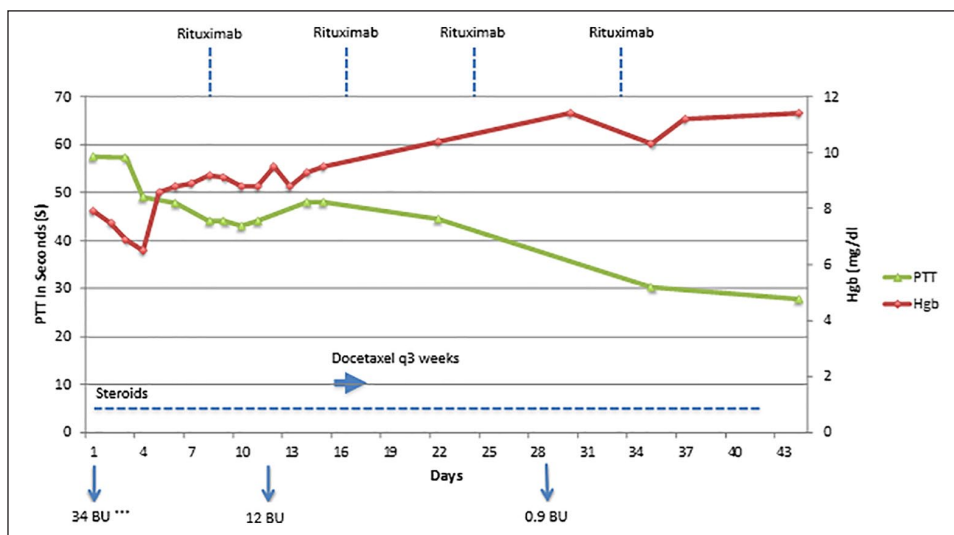


Figure 5. Graphic representation of Hb and PTT trend over time, with specific treatments received for factor VIII deficiency. ***Factor VIII inhibitor level in Bethesda Units (BU).

inhibitor bypassing activity (FEIBA), and switching if the other fails. However, for patients with low-titer inhibitors, treatment with porcine factor VIII concentrates can be considered.^{5,17} Bleeding can persist for days to weeks and inhibitors can recur even after successful initial elimination.¹⁷

The 2010 GTH study identified FVIII > 1% to have increased survival and improved rates of remission; however, among other factors, being male, age > 74 years, > 20 BU, and malignancy associated with poor overall survival.¹⁸ Although the GTH protocol of steroid alone and then adding either cyclophosphamide or rituximab on first-line therapy failure could be considered, in the setting of his poor prognostic indicators, symptomatic anemia refractory to transfusion and suspicion acute bleeding our goal was to treat him aggressively.

According to a systematic review of 47 cases of Factor VIII inhibitors in cancer patients, post-treatment inhibitor levels appeared to be the best prognostic indicator

with treatment responders (defined as >50% reduction in baseline Factor VIII inhibition level) having an overall survival of 41 months compared with 2 months for non-responders.¹⁹ In stratifying treatment response, a retrospective study of 41 cancer patients with AHA showed that 66% of non-responders had advanced or metastatic malignancy.¹

Providing costly care with these treatments to a geriatric patient with metastatic refractory cancer involves an evaluation of the multidimensional nature of aging in the clinical assessment. This includes the functional and cognitive domains of the patient, with constant evaluation of risk versus benefit. Although this patient had advanced prostate cancer, it was believed that if his AHA was controlled he may be able to receive treatment for his cancer with chemotherapy for another few years. As his baseline functional performance status was acceptable, aggressive therapy was chosen and all available treatments utilized.

Conclusion

This case report illustrates an unusual presentation of hemarthrosis in AHA, resembling that of congenital hemophilia A. With only a few documented cases of hemarthrosis in the setting of AHA, and, to our knowledge, few in the setting of malignancy, this presentation showcases a particularly challenging diagnosis of an uncommon condition. This case also demonstrates the successful elimination of acquired factor VIII inhibitors and the achievement of long-term remission with prednisone, rituximab, and chemotherapy for the treatment of the underlying metastatic castrate-resistant prostate cancer.

Author contributions

A.L. and J.J. managed the patient's care and drafted the manuscript. N.P. and B.B. contributed and assisted in the literature search and interpretation of the sources. A.L. finalized, evaluated, and edited the case report along with C.L. All authors have read and approved the final manuscript.

Declaration of conflicting interests

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Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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