Case – Acquired hemophilia A in a patient with metastatic castration-resistant prostate cancer

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Cite as: Poscente M, Gan CL, Heng DYC, et al. Case – Acquired hemophilia A in a patient with metastatic castration-resistant prostate cancer. *Can Urol Assoc J* 2021;15(9):E519-21 http://dx.doi.org/10.5489/cuaj.7089

Published online February 12, 2021

Introduction

Hematological abnormalities in patients with non-hematological malignancies are relatively common, with nearly 10% experiencing abnormal bleeding.[1,2] The etiology ranges from bone marrow suppression to more acutely life-threatening conditions such as disseminated intravascular coagulation (DIC) or trauma to highly vascularized neoplastic tissue.[3] Acquired hemophilia A (AHA) is a rare condition, with an incidence of 1.5 in 1 000 000 annually[4] and is associated with the development of autoantibodies to clotting factor VIII.[2] AHA can be caused by autoimmune disease, drug exposure, post-partum, and malignancies.[5]

Case report

A 62-year-old male with metastatic castrate-resistant prostate cancer (mCRPC) presented to emergency medical attention with a two-day history of swelling and bruising in the right hand in the context of four months of spontaneous bruising and a recent non-traumatic psoas muscle hematoma. His medical profile was significant for prostate cancer. Initial prostate biopsy four years prior to this presentation revealed intermediate-risk prostate adenocarcinoma with Gleason 4+3=7 disease and a pretreatment prostate-specific antigen (PSA) of 12.5 ug/L. He was treated with external beam radiotherapy and short-term androgen deprivation therapy (ADT) in the form of leuprolide acetate given subcutaneously (Fig. 1). Post-treatment toxicity included intermittent rectal bleeding. Biochemical recurrence of his prostate cancer occurred 17 months later and the patient was restarted on ADT, subsequently given continuously. He developed metastatic castrate-resistant disease and was commenced on abiraterone and prednisone 30 months after his initial diagnosis, with biopsy-proven lymphadenopathy. Eventually, the patient developed bone metastases and he was switched to second-line mCRPC therapy with docetaxel chemotherapy after being on abiraterone and prednisone for 16 months. Docetaxel was commenced at 75% dose for tolerability one month prior to his emergency room presentation.

The patient's presenting concern in the emergency department was significant bruising in his right hand (Fig. 2A). Two days prior to presentation, he noted opening a jar, which caused swelling, pain, and decreased range of motion. There was no epistaxis, hematemesis, melena, headaches, or focal neurological symptoms, and the small amount of rectal bleeding was unchanged. He did not have clinical features consistent with compartment syndrome. He noted gross hematuria three weeks prior, which had spontaneously resolved, with ongoing blood-tinged urine. There was no history of personal or familial hematological disorders. The patient had been finding it easier to bruise since January of 2020, with progression of severity. He was found to have an intramuscular psoas hematoma related to a ground level fall in May of 2020, which was conservatively managed.

His medications included acetylsalicylic acid 81 mg orally (PO) for a remote vertebral artery stroke, prednisone 5 mg PO twice daily (BID) started with the docetaxel, alendronate 70 mg weekly, hydromorphone as needed, pantoprazole 40 mg PO, and rosuvastatin 5 mg at bedtime, as well as calcium and vitamin D supplements. Vital signs were stable. Initial blood work revealed low hemoglobin of 63 g/L (137–180), normal international normalized ratio (INR) of 1.2, elevated partial thromboplastin time (PTT) of 63.4 seconds (28–38), elevated fibrinogen of 4.2 g/L (1.6–4.1), and elevated D-dimer at 4.85 mg/L (<0.5). DVT of the upper extremity was ruled out with ultrasound.

The patient was admitted to hospital for further workup and management, including red blood cell transfusions and tranexamic acid. Initially, the patient was managed with Factor VII 7 mg intravenous (IV) three times daily (TID) (90 mcg/kg)[6] with Factor VIII (FVIII) 7200 IU IV BID while awaiting hemostasis studies. Two days later, inhibitor to factor VIII was confirmed at a level of 11 BU/ml (Fig. 3). FVIII

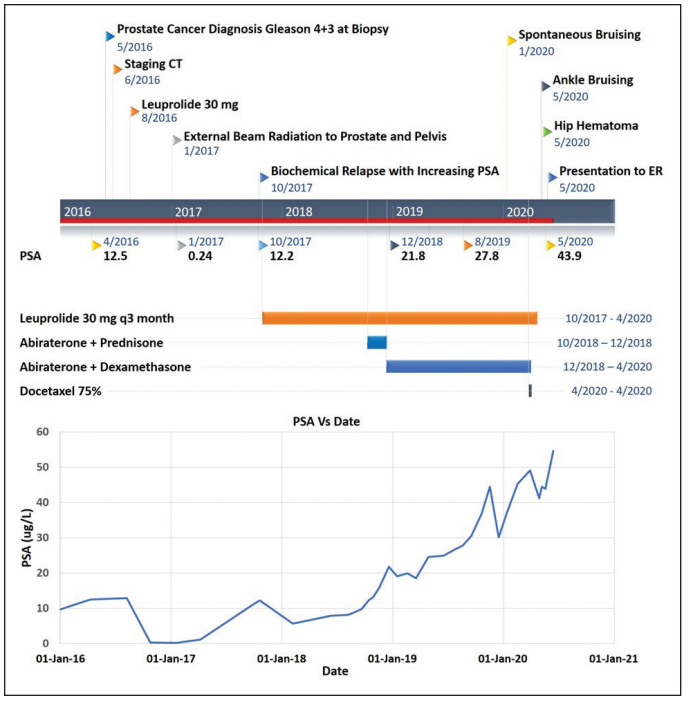

Fig. 1. Timeline of disease diagnosis, management, and progression. Serial prostate-specific antigen (PSA) measurements are presented in graph form.

3500 IU IV BID was given for four days. The patient was given prednisone 70 mg PO daily (1 mg/kg) for 11 days, 60 mg PO daily for 20 days, and 50 mg PO daily for 14 days. Rituximab 710 mg (375 mg/m x 2) was started one week after presentation due to a lack of improvement on steroids and was repeated every seven days three times.

As the perfusion of his hand improved, the bruising extended up the arm (Fig. 2B). The range of motion in his hand improved as swelling decreased. He developed further episodes of lower extremity hematoma after early physiotherapy, however, these improved as his clotting factors normalized and he returned to his baseline mobility. To treat his underlying malignancy, enzalutamide 160 mg was started once the patient was clinically stable and was continued as an outpatient. At discharge after three months of hospital stay, the patient was biochemically and physiologically stable on a prednisone taper, prophylaxis for Pneumocystis jirovecii pneumonia, enzalutamide 160 mg daily, tamsulosin 0.4 mg daily, and his other home medications. The patient ultimately did not respond to enzalutamide and was started on cabazitaxel chemotherapy with good clinical and PSA response; his factor VIII levels normalized (0.5–1.5 U/ml) and his inhibitor levels are nearly undetectable (Fig. 3).

Discussion

AHA is a rare and serious disease caused by the development of autoantibodies against factor VIII. Due to its rarity, the true incidence of acquired hemophilia is unknown. The

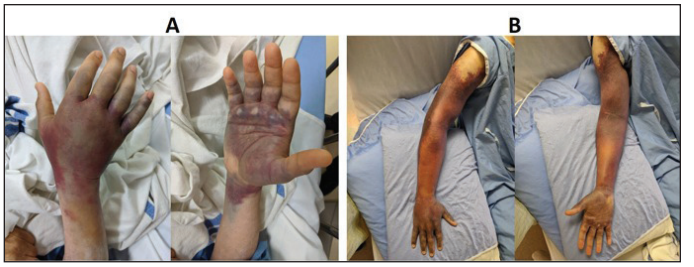

Fig. 2. (A) Initial bruising in the hand. ***(B)*** Progression of the bruising four days later.

best estimate of the incidence of AHA comes from a series of 172 patients in a two-year national surveillance study by the U.K. Hemophilia Centre Doctors' organization, where an incidence of 1.48 cases/million/year were reported.[4] In this series, underlying malignancy accounted for 15% of the cases, of which 2% (three patients) had prostate cancer. In another series of 41 patients with AHA, six patients were found to have underlying prostate cancer.[7]

There are numerous causes of abnormal bleeding in the cancer patient, and this case was complicated by long-term steroid use, ASA,[8] and recent commencement of chemotherapy, which initially was considered as a potential cause of the development of AHA. As in this case, patients with AHA often present with spontaneous mucosal bleeding, hematomas, or hematuria, and contrary to inherited hemophilia, hemarthrosis is rare.[9] Presentation may be related to surgery or interventions,[10] and rarely may represent initial presentation of malignancy.[11] In this case, the patient's progressive disease may have triggered the development of AHA. Most patients have a high response to immunosuppression, with a median time to remission of five weeks.[12] The mortality of AHA ranges from 17–22% of cases.[13] Survival outcomes are related to FVIII levels, while higher inhibitor concentration, age >74, male gender, and associated malignancy have been shown to be negative prognostic factors.[14]

The goal of treatment of AHA is to achieve hemostasis and eradicate antibodies.[15] Eradication is achieved with

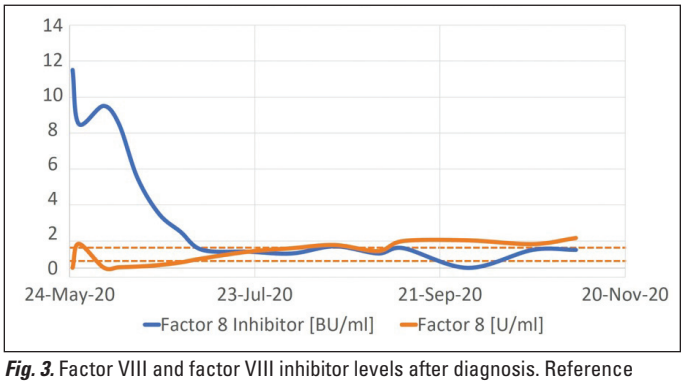

Fig. 3. Factor VIII and factor VIII inhibitor levels after diagnosis. Reference ranges for Factor VIII activity provided with dotted orange lines. In the case of the FVIII inhibitor, any activity is considered abnormal

immunosuppressive therapy, with the most common therapy being cyclophosphamide and steroids.[12] In this case, rituximab with steroids was chosen instead, given the patient's recent chemotherapy and the concern of added toxicities from further chemotherapy.[16] If possible, treating the underlying malignancy eradicates FVIII antibodies faster,[7] and so this patient was started on enzalutamide in hospital and cabazitaxel in the community for treatment of progressive metastatic castrate-resistant disease. Given the mortality associated with complications from immunosuppressive therapy,[14] prophylactic antibiotics and monitoring for metabolic/cardiovascular derangements continued as an outpatient. In this case, the patient survived and has no further hematological concerns.

Conclusions

AHA is an uncommon complication of malignancy. Because of its rarity, a high index of suspicion and prompt recognition of potential bleeding diathesis in a cancer patient is crucial to the investigation and management of this life-threatening condition. The involvement of a multidisciplinary team with members from the oncology, hematology, and blood bank is critical in the management of this highly lethal condition. Immunosuppression and treatment of the underlying malignancy appears to play a central role in management, as demonstrated in our case.

Competing interests: Dr. Heng has been an advisory board member for Astellas, BMS, Esai, Ipsen, Janssen, Merck, Novartis, and Pfizer; and has received research funding from BMS, Exelixis, Ipsen, Novartis, and Pfizer. Dr. Alimohamed has been an advisory board member for Astellas, AstraZeneca, Janssen, Merck, and Pfizer. The reaining authors do not report any competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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