Acquired hemophilia A: A rare cause of gross hematuria

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Abstract

Acquired hemophilia A is a rare condition caused by spontaneous development of factor VIII inhibitor. This condition most commonly presents with multiple hemorrhagic symptoms and isolated hematuria is exceedingly rare. Early diagnosis is important, as this condition carries a high mortality rate (13–22%). We present a case of an 82-year-old man with isolated hematuria caused by a factor VIII inhibitor who was successfully treated with recombinant activated factor VII concentrate, as well as prednisone and cyclophosphamide.

Case report

An 82-year-old man presented to the emergency department with an eight-day history of painless gross hematuria. Past medical history included a left lung lobectomy for squamous cell carcinoma two months prior and radical prostatectomy with salvage radiation for prostate cancer 15 years prior. Most recent prostate-specific antigen (PSA) was <0.04 ng/mL. He was not taking any antithrombotic medications. Physical exam revealed moderate left flank pain, but was otherwise normal. Hemoglobin was 82 g/L, white blood cells 9 x 10^3/L, platelets 278 x 10^9/L, creatinine 158, international normalized ratio (INR) 1, partial thromboplastin time (PTT) 71 s (normal 26–38 s). Urinalysis showed >900 red blood cells per high-power field and 41 white blood cells per high-power field. The patient was treated empirically for a suspected urinary tract infection and referred to urology for cystoscopy.

Cystoscopy revealed significant active bleeding from the left ureteric orifice. An enhanced computed tomography (CT) revealed a 9.3 cm retroperitoneal hematoma in the right ileopsoas region and a 3.4 cm non-enhancing left lower pole renal lesion that was felt to be in keeping with a spontaneous hemorrhage of a previously seen renal cyst, although a cystic mass could not be ruled out (Fig.1). There was no recurrent or metastatic disease seen.

The patient continued to have gross hematuria and developed subcutaneous hematomas of both forearms. A PTT correction study revealed the presence of a coagulation inhibitor, as the PTT only corrected to 42 s. The Bethesda test confirmed an elevated level of factor VIII inhibitor at 6.16 IU/mL (normal 0.0 IU/mL) and a low level of factor VIII at 0.02 IU/mL (normal 0.5–1.50 IU/mL), confirming a diagnosis of acquired hemophilia A. No endoscopic investigations were performed on the advice of the hematology service, due to the risk of hemorrhage.

The patient was transferred to the hematology service and started on recombinant activated factor VII concentrate (NiaStase®) and oral prednisone 1 mg/kg daily. After seven days of treatment, his hemoglobin stabilized and his hematuria resolved. The NiaStase was discontinued. The patient was started on oral cyclophosphamide 100 mg daily, along with continued prednisone. He was discharged five days later in good condition, with a PTT of 49 s, factor VIII level of 0.09 IU/mL, factor VIII inhibitor level of 2.34 Bethesda Units/mL, and creatinine of 105 μmol/L. Within two weeks, his factor VIII level was normal at 0.75 IU/mL and the factor VIII inhibitor level was undetectable. He was gradually weaned off cyclophosphamide and prednisone. Followup imaging ruled out the presence of a left lower pole renal mass.

Discussion

Gross painless hematuria is a common presenting symptom for many urological conditions. Hematological disorders are a rare cause of hematuria and typically present with hemorrhagic symptoms. Here, we present a case of acquired hemophilia A presenting as isolated hematuria in an 82-year-old male with a recent diagnosis of squamous cell lung carcinoma treated with lung resection. To the best of our knowledge, there are only seven previous cases reported of acquired hemophilia A presenting with isolated hematuria.[1–6]

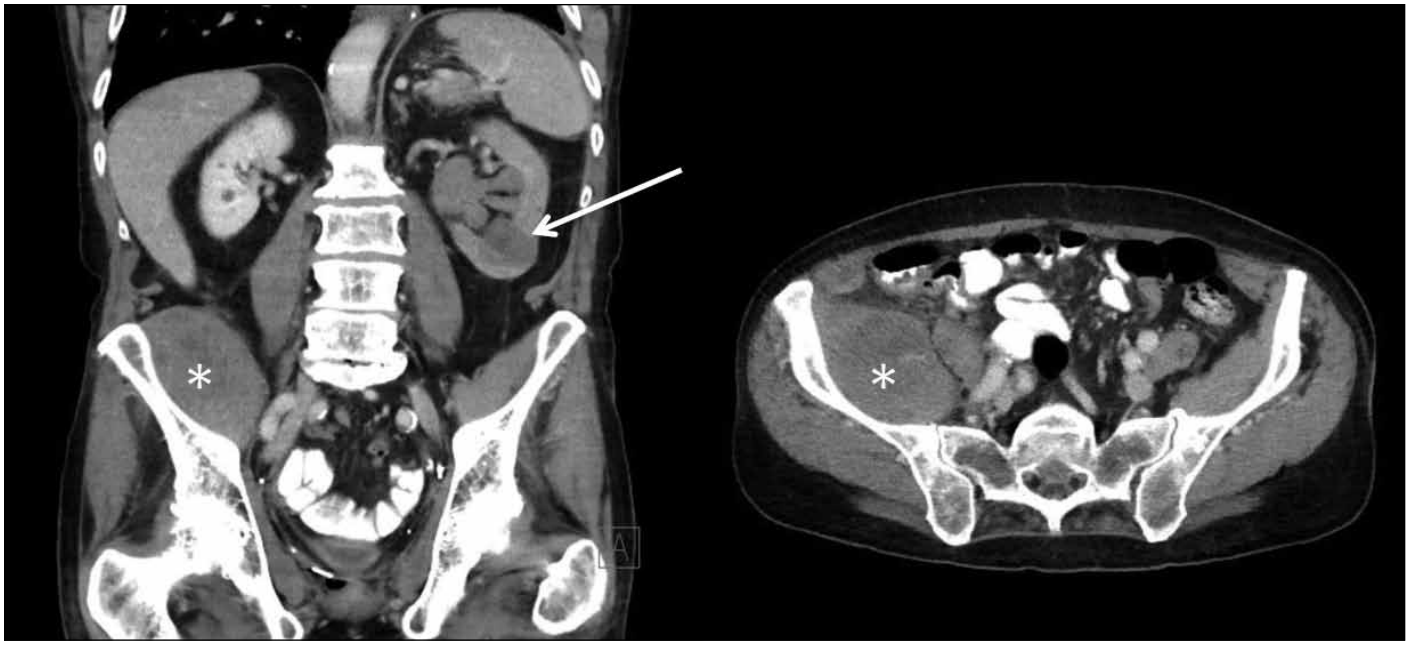

Fig.1. Enhanced abdominal CT showing 9.3 cm retroperitoneal hematoma (*), a 3.4 cm non-enhancing left lower pole renal lesion (arrow), and left hydronephrosis.

Acquired hemophilia A is a rare condition with an incidence of about one case per million.[1,2,7-9] Acquired hemophilia A typically presents with multiple hemorrhagic complications, including ecchymoses or hematomas (94%), hematuria (30%), compressive neuropathy (24%), and hemarthrosis (9%).[2] Prolonged bleeding from intravenous (IV) sites and other iatrogenic sources is also common.

The disorder most commonly affects patients older than age 60 and affects men and women equally.[1,2,7,9] It is fatal in 13–22% of patients, however, more recent studies have found the mortality rate to be closer to 4.5%, which may reflect improved outcomes with treatment advances.[9] The most common cause of death is retroperitoneal hemorrhage.[1-3] Underlying disorders are associated with the development of a factor VIII inhibitor in about half of cases, with the most common being autoimmune disorders (12%), malignancy (7–15%), pregnancy or post-partum (10%), drug reactions (3–6%), and dermatological disorders (2-5%).[1,2,7,9] Squamous cell lung cancer has been described in three cases prior to ours, however, no causal mechanism has been identified.[10-12]

Acquired hemophilia A is caused by the spontaneous development of an auto-antibody directed against factor VIII that impairs its function in the coagulation pathway.[13] The diagnosis is based on an isolated prolongation of PTT that is not corrected by a mixing study and confirmed by a reduced factor VIII level and a positive Bethesda assay.[13]

Treatment consists of maintaining hemostasis and eradicating the factor VIII inhibitor. First-line therapy for hemostasis is recombinant activated factor VII or activated prothrombin complex, which bypasses the factor VIII inhibitor in the coagulation cascade.[13] If bypassing agents are not available or the inhibitor titer level is low (<5 Bethesda units), factor VIII replacement can be used alone or in combination with desmopressin, which increases endogenous factor VIII levels.[13] Typically bypassing agents are recommended since they are associated with significantly lower rates of bleeding compared to FVIII concentrates or desmopressin (6.7% vs. 31.7%).[14] To eradicate a factor VIII inhibitor, corticosteroids and immunosuppressant drugs, such as cyclophosphamide, azathioprine, vincristine, cyclosporine ,and rituximab, are used alone or in combination.[13,15]

Although prospective randomized control studies are lacking, current evidence suggests that steroids and cyclophosphamide should be used as first-line agents. Steroids combined with cyclophosphamide result in more stable and complete remissions (70%) compared to steroids alone (48%) or rituximab-based regimens (59%).[13,15] Relapse was reported in 18% of patients treated with steroids and cyclophosphamide who achieved complete remission, indicating the need to follow patients closely after inhibitor eradication.[13,15] Patients should be educated about the signs and symptoms of recurrence and urged to promptly report any bleeding or bruising

Conclusion

Acquired hemophilia A is a rare cause of gross hematuria, but should be considered in the presence of isolated prolongation of PTT. Rapid identification and treatment is needed,

as the mortality of this condition is high. Instrumentation should be avoided in these patients unless absolutely necessary, to limit the risk of iatrogenic hemorrhagic complications.

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