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Acquired haemophilia as complicating factor in the treatment of non-muscle invasive bladder cancer: A case report

Ryšánková K *et al*. Patients with AH and bladder cancer

Abstract

BACKGROUND

Acquired haemophilia (AH) is a serious autoimmune haematological disease caused by the production of auto-antibodies against coagulation factor VIII. In some patients, AH is associated with a concomitant malignancy. In case of surgical intervention, AH poses a high risk of life-threatening bleeding.

CASE SUMMARY

A 60-year-old female patient with multiple recurrences of non-muscle invasive bladder cancer underwent transurethral tumour resection. A severe haematuria developed postoperatively warranting two endoscopic revisions; however, no clear source of bleeding was identified in the bladder. Subsequent haematological examination established a diagnosis of AH. Treatment with factor VIII inhibitor bypass activity and immunosuppressive therapy was initiated immediately. Patient responded well to the therapy and was discharged from the hospital 21 d after the primary surgery. On 38-mo follow-up, both AH and bladder cancer remain in complete remission.

CONCLUSION

AH is a rare, life-threatening haematological disease. AH should be considered in patients with persistent severe haematuria or other bleeding symptoms, especially if combined with isolated activated partial thromboplastin time prolongation.

Key Words: Acquired haemophilia A; Bladder cancer; Bleeding; Complication; Surgery; Case report

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Core Tip: Patients with autoimmune disease - acquired haematuria A, even those who have never experienced any previous haemorrhagic event, are at high risk of severe life-threatening bleeding in case they need surgery. It is a rare disease that is often overlooked in the differential diagnosis, resulting in a delay with the risk of life-threatening consequences. Therefore, it is essential to avoid underestimating of the isolated prolongation of the activated partial thromboplastin time or other altered coagulation parameters detected prior to surgery.

INTRODUCTION

Haemophilia is a gonosomal, recessively inherited bleeding disorder. Haemophilia A is caused by a mutation in the gene that encodes coagulation factor VIII, while haemophilia B is caused by a mutation in the gene that encodes coagulation factor IX. The prevalence of haemophilia A is 1/5000 and the prevalence of haemophilia B is 1/30000[1]. Haemophilia is diagnosed based on typical clinical symptoms, laboratory evaluation and genetic tests. In most cases, it is treated with coagulation factors substitution.

Acquired haemophilia (AH) is much less understood. This serious haematological disease is caused by the production of auto-antibodies against coagulation factor VIII. The estimated incidence is 0.2-1.5/1000000, but many cases remain undiagnosed[2,3]. The pathogenesis of AH is unknown. In some patients, AH is associated with a concomitant malignancy or autoimmune disease. The association of AH with bladder cancer is rare[2]. Here, we describe a previously undiagnosed patient with AH, in whom an uncomplicated transurethral resection of non-muscle invasive bladder cancer led to severe haematuria.

CASE PRESENTATION

Chief complaints

A 60-year-old female who developed severe haematuria after elective endoscopic surgery - transurethral resection of multiple recurrent bladder tumours.

History of present illness

In August 2019, a small recurrence developed, and patient was referred for another transurethral resection of the bladder tumour (TURBT). At the time of hospital admission, the patient had a normal prothrombin time, however her activated partial thromboplastin time (APPT) was prolonged. This abnormal laboratory finding was initially missed. Immediately after the TURBT, severe haematuria developed. The precipitous drop of haemoglobin to a value of 70 g/L and haemorrhagic shock required intensive care including blood transfusions and coagulation factors substitution. In order to identify the source of bleeding, two consecutive endoscopic revisions were performed within the next seven days. No clear source of haematuria was identified.

History of past illness

In July 2018, a bladder tumour was diagnosed during an ultrasound examination, and a TURBT was performed. Histology has revealed a non-invasive low-grade urothelial carcinoma. A single dose of intravesical therapy with mitomycin was administered. At that time, all coagulation parameters were normal, and no postoperative complications developed. In March 2019, multiple superficial recurrences were identified, warranting another TURBT. A histological examination confirmed a non-invasive, low-grade urothelial carcinoma. There were no complications during or after this surgery as well.

Personal and family history

Patient had a history of hypertension and osteoporosis, but no other severe comorbidities. She did not report any previous symptoms of coagulopathy. Her family history regarding bleeding disorders was negative.

Physical examination

Patient's physical examination revealed only haematuria, without other bleeding symptoms.

Laboratory examinations

Changes in the coagulation factors over time are shown in Table 1.

Imaging examinations

Ultrasound examination of the upper urinary tract did not reveal any major pathology.

FINAL DIAGNOSIS

Seven days after the primary surgery, due to persistent haematuria, a haematological examination was performed. At this time point, haematologist included AH in differential diagnosis for the first time. Subsequently, at day ten after the primary TURBT, the final diagnosis of AH was confirmed. Changes in the coagulation factors over time are shown in Table 1.

TREATMENT

Two consecutive endoscopic revisions were performed before final diagnosis was established. Before the final diagnosis was made, patient received eight units of plasma, four units of erythrocytes without buffy coat, and activated recombinant Factor VII (NovoSeven, Novo Nordisk A/S, Denmark) with no effect on bleeding. After confirmation of AH, treatment with factor VIII inhibitor bypass activity and immunosuppressive therapy (prednisone with cyclophosphamide) was immediately initiated, according to current guidelines[4]. In course of six days, the bleeding subsided and haematuria gradually stopped. On the day 10 after treatment initiation, normal activity of the factor VIII was confirmed and level factor VIII antibodies decreased.

OUTCOME AND FOLLOW-UP

On day 21 after the primary TURBT, the patient was discharged from the hospital. The immunosuppressive therapy dose was gradually reduced, but in February 2020, a relapse of AH was detected in laboratory results, without bleeding symptoms. Thus, a

second line of immunosuppressive treatment was started, with a monoclonal antibody against the CD20 antigen (rituximab). Gradually, the laboratory parameters normalized, and disease remission was achieved. In June 2020, another recurrence of bladder cancer was detected. No specific preventive haematologic measures were adopted prior to surgery, as coagulation parameters were normal at that time. The TURBT and the postoperative course were without complications. Subsequently, the patient received a one-year course of intravesical chemotherapy, as recommended by the European Association of Urology guidelines[5]. As of February 2023, both AH and bladder cancer are in complete remission. The patient attends regular urology and haematology follow-ups.

DISCUSSION

AH is a rare, potentially life-threatening autoimmune disease. In general, the AH incidence is similar in both sexes. It is higher in women between 20 and 40 years of age, as AH may develop after childbirth[6]. Additionally, the incidence is known to increase in both men and women over 60 years of age.

AH frequently manifests as a subcutaneous haematoma or bleeding into the muscles, gastrointestinal or urogenital tract, epistaxis, or intracranial bleeding. Bleeding into the joints, typical for congenital haemophilia, occurs infrequently in AH[7,8]. Up to 10% of patients with AH remain asymptomatic. AH-related mortality is estimated to be 3%[9]. Even after successful treatment, 12%-18% of patients are at risk of relapse; therefore, all patients require long-term monitoring[4].

The aetiology of AH is unknown. About half the cases are idiopathic, and the other half is associated with various conditions, including malignant tumours (most frequently lung or prostate cancer), autoimmune diseases, drug abuse or allergy. AH in patients with bladder cancer is extremely rare, with only three cases reported to date[10]. Unlike in our case report, a number of risk factors for AH development were reported in all previously reported cases. These included sepsis or lupus anticoagulant. In our case the only potential risk factor for AH development was bladder cancer[2,3,11] (Table

2). In this case the only symptom was severe post-TURBT haematuria. In contrast, in all three previously reported cases other bleeding symptoms were present, including subcutaneous and intramuscular hematomas, that led to earlier inclusion of coagulopathy in the differential diagnosis.

The AH diagnosis is based on laboratory tests. It is associated with isolated APTT prolongation and antibodies against factor VIII, which reduce its coagulation activity. Both the prothrombin time and the number of platelets is normal. The mixing plasma test is the initial diagnostic tool, but the Bethesda test is considered confirmatory in making the final diagnosis[4]. Neither the level of anti-factor VIII antibodies, nor factor VIII activity are directly proportional to bleeding severity, but both may predict disease progression, the treatment response, and overall survival rate[9].

Kreuter *et al*[3] suggested that patients with malignancies that fail AH therapy often have advanced or metastatic disease. They also reported that in 20% of patients, curing malignancy led to the disappearance of anti-factor VIII antibodies. The prompt response to immunosuppressive treatment of AH in our patient could be related to her younger age and favourable stage of the disease[12,13].

Since AH is considered a sporadic disease, the European Acquired Haemophilia registry was founded[14] to promote the development of internationally accepted diagnostic and treatment guidelines. Treatment of AH consists of haemostatic and immunosuppressive therapy. The treatment in patients with mild form of AH starts with corticosteroids. In cases where the levels of anti-factor VIII antibodies are high, combination with cyclophosphamide or rituximab is recommended. Adverse events of immunosuppressive therapy occur in more than 50% of patients[4]. They may include cardiovascular events such as stroke or myocardial infarction, diabetes mellitus, neutropenia, sepsis, psychiatric disorders[7]. In addition, the rebound elevation of factor VIII may lead to thromboembolic events.

In clinical practice, early diagnosis is important for successful treatment. However, an appropriate diagnosis and subsequent treatment is often delayed, because patients with AH-related bleeding are mostly encountered by physicians without expertise in

haematology. In the present case study, the patient was admitted to the hospital with laboratory signs of AH, and despite APTT values in the pathological range and severe bleeding, the diagnosis was delayed by ten days. It is therefore important that the urologists and other surgical specialists include this disease in their differential diagnosis when encountering prolonged bleeding. Patients with AH, even those who have never experienced any previous haemorrhagic event, are still at high risk of severe life-threatening bleeding associated with surgery. Therefore, it is essential to avoid underestimation of the isolated prolongation of the APPT or abnormalities in any other coagulation parameters detected prior to surgery[4].

CONCLUSION

AH is a rare, potentially life-threatening haematological disease. It is important to consider AH in the differential diagnosis of patients with haematuria, or other bleeding symptoms, when combined with isolated APTT prolongation.

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