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A case report of bladder cancer-related acquired hemophilia A

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Abstract

Acquired hemophilia A (AHA) is an extremely rare (incidence of 1.5/1,000,000) and potentially life-threatening disorder characterized by the production of autoantibodies against coagulation factor VIII with a consequent increased bleeding risk; it mainly affects elderly people, and approximately 6-22% of the cases are cancer-related. We report the case of an 84-year-old man who presented with subcutaneous hematomas and anemia; he had prolonged activated partial thromboplastin time, coagulation factor VIII deficiency, and high levels of factor VIII antibodies, and he was successfully treated with prednisone, cyclophosphamide, and recombinant activated factor VII as a bypassing agent.

Introduction

Acquired hemophilia A (AHA) is a rare autoimmune bleeding disorder caused by autoantibodies against coagulation factor VIII, resulting in inhibition of the coagulation intrinsic pathway and an increased bleeding risk.¹ Incidence is about 1.5/1,000,000, involving people with a median age of 71-75 years without difference between genders, except for a minority of cases triggered by pregnancy. 50% of cases are idiopathic, but the other 50% have an underlying cause such as malignancy (solid or hematologic), autoimmune disorders (mostly systemic lupus erythematosus and rheumatoid arthritis), drug-related, and dermatological conditions. Cancer can be found in 6-22% of the cases of AHA; a quarter of patients have a lung tumor, and 20-25% have prostate cancer or a gastrointestinal malignancy; the prevalence of bladder cancer is unknown at this time.

There is a wide range of clinical presentations that can vary from a mild degree (self-limiting, without anemia) and even rare, lethal hemorrhages. Typical presentation is with subcutaneous and muscular hematomas, and mucosal bleeding (gastrointestinal, urogenital); intracranial bleeding and hemarthrosis are less frequent.² The isolated relief of activated partial thromboplastin time (aPTT) prolongation is pathognomonic, due to deficiency of the coagulation factor VIII (FVIII) and high levels of antibodies against FVIII.³

The aim of treatment is first and foremost to reduce bleeding risk using bypassing agents such as recombinant activated factor VII (rFVIIa), activated prothrombin complex concentrate, or recombinant porcine FVIII in bleeding patients, then to reduce the inhibitor's level by immunosuppressive therapy (prednisone, cyclophosphamide, rituximab).⁴ If it is possible, the underlying cause should be removed.

AHA represents a clinical challenge because of its rarity and lack of knowledge about it; moreover, the treatment management is extremely delicate and involves unusual drugs that should be managed mostly in HUB centers.

Case Report

An 84-year-old man was admitted to the emergency room due to the appearance in the last 2 days of spontaneous hematomas at the right upper extremity and the distal third of the right thigh. He was previously examined by the attending physician, who suspended antiplatelet therapy and recommended access to the emergency room.

His medical history included: severe cognitive impairment of likely polyfactorial nature, hypothyroidism on replacement therapy, hypertension on therapy with angiotensin II receptor 1 antagonist, benign prostatic hypertrophy, dyslipidemia on statin therapy, previous bladder neoplasm (2018), chronic peripheral arterial disease on acetylsalicylic acid therapy, chronic kidney disease stage III, sub renal abdominal aortic aneurysm of about 5.24 cm. Family and personal history were negative for hemorrhagic syndromes. A targeted ultrasound was performed, which confirmed the presence of diffuse tissue hematoma. Laboratory testing found a severe anemia [hemoglobin (Hb) 8.8 g/dL] and elongation of aPTT 98.4 sec (reference values 26.5-37.5 sec) with prothrombin time (PT) within limits (1.08; reference values 0.8-1.2). The patient was treated with plasma (2 units) and tranexamic acid (1 g) infusion; computed tomography (CT) scan was not performed due to renal insufficiency (creatinine 2.58 mg/dL) and accordingly to the hemodynamic stability.

The patient was then transferred to the internal medicine department (which was also a HUB center for hemostasis and thrombosis diseases) for further investigations. Onward admission Hb was 7.5 g/dL, aPTT 102.9, and PT and fibrinogen were in range. On suspicion of acquired hemophilia, systemic steroid therapy (1 mg/kg/day) was immediately started.

The diagnosis of AHA was then confirmed by the findings of very low levels of FVIII activity (1.5%; reference values 60-120%), uncorrected aPTT by mixing test, and the presence of anti-FVIII antibodies (50). Lupus anticoagulant, antiphospholipid antibodies, Von Willebrand factor, factor IX, and factor VII levels were in the normal range; mild factor XI deficiency was registered.

To reduce the hemorrhagic risk, as the first therapy was not chosen a bypassing agent because of the patient's age, comorbidity, and hemodynamic stability; desmopressin (0.3 mcg/kg, 22.5 mcg/day) has been administered for 5 days without response on aPTT, FVIII and FVIII-inhibitor levels, furthermore, due to the upcoming tachyphylaxis of the drug it was discontinued.

Due to the appearance of a new hematoma in the left scapular region also extended to the ipsilateral hip (Figure 1), hemostatic treatment was introduced: rFVIIa (novoseven) 90 mcg/kg, without adverse reaction (Figure 2). At the same time, it was improved immunosuppressive therapy introducing cyclophosphamide (50 mg 2/day) and increasing steroid therapy (2 mg/kg/day) (Table 1): over the next few days, reduction of the hematomas and stabilization of the Hb levels were observed, there was a marked therapeutic response with progressive normalization of aPTT, increase in FVIII and decline in FVIII-inhibitor titer. At discharge, values were as follows: Hb 9.3 g/dL, aPTT 35.9, FVIII 40, inhibitor titer 7.75 (Figure 3).

Because acquired hemophilia is often secondary to other conditions, in-depth instrumental investigations were performed. Abdominal ultrasonography showed a distended bladder with the presence of a projecting lesion on the left; the suspect was confirmed by abdominal CT with contrast agent, but with a negative cytological test on the urine. The case was discussed with urology colleagues who recommended cystoscopy and transurethral resection of the bladder tumor of likely bladder neoplasm recurrence, but the procedure was refused by the patient and family members.

During hospitalization, an electrocardiogram showed an undated atrial fibrillation. The case was collegially discussed, and because of the high risk of bleeding, it was decided not to introduce anticoagulant therapy.

The patient was discharged in good hemodynamic compensation; it was recommended to continue steroid therapy in decalage (100 mg/day) and cyclophosphamide until the follow-up visit (Figure 4). One month later, at the follow-up visit, the hematomas were small, no new bleeding was recorded, the coagulation parameters and FVIII were normal (PT 12.9 sec, aPTT 28.9 sec, FVIII 75%) as well as Hb level (13.6 g/dL). Due to clinical and laboratory evolution, both immunosuppressive drugs were reduced as reported: methylprednisolone 1 mg/kg/day and cyclophosphamide 50 mg/day. At the next visit (1 month later), clinical conditions were unchanged without new bleeding episodes; Hb was 11.5 mg/dL and aPTT was 28 sec. The steroid therapy was further reduced (0.5 mg/daily) while cyclophosphamide was kept unchanged. One week after the visit, unfortunately, the patient entered the emergency room due to dyspnea and hypoxemia. The patient was admitted to the medical department of another hospital, under suspicion of heart failure. The patient's condition worsened in a few days with a fever of new onset, impaired consciousness, worsening of renal function, and increased inflammation indices. Despite the broad-spectrum antibiotic therapy, including an antifungal drug and supportive care, the patient died 10 days later.

Discussion and Conclusions

Acquired hemophilia can show a wide pattern of clinical presentations, ranging from asymptomatic to rare cases of fatal hemorrhage; however, the typical presentation is represented by subcutaneous hematomas arising within days/weeks, as in the case of this patient. In addition, the presence of an underlying trigger is detected in about 50% of cases, and in about 6-22% of cases is represented by cancer.²⁻⁵ Therefore, hemophilia is considered paraneoplastic. Prostate and lung cancer occur with the highest frequency among solid tumors, while lymphoproliferative disorders are the most predominant (66.7%) hematologic cancers. AH in patients with bladder cancer is extremely rare, with only three cases reported to date.⁶ However, it is intuitive to understand that patients with such a high hemorrhagic risk are unlikely to undergo surgery, but at the same time, if the underlying cause is not removed, there is a real risk of recurrence (typically in the first year after treatment discontinuation).⁷ Compared to the general population of patients with AH, patients with cancer are

more likely to experience recurrent bleeds and less likely to be successful in achieving a complete response with complete eradication of the neutralizing autoantibody.⁶

Another key consideration concerns the use of monitoring FVIII and inhibitor levels to assess the progress of the disease; while the 2009 guidelines did not suggest a correlation between these values and the clinical presentation, the 2020 guidelines suggested the use of these values as prognostic markers to individualize immunosuppressive therapy.

Therefore, monitoring of Hb values and the progress of hematomas are still the major criteria for direct therapeutic decisions.⁸ All the bladder cancer-associated acquired hemophilia cases described (Kreuter *et al.*, Taza *et al.*, Onitilio *et al.*) were characterized by elevated anti-FVIII antibody levels and reduced residual FVIII function (1-2%). Three of these cases were treated with steroid therapy, cyclophosphamide, and rituximab. In cases of malignancy-associated AHA, a retrospective analysis demonstrated that successful treatment of the underlying malignancy with chemotherapy or surgery was associated with eradication of the acquired FVIII inhibitor.⁹⁻¹¹

Another important point of discussion concerns the thromboembolic risk to which patients are exposed when we administer bypassing agents (drugs not available in all hospitals and very expensive); rFVIIa is associated with a significant increase in thromboembolic risk (about 5%), a risk that is often already high because patients are typically elderly and pluri-comorbid (cancer, atrial fibrillation, bedridden, co-presence of venous thromboembolism).¹² At the same time, patients who should be anticoagulated cannot be because of the hemorrhagic risk.

From all these issues, it is clear that the management of the patient with acquired hemophilia is delicate and should be managed by specialized HUB centers; however, few data are available on the long-term treatment, the management of the condition and the link between the development of cancer and the synthesis of autoantibodies against FVIII, so further studies are needed to increase the evidence and improve the quality of care.

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Figure 1. Onset of new hematoma in the left scapular region extended to the ipsilateral hip during hospitalization.

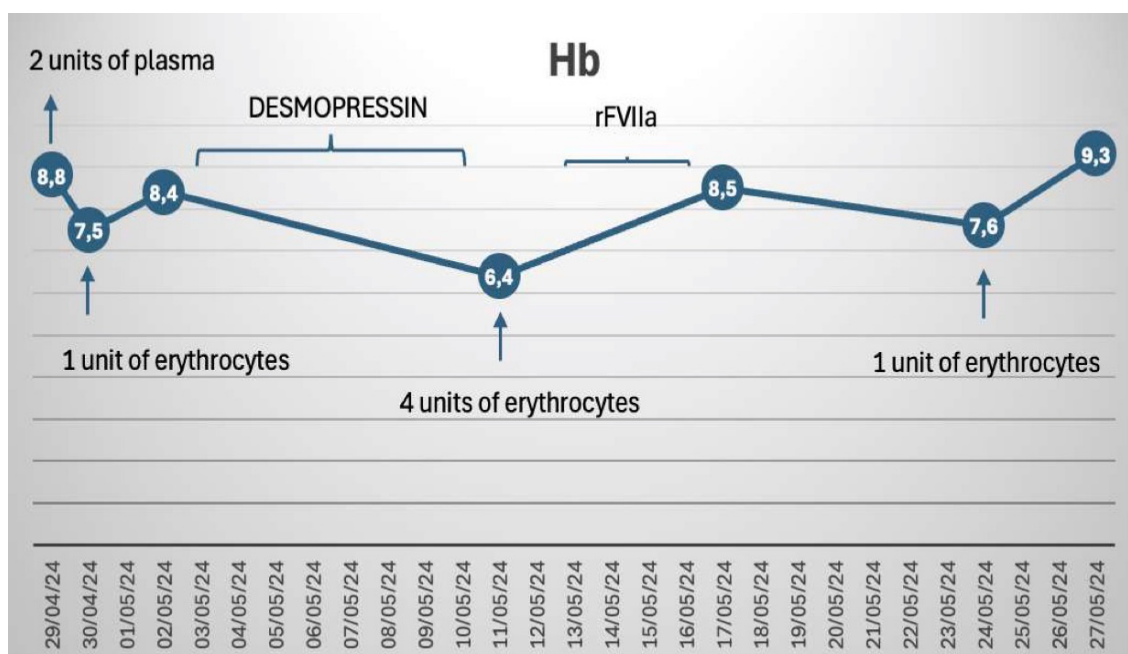


Figure 2. Hemoglobin levels and hemostatic treatment performed.

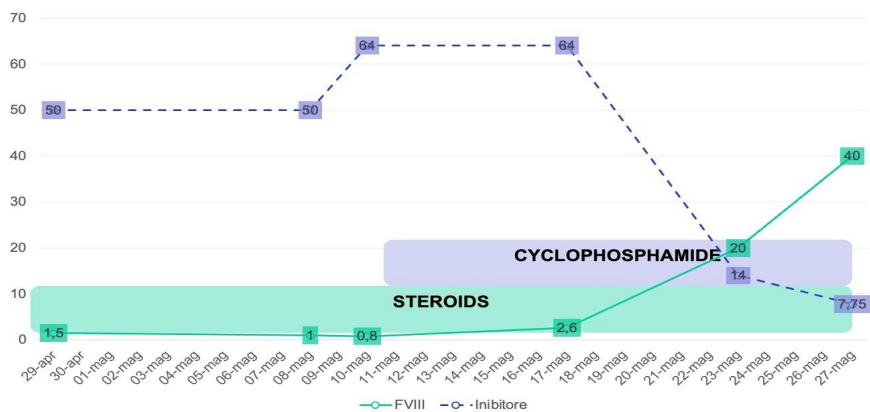


Figure 3. The graph shows the therapeutic response in terms of FVIII and FVIII inhibitor titer.



Figure 4. The image shows the resolution of hematomas at the discharge.

Table 1. Immunosuppressive therapy administered during hospitalization.

	Steroids	Cyclophosphamide
Start	30/04/2024	11/05/2024
Initial dose	1 mg/kg/die until 9/05 included 2 mg/kg/die until 29/05	1.5 mg/kg/die
	From 29/05 100 mg/day until next checkup c/o Thrombosis Outpatient Clinic 1 month later	Continued 100 mg/day until next checkup c/o Thrombosis Outpatient Clinic 1 month later