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CASE REPORT

A perioperative uncontrollable bleeding in an elderly patient with acquired hemophilia A: a case report

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Key Clinical Message

Acquired hemophilia A should be taken into account in the differential diagnosis of perioperative bleeding in patients without any apparent reason for activated partial thromboplastin time prolongation.

Keywords

Acquired hemophilia A, bleeding disorders, bypassing agents.

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Introduction

Acquired hemophilia A (AHA) is a rare and potentially life-threatening hemorrhagic disorder. It is caused by the production of autoantibodies against factor VIII (FVIII) [1]. It could be associated with several underlying conditions as pregnancy, autoimmune disorders, drugs, and malignancies. However, etiology remains unknown in up to 50% of cases [2]. Bleeding usually involves soft tissues, muscles, insertion sites of vascular accesses, retroperitoneal space and, eventually, traumatized tissues and organs. The diagnosis of AHA is usually based on an isolated prolongation of activated partial thromboplastin time (APTT) in a bleeding patient without known coagulation disorders, a low level of FVIII activity and a high level of FVIII antibodies [3]. We report the case of a man admitted to our general intensive care unit (ICU) because of a perioperative uncontrollable acute bleeding, severe anemia, and isolated prolongation of APTT.

Case Report

An 82-year-old Caucasian man presented to the emergency room (ER) of the University General Hospital (Policlinico P. Giaccone) in Palermo, Italy, because of a 3-day history of right lower back pain radiating to the abdomen and superficial bruising on the right lumbar region. The day before, he had fallen in the bathroom during a lipothymic episode. Thus, his general physician referred him to the ER, where he was admitted as "yellow code" (necessitating urgent care). His past medical history included hypertension (treated with carvedilol and furosemide), chronic renal failure (stage II) [4], glaucoma, and cancer (hemicolecotomy 7 years before and nephrectomy 6 months before). Once arrived to ER, he was febrile (38°C), tachypnoic (26 breaths/min), and tachycardic (106 beats/min). Noninvasive blood pressure was 110/70 mmHg and peripheral O₂ saturation was 99% on air. Inspection revealed bruising on the legs and on the right

lumbar region. Physical examination revealed a rigid, tender abdomen. Arterial blood gas analysis showed a pH of 7.49, PaCO₂ of 23 mmHg, PaO₂ of 104 mmHg, HCO₃⁻ of 17.4 mEq/L, and a base excess of -4.9 mmol/L. Laboratory tests revealed a hemoglobin (Hb) level of 7.6 g/dL, white blood count of $18.56 \times 10^3 \mu\text{L}$, serum creatinine of 4.26 mg/dL, potassium of 7 mEq/L, and a myoglobin of 1025 ng/mL. His first-line coagulation parameters were platelets $356 \times 10^3 \mu\text{L}$, international normalized ratio (INR) 0.96, APTT 101 sec (normal range 24–36 sec), and fibrinogen 705 mg/dL. Once asked, the patient denied any bleeding episodes or family history of coagulation disorders. A computerized tomography (CT) with contrast revealed an active retroperitoneal bleeding. As soon as called on consultation, the surgeon suggested an explorative laparotomy, due to the active retroperitoneal bleeding and the recent trauma history. A preoperative dialysis without heparin was executed because of the high potassium level and the finding of peaked T-waves on electrocardiogram. After hemodialysis, potassium level decreased to 3.9 mEq/L and the patient was conducted to the operating theater where general anesthesia was induced without complications. The explorative laparotomy revealed a blood congested right ileo-psoas muscle with an active, oozing and diffuse hemorrhage. Intraoperative arterial blood gas analysis and coagulation tests showed a reduction in Hb level (6.6 g/dL) and an APTT >220 sec. The anesthesiologist started a transfusion of fresh frozen plasma (FFP) and packed red blood cells (PRBCs). As an adequate hemostasis was not achievable, the surgeon positioned two retroperitoneal drains and sutured the bleeding abdominal wall. Then, the patient was admitted to our ICU under mechanical ventilation and sedation. Despite the preload optimization, he was hemodynamically unstable and norepinephrine infusion was started. The intensivist continued the transfusion of PRBCs and FFP and required clotting factors dosages. FVIII level was <2% (normal range: 50–150%). Lupus anticoagulant activity test was negative. Suspecting an AHA, he requested the dosage of FVIII inhibitors and the result was 20.64 Bethesda Units/mL. The hematologist suggested the administration of FVIII inhibitor bypass activity (FEIBA[®], Baxter AG, Vienna, Austria) 50 international units/kg (I.U./kg) twice a day and methylprednisolone 125 mg once a day. Despite antihemorrhagic therapy, clinical status and coagulation tests did not improve significantly. After an initial decrease (APTT 63 sec on day 1), APTT remained >100 sec and Hb levels continued to lower. Bleeding was clinically evident from the surgical wound, requiring several changes of surgical dressing (Figs. 1 and 2). Moreover, it was also evident from arterial line and venipuncture sites. On day 4, the intensivist, after a new hematology consultation, started a second-line bypassing



Figure 1. New surgical dressing. Day 1: 8.30 AM.



Figure 2. Bleeding from surgical wound and insertion sites of surgical drains. Day 1: 10.30 AM.

therapy with recombinant activated FVII (rFVIIa; NovoSeven RT[®], Novo Nordisk AS, Bagsvaerd, Denmark) 90 $\mu\text{g/kg}$ every 3 h and added a prothrombin complex concentrate (UmanComplex D.I[®], Kedrion, Castelvechio Pascoli, Italy) 2000 I.U. twice a day. Immunosuppressive therapy was shifted to dexamethasone 8 mg/die. On day 9, bleeding increased from the cited sites. Conjunctival and mucosal hemorrhage and diffuse ecchymosis in the back appeared. He died on day 11.

Discussion

AHA is a rare hemorrhagic disorder with an estimated incidence of 0.2–1 million/year and a mortality rate of 7.9–22% [3]. Demographic and clinical data of 501 patients with AHA, included in the European Acquired Haemophilia Registry (EACH2), have been recently published [5]. According to previous case series, no associated medical condition is identified in 51.9% of cases [6]. The average age at diagnosis is 74 with a positive linear correlation between incidence and age [5]. Cancer is associated with AHA in 11.8% of cases. The relationship between hematologic malignancies and production of FVIII inhibitors is well established but the correlation with solid tumors is still unclear [6]. Although cancer was reported in the past medical history of our patient, a review of his medical records revealed that both the colon adenocarcinoma and the renal pelvis urothelioma were treated with radical surgery and neither signs (i.e., physical examination and abdominal CT scan) nor symptoms were suggestive of a cancer recurrence or metastases. The cancer markers, CEA and CA19.9, dosed 1 month before as part of a periodic follow-up, resulted within normal range. Therefore, a definitive relationship between cancer history and AHA could not be established. Associated autoimmune disorders are present in 11.6% of AHA cases [5]. In these patients, the level of inhibitors is usually high and do not decrease with steroid therapy alone [6]. In our patient, despite the high level of inhibitors and the poor response to steroidal therapy, the diagnosis of an underlying autoimmune disease was refuted by negative autoantibodies screening tests, negative personal and family history and the absence of any other clinical finding consistent with an autoimmune disorder. A drug-induced AHA was excluded as his chronic therapy had remained stable for years without previous bleeding episodes, even during his previous two surgical interventions. Initial bleeding event is spontaneous in the majority of cases (77.4%). Trauma is recognized as the cause of the initial bleeding episode in only 8.4% of cases [5]. Although relatives reported a traumatic event during the lipothymic episode, a source of bleeding was not identified during surgery. Moreover, it could be possible that the lipothymic episode was a consequence of the hypotension and the low Hb level due to the underlying, spontaneous bleeding. After a benefit-risk analysis, surgery represented the first-line treatment because of the CT-scan finding of an active retroperitoneal bleeding and history of trauma. As soon as the diagnosis of AHA was confirmed, an anti-hemorrhagic treatment strategy was promptly started. Cornerstones of therapy are hemostatic treatment with bypassing agents and inhibitor eradication with immunosuppressive therapy [7]. Bypassing agent is a definition

for a drug with the property of promoting thrombin generation bypassing platelets surface activity of activated FVIII and IX (FVIIIa–FIXa, tenase complex) which is lacking in AHA [8]. Both rFVIIa and FEIBA mechanisms of action were reinterpreted in light of the cell-based model of hemostasis which, in contrast to the coagulation cascade model, provides an explanation of bleeding episodes in AHA in spite of two different, though converging, coagulation pathways [9]. The mechanism of action of FEIBA mainly relies on the presence of the activated factor X (FXa) complex with prothrombin (factor II, FII), which protects FXa from inhibition and enhances the formation of prothrombinase complexes on platelet surfaces. Conversely, rFVIIa acts activating small amounts of FX on platelet surface bypassing tenase complex activity and then promoting thrombin generation and fibrin clot formation. FEIBA and rFVIIa are the only bypassing agents coagulation factor concentrates available at the moment for bleeding control in AHA [1, 2]. Although not directly compared for AHA treatment, rFVIIa and FEIBA seem equally efficacious for bleeding control, according to the observational data of the EACH2 registry. We decided to adopt FEIBA as the first-line bypassing agent [8]. Bypassing therapy response was primarily monitored on a clinical basis. As no adequate bleeding control was achieved with FEIBA, NovoSeven[®] was started as a second-line bypassing therapy. UmanComplex D.I[®] (containing FII, FIX, and FX) was added as a prothrombin complex concentrate in order to supply a balanced coagulation factor composition.

The aim of immunosuppressive therapy is to eradicate the inhibitor suppressing its production by responsible cell clone and to normalize the FVIII level [6]. Steroids are the most commonly used drugs for this therapeutic goal though several authors described their association with cyclophosphamide. To date, no definitive data support combined steroids and cyclophosphamide therapy in AHA [2, 10]. Although remission rate seems to be higher with combined immunosuppressive therapy, final outcome is not influenced by the initial immunosuppressive regimen, possibly reflecting the higher morbidity (i.e., infections, cytopenia) associated with the combined immunosuppressive therapy [10]. Moreover, advanced age and comorbidities may preclude an aggressive immunosuppressive treatment and influence the final outcome.

Conclusion

Although AHA is a rare disease, it should be taken into account in the differential diagnosis of elderly patients with a history of recent onset bleeding and a prolonged APTT. Identifying a relationship between AHA and an

associated disease could be challenging and even in our patient's case no definitive cause was found despite an accurate review of old medical records and an extensive investigation through imaging and laboratory tests. As bypassing agents represent the first-line therapy, they should be promptly started after laboratory diagnosis confirmation of AHA.

Conflict of Interest

None declared.

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