Acquired hemophilia A in a case of purple urine bag syndrome

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ABSTRACT

The rare hemorrhagic disorder known as acquired hemophilia A (AHA) is brought on by the spontaneous development of autoantibodies against coagulation factor VIII (FVIII). It may be secondary to autoimmune diseases or cancers, or it may be idiopathic. Less than 10% of cases may have an infection as a secondary cause. We present the case of a 90-year-old anemic woman who was admitted to the hospital. She contracted a urinary tract infection (UTI) while in the hospital, and her urine took on a distinct purple hue. She had poor hemorrhagic manifestations and a prolonged partial thromboplastin time. After ruling out autoimmune and neoplastic causes, we diagnosed AHA as a result of a UTI caused by *Enterococcus faecalis*.

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Introduction

AHA is a rare hemorrhagic syndrome (1.5 in $1x10^6$ patients/year) with autoimmune pathogenesis, due to the development of autoantibodies directed against various epitopes of the FVIII molecule that neutralize its coagulant activity (inhibitors). In 50% of cases, it is idiopathic, in secondary forms the most frequent cause, especially in the elderly, is neoplasms, while infections account for less than 10% of cases; some other causes are pregnancy and medications.[1] In this case, the patient had a urinary tract infection (UTI) caused by *Enterococcus faecalis*, a Gram-positive agent, which also caused the peculiar purple coloration of the urine, which is referred to in the literature as purple urine bag syndrome (PUBS). It is a rare syndrome caused by increased levels of indigo and indirubin, two pigments related to the metabolism of the amino acid tryptophan. It is most common in female and older persons with dementia, chronic renal failure, dehydration, urinary catheter wearers, and long-time bedridden.[2]

Case report

A 90-year-old woman was admitted to the internal medicine department due to marked asthenia caused by severe anemia. Vital signs were normal. Her medical history included hypertensive heart disease, renal failure, and a previous right femur fracture. No personal history of hemorrhages or thrombosis was reported. At the admission, laboratory tests showed: hemoglobin 5.8 g/dl, mean corpuscular volume 86 fl, mean corpuscular hemoglobin 27 pg, white blood cells 10.42 10^3/mm^3, platelets 336,000 10^3/mm^3, creatinine 3.8 mg/dl, C-reactive protein (CRP) 3.86 mg/dl, d-dimer 2178 microg/L, fibrinogen 502 mg/dl, prothrombin activity 107%, international normalized ratio 0.96, partial thromboplastin time (APTT) 45 sec with ratio 1.49. At phys-

ical examination, the patient appeared drowsy, arousable to verbal stimuli, and, confused, obeyed simple commands. She also had dehydrated skin and mucous membranes. No active sources of bleeding were objectified, except for the presence of ecchimosis at the venipuncture sites. At the bladder catheterization purple urine was outputted (Figure 1.). For this reason, a urine sample for urgent culture was performed, and in the suspicion of UTI, broad-spectrum antibiotic therapy with piperacilline/tazobactam was started (corrected for renal function). Also two units of compatible packed red blood cells were transfused. The Sequential Organ Failure Assessment score was 4, so also blood cultures were performed, but the results were negative. At routine laboratory tests, a steady prolongation of the APTT was observed (50 sec, ratio 1.67), in the absence of heparin therapy. Therefore, in the hypothesis of acquired coagulopathy, the following blood tests were prescribed: APTT plasma mixing test, assay of intrinsic coagulation pathway factors (FVIII, FIX, FXI, FXII), lupus anticoagulant (LAC), Von Willebrand factor (vWF) antigen and ristocetin cofactor (vWF:RCo). APTT mixing test was conducted to determine if a prolonged APTT was due to a coagulation factor deficiency or due to the presence of an inhibitor. The test is performed after incubation of the patient's plasma with normal plasma for two hours at 37°C. APTT remained prolonged (2-hour mixing test ratio 1.47), suggesting the presence of a direct inhibitor against FVIII.[3] The diagnosis of AHA was confirmed by a low concentration of FVIII (30%) with the presence of FVIII antibodies at a titer of 4 U.B./ml (Bethesda Units). The other intrinsic pathway factors, vWF, and vWF:Rco were normal (Table 1). Due to the lack of severe bleeding symptoms and the high thromboembolic risk (sepsis, immobilization, older age), we refrained from prescribing antihaemorrhagic therapy, while immunosuppressive therapy with steroids (Prednisone 1 mg/kg) was started. Two days after admission the urine culture showed the presence of Linezolid-sensitive *Enterococcus faecalis*, so antibiotic therapy was modified according to the antibiogram. In order to rule out a neoplastic disease, on day 3, the patient underwent a total-body computed tomography scan that resulted negative for neoplasm except for a bladder mass of undetermined origin. She also tested negative for autoimmune disease. On day 7 of hospitalization, the patient presented severe hematuria, therefore one unit of compatible packed red blood cells was transfused, and antihemorrhagic therapy with recombinant activated factor VII (FVIIa) at a dosage of 90 mcg/kg was prescribed successfully, resulting in rapid cessation of bleeding. The subsequent cystoscopic examination was negative for exophytic endoluminal neoformations and showed the presence of an ulcerated lesion due to catheter decubitus at the posterior wall of the bladder and a voluminous floating clot. Ruled out the neoplastic and autoimmune causes, according to the patient's clinical picture, the diagnosis of AHA secondary to *Enterococcus faecalis* infection was made. During the hospital stay, CRP levels gradually decreased, and stable values of hemoglobin were observed, while another negative urine culture was performed showing that antibiotic therapy was effective. Steroid therapy (Prednisone 1 mg/kg) was continued, then gradually de-escalated and suspended. Hemostatic control was obtained at the same time with a progressive reduction and normalization of aPTT (31 sec, 1.04 ratio) while the serum inhibitor became no longer detectable. The patient was dismissed with a one-month ambulatorial appointment.

Figure 1. Urine bag with purple-like colored urine.

Discussion

We know that in 50% of the cases, AHA is idiopathic. In the other half of cases, it is secondary to malignancies, autoimmune disorders, or infections (>10%).[1] AHA is often complicated by life-threatening hemorrhages that require immediate therapy for bleeding arrest and eradication of the inhibitor, that's why it should be suspected in all patients,

Table 1. Laboratory test results.

Laboratory tests	Results
aPTT	1.67
aPTT (after incubation for 2 hours at 37°C of the patient's plasma with normal plasma	1.47
Lupus anticoagulant	Normal
vWF:Ag and vWF:Rco	Normal
Intrinsic coagulation factors: FIX, FXI, FXII	Normal
FVIII and FVIII inhibitor	30% - 4 U.B./ml

aPTT, partial thromboplastin time; vWF:Ag, Von Willebrand factor antigen; vWF:Rco, Von Willebrand factor ristocetin cofactor; F, factor.

especially in elderly, with recent onset of abnormal bleeding, or with isolated prolongation of APTT and normal physical therapy; also in non-bleeding patients with prolonged APTT (not under anticoagulant therapy), which have a mixing study consistent with the presence of an inhibitor directed against FVIII, and a negative LAC.[4] Bleeding patterns are different from the one observed in congenital hemophilia. The main bleeding pattern is subcutaneous (>80%), followed by gastrointestinal (>20%), muscle (>40%), and genitourinary, retroperitoneal, and other sites (<10%). Therapy consists mainly in bleeding arrest. The choice of therapy depends on the severity of the bleeding and on the inhibitor title. Guidelines recommend the utilization of FVIII bypassing agents such as recombinant FVIIa or activated prothrombin complex concentrates.[5] The use of desmopressin acetate for the management of bleeding should be reserved for minor bleeding in patients with low inhibitor titers (<2 B.U./mL) and FVIII levels >5 IU/ml.[4] Also, immunosuppressive therapy is indicated (corticosteroids, corticosteroids plus cyclophosphamide, or corticosteroids plus rituximab). The association between AHA and sepsis is only described in other three reports.[5-7] We report the first case of AHA secondary to a UTI caused by *Enterococcus faecalis*. We also objectified the urine discoloration, named PUBS.[2] It was first reported in 1978, and it is not so uncommon to see this condition; its prevalence has been reported to be as high as 9.8%,[2] especially in elderly patients, typically females, with many comorbidities, such as chronic kidney disease, constipation, prolonged catheterization with urinary catheters, dehydration, and recurrent UTIs.[8,9] Pathophysiology refers to the metabolism of tryptophan (an α-amino acid used in the biosynthesis of proteins) that leads to urinary by-products: indirubin (red) and indigo (blue). The mixture of those 2 pigments is responsible for converting urine into purple.[6] PUBS is mainly caused by the following microbes: *E. Coli* (20.8%), *Proteus Mirabilis* (15%), *Klebsiella Pneumoniae* (13.6%), *Enterococcus* spp 9.1%).[2]

Conclusions

We reported the case of a 90-year-old woman who had isolated prolonged APTT and normal PT, with no active sources of bleeding, except for the presence of ecchymosis at the venipuncture sites. AHA is idiopathic in 50% of the cases; otherwise, it can be secondary to malignancies and autoimmune disorders. Less than 10% of the cases are attributable to infections.[1] The main bleeding pattern is subcutaneous bleeding, followed by muscle, gastrointestinal, genitourinary, and retroperitoneal.[4] In this particular case, neoplastic and autoimmune diseases were excluded, we objectified ecchymosis at venipuncture sites, and hematuria due to ulcerated lesions caused by the catheter decubitus at the posterior wall of the bladder. Furthermore, urine culture was positive for *Enterococcus faecalis*. AHA secondary to sepsis is only described in other three cases,[5-7] but this is the first report of an AHA associated with a UTI caused by *Enterococcus faecalis*. Due to the association with life-threatening bleeding, it should be suspected in all patients who experience abnormal bleeding, or with prolonged APTT and normal PT, and in non-bleeding patients with isolated prolongation of APTT (not under anticoagulant therapy).

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