Case Report

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Acquired Hemophilia: Rare or Underdiagnosed Pathology. Report of Two Cases

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ABSTRACT

Background: Acquired hemophilia (AH) is caused by the presence of factor VIII inhibitor and can be associated with various etiologies: hematological neoplasms or solid tumors, drugs, autoimmune diseases, pregnancy, etc. Through a review of medical records, two cases of the disease are described in male patients older than 70, diagnosed over three years: from 2019 to 2021 in our hospital.

Case Presentation: The first case refers to a 72-year-old patient with hematuria, who developed ecchymosis and subcutaneous hematomas associated with prolonged activated thromboplastin time (aPTT), reduced blood levels of factor VIII and factor VIII inhibitor. The second case refers to an 89-year-old patient with major anemia, ecchymosis and hematomas all over the body and the same hematological profile as the first case. Both cases responded to the immunosuppressive therapy with complete remission of clinical and laboratory abnormalities. We report the clinical manifestations on admission, the laboratory abnormalities, and the therapeutic regimen in each case. Acquired hemophilia (AH) is a disease little known by the medical community. Its main signs are hemorrhagic phenomena associated or not with anemia, prolonged aPTT, drop in serum factor VIII levels and presence of factor VIII inhibitor.

Conclusion: High-level clinical suspicion is imperative to diagnose the disease and start the proper therapy.

Introduction

Acquired hemophilia (AH) is a rare disease caused by the presence of blood clotting factor VIII inhibitor antibodies (autoantibodies) which, in most cases, has no identified cause and is therefore classified as idiopathic. Other cases are associated with infections, pregnancy or puerperium, malignant hematological diseases, solid tumors, autoimmune diseases, dermatological or drug-induced diseases. Unlike hereditary hemophilia transmitted by genes, AH manifests throughout life. Elderly individuals aged 70 on average are the main group affected [1]. The main clinical manifestations are hemorrhagic phenomena that can involve any organ, but mostly cause voluminous subcutaneous hematomas in the limbs or retroperitoneum. Diagnosis requires high-level clinical suspicion associated with prolonged activated thromboplastin time (aPTT), reduced serum factor VIII levels, and serum detection of factor VIII inhibitor [2,3]. This report describes two cases of AH whose diagnoses and treatments contributed to a positive outcome in both cases.

Case Report

The first case refers to a 72-year-old male patient with a history of systemic arterial hypertension (SAH), diabetes mellitus (DM),

paroxysmal atrial fibrillation, previous cardioembolic stroke, stable chronic coronary artery disease, chronic obstructive pulmonary disease (COPD), former smoker, moderate alcoholic, partial colectomy for malignant colon neoplasia 10 years prior, obesity and chronic degenerative joint disease. The patient was hospitalized for investigation of macroscopic hematuria and low back pain. He was on regular use of ramipril, metformin, linagliptin, amiodarone, atorvastatin, weekly vitamin D, warfarin and clopidogrel. Although the regular use of anticoagulant (warfarin) and antiplatelet agent (clopidogrel) was suspended due to hematuria, the onset of low back pain led to hospitalization for diagnostic clarification. On admission, vital signs were normal, and abnormalities included hyperemia and right lower limb edema. Radiological examination identified a tumor and hydronephrosis in the right kidney. Surgery for decompression and biopsy of the tumor was indicated. Double-J catheter was placed for decompression and a biopsy of the renal mass was performed, which only identified blood cells compatible with a clot.

While in hospital, hematuria persisted and ecchymoses and bruises appeared on the limbs. As there was no well-defined cause for the hematomas, hematology tests revealed prolonged aPTT and reduction of factor VIII. Factor VIII inhibitor levels were then measured and found to be high. (Table 1) With the confirmed diagnosis of AH, immunosuppressive treatment was started with cyclophosphamide (400 mg/m^2), rituximab (375 mg/m^2) and methylprednisolone (200 mg) on a weekly basis for a total of 4 cycles. The patient progressed with cessation of hematuria and reduction of ecchymosis and hematomas along with normalization of coagulation abnormalities (Table 1) discharged for outpatient follow-up. The time between admission and diagnosis was approximately five days. The second case refers to an 89-year-old patient with history of SAH, DM, dyslipidemia, former smoker, COPD, hearing loss, hepatitis B, degenerative joint disease, left ankle fracture complications requiring orthosis for walking purposes, and dementia syndrome. The patient was admitted due to a significant drop in hemoglobin levels after an exhaustive outpatient investigation of iron deficiency anemia.

Table 1: Tests — Case 1.

Date	09.02.19	14.02.19	27.03.19
Hb	15.5	12.3	10
Platelets	230.000	228.000	282.000
aPTT	62.2	83.7	43.4
P/C ratio	1.86	2.63	1.39
Factor VIII	2	1	11
Inhibitor		140	0.5

The patient was on regular use of losartan, amlodipine, metformin, atorvastatin, donepezil, memantadine, zolpiden, pregabalin, levomeprazine and vitamin D on a weekly basis.

On admission, there were bruises and ecchymoses all over the limbs and trunk, and spontaneous bleeding in skin lesions and vascular punctures. On admission, blood test revealed signs of significant anemia: hematocrit 12.8% and hemoglobin 4.3 g/dL, with normal platelet count (217,000). Two red blood cell concentrates (RBCC) were administered on admission and another 15 RBCC and 4 bags of fresh plasma (FP) during hospitalization. As there were no signs of digestive or urinary bleeding, hematology tests were performed, revealing prolonged aPTT with P/C ratio of 2.94 and reduced levels of factor VIII. Because of this, measurement of factor VIII inhibitor levels was requested. The levels were high (27 IU), which characterized the diagnosis of AH. Treatment with prednisone 1.5 mg/kg/day was started and, after 30 days, rituximab (375 mg/m^2) was started on a weekly basis, totaling four doses. Prednisone was progressively reduced and maintained on a daily basis. With this therapy, there was regression of hematomas and ecchymoses, reduction in aPTT, normalization of factor VIII levels and reduction of factor VIII inhibitor levels, as shown in (Table 2). Between admission and diagnosis of AH there were about five days. The patient was discharged from the hospital for outpatient follow-up and has no signs of bleeding 18 months after discharge.

Table 2: Tests — Case 2.

Date	12.01.21	23.01.21	10.02.21	20.02.21	02.03.21	10.03.21
Hb	5.2	8	7.9	7	7.8	7.8
Platelets	167,000	249,000	134,000	165,000	196,000	204,000
aPTT	74.2	57.2	44.1	42.7	36.8	31.3
P/C ratio	2.69	2.75	1.63	1.58	1.34	1.22
Factor VIII	1.3	2.4	4.9	6.5	12.8	34.3
Inhibitor	27.2	18	16	3.2	2	0

Discussion

This report highlights the importance of a high level of clinical suspicion for the diagnosis of AH, which is considered a rare disease, but has been reported more frequently in recent years [2]. Perhaps the severity of bleeding at admission of elderly patients with multiple comorbidities, such as in the second case described, associated with the lack of knowledge about the disease, makes it difficult to establish a diagnosis and prevents similar cases from being diagnosed and, therefore, published [4] Because it is difficult to diagnose or hard to learn about the disease, a group of international experts proposed recommendations for the diagnosis and treatment of AH [1]. Although it is widely known in the medical community that isolated abnormalities in laboratory tests to assess coagulation in the general population are not able to predict the development of bleeding events, it is not recommended to order these tests. In the event of hemorrhagic conditions, laboratory tests and interpretation of results are imperative to confirm the diagnosis and support specific hemostatic therapy [2].

AH is characterized by factor VIII neutralizing autoantibodies that affect both men and women with a presumed incidence of 1 to 1.5 per million individuals per year [2,4]. In general, it affects the elderly aged 64 to 78 with many comorbidities and on various medications, including anticoagulants and antiplatelet agents, as in the first case described, which can influence the clinical picture and require an individualized therapeutic approach [5].

In more than half of the cases there is no clear cause and AH is considered idiopathic. However, AH has been associated with pregnancy, autoimmune diseases, malignancies, and some medications, including clopidogrel as in the first case [6-8]. The bleeding phenotype varies from life-threatening bleeding to light or no bleeding, in which case the diagnosis is based on prolonged activated partial thromboplastin time (aPTT) associated with reduced levels of factor VIII and the presence of antibodies inhibiting this factor, as observed in the two cases reported here [3,8-10]. Subcutaneous hematomas are typical of AH and may be the key to the diagnostic suspicion of the disease, as in the second case described here. Muscular, gastrointestinal, genitourinary and retroperitoneal hemorrhages may also occur and, unlike hereditary hemophilia, hemarthrosis is rare [9,11]. As AH is rare or little suspected, diagnosis is often delayed. Schep et al. from the Dutch Society of Hemophilia Treaters found a delay of up to 22 days for the diagnosis of AH [12].

The European Acquired Hemophilia Registry (EACH2) found that definitive diagnosis of hemophilia was reached within one day in 37% of patients, within one week in 26% and within one month in approximately 10% of patients [8,9]. It has been confirmed that the pattern and severity of bleeding are not directly related to serum levels of factor VIII activity [9]. Severe or potentially lethal bleeding requires hemostatic treatment or transfusion in 70 to 90% of patients. It is fatal in 5 to 10% of cases [9]. Mortality increase is directly related to the severity of bleeding, delay in diagnosis, inadequate treatment and bleeding complications during invasive bleeding control procedures. Mortality also increases due to underlying conditions such as infections or sepsis [10,11]. Treatment of AH requires maintenance of hemostasis and eradication of factor VIII inhibitor. Although spontaneous resolution may occur in up to 25% of cases, especially in those induced by drugs or pregnancy, prognosis is unpredictable [9]. According to a review by Delgado et al., total mortality of untreated patients may reach 41%, while it is reduced to 20% in those treated with immunosuppression.

Therefore, treatment should be started soon after AH is diagnosed [13]. The recommended therapy for factor VIII inhibitor eradication is immunosuppressive therapy, which must be carefully conducted in the elderly [3]. The first line of therapy recommended are corticosteroids, typically prednisone 1 mg/kg in association with cyclophosphamide or rituximab, as this association increases the chances of complete remission of the disease [11]. The rate of relapse after cessation of immunosuppression is around 25% of cases, which implies alerting patients to watch for the onset of ecchymosis or unexplained bleeding [3]. There is no definition on how often to check aPTT or factor VIII levels, but it is recommended to be monthly, for 3 to 6 months, after cessation of immunosuppression [3]. It is worth mentioning that the use of immunosuppressive drugs as a therapeutic approach to the disease was partially different in the way they were administered, but both patients presented good response to treatment.

Declarations

Ethics Approval and Consent to Participate

This report was submitted to the teaching and research committee (CEP) through the Plataforma Brasil https://plataformabrasil.saude.gov.br, and obtained approval under number 5.467.899 on 16th September 2022, without any recommendations or requirements.

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of Supporting Data and Materials

Not applicable in this case, because it is a case report.

Competing Interests

All the authors disclose no conflicts of interest relevant to this publication.

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Authors Contributions

The conception and design of this publication, as well as the collection of data from the medical record, and the analysis and interpretation of data was the responsibility of DCSC, with help from FEN and JS, and ASCR who participated in the other phases of the process, mainly writing the report and received help from PRDS as responsible for a critical analysis of the final manuscript.

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