Acquired hemophilia in an elderly person

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Abstract

Acquired hemophilia is a rare but highly fatal hemostatic disorder that occurs predominantly in elderly people. It is a disorder secondary to the development of specific autoantibodies directed against coagulation factor VIII. It is characterized by potentially fatal gastrointestinal, pulmonary, retroperitoneal, soft tissue or intracranial hemorrhages, so it requires early diagnoses and effective treatments. The present case is of a 78-year-old man with sudden onset gastrointestinal hemorrhage associated with ecchymosis and hematomas in soft tissues, with the complication of a laryngeal hematoma. He had a prolonged partial thromboplastin time (PTT), elevated factor VIII levels and elevated factor VIII inhibitorst. **(Acta Med Colomb 2019; 44. DOI: https://doi.org/ 10.36104/amc.2019.1207).**

Keywords: *acquired hemophilia, factor VIII, inhibitor, coagulopathy.*

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Introduction

Acquired hemophilia is a hemorrhagic disorder secondary to the development of specific autoantibodies which inhibit one of the coagulation factors (1). It occurs spontaneously in individuals with previously normal hemostasis, who are not hemophiliacs, and who do not have a family history of blood dyscrasias (2). Factor VIII (FVIII) is the most frequent target of these antibodies, known as acquired hemophilia A (3), but inhibiting factors of other coagulation components may also be produced. These neutralize the specific function of the coagulation factor at which they are aimed, causing a propensity for bleeding (4) leading to the serious hemorrhagic episodes produced in up to 90% of affected patients and associated with the 8-22% patient mortality (2, 5-8).

Acquired hemophilia is more prevalent in elderly patients and men, with a risk ratio directly proportional to age; thus, between 65 and 85 years of age there are nine cases per million inhabitants, and in those over 85, 15 cases per million (9-22).

The lack of knowledge regarding the presentation of the disease, the diagnostic process and the severity of presentation contribute to the high rate of morbidity and mortality (9). Likewise, the clinical presentation and its severity are not correlated with the level of factor VIII or the titer of the inhibitor, constituting a failure in the prognosis and forging a persistent and potentially fatal risk of spontaneous bleeding until the inhibitor has been eradicated (1, 13). We present the case of an elderly male patient who debuted with hemorrhagic manifestations secondary to the presence of factor VIII inhibitor, with multiple morbidities which modify the clinical phenotype of the disease and condition its treatment.

Case report

A 74-year-old male patient consulted due to 12 hours of episodes of hematochezia and then three episodes of rectorrhagia along with moderate, diffuse abdominal pain.

His past medical history included arterial hypertension being treated with acetylsalicylic acid 100 mg/day, atorvastatin 40 mg/day and enalapril 20 mg/day. He had no other significant medical history. On a review of systems, he reported the appearance of multiple ecchymoses on his extremities beginning two weeks prior.

Functionally, he was independent in activities of daily living. He had no memory complaints and the mini mental test was applied with a score of 30/30. He had no mood changes and had an adequate support network.

On the admission physical exam he was hemodynamically stable, with hypochromic conjunctivas, and oropharyngeal ecchymosis. He had ecchymoses on the anterior cervical region of the neck. On his chest, he had ecchymoses in the sternal and bilateral supraclavicular regions. Tachycardic heart sounds, without murmurs. Normal breath sounds. Normal abdomen, residual melena on rectal exam. There were multiple ecchymoses on his upper and lower extremities. No neurological alterations.

Paraclinical exams documented a hemoglobin of 6.4 g/dL, and an upper gastrointestinal endoscopy reported antral vascular malformation (Dieulafoy) which was treated with sclerotherapy and argon plasma, and proton pump inhibitor treatment was prescribed. A colonoscopy showed hemorrhoidal disease, without bleeding.

The patient had a prolonged PTT, without involvement of other blood lines, a normal C3 and C4, negative ANAS,

negative direct Coombs, and negative lupus anticoagulant. The PTT mixing studies showed no correction pre and post incubation, positive for circulating anticoagulant, without autoimmune stigmata. A peripheral blood smear evidenced microcytes and hypochromia (Table 1).

Seven days after admission the patient presented tachycardia, arterial hypotension, tachypnea and respiratory difficulty, extensive sternal and cervical ecchymosis and a 2 gr decrease in hemoglobin, without evidence of active bleeding. He was seen by hematology, who, due to the mixing study evidence compatible with a coagulation inhibitor and a negative lupus anticoagulant, in the absence of autoimmune stigmata, determined that the presence of a specific inhibitor should be ruled out (acquired hemophilia).

The study results suggested acquired hemophilia with moderate factor VIII deficit (2.5%). It was decided to begin treatment with prednisone 100 mg per day and cyclophosphamide 50 mg per day by mouth and broaden the study in search of a primary pathology as the cause of the secondary coagulopathy.

During the course of his disease, the patient presented hoarseness, mild stridor, dysphagia and progressive desaturation, and growing ecchymoses and hematomas on the anterior neck and chest. The paraclinical exams showed a 3 gr decrease in hemoglobin despite transfusion therapy. Nasofibrolaryngoscopy showed evidence of a pharyngeal hematoma affecting the esophageal lumen and the airway. Bypass therapy with FEIBA was begun, administered for 28 days at an average adjusted dose of 4,000 IU every eight hours (60 IU/kg/dose), achieving adequate hemostasis, and adjusting the dose according to the response (Table 2). Follow up factor VIII levels were at 30%, with no decrease in hemoglobin, and a possible related malignancy or autoimmune disease was also ruled out.

Table 1. *Lab exams performed on the patient.*

	Day 1	**Day 5**	**Day 7***	**Day 9≈**	**Day 10**	**Day 14**	**Day 30**
Hb g/dl	6.4	8.4	6.3	9.3	6	10.8	11.4
Platelets x10^3	364	418.3	422.3	467.1	432	452.1	480.2
PTT (control 28 sec)	64	78			63		30
ANAS	Negative						
C3: (88-165 mg/dL)		109					
C4: (14-44 mg/dL)		34					
Lupus anticoagulant		Negative					
Direct Coombs		Negative					
Factor VIII % (average control 99.2%)			2.045		9.1	9.8	30.1
Factor VIII Inhibitor UB/ml (0-0.6)			1.8		1.3	1.2	0.8
PTT mixing test (Day 7)			**Preincubation**	**Postincubation**			
1. Normal control			27.5 sec	29.8 sec			
2. NC 80% + Patient 20%			30.2 sec	42.3 sec			
3. NC 50% + Patient 50%			39.3 sec	49.9 sec			
4. NC 20% + Patient 80%			53.2 sec	62.3 sec			
5. Patient			76.6 sec	77.3 sec			
INTERPRETATION			Does not correct	Positive for circulating antibody			
Others:	Total bilirubin 1.8 mg/dL Direct bilirubin 0.45 mg/dL Indirect bilirubin 1.35 mg/dL. AST 67 mg/dL, ALT 33 mg/dL PSA: 0.17 ng/mL. CEA1.86 ng/ml (0.00-5.00). CA 19 - 9: 23.46 U/mL (0-39). IGM Beta 2 glycoprotein 1: IgM antibodies: 4.04 U Negative. IgG antibodies: 0.86 U Negative. IGG cardiolipin 4.85 GPLU/mL (negative less than 19.9 GPL). Fibrinogen: 518.0 mg/dL. LDH 713.00 U/l						

***Began prednisone at 100 mg per day, cyclophosphamide 50 mg per day, by mouth**
≈ Transfusion of 2 IU PRBCs, began FEIBA treatment

Discussion

When faced with an elderly patient with a suspected coagulopathy, a diagnostic sequence should be established to determine the cause, in order to instate the correct therapeutic strategy. First, a detailed clinical history should be taken including the use of antithrombotic medications, diseases which alter the coagulation cascade cells and proteins, and the lack of a family history of hemorrhagic disorders. When this is associated with the acute onset of hemorrhagic lesions or severe hemorrhages, without blood cell disorders and with unexplained prolonged PTT, a diagnosis of coagulopathy due to inhibitors, or acquired hemophilia, should be considered (12, 14).

The presented patient debuted with soft tissue ecchymoses and hematomas followed by hemorrhages with a high risk of mortality, such as the gastrointestinal bleeding and the laryngeal hematoma. The typical clinical presentation of acquired hemophilia includes generalized subcutaneous hemorrhages in 80% of cases, gastrointestinal and mucosal hemorrhages, muscular hematomas, neurovascular injury and urogenital tract hemorrhage (1, 2, 7).

The diagnostic process depends on the expertise of the clinician in the approach to the coagulopathy syndrome. As was pointed out in this case, PTT mixing tests and factor VIII quantification must be carried out to identify inhibitors and a deficit of the factor against which the antibodies are directed (15).

The etiology of the development of factor VIII inhibiting antibodies in most cases is idiopathic, once autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, rheumatic polymyalgia and hypo- and hyperthyroidism have been ruled out (1, 6, 16).

Other conditions to be ruled out include lymphoproliferative diseases such as chronic leukemia and multiple myeloma and solid tumor carcinomas of the lung, breast and pancreas (17, 18). Also, skin diseases such as pemphigoid psoriasis and pemphigus vulgaris; medications such as penicillins, sulphonamides, phenytoin, Alpha interferon and rituximab (19), among others; and inflammatory pulmonary conditions such as asthma and COPD (1, 2, 16, 20). In this patient´s case, a complete study was performed, ruling out these causes, and concluding an idiopathic origin of the coagulopathy.

Once the diagnosis has been made, treatment should be instated aimed at controlling the bleeding, transfusing blood products, if the patient requires them, treating complications promptly, avoiding invasive procedures, eradicating the inhibitor and treating the underlying disease (1, 13, 21).

The hemostatic treatments used in acquired hemophilia are implemented thanks to their efficacy and the need to achieve rapid hemostasis (4, 21).

The current guidelines recommend the use of recombinant activated factor VII (rFVIIa), plasma-derived activated prothrombin complex (pd-aPCC) concentrate and factor VIII inhibitor bypass activity (FEIBA) as first line hemostatic treatment (1, 21, 22). In the patient in this case the latter was used, achieving an adequate response after 21 days of treatment, with follow-up of hemoglobin, PTT and factor VIII levels. Treatment to eradicate the inhibitor has proven to decreases mortality and morbidity in patients, as well as length of hospitalization and the need for transfusions (2, 7, 8).

Corticoids may be used alone or together with cyclophosphamide or rituximab for this purpose. Despite this, the possibility of a relapse is very high, especially in elderly patients (9, 20).

Table 2. Evaluation of the patient´s imaging studies.

Upper GI Endoscopy	Dieulafoy vascular lesion at the antrum-corpus junction. Successful endoscopic treatment with argon plasma.
Colonoscopy	Mixed hemorrhoids (internal, complicated grade 2)
Abdominal and chest CT with contrast	There is no adenomegaly. No pulmonary nodules or masses.
Cervical CT	Thickening of the soft tissues of the cervical and upper thoracic region, without hematomas.
NMR of the Cervical Spine with Gadolinium	No evidence of focal lesions or areas of enhancement following gadolinium injection.
Brain NMR with Gadolinium	No hemorrhage or other lesions.

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