Acquired hemophilia A – a case report

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Abstract

Acquired Hemophilia A (AHA) is a rare but potentially serious disorder that results from the presence of circulating antibodies specific to several domains of the factor VIII molecule. The clinical condition is significantly different from the congenital form of hemophilia A, presenting mainly with soft tissue haematomas, gastro-intestinal bleeding and hematuria.[1,2]

We report a case of a 66 year-old man presenting a bleeding disorder of acute onset. We determined the presence of antibodies directed against factor VIII. The patient was successfully treated with activated recombinant factor VII (rFVIIa), steroid and gamma globulin. We review the clinical picture, etiological associations and therapy of acquired hemophilia A.

Key words: Acquired hemophilia A, Activated recombinant factor VII, acquired bleeding disorder.

CLINICAL CASE

A 66 years-old male patient, transferred to our hospital subsequently to an out of control hemorrhage after a forearm muscle groups fasciectomy due to a compartmental syndrome.

The patient was asymptomatic until about a month before admission, time in which he started complaining about total hematuria without any other urinary or systemic symptoms. It is also relevant the non-existence of other hemorrhagic phenomenon namely cutaneous, muscles or joints, gingiva hemorrhages, epistaxis, melaena, rectorrhagia, haematemesis, haemoptysis. He did not have a personal history of coagulopathy, trauma, antibiotic ingestion or another therapy, malignant disease, liver disease, alcohol consumption, smoking or a family history of coagulopathy or neoplastic disease.

A cystoscopy was carried out in the out-patients practice which was inconclusive due to the presence of intravesical live blood.

On the sequence of the venous puncture it was seen a forearm extensive muscular haematoma with compartmental syndrome having been carried out a fasciectomy of the anterior muscular groups. Due to the persistence of the clinical condition, with a surgical wound hemorrhage he was transferred to our hospital.

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On admission the patient was haemodynamically stable, with increased blood pressure values, frank total hematuria, forearm haematoma and inguinal regions and right forearm bleeding surgical wound. Without any other evident sign of hemorrhage namely at the joints.

From the baseline laboratorial evaluation it can be highlighted: hemoglobin 8.9 g/dL with normal corpuscular volume and hemoglobin concentrations, platelet count of: 375,000 platelets/uL, noalterations on peripheral blood swabs, leukogram: 9200 white blood cells with 88% of neutrophils, prothrombin time: normal (INR:1.0), activated prothrombin time: above 200 seconds, C protein reactive: 3.4 mg/dL.

Clotting factors activity was normal except for factor VIII with an undetectable activity having been determined the presence of anti-factor VIII antibodies (eight Bethesda units), which has confirmed a diagnosis of Acquired Hemophilia A (Hemorrhage Dyscrasia secondary to the presence of anti-factor VIII antibodies).

From the reminder of the immunology study carried out, we highlighted a lupus anticoagulant, antiphospholipids antibodies, antinuclear antibodies, rheumatoid factor: persistently negative.

From the tests performed in order to try to ascertain an etiology, it is to highlight:

- Positive serum tests for Epstein Barr Virus, namely positive EBNA, positive IgG and positive IgM, compatible with an acute infection on the date the patient's complaints started.

The reminder viral serology, namely HIV and B and C hepatitis were negative

A prostatic node was detected through abdominal

CAT scan and subsequently confirmed by transrectal ultrasound with imaging features of benignity (adenomatous node). The total dosed PSA was within the reference range.

The patient also underwent a cystoscopy which did not show any lesions on the bladder walls.

A rFVIIa therapy was started to control the acute hemorrhage. 100µg/Kg doses every 2 hours to start with and than were increased (4/4h, 6/6h) according to the clinical response, were administered. One week after admission, FVIII inhibitors had raised to 64, and in the sequence of a new worsening of the clinical condition, 3 takes of 125 µg/Kg rFVIIa were administered every 2 hours, followed by takes at wider intervals and smaller doses (100µg/Kg every 3 hours; every 4h; every 6h). After a 2 weeks treatment, a maintenance therapy was started with rFVIIa in two daily doses and previously to invasive procedures or blood samples collection.

During the 29 days of admission, a total of 69 rFVIIa takes were administered, being 17 in the first 3 days.

He was medicated with oral acyclovir on a 400 mg dose every 4 hours which was taken for eight days (due to a suspicion of EBV as an etiologic agent and as it inhibits the EBV replication by acyclovir in vitro). EBV repeated serology after twenty days indicate an ongoing seroconversion keeping a positive IgG and an equivocal IgM.

The patient was medicated with oral prednisolone in the dosage of 1mg/kg/day and endovenous gammaglobulin (400 mg/kg/day for five days) and then it was seen a progressive decrease on the circulating antibodies titer.

On the 26th day of immunosuppressant therapy he showed a total hematuria remission and an APTT return to normal, absence of detectable antibodies (Negative FVIII inhibitors) and an FVIII dosage of 3% of a progressive increase on the follow-up visit), reason why it was started a prednisolone progressive reduction of the daily dosage keeping normal clotting times. After a total withdrawal of the immunosuppressant therapy, the patient had no new hemorrhage events keeping normal clotting times in the follow-up visit at 6 months and subsequently 1 year afterwards.

DISCUSSION

Before a patient with delayed APTT and a normal PT, hypotheses as von Willebrand's disease, clotting intrinsic pathway factors deficit, presence of circulating inhibitors or a presence of anti-phospholipids antibodies or lupus anticoagulant are raised.

In this case, due to the hemorrhagic condition, the most likely would be a deficit of VIII, IX or XI factors. FXII factors, prekallikrein or kininogen of low molecular weight do not cause hemorrhage and the presence of anti-phospholipids antibodies or lupus anticoagulant usually leads to thrombotic conditions.

In this patient case it was confirmed at a later stage a serious FVIII (<1%) deficit. In the absence of a personal or family background of hemorrhages and being FVIII undosable, it could be excluded a congenital Hemophilia A, which being serious would manifest itself previously.

Therefore the hypothesis of acquired Hemophilia A remained, and was later confirmed with the research of FVIII inhibitors.

Acquired hemophilia is a severe coagulopathy with a mortality between 15 to 20% in need of a quick diagnosis and treatment.[3]

This patient treatment is simultaneously complicated and expensive.[2]

The two main objectives are controlling the bleeding and eradicating the inhibitor, but it is also very important the prevention, i.e., to avoid situations leading to hemorrhage, in which can be included surgical or invasive diagnosis procedures, intramuscular injections, acetylsalicylic acid administration or other drugs interfering in the platelet function.[1,4]

The therapy choice depends on the hemorrhage severity and on the inhibitors titer. FVIII high doses can be useful in patients with lower inhibitor titers (<5 UB)[1] but when these titers are higher, usually it does not work as the administered factor is neutralized.[4] In patients with higher titers, as it was our case, bypassing agents (FEIBA or rFVIIa) should be used.[2,3]

These products are effective, safe and usually well tolerated.[2]

Bypassing agents are also a first choice when the inhibitors titers are not known.[2]

Since October 2006 that FDA approved rFVIIa in the therapy of hemorrhagic events in patients with Acquired Hemophilia as well as preventing bleeding in surgical interventions or invasive procedures in such patients.[5]

Most authors recommend the following FEIBA dosages: 50 to 200U/Kg/day split in 2 to 3 takes or rFVIIa: 90 to 120µg/Kg/every 2 or 3 hours until the hemorrhage is under control.[4,6,1]

Less severe hemorrhages are usually treated with 2 or 3 takes of rFVIIa but major hemorrhages may need therapy for a few days.[1]

In this case, rFVIIa was started with a dosage of 100µg/Kg/every 2 hours with the intervals increased when the clinical condition enabled to do so.

After starting therapy for an acute hemorrhage it is necessary to ascertain its etiology suppressing the circulating antibody.

Regarding the possible etiologies, in this case, we raised the following hypotheses: paraneoplastic phenomenon with a prostatic pathology origin, presenting non clarified hematuria, auto-immune pathology, namely systemic erythematous lupus or rheumatoid arthritis in a patient without a history or other suggestive findings, with a negative lupus anticoagulant and negative antiphospholipid antibodies or infectious intercurrence, non described as an usual cause of acquired hemophilia but to be considered in patients with increased inflammatory endpoints.

A review of the available literature was carried out after search in a Medline (words searched: Acquired Hemophilia, Acquired Hemophilia, Acquired inhibitor to factor VIII and Autoantibodies against factor VIII).

About half of Acquired Hemophilia cases are related with an underlying pathology[7]. Namely autoimmune diseases (LED, rheumatoid arthritis, asthma), viral diseases, malignant diseases (particularly lymphoproliferative disorders) and pregnancy.[8,3,4] In 50% of cases are idiopathic.

Several cases associated to neoplasms are described, and patients usually have lower circulating inhibitor titers.[9] It is suggested an association between acquired hemophilia and a change on the patient's immune condition with higher prevalence of acquired hemophilia in lymphoproliferative disorders as chronic lymphocytic leukemia,[10,11,12] non-Hodgkin lymphoma,[13] as well as multiple myeloma and Waldenström macroglobulinemia.[12]

In patients with solid neoplasms are described cases of acquired hemophilia whilst paraneoplastic phenomenon in cases of: lung small cells carcinoma,[14] colon adenocarcinoma,[15] lung adenocarcinoma,[16] gastric signet ring cell carcinoma,[17] renal cells carcinoma,[15] prostate carcinoma.[15]

A retrospective study of 41 oncologic patients with acquired hemophilia has revealed a predominance of 64% adenocarcinomas, being the most common the respiratory tract and prostate tumors.[18]

No evolution factor is demonstrated in the progression of neoplasm associated to acquired hemophilia, whether the presence or not of widespread disease, and the inhibitor often is not eradicated after a well succeeded therapy of neoplasm as well as a new episode of acquired hemophilia it is not an indicator of neoplasm recurrence.

Apart of acquired hemophilia whilst a paraneoplastic phenomenon, multiple cases of association with autoimmune diseases are also described. Most cases are associated to systemic erythematous lupus,[19,20,21] rheumatoid arthritis,[22,23] and associated to the presence of antiphospholipid antibodies.[24]

Other auto-immune phenomena related with acquired hemophilia are described, namely: Sjogren's syndrome,[25] temporal arteritis,[22] auto-immune hemolytic anemia[26] and thyroid auto-immune pathology, Graves's disease[27] and auto-immune hypothyroidism.[26]

Other diseases were also related with an inhibitor present in circulation and hemorrhagic dyscrasia, namely a case of myocardial acute infarction,[28] acute pancreatitis,[29] respiratory diseases as asthma and chronic obstructive pulmonary disease,[22] dermatologic diseases,[22] myasthenia gravis[22] and acute infection by the C Hepatitis virus.[30] It is not described, in our knowledge, any association with EBV infection.

Another defined association it is the presence of anti-factor VIII antibodies in the post-partum period, mainly after a first labor, with spontaneous remission in most cases in an average period of about thirty months.[31,32,33]

Finally, there are still described cases of drugs interaction,[32] namely after the use of penicillin in children with streptococcal pharyngitis.[34]

A 1981 retrospective study with 215 patients with acquired hemophilia has shown that in 46% of patients it was not possible to name an etiologic cause for the inhibitor presence.[22]

CONCLUSION

Acquired Hemophilia is a rare disease in which the physiopathology mechanism only now is starting to be clarified. There is no consensus or guidelines to

a uniform therapy to be made in patients presenting a hemorrhagic dyscrasia and circulating anti-factor VIII antibodies.

In the case we present the therapy was successful administering activated recombinant Factor VII, prednisolone and gammaglobulin as well as acyclovir in the presence of detected EBV infection.

From the review made it is to be highlighted the absence of any previous finding referring to the association between viral infections, namely an acute EBV infection and acquired hemophilia. The main etiologies found are neoplastic diseases (mainly lymphoprolipherative disorders), autoimmune diseases (mainly rheumatoid arthritis and systemic erythematous lupus). ■

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