Acquired hemophilia: a clinical case

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Abstract

The authors emphasize points of particular importance, essential Spontaneous development of autoantibodies against factor VIII protein in a non-hemophiliac patient is a rare but significant clinical occurrence that frequently is associated with life-threatening haemorrhagic complications.

Acquired hemophilia has been associated with several disorders, namely neoplastic diseases, but often no cause is found.

The authors present a short revision of this condition, based upon a case report of a 73-year-old female admitted with a severe haemorrhagic diathesis.

Keywords: acquired hemophilia, factor VIII inhibitor, haemorrhagic diathesis.

Introduction

Factor VIII (FVIII) inhibitors are pathologic, circulating antibodies that reduce the activity of F VIII. Several autoantibodies against each of the coagulation factors have been described; however, FVIII antibodies are undoubtedly the most common ones. They may appear as alloantibodies in classical hemophilia or as autoantibodies in non-haemophilic patients.[1,2]

The incidence of acquired haemophilia is extremely rare (1 in 1,000,000);[1] conversely, 10% to 20% of haemophilic patients who receive FVIII concentrate transfusions develop alloantibodies.[3]

FVIII antibodies are composed predominantly of polyclonal immunoglobulin G, subclass IgG 4.[4,5] These heterogeneous autoantibodies, which do not precipitate and are not bound to the complement, directly target functional epitopes (antigenic sites) of the FVIII large molecule. This reaction is dependent on temperature (37ºC) and time. They are species-specific, and react in a slow, incomplete and insufficient manner against FVIII isolated from other animals, which has been applied in the control of hemorrhagic complications with administrations of purified porcine FVIII concentrate.[3]

These anti-FVIII antibodies appear as epiphenomena of various autoimmune pathologic conditions, or trigger an immunological dysfunction component.[3,4] In the most relevant case series published by Green and Lechner[1,6] (1981), of 215 nonhemophilic patients with spontaneous FVIII inhibitors, 46% did not have an identifiable associated disease. Autoimmune diseases were the most frequently associated with the appearance of these autoantibodies (18%), particularly rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).

Specific FVIII inhibitors have also been described in association with malignancies (7%), hematological diseases (plasma cell dyscrasia, lymphoproliferative diseases) and non-hematological diseases (lung, colon, pancreas, and prostate neoplasms and hypernephroma, among others).

Some drugs have also been associated with the appearance of inhibitors (5%), the penicillin group being the most common. In 5% of cases, a relation was observed with skin changes (psoriasis, exfoliative dermatitis and erythema multiforme). Another condition associated with acquired hemophilia is puerperium (7%). The antibodies may appear at the end of the pregnancy or immediately after delivery, suggesting that their appearance is due to a change in the immunological system in the third quarter of pregnancy and during delivery, and, usually, no recurrence is experienced in subsequent pregnancies. The remaining 12%, the patients presented asthma, mellitus diabetes, hepatitis, and multiple transfusions, among other conditions.

Age is another important etiological factor. Although it can occur at any age, this pathology has a higher incidence between 60 and 80 years. It is also in this age group that, in most cases, no identifiable associated diseases are found.

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Clinical presentation

Factor VIII inhibitors that cause acquired hemophilia may develop spontaneously, in a sudden and severe way or, in milder cases, they may have more subtle onset, manifesting only when the tissues have suffered trauma, or due to excessive bleeding in venipuncture or biopsy sites. They can also be an unexpected finding when a prolonged activated partial thromboplastin time (aPTT) is detected in laboratory tests.[7]

In other cases (87% of the cases in the Green and Lechner series), the clinical presentation can be dramatic, particularly with the occurrence of large ecchymosis, epitasis in abundance, hematuria, cerebral and gastrointestinal hemorrhage or bleeding after surgical procedures, and can cause hypovolemic shock and acute anemia.[1,2,4] Retroperitoneal hemorrhage is not uncommon, and can cause large masses that simulate tumours, make diagnosis difficult, and are often fatal.[4] Sometimes, the large muscle hematomas that are developed due to a mild trauma can cause compartment syndrome, which forces a rapid surgical decompression that can cause uncontrollable hemorrhages.

The nature and degree of the hemorrhage in patients with autoantibodies differs from that observed in patients with haemophilia A who have developed inhibitors. In these patients, the bleeding occurs in the joints, muscles and soft tissues, and the presence of inhibitors does not increase the frequency of hemorrhagic episodes.[1]

Patients with acquired hemophilia are usually adults. The hemorrhage is more severe and abrupt, and although hemarthroses may also occur, these are less common.[7] The mortality rate is high (22%).[1] The causes of death may be related to hemorrhagic episodes and/or treatment complications (e.g., sepsis secondary to immunosuppression).[8]

Diagnosis

For the diagnosis of acquired hemophilia, it is important to consider the clinical presentation, the absence of history of hemorrhagic diathesis, and the laboratory findings, namely prolonged activated partial thromboplastin time (aPTT), prothrombin time (PT), fibrinogen, thrombin time (TT) and normal platelet count, and low FVII activity.[3,9] The presence of prolonged aPTT and normal PT only indicates that there is a deficit in one of the factors of the intrinsic pathway of coagulation (factor VIII, IX, XI or XII) or in an antiphospholipid antibody, but does indicated which factor is decreasing, or if the deficiency is congenital or acquired.[3,9]

In the presence of a FVIII inhibitor, mixing normal plasma with the patient's plasma in equal parts, during incubation at 37ºC, for a period of one to two hours, will not correct the aPTT; on the contrary, it will cause it to be prolonged. In congenital hemophilia, prolonged aPTT is corrected with the administration of plasma and/or factor VIII. It is also important to differentiate between FVII acquired inhibitor and lupus anticoagulant inhibitor, which is more common and does not cause hemorrhage. While the inhibitor becomes more potent with incubation, the lupus anticoagulant that reacts against the phospholipid immediately responds, and is not potentiated by the incubation.[7]

The quantitative methods for determining factor VIII inhibitors are based on the determination the amount of factor VIII inactivated by the patient's plasma. The main differences between the two methods mostly commonly used include the origin of the FVIII (normal plasma or concentrates), the duration of incubation, the relationship between FVIII with the patient's plasma, and the quantity of FVIII that must be inactivated to establish an inhibitor unit. The New Oxford method is used exclusively in the United Kingdom, while the Bethesda method, which was standardized by a group of American hematologists who met in Bethesda in the middle of the 1970s, is the most commonly used.[9] This method uses normal plasma containing 100 units of FVIII/dL as the origin of FVIII, which are incubated in equal proportions with the patient's plasma for two hours. Thus, the amount of inhibitor that inactivates half of the FVIII in the mixture is defined as the inhibitor unit (Bethesda unit). One Bethesda unit is equivalent to 1.21 New Oxford units.[9] Both inhibitor determination methods can be modified as to determine the porcine FVIII inhibition, using the said factor as FVIII source, which can be important in the therapeutic regimen adopted.[9]

Human FVIIII antibodies do not recognize porcine FVIII, therefore the degree of porcine FVIII inhibition is usually lower, which allows for excellent hemostatic responses after its infusion.[9]

Therapy

The main objective in the treatment of acquired hemophilia, in addition to controlling acute hemorrhage

episodes, is the disappearance of the anti-factor VIII antibodies. In this context, the natural history of these inhibitors is important. Therefore, in the patients in whom the appearance of the inhibitor is directly related to an alteration in the immune system (SLE, RA), the use of immunosuppressant is associated with a good therapeutic response. Spontaneous remissions are observed in female patients with inhibitors acquired after delivery, or in patients with an inhibitor associated with drug reactions.[10]

In patients with acquired inhibitor but no active hemorrhage, prevention is important, especially to avoid conditions such as minor trauma, intramuscular injections, dental procedures, or the use of drugs that interfere with platelet count.[7] Once hemorrhage starts, it is often severe and must be immediately controlled by increasing the FVIII plasma levels. The dose administered should be sufficient to neutralize the circulating antibodies and cause an additional increase in this factor.[11] When FVIII concentrates are used and the inhibitor plasma levels are known, the initial dose is 20 U FVIII/Kg for each inhibitor Bethesda unit, followed by an additional dose of 40 U FVIII/Kg. If the level of antibodies is not known, a dose of 240 U FVIII/Kg should be administered. When a human FVIII concentrate is used, it should be observed whether viral inactivation occurred as to avoid the risk of transmission of hepatitis B or C, or infection by the human immunodeficiency virus (HIV).[11]

An alternative to the use of human FVIII is the administration of porcine FVIII, which has some advantages, in particular, the fact that the inhibitors react less potently when the porcine factor is administered, their effects are predictable and can be monitored through laboratory tests, and they do not carry virus like HIV and hepatitis.[11,12] According to Kernoff, the initial dose should be 20 to 50 U porcine FVIII/Kg in patients with inhibitor below 5 B U; 50 to 100 U porcine FVIII/Kg when the inhibitor titer is 5 to 50 B U; and 100 U porcine FVIII/Kg when the inhibitor titer is above 50 B U.[13,14]

The major secondary effects of the porcine FVIII concentrate are thrombocytopenia, amnesic reactions and tremor. It can be administered safely for several years and only 20% of patients develop porcine anti-FVIII antibodies. It therefore plays an important role in the long-term treatment of the inhibitors in acquired or congenital haemophilia.[11,15,16,17]

Other options include the use of recombinant factor VIII concentrate (using the recombinant DNA technology in hamster cells), factor IX concentrates or recombinant factor VIIa concentrates.[18,19]

The F IX concentrate, also known as prothrombin complex concentrate, works by bypassing the inhibitor blockade and providing large levels of factors X, VII and perhaps VIIa, promoting hemostasis by activating the extrinsic pathway. Adverse effects include the occurrence of thrombotic events, disseminated intravascular coagulation and acute myocardial infarction. Although minimal, the risk of contamination by virus is possible. Its use is restricted to patients for whom other options are not effective in the control of haemorrhage.[18]

The recombinant VIIa factor, which is still being investigated, has been used in situations where all other options have failed, and as a "compassionate case". It does not transmit viral diseases, but due to its short half-life, it has to be administered frequently, at a dose of 90 mg/Kg.

In patients with low inhibitor titers and hemorrhage, desmopressin (DDAVP) has been used. After an intravenous injection of 0.3 mg/Kg DDAVP, a rapid rise in FVIII plasma levels is observed, as well as of other coagulation factors, which may be sufficient to neutralize the circulating inhibitor and obtain hemostatic F VIII levels.[11]

In the patients with high inhibitor titers, options include reduction of the inhibitor titers by plasmapheresis, although temporary, and extracorporeal immunoadsorption, before the administration of F VIII, F IX concentrates or recombinant F VIIa.[11]

A decrease in inhibitor titers has been described in some patients with acquired hemophilia and treated with intravenous gammaglobulin.[7,20]

Sultan et al used intravenous gammaglobulin infusion in two patients with anti-F VIII antibodies at a dose of 0.4 g/kg/day for 5 days, and observed, with this first cycle, a decrease in the antibodies titers of approximately 97%. A 2nd cycle with the same dose for 2 days, and a 3rd cycle for 5 days, did not result in different responses from the 1st cycle.[21,22] The action of the gammaglobulin is related to the presence of FVIII inhibitor anti-idiotypic antibodies in the gammaglobulin preparations. The origin of these antibodies in gammaglobulin preparations from different donors is not clear, but it seems they can exist in healthy donors, particularly in the elderly. Gammaglobulin also seems to suppress the synthesis of autoantibo-

dies, since the inhibitor titers never reach preinfusion levels. When effective, it decreases the antibody titers within 24 and 48 hours.[11,22,23]

Attempts to eliminate the autoantibodies are dependent on the use of immunosuppressant agents, which will eliminate or suppress the clone of the cells responsible for the synthesis of autoantibodies. A favourable response to corticosteroids has been described for several patients. Other agents, such as azathioprine, 6-mercaptopurine, cyclophosphamide and vincristin, even if in association with corticosteroids, have also been reported as beneficial in the treatment of these patients.[10,24] The majority of studies report the use of cyclophosphamide, a cytotoxic drug, the secondary effects of which are related to the dose and duration of treatment. In acquired hemophilia, this drug should not be administered for longer than six weeks, even if a favourable response is not observed, since prolonged treatment would only increase the likelihood of secondary effects. Cyclophosphamide should not be administered in pregnant women or those attempting to become pregnant.[4,10]

Despite the interest in this pathology for more than three decades, only recently a randomized trial was carried out on the use of immunosuppressant agents in the treatment of anti-F VIII antibodies, given the rarity of this situation. In 1987, a prospective trial was begun to determine the efficacy of prednisolone, cyclophosphamide or a combination of both drugs, in the suppression of anti-F VIII antibodies. Until now, the study has included only 30 patients, and its conclusions indicate that immunosuppression treatment should start with *1 mg/Kg prednisolone for 3 weeks if there is evidence that the inhibitor titer is decreasing; otherwise, 2mg/Kg oral cyclophosphamide is combined for 6 weeks, withdrawing the corticosteroids progressively over 3 to 6 weeks. It is a regimen that is generally proposed for patients with an inhibitor titer of below 100 B U. The administration of FVIII concentrate depends on the presence of hemorrhagic events.[4,10] Recently, Lian and colleagues used prednisolone, cyclophosphamide and vincristin in association, in an attempt to achieve higher immunosuppression, and they observed the disappearance of antibodies in 11 of the 12 patients.[25] In the patients with an inhibitor titer above 100 B U, cycles of 3 or 4 weeks with 100 U/Kg FVIII concentrate, prednisolone 100 mg/day (D1-D5), intravenous cyclophosphamide 500 mg (D1), followed by 200 mg, and vincristin 2 mg on the day 1 have been administered.[25]

Garvey also suggests the use of cyclosporine or a-interferon when no response to cyclophosphamide is observed.[7]

According to Kasper,[26] the approach to be used for all patients, at the time of diagnosis includes:

1. Determination of the factor VIII plasma level, and quantification of human and porcine inhibitor (weekly).
2. Immunosuppressant therapy with prednisolone 1 mg/Kg/day, which should be suspended after 3 weeks if the inhibitor has disappeared and factor VIII plasma levels are normal. If the inhibitor reduces to a titer equal to or below 50%, maintain prednisolone for a further 3 weeks and consider the use of intravenous gammaglobulin, at 400 mg/Kg/day, for 5 days. If the inhibitor does not disappear, start administration of 2 mg/Kg/day oral cyclophosphamide for a maximum of 6 weeks.
3. Check for possible hemorrhage. In patients with no bleeding, or those in whom hemorrhage is mild, prevention should be carried out, that is, do not use acetylsalicylic acid, and avoid traumas that may cause hemorrhage; also, advise patients of the possible symptoms that could occur, and what should be done in case of a hemorrhage.

In the case of serious hemorrhage, if the porcine factor VIII inhibitor is equal to or below 10 BU, administer 20 units of porcine factor VIII /Kg/BU, followed by 40 units/Kg, and determine the plasma level of factor VIII after infusion. If the plasma level is equal to or above 30 units/dL, hemorrhage must be controlled. If the plasma level is below 30 units/dL, repeat factor VIII at the same doses until the hemorrhage is controlled or the factor VIII level is above 30 units/dL.

When porcine FVIII titers cannot be determined, but the anti-FVIII antibody titers are known, the porcine anti-F VIII antibody is estimated to be around 5% that of the anti-F VIII antibody. When both titers are unknown, begin therapy as if the titers were below 10 B U. If porcine F VIII concentrate cannot be used, use human FVIII concentrate at the doses described above. If the titers of porcine factor VIII inhibitor are above 10 BU, consider: plasmapheresis or intravenous gammaglobulin (1 mg/Kg/day for 2 days), followed by 240 units of porcine factor VIII /KG; factor IX complex (75 to 100 units/Kg at an interval of 8/8 hours, at a maximum of 4 doses), if hemorrhage persists.

TABLE I

Laboratory evolution with therapy

	7/10/94	11/10/94	17/10/94	21/10/94	25/10/94	4/11/94
Hg(gr/dL)	4.8	9.8	4.7	6.2	8.2	10.7
aPTT(sec)	77.4 (31)	60.8 (32)	75.8 (29)	64.7 (29)	68.2 (34.5)	67.5 (28)
F. VIII(%)		< 1.6			0.1	0.7
INIB.(Beth.U)						128
				[cyclophosph]		L
Cyclosp						
				[_____Ig_____]		
			[60 mg _____ Prednisolone _____ 40 mg _____ 20 mg]			

Clinical case

B.S.S.A, 73 years, female, White, admitted to the Medicine I Service of Hospital de Egas Moniz in October 1994 due to serious hemorrhagic dyscrasia. The current disease first appeared in August 1994, resulting in hospitalization in the Urology Service for total hematuria, with a hemoglobin count of 5.2 gr/dL and aPTT of 73 seconds (control=29.5), and normal PT and platelet count.

To evaluate the condition, renal and vesical echography was performed, revealing a pyelocalyceal and right ureteral dilatation; elimination urography, revealing left ureteral dilatation and non-visualization of distal two-third right ureteral segment; cystoscopy, identified a bladder with organized clots; and the second third right ureteral segment could not be seen on ascending pyelography. These findings match the presence of clots, which would cause urinary obstruction or an urothelial tumour.

Complete regression of the hematuria was observed only with antibiotherapy and transfusional support; however, prolonged aPTT was maintained. The patient was discharged, and referred to the outpatient hematology clinic.

A reassessment abdominal CT showed normal renal function, revealing only one solid formation on the left suprarenal gland, with dimensions of 3.2 x 3.3 cm.

In October 1994, the patient was admitted to the Medicine Service due to signs of acute anemia, several hematomas, some hemorrhagic suffusion and a massive, non-pulsatile mass of hard consistency, covering the hypogastric area and right quadrants. Personal history did not include hemorrhagic dyscrasia, blood transfusion, or administration of drugs interfering on coagulation. It is worth pointing out psoriasis and cholecystectomy in July 1994 for symptomatic bile duct lithiasis; at that time, coagulation analysis showed normal results.

The laboratory results were Hb 4.8 g/dL, Hct 15%, aPTT 77 sec (control=31.2), PT 15.3 sec (control=13.2), platelet count 359,000/mm^3 , fibrinogen 522 mg/dL. Incubation of the patient's plasma at 37ºC, for two hours with normal plasma, revealed a prolonged aPTT that rose to 84 seconds, indicating the presence of the inhibitor. For the subsequent evaluations, the presence of FVIII inhibitor was confirmed by a titer of 128 Bethesda U and F VIII activity below 0.5%.

To investigate the intra-abdominal mass and rule out the conditions most frequently associated with acquired hemophilia, an abdominal pelvic CT was performed, which revealed a solid mass surrounding the duodenal bulb, moderate right hydroureteronephrosis, solid mass on the left suprarenal gland, and iliopsoas muscle hematoma causing a left deviation of the urinary bladder. Tumour markers, ANA, ENA system, anti-DNA antibodies, determination of immunoglobulins, complements and anti-cardiolipin antibody were negative or within the normal parameters.

As therapy, and in addition to the transfusional support with erythrocyte concentrate, oral corticosteroid therapy with 1 mg/kg/day prednisolone was begun. On day 7, because clinical worsening was observed, i.e. the abdominal mass increased and con-

TABLE II

Laboratory evolution in an outpatient setting

	Dec. 1994	March 1995	June 1995	Sept 1995	Nov 1995	March 1996	Nov 1996
Hg(gr/dL)	10.1	10.9	12.0	11.3	12.1	12.4	12,5
aPTT(sec)	94 (32)	69 (31)	43 (30)		42 (32)	39.3 (34)	36 (34)
F. VIII(%)	0.1	0.6	31.2	28.1	36.8	29	41,9
INHIB.(Beth.U)	256	64		2	1	0.5	0
[_____ ciclosp _____]							

junctival hemorrhage occurred, and due to decreased hemoglobin levels, intravenous immunoglobulin was administrated in association, at a dose of 0.4 g/kg/day for 5 days. On day 12, as clinical symptoms and laboratory data remained the same, administration of IV cyclophosphamide was begun (500 mg on day 1, 200 mg from day 2 to 4), resulting in clinical improvement, with complete regression of hematomas and progressive reduction of the abdominal mass, as well as stabilization of hemoglobin levels. However, prolonged aPTT values and decreased factor VIII levels remained the same (*Table I*).

The patient was discharged in November 1994, continuing with the same immunosuppressant therapy with cyclosporine, at a dose of 15mg/Kg/day for 2 weeks, which was progressively reduced due to normalization of the clotting values and F VIII, until its suspension within 1 year of therapy (October 1995) (*Table II*).

A reassessment abdominal pelvic CT was performed in March 1996, revealing only a slightly increased mass on the left suprarenal gland (3.8X3.4 cm), for which a hormone analysis was performed (D_4 androstenedione, dehydroepiandrosterone, free testosterone, total metanephrines and vanillylmandelic acid), with normal results. Also, because the laboratory data allowed, aspiration biopsy of the left suprarenal gland was performed, which was negative for neoplasm cells.

The patient is now asymptomatic, with hemoglobin levels of 12.5 g/dL, Hct 35.9%, platelet count 289,600/mm^3, aPTT 36 sec (control=34), PT 13.3 sec (control=12.3), F VIII activity 41.9% and disappearance of the inhibitor (Nov 96).

Discussion

The spontaneous development of FVIII antibodies, also known as acquired hemophilia, is a clinical entity with an extremely rare incidence and unknown aetiology. These autoantibodies act against functional epitopes of the FVIII large molecules. They may be associated with several pathologies, including autoimmune diseases, hematologic and non-hematologic neoplasms, drug reactions, skin alterations, or puerperium; but in most cases, no such association is identifiable. Although it may occur at any age, this pathology has its highest incidence between 60 and 80 years.

In our case, a causal relation with surgery can be established, although in addition to the surgery, the patient had been given different drugs - anaesthetic and antibiotics - in some cases, these may be also responsible for the appearance of anti F VIII auto-antibodies, as no cause of neoplasm was detected. The follow-up abdominal CT did not show the initial mass; therefore, we concluded that it was a case of retroperitoneal hematoma. The left suprarenal tumour was nothing more than an "incidentaloma".

For the diagnosis, it is important to take into account the clinical presentation, absence of bleeding diathesis and laboratory findings, including prolonged aPPT, and normal PT, fibrinogen, TT, platelet count, low FVIII activity and the presence of inhibitor.

The therapeutic options are varied, and also depend on the existing inhibitor titers. In patients with acquired inhibitor but no evidence of active bleeding, prevention of hemorrhagic events is important.

Once hemorrhage occurs, immediate action should be taken, and acute bleeding episodes controlled by increasing the FVIII plasma levels, with the administration of human or porcine FVIII concentrate.

Other options include the use of F IX and recom-

binant F VII concentrate, but these should be reserved for conditions where the first options are ineffective. Intravenous gammaglobulin has also been used with some degree of success.

The use of prednisolone is generally agreed upon, should be administered immediately after the diagnosis, and can be associated with cyclophosphamide later. When this regimen is ineffective, other immunosuppressant agents have been used.

In our case, the therapy with corticosteroid and immunoglobulin was not effective. Porcine F VIII was not used because it was difficult and expensive to obtain (in this case, a cost of approximately 60 million Portuguese escudos for every 15 days of treatment). Immunosuppression with cyclophosphamide resolved the patient's acute bleeding. After discharge, and once there was no bleeding dyscrasia, but a prolonged aPTT, high inhibitor titer and low FVIII activity remained, which predicted a prolonged therapy, we opted for immunomodulation therapy with cyclosporine. This therapy, when administered over the long term, has less adverse effects than cyclophosphamide, which is not indicated for treatments longer than 6 weeks in acquired hemophilia. A gradual reduction of the inhibitor titer was observed with cyclosporine, and even after its suspension, laboratory parameters showed improvement until the inhibitor disappeared.

Garvey suggests the use of cyclosporine when other therapy regimens fail, but the doses or duration of treatment were not reported.

Despite the fact this this is a clinically heterogeneous disease with multiple therapy options, more randomized trials are necessary to find new treatments. Thus, future improved approaches to these patients will be based on advances on the knowledge of the factor VIII molecule and the immune response.[27] ■

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