Symptomatic Acquired Haemophilia Due to Circulating Antibodies Against Both Factor VIII and IX in a Non-haemophiliac Patient

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Abstracts Acquired haemophilia is a very rare condition, occurring in less than 2 per million populations. This condition is caused commonly by acquired antibodies against factor VIII and rarely by antibodies against factor IX. Here we describe an extremely rare presentation of idiopathic acquired haemophilia in an otherwise healthy male patient, caused by simultaneous occurrence of circulating antibodies against both factor VIII and IX.

Keywords Acquired haemophilia · Factor VIII inhibitor · Factor IX inhibitor

Introduction

Acquired hemophilia is a rare condition caused by occurrence of inhibitor antibodies to factor VIII or IX [1]. The estimated annual incidence is around 1–1.5 per million populations and acquired haemophilia A is the most common subtype [1]. Acquired haemophilia B is extremely rare and only few cases have been described [2]. Usually acquired haemophilia is seen in older patients, with a median age at diagnosis of 75 years. There are no sex predilections, though it can occur during pregnancy more commonly. Most common causative factors identified so far have been autoimmune disorders (17 %), malignancy (7–15 %), pregnancy (5–10 %), drug reactions and skin diseases (<5 % each).

However in about 50 % of patients no causes are found and are labelled as idiopathic acquired haemophilia [1, 3, 4]. The common clinical manifestations include spontaneous haemorrhages into the skin, muscles or soft tissues or excessive bleeding during surgery with an extremely high mortality due to major bleeding episodes. However the haemorrhages which are hallmark of congenital haemophilia seldom occur in these patients [1, 3, 4]. The literature survey shows only about five case reports of simultaneous occurrence of acquired inhibitors to both factor VIII and IX [5–9]. To the best of our knowledge this is the first case report of occurrence of idiopathic acquired haemophilia with inhibitors to both factor VIII and IX in adults.

Case Report

A previously healthy 59 year old gentleman with no prior history of bleeding disorders presented to us with history of spontaneous swelling in right thigh and left calf region of around 10 days duration. There was no preceding history of trauma or fever. On evaluation he was found to have intramuscular hematomas in right hamstring and left gastrocnemius muscles along with several ecchymotic patches on the skin. Preliminary lab investigations showed microcytic anemia with normal WBC and platelet counts (Hb-7.8 g%, WBC-9800/ μ L, Neutrophilic predominant differential count, Platelet-2,71,000/ μ L). His coagulation work up showed a prolonged aPTT with a control of 28.5 s which was not correcting with normal plasma, and PT of 12.6 s with control of 12.2 s and an INR of 1.03. The fibrinogen levels were 334.5 mg%. The DIC panel, renal and liver function tests were normal. Patient had very low levels of coagulation factors VIII and IX (0.7 and 1.2 % respectively) done at our lab. Repeat tests at outside

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reference lab also confirmed extremely low levels of both factor VIII and IX levels along with high level inhibitor (details given below). Von Willebrand's antigen assay was within normal limits (120 %). Etiological evaluation with serology for HIV, HBV and HCV were negative. Autoantibody panel for collagen vascular diseases was also negative. A whole body PET CT scan done to rule out occult malignancy was also normal. Patient was not on any medications previously.

Factor Assays and Inhibitor Profile

Factor VIII: C 2.3 %. Factor IX: C 1.5 %.

Bethesda assay	1st visit	2nd visit	3rd visit
Factor VIII: C inhibitor BU/ml	486	90	19.2
Factor IX: C inhibitor BU/ml	27.2	7.2	16

Management of Patient

Patient was given two doses of activated factor VII to prevent ongoing bleeding. He was also supported with recombinant factor VIII and IX supplements and injectable tranexamic acid. Patient was started on immunosuppressive therapy to reduce the inhibitor levels. A pulse dose of methylprednisolone was given at a dose of 10 mg/kg/day for 3 days followed by oral prednisolone at 1 mg/kg day. He was also given a single dose of Rituximab at 375 mg/m². Later he was started on steroid sparing therapy with Azathioprine at 0.5 mg/kg/day and later hiked it up to 1 mg/kg day. He was also given blood transfusion and oral iron supplements. The haematoma size reduced with reduction in pain over a period of 2 weeks. He was discharged in a stable condition after 14 days of hospitalization. At the end of 3rd week of follow up, patient is clinically stable with no fresh episodes of bleeding. His inhibitor levels are showing a decreasing trend as described in above table. Patient has been on out patient follow-up with gradually decreasing inhibitor titres and recovering factor levels. Mutation analysis was not carried out. The patient has been on follow up for more than 6 months now and both his factor levels have normalized and he is off immunosuppression.

Discussion

A review of literature for simultaneous occurrence of inhibitors to multiple coagulation factors yielded 5 case reports.

One of the earliest reports is by Reussi C et al. [5] in 1966 where they describe a case of young girl with combined inhibitors against both factor VIII and IX. In 1976, Moake et al. [6] describe a 64 year old man with multiple sclerosis developing circulating IgG antibodies against both factor VIII and IX. In 1985 Gouyon et al. [7] describe a child with Henoch Schonlein disease developing both antibodies. Similarly, in 2007, Carmassi et al. and in 2011 Campos-de-Magalhaes describe similar cases. While Carmassi et al. [8] reports the occurrence of combined inhibitors in a patient with Sjogren's syndrome, Campos-de-Magalhaes's [9] patient developed the antibodies during therapy with pegylated interferon with ribavirin for chronic hepatitis C infection. All these instances appear to be cases of secondary acquired inhibitors. In our patient, after extensive search yielded no precipitating cause, we think it is a case of idiopathic acquired inhibitors. We believe this is the first case report of simultaneous occurrence of idiopathic acquired haemophilia A and B due to spontaneous development of auto-antibodies against factor VIII and IX.

The treatment of acquired haemophilia is complex and associated with a mortality rate of around 10–20 % due to occurrence of fatal haemorrhages. In 2009, Huth-Kunhe et al. [10] published the international recommendations on the diagnosis and treatment of acquired haemophilia. Supplements with recombinant or plasma derived factor VIII and IX are usually ineffective for acute bleeding episodes due to the presence of inhibitors. These patients need multiple doses of factor bypassing agents like activated recombinant factor VII or activated prothrombin complex concentrates (APCC) or factor eight inhibitor bypass activity (FEIBA) concentrates. If the patients have low titres of inhibitors, they can be managed with antifibrinolytics like tranexamic acid, DDAVP (1-deamino-8-D-arginine vasopressin) along with high doses of factor VIII and IX. Sometimes porcine factor VIII can be used in milder cases [3]. However the primary aim of the treatment is to reduce the inhibitor levels by immunoadsorption, immunosuppression or immune tolerance induction along with treating the underlying condition. If the patient is young and fit, immunosuppressive therapy with cyclophosphamide and steroids can be given. If the general condition is not permitting the use of cytotoxic therapy, or in case of refractoriness to immunosuppressive therapy, the anti-CD20 antibody rituximab can be used as a single agent or in combination. In a metanalysis of 249 cases, Delgado et al. [11] observed a complete remission rate of 74 % after a median follow-up of 12 months with immunosuppressive therapy. The inhibitor-related mortality rate was around 11 % with following poor prognostic features identified in the review: Age at diagnosis (<65 better than ≥65 years); Achievement of a complete remission (yes better than no); and the nature of underlying disease (malignant disease

worse than others). Since our patient's general condition was not stable, we started him on pulse methylprednisolone with rituximab. Later he was switched to low dose steroids and azathioprine. With this protocol, patient's condition has improved with reduction in inhibitor levels and reduction in need for factor supplements.

Conclusions

Occurrence of acquired haemophilia is a rare condition with wide variety of underlying causes. During routine testing, the only clue may be an isolated aPTT that is not correcting by the addition of normal plasma and a low level of factor VIII. Though the factor VIII inhibitor antibody can cross react with factor IX to give a false impression of presence of low titre inhibitor to factor IX, the occurrence of low levels of factor IX in circulation should arise the suspicion of presence of additional anti factor IX antibodies. A very high index of suspicion is the only way one can arrive at a diagnosis of such rare but serious conditions.

References

1. Green D, Lechner K (1981) A survey of 215 non-hemophilic patients with inhibitors to factor VIII. *Thromb Haemost* 45: 200–203
2. Jedidi I, Hdiji S, Ajmi N, Makni F, Masmoudi S et al (2011) Acquired haemophilia B: a case report and literature review. *Ann Biol Clin (Paris)* 69(6):685–688
3. Morrison AE, Ludlam CA, Kessler C (1993) Use of porcine factor VIII in the treatment of patients with acquired hemophilia. *Blood* 81:1513–1520
4. Collins PW, Hirsch S, Baglin TP, Dolan G, Hanley J et al (2007) Acquired haemophilia A in the UK: a 2-year national surveillance study by UK Haemophilia Centre Doctors' Organisation. *Blood* 109:1870–1877
5. Reussi C, Altman R, Rouvier J, Maino R (1966) Combined factor VIII and IX inhibitors in a girl. *Thromb Diath Haemorrh* 16(3):549–558
6. Moake JI, Kent CJ, Meta LD, Wright LC (1976) Circulating IgG antibodies against Factors IX and VIII in multiple sclerosis. *Acta Haematol* 55:53
7. Gouyon JB, Seiller F, Deries X, Alison M, Lorenzini JL et al (1985) Inhibitors of factors VIII and IX in a child with Henoch-Schönlein syndrome. *Am J Pediatr Hematol Oncol* 7(4):376–377
8. Carmassi F, Giannarelli C, De Giorgi A, De Negri F (2007) Combined factor VIII and IX inhibitors in a non-haemophilic patient: successful treatment with immunosuppressive drugs. *Haemophilia* 13:106–107
9. Campos-de-Magalhaes M, Brandao-Mello CE, Pires MLE, Salgado MCF, de Brito SB et al (2011) Factor VIII and IX deficiencies related to acquired inhibitors in a patient with chronic hepatitis C virus infection receiving treatment with pegylated interferon plus ribavirin. *Hematology* 16(2):80–85
10. Huth-Kuhne A, Baudo F, Collins P, Ingerslev J, Kessler C et al (2009) International recommendations on the diagnosis and treatment of patients with acquired haemophilia A. *Haematologica* 94:566–575
11. Delgado J, Jimenez-Yuste V, HernandezNavarro F, Villar A (2003) Acquired haemophilia: review and meta-analysis focused on therapy and prognostic factors. *Br J Haematol* 121(1):21–35