Rare Case of Acquired Haemophilia and Lupus Anticoagulant

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Abstract Acquired haemophilia or factor VIII (FVIII) deficiency, caused by FVIII inhibitor antibodies, is a very rare condition that commonly results in severe haemorrhagic complications. We report a case of acquired haemophilia presenting with multiple bluish patches affecting face, neck, upper & lower limbs, history of gum bleeding and left knee hemarthrosis. The patient was found to have acquired FVIII inhibitor and lupus anticoagulant (LAC). The simultaneous presence of LAC and FVIII inhibitor is exceedingly rare. The differentiation between these two conditions is crucial, because both result in a prolongation of the activated partial thromboplastin time test, which does not correct when mixed with the plasma of a normal control; however, the clinical manifestations range from thrombosis in the presence of LAC to massive haemorrhage with FVIII inhibitors.

Keywords Acquired haemophilia · Factor VIII inhibitor · Lupus anticoagulant

Introduction

Acquired haemophilia or factor VIII (FVIII) deficiency, caused by FVIII inhibitor antibodies, is a very rare condition, which commonly results in severe haemorrhagic complications [1]. This condition has been reported in association with pregnancy, autoimmune disorders, malignancy and drug reactions [1]. The lupus anticoagulant (LAC) is an antiphospholipid antibody associated with thrombotic complications. The simultaneous presence of LAC and FVIII inhibitor is exceedingly rare [2]. About 80 % of patients with FVIII autoantibodies hemorrhage into the skin, muscles, or soft tissues and mucous membranes (e.g., epistaxis, gastrointestinal and urological bleeds, retroperitoneal hematomas), whereas hemarthroses, typical of congenital FVIII deficiency, are unusual.

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Case Report

A 69 year old lady, known hypertensive presented to haematology clinic with complaints of bluish patches all over the body, history of gum bleeding and swelling left knee joint of 3 weeks duration (Fig. 1). She denied any family history of bleeding diathesis or any other previous nontraumatic or unexplained bleeding prior to this episode. There was no history of any drug intake. On physical examination she was found to have pallor and a haematoma measuring 2 × 2 × 2 cm on tongue. The knee swelling was nontender and had a positive patellar tap.

Fig. 1 Ecchymotic patches over neck and upper limb

Investigations done revealed a normal erythrocyte sedimentation rate, blood urea nitrogen, creatinine, serum calcium, prothrombin time, bleeding time and platelet aggregation. Her activated partial thromboplastin time (aPTT) was prolonged (110.2 s) with failure to correct (59.2 s) with 1:1 mixing studies. Repeat aPTT was performed two additional times that day to confirm the results and use of appropriate tubes was ensured. Fibrinogen level was 394 mg/dl (normal 200–400 mg/dl) and D-dimer was 8 µgm/dl (normal <5 µgm/dl).

Lupus anticoagulants were positive as evaluated by the Dilute Russell Viper Venom test (dRVVT). An abnormal dRVVT assay was followed by a confirmatory test with hexagonal phospholipids. In this test the inhibitory effects of lupus anticoagulants on phospholipids in the dRVVT was overcome by adding an excess of phospholipids to the assay (phospholipid neutralization test). Systemic lupus erythematosus work-up showed a negative antinuclear and anti-DNA antibodies. The von Willebrand factor, cardiolipin antibody, factor IX, factor XI and factor XII assays were normal.

Serum protein electrophoresis, serum free light chain assays, bone marrow studies and skeletal survey were normal.

Quantification of the coagulation factors revealed the presence of 04 % FVIII activity (measured by FVIII assay in which the percentage of FVIII in plasma is determined by the degree of correction obtained when patient plasma is added to human plasma that has been depleted of FVIII but contains normal concentrations of all other coagulation factors).

Anti-human FVIII inhibitor concentration, as quantified by the Bethesda assay [3] (Table 1) was 08 Bethesda units (BU).

A diagnosis of acquired haemophilia with lupus anticoagulant was made and she was started on oral steroids (prednisone 30 mg daily), and she received two doses of recombinant factor VIIa (rFVIIa) (2.4 & 4.8 mg/dose),

Table 1 The Bethesda Assay

Control plasma	Factor activity 100 %
Dilution 1:2	Factor activity 66%
Dilution 1:4	Factor activity 61%
Dilution 1:8	Factor activity 53%
Dilution 1:16	Factor activity 16%
Dilution 1:32	Factor activity 19%
Dilution 1:64	Factor activity 18%
Dilution 1:128	Factor activity 13%
Dilution 1:256	Factor activity 10%
Dilution 1:512	Factor activity 09%
Dilution 1:1024	Factor activity 07%
Dilution 1:2048	Factor activity 06%

Dilution of patient plasma were incubated with equal volume of normal pooled plasma at 37 °C for 2 h and FVIII assay was done on each of the dilutions. Inhibitor strength was calculated from residual factor activity versus inhibitor units. Inhibitor in Bethesda unit: 8 B.U. Interpretation: Inhibitor with complex kinetics

Tablet Azathioprine (50 mg/daily), Inj IVIG 2 g/kg twice, Inj Rituximab 600 mg infusion on D1/D7/D14/D28.

This treatment regime was followed by marked improvement in her aPTT (which decreased from 35/109.2 to 35/46 s), increase in FVIII levels (4–96 %) and control of bleeding. No adverse reactions were encountered.

The patient was discharged and after one month she was re-evaluated.

No haemorrhagic or thrombotic complications were reported and her coagulation parameters were normal.

Discussion

We report the case of an elderly lady with the simultaneous occurrence of acquired FVIII inhibitors and LAC. The simultaneous presence of LAC and FVIII inhibitor is a rare occurrence, first reported in 1993 [4] and described in association with haemophilia A, myeloproliferative disorders, connective tissue diseases and with no other associated conditions [5]. Though no thrombotic complications were noticed in our case, but in combined FVIII inhibitors with LAC, it is known to occur. Both FVIII inhibitors and LAC will cause prolongation of aPTT; the difference between the two, however, lies in their mechanism of inhibition. The effects of LAC can be confounding when investigating a prolonged aPTT so different aPTT reagents may be used to minimize these effects and increase the sensitivity. A single positive test should be repeated 6–8 weeks later which was positive in our case, because a transient positive may be the result of intercurrent illness or medication [6].

Also in a complex cases a FVIII antibody ELISA may be useful to distinguish between a lupus anticoagulant and an acquired FVIII inhibitor [7].

Inhibitors to FVIII tend to occur in 5–25 % of patients with classical haemophilia receiving FVIII infusion concentrates; however, in nonhaemophilic patients FVIII inhibitors are rare [8]. In more than half the cases, the FVIII autoantibodies occurrence is not related to any disease or clinical condition. Such a form of acquired haemophilia is called idiopathic. Quite a significant percentage of acquired haemophilia patients (20 %) represent individuals with a coexisting autoimmune disease, usually systemic lupus erythematosus, but also with rheumatoid arthritis, ulcerative colitis or a lymphoproliferative disease [9]. 10 % of cases of acquired haemophilia occur postpartum. In nearly 90 % of cases acquired haemophilia manifests itself in a severe hemorrhagic diathesis causing death of 7.9–22 % of patients within a few days [10].

In contrast to classical haemophilia which presents with joint haemarthrosis, mucocutaneous bleeds are more common in cases of acquired haemophilia.

Acquired haemophilia should therefore be suspected in patients with no prior tendency to bleeding for the major part of their lives who suddenly present with symptoms of severe hemorrhagic diathesis, as was seen in our case. Acquired hemophilia is definitely confirmed by detecting the FVIII inhibitor in laboratory tests. These tests are unfortunately only available in specialized hematological laboratories. The time in diagnosing is hence extended, which delays initiation of appropriate treatment leading to decreased survival rates.

The presence of the circulating anticoagulants is definitely confirmed by the APTT prolongation in the mixture of equal volumes of examined serum and of normal serum (so called correction test). Normal plasma mixed with a plasma containing an immediately acting inhibitor will have little or no effect on the prolonged clotting time. In contrast, if normal plasma is added to a plasma containing a time dependent inhibitor the clotting time will be shortened giving a false result. It is therefore necessary to follow a corrected immediate mix study with a incubated mix study to detect time dependent inhibitor. Next it is then essential to determine the FVIII activity, which in healthy individuals ranges between 50 and 150 % of normal values, and in AH patients—0 to 15 % of normal values. The last stage of FVIII inhibitor laboratory diagnosis is to measure its concentration, that is its titer, expressed in Bethesda units (B.U./ml). One B.U. is defined as the titer of antibodies inactivating 50 % of the FVIII activity in the mixture of equal volumes of examined plasma and normal plasma, after a 2 h incubation in a temperature of 37 °C [11].

To differentiate LACs from FVIII inhibitors we used phospholipids dependent tests. The dRVVT test is more sensitive than the aPTT test for the detection of lupus anticoagulant, because it is not influenced by deficiencies or inhibitors of clotting factors VIII, IX or XI.

During the acute stage, effective control of bleeding is the primary objective.

Measures include administration of human FVIII and desmopressin (DDAVP) to patients with low (<5BU) inhibitor titres. Patients with high (>5B.U) FVIII inhibitor titres often require administration of porcine FVIII, activated prothrombin complex concentrate with FVIII bypassing agent (e.g. FEIBA), or more recently recombinant human factor VII (Novoseven). The ultimate therapeutic goal is elimination of the inhibitor. Our patient received rFVIIa infusion to control her bleeding; this modality of treatment has been successfully used for treatment of bleeding in patients with congenital and acquired haemophilias [12, 13]. Other modalities of treatment included use of immunosuppressive therapy with prednisolone, azathioprine, Inj IVIG and Inj Rituximab. Immunosuppressive agents must be used with caution due to the adverse effects such as infection or infertility from cytotoxic agents [14].

In summary, acquired haemophilia (FVIII inhibitors) is a complex disorder because bleeding is severe a prompt and accurate diagnosis is necessary in order to provide adequate therapy. This particular case was interesting since our patient was found to have both a lupus anticoagulant and FVIII inhibitor without a prior history of thrombosis or bleeding.

References

1. Gawryl MS, Hoyer LW (1982) Inactivation of factor VIII coagulant activity by two different types of human antibodies. *Blood* 60:1103–1109
2. Saxena R, Mishra DK, Kashyap R, Choudhry VP, Mahapatra M, Bhargava M (2000) Acquired haemophilia—a study of ten cases. *Haemophilia* 6:78–83
3. Sahud MA (2000) Factor VIII inhibitors. Laboratory diagnosis of inhibitors. *Semin Thromb Hemost* 26:195–203
4. Saxena R, Dhot PS, Saraya AK, Singh H, Malhotra OP (1993) Simultaneous occurrence of factor VIIIc inhibitor and lupus anticoagulant. *Am J Hematol* 42:232–233
5. Brings HA, Waas JK, McCrae KR, Baele HR, Goldstone J (2002) Successful management of life-threatening hemorrhage in a patient with synchronous lupus anticoagulant and factor VIII inhibitor. *J Vasc Surg* 36:853–855
6. Jennings I, Kitchen S, Woods TA et al (1997) Potentially clinically important inaccuracies in testing for the lupus anticoagulant: an analysis of results from three surveys of the UK National External Quality Assessment Scheme (NEQAS) for blood coagulation. *Thromb Haemost* 77:934–937

7. Sahud MA, Pratt KP, Zhukov O, Qu K (2007) Thompson ar. ELISA system for detection of immune responses to FVIII: a study of 246 samples and correlation with the Bethesda assay. *Haemophilia* 13:317–322
8. Sallah S (1997) Inhibitors to clotting factors. *Ann Hematol* 75:1–7
9. Green D, Lechner K (1981) A survey of 215 non-hemophilic patients with inhibitors to factor VIII. *Thromb Haemost* 45: 200–203
10. Sallah S, Wan JY (2001) Inhibitors against factor VIII in patients with cancer. Analysis of 41 patients. *Cancer* 91:1067–1074
11. Kasper CK, Pool JG (1975) Letter: measurement of mild factor VIII inhibitors in Bethesda units. *Thromb Diath Haemorrh* 34:875–876
12. Schulman S (2000) Continuous infusion of recombinant factor VIIa in haemophilic patients with inhibitors: safety, monitoring, and cost effectiveness. *Semin Thromb Haemost* 26(4):421–424
13. Roberts HR, Monroe DM, White GC (2004) The use of recombinant factor VIIa in the treatment of bleeding disorders. *Blood* 104:3858–3864. doi:[10.1182/blood-2004-06-2223](https://doi.org/10.1182/blood-2004-06-2223). PMID:15328151
14. Franchini M, Tagliaferri A, Mannucci PM (2007) The management of haemophilia in elderly patients. *Clin Interv Aging* 2:361–368