DOI: 10.7860/JCDR/2017/21598.10109

Case Report

Pathology Section

Acquired Inhibitor of Factor VIII Presenting as Delayed Wound Healing

SUSHMA NAYAR[1], KISHORE BABU ESAKKIMUTHU PARVATHI[2], MAYILANANTHI KALIANNAN[3], PREMLATHA SIVASAILAM[4]

ABSTRACT

Acquired coagulation factor VIII inhibitor leads to a rare disease i.e., acquired haemophilia which is idiopathic in majority of cases and is seen with autoimmune diseases, haematologic and solid tumours, infections, in the post-partum period and also with certain long-term use of drugs like penicillin and its derivatives, phenytoin, sulfa antibiotics, chloramphenicol, methyldopa, chlorpromazine, levodopa, interferon-α, fludarabine, clopidogrel. We report a case here, with acquired Factor VIII (FVIII) inhibitor acquisition which presented with delayed wound healing as a result of protracted bleeding into the wound. The inhibitor was acquired due to prolonged chlorpromazine use.

Keywords: Chlorpromazine, Idiopathic, Protracted bleeding

CASE REPORT

A 55-year-old male was admitted following a road traffic accident with scalp suture infection, right preseptal cellulitis and right parotitis. He was treated at a local hospital where primary suturing was done and was referred to our tertiary care hospital following non-healing of wound for further management. There was an eschar on the right side of the face. He had a past history of delusions and hallucinations 22 years back for which he was on chlorpromazine and diazepam. There was no family history of bleeding disorder. On examination, patient was febrile, pale with a pulse-rate of 100 beats/minute, blood pressure of 110/70 mmHg. There were no abnormal heart sounds and the lungs were clear. The abdomen was soft and there was no organomegaly clinically. On admission his haemoglobin was 9.5 gm/dL, total count-7,400 cells/mm^3 with a normal differential count, platelet count 90,000/mm^3 of blood.

The peripheral smear showed normocytic normochromic RBCs, erythropenia with few macrocytes, there were no schistocytes, the white blood cells were within normal limits and there was mild thrombocytopenia. The reticulocyte count was 0.1%. Blood urea was 10 mg/dL, creatinine 0.92 mg/dL, serum sodium 139 meq/L, serum potassium 3.9 meq/L and chloride 105 meq/L. The random blood sugar was 96 mg/dL, serum bilirubin 0.4 mg/dL, SGOT-33 units/L, SGPT 53 units/L, serum alkaline phosphatase-98 units/L, gamma glutamyl transferase of 59 units/L, total protein 3.4g/dL. The urine routine was normal. The prothrombin time was normal (15.6 sec with a control of 14.1 sec). The activated partial thromboplastin time was prolonged, 60.6 sec with a control of 29.2 sec. The D-dimer test was negative, ruling out disseminated intravascular coagulation. The bleeding time was normal. The chest X-ray was normal.

The X-ray skull showed no evidence of bony injury to the facial bones and there was no evidence of osteomyelitis. The CT scan facial bones showed no evidence of bony injury and CT of the brain was normal. The ultrasound of the right parotid region showed parotitis and multiple enlarged deep cervical lymph nodes on both sides. The ultrasound abdomen showed splenomegaly. There was no evidence of papilloedema. The wound swab culture and sensitivity showed a moderate growth of *Staphylococcus aureus* which was sensitive to a large number of antibiotics. In view of the prolonged activated partial thromboplastin time, mixing test using normal plasma was done to rule out factor deficiency. The Activated Partial Thromboplastin Time (APTT) did not correct with normal plasma ruling out factor deficiency. Further, mixing study to demonstrate inhibitor was done which demonstrated time dependent inhibitor. The repeat platelet count the following day after admission was 1.2 lacs/mm^3 of blood which further increased to 2.39 lacs/mm^3 of blood three days after admission.

Long term intake of chlorpromazine is known to cause the presence of a time dependent inhibitor. Factor VIII inhibitor was 2.6 Bethesda Units (BU)/ml. Antibody tests for lupus anticoagulant (dilute Russell's viper venom test, kaolin clotting time) were not prolonged. Clot solubility test for FXIII was normal. FVIII levels were 13% of normal.

The patient was started on antibiotics based on the culture and sensitivity reports. The chlorpromazine and diazepam were stopped and patient started on steroids. Slough was excised near the outer canthus of the eye. The patient was managed conservatively and discharged after seven weeks, on antibiotics, steroids, zolpedem and trypsin and chymotrypsin as the wound was showing granulation tissue and was healing well. At the time of discharge, the APTT was 41.1 sec with a control of 29.2 sec.

The patient was re-admitted after a week with pain and swelling of bilateral frontal region of the scalp. On examination, there was a 2 x 2 cm ulcer in the parietal region of the face. In addition there were two irregular ulcers with granulation tissue just below the first scar. Laboratory parameters revealed hyperglycaemia (HbA1C 7.3%). The hyperglycaemia was attributed to the steroids. The APTT was 40.0 sec with a control of 29.2 sec. The patient developed bronchitis during his stay in the hospital which was treated with appropriate antibiotics and bronchodilators. The hyperglycaemia was controlled by oral hypoglycaemic drugs. The wound showed healthy granulation tissue at the end of two weeks and patient was discharged with advice to come for follow-up. However, the patient was lost to follow-up.

DISCUSSION

Acquired FVIII inhibitors are idiopathic or secondary to hereditary haemophilia. Auto-immune inhibitor may be seen with the post-partum state, other autoimmune diseases, malignancies or

drugs. The drugs which are commonly implicated are antibiotics, psychotropics, fludarabine and interferon [1-6]. Drugs like chlorpromazine, hydrallazine, phenytoin, quinine and procainamide may induce the formation of lupus anticoagulants and anti-phospholipid antibodies [5].

Chlorpromazine usage has been associated with autoimmune FVIII inhibitor activity [5-7]. In one study, three patients with chronic schizophrenia on long term chlorpromazine therapy developed asymptomatic IgM inhibitors of the factors involved in the intrinsic phase of blood coagulation. The anticoagulant resulted in decreased levels of all of the clotting factors in the intrinsic pathway (factors VIII, IX, XI, XII, Fletcher factor and Fitzgerald factor). To find the relationship between drug therapy and these IgM inhibitors, nine schizophrenic patients who were on long term chlorpromazine therapy were studied. These patients had inhibitors of coagulation but were asymptomatic [6]. In another study, 75 patients with schizophrenia treated with chlorpromazine or with other anti-psychotic drugs showed abnormalities in coagulation. Patients on long term chlorpromazine therapy had increased levels of serum IgM and there was prolongation of the activated partial thromboplastin time. A circulating inhibitor similar to that seen in patients with systemic lupus erythematosus, was detected. The IgM level had a positive correlation with the prolongation of partial thromboplastin time. There was a direct relationship with the dose and duration of treatment with chlorpromazine [6-8].

An occasional case report of an association between mycoplasma pneumonia infection auto-immune FVIII acquired inhibitory activity has also been noted [9].

Clinical features of auto-immune acquired FVIII inhibitor activity are different from acquired FVIII inhibitor activity in congenital haemophilia. Congenital haemophilia is more common in males whereas Autoimmune Aquired Haemophilia (AAH) is seen in both sexes. Regarding age, in autoimmune FVIII inhibitor there is a bimodal peak whereas congenital haemophilia is seen in a younger age group. A small peak is seen at 20-30 years and a major peak is seen between 68-80 years of age. Our patient was 55-year-old which is closer to the second peak. The high incidence in women aged 20-40 years is related to pregnancy. There is no family history or past history of bleeding disorders in these patients, in contrast to patients with congenital haemophilia [1,3]. Patients with congenital haemophilia have haemarthrosis in contrast to patients with autoimmune acquired FVIII inhibitors in whom haematoma formation in fascial planes or mucosal bleeding and purpura are common as it was seen in our patient. In addition, our patient had delayed wound healing probably as a result of protracted bleeding into the wound. Haemorrhagic manifestations in Auto-immune Acquired Haemophilia A (AAHA) may be severe. An initial presentation of upper and lower gastrointestinal bleeding in previously healthy patients may be seen [2,9].

The laboratory diagnosis of AAHA is based on: 1) the initial detection of an isolated prolonged APTT, which cannot be corrected by addition of normal plasma even after incubating for two hours at 37°C (mixing study); 2) identification of reduced FVIII level with evidence of FVIII inhibitor activity (Bethesda assay). In our case, there was prolongation of APTT with reduced FVIII activity. In addition, our case had an initial platelet count which was low and D-dimer levels were normal. The platelet levels returned to normal in three days without any treatment. This could be attributed to the unexplained splenomegaly as the patient did not have any haemolysis (normal peripheral smear and reticulocyte count). The kinetics of FVIII inhibitory activity is linear in cases of inhibitors associated with congenital haemophilia, in contrast to patients with AAHA. In AAHA the inhibitor activity is non-linear with some FVIII activity being noted after prolonged incubation at 37°C. There is an initial rapid inactive phase followed by a slower phase of equilibrium where some FVIII activity can be measured. Prolongation of partial thromboplastin time can also be elevated with heparin contamination and lupus anti-coagulant, which in our case was negative [2,10,11].

The management of AAHA includes elimination of the underlying disorder, treatment of the acute bleeding and lowering of the antibody titre. About 36% cases have a spontaneous disappearance of their auto-antibodies. However, predictors of such occurrences are not known [1,9,10]. In case of drug administration, discontinuation of the drug and alternate therapy is started as was done in our case.

Suppression of inhibitor formation: Corticosteroids and cyclophosphamide have been used. In approximately 50% of cases, there is disappearance of the antibody within six to eight weeks. Other combinations used are prednisone with azathioprine or prednisone with cyclophosphamide. Patients with severe haemorrhage are treated with large doses of Factor VIII combined with cyclophosphamid [4,10]. Cyclosporine with or without prednisone have been used. Anti-CD20 monoclonal antibody leads to reduction of antibody titre and a durable remission [2]. Intravenous immunoglobulins have also been used in treatment [9]. Plasmapheresis has been tried to reduce levels of inhibitor sufficiently to make replacement therapy possible [2,4]. Relapse is common once the drugs are stopped [10].

Treatment of acute bleeding: Activated FIX can also be used [3]. 1-deamino-8-D-arginine or infusions of FVIII (either human or porcine) increase FVIII levels. FVIII bypassing agents like activated prothrombin complex concentrate recombinant FVIIa. The use of these agents depends on the site of bleeding, severity of bleeding and any co-morbidity. Response to treatment is unpredictable with those in the post-partum period and those following drug use having a favourable outcome. The antibodies tend to disappear spontaneously within a few months after delivery or after the discontinuation of drug therapy [10]. Treatment of the acute bleeding includes activated prothrombin complexes (such as FEIBA, which contains activated Factors VII, IX, and X) or recombinant FVII [10,11].

CONCLUSION

In conclusion, patients on long term chlorpromazine and other antipsychotic drugs may develop inhibitors to Factor VIII. Hence, coagulation profile including APTT with correction studies may be done in cases presenting with protracted bleeding. Discontinuation of the offending drug may lead to correction of the bleeding.

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PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Pathology, Chettinad Hospital and Research Institute, Rajiv Gandhi Salai, Kelambakkam, Kanchipuram, Chennai, Tamil Nadu, India.
2. Assistant Professor, Department of Surgery, Chettinad Hospital and Research Institute, Rajiv Gandhi Salai, Kelambakkam, Kanchipuram, Chennai, Tamil Nadu, India.
3. Associate Professor, Department of Medicine, Chettinad Hospital and Research Institute, Rajiv Gandhi Salai, Kelambakkam, Kanchipuram, Chennai, Tamil Nadu, India.
4. Professor, Department of Surgery, Chettinad Hospital and Research Institute, Rajiv Gandhi Salai, Kelambakkam, Kanchipuram, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Sushma Nayar,
Associate Professor, Department of Pathology, Chettinad Hospital and Research Institute, Rajiv Gandhi Salai,
Kelambakkam, Kanchipuram District, Chennai-603103, Tamil Nadu, India.
E-mail: divya_s35@hotmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **May 24, 2016**
Date of Peer Review: **Aug 19, 2016**
Date of Acceptance: **Mar 31, 2017**
Date of Publishing: **Jun 01, 2017**