Acquired hemophilia A

Poudyal B*
* Clinical Hematologist and hemato-oncologist, NAMS.

ABSTRACT

Acquired hemophilia A is a rare bleeding disorder caused by auto antibodies directed against clotting factor VIII and associated with increased morbidity and mortality. This autoimmune disorder most commonly occurs in the elderly. Although it may be associated with several underlying pathologies, up to 50% of reported cases remain idiopathic. In contrast with congenital hemophilia which is commonly characterized by hemoarthrosis, hemorrhages in patients with acquired hemophilia involve most frequently soft tissues. Here I present the case of acquired hemophilia A successfully treated with oral cyclophosphamide and prednisolone without any adverse outcome.

INTRODUCTION

It is estimated that acquired factor VIII auto antibodies are seen in 0.2 to 1.0 persons/million population annually1. The incidence of acquired hemophilia A increases with age, being very uncommon in children2. Indeed, the incidence in children younger than 16 years has been estimated to be 0.045 per millions/year to compared with 14.7 per million/year in the elderly aged older than 85 years of age3. The diagnosis of acquired hemophilia A in a patients with no previous personal or family history of bleeding is typically based on 1) the initial detection of an isolated prolongation of activated partial thromboplastin time (APTT) which cannot be corrected by incubating for 2 hours at 37 degree centigrade equal volume of patients plasma and normal plasma (mixing study) and 2) Subsequent identification of reduced factor VIII level with evidence of factor VIII inhibitor activity.

CASE REPORT

A 90 years old gentleman was referred to hematology unit for two days history of diffuse large ecchymosis of right thigh and right arm. Physical examination revealed swollen right arm with 6cm × 4cm tender hematoma on anterior portion of right arm. Similarly large hematoma measuring 8cm × 6cm was present in right anterior thigh, which was tender and has restricted the movement of right lower limb. There was no history of trauma. Patient was not in any kind of anticoagulant/anti platelet drugs and denies intake of any other drugs. He denies history of jaundice and any other stigmata of liver disease. He is non alcoholic and non smoker and there is no history of diabetes mellitus and high blood pressure. He denies any similar episodes in past and gives no history of gum bleeding, purpuric rash, melena or hematuria. There is no significant family history. On routine blood examination his Hb is 13g/l, WBC is 6700/ul (N 69%, L 30%, M 1%), platelet count is 300000/ul. Kidney function test and liver function test were found to be within the normal range. USG examination, echo cardiogram and chest x ray didn’t reveal any abnormal findings. RA factor and ANA was negative. Urine and stool test were normal. APTT was 92 sec and PT was found to be normal with INR 1.2. Factor VIII assay revealed 3% of factor VIII activity. Mixing study was done and patient APTT was not corrected even after adding of equal volume
of normal plasma, thus the presence of inhibitor was noted. Patient was prescribed oral cyclophosphamamide (120mg) and prednisolone (60mg). Patient didn’t develop new ecchymotic lesion and his symptoms gradually subsided. Oral cyclophosphamidem was continued till his APTT was corrected and gradually tapered within a month. Since then (for six month) patient is in regular follow up and is completely asymptomatic and enjoying sound health.

DISCUSSION

Acquired inhibitor against factor VIII is termed acquired hemophilia A and it occurs rarely in non hemophilic population. Although uncommon, these auto antibodies are associated with high rates of morbidity and mortality as severe bleeds occurs up to 90% of affected patients and mortality is high, ranging from 85% to 22%. For these reasons patients with acquired hemophilia represents demanding clinical challenge.

The bleeding pattern of acquired hemophilia A is rather different from that of congenital hemophilia A. Thus, most patients with factor VIII auto antibodies have hemorrhages into skin, muscles or soft tissues, and mucus membranes, where as hematosis, a typical feature of congenital factor deficiency, are uncommon. Our patient is 90 years old and he presented with skin bleeding. Monospecific antibodies to factor VIII can arise spontaneously in association with various autoimmune and chronic inflammatory diseases, such as systemic lupus erythematosis, rheumatoid arthritis, and ulcerative colitis. Acquired hemophilia may also be seen in association with hematological malignancy and solid tumors. Certain medication such as penicillin, sulfa antibiotics and phenytoin and dermatological conditions such as psoriasis and pemphigus vulgaris can also present as acquired hemophilia. Most often, acquired factor VIII antibodies are idiopathic, particularly in older patient without apparent underlying disease. I believe our patient falls into idiopathic category since I have ruled out all above mentioned conditions with thorough investigation and clinical history.

Two options are currently available for hemostatic control of acute bleeding: the use of bypassing agents and strategies aimed to raise the level of circulating Factor VIII. Of note any potential additional risk situation for bleeding, such as intramuscular injections, invasive procedure, or use of antplatelet agents should be avoided by passing agents are currently the most used first line treatment, and both the recombinant activated factor VIII and activated prothrombin complex concentrate (APCC) factor VIII inhibitor by passing activity (FEIBA) have been proven effective in the treatment of acquired hemophilia. Both of these drugs are very expensive and not available in Nepal.

Regarding possible therapeutic strategies aimed to raise the levels of circulating FVIII, plasma derived porcine F VIII, which has been successfully used in past to achieve hemostatic levels in situation where human factor VIII was in effective, is not routinely available for clinical use. Human factor VIII concentrates usually represent an in adequate haemostatic therapy unless inhibitor titer is low (ie less than 5 Bethesda unit) but should be used in very high dose to overwhelm the inhibitor again the factor VIII is not easily available and is very expensive options in our context. Other options includes using of high dose intravenous immunoglobulin, immunoadsorption , rituximab and immune tolerance which are expensive modes of treatment and not easily accessible to all the patients.

While numbers of studies have been published on the immunosuppressive therapy of patients with acquired hemophilia, the great majority of them are case reports or small single center retrospective surveys. In one study 31 patients were initially treated with prednisolone at a dose of 1mg/kg for three weeks. If the antibodies were still detectable, the patients were then randomised to receive for an additional six weeks prednisolone alone or prednisolone with oral cyclophosphamide or cyclophosphamide alone (2mg/kg). Approximately one third of patients responded to initial prednisolone course, while approximately 50% of the steroid resistant patients responded to cyclophosphamide containing regimen. The combined data available from uncontrolled cohort studies recently reviewed by Collins, suggested a benefit for combined steroids and cytotoxic drugs. We treated our patients with prednisolone 1 mg/kg and cyclophosphamide 2 mg/kg until the APTT is corrected and slowly tapered the both drug over one month. It took 21 days for APTT to be corrected and one month for factor VIII level to revert back to normal level. Immunosuppressive therapy should be strictly tailored to the patients characterstics (age, sex, and general health status to minimize the treatment related adverse effect. The most feared complication in old age patient is neutopenia related
infection. Thus it should be cautiously used in elderly patients.

CONCLUSION

Acquired hemophilia A is a rare but curable disease. Elderly patient with bleeding diathesis should be screened for acquired hemophilia A. Diagnosis is easy to make and can be done in most of the laboratories. As other forms of treatment are expensive and not easily assessable, patients with acquired hemophilia can be treated with immunosuppressive drugs with careful and regular follow up to avoid neutropenia associated infection.

REFERENCE