ACQUIRED HAEMOPHILIA A CASE REPORT

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SYPNOSIS

A 70 year old man presented initially with anaemia and swelling of the right leg which was diagnosed as deep vein thrombosis. Three weeks later he developed extensive bruising due to circulating factor VIII inhibitors. He had responded well to cyclophosphamide, steroids and fresh frozen plasma therapy.

INTRODUCTION

Factor VIII inhibitors occur in 5-20% cases of haemophiliacs especially those treated with repeated transfusions. These can also develop in non-haemophiliacs especially in the elderly and female patient. We report here a case of acquired haemophilia without any obvious cause.

CASE REPORT

A 70 year old Chinese man was admitted on 21.11.81 for swelling of the right leg up to the midthigh. On 18.11.81 he had sprained his right foot followed by bruising over the dorsum of the same foot. This was followed by pain over the right calf associated with progressive swelling of the leg up to the thigh. He also noted bruises over the right thigh after vigorous massage and bruises over the right palm after pressure from the walking stick. He had no past history of easy bruisability or family history of bleeding tendency. He had diabetes since 1962 controlled on diet alone.

On admission he was noted to be pale. The right lower limb was swollen up to the mid-thigh and was tender and warm. Ecchymoses were present over the anterior aspect of the thigh. There were no other

significant findings of note.

Initial investigations showed:- Hb 5.1 g% TWC 7,500 Platelet 150,000 PT 13 secs PTT 38 secs (Control 13, 38 respectively).

He was managed as for deep vein thrombosis of the right leg and he improved with anticoagulant therapy.

No venogram was done as the subsequent coagulation profile was abnormal.

Relevant investigations for the anaemia showed: PBF:- Hypochromic, microcytic with moderate anisocytosis and few macrocytes. Serum Iron: 100 ug/dl TIBC: 240 ug/dl Serum folate 10.3 ug/l. Vit B12: 150 ug/l ESR 85 mm/hr Retic count: 1.3% Direct Coomb's test:- negative LE/RA/ANF were negative. Stools for ova and cysts were negative. Gastroscopy showed non-active prepyloric ulcer. Stools were negative for occult blood. He was given intramuscular B12 injections and other hematinics and his haemoglobin rose to 10 g% with transfusion. He had earlier been given intravenous ampicillin on admission and had developed moderately severe allergic rashes to the ampicillin.

On the third intramuscular injection of B12 he developed intramuscular hematoma over the right thigh. Subsequently spontaneous bruises appeared over the right arm, left thigh and the sacral area.

Repeat haemoglobin had fallen to 8.5 g%. His thrombotest, however, had remained stable ranging from 6 to 14% PT/PTT done on 9.12.81 showed a PT of 16 secs (13 control) and PTT more than 2 mins (control 38 secs). Despite fresh frozen plasma and intravenous Vitamin K injections his ecchymoses had worsened and he developed a large hematoma over the right thigh and haemarthrosis of the right knee.

A full coagulation profile done on 14.12.81 showed: Hb: 5.2 g% TWC: 13,300 Platelet: 150,000 PTT: 64 secs (control 34 secs) PT 13 secs (control 14 secs) PTT (50% patient's plasma: 50% normal plasma) 64 secs (control 34 secs) Thrombin time: 10 secs (control 10 secs). Factor VIII inhibitor level: 1/32.

Based on these investigations the diagnosis of acquired haemophilia was made.

Therapy was started on 16.12.81 with fresh frozen plasma and intravenous hydrocortisone and oral cyclophosphamide. On 29.12.81 his PTT had reverted to normal and the bruises subsided except for residual right thigh haematoma and haemarthrosis. His PTT remained normal and he was given altogether 52 pints of fresh frozen plasma between 16.12.81 and 31.12.81. The factor VIII inhibitor level was less than ½ on discharge.

DISCUSSION:

This patient presented initially with swelling of the right leg associated with anaemia. Our initial impression of deep vein thrombosis rather than bleeding into the leg was based on the normal initial coagulation profile and the good response to anticoagulant therapy. However, in retrospect, this diagnosis was in doubt as it is not possible to have a hypercoagulable state to be followed shortly by a haemorrhagic haemophilia-like state. It is also uncommon to observe ecchymoses and bruising in de novo deep vein thrombosis. The anaemia of 5.1 g% on admission could not be well explained by any obvious cause except for bleeding into the leg.

The leading clue to the diagnosis of this particular bleeding disorder was the normal prothrombin time and the prolonged partial thromboplastin time which was present three weeks after heparin had been stopped. Thus this abnormal coagulation pattern could not be explained by the effect of heparin. Since the prothrombin time was normal and the partial thromboplastin time was prolonged, the defect might be due to factors VIII, IX, XI or XII deficiencies. A congenital cause seemed unlikely as there was no family history of bleeding tendency and because of the late onset of this bleeding disorder. The final diagnosis was made after assay of factor VIII inhibitors.

Acquired haemophilia is caused by the development of

Coagulation Profile of the patient

Date	PT (secs)	PTT (secs)	Thrombotest	Factor VIII inhibitor	Management
21.11.81	14	38			Anticoagulant therapy started
22.11.81	20	60	14		
23.11.81	16	61	10		
24.11.81	16	90	9.5		
25.11.81	16	90	10		
9.12.81	16	>120	13		Anticoagulant therapy stopped
10.12.81	16	180	14		
16.12.81	14	75	16	1/32	Started on Fresh Frozen Plasma Cyclophosphamide Hydrocortisone Prednisolone
31.12.81	14	35	12.5	1/2	Fresh Frozen Plasma stopped (52 pints)
19.1.82 (discharged)	13	34		<1/2	Prednisolone (25 days) Cyclophosphamide (35 days)

IgG antiboties which neutralise clotting factor VIII. In haemophilia, the development of such antibodies may be related to replacement therapy with factor VIII in 5 to 20% of cases and most commonly in those severely affected (1, 2). However, in non-haemophiliac cases as in the patient reported here, inhibitors can also develop usually in the elderly and may be idiopathic. They can also occur in women after childbirth especially when there is rhesus incompatibility; in association with autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus; inflammatory bowel conditions as in ulcerative colitis and Crohn's disease; malignancies especially lymphomas; inflammatory skin conditions such as pemphigus and erythema multiforme; and allergy to drugs such as penicillin and sulphonamides (3). In younger age groups, acquired haemophilia is most often seen after a normal pregnancy and in the elderly age group it may be idiopathic. We have been unable to find any evidence of autoimmune disease or malignancy in this patient and further follow-up will be necessary. The clinical setting favouring the development of these antibodies in our case are allergy to ampicillin and the elderly age group.

The laboratory diagnosis resembles those seen in haemophilia A. Factor VIII levels may be nil in those severely affected but may range to 10% or higher. Prothrombin time and bleeding times are normal. Partial thromboplastin time may be prolonged despite 50% dilution with normal plasma.

Patients with factor VIII antibodies pose a difficult problem of management as life-threatening haemorrhage is a potential risk especially in surgery.

The first prinicple in the management is the avoidance of factors provoking haemorrhage such as surgery, invasive procedures, careless venepunctures and intramuscular injections.

Large amounts of factor VIII concentrates may produce remission in some especially if the antibody titre is low and kinetic studies show complex neutralisation of factor VIII (4). Blatt (5) used an arbitrary loading dose of 10,000 units of high potency concentrates followed by 300—1000 units per hour by continuous infusion in adults. The disadvantages of large doses include (a) amnestic response (b) cost (c) haemolysis from blood group isoantibodies (d) high fibrinogen levels (e) transmission of hepatitis and (f) thrombocytopenia from the use of porcine concentrates. (6) There are two types of immunological response to factor VIII concentrates. In the high responder group, amnestic response occurs with increased antibodies as more concentrates are given while in the low responder group, there is no amnestic response. Thus therapy needs to be prompt and vigorous as once haemostasis is secured, the rise of inhibitors is not as harmful as before therapy. Due to the cost of factor VIII concentrates and the danger of amnestic response, we did not give our patient any factor VIII transfusion.

Fresh frozen plasma infusion is generally useless because of the small content of factor VIII can be readily inactivated by circulating antibodies that are present (7). Also the large volumes which need to be given may cause cardiac failure as in our patient.

Steroids are generally ineffective unless the primary disease is responsive to steroids. Immunosuppressants may be ineffective in haemophiliacs but for the spontaneous group, antibodies may disappear with therapy. The combination of steroids and cyclophosphamide may be useful (7). The main disadvantages of immunosuppresants are that of interference with wound healing and the risk of infections in patients undergoing surgery. We had started our patient with steroids and cyclophosphamide right from the start after the diagnosis. Factor VIII antibodies disappeared two months after therapy but we are uncertain whether this could be due to the drug therapy or the natural remission of his illness.

Activated prothrombin complex concentrates, a complex containing prothrombin, factors VII, IX, X and XI, has been successfully used for the treatment of haemorrhagic episodes in patients with factor VIII inhibitors (Kurczynski et al 1974). The activated factor bypasses the contribution of factor VIII and directly activates steps in coagulation. The potential complications here, which are of great concern are its thrombogenic properties and hepatitis. Although activated prothrombin complex is an effective form of therapy, it is useful only if there are no alternatives in view of the potential dangers present.

Intensive plasma exchange has been found to be useful in the prevention and management of haemorrhage in patients with inhibitors to factor VIII (8). This method is particularly useful for patients about to undergo major surgery when haemostasis is required over a long period. Further experience is required in the management of patients whose lives are threatened by haemorrhage due to the inhibitors.

In summary, the most important principle in the management is the prevention of trauma. Most of the methods described have risks and are very expensive. Clinical trial evidence of effectiveness is scanty. To be effective, therapy needs to be aggressive and sustained. Spontaneous remission may sometimes occur and maybe only weakly related to the activity of the associated disease.

ACKNOWLEDGEMENT:

We wish to thank Dr Goh Choo Ngoh for her assistance in the relevant haemotological investigations and management of this patient.

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