Circulatory Factor VIII Inhibitor Associated with Pregnancy

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A 35-year-old female patient developed persistent painless haematuria during her third pregnancy and severe life-threatening bleeding occurred shortly after delivery. Laboratory findings were consistent with the presence of factor VIII inhibitor. The initial symptoms started 6 weeks after she was transfused with red blood cells.

Factor VIII inhibitors occur in 5-10% of all patients with haemophilia-A. Rare cases have been reported to occur in the postpartum state, in association with underlying autoimmune disease and de novo in the elderly.

In this report we describe a patient in whom a factor VIII inhibitor was detected shortly after delivery but whose initial symptoms started during pregnancy, 6 weeks after she had a packed red cell transfusion. A review of the literature is included.

Method
Prothrombin time (PT) was measured using rabbit thromboplastin Manchester reagent. Activated partial thromboplastin time was measured using Cephaloplastin reagent (Dade Company, Baxter Health Care Corporation, Dade Division, Miami FL 33157-0672, USA). Bleeding time was determined according to the template method. Thrombin time was measured using human thrombin (Fibrinex, Ortho Diagnostic Systems Inc., a Johnson & Johnson Company, Rariton, NJ 08869 USA). Factors VIII, IX, XI, XII activities were determined using a one-stage method. The fibrinogen level was determined using the FBG method (Dupont aca™ 111 analyzer, Dupont Clinical Systems Division, Wilmington, DE 19898 USA), normal range 0.2-0.4 g/l.

The presence of an inhibitor was demonstrated by performing serial activated partial thromboplastin time (aPTT) on a 50:50 mixture of patient plasma and normal pooled fresh plasma incubated at 37 °C for 120 min. Normal pooled fresh plasma served as control.

Case Report
The patient, a previously healthy 35-year-old Egyptian woman, with no history of bleeding diathesis, was found to be severely anaemic in the 27th week of the pregnancy. The haemoglobin was 6 g/dl, HCT 21.7 and MCV 66 fl. On 25 May 1989, she was transfused with two units of packed red blood cells (RBCs) with a rise in the Hb to 8.3 g/dl and subsequently maintained on oral iron and folic acid.

On 12 July 1989 the patient was admitted with gross painless haematuria of 3 days duration. Urine analysis showed many RBCs but no casts and urine culture was negative. Renal ultrasound was normal. Mild haematuria persisted throughout her pregnancy with no bleeding from any other sites. On 8 October 1989, she delivered two healthy fraternal twins by an uncomplicated vaginal delivery. The estimated blood loss was 300 ml. An intravenous pyelogram 2 days after delivery because of the persistent haematuria was normal. One week after delivery the patient was readmitted through the emergency room because of severe vaginal bleeding. She was shocked and hypotensive. The Hb was 3.3 g/dl, platelet count 301 × 10^9/l, PT: 12.3 s, aPTT: 87.7 s, serum fibrinogen 3.25 g/l, fibrinogen degradation products were not detectable. Her condition quickly stabilized and the bleeding diminished after the infusion of 3 units of packed red cells and 3 units of fresh frozen plasma (FFP). Dilatation and curettage were performed the day after admission without complications.

Blood clots and some residual decidua tissue were evacuated. When seen by the haematology team there was
Table 1

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Incubated mixture</th>
<th>Normal control plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>45</td>
<td>40.5</td>
</tr>
<tr>
<td>15</td>
<td>46</td>
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<td>41.5</td>
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<tr>
<td>120</td>
<td>90</td>
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</tr>
</tbody>
</table>

aPTT: Activated partial thromboplastin time.

mild vaginal bleeding and oozing from venipuncture sites. Additional laboratory tests showed the thrombin time to be 7.5 s. The bleeding time was 7 min.

A serial aPTT done on a 50:50 mixture of the patient’s plasma and normal pooled plasma incubated over 120 min at 37 °C showed a progressive prolongation of aPTT of the mixture as shown in Table 1.

The activities of various factors were: factor VIII 2.8%, factor IX 60%, factor XI 74%, factor XII 28%; ANA and rheumatoid factor tests were negative. The anti-DNA test was not performed. Two days after admission vaginal bleeding became more severe and the patient was started on intensive replacement therapy with factor VIII concentrate; 5000 units were administered as an i.v. bolus followed by 2000 units i.v. every 3 h. In addition she received a daily average of 6 units of cryoprecipitate and 5 units of FFP. She also received oxytocin and oral mephargoine. However, the vaginal bleeding persisted and on several occasions was quite severe requiring the transfusion of packed erythrocytes. On 24 August 1989 the patient developed a large ecchymosis involving the whole right arm. For this reason she was subjected to plasmapheresis using FFP as partial replacement fluid. She was also started on immunosuppressive therapy in the form of 60 mg prednisone and 100 mg cyclophosphamide daily. On 5 September 1989 immunosuppressive therapy was changed to an intermittent modified COP regimen (a combination of cyclophosphamide, vincristine and prednisone) after perusal of a recent report indicating a favourable result using this regimen combined with factor VIII infusion in patients with spontaneously acquired factor VIII inhibitor. On this intensive therapy bleeding from all sites gradually ceased and on discharge on 26 September 1989 the patient was completely asymptomatic. The aPTT on the day before discharge was 68.2 s.

During her hospital stay this patient had received a total of 15 units of packed RBC, 142 units of FFP, 139 units of cryoprecipitate and 4 units of whole blood. The assay of factor VIII activity was repeated on several occasions during her stay and it showed minimal improvement as shown in Table 2.

This patient was seen on 3 October 1989 as an outpatient and was still asymptomatic. The repeated aPTT was 88.6 s. Another course of the modified COP protocol was administered. She was lost to follow-up after this visit.

Her husband was contacted about 2 months after the last clinic visit and he indicated that they left to go to Egypt shortly after 3 October 1989. While in Egypt they consulted a gynaecologist who subjected the patient to hysterectomy. The patient died soon after the surgery as a result of uncontrollable bleeding from the surgical site. The indication for this surgery was not clear. The husband stated that the patient did not experience any bleeding after she left Qatar and up to the time of the surgery. He was not told of any abnormalities in the surgical specimen.

Discussion

About 35 cases of factor VIII inhibitor have been reported in the postpartum period, but only one case was diagnosed during pregnancy. Our patient had her initial symptoms during pregnancy and it is possible that the inhibitor was present at that time.

The aetiology of pregnancy-associated factor VIII inhibitor is unknown. Only three cases were reported to have an underlying autoimmune disease. One hypothesis is that allotypes to factor VIII exist and the mother develops antibodies against paternal allotypic determinants inherited by the fetus which cross-react with her own factor VIII. The symptoms in our patient started 6 weeks after the transfusion of packed RBC, raising the possibility of an immune reaction against an allotypic factor VIII in the transfused blood.

The presence of factor VIII inhibitor can cause severe life-threatening bleeding. Our patient, required intensive multimodality therapy before we were able to control her bleeding. The subsequent course after the acute bleeding seems to be variable. Ten patients with postpartum factor VIII inhibitor were reported to have had a normal second pregnancy without bleeding complications. Six were in remission at the time of second pregnancy and did not relapse. One patient developed a rising factor VIII inhibitor titre during the second pregnancy but she did not develop any bleeding complications. In 11 patients the inhibitor disappeared spontaneously. The factor VIII level of our patient was measured on several occasions during her hospital stay and showed only minimal improvement as shown in Table 2. Her rather premature death from uncontrollable bleeding following hysterectomy done at another hospital, after she survived the initial bleeding episode, emphasizes the seriousness of this disorder and the great difficulties encountered in controlling bleeding in factor VIII inhibitor patients.

Table 2

<table>
<thead>
<tr>
<th>Date</th>
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<tr>
<td>26 August 1989</td>
<td>2.5</td>
</tr>
<tr>
<td>4 September 1989</td>
<td>3.0</td>
</tr>
<tr>
<td>19 September 1989</td>
<td>6.0</td>
</tr>
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<td>25 September 1989</td>
<td>9.0</td>
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The management of acute bleeding episodes in patients with factor VIII inhibitor is one of the most difficult and challenging of medical problems. Several therapeutic modalities have been utilized, but none have been proven to be satisfactory.

Continuous infusion of high dose of factor VIII is commonly used in an effort to neutralize the inhibitor and raise factor VIII activity, taking advantage of the time dependence of the neutralizing antibody. This procedure is more effective in patients with low inhibitor titres than in those with higher titres; it may provoke an anamnestic rise in the anti-factor VIII levels in susceptible haemophilic patients (‘high responders’).

Both activated and non-activated prothrombin complex concentrates were shown to be effective in controlling haemarthrosis and muscle bleeding in haemophilic patients with factor VIII inhibitors.11,12

Exchange plasmapheresis can be utilized transiently to lower the antibody titre, after which infusion of factor VIII concentrate may achieve a haemostatic level.1,13

Human factor VIII antibodies are generally less reactive with bovine and porcine factor VIII.14 Porcine factor VIII concentrates have been used to treat patients with factor VIII inhibitors. The crude factor VIII concentrate which was used in the past caused considerable adverse reactions including allergic reactions, thrombocytopenia and progressive loss of activity.1 The polyelectrolyte fractionated concentrate (PE Porcine VIII, Hyate: C, Spewood, Wrexham, Wales), which became available in 1980 has been effectively used in the treatment of severe bleeding episodes in high responding haemophilic patients and in patients with spontaneously acquired factor VIII antibodies.14,15

Adverse reactions were reported to be mild and considerably less than the reactions associated with the earlier preparation.

The long-term goal of management in patients with factor VIII inhibitors is to attempt to eliminate the inhibitor and to prevent anamnesis. To achieve this goal immunosuppressive therapy, utilizing corticosteroids, cytotoxic drugs or a combination of both is commonly used. The efficacy of such therapy can be difficult to evaluate due to the small number of patients in most reports and because the inhibitors disappear spontaneously in some patients.

Most reports of immunosuppressive therapy in patients with factor VIII inhibitors suggest that such therapy is effective in patients with spontaneously acquired factor VIII inhibitors in contrast to haemophilia-A patients with inhibitors who were not shown to respond to immunosuppressive therapy.16–18 Recently, intermittent cyclophosphamide, vincristine and prednisone combined with factor VIII infusion resulted in elimination of the inhibitor antibodies in 11 out of 12 patients with spontaneously acquired factor VIII inhibitors; the same therapy was ineffective in five haemophilic patients with inhibitors.2

Intravenous infusion of high-dose immunoglobulin was reported to be followed by a prolonged decrease in the level of the inhibitors in four non-haemophilic patients with factor VIII inhibitors.19,20 Two haemophilic patients with inhibitors did not respond to high dose i.v. IgG, moreover, two additional non-haemophilic patients with factor VIII inhibitors failed to respond to high dose i.v. IgG.21 The role of high dose i.v. immunoglobulin in the management of factor VIII inhibitor patients remains controversial.

A combination of factor VIII infusion, cyclophosphamide and high dose i.v. immunoglobulin followed by regular prophylactic treatment with factor VIII was successful in eliminating factor VIII inhibitors in nine out of 11 haemophilic A patients with inhibitors.22 Patients with high inhibitor titres had the inhibitor levels lowered by absorption to protein A before therapy was initiated. This is a rather promising approach especially since tolerance was achieved in a few weeks even in high-responding patients.

Another encouraging report involves five haemophilic patients who initially had high titres, high-responding anti-human factor VIII inhibitors and were lacking anti-porcine factor VIII activity. They received home therapy with porcine factor VIII for between 2 and 8 years. All five patients lost their initial anti-human factor VIII inhibitors after treatment with porcine factor VIII was started.23 In three patients, treatment with human factor VIII was reintroduced after 2 to 3 years of treatment without the recurrence of the inhibitor in any of them. Porcine factor VIII therapy may have a role in the desensitization of some patients who possess a factor VIII inhibitor.

References


