Acquired Factor VIII Inhibitor

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Surgery, head page at the beginning of this issue. ANESTHESIOLOGY’s articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of this issue.
Discussion

Our case report demonstrates the catastrophic consequences of performing extensive visceral surgery in a nonhemophilic patient with a newly acquired Factor VIII inhibitor and insufficient preoperative preparation. If a patient is scheduled to undergo major surgery and presents with an abnormal coagulation study, the pathologic results should be verified preoperatively. Should the repeat study generate an abnormal value, the patient should be specifically asked about signs of a bleeding disorder (e.g., soft tissue hematoma) and a coagulation expert should then be consulted.

Patient Presentation and Demographic Characteristics

Our patient was 57-yr-old, previously healthy with no congenital hemophilia, and presented with progressively more severe postoperative bleeding. In a prospective cohort study, nonhemophilic patients with autoantibodies to coagulation factors (acquired hemophilia) were studied by the United Kingdom Hemophilia Centre Doctors’ Organization.3 Over a 2-yr period they identified 178 patients. Patients were mostly older than 65 yr (85%; median age 78 yr) and had no coexisting disease (63%). Acquired hemophilia was associated with malignancy (15%), autoimmune or collagen vascular disease (15%), pregnancy (2%, mostly postpartum) or dermatologic diseases (3%), and these coexisting diseases are significantly more frequent in younger patients. Spontaneous bleeding frequently occurs subcutaneously (25%), in muscle (45%), or in the gastrointestinal tract (22%). Fatal bleeding is present in 9% (gastrointestinal, intracranial, retroperitoneal, and perioperative).

Establishing the Diagnosis of Acquired Hemophilia

If unexpected bleeding occurs, adequate first-line treatment should be given.# Our patient presented with diffuse bleeding and a prolonged aPTT. This can be because of factor deficiencies (VIII, IX, XI, XII, or fibrinogen), von Willebrand syndrome, lupus anti-coagulants, medication effects (e.g., heparin, hirudin, activated protein C), fibrinogen split products, or acquired hemophilia with antibodies against coagulation factors (treatment-related alloantibodies in hemophilic patients or autoantibodies in nonhemophilic patients). In the case of acquired Factor VIII inhibitors as a result of autoantibodies, a decreased Factor VIII is found and the pathologic aPTT is not corrected if aPTT is determined after mixing patient and pool plasma. Other coagulation studies such as international normalized ratio and factor concentrations (fibrinogen, Factors II, IX, XI, XII, XIII, and von Willebrand factor ristocetin cofactor and antigen, table 1) are within normal limits. Lupus coagulants

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Table 2. Outcome of Surgery in Patients with Unknown Acquired Factor VIII Inhibitor

<table>
<thead>
<tr>
<th>Underlying Disease</th>
<th>Type of Surgery</th>
<th>Time (Surgery to Bleeding)</th>
<th>Treatment of Bleeding</th>
<th>Outcome</th>
<th>Preop. aPTT (s)</th>
<th>Factor VIII Inhibitor (BU)</th>
<th>Inhibitor Elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis (infected hip arthroplasty)</td>
<td>Girdlestone arthroplasty</td>
<td>None</td>
<td>&gt;100 PRBC, aPCC, tranexamic acid</td>
<td>Hip excitation</td>
<td>45-65</td>
<td>n.d.</td>
<td>Steroids, IVIG</td>
</tr>
<tr>
<td>Posttraumatic soft tissue necrosis</td>
<td>Free muscle flap</td>
<td>None</td>
<td>40 PRBC</td>
<td>No sequelae</td>
<td>32.6</td>
<td>50</td>
<td>Steroids, plasma exchange</td>
</tr>
<tr>
<td>Chronic low back pain</td>
<td>Lumbar discectomy</td>
<td>8 days</td>
<td>16 PRBC, factor VIII (human), rFVIIa, tranexamic acid</td>
<td>No sequelae</td>
<td>44</td>
<td>9</td>
<td>Steroids</td>
</tr>
<tr>
<td>Lower extremity compartment</td>
<td>Hematoma evacuation</td>
<td>None</td>
<td>&gt;10 PRBC, factor VIII (human), aPCC</td>
<td>No sequelae</td>
<td>148</td>
<td>64</td>
<td>Steroids, cyclophosphamide</td>
</tr>
<tr>
<td>Upper extremity compartment</td>
<td>Fasciotomy (forearm)</td>
<td>None</td>
<td>No PRBC, factor VIII</td>
<td>No sequelae</td>
<td>51</td>
<td>n.d.</td>
<td>None</td>
</tr>
<tr>
<td>Acute cholecystitis</td>
<td>Open cholecystectomy</td>
<td>None</td>
<td>6 PRBC, factor VIII</td>
<td>Sudden death (12 h later)</td>
<td>n.d.</td>
<td>6</td>
<td>IVIG</td>
</tr>
<tr>
<td>&quot;Recent&quot; cholecystitis</td>
<td>Cholecystectomy</td>
<td>4 days</td>
<td>&quot;Multiple&quot; PRBC, factor VIII</td>
<td>Recurrence of inhibitor</td>
<td>Normal</td>
<td>5</td>
<td>None</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Cholecystectomy</td>
<td>18 days</td>
<td>4 RBC, rFVIIa, &quot;Multiple&quot; PRBC, factor VIII</td>
<td>Death (bleeding)</td>
<td>Normal</td>
<td>22.4</td>
<td>—</td>
</tr>
<tr>
<td>Ischemic bowel disease</td>
<td>Bowel resection</td>
<td>4 days</td>
<td>Unknown number of PRBC, rFVIIa, factor VIII</td>
<td>No sequelae</td>
<td>Normal</td>
<td>3.25</td>
<td>Steroids, IVIG, plasma exchange</td>
</tr>
<tr>
<td>Abdominal wall hernia</td>
<td>Hemia repair</td>
<td>4 days</td>
<td>Unknown number of PRBC, factor VIII</td>
<td>Recurrence of inhibitor</td>
<td>Normal</td>
<td>10.4</td>
<td>Steroids, IVIG, cyclophosphamide</td>
</tr>
<tr>
<td>Vaginal delivery with episiotomy</td>
<td>Curettage, then laparotomy</td>
<td>6 days</td>
<td>Unknown number of PRBC, factor XI concentrate</td>
<td>Death (bleeding)</td>
<td>n.d.</td>
<td>19</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>Unruptured cerebral aneurysm</td>
<td>Aneurysm clipping</td>
<td>7 days</td>
<td>No PRBC, factor VIII</td>
<td>Intracranial bleeding</td>
<td>Normal</td>
<td>2 BU</td>
<td>Steroids, cyclosporine</td>
</tr>
<tr>
<td>Retropharyngeal hemorrhage with airway obstruction</td>
<td>Hematoma evacuation</td>
<td>None</td>
<td>No PRBC, rFVIIa, aPCC</td>
<td>Temporary tracheostomy</td>
<td>Ratio 2.2</td>
<td>67</td>
<td>Steroids</td>
</tr>
<tr>
<td>Dental decay</td>
<td>Extraction of teeth</td>
<td>None</td>
<td>&gt;18 PRBC, rFVIIa, aPCC, aminocaproic acid, 4 PRBC, factor VIII</td>
<td>Retroperitoneal hemotoma</td>
<td>59</td>
<td>10.4 BU</td>
<td>Steroids, IVIG, cyclophosphamide</td>
</tr>
<tr>
<td>Cataract</td>
<td>Cataract surgery</td>
<td>12 hours</td>
<td>&gt;18 PRBC, rFVIIa, aPCC</td>
<td>Loss of vision</td>
<td>n.d.</td>
<td>61</td>
<td>Steroids, IVIG</td>
</tr>
</tbody>
</table>

aPCC = activated prothrombin complex concentrate; IVIG = intravenous immune globulin; n.d. = not determined; PRBC = packed red blood cell concentrates.

are not present. Thrombocyte count and function are also normal. Factor VIII inhibitor concentrations are determined by mixing patient and control serum in a dilution curve using an enzyme-linked immunosorbent assay. One Bethesda unit describes a 50% decrease in Factor VIII activity (Nijmegen-Bethesda protocol). Importantly, neither Factor VIII levels nor inhibitor concentrations accurately predict bleeding intensity. A Factor VIII gene analysis is not indicated, since it is an acquired disease without a genetic background.

A number of case reports describe the clinical course and outcome of surgeries in patients with acquired Factor VIII inhibitor but no accompanying congenital hemophilia A (table 2). Patients will sometimes not be identified preoperatively for several reasons (table 2). Coagulation studies can be near or even within normal limits before surgery. Alternatively, hospital policy or national guidelines do not demand these studies for minor surgical procedures, and these will thus not be available preoperatively. Mistakes can occur and surgery is performed despite abnormal values, or the risks are underestimated. However, even minor surgical procedures (e.g., insertion of central lines or extraction of teeth) can have devastating consequences in these patients (table 2). Bleeding can occur during or immediately after surgery, but often involves a time delay of several days.

Treatment of Acute Bleeding

Our patient presented with two major episodes of acute bleeding. During the first episode, diffuse bleeding was noticed on surgical reexploration and was controlled by aFVIIa by POD 14. De novo and massive bleeding started again on POD 29. It originated from the gastroduodenal artery and was probably a result of an erosion caused by a drainage tube. It finally was controlled by surgical ligation, abdominal packing, and rFVIIa treatment.

While patients with congenital hemophilia A are treated with Factor VIII concentrates, this is not recommended in patients with acquired hemophilia. Our patient was initially treated with fresh frozen plasma and Factor VIII concentrates. Especially Factor VIII concentrates are ineffective, and might even increase bleeding since they can boost the formation of autoantibodies. Thus, two treatment options exist that are recommended in international consensus guidelines: aPCC (50–100 units/kg every 8–12 h with a maximum daily dose of 200 units/kg), and rFVIIa (90 μg/kg, up to every 2 h because of its short half-life). If either aPCC or rFVIIa is ineffective, the other should be tried. aPCC is an activated prothrombin complex and bypasses the necessity of Factor VIII activation. rFVIIa induces supraphysiologic concentrations of Factor VIIa, which bind to
thrombocytes and thereby directly activate Factor X and subsequently thrombin. Both aPCC and rFVIIa are very expensive, and daily treatment costs can exceed $20,000.

Importantly, bleeding can persist for days or even weeks. Furthermore, inhibitors can reoccur after successful elimination, leading to recurring bleeding episodes. In our patient, bleeding persisted for almost 10 weeks, leading to massive transfusion requirements (fig. 1), but was finally controlled.

**Factor VIII Inhibitor Elimination and Surgery in Patients with Known Acquired Hemophilia**

Inhibitor elimination aims to suppress autoantibody production using immunosuppressive agents. Treatment should involve steroids (prednisolone 1 mg · kg⁻¹ · day⁻¹) with or without cyclophosphamide (1.5–2 mg · kg⁻¹ · day⁻¹) for 4–6 weeks. Rituximab is considered a second-line treatment. For high-risk patients, plasmapheresis with immune adsorption and intravenous immunoglobulin treatment with or without Factor VIII substitution has been recommended. Complete remission can be achieved in 70–80% of patients, and involves a median time of 40–60 days (range, 2–560 days). Since acquired hemophilia A is more frequent in older patients, it is important to note that inhibitor elimination occurs faster in older patients than in the younger age group.

We achieved complete remission in 70 days using corticosteroids, immune adsorption, and high-dose intravenous immunoglobulins. Cyclophosphamide was not used, and only a single dose of rituximab was given because of the recurrent infectious complications.

If patients with acquired hemophilia are identified preoperatively, surgery should be postponed except for life-threatening emergencies. Prior inhibitor elimination should be seriously considered in collaboration with coagulation experts. If successful, surgery has been reported to occur without bleeding complications (e.g., lobectomy). If surgery cannot be postponed, prophylactic treatment with FEIBA or rFVIIa should be seriously considered.

In summary, acquired hemophilia A is caused by autoantibodies (so-called inhibitors) to coagulation factors (mostly Factor VIII). Patient can be often identified by a history of unexplained bleeding episodes and by a prolonged aPTT. Before surgery, inhibitor elimination should be attempted. If surgery is urgent or unexpected bleeding occurs, treatment options include aPCC or rFVIIa.

**References**