A CQUIRED HEMOPHILIA A occurs as a result of development of inhibitory autoantibodies to factor VIII in the coagulation cascade.1 These antibodies result in impaired hemostasis and bleeding disorders of variable severities through varied mechanisms including impairment of binding of factor VIII to membrane phospholipids, factor IX, and/or von Willebrand factor.2 Common presentation includes mucocutaneous and soft tissue hemorrhage, although hemarthroses typically seen in severe congenital hemophilia A are rare.1,2 Most patients are diagnosed during the course of evaluation of bleeding symptoms, and for such patients requiring cardiac surgery, management has been described previously.3,4 The successful postoperative management of a case of acquired hemophilia A diagnosed perioperatively after cardiac surgery is reported here.

CASE REPORT

A 55-year-old male with bileaflet mitral valve prolapse, severe mitral regurgitation (regurgitant volume 80 mL and effective regurgitant orifice 0.52 cm²), normal biventricular function, mild left ventricular enlargement, mild coronary artery disease, and New York Heart Association Class II symptoms presented for minimally invasive mitral valve repair. Past medical history was significant for psoriasis, psoriatic arthritis, iron deficiency anemia, and chronic lymphocytic leukemia (CLL) that had been in remission for 1 year. Preoperative medications included alendronate, aspirin, 81 mg, hydroxychloroquine, naproxen, and sulfasalazine. He was seen 3 weeks preoperatively by his hematologist regarding his CLL and was found to be in optimal condition to proceed with cardiac surgery. Approximately 1-2 weeks before surgery, the patient underwent a shoulder injection and cardiac catheterization, with minor bruising noted on the patient’s arm and thigh the day before surgery. He denied personal or family history of bleeding and had undergone prior operations without notable bleeding. Standard preoperative testing for patients undergoing cardiac surgery at this institution revealed prothrombin time (PT) 13.4 seconds (normal range 9.5-13.8 sec), international normalized ratio (INR) 1.1, and platelet count 250 x10⁹/L (normal range 150-450 x10⁹/L). After discussion with his hematologist, the minor bruising was thought to be secondary to aspirin and sulfasalazine, and it was deemed appropriate to proceed with surgery.

After induction of general anesthesia and before unfractionated heparin (UFH) administration, a baseline activated coagulation time (ACT) was noted to be prolonged at 257 seconds (normal range 84-139 sec), and this was reconfirmed on the same (269 sec) and a second instrument (308 sec). In pursuit of the prolonged baseline ACT, intraoperative testing found a normal PT of 13.5 seconds (INR 1.2) and platelet count 179 x10⁹/L; however, the activated partial thromboplastin time (aPTT) was prolonged at 47 seconds (normal range 23-38 sec). By the time the data were available, surgical exposure had been undertaken through a 3-cm right mini-thoracotomy, 2 small port incisions, and a groin incision to expose the femoral vessels. Given that all incisions showed no evidence of bleeding, specimens for special coagulation testing were collected before heparin administration, but the surgery proceeded based on the presumption that the patient had a lupus anticoagulant in association with the CLL. Mitral valve repair and annuloplasty band were performed uneventfully with a cross-clamp time of 36 minutes and total cardiopulmonary bypass time of 50 minutes; peak UFH concentration achieved was 4.1 U/mL. The UFH was reversed with protamine, the surgical field remained without evidence of bleeding, the patient was extubated in the operating room and transferred to the surgical intensive care unit (SICU).

While in the SICU, results of special coagulation testing became available. Mixing study of the prolonged aPTT showed weak inhibition, and the factor VIII activity (FVIII:C) was noted to be 5% (normal range 55%-200%). Based on the possibility of the presence of a low titer FVIII inhibitor, high-dose recombinant human factor VIII concentrate (Helixate FS, Bayer HealthCare LLC, Tarrytown, NY) 50 U/kg bolus was administered and a 4 U/kg/h infusion was initiated in an attempt to overwhelm the inhibitor. A goal FVIII:C of 80% to 120% was chosen, considering that the patient had just undergone cardiac surgery. Because of a suboptimal 15-minute post-bolus recovery (FVIII:C 20%), an additional bolus (100 U/kg) was administered, and the infusion was increased to 8 U/kg/h. Several hours later the factor VIII activity level was 32%.

Because the chest tube output increased to 150 mL/h over the first 12 hours postoperatively, development of a right hemotorax, suboptimal post-bolus FVIII:C (32%), and essentially a flat line on the thromboelastogram (TEG) (Fig 1A), hemostatic management was changed to recombinant activated factor VII (rFVIIa) (Novo Seven, Novo Nordisk A/S, Bagsvaerd, Denmark) 90 µg/kg every 2 hours. A postinfusion TEG showed improvement in clot formation (Fig 1B); however, because of continued chest tube drainage and an

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expanding hemothorax, the patient returned to the operating room early the next morning (postoperative day 1) for evacuation of the hemothorax. The operative field revealed diffuse oozing. By this time, the factor VIII inhibitor titer performed on the intraoperative specimen returned at 66 Bethesda units (BU) (normal value 0 BU). At this time it was decided, given the extremely high titer of the inhibitor, to switch to a combination of factor VIII inhibitor bypassing activity (FEIBA) at 75 units/kg every 6 hours alternating with rFVIIa every 6 hours, as outlined by Young et al, which resulted in successful hemostasis and was continued until postoperative day 3, after which he received FEIBA until discharge. To decrease factor VIII inhibitor titers, he received methylprednisolone (postoperative days 1 to 3), prednisone (beginning day 4), and cyclophosphamide (beginning day 6). The remainder of his hospital course was uneventful. The patient was discharged home on postoperative day 12 and received in total 12 units of red blood cells and 1 unit of platelets. On day 27 of cyclophosphamide therapy, his factor VIII inhibitor titer increased to 87 BU; however, he experienced no bleeding symptoms. By day 61, the FVIII:C and inhibitor titer were 26% and 3 BU, respectively. Approximately 3 months after initiation of cyclophosphamide, FVIII:C was normal.

DISCUSSION

Acquired factor VIII inhibitors are rare, with an incidence of 1-4:1,000,000 per year. Although patients of all ages may be affected, typically, the median age at diagnosis is 70 years. Most cases of autoimmune hemophilia A are idiopathic; however, it may occur in association with malignancies, autoimmune disorders, pregnancy, respiratory disorders, diabetes, infections, and drug reactions. Bleeding has been reported in greater than 95% of patients with this condition, with 9% experiencing fatal bleeding, and factor VIII activity levels do not necessarily correlate with bleeding severity. Delayed bleeding is characteristic of defects in secondary hemostasis such as acquired hemophilia A. Primary hemostasis is achieved by platelet plug formation, which is intact in patients with acquired hemophilia A. However, the platelet plug is a weak hemostatic plug and frequently gets dislodged with defects in secondary hemostasis, leading to initial lack of bleeding followed by delayed bleeding.

Management of acquired hemophilia can be divided broadly into management of hemostasis and elimination of the inhibitor (immunosuppression) (Fig 2). High doses of recombinant factor VIII (rFVIII) may stop hemorrhage in patients with low factor VIII inhibitor titers (≤ 5 BU) but may be ineffective in the presence of higher inhibitor levels (> 5 BU). In such cases, FEIBA, an activated prothrombin complex concentrate, and rFVIIa serve as bypassing agents to manage severe hemorrhage associated with this condition.

This unique case of unknown acquired hemophilia A manifesting and diagnosed perioperatively after cardiac surgery raised several aspects of diagnosis and management that warrant discussion. Of the multiple preoperative issues that merit evaluation, adequacy of hemostasis is an important one. The most useful preoperative hemostatic assessment in patients involves a personal and familial bleeding history in conjunction with a review of a patient’s medications and herbal supplements. Routine preoperative laboratory testing has a low yield, as reported in a systematic review.
PT and aPTT were encountered in up to 4.8% and 15.6%, respectively, of routine preoperative testing and “very rarely [led] to change in the clinical management of patients.” Another study found that patients may safely undergo an operation without preoperative hematologic testing unless indicated by preoperative history or physical exam.15 Given that the patient described here had no history of postsurgical bleeding and had undergone recent interventions (shoulder injection and coronary angiography) with resulting bruising that was not unexpected for the procedures, in-depth coagulation testing was not undertaken before cardiac surgery. Although initial testing limited to a platelet count and a PT were normal, performance of an aPTT would have had a higher yield, as an abnormal aPTT test may detect congenital hemophilia (A and B), autoimmune hemophilia A, and factor XI deficiency.

As encountered in this case, there are multiple potential causes of a prolonged ACT and aPTT (Table 1). In a patient with CLL, in the absence of heparin administration, the most likely causes of a prolonged ACT and aPTT are lupus anticoagulant, acquired hemophilia A, and acquired von Willebrand disease. Given that the surgical field was without evidence of bleeding, it was assumed that the patient had a lupus anticoagulant and, thus, the surgery proceeded while awaiting results of special coagulation testing.

Table 1. Causes of Coagulation Testing Abnormalities

<table>
<thead>
<tr>
<th>Causes of Prolonged ACT</th>
<th>Causes of Isolated Prolonged aPTT</th>
<th>Potential Causes of Prolonged ACT and aPTT in a Patient with CLL</th>
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</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>Heparin</td>
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<tr>
<td>Lupus anticoagulant</td>
<td>Lupus anticoagulant</td>
<td>Lupus anticoagulant</td>
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<tr>
<td>Coagulation factor deficiencies (eg, decreased factors VIII, IX, XI, XII, fibrinogen; liver disease, warfarin)</td>
<td>Coagulation factor deficiencies (eg, decreased factors VIII, IX, XI, XII)</td>
<td>Acquired factor VIII inhibitor</td>
</tr>
<tr>
<td>Severe thrombocytopenia (platelets &lt; 50 × 10⁹/L)</td>
<td>Contact factor deficiencies (eg, decreased pre-kallikrein, high-molecular-weight kininogen)</td>
<td>Acquired von Willebrand disease</td>
</tr>
<tr>
<td>Hemodilution</td>
<td>Newer oral anticoagulants (dabigatran and rivaroxaban)</td>
<td>Acquired factor XI inhibitor prolonged PT and aPTT</td>
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<tr>
<td>Hypothermia</td>
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<td>Aprotinin (celite-based ACT, but not kaolin-based ACT)</td>
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<tr>
<td>Newer oral anticoagulants (dabigatran and rivaroxaban)</td>
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</tbody>
</table>

Abbreviations: ACT, activated clotting time; aPTT, activated partial thromboplastin time; CLL, chronic lymphocytic leukemia; PT, prothrombin time.
Upon availability of additional data as described in the case report, management was altered to rFVIII concentrate, rFVIIa, and, subsequently, to a combination of FEIBA and rFVIIa. The eventual availability of the inhibitor titer reaffirmed the clinical management plan. Given that primary hemostasis is driven primarily by the endothelium, platelet, and von Willebrand factor interactions, it generally is accepted that patients with coagulation factor deficiency undergoing surgery, without any factor replacement, typically experience bleeding within 4 to 6 hours postoperatively, given the suboptimal fibrin clot formation. This patient’s intraoperative course reaffirmed this impression.

CONCLUSION

Given its low incidence in the general population, acquired factor VIII inhibitors are a rare cause of perioperative bleeding; most patients are diagnosed during the course of evaluation of spontaneous bleeding symptoms. Rarely, evaluation of postoperative hemorrhage may lead to the diagnosis. This unique case describes a patient with a previously undiagnosed auto-antibody against FVIII undergoing such a major surgical procedure with minimal intraoperative complications and severe postoperative bleeding.

REFERENCES