

An Acquired Bleeding Disorder in the Perioperative Setting

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Patient Profile: Albert H.

- 71-year-old Caucasian male
- Medical Hx
 - Unremarkable
- Surgical Hx
 - Appendectomy 40 years earlier
- No personal or family history of bleeding problems
- Medications
 - None
- ED presentation
 - Abdominal cramping and sharp pain over past 24 h
 - Episodic nausea and vomiting, past 2 wk
 - Abdominal distention
 - Diarrhea
- Labs
 - White count: 25K/mm³
 - Platelets: 250K
 - Hb: 14 g/dL
 - Hct: 43%
 - PT: 11 sec
 - aPTT: 32 sec
 - INR: 1.0

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When Albert H. presents to the ED with acute abdomen, there is nothing in his personal or family medical history to suggest that this otherwise healthy 71-year-old has a bleeding disorder. Except for an elevated white blood cell count, his initial lab values are unremarkable.

Patient Profile: Albert H. (cont)

- **Physical exam**
 - Remarkable for hyperactive, high-pitched peristalsis
 - Rushes coinciding with cramps
 - No abdominal tenderness
- **Imaging**
 - CT scan reveals small and large bowel loops
- **Diagnosis**
 - Partial small bowel obstruction
- **Conservative treatment initiated**
 - Hospital admission for observation

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Efforts are directed at relieving Albert H.'s acute symptoms, which are consistent with a bowel blockage. Findings of the physical exam and abdominal CT scan confirm a diagnosis of partial small bowel obstruction.

The patient is admitted to the hospital for observation, as conservative treatment is initiated, including insertion of a nasogastric tube, fluid therapy to reverse dehydration, and administration of antiemetics and analgesia.

Hospital Days 2 to 4

- No clinical improvement over 48 h
- Repeat CT scan
 - Multiple fluid- and gas-filled loops of small bowel
 - Retroperitoneum unremarkable

Hospital day 4

- Exploratory laparotomy
- Preoperative labs
 - White count: 30K/mm³
 - Platelets: 200K
 - Hb: 11.9 g/dL
 - Hct: 40%
 - PT: 11 sec
 - aPTT: 36 sec
 - INR: 1.2

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There has been no improvement observed in the patient over the past 48 hours with administration of a conservative course of treatment. Repeat imaging studies reveal multiple fluid- and gas-filled loops of the small bowel.

Based on patient unresponsiveness to treatment thus far, a decision is made by the medical /surgical team to perform an exploratory laparotomy on hospital day 4.

Preoperative lab values are still within the normal range, although the white blood cell count has risen, but there are no red flags at this juncture to alert the medical/surgical team of potential bleeding problems. However, the aPTT is in the outer limit of normal and slightly more elongated than that of the initial blood workup.

Hospital Day 4

- **Surgical findings**
 - Duodenal adhesions; lysis performed
 - Uneventful closure
 - Minimal blood loss
- **Recovery**
 - Hemodynamic instability
 - Abrupt onset of bleeding
 - EBL: 250 mL/h
- **Resuscitation**
 - Packed red blood cells (PRBCs)
 - Cryoprecipitate
 - Fresh frozen plasma (FFP)
 - Recombinant factor VIIa (rVIIa)
- **Imaging**
 - 1 L blood collection
- **Decision made to reopen patient**

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During the laparotomy procedure, duodenal adhesions are discovered and lysis performed. Surgical events proceed normally until the patient is brought to Recovery, where he soon becomes coagulopathic. There is abrupt onset of bleeding, and resuscitation methods, including transfusional and nontransfusional strategies, are employed to reverse coagulopathy. A repeat abdominal CT scan shows a 1-L collection of blood. As a result, the patient is sent back to the OR for re-exploration.

At this juncture, the medical/surgical team has not identified a bleeding source, and preliminary lab work has been within the normal range for most parameters. However, in this case, the sudden onset of excessive bleeding following surgery may be an indicator of autoantibodies directed against specific coagulation factors, with factor VIII autoantibodies being the most common.¹ Spontaneous inhibitors to coagulation factors are not uncommon in elderly patients and can present as excessive bleeding following trauma or surgery.² At this time in the case, however, the possibility of inhibitor involvement is not acted upon, and the patient is treated for a surgically acquired coagulopathy.

References

- 1.Green D. *Clin Lab Haematol.* 2000;22(suppl 1):21-25.
- 2.Franchini M, et al. *Blood.* 2008;112:250-255.

Hospital Day 4 (cont)

- **Surgical re-exploration**
 - Large hematoma at operative site
- **Intraoperative labs**
 - White blood cell count: 18K/mm³
 - Platelets: 125K
 - Hb: 8.4 g/dL
 - Hct: 20%
 - aPTT: 70 sec
 - INR: 2.3
- **SICU**
 - Persistent bleeding
 - Resuscitation
 - PRBCs
 - Cryoprecipitate
 - rVIIa
- **Postoperative labs ordered**

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Surgical re-exploration reveals a large hematoma at the operative site, necessitating the drainage of 1 liter of blood. Intraoperative lab values indicate declining hemoglobin and hematocrit levels and, significantly, a prolonged activated partial thromboplastin time (aPTT).

In the SICU, postoperatively, the patient experiences persistent bleeding and receives multiple units of packed red blood cells, cryoprecipitate, and, ultimately, recombinant factor VIIa for what is still believed to be a surgically acquired coagulopathy. Nonetheless, additional blood work is ordered, including a mixing study and a Bethesda assay, as the aPTT suggests the presence of an inhibitor.

With the mixing study, the patient's plasma is mixed in a 1/1 ratio with normal control plasma for 1 to 2 hours at 37°C. An inhibitor is present if mixing fails to fully correct the test value to the normal range.¹ The Bethesda assay is a measurement of inhibitor strength.¹

Reference

1. Ma AD, et al. *American Society of Hematology Education Program Book*. 2006;1:432-437.

Hospital Day 5

Inhibitor involvement suspected

- **Differential diagnosis**
 - **Vitamin K deficiency**
 - **Disseminated intravascular coagulation (DIC)**
 - **Fibrinolysis**
 - **Exclude presence of heparin**
 - **Lupus anticoagulant?**
 - **Warfarin?**
 - **Biologic abnormalities**
 - **Platelet dysfunction**
 - **von Willebrand defect**
 - **Coagulation factors II, V, VII, IX, X, XI, XIII**

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The medical/surgical team now suspects inhibitor involvement, based on bleeding severity, prolonged aPTT, and the large surgical hematoma found on re-exploration. With inhibitors to factor VIII, specifically, hematomas are a common clinical manifestation of the disorder.¹ Repeat coagulation testing is conducted as well as specific factor assays. The differential diagnosis includes such disorders as vitamin K deficiency and disseminated intravascular coagulation, coagulation disorders that can occur in the postoperative setting.²

The presence of heparin and lupus anticoagulant are excluded, as these can prolong the aPTT,¹ and although Albert H. has not received warfarin, it and other oral anticoagulants have been known to prolong the aPTT as well as the PT, and their use should be considered when coagulation testing is conducted.³

Platelet dysfunction can occur in the postoperative setting, and should be a consideration,² as should antibodies directed against coagulation factors V, IX, XI, and XIII, as well as von Willebrand factor and vitamin K-dependent factors II, VII, and X.⁴

References

- 1.Ma AD, et al. *American Society of Hematology Education Program Book*. 2006;1:432-437.
- 2.Rice L. *Clin Lab Haematol*. 2000;22 (suppl 1):17-20.
- 3.Vadikolia CM, et al. *Int J Lab Hematol*. 2007;29:64-68.
- 4.Cohen AJ, et al. *Baillière's Clin Haematol*. 1996;9:331-354.

Hospital Day 5 (cont)

- Postoperative labs
 - White blood cell count: 18K/mm³
 - Platelets: 100K
 - Hb: 7 g/dL
 - Hct: 17%
 - PT: 12.3 sec
 - aPTT: 88 sec
 - INR: 2.7
 - Fibrinogen levels (within normal range)
 - Factor VIII: 3%
 - All other factors tested in normal range
 - Bethesda assay
 - Factor VIII titer: 10 BU

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In Albert H.'s case, the last set of labs ordered reveal an aPTT that didn't correct in the mixing study, and the Bethesda assay indicates that the patient has a factor VIII inhibitor titer of 10 Bethesda units. Additionally, his factor VIII level is only at 3%, not the requisite 30% to 50% to achieve hemostasis.¹

Armed with the knowledge that Albert H. has an acquired inhibitor to factor VIII, a treatment strategy is put into place by his medical/surgical team.

Reference

1. Ma AD, et al. *American Society of Hematology Education Program Book*. 2006;1:432-437.

Hospital Days 5 to 30

- **Diagnosis**
 - **Acquired hemophilia A**
- **Treatment**
 - **rVIIa 90 mcg/kg q3h**
- **Long-term management**
 - **Prednisone 1 mg/kg OD for 3 wk**
- **Discharge**
 - **Hospital day 30**

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The treatment strategy for acquired hemophilia A is 2-pronged: management of acute bleeding and eradication of the inhibitor.^{1,2}

In Albert H.'s case, it is decided that recombinant factor VIIa (rVIIa) should be administered. Because studies of acquired hemophilia A have demonstrated good hemostatic efficacy with a dosage of 90 mcg/kg every 3 hours,^{3,4} the patient is placed on this regimen until resolution of bleeding is achieved.

Although factor VIII replacement and desmopressin are treatment options, given Albert H.'s high titer (greater than 5 Bethesda units), a bypassing agent is indicated (eg, FEIBA or, in this case, rVIIa) for raising the level of circulating factor VIII.⁵

Corticosteroids alone or in combination with a cytotoxic agent such as cyclophosphamide have proven successful in eradicating the inhibitors associated with acquired hemophilia A.² However, because of the adverse effects associated with corticosteroids, clinicians should be judicious when using these agents in the elderly and tailor their drug choices and dosages to the individual patient's age.⁶

High-dose IV immunoglobulin is another treatment method by which the factor VIII autoantibodies can be eliminated, and rituximab has shown promise as a novel therapy for the safe and effective eradication of autoantibodies.²

For the long-term management and eradication of Albert H.'s inhibitor, he is placed on a regimen of prednisone 1 mg/kg daily for 3 weeks. Treatment proves successful, and he is ultimately discharged from the hospital on day 30.

References

1. Evans EN, et al. *BMJ*. 1995;311:679.
2. Franchini M, et al. *Blood*. 2008;112:250-255.
3. Hay CRM, et al. *Thromb Haemost*. 1997;78:3-7.
4. Croom KF, et al. *Biodrugs*. 2008;22:121-136.
5. Dragani A, et al. *Aging Clin Exp Res*. 2004;16:487-489.
6. Franchini M, et al. *Clin Interv Aging*. 2007;2:361-368.