A 54-Year-Old Woman With Acute Airway Obstruction*

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A 54-year-old African-American woman presented with sore throat and bilateral ear pain and was initially treated with oral cephalaxin. Ten days into her illness, she presented to an outpatient clinic with swelling of the right neck and an enlarged right submandibular gland. She complained of dysphagia and odynophagia. She was admitted to the inpatient medical ward for observation and was begun on IV antibiotics for treatment of pharyngitis.

Her medical history was remarkable for type 2 diabetes mellitus and hypertension. A recent spontaneous right-calf hematoma had prompted a coagulation workup that showed a prolonged partial prothrombin time (PTT). A diagnosis of acquired hemophilia (antibodies to factor VIII) was made, but no treatment was deemed necessary. Her medications included insulin, benazepril, oxycodone as needed for pain, and cephalaxin.

**Physical Examination**

Initial examination revealed an obese woman in no distress with a normal voice. Vital signs were normal. Examination of her throat revealed erythema and an ecchymosis over the right tonsil without hypertrophy or exudate, and no deviation of the soft palate. The right tympanic membrane was erythematous. Neck examination revealed an enlarged right submandibular gland with surrounding edema crossing the midline and ecchymotic skin changes in the suprasternal area. The remainder of the physical examination was normal.

**Laboratory Findings**

A CBC, urinalysis, and routine chemistry findings were normal. The prothrombin time was normal (11.1 s; normal range, 10.4 to 12.8 s). The PTT was prolonged (62 s; normal range, 20 to 29 s). Chest radiographic findings were normal except for soft tissue swelling of the neck. A CT scan of the neck confirmed enlargement of the right submandibular gland, and showed right aryepiglottic fullness with a patent airway but with leftward shift (Fig 1).

**Clinical Course**

Laryngoscopic examination on hospital admission showed a red epiglottis with edema, but with a patent airway. Several hours after hospital admission, acute stridor developed with gross swelling and purplish discoloration of the tongue and neck (Fig 2). The patient was quickly transferred to the ICU. Massive upper-airway swelling prevented endotracheal intubation.

Attempts at blind nasotracheal intubation as well as intubation via bronchoscopy were unsuccessful. Emergent cricothyroidotomy was life-saving.

What is the most likely diagnosis?

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Figure 1. Neck CT demonstrating an enlarged right submandibular gland, right aryepiglottic fullness, and a patent airway but with leftward shift.

Figure 2. Gross swelling and discoloration of the tongue.
Acquired hemophilia is a rare disorder caused by autoantibodies to factor VIII that neutralize circulating factor VIII, usually to a very low level (< 0.01 IU/mL). Antibodies to factor VIII in normal patients occur in approximately one in 1 million of the population each year. This is likely an underestimation, because diagnosis is often missed due to a low index of suspicion. The etiology is uncertain but can be associated with disorders such as lupus, lymphoproliferative malignancy, pregnancy, and transfusion. The mortality is estimated to be approximately 20% and is usually secondary to hemorrhage.

The diagnosis of acquired hemophilia is usually suggested by the spontaneous onset of severe bruising and hemorrhage in a patient with no bleeding history. Many of the patients will present with life-threatening hemorrhage. Spontaneous ecchymoses, retroperitoneal and cerebral hemorrhages, gross hematuria, muscle bleeding, and intractable epistaxis are common. This pattern of bleeding is in contrast to patients with hemophilia A, which is characterized by bleeding into joints or soft tissues. Acquired hemophilia typically occurs in adults with a median age of 60 to 67 years, and is more common in women due to its association with pregnancy and autoimmune disorders.

Bleeding in acquired hemophilia can be life-threatening as illustrated in this patient, when acute pharyngitis developed into massive bleeding into the soft tissues of the neck and tongue causing airway obstruction. The bleeding seemed to occur after direct laryngoscopy, although a causal relationship of the procedure to the bleeding is unproven.

The differential diagnosis of the airway obstruction in this patient also included infection such as pharyngitis, hereditary angioedema, epiglottitis, and severe allergic reaction. These disorders were quickly dismissed in this case.

Autoantibodies have been described to all clotting factors, but those directed against factor VIII are the most common. The antibodies against factor VIII are usually IgG1 and IgG4 subclasses with binding that interferes with factor VIII procoagulant activity. These antibodies are polyclonal and are not light-chain restricted, which is reflected in their usually complex second-order reaction kinetics. This is in contrast to the inhibitor isoantibodies seen in congenital hemophilia, which typically inactivate factor VIII progressively in direct proportion to their concentration ("first-order kinetics").

The diagnosis is established by demonstrating an isolated prolongation of the PTT, which initially corrects with the addition of normal plasma. These findings occur in association with a reduced factor VIII level and evidence of factor VIII inhibitor activity in a patient with no previous personal or family history of bleeding. The reaction between factor VIII and its inhibitor is both time dependent and driven by the potency of the inhibitor. Due to complex reaction kinetics, inexperienced coagulation laboratories may have difficulty interpreting inconsistent or unexpected results. The inhibitor can be roughly quantified using the Bethesda assay against both human and porcine factor VIII. The Bethesda unit (BU) is defined as the amount of inhibitor that would inactivate 50% of a control amount of factor VIII. Assays can measure inhibitor reactivity to both human factor VIII as well as to porcine factor VIII, which can be useful when trying to determine the best treatment option.

The primary goals of the treatment of acquired hemophilia are to eliminate the inhibitor and to treat the hemorrhagic complications. First, bleeding risks should be minimized. Avoidance of minor traumatic injuries, IM injections, careless venipunctures, dental procedures, and use of aspirin or other platelet-interfering drugs are important. The inhibitor level should be lowered as much as possible to prevent bleeding, which usually involves immunosuppression in the form of prednisolone and cyclophosphamide. High-dose Ig and cyclosporin A have been successful in some refractory cases. Patients with underlying disorders of immune regulation such as lupus usually have the best response. Although most patients respond to immunosuppression within 3 to 6 weeks, the response can be slower in some cases taking many weeks to months.

For acute bleeding, raising factor VIII levels to at least 30% is usually sufficient to establish hemostasis. There are several options available with different mechanisms of each. These include 1-desamino-8-D-arginine vasopressin (DDAVP), porcine factor VIII, human or recombinant factor VIII, factor IX prothrombin complex concentrates, activated factor VIIa, exchange plasmapheresis, and high-dose Ig. Decision to use one option over the other will depend on availability, cost, individual patient considerations, degree of bleeding, and level of the inhibitor.

DDAVP is most useful for non-life-threatening hemorrhage in patients with inhibitor levels < 3 BU and a residual factor VIII level that is measurable. It works by increasing blood levels of factor VIII, von Willebrand factor, and plasminogen activator. DDAVP is administered IV, usually at a dose of 0.3 μg/kg.

Human factor VIII concentrate is clinically ineffective in most patients with acquired hemophilia.
unless used in massive doses in patients with low-level inhibitors. However, porcine factor VIII has shown to be very effective in controlling bleeding episodes, with most inhibitors having little or no cross-reactivity to porcine factor VIII in the Bethesda assay. It is usually administered as an initial bolus followed by a continuous infusion. The principal side effects of porcine factor VIII are transfusion reactions and a postinfusion fall in platelet count.

Factor IX, or prothrombin complex concentrates, are used to “bypass” the factor VIII level of coagulation, though the precise mechanism is not fully understood. Factor IX is prepared from human plasma derived from a large number of donors. In the United States, all factor IX is subject to heat inactivation for HIV. Complications of administration include disseminated intravascular coagulation, thromboembolism, and acute myocardial infarction. An amnestic rise in inhibitor can be seen since these products do contain small amounts of factor VIII. The clinical response can be unpredictable, and their use is recommended when more effective alternatives are unavailable.

Activated factor VIIa, a recombinant product that binds with tissue factor to activate factor X to Xa, is a newer product being used with increasing frequency. Advantages are that the product is genetically engineered, has no risk for viral transmission, has no amnestic response, has no anaphylactic reaction, and has a low thrombogenic potential. Disadvantages are that the product is not universally effective, has a short half-life of 2 h necessitating frequent dosing, and lacks an assay for serial measurements.

For patients with extremely high levels of inhibitor exchange, plasmapheresis can reduce the inhibitor level in half with factor VIII given immediately afterwards. Alternatively, IV γ-globulin (IVIG) can be administered to neutralize the inhibitor by providing anti-idiotypic antibodies contained in pooled IVIG. The use of IVIG has been tested in a prospective study in which there was a 37% response rate. Many of the patients had been poor responders to other modalities of therapy.

Factor VIII antibodies in this patient were quantified as being > 70 BU. Factor VIII levels were 5% (normal range, 50 to 200%). For this reason, factor IX replacement (3,500 U IV q8h) was administered. The patient steadily improved with a gradual decrease in size of the hematoma involving her neck and tongue. Mechanical ventilation was discontinued after 3 days. She was discharged home on day 15, and the tracheostomy was subsequently removed. She was followed up in the Hematology Clinic, and no further bleeding episodes occurred. Her acquired hemophilia spontaneously resolved 2 years later.

**Clinical Pearls**

1. Congenital and acquired disorders of coagulation can lead to upper-airway obstruction. Inciting events may be infection or diagnostic procedures involving the upper airway.

2. Specific therapy exists to correct the coagulopathy under emergent conditions. This therapy can be thrombogenic.

3. The PTT is frequently prolonged in these disorders but cannot be used to monitor the effectiveness of therapy.

4. Hemophilia patients admitted to the ICU should have prompt correction of coagulopathy to prevent bleeding complications from invasive procedures and critical illness.

**Suggested Readings**


Lottenberg R, Kentro TB, Kitchens CS. A natural history study of 16 patients with factor VIII inhibitors receiving little or no therapy. Arch Intern Med 1987; 147:1077–1081


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