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ACQUIRED HEMOPHILIA PRESENTING AS PROFOUND HEMATURIA: EVALUATION, DIAGNOSIS, AND MANAGEMENT OF ELUSIVE CAUSE OF BLEEDING IN THE EMERGENCY DEPARTMENT SETTING

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□ **Abstract—Background: There are numerous causes of bleeding that may present to the Emergency Department (ED). Although rare, acquired hemophilia is a potentially life-threatening bleeding disorder, with reported mortality rates ranging from 6% to 8% among patients who received proper diagnosis and treatment. Approximately two thirds of patients with this condition will present with major bleeding, the magnitude of which may necessitate urgent evaluation and care. Objectives: The aim of this article is to provide an overview of the evaluation, differential diagnosis, and management of acquired hemophilia for the emergency physician. Case Report: A case report of a patient who presented to the ED with gross hematuria secondary to undiagnosed acquired hemophilia is described to facilitate a review of the laboratory evaluation, differential diagnosis, and treatment of acquired hemophilia. Conclusion: Patients with acquired hemophilia–related bleeding may present to the ED for care, given the often serious nature of their bleeding. Delayed diagnosis may postpone the initiation of targeted, effective treatments for achieving hemostasis, with potentially catastrophic consequences, particularly in patients who require emergent invasive procedures. Recognition of the potential for an underlying bleeding disorder and subsequent consultation with a hematologist are critical first steps in effectively identifying and managing a patient with acquired hemophilia who presents with bleeding.** © 2013 Elsevier Inc.

□ **Keywords—blood coagulation disorders; bleeding inhibitor; hemophilia A; hematuria; hemostasis**

INTRODUCTION

Acquired hemophilia is a rare but potentially life-threatening autoimmune bleeding disorder that often presents with severe bleeding. This condition arises from the presence of autoantibodies, or inhibitors, directed against clotting factors, most often factor VIII, though antibodies against factor IX, XI, and XII have also been described (1–6). The estimated incidence is approximately one to four per million per year among the general population (7). Unlike congenital hemophilia, which occurs primarily in males and is often diagnosed before adolescence, acquired hemophilia occurs with roughly equal incidence in men and women and is predominantly a condition of adulthood (8). The age distribution is bimodal, with a small peak among young women in the postpartum period (reported incidence 1/350,000 births) and a second, larger peak among older adult patients (reported incidence 6/1,000,000 in those aged 65–85 years and 16.6/1,000,000 per year in those older than 85 years) (9,10). In approximately half of cases, there is a co-existing underlying condition

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characterized by immune dysregulation, such as autoimmune or malignant disease (11). However, in the other half of cases, there is no such association (11).

Acquired hemophilia may present with excessive bleeding after trauma, surgery, or other invasive procedures or with spontaneous bleeding (8,11). Nearly two thirds of patients with acquired hemophilia present with major bleeding, typically involving the skin, soft tissues, or mucosa of the gastrointestinal or genitourinary tract (11). Rare cases of spontaneous intracranial bleeding also have been reported (12,13). Complications of bleeding into closed spaces, such as a compartment syndrome secondary to intramuscular bleeding, may contribute to the morbidity of acquired hemophilia–related bleeding and may require urgent surgical intervention. When such an intervention is indicated, failure to promptly identify acquired hemophilia as the etiology of the original bleeding event may prove catastrophic. In one series, four of the five total reported deaths occurred in patients who underwent surgical interventions before the diagnosis of acquired hemophilia was rendered (14). Because acquired hemophilia–related bleeding is not likely to respond to standard hemostatic treatments, the prognosis in patients who require surgery or who have active bleeding depends primarily on the rapidity with which the diagnosis is made (14). Yet, diagnostic delays are common with this condition. In an analysis of data from a multinational European registry composed of 501 patients with acquired hemophilia, the average time to diagnosis was 22 days after the finding of an abnormal activated partial thromboplastin time (aPTT), which is the hallmark initial laboratory finding in this condition (15). Even when acquired hemophilia is properly diagnosed and treated, the mortality attributable to this condition is relatively high; published mortality rates range from 6% to 8%, mostly due to rebleeding (16,17).

Prompt diagnosis of acquired hemophilia is dependent upon recognition of the potential existence of an underlying bleeding disorder in an affected patient who presents with recent- or acute-onset bleeding symptoms. The presence of a bleeding disorder should be considered when there is no identifiable source of or cause for bleeding, such as neoplasm or trauma, or in the case of the latter, when bleeding is out of proportion to the magnitude of injury. Abnormalities in subsequently obtained basic coagulation studies confirm the presence of an undiagnosed bleeding disorder, prompting consultation with a hematologist for further definitive evaluation and management. In this article, we describe a case of acquired hemophilia manifested by profound hematuria, as a means to familiarize the emergency physician with the clinical presentation and initial work-up and management of this condition. The diagnostic approach to this elusive cause of bleeding, both in the ED and beyond, is reviewed in the case presentation and discussion that follows to provide an overview of the evaluation and differential diagnosis of the sentinel laboratory finding in acquired hemophilia: an isolated prolonged aPTT. Finally, therapeutic options for managing active bleeding and, in the long term, eradicating the inhibitor in acquired hemophilia are discussed.

CASE REPORT

A 54-year-old woman presented to the Emergency Department (ED) with a chief complaint of profuse urinary tract bleeding. The patient noticed that her urine appeared blood-tinged the day before presentation. On the day of presentation, her urine was grossly bloody and contained blood clots, findings that caused the patient concern and led her to the ED for evaluation. The patient denied having experienced any previous bleeding episodes, even during dental work and three previous surgeries (which included one cesarean section for childbirth). She denied any trauma, abdominal pain, back pain, fever, nausea, or vomiting. Review of symptoms was also negative for chest pain or discomfort, shortness of breath, headache, or dizziness. Medical, social, and family histories were unremarkable.

The patient's vital signs on presentation included a heart rate of 110 beats/min, blood pressure of 148/88 mm Hg, respiratory rate of 18 breaths/min, temperature of 37°C, and oxygen saturation of 99% on room air. The patient was in no obvious distress. The physical examination was remarkable for tachycardia and two large areas of ecchymosis on her forearms. When questioned about the bruises, the patient stated that they were from intravenous line attempts during the current visit.

Laboratory test results revealed a prolonged aPTT of 41 s (normal 26–36 s), but normal prothrombin time (PT) index, which was 82% (normal 70–130%). Other values within normal ranges included bleeding time of 5 min 20 s (normal < 10 min) and platelet count of 366 cells $\times 10^9$/L (normal 130–400 cells $\times 10^9$/L); hemoglobin was at the patient's baseline of 10.5 g/dL. Urinalysis was normal, except for gross hematuria.

Given the laboratory findings and lack of prior history, the patient was presumed to have an emergent bleeding diathesis. The on-call hematologist was consulted to assist with diagnosis and treatment of the underlying cause of bleeding. An initial differential diagnosis was generated based, in part, on the initial laboratory findings (Table 1). The sudden presence of gross hematuria and extensive ecchymosis in an older adult without significant trauma or known bleeding disorder raised the clinical suspicion of a clotting factor inhibitor, as did the laboratory