Title

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CLINICAL VIGNETTE

An Unusual Cause of Recurrent Hematuria in a Geriatric Patient

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Case Report

An 84-year-old female with a history of colon cancer status post resection 10 years prior, osteoporosis, atrial fibrillation, osteoarthritis, severe Alzheimer's dementia, depression, and chronic lower back pain status post laminectomy presented with two days of gross hematuria, increasing back pain, nausea, vomiting and generalized weakness. Medications on presentation included only a multivitamin and citalopram. Social history was significant for 45-pack year tobacco use. There was no known family history of bleeding disorders.

Physical examination revealed a frail appearing woman in no acute distress. She was afebrile, no abdominal masses were palpable, there was no abdominal or CVA tenderness, and no significant ecchymoses were noted. Laboratory examination revealed acute kidney injury with creatinine of 1.7 mg/dL (baseline creatinine 1.0 mg/dL) and a leukocytosis of 20.4 x10E3/μL with 89.5% neutrophils. Platelets were within normal limits and she was not anemic. Urinalysis showed 3+ blood, 2+ protein, >1000 RBCs/μL and 26 WBCs/μL. Prothrombin time (PT) was 11.5 seconds, INR was 1.1, and activated partial thromboplasin time (APTT) had not been obtained. CT KUB without contrast showed mild right hydronephosis with a high-density material, which was likely blood, within the right renal collecting system as well as right perinephric stranding. Her hospital course was uncomplicated, and she was discharged on oral antibiotics for presumptive pyelonephritis, although urine cultures from admission were negative.

Outpatient cystoscopy revealed ecchymoses of the mucosa on the left side that was thought to be secondary to foley catheter. However, no cause for hematuria or tumors was identified and urine cytology was negative for malignant cells.

A few weeks later the patient presented to the emergency room with increasing agitation and a recurrence of hematuria. The patient was again afebrile and the exam remained unremarkable except for notable hematuria. Urinalysis showed 4+ blood, 4+ protein, 3+ leukocyte esterase, >100 RBCs/μL and >100 WBCs/μL with many bacteria. Coagulation testing revealed an INR of 1.1 and a mildly elevated APTT of 40.8 seconds. Her white blood cell count was elevated at 14.26 x 10E3/μL, platelets were normal, and creatinine was 1.3 mg/dL. CT urogram with IV contrast showed resolution of the previous right hydronephrosis and right perinephric stranding. However, there was a new mild left hydronephrosis without an identifiable stone. Urine cultures were significant for E. Coli; and the patient was again discharged to complete an antibiotic course for presumptive pyelonephritis with associated hematuria.

The patient later represented to clinic with development of multiple ecchymoses on her chest and no known history of trauma. Admission labs revealed a new anemia with hemoglobin of 8 g/dL (baseline hemoglobin 12.9 g/dL), PT of 10.9 seconds, INR of 1.1, and an APTT 66.4 seconds. Workup of her elevated APTT on this admission showed a low factor VIII activity (1%); and a mixing study was positive for an inhibitor. Factor VIII Bethesda titer was 72.2 BU/ml. The patient was diagnosed with acquired hemophilia A and treatment with rituximab and recombinant factor VIIa was initiated. The treatment course was complicated by a DVT, thought to be secondary to recombinant factor VIIa. Prednisone was added to augment the treatment regimen and the coagulation profile returned to normal without further bleeding events.

Although an initial workup for autoimmune disease or underlying malignancy was unrevealing, the patient later developed an obstructive, painless jaundice. Endoscopic ultrasound revealed a 3.2cm, poorly-demarcated, homogeneous, hypoechoic mass in the pancreatic head. A stent was placed for palliative decompression of her billiary tree; and a fine

needle aspiration of the mass was definitive for adenocarcinoma. The patient was discharged home with hospice.

Discussion

Acquired hemophilia A is a rare and potentially life threatening bleeding disorder caused by development of autoantibodies directed against coagulation factor VIII in non-hemophilic patients. Incidence of acquired hemophilia A has been shown to occur at a rate of about 1 person per million each year[1]. In contrast to congenital hemophilia, where bleeding episodes are primarily spontaneous hemarthroses, acquired hemophilia typically causes soft tissue, mucocutaneous, gastrointestinal and urogenital bleeds[2]. Bleeding is often severe, and the disease frequently manifests as excessive bleeding after trauma, surgery, or cerebral hemorrhage[3]. In one study, 87% of patients required transfusion[4]. Mortality rates are high, and have been shown between 8-22%[5].

Acquired hemophilia A has a biphasic age distribution with a small peak between 20-40 years of age and the majority of those diagnosed between 68-80 years of age.[2] Male to female ratios are similar in the older age group, however, female patients predominate the younger age group, likely secondary to rates of acquired hemophilia A in the postpartum period[3].

Acquired hemophilia has been correlated with multiple disease states including malignancy, rheumatic disease, infections, postpartum period, and medication related, however, in up to 50% of the cases the cause remains unknown. (Table 1) An autoimmune correlation has been noted to be present in 17-18% of cases of acquired hemophilia A[6]. About 10% of acquired hemophilia A cases are associated with underlying malignancy[1, 3]. Although the exact etiology of solid tumor related formation of factor VIII inhibitors is not known, they are thought to represent an auto-immune response to tumor antigens that resemble factor VIII[7].

Workup for acquired hemophilia A should be done in a patient with isolated prolongation of the APTT. The differential of an isolated prolonged APTT includes deficiencies or inhibitors of factors XI, IX, or VIII, von Willebrand disease, the use of heparin, and antiphospholipid antibodies. To help clarify, a mixing study should be done in which the patients plasma and pooled normal plasma are mixed at equal amounts. An APTT that does not correct after incubation for 2 hours at 37^0C is positive for an inhibitor. Nonspecific inhibitors (heparin and lupus anticoagulant) should be ruled out. The Bethesda assay is completed in which serial dilutions of the patient's plasma are incubated with normal plasma and factor VIII activity is measured using a clotting assay. This gives a value for the strength of the inhibitor, which is reported in Bethesda units (BU). One unit inactivates 50% of the factor VIII in an equal volume of normal plasma[7]. Factor VIII levels and inhibitor titers have not been shown to correlate with severity of clinical bleeding episodes, however, they may be helpful to guide inhibitor eradication therapy[2].

Treatment of acquired hemophilia A is complex and varies depending on clinical presentation and co-morbidities. Treatment is aimed at control of bleeding episodes, eradication of inhibitors with the use of immunosuppressants, and treatment of underlying disease processes. Treatment of acute hemorrhages includes use of the bypassing agents recombinant activated FVII (rFVIIa) and activated prothrombin complex concentrates (aPCCs)[6,8,9]. Factor VIII concentrates and desmopressin should be used only if rFVIIa or aPCCs are unavailable[8]. Inhibitor eradication involves the use of immunosupressants and cytotoxic agents; corticosteroids, cyclophosphamide and rituximab have been shown to be beneficial[6,8,9]. Underlying malignancy is not a contraindication to treatment of acquired hemophilia A with immunosupressants[9]. Treatment of the underlying disorder if one is identified is recommended, and factor VIII autoantibodies have disappeared with removal of the tumor in at least one case[10].

Acquired hemophilia most often occurs in elderly patients who may have multiple underlying medical conditions and take several medications, including antiplatelet agents that may contribute to easy bruising and bleeding. In the case described above, the workup for acquired hemophilia A was not done initially, as pyelonephritis was thought to be the cause of her hematuria. Although APTT was not obtained during her first admission, she was noted to have an abnormal value of 40.8 seconds on subsequent admission. Even though Bethesda titers and factor VIII levels were not obtained during that episode of hematuria, given the abnormal APTT, acquired hemophilia A related

to her underlying malignancy could have been contributing at that time. Ultimately, her pancreatic cancer was felt to be the underlying etiology for the development of factor VIII autoantibodies. In this patient, effective treatment with rituximab and prednisone corrected her coagulation abnormalities and allowed her to return home where she was able to spend the rest of her days with her family.

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Table 1- Etiology of Acquired Hemophilia A [2,5,7,11]
Idiopathic
Pregnancy-related (typically 1-4 months postpartum)
Autoimmune diseases Systemic lupus erthematosus Rheumatoid arthritis Multiple sclerosis Psoriasis Pemphigus vulgaris Temporal Arteritis Sjögren syndrome Inflammatory bowel disease Goodpasture syndrome Graft-versus-host disease Myasthenia gravis Graves disease Autoimmune hemolytic anemia Autoimmune thyroid disease
Malignancy Hematologic: Chronic lymphocytic leukemia Non-Hodgkin lymphoma Multiple myeloma Waldenström macroglobulinemia Myelodysplasic syndrome Myelofibrosis Erythroleukemia Solid organ tumors: Prostate Lung Colon Pancreas Stomach Choledochus Head and neck Cervix Breast Melanoma Kidney
Drug-induced Beta-lactam antibiotics Sulfonamides Phenytoin Chloramphenicol Methyldopa Bacillus Calmette-Guerin vaccination Interferon alpha Fludarabine Depot thioxanthene NSAIDs Clopidogrel
Infections

Hepatitis B Hepatitis C