Acquired hemophilia complicated by cardiorenal syndrome type 3

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Abstract
Development of autoantibodies against coagulation factor VIII (FVIII) leads to a rare condition defined as acquired hemophilia (AH). If not diagnosed and treated early, AH may be associated with high mortality and morbidity. A 65-year-old woman presented with history of macrohematuria, acute renal failure, cardiogenic shock, and acute respiratory failure. Blood investigation revealed azotemia, prolonged activated partial thromboplastin time (aPTT), coagulation FVIII level of <1%, and presence of FVIII inhibitor. Echocardiography showed global hypokinesia and ultrasonography and computed tomography (CT) revealed bilateral hydroureteronephrosis. The final diagnosis was acquired hemophilia A, complicated by acute obstructive renal failure and cardiorenal syndrome (CRS) type 3. Patient was managed with mechanical ventilation, heparin-free hemodialysis, negative fluid balance, recombinant activated factor VII, and prednisolone. Hematuria was relieved, renal function improved, and cardiac function showed improvement on repeat echocardiography. Patient was discharged on prednisolone with subsequent follow ups.

Keywords: Acquired hemophilia, cardiorenal syndrome, factor VIII inhibitor, recombinant activated factor VII

Introduction
Acquired hemophilia (AH) is a rare bleeding diathesis characterized by development of autoantibody against coagulation factor VIII (FVIII) and significant bleeding episodes causing high morbidity and mortality.1 The severity of presentation, along with the rarity of AH, makes it a challenge for diagnosis and treatment. However, rapid diagnosis is a primary determinant of prognosis because AH does not respond to customary management of bleeding disorders.2

Case Report
A 65-year-old female with history of healed traumatic amputation of left 5th toe 2 months back, transferred to our hospital on mechanical ventilator and dopamine infusion with the complaints of hematuria for 1.5 months, subcutaneous hemorrhage for 15 days, oliguria for 3 days, and respiratory failure for 1 day. At presentation, she was alert, afebrile, and tachycardic, with high oxygen requirement. On examination, she was volume overloaded with multiple ecchymotic patches over limbs [Figure 1], back, and buttocks.

Ultrasoundography of abdomen showed hepatomegaly, right pleural effusion, bilateral hydronephrosis, and hydroureter with no calculus or focal mass lesion and normal blood flow bilaterally in the renal arteries and veins. ECG showed tall T-waves and arterial blood gas analysis (ABG) indicated metabolic acidosis with a base deficit of 6.8. Other investigations were hemoglobin 8.7 gm/dL, total leukocyte count 12,100/μL, platelet 297,000/μL, international normalized ratio 1.1, activated partial thromboplastin time (aPTT) 55.4 s (control 27 s), urea 117 mg/dL, creatinine 7.1 mg/dL, sodium 120 mEq/L, potassium 5.6 mEq/L. Chest radiograph showed bilateral pleural effusions with basal atelectasis [Figure 2]. Her
liver function tests were normal. Echocardiography showed global hypokinesia with dilated cardiac chambers and left ventricular ejection fraction (LVEF) 25-30% [Figure 3]. Patient was immediately administered heparin-free hemodialysis with low sodium dialysate and a target ultrafiltrate of 3 L. Packed red blood cells (RBCs) and fresh frozen plasma were transfused during dialysis. All serological tests were normal.

Over the next 3 days, her general condition improved with correction of dyselectrolytemia, discontinuation of vasopressors, and weaning from the ventilator; but she continued to have hematuria with a raised aPTT. Blood, urine, and tracheal secretions cultures were negative. Blood FVIII level was less than 1% and FVIII inhibitor was detected in serum. Recombinant activated factor VII (rFVIIa) was given in a dose of 90 µg/kg as intravenous bolus and repeated after 4 h. Hematuria was relieved followed by normalization of creatinine. She
was started on tablet metoprolol 25 mg/day and tablet prednisolone 50 mg/day. Patient was shifted out of ICU on 5th day of admission.

Drug treatment for cardiac failure was optimized. Repeat echocardiography on the 10th day showed LVEF of approximately 35%. Dobutamine stress echocardiography was negative for reversible ischemia with significant improvement in LVEF. The patient was discharged on the 12th day of hospitalisation.

**Discussion**

AH is a rare but life-threatening hemorrhagic disorder caused by spontaneous appearance of autoantibody or inhibitor against coagulation FVIII. The diagnosis of AH should be considered in the actively bleeding patient, with no personal or family history of bleeding diatheses, particularly in the elderly and during postpartum. Our patient had 1.5 months, history of hematuria and ecchymosis without any obvious cause. Although she had traumatic amputation of toe 2 months back, no treatment records were available. AH can be associated with autoimmune disorders, malignancies and drug exposures such as penicillin, sulfonamides, phenytoin, methyldopa, and interferon alpha. However, in approximately 50% of cases, AH is idiopathic. Median age at diagnosis ranges from 55 to 78 years. More than 80% of patients experience hemorrhages affecting the skin, soft tissues, gastrointestinal, or genitourinary tracts; but hemarthrosis (common in congenital hemophilia) is rare in AH.

AH is diagnosed by demonstration of an isolated prolongation of aPTT, with low FVIII levels and evidence of FVIII inhibitor. AH and von Willebrand disease (vWD) are the only conditions associated with isolated prolonged aPTT that manifest with a bleeding phenotype. vWD was ruled out by absence of relevant family history and absence of mucous membrane bleeding. aPTT of the patient was 55.4 s (control 27 s), FVIII level less than 1%, and FVIII inhibitor was positive. Quantitative estimation of the FVIII inhibitor could not be done because of nonavailability of the test in our institution.

She developed obstructive renal failure due to hematuria, which was confirmed with ultrasonography and noncontrast CT (NCCT) of the abdomen. There are multiple case reports of obstructive renal failure associated with AH. On presentation she was fluid overloaded, hyperkalemic, and in metabolic acidosis. She had no previous symptom or history of cardiac illness. However, at presentation, she was in cardiogenic shock with low LVEF. She had no fever, thin layer chromatography (TLC) was slightly raised and all the cultures were sterile. She had rapid recovery with a single hemodialysis and negative fluid balance. Her hemodynamic improvement paralleled improvement in serum creatinine. In view of the above findings, echocardiography was repeated on day 10, which showed improvement of LVEF. Myocardial ischemia was excluded by a negative Dobutamine stress echocardiography.

Acute kidney injury affects the heart through multiple mechanisms; volume overload, acidosis, and hyperkalemia; resulting in myocardial systolic dysfunction, arrhythmias, and pulmonary congestion. As AH has no direct effect on myocardium, in the absence of sepsis and history of cardiac illness, the effect on the myocardium could be secondary to obstructive renal failure. Acute obstructive renal failure resulted in acute heart failure, named as cardiorenal syndrome (CRS) type 3. CRS identifies the disorder of heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ. CRS is classified into five subtypes:

- **CRS type 1**: Acute worsening of heart function leading to kidney injury and/or dysfunction
- **CRS type 2**: Chronic cardiac dysfunction leading to kidney injury and/or dysfunction
- **CRS type 3**: Acute kidney injury (AKI) leading to heart injury and/or dysfunction
- **CRS type 4**: Chronic kidney disease leading to heart injury, disease, and/or dysfunction
- **CRS type 5**: Systemic conditions leading to simultaneous injury and/or dysfunction of heart and kidney.

Treatment strategy in AH is based on the severity of hemorrhage and the level of the inhibitor. When the inhibitor level is low and bleeding is less severe, FVIII concentrate or desmopressin can be given. However, for high inhibitor titers or severe bleeding regardless of the titer, bypassing agents are the primary treatment of choice. Activated prothrombin complex concentrates (APCC) or recombinant activated factor VII (rFVIIa) are effective bypassing agents. In addition, inhibitor elimination may be achieved by corticosteroids alone or in association with cyclophosphamide. rFVIIa promotes hemostasis by activating extrinsic pathway of coagulation cascade. Patient was given rFVIIa along with prednisolone. Hematuria was relieved followed by normalization of serum creatinine.
Although the patient presented to us with multiple organ failure, with rapid diagnosis and treatment, patient recovered relatively quickly. She was extubated on day 3 and discharged on day 12 of hospitalisation. On the patient and family’s request, she was not investigated further to define the etiology of AH but she is on routine follow up. In conclusion, rapid diagnosis and treatment are the two key factors for a successful outcome in the AH patient.

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