中文題目：Furosemide 誘導溶血性貧血

英文題目：A Rare of Furosemide-Induced Hemolytic Anemia

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Introduction

Furosemide is a keystone in treatment for heart failure and is commonly used to relieve congestion, improve symptoms and prevent worsening heart failure.[1] Though generally well tolerated, major adverse reactions have been documented including electrolyte abnormalities, acute kidney injury, hypersensitivity reactions and ototoxicity. Direct hematological side effects such as agranulocytosis, anemia, aplastic anemia, hemolytic anemia, leukopenia, purpuric disease, thrombocytopenia have been described only in extremely limited cases. [2-4]

Drug-induced immune hemolytic anemia (DIIHA) is a rare complication. The incidence was reported only about 1 per million/year. [5] However, once a patient develops drug-induced hemolytic anemia, it can be fatal with acute severe hemolysis, and it is challenging in evaluation. Most common medications reported to be associated with DIIHA are antibiotic and non-steroidal anti-inflammatory drugs (NSAID). [6, 7]

Furosemide-induced hemolytic anemia is extremely rare and it was only reported in some sporadic cases.[8] In this case, we introduce a 91-year-old male who developed acute hemolytic anemia three days after starting furosemide in the treatment of myocardial infarction complicated with acute decompensated heart failure.

Case Presentation

A 91-year-old male presented to the Emergency Department (ED) with acute onset of chest tightness and dyspnea. He had a previous medical history of coronary artery disease status post bare metal stent placement on left circumflex artery (LCX) nine months ago, chronic heart failure, hypertension, hyperlipidemia, and chronic kidney disease. Regular medications initiated more than half years prior included clopidogrel, isosorbite-5-mononitrate, tamsulosin, spironolactone, atorvastatin, valsartan. No allergies, tobacco, or alcohol exposures were known, and he had no other relevant personal or family history. He also denied other relevant symptoms, including fever, melena, and other evident blood losses.

On examination, his vital sign was stable and physical findings were unremarkable

except bilateral rales breathing sounds and lower limbs pitting edema (1+). No fever or other abnormalities were noted.

ECG showed lateral and inferior lead ST segment depression and blood tests revealed elevated troponin I level. With the impression of myocardial infarction complicated with acute decompensated heart failure, initiation of intravenous furosemide and urgent coronary angiography was performed which disclosed LCX in-stent restenosis. Further plain old balloon angioplasty was then applied smoothly.

However, three days later, his hemoglobin level dropped from 8.7 g/dL to 6.5 g/dL, and the total bilirubin level rose from 0.9 mg/dL to 2.25 mg/dL, at the expense of unconjugated bilirubin (conjugated bilirubin: 0.68 mg/dL). There was no evidence of active bleeding, and the coagulation profile was normal. Further laboratory tests for anemia showed reticulocytosis (6.7%), elevated lactic dehydrogenase (519 UI/L) and haptoglobin level was undetectable. Serum iron concentration, total iron-binding capacity, folic acid, or vitamin B12 were within normal range. Blood tests for autoimmune disease including antinuclear antibody (ANA), cryoglobulin, and extractable nuclear antigens (ENA) were negative and C3, C4 levels were in normal range. Peripheral blood smear did not reveal schistocyte or spherocyte. The direct antiglobulin test (DAT) and indirect antiglobulin test were also negative. Results of a serologic workup were negative for human immunodeficiency virus (HIV), hepatitis B, and hepatitis C. Glucose-6-phosphate dehydrogenase levels were within the normal range. Flow cytometry for CD55 and CD59 were also within normal limits. The patient was diagnosed with a drug-induced hemolytic anemia considering the previous history of unknown hyperbilirubinemia after exposure to Furosemide half a year ago.

With suspicion of DIIHA, furosemide was discontinued on day 8. Hemoglobin level gradually up-trended and total bilirubin level down-trended four days after withdrawal of furosemide. Nonetheless, due to symptoms related to fluid overload, we tried intravenous bumetanide instead of furosemide on day 12. His hemoglobin level dropped, and bilirubin level gradually rose again after three days of bumetanide administration. Experimentally, the patient was started on 62.5 mg of methylprednisolone per day (1 mg/kg/day) for three days and tapered every three days. His hemoglobin level gradually up-trended and total bilirubin level down-trended to normal range. After a stable condition, the patient was discharged.

Discussion

DIIHA is diagnosed by well-defined hemolytic anemia and good chronological relevance with the suspected drugs.[9] Early diagnosis and suspension of the offending drugs is the first approach to therapy.[9] After discontinuation, condition

usually improves within 1-2 weeks. However, in severe cases, patients may require intensive care, and repeated blood transfusion. In a case-control study including all 124 immune hemolytic anemia cases reported 55% of patients with DIIHA needed blood transfusion.[7]

In a review, 136 drugs had been documented to account for DIIHA. [8] The most common medication associated with DIIHA are piperacillin, followed by cefotetan and ceftriaxone. Furosemide was only reported in some sporadic cases and hemolytic anemia did not occur even with a positive test of DAT. [8] In our case, based on criteria of WHO-UMC system for standardized case causality assessment, we assure that Furosemide is probable medication for DIIHA.[10] The patient had definite hemolytic anemia after furosemide administration and we had excluded other possible etiologies. After withdrawal of furosemide, the condition soon improved.

The DAT is a crucial test to evaluate immune dependent hemolytic anemia. Though negative result of DAT in our patient, it does not preclude the diagnosis of DIIHA. In a case series, DAT was positive in 72 of the 73 patients. And the remaining one tested positive result 6 months after hemolysis. 65 patients (89%) had a C3d-positive DAT, 6 patients had only an IgG-positive DAT, and in 1 patient only IgA was detectable.[11] Another hypothesis is that negative DAT test can be due to the sudden massive hemolysis after drug administration. Hence, sensitized RBC with C3d and IgG cannot be detected. This phenomenon have been described in ceftriaxone-induced immune hemolytic anemia.[12]

We tried bumetanide instead of furosemide. Nonetheless, hemolysis still occurred. Explanation for the situation may result from similar chemical structure between bumetanide and furosemide.[13] Both are 5-sulfamoylbenzoic acid derivatives. However, cross-reactivity in DIIHA had only been studied in ceftriaxone and in vitro data. The result showed very weak cross-reactivity between ceftriaxone antibodies and cefotaxime, cefamandole, and cefoperazone. [14] There was no data to indicate whether the in vitro data relate to in vivo reactivity. We speculate cross-reactivity of bumetanide and furosemide antibodies may play a role in hemolysis.

Glucocorticoids was generally used to treated autoimmune hemolytic anemia (AIHA) as first-line agents especially symptomatic patients.[15] An initial dose of 1 mg/kg or a dose of 60 to 100 mg daily prednisone was recommended. However, the benefit of steroids in DIIHA remains controversial. Because the suspected drugs were withdrawn simultaneously with the administration of steroids in most cases, the benefit of steroid is difficult to be proved. Therefore, the decision whether to use steroids should depend on the severity of hemolysis and clinical condition individually.[9] In our case, our patient was treated with methylprednisolone

intravenously (1 mg/kg/day of equivalent prednisone) and we tapered gradually every three days. The hemoglobin and bilirubin remarkedly improved and stabilized. Eventually, our patient was discharged under stable condition.

Conclusion

DIIHA is a rare complication, but it can be fetal without early diagnosis and early discontinuation of offending medication. We provide a rare case of furosemide-induced hemolytic anemia.

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