CLINICAL VIGNETTE

Drug Induced Immune Hemolysis: A Rare Cause of Post-operative Anemia

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Case Report

A 73-year-old woman presented with syncope. Two weeks prior she underwent elective ventral hernia repair at an outside hospital and was discharged without complication on post-operative day 3. She was doing well until 2 days prior to presentation when she developed fatigue and dyspnea on exertion. She was standing washing dishes when she lost consciousness for approximately one minute. The patient denied antecedent symptoms of chest pain or palpitations, but did report feeling dizzy prior to the event.

Vital signs in the ER including orthostatics were normal. Physical exam revealed pale conjunctiva, a mid systolic murmur at the right upper sternal border without radiation and a benign abdomen with a well-healing surgical incision.

Laboratory studies were significant for marked anemia with hemoglobin of 6.2mg/dL; there was macrocytosis with mean corpuscular volume of 95. Total bilirubin was elevated at 4.5mg/dL and direct bilirubin was normal.

The patient was admitted to the hospital with a presumptive diagnosis of syncope secondary to symptomatic anemia, likely hemolytic in etiology. Additional laboratory studies were obtained. LDH was elevated at 1500, haptoglobin was low at 8, and reticulocyte count was elevated at 10%. Peripheral smear showed spherocytes without schistocytes. Renal function was normal. Direct Anti-Globulin Test (DAT) was positive for IgG antibodies confirming immune mediated hemolytic anemia. Elution studies were negative, ruling out auto-antibodies. Drug testing demonstrated that the patient's serum caused marked hemolysis of cefotetan coated red blood cells. Outside records from the recent hospitalization confirmed the patient had received a single dose of cefotetan perioperatively for routine surgical prophylaxis. A diagnosis of cefotetan-induced immune hemolytic anemia was made.

Background

Autoimmune mediated hemolytic anemia (AIHA) is caused by antibodies directed against antigens on red blood cells (RBCs) causing RBC lysis. Drug induced immune hemolytic anemia (DIIHA) was first described in 1954. A patient taking stibophen—a drug used to treat schistosomiasis—developed a hemolytic anemia that was DAT positive. The patient's serum was shown to react with allogenic red blood cells only when the drug was present. The patient had taken a course of stibophen 10 years prior without complication[1, 2].

Today, approximately 125 drugs have good evidence documenting DIIHA[3]. The reported incidence is relatively rare—1 per million of population. However, this may be an underestimate as typically only severe cases are reported[4].

Mechanism

Several mechanisms for hemolysis in DIIHA have been proposed, but the most widely accepted is the "drug-absorption" mechanism initially described with penicillins. The penicillin molecule coats the red blood cells. IgG-penicillin antibiodies present in the patient's serum react with the RBC bound penicillin resulting in destruction of IgG coated RBCs by macrophages[1]. Reportedly, DIIHA is caused by either IgG or IgM antibodies and has no relationship to anaphylactoid reactions which are IgE mediated.

Diagnosis

AIHA is typically diagnosed with the Coombs' test or Direct Anti-Globulin test. The red blood cells of a patient's serum are washed of adherent proteins and reacted with monoclonal antibodies against immunoglobulins, typically IgG and C3. RBC agglutination confirms the presence of reacting antibodies on the red cell surface membrane[5]. If the eluate from the patient's

serum shows drug-independent antibodies (i.e. auto-antibodies) idiopathic warm antibody immune hemolytic anemia should be considered (WAIHA). This entity is far more common than DIIHA. If DAT is positive, but no drug-independent antibodies are found and the history strongly suggests DIIHA, drug-specific testing should be done. This typically requires a referral to a specialty lab that is familiar with the technique. In our case the patient's serum was sent to the American Red Cross.

A detailed history typically reveals recent use of the offending drug. Patients often have had prior exposure to the drug (or a biochemically similar drug) without complication leading to circulating antibodies. Interestingly, cefotetan antibodies can be found in the plasma of 75% of random individuals[1]. The mechanism for the presence of these antibodies is unclear, but it has been postulated that they are derived from ingestion of farmed animals that have been treated with prophylactic antibiotics[1].

Causative Drugs

The majority of drugs reported to cause DIIHA are antimicrobials (42%). The phenomenon has also been reported with NSAIDS, anti-neoplastics and anti-hyertensives. Among anti-microbials, cefotetan is the most common (54%) followed by ceftriaxone (16%), and then piperacillin (9%). Cefotetan is most commonly associated with fatal DIIHA. The vast majority of cases with DIIHA attributed to cefotetan involve a single dose of the drug given in the peri-operative setting. Ceftriaxone is associated with fatal DIIHA in children but typically causes more mild symptoms in adults[6].

Treatment

The mainstay of treatment for DIIHA is supportive care through blood transfusion and discontinuation of the offending agent. Most drugs are cleared from the system quickly and the drug-dependent antibodies do not adhere without presence of the drug on the RBC membrane[7]. There are limited data to suggest the utility of steroids, and plasma exchange has been reported successful in severe cases[8]. It is recommended that the patient avoid any further exposure to the entire class of offending drugs (e.g. cephalosporins), however in vitro studies show surprisingly little cross-reactivity[9]. With regard to cephalosporin–penicillin cross-reactivity, early cephalosporin antibiotics contained trace amounts of penicillin. Thus, early studies may have over-estimated the degree of cross-reactivity between the two groups. Nevertheless, it is generally accepted that there is an approximate 5-8% incidence of cross-reactivity[10].

Conclusion

Clinical concern for DIIHA should arise in a patient with evidence of hemolytic anemia, positive DAT and recent history of exposure to an inciting drug. If elution studies show no auto-antibodies to suggest WAIHA, drug testing should be performed to confirm the diagnoses of DIIHA. Treatment is typically supportive care and cessation of the offending drug. The patient in our case received a single blood transfusion on admission with appropriate response in blood counts and good relief of her fatigue and dyspnea. Her blood counts remained stable and she was discharged on hospital day 3 with instructions that she had confirmed allergy to cefotetan.

REFERENCES

1. **Garratty G**. Immune hemolytic anemia associated with drug therapy. *Blood Rev*. 2010 Jul-Sep;24(4 5):143-50. Epub 2010 Jul 21.
Review. PubMed PMID: 20650555.
2. **Harris JW**. Studies on the mechanism of a drug-induced hemolytic anemia. *J Lab Clin Med*. 1956 May;47(5):760-75. PubMed PMID: 13319885.
3. **Garratty G, Arndt PA**. An update on drug-induced immune hemolytic anemia. *Immunohematology*. 2007; 23(3):105-19. PubMed PMID: 18284300.
4. **Petz LD et al**. Immune Hemolytic Anemias, 2nd ed. Philadelphia: Churchill Livingstone: 2004.
5. **Chaplin H Jr**. Clinical usefulness of specific antiglobulin reagents in autoimmune hemolytic anemias. *Prog Hematol*. 1973;8:25-49. PubMed PMID: 4545113.
6. **Kelkar PS, Li JT**. Cephalosporin allergy. *N Engl J Med*. 2001 Sep 13;345(11):804-9. Review. PubMed PMID: 11556301.
7. **Salama A**. Drug-induced immune hemolytic anemia. *Expert Opin Drug Saf*. 2009 Jan;8(1):73-9. Review. PubMed PMID: 19236219.
8. **Doratotaj S, Recht M, Garratty G, Krupicka M, Thomas GA, Boshkov L**. Successful treatment of life-threatening ceftriaxone-induced hemolysis by plasmapheresis in a 4-year old girl. *Transfusion*. 2009; 49(S):13A.
9. **Arndt PA, Garratty G**. Cross-reactivity of cefotetan and ceftriaxone antibodies, associated with hemolytic anemia, with other: cephalosporins and penicillin. *Am J Clin Pathol*. 2002 Aug;118(2):256-62. PubMed PMID: 12162687.
10. **Saxon A, Beall GN, Rohr AS, Adelman DC**. Immediate hypersensitivity reactions to beta-lactam antibiotics. *Ann Intern Med*. 1987 Aug;107(2):204-15. Review. PubMed PMID: 3300459.

Submitted on December 13, 2011