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Case report

Cefazolin-induced hemolytic anemia in septic arthritis: A case report

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ABSTRACT

A 50-year-old woman living with untreated HIV and injection drug use presented with right shoulder pain. The shoulder exam and computed tomography (CT) scan were concerning for septic arthritis. She was started on empiric vancomycin and cefepime and underwent right shoulder debridement and humeral head resection. Bone cultures grew methicillin sensitive *Staphylococcus aureus* (MSSA); empiric broad-spectrum antibiotics were changed to cefazolin. The patient subsequently developed severe anemia refractory to blood transfusions approximately 6 days later. Further evaluation disclosed hemolytic anemia attributable to cefazolin. Antibiotic therapy was switched from cefazolin to daptomycin, and the patient was started on prednisone. She had sustained improvement in hemoglobin values above 6 g/dL without requiring further transfusions prior to hospital discharge. Drug-induced immune hemolytic anemia from cefazolin is rare but has been reported primarily in the perioperative setting. Here, we present a case following initiation of treatment for septic arthritis.

Case Report

A 50-year-old woman with a history of untreated Human Immunodeficiency Virus (HIV) infection, Hepatitis B and C, and injection drug use presented with ten days of right shoulder pain. Past surgical history included muscle flap placement in the right shoulder for multiple abscesses over preceding 10 years without adverse reactions to perioperative antibiotics, including cefazolin. Shoulder exam was notable for a draining wound from a prior incision, diffuse tenderness, and decreased range of motion. Laboratory examination revealed a baseline hemoglobin of 8.7 g/dL (11.9–15.7), with an elevated Erythrocyte Sedimentation Rate (ESR) of 121 mm/h (0–30) and C-reactive protein (CRP) of 4.7 mg/dL (< 1.0).

A computed tomography (CT) scan of the shoulder showed new articular erosive change in the humeral head and glenoid concerning for septic arthritis. Empiric vancomycin and cefepime were started after drawing blood cultures. On hospital day 2, the patient underwent operative debridement of the right humeral shaft and resection of the humeral head, with copious pus visualized in the humeral canal. Estimated blood loss was 200 mL. Intraoperative cultures grew methicillin sensitive *Staphylococcus aureus* (MSSA). Subsequently, antibiotics were narrowed to cefazolin 2 g every 8 h infused over 30 min. Dosing was appropriate given patient's weight of 54.4 kg and creatinine clearance greater than 50 mL/min at the time (using Cockcroft-Gault equation).

On hospital day 9, the patient's hemoglobin acutely dropped to 5.5 g/dL, and she was transfused two units of packed red blood cells (pRBCs). However, after a brief post-transfusion increase in hemoglobin to 7.8 g/dL on day 10, subsequent hemoglobin values remained below 7 g/dL and refractory to further transfusion with another unit of pRBCs on day 11, hitting a nadir of 5.8 g/dL on day 13. In total, 3 units pRBCs were transfused during the hospitalization (Fig. 1). A CT angiogram of the abdomen and pelvis showed no obvious blood extravasation or hematoma. Repeat CT scan of the right shoulder showed no significant hematoma. The patient additionally reported dark-colored urine. Further laboratory workup was significant for a rising alkaline phosphatase and total bilirubin, with peaks to 700 units/L (38–126) and 2.0 mg/dL (0.3–1.2), respectively. Serum lactate dehydrogenase (LDH) was 5774 units/L (313–618), reticulocyte percentage 6.34 % (0.59–2.79), and haptoglobin < 20 mg/dL (30–178). A direct Coombs test was positive. Of note, renal function declined primarily after the drop in hemoglobin

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(Fig. 1). On hospital day 10, cefazolin dosing was adjusted to 2 g every 12 h due to decrease in creatinine clearance below 50 mL/min. Subsequently, cefazolin was changed to daptomycin on day 11 due to concern for drug-induced immune hemolytic anemia (DIIHA). Hematology was consulted and recommended initiation of a prednisone taper, starting with 60 mg for 5 days followed by decreases every 5 days to 40 mg, then 20 mg, then 10 mg, and finally 5 mg prior to stopping. Following cefazolin discontinuation and prednisone initiation, the patient clinically improved with resolution of dark urine and a rise in hemoglobin to 7.3 g/dL prior to discharge on day 24 (see Fig. 1 for trend). Subsequent post-discharge hemoglobin values were 9.6 g/dL (2 weeks after discharge) and 10.5 g/dL (6 months after discharge).

Discussion

DIIHA is extremely rare, estimated to occur at a rate of approximately one in one million people [1,2]. Although the exact immunologic mechanisms of DIIHA are not fully understood, it is thought to be mediated by drug-induced antibodies and non-immunologic protein adsorption [3–5]. The hapten theory, in which the drug binds with high affinity to a carrier protein to elicit an IgG anti-hapten-specific immune response, seems to be most plausible for beta-lactam-related DIIHA [2,6,7]. The beta-lactam moiety is thought to be the hapten in these reactions [8].

The cephalosporins cefotetan and ceftriaxone are most commonly associated with DIIHA as they cause hemolytic anemia via multiple mechanisms, including the hapten-carrier complex mechanism [2,6,7]. Reports of DIIHA attributed to cefazolin are exceedingly rare. In 50 years of clinical use, only 6 case reports of cefazolin-induced DIIHA have been published, most of which occurred in the perioperative setting [9–12]. Recently, a case of direct Coombs test-negative DIIHA due to cefazolin usage for MSSA endocarditis was reported [13]. The timing to development of DIIHA after cefazolin use has ranged from hours to 7 days, which is congruent with the timing observed with our patient [9,10,13].

Although HIV is known to be an independent risk factor for immune hemolytic anemia (IHA), the incidence of IHA from HIV alone is reported to be less than 5 % [14,15]. Additionally, active use of antiretroviral therapy has been linked to higher likelihood of IHA in people living with HIV (PLWH) [14]. Therefore, although HIV increased the underlying risk for IHA in our patient and likely contributed to her baseline anemia, the temporal relation of hemoglobin decline and symptomatology to drug initiation followed by improvement after cessation argue more for cefazolin as the likely cause. Furthermore, we calculated an Adverse Drug Reaction Probability Scale (Naranjo) score of 8 in relation to cefazolin, indicating that the drug is the probable cause for the IHA [16].

Here, we present a case of DIIHA due to cefazolin. The diagnosis is supported by temporal relation, laboratory data indicative of immune-mediated hemolysis, and clinical improvement with discontinuation of cefazolin and treatment with prednisone. Cefazolin dosing was appropriate based on renal function, making DIIHA an adverse effect strictly due to inappropriate dosing less likely. Given paucity of reported cases in the literature, no definitive predisposing factors have been established between cefazolin use and development of IHA, although the risk may be higher in patients with other underlying diseases such as HIV or prior penicillin allergy [13]. Further evaluation is necessary to definitively delineate risk factors for development of DIIHA from cefazolin. However, this case report serves as an important reminder of the need to be vigilant for both common and uncommon side effects with antibiotic treatment.

CRediT authorship contribution statement

Shah Zafar: Writing – review & editing, Writing – original draft, Visualization, Investigation, Conceptualization. **Zachary Wynne:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Thomas John:** Writing – review & editing, Writing – original draft. **Lauren Buzzalino:** Writing – review & editing,

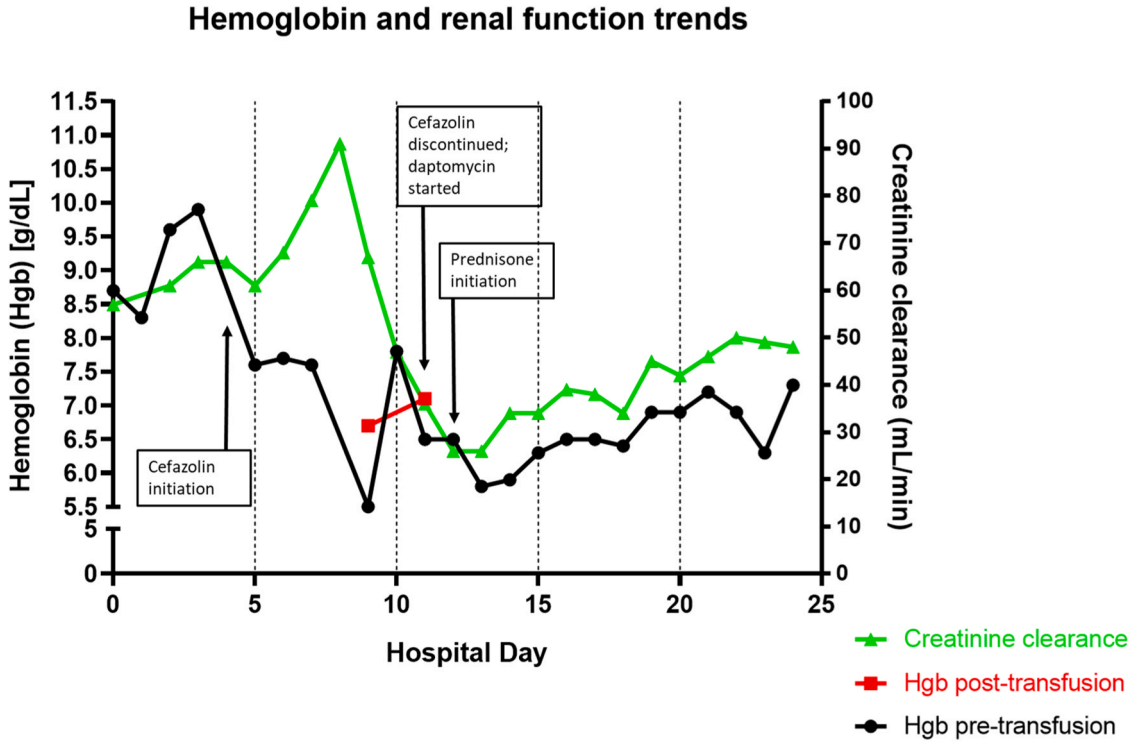

Fig. 1. Temporal relationship between hemoglobin (g/dL) and renal function, as represented by creatinine clearance in mL/min, and antibiotic plus steroid use over hospital course. Black points and line represent hemoglobin values on routine checks. Red points and line represent hemoglobin values checked 30 min to 2 h post-transfusion. Patient was transfused 2 units pRBCs on hospital day 9 and 1 unit pRBCs on hospital day 11.

Investigation. **Akira Shishido:** Writing – review & editing, Investigation. **David Riedel:** Writing – review & editing, Supervision, Investigation.

Consent

Written informed consent was obtained from the patient's next of kin for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Ethical approval

N/A.

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All the authors had access to the patient record and contributed to this work.

Conflicts of Interest

All of the authors have no conflicts of interest to declare.

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