Severe piperacillin–tazobactam-induced hemolysis in a cystic fibrosis patient

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Key Clinical Message

Piperacillin–tazobactam is one of the most common causes of drug-induced immune hemolytic anemia (DIHIIA) and is frequently utilized, especially in patients with cystic fibrosis (CF). Here, we report a case of life-threatening piperacillin–tazobactam-associated DIHIIA in a 30-year-old woman with CF and propose management recommendations for piperacillin–tazobactam-associated DIHIIA in CF patients.

Keywords

Anemia, cystic fibrosis, hemolysis, piperacillin, tazobactam.

Introduction

Drug-induced immune hemolytic anemia (DIHIIA) is rare but life-threatening [1]. Piperacillin–tazobactam, a ubiquitous antibiotic and one of the most common causes of DIHIIA, is frequently utilized in cystic fibrosis (CF) patients [1]. The management of piperacillin–tazobactam-associated DIHIIA in CF patients is incompletely described. Here, we present a case of severe piperacillin–tazobactam-associated DIHIIA in a CF patient and management recommendations.

Case Report

A 30-year-old woman with cystic fibrosis (CF) presented to a local emergency department with acute dyspnea and palpitations. Four days prior, she had been discharged after a pulmonary exacerbation. She was on day 11 of 14 of piperacillin–tazobactam and ciprofloxacin. Past medical history included pulmonary exacerbations with multi-drug-resistant *Pseudomonas*, allergic bronchopulmonary aspergillosis, sinus disease, gastroparesis, pancreatic insufficiency, and iron deficiency anemia. Home medications included: arformoterol, tiotropium, albuterol, hypertonic saline, dornase alpha, inhaled aztreonam and tobramycin, azithromycin, fluconazole, lipase–protease–amylase, lansoprazole, multivitamin, ferrous sulfate, calcium, vitamin D, lactobacillus, metoclopramide, polyethylene glycol, ondansetron, dextroamphetamine, lorazepam, bupropion, and buspirone. She had no known allergies. Presenting vital signs and examination were notable for tachycardia (144 beats/min), altered cognition, conjunctival pallor, and diffuse jaundice. The white blood cell (WBC) count was 38.9 × 10⁹/L, hemoglobin 3.1 g/dL, mean corpuscular volume (MCV) 78 fl, platelets 457 × 10⁹/L, total bilirubin 7.0 mg/dL, direct bilirubin 1.7 mg/dL, international normalized ratio 1.2, reticulocyte count 489.5 × 10⁹/L (25.6–96.6), lactate dehydrogenase (LDH) 1620 U/L (102–199), and haptoglobin <6 mg/dL (36–195). A blood smear showed microspherocytes. Ten days prior, her
hemoglobin was 10.0 g/dL, MCV 81 fL, ferritin 13 µg/L (12–160), serum iron 19 µg/dL (29–189), transferrin 230 mg/dL (182–360), and transferrin saturation 6% (10–47). After receiving 3 units of O-negative blood, she was transferred to our hospital.

Direct antiglobulin test (DAT) was IgG and C3-positive with a nonreactive eluate. Cold agglutinins were negative. Drug-induced immune hemolytic anemia (DIIHA) was suspected, and antibiotics were withheld. Oral folate was given. The reticulocyte count, bilirubin, and LDH decreased, while hemoglobin improved to 7.2 g/dL. She remained dyspneic and tachycardic. To reduce alloimmunization risk, and to treat her absolute iron deficiency, 200 mg of intravenous iron sucrose was administered instead of further transfusion. Her symptoms improved, and she was discharged.

Testing returned positive for piperacillin–tazobactam-dependent red cell antibodies and negative for ciprofloxacin-dependent antibodies. This was her fifth course of piperacillin–tazobactam; courses 3 and 4 were associated with drops in hemoglobin (11.7–9.3 and 11.2–8.8, respectively). One week later, her hemoglobin was 8.3 g/dL. She was seen in pulmonology clinic five months after hospital discharge and had a hemoglobin level of 12.0 g/dL.

Discussion
Our case builds upon previous reports of piperacillin–tazobactam-associated hemolytic anemia [2, 3]. Although DIIHA is rare (1:1,000,000 in the general population), piperacillin–tazobactam is a common culprit [1]. Forty percent of DIIHA cases occur in CF patients, in whom piperacillin–tazobactam is commonly used; nearly two in five CF patients require IV antibiotics annually for pulmonary exacerbations [4]. Up to 7% of piperacillin–tazobactam-associated DIIHA may be fatal [1]. The young age of piperacillin–tazobactam-associated DIIHA cases (typically < 35 years old) [2, 3] is likely due in part to the early age and frequency at which CF patients receive IV antibiotics. It is unclear whether CF patients are more susceptible to DIIHA or whether this represents a reporting bias in a closely monitored patient population. CF patients may be more predisposed to DIIHA via decreased nitrous oxide production leading to vasoconstriction and intravascular sludging [3].

DIIHA should be suspected in patients receiving piperacillin–tazobactam who develop new/worsening anemia. Symptoms occur 24 h to 2 weeks after piperacillin–tazobactam initiation [1]. The typical hemoglobin nadir is 3–5 g/dL [2, 3], although mild cases are likely underreported [5]. Upon chart review, our patient had decreases in hemoglobin levels during prior piperacillin–tazobactam courses that may have been missed DIIHA. As with other hemolytic anemias, LDH, indirect bilirubin, and reticulocyte count are elevated, and haptoglobin is decreased. Hemoglobinuria may not be present as hemolysis is predominantly extravascular. DAT positivity with nonreactive eluate characterizes DIIHA; contrastingly, warm autoimmune hemolytic anemia has a reactive eluate. Drug-dependent antibodies are confirmatory [6].

When concern for DIIHA exists, piperacillin–tazobactam should be stopped and an alternate antipseudomonal agent started, if still indicated. Because the antibody in DIIHA should no longer react in the absence of drug, steroids and intravenous immunoglobulin are not recommended [6].

If the patient is stable with only mild symptoms, transfusion should first be discussed with CF and hematology experts, as resultant alloimmunization could increase the patient’s future likelihood of lung transplant rejection. Folate should be given to support erythropoiesis. The role of empiric iron therapy in CF patients with DIIHA is unclear, but IV iron may be a reasonable alternative to transfusion in stable patients with mild anemia as concomitant iron deficiency is common in CF; intestinal absorption is often impaired in CF patients, rendering the parenteral route more reliable for iron delivery.

Erythropoiesis-stimulating agents have demonstrated benefit in other anemias of chronic disease [7] and may be considered in patients with refractory anemia and low erythropoietin levels. While improvement is expected with drug cessation alone, the time to anemia resolution is variable and depends on the amount of transfusion support provided as well as the rapidity of piperacillin–tazobactam [6].

DIIHA is a likely underdiagnosed and potentially fatal complication of piperacillin–tazobactam and is most common in CF patients. High clinical suspicion, piperacillin–tazobactam cessation, and supportive care are required. Alternatives to unnecessary blood transfusion when appropriate are desirable in this population.

Conflict of Interest
The authors have no conflict of interests to report.

Authorship
ADK and SB: wrote the first draft of the manuscript. All authors: participated in direct patient-care activities, commented on manuscript drafts, and approved the final version of the article.

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