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CASE REPORT

Immune Hemolytic Anemia Associated with Prophylactic Use of Cefotetan during Pelvic Reconstructive Surgery: A Case Report and Review of the Literature

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Abstract

We describe the first case of cefotetan-induced immune hemolytic anemia (IHA) following sacrocolpopexy. A 65-year-old female status post uncomplicated sacrocolpopexy presented on postoperative day 15 for worsening fatigue. Her exam was notable for jaundice and icteric sclerae. Hemoglobin and hematocrit were 5.5 g/dL and 17.2%, respectively and direct anti-globin test was positive. She was successfully managed with a blood transfusion and oral prednisone, then discharged home. Cefotetan is the most common culprit in drug-induced IHA and a widely used perioperative antibiotic, particularly in gynecology and pelvic reconstructive surgery. Symptoms of anemia and its clinical sequelae occur 1 to 3 weeks following exposure to cefotetan, so a high index of suspicion is needed to quickly diagnose and manage this rare and life-threatening condition.

PRECIS: Cefotetan-induced immune hemolytic anemia is a rare but potentially life-threatening condition involving a commonly used perioperative prophylactic antibiotic in gynecology and pelvic reconstructive surgery.

Keywords

Cefotetan, Cephalosporins, Drug-induced hemolytic anemia, Perioperative antibiotics

Introduction

Drug-induced immune hemolytic anemia (DIIHA) is a rare and life-threatening condition, with an estimated incidence of 1 in 1,000,000 [1]. The condition is precipitated by the administration of medications which trigger the production of antibodies against moieties on red blood cells (RBC). These antibodies cause RBC destruction, resulting in hemolysis, severe anemia, and its associated clinical sequelae, such as renal failure. Various medications have been implicated as causative agents of DIIHA, including non-steroidal anti-inflammatory drugs, fluoroquinolones, nitrofurantoin, and levodopa. Cephalosporins account for 70% of all reported DIIHA cases; of these cases, most were due to Cefotetan [2].

Cefotetan is a second-generation cephalosporin commonly used for prophylaxis against surgical site infections. Due to its extended antimicrobial spectrum, it is a perioperative antibiotic of choice in pelvic reconstructive surgeries employing mesh augmentation [3]. With over 300,000 pelvic reconstructive surgeries performed annually in the United States, the likelihood of encountering DIIHA secondary to perioperative antibiotic prophylaxis is not negligible [4]. To the best of our knowledge, there are four existing publications on cefotetan-induced hemolysis following perioperative prophylactic antibiotic use during obstetric and gynecologic procedures, with the most recent publication in 2004 (Table 1) [5-8]. Of these publications, there were only two cases of cefotetan-induced immune hemolytic anemia (IHA) following pelvic reconstructive surgery [7,8]. In an effort to increase awareness among surgeons in our field, we describe the first case of

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Table 1: Drug-induced immune hemolytic anemia secondary to perioperative prophylactic use of cefotetan in obstetrics and gynecology.

Case	Publication	Procedure	Initial postoperative Hgb or HCT	Cefotetan-induced immune hemolytic anemia						
				Postoperative time to diagnosis (days)	Hgb or HCT	Reticulocyte count (%)	Bilirubin, Total (mg/dL)	Bilirubin, Indirect (mg/dL)	Lactate dihydrogenase (U/L)	Haptoglobin (mg/dL)
1	Shariatmadar [5]	Cesarean	---	2 weeks	14.80%	15	3.5	---	750	Normal
2	Naylor [6]	Cesarean	29%	13	11%	6.8	2.5	2.3	---	< 6
3		Cesarean	35%	9	23%	9.1	1.9	---	338	7
4		Cesarean	---	9	8%	11.1	5.4	4.8	448	---
5	Garratty [7]	Enterocele repair	11.6 g/dL	9	6.8 g/dL	---	---	6.1	---	< 5
6		Cesarean	7.5 g/dL	10	3.5 g/dL	30.6	---	5.4	607	< 50
7		Cesarean	9.9 g/dL	12	4.0 g/dL	---	---	2.2	1987	---
8		Cesarean	---	14	6.1 g/dL	---	---	---	---	---
9		Cesarean	9.6 g/dL	9	2.6 g/dL	---	5.3	---	1849	---
10		Cesarean	---	9	3.4 g/dL	---	27.6	---	2150	< 6
11		Cesarean	10.8 g/dL	9	3.7 g/dL	5.1	5	---	2967	---
12		Curettage	---	14	7.6 g/dL	2.5	---	3.1	233	< 6
13	Mohammed [8]	Colporrhaphy	11 g/dL, 32%	6	4.8 g/dL, 12.8%	3.2	5.2	---	1170	---

Hgb: Hemoglobin; HCT: Hematocrit

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cefotetan-induced IHA following an uncomplicated sacrocolpopexy and present a review of the existing literature on the diagnosis and management of this potentially fatal condition. Both patient consent and Institutional Review Board exemption have been obtained.

Case Description

A 65-year-old Hispanic female with stage 3 pelvic organ prolapse and stress urinary incontinence underwent surgical treatment with robotic-assisted laparoscopic supracervical hysterectomy, bilateral salpingo-ophorectomy, sacrocolpopexy, posterior colporrhaphy, perineorrhaphy, retropubic synthetic mid-urethral sling, and cystoscopy. Her surgical history was significant for a remote cholecystectomy, and her medical history was notable for moderately controlled type 2 diabetes mellitus (hemoglobin A1C 8.0%). She reported no known drug allergies. Preoperative hemoglobin and hematocrit (H&H) were 13.9 g/dL and 44.3%, respectively.

The patient received 2 grams of cefotetan intravenously for prophylaxis against surgical infection prior to incision. Her surgery was uncomplicated, with an estimated blood loss of 150 mL. She had an uneventful hospital course and was discharged home in stable condition on postoperative day 1 with a H&H of 12.5 g/dL and 37.7%, respectively.

On postoperative day 15, the patient presented to clinic for progressively worsening fatigue, fever, chills, headache, and shortness of breath. She was afebrile, normotensive, and tachycardic to 115 beats per minute. Exam was notable for jaundice with icteric sclerae. Her abdomen was soft, non-distended, and minimally tender to palpation. There was no vaginal bleeding on pelvic exam, and her urine was noted to be a dark amber color. Her H&H were 5.5 g/dL and 17.2%, respectively, and renal function was normal. The patient was transferred to the emergency department for further evaluation and treatment of her severe anemia.

In the emergency department, computed tomography of the abdomen and pelvis was negative for any acute intraabdominal process, including fluid collection, abscess, hematoma, or gastrointestinal abnormality. Additional anemia workup was initiated and was significant for elevated reticulocyte count (12.8%), elevated total bilirubin (2.2 mg/dL), elevated lactate dehydrogenase (LDH, 445 U/L), and low haptoglobin (< 9 mg/dL), all of which supported a diagnosis of hemolytic anemia. Her direct anti-globin test (DAT), also known as a direct Coombs test which detects the presence of RBC antibodies, resulted as positive, confirming her diagnosis of IHA.

She was admitted to the hospital, transfused one unit of packed RBC, and started on oral prednisone. She was discharged on hospital day 6 with symptomatic improvement, a H&H of 8.0 g/dL and 25.8%, respectively, and a prednisone taper. Following hospital discharge, H&H was trended weekly and a prednisone taper was continued for approximately 2.5 months. Following completion of the treatment course, her H&H was 12.9 g/dL and 37.9% with resolution of all symptoms and associated lab abnormalities.

Conclusions

We present a case of IHA in the setting of cefotetan exposure in a post-surgical patient who had no history of autoimmune disease, known adverse reactions to antibiotics, or any other inciting drug linked to the condition. She presented with an acute and severe hemolytic episode that resulted in significant symptomatology and hospitalization after approximately 15 days from cefotetan exposure, which is similar to previously published cases that ranged from postoperative days 6 to 14 [5-8].

Mechanisms for DIIHA can be broadly categorized as drug-independent and drug-dependent antibodies [2]. Drug-independent antibodies occur when the drug triggers the immune system to produce RBC antibodies, and subsequently, the RBC antibodies can be detected in the absence of the drug. Drug-dependent antibodies react only in the presence of the drug and are directed at drug surface antigens or the drug-RBC complex. Cefotetan responds in a drug-dependent, dose-dependent manner by covalently binding to the RBC membrane. This is a benign process, unless the immune system creates IgG antibodies against cefotetan, resulting in RBC destruction.

In the presence of hemolysis, DAT is a necessary serologic assay used to distinguish immune-mediated hemolysis from other nonimmune causes. The test confirms the presence of RBC-bound antibodies or complement circulating in the bloodstream with a 5 to 10% false-negative rate [9]. False-negatives can result from severe hemolysis (rapid destruction), IgA- or IgM-mediated hemolysis, IgG levels below detectable limits, low-affinity antibodies, or technical error [10]. Enzyme-linked antiglobulin tests and complement-fixing antiglobulin consumption tests are more sensitive and time-consuming than DAT, and these tests can be considered in the event of a negative DAT with a high clinical suspicion for DIIHA.

Given the significant health implications of severe DIIHA, prompt diagnosis and management are critical. In practice, the acute hemolytic reaction occurs approximately 1 to 3 weeks after exposure to the medication, a time period in which most post-surgical patients are no longer under direct clinical supervision. Symptoms of anemia will be apparent in addition to lab abnormalities, including a decreased H&H and haptoglobin and/or an increased bilirubin and LDH. In the setting of a negative work-up for postoperative

complications, like hematoma and infection, and other etiologies such as gastrointestinal bleeding or malignancy, patient medications should be reviewed and a DAT should be ordered to help establish an immune etiology for the hemolytic anemia. If DIIHA is suspected or serologic tests are positive, hematology should be consulted promptly.

Generally, DIIHA is a self-limiting condition once the inciting drug is discontinued [2]. However, cefotetan-induced IHA is unique given its proven ability to remain adherent to the RBC membrane for much longer than other drugs. Thus, in addition to a blood transfusion for improving symptoms and end-organ perfusion, the use of corticosteroids may be necessary. Second-line treatment options include rituximab, intravenous immunoglobulin, plasma exchange, splenectomy, and immunosuppressive drugs; there have been no comparative trials of second-line treatment options, so a standard approach does not exist. Close outpatient follow-up is needed to assess patient symptoms and to ensure a persistent rise in H&H until baseline levels are met. Experts recommend avoidance of all cephalosporins in patients with a history of cefotetan-induced IHA given that repeat episodes of IHA are often more severe than the prior episode.

Our case demonstrates the severity of cefotetan-induced IHA, a rare but potentially life-threatening condition involving a commonly used drug in gynecology and pelvic reconstructive surgery. Postoperatively, it is important to educate patients on how to (1) Recognize signs and symptoms of hemolysis and (2) Encourage prompt communication regarding such findings with their provider, both of which will help ensure timely evaluation and management. Providers should also be aware of this condition, and it should be highly considered on the differential in the setting of a similar presentation. Medications should be thoroughly reviewed, and potential inciting drugs should be stopped immediately. Previous reports have suggested discontinuation of cefotetan as a choice for antibiotic prophylaxis. However, we surmise that the rarity of the condition be thoroughly considered against the effectiveness of the drug as a prophylactic agent and overall low side effect profile before such a recommendation is advised.

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Conflicts of Interest

The authors declare that they have no actual or potential conflicts of interest.

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