Case Report

Refractory Unforeseen Anaphylaxis Case in a Rural OR Unit

Sayed Hafizi, Christine Nadeau, Mohamed Gazarin, and Emily Mulligan

Winchester District Memorial Hospital, 566 Louise St, Winchester, ON, Canada K0C 2K0

Correspondence should be addressed to Mohamed Gazarin; mgazarin@wdmh.on.ca

Received 4 June 2019; Revised 21 October 2019; Accepted 23 December 2019; Published 28 January 2020

1. Introduction

Assessment and management of serious allergies is a key component in patient safety in all clinical environments. An accurate and detailed allergy history is the standard of care, and in most cases, prevents the rare occurrence of anaphylaxis and its associated morbidity and mortality. However, despite our very best efforts, some sentinel events can occur which call into question the mechanism behind certain drug reactions, and require critical care to stabilize an affected patient. This particular case was striking in the speed of onset, severity of symptoms, the known history of previous cephalosporin administration without adverse reaction, and subsequent negative allergy test results.

2. Case

The patient was admitted into day surgery at Winchester District Memorial Hospital for an elective posterior vaginal repair. Her past medical history was significant only for a skin and soft tissue infection treated safely with PO cephalexin in 2013, and for an upper respiratory tract infection treated with amoxicillin in December 2016; surgical history was significant only for an uneventful total hysterectomy and tension-free vaginal tape (TVT) to correct a vaginal prolapse in 2016, during which she had received prophylactic intravenous (IV) cefazolin without adverse reaction. The patient had a documented incident of adverse reaction to ciprofloxacin, which caused nausea and vomiting.

As summarized in Table 1, the patient was feeling well at the time of admission and had followed preoperative fasting instructions. A routine infusion of Ringer’s lactate was initiated. After the anesthetist had reviewed the patient’s history and examined the patient, she was transferred into the operating theatre where the team was waiting. The patient’s preoperative vitals were as follows: blood pressure (BP) 111/94 mmHg, heart rate (HR) 54 beats per minute (bpm), and oxygen saturation (O2Sat) 97%. Monitors were applied and the “time-out” was performed. Intravenous infusions of cefazolin 2 g and midazolam 2 mg were initiated. Approximately 2 minutes after the medications began infusing, the patient stated she felt a sense of doom and was itchy. In the time it took to ask her where she was uncomfortable, she had become deeply flushed and was in respiratory compromise. The patient then lost consciousness. Within seconds she received a first dose of 0.4 mg intramuscular epinephrine but became profoundly hypotensive nonetheless. Patient vitals at that time were BP 70/45 mmHg, HR...
blood count (CBC), electrolytes, renal function, and noncon-

tributory chest X-ray. She stabilized clinically over the follow-

ing 16 hours and was discharged the following day.

3. Discussion

Anaphylactic reactions are quite rare in perioperative set-

tings. According to studies conducted in Europe, Australia, and New Zealand, one out of every 4,000 to 20,000 patients experiences a perioperative anaphylactic reaction [1–8]. Neuromuscular blocking agents, latex, and antibiotics account for the majority of perioperative anaphylactic reaction triggers [9].

Of all perioperative anaphylactic reactions, antibiotics cause approximately 15% [10]. Cefazolin is an example of a cephalosporin antibiotic commonly used in perioperative settings to lower the risk of postoperative infections [11]. It exerts its effects by inhibiting bacterial cell wall synthesis [12]. Some individuals activate an immune response against cefazolin as their immune systems identify it as a foreign invader or allergen. In turn, the body increases the number of IgE antibodies against the specific allergen. In addition, the IgE antibodies also prime mast cells and basophils, thus triggering the release of histamine, tryptase, and other mole-
cules. Once these molecules are released, a cascade of events are actuated including the inflammatory response, broncho-
constriction, and increased mucus secretion—all of which were present in the patient [9] (Table 1). Cefazolin-
provoked anaphylaxis, although rare, has been noted to occur in some patients [1, 13–16]. Anaphylactic reactions caused by cefazolin can be very severe and result in death 3% to 9% of the time [1, 17, 18]. For this reason, extreme care must be taken to prevent such occurrences.

The patient’s clinical symptoms support that she had suf-

fered an anaphylactic shock. Since the patient had undergone previous surgery with similar preoperative procedures with no notable adverse reactions, it was almost impossible to pre-
dict that such a life-threatening reaction would occur during this procedure. Moreover, the patient’s medical history reveals that she safely received PO cephalaxin in 2013 and IV cefazolin in 2016.

After the anaphylactic incident, the patient underwent intradermal allergy testing for multiple agents including major and minor penicillin determinants. The major deter-

minant antigen contained penicilloyl-polysylne whereas a minor determinant mixture was composed of benzylpenicillin, benzylpenicilloate, and benzylpenilloate. The patient was also tested for cefazolin, latex, midazolam, and chlorhex-
idine allergies. Interestingly, the patient did not elicit a posi-
tive reaction to any of the tested agents; therefore, the allergy consultant was left to determine the causative agent based on probability. Because midazolam was statistically unlikely to be the causative agent, the most likely reason for the anaphylaxis was determined to be cefazolin.

According to one study by Romano et al., 13 out of 76 adults who displayed immediate reactions to cephalosporins had received negative results to all cephalosporin allergologic tests. After eight of the 13 subjects consented to be challenged and reevaluated, two (25%) who initially tested negative reported positive [19]. It is important to note that there are

| Timeline of events | Time (min) |
|--------------------|------------|
| Patient preop vitals BP 111/94 mmHg, HR 54 bpm, and O2Sat 97%. Patient was brought into the operating theatre, feeling well. Monitors applied to patient, “time-out” done. Cefazolin 2 g IV infused, followed by midazolam 2 mg IV. | 12:15 |
| A few seconds after midazolam was initiated, she reported a feeling of “doom,” itching in the face and chest, followed by difficulty in breathing and loss of consciousness. Prominent flushing was noted over face and chest. Profound hypotension (BP of 70/45 mmHg) despite a first dose of epinephrine 0.4 mg IM within one minute of symptoms. Patient heart rate was 115 bpm and O2Sat was 80%. | 12:17 |
| Diphenhydramine 50 mg IV, ranitidine 50 mg IV, and dexamethasone 8 mg IV were given. 2 L fluid bolus was started under pressure. Pulse was nonpalpable for less than 10 seconds, code blue called with rapid response from OR team. The airway remained patent and pulse returned spontaneously before compressions were initiated. | 12:18 |
| Salbutamol was administered, second dose of epinephrine 0.4 mg IM given, along with two boluses of 5 mcg IV epinephrine followed by a continuous infusion. Patient regained consciousness, after approximately 3-4 minutes of absence. She continued to feel weak and reported that her face was swollen. | 12:21 |
| Received odansetron IV for nausea. The airway was continuously monitored out of concern for a need to intubate; however, it remained patent and oxygen was supplemented via nasal prongs. On auscultation, there was no significant wheezing. She improved clinically with the epinephrine infusion. | 12:30 |
three major challenges with cephalosporin skin testing: (1) there are several cephalosporin allergenic determinants that have not been conclusively defined and understood, (2) cephalosporin-protein conjugate reagents for testing are not commercially available, and (3) the negative and positive cephalosporin testing predictive values are not well established. Therefore, a negative response to the test means that the patient could have been allergic to a metabolite or to a metabolite-protein complex [20]. Thus, such a result in our case must be interpreted cautiously and cannot be used to deem cefazolin as a noncausative agent for the anaphylactic reaction [21, 22].

Since allergy testing for cephalosporins may be insufficiently sensitive, procedures such as basophil activation test and/or oral provocation tests may be carried out to verify the drug responsible for the adverse reaction [23]. Unfortunately, neither of the two tests were conducted in our case.

Looking back at the case, we realize that it may have been useful to obtain a serum tryptase level within 15 minutes to 3 hours after onset of anaphylaxis symptoms and then 24 hours after all signs and symptoms had resolved. Elevated levels of mature or total tryptase in serum may have been useful for differentially diagnosing anaphylaxis from other conditions such as systemic mastocytosis, vasovagal reactions, or septic shock [24].

This case highlights the severity of anaphylactic reactions and the importance of a proactive healthcare team. The patient had a severe anaphylactic shock to cefazolin which was successfully treated due to the immediate and aggressive response by healthcare providers. In this regard, mock drills for intraoperative emergencies, such as anaphylactic shock, would be beneficial to practice recognition and the skills required to react quickly and appropriately. In our case, the team felt that having an anesthetist with an extensive emergency room experience played a role in the swift recognition and handling of the case. Furthermore, this case also illustrates the possibility of any patient presenting a false negative result to cephalosporin allergy testing. As a result, healthcare providers must interpret such results cautiously and remain proactive to prevent and treat anaphylactic reactions. This patient was otherwise healthy and had once previously received cefazolin in an operative setting without any adverse reaction.

**Consent**

The patient was informed of and consented to this case report.

**Disclosure**

The attached case report is original and has not been published or submitted for publication elsewhere. The views expressed in the submitted article are of the authors’ and not an official position of Winchester District Memorial Hospital.

**Conflicts of Interest**

The authors declare that they have no competing interests.

**Acknowledgments**

The authors acknowledge the support and cooperation of the involved staff at Winchester District Memorial Hospital.

**References**

[1] A. Gonzalez-Estrada, L. C. Pien, K. Zell, X.-F. Wang, and D. M. Lang, "Antibiotics are an important identifiable cause of perioperative anaphylaxis in the United States,” The Journal of Allergy and Clinical Immunology: In Practice, vol. 3, no. 1, pp. 101–105.e1, 2015.

[2] J. Pepys, E. Pepys, B. Baldo, and J. Whitwam, “Anaphylactic/anaphylactoid reactions to anaesthetic and associated agents skin prick tests in aetiological diagnosis,” Anaesthesia, vol. 49, no. 6, pp. 470–475, 1994.

[3] T. Harboe, A. Guttormsen, A. Irgens, T. Dybendal, and E. Fløraaag, "Anaphylaxis during anesthesia in Norway: a 6-year single-center follow-up study,” Anesthesiology, vol. 102, no. 5, pp. 897–903, 2005.

[4] L. Garvey, J. Roed-Petersen, T. Menne, and B. Husum, “Danish Anaesthesia Allergy Centre - preliminary results,” Acta Anaesthesiologica Scandinavica, vol. 45, no. 10, pp. 1204–1209, 2001.

[5] M. Laxenaire, P. Mertes, and Groupe d’Etudes des Réactions Anaphy lactoides Peranesthésiques, "Anaphylaxis during anaesthesia. Results of a two-year survey in France,” British Journal of Anaesthesia, vol. 87, no. 4, pp. 549–558, 2001.

[6] P. M. Mertes, F. Alla, P. Tréchot, Y. Auroy, and E. Jougl, "Anaphylaxis during anesthe sia in France: an 8-year single-center follow-up study,” Journal of Allergy and Clinical Immunology, vol. 128, no. 2, pp. 366–373, 2011.

[7] M. M. Fisher and B. A. Baldo, "FrequenCe et aspects cliniques des reactions anaphylactiques peranes thesi ques en Australie,” Annales Françaises d’Anesthésie et de Réanimation, vol. 12, no. 2, pp. 97–104, 1993.

[8] P. M. Mertes, K. Tajima, M. A. Regnier-Kimmoun et al., “Perioperative anaphylaxis,” Medical Clinics of North America, vol. 94, no. 4, pp. 761–789, 2010.

[9] W. Reisacher, "Anaphylaxis in the operating room,” Current Opinion in Otolaryngology & Head and Neck Surgery, vol. 16, no. 3, pp. 280–284, 2008.

[10] S. Caimmi, D. Caimmi, E. Lombardi et al., “Antibiotic allergy,” International Journal of Immunopathology and Pharmacology, vol. 24, pp. 47–53, 2011.

[11] T. Chopra, J. Zhao, G. Alangaden, M. Wood, and K. Kaye, “Preventing surgical site infections after bariatric surgery: value of perioperative antibiotic regimens,” Expert Review of Pharmacoeconomics & Outcomes Research, vol. 10, no. 3, pp. 317–328, 2010.

[12] Ancef, Food and Drug Administration, Durham, NC, USA, 2004, August 2017, https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/50461slr139_ancef_lbl.pdf.

[13] H. J. Carson and B. A. Cook, "Mast cell tryptase in a case of anaphylaxis due to repeat antibiotic exposure," Legal Medicine, vol. 11, no. 5, pp. 234–236, 2009.
[14] C. Tayman, E. Mete, O. Bayrak, F. Catal, and B. Usta, "Unexpected cefazolin anaphylaxis in a 5-month-old girl," *Pediatric Emergency Care*, vol. 24, no. 5, pp. 344-345, 2008.

[15] J. Culp, R. Palis, M. Castells, S. Lucas, and L. Borish, "Perioperative anaphylaxis in a 44-year-old man," *Allergy and Asthma Proceedings*, vol. 28, no. 5, pp. 602–605, 2007.

[16] L. Chyh-Woei and M. Castells, "Perioperative anaphylaxis to cefazolin," *Allergy and Asthma Proceedings*, vol. 25, no. 1, pp. 23–26, 2004.

[17] H. Mitsuhata, S. Matsumoto, and J. Hasegawa, “The epidemiology and clinical features of anaphylactic and anaphylactoid reactions in the perioperative period in Japan,” *Masui The Japanese Journal of Anesthesiology*, vol. 41, no. 10, pp. 1664–1669, 1992.

[18] K. Light, A. Lovell, H. Butt, N. Fauvel, and A. Holdcroft, "Adverse effects of neuromuscular blocking agents based on yellow card reporting in the U.K.: are there differences between males and females?,” *Pharmacoepidemiology and Drug Safety*, vol. 15, no. 3, pp. 151–160, 2006.

[19] A. Romano, R. M. Gueant-Rodriguez, M. Viola et al., "Diagnosing immediate reactions to cephalosporins," *Clinical Experimental Allergy*, vol. 35, no. 9, pp. 1234–1242, 2005.

[20] M. Blanca, A. Romano, M. J. Torres et al., “Update on the evaluation of hypersensitivity reactions to betalactams,” *Allergy*, vol. 64, no. 2, pp. 183–193, 2009.

[21] S. Yoon, S. Park, S. Kim et al., "Validation of the cephalosporin intradermal skin test for predicting immediate hypersensitivity: a prospective study with drug challenge," *Allergy*, vol. 68, no. 7, pp. 938–944, 2013.

[22] M.-H. Kim and J.-M. Lee, "Diagnosis and management of immediate hypersensitivity reactions to cephalosporins," *Allergy, Asthma & Immunology Research*, vol. 6, no. 6, pp. 485–495, 2014.

[23] S. Y. Kim, J. H. Kim, Y. S. Jang et al., "The basophil activation test is safe and useful for confirming drug-induced anaphylaxis," *Allergy, Asthma & Immunology Research*, vol. 8, no. 6, pp. 541–544, 2016.

[24] L. B. Schwartz, "Diagnostic value of tryptase in anaphylaxis and mastocytosis," *Immunology and Allergy Clinics of North America*, vol. 26, no. 3, pp. 451–463, 2006.