ELMER PRESS

Case Report

J Med Cases. 2022;13(4):159-162

Intraoperative Anaphylaxis Following Injection of a Bleomycin-Gelatin Solution for Sclerotherapy

Laura Roberts[a], Leah Braswell[b], Gregory Maves[c, d], Kimberly Stumpf[c], Margaret Redmond[e], Joseph D. Tobias[c, d, f]

Abstract

During the perioperative period, the most commonly identified agents that are responsible for acute allergic reactions include antibiotics, neuromuscular blocking agents, opioids, chlorhexidine, and iodinated dyes for radiologic imaging. However, whenever an allergic reaction is suspected, all of the agents to which the patient has been exposed must be considered. Although bleomycin is utilized as the primary agent for sclerotherapy in the treatment of vascular malformations, other substances such as Surgiflo® may be added to the bleomycin solution to increase its efficacy and promote thrombosis of the smaller vessels. These products are derived from animal collagen and contain gelatin which may lead to an allergic reaction. We present an 11-year-old girl undergoing sclerotherapy treatment of an extensive left lower extremity venous malformation who subsequently developed perioperative hemodynamic instability requiring intervention after receiving an injection of a bleomycin and Surgiflo® solution. Further investigation identified gelatin in the Surgiflo® as the causative agent of the allergic event. Previous reports of such reactions are reviewed and the perioperative care and treatment of patients who experience anaphylaxis is addressed.

Keywords: Anaphylaxis; Anaphylactoid reactions; Intraoperative care; Bleomycin; Allergic reactions; Sclerotherapy; Gelatin; Case report

Introduction

Although rare, anaphylaxis remains a life-threatening complication in the perioperative setting [1]. Acute drug reactions may be anaphylactic or non-immune-mediated (anaphylactoid). Anaphylactic reactions result from the cross-bridging of an antigen with IgE antibodies that are attached to mast cells and basophils with the release of histamine, kinin, slow-reacting substance of anaphylaxis, eosinophilic chemotactic factor, platelet activating factor, and prostaglandin. Non-immune, anaphylactoid reactions result from the direct, non-IgE-mediated activation of mast cells and basophils. Antibiotics, opioids, iodinated contrast agents, chlorhexidine, and neuromuscular blocking agents (succinylcholine, rocuronium, or vecuronium) have been identified as the most common causes of perioperative acute drug reactions [2, 3].

The potential role of allergic reactions must be considered when treating intraoperative hemodynamic instability or cardiorespiratory deterioration as prompt identification of the provocative agent, prevention of further exposure, and treatment according to fixed algorithms are essential in ensuring a successful outcome [4]. We present an 11-year-old girl who experienced acute hemodynamic and respiratory compromise following the injection of a bleomycin solution for sclerotherapy. The potential perioperative implications of allergic reactions are discussed, pathways for the identification of the offending agent are presented, and treatment strategies are suggested.

Case Report

Investigations

The patient was an 11-year-old, 57.4 kg girl with an extensive multifocal venous malformation of the entire left lower extremity and abdominal wall who was scheduled with interventional radiology to receive sclerotherapy treatment with injection of a bleomycin solution to the left foot and left thigh.

Diagnosis

The patient had received sclerotherapy treatment for the malformation several times previously over the past 7 years without difficulties. Those treatments were performed with mixtures of 3% Sotradecol® (sodium tetradecyl sulfate injection), Lipiodol® (ethiodized oil injection), and Surgiflo® hemostatic matrix. She was being followed by the plastic surgery and he-

Manuscript submitted January 25, 2022, accepted March 4, 2022
Published online March 25, 2022

[a]Heritage College of Osteopathic Medicine - Dublin Campus, Dublin, Ohio and Ohio University, Athens, OH, USA
[b]Department of Radiology, Nationwide Children's Hospital, Columbus, OH, USA
[c]Department of Anesthesiology & Pain Medicine, Nationwide Children's Hospital, Columbus, OH, USA
[d]Department of Anesthesiology & Pain Medicine, The Ohio State University College of Medicine, Columbus, OH, USA
[e]Department of Pediatrics, Division of Allergy & Immunology, Nationwide Children's Hospital, Columbus, OH, USA
[f]Corresponding Author: Joseph D. Tobias, Department of Anesthesiology & Pain Medicine, Nationwide Children's Hospital, Columbus, OH 43205, USA. Email: Joseph.Tobias@nationwidechildrens.org

doi: https://doi.org/10.14740/jmc3906

Articles © The authors | Journal compilation © J Med Cases and Elmer Press Inc™ | www.journalmc.org
This article is distributed under the terms of the Creative Commons Attribution Non-Commercial 4.0 International License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited

matology services and had previously been trialed on sirolimus as treatment prior to sclerotherapy for the vascular malformations, but it was discontinued due to patient intolerance. Current medications included rivaroxaban (for prevention of thrombosis), which was held prior to the sclerotherapy. The patient and family reported no known drug, animal, or environmental allergies. Her past medical history included eczema as well as a family history of asthma in her brother, but no other family history of atopy.

Treatment

The patient was held *nil per os* for 8 h and brought to the interventional radiology (IR) suite where standard American Society of Anesthesiologists' (ASA) monitors were placed. She was positioned supine on the bed, followed by the induction of anesthesia with the inhalation of sevoflurane in air and oxygen. A 20-gauge peripheral intravenous cannula was then placed followed by the administration of propofol (200 mg), dexamethasone (4 mg), dexmedetomidine (8 µg), fentanyl (100 µg total), and hydromorphone (0.5 mg). The patient's trachea was intubated with a 6.0 mm cuffed endotracheal tube (ETT). Maintenance anesthesia included 2-3% sevoflurane in air and oxygen. The left foot was prepped with chlorhexidine. Eight 23-gauge needles were placed into the left foot vascular malformation with ultrasound guidance and successful venous return. Ioversol (Optiray® 320) was instilled evenly into each needle under the assistance of fluoroscopic guidance to confirm lesion flow dynamics and favorable needle position. A sclerotherapy solution was generated using the following components: 10 units (2 mL) of bleomycin, 2 mL of albumin, and 4 mL of Surgiflo® that had been reconstituted with saline per package instructions. The solution was then injected in equally divided amounts through the eight needles. Shortly after injection, the patient developed tachycardia with an increase in heart rate from 100 to 160 - 170 beats/min and hypotension (blood pressure decreased from 102/45 to 47/22 mm Hg) with ST segment depression and oxygen desaturation to 85%. The patient was also noted to be flushed. The lungs were clear to auscultation bilaterally with no change in resistance. The needles that were used for the injection were aspirated and removed. The volatile anesthetic agent was discontinued and controlled ventilation provided with 100% oxygen. Resuscitation included intermittent doses of epinephrine (total dose of 250 µg), intermittent doses of phenylephrine (total dose of 700 µg), and isotonic fluids. An arterial cannula and a second peripheral intravenous cannula were placed. The patient was also noted to have eyelid, lip, and tongue swelling. Albuterol (6 puffs), hydrocortisone (100 mg), and diphenhydramine (25 mg) were also administered. Midazolam (2 mg) was administered to ensure amnesia. The patient's heart rate and blood pressure stabilized after approximately 30 min of resuscitation and her trachea was extubated in the IR suite. She was transferred to the post-anesthesia care unit and the remainder of her postoperative course was unremarkable. The planned sclerotherapy to the left thigh was not performed. She was admitted to the hospital for further observation, monitoring, and workup for the presumed allergic reaction.

Follow-up and outcomes

A tryptase level obtained within 1 h of the event was elevated at 35.3 ng/mL (normal ≤ 10 ng/mL). Following admission, the patient remained stable and her symptoms continued to improve. She was discharged home the following day with only mild swelling of the upper eyelids. Follow-up was arranged with the Allergy and Immunology Service. Additional history was elicited, and the patient reported lip swelling and throat discomfort after eating marshmallows, Rice Krispies Treats™, or gummy-based products. Serum IgE testing for gelatin was obtained. Porcine gelatin IgE was elevated to 12.42 kU/L (reference value ≤ 0.35 kU/L) and bovine gelatin IgE was elevated to 1.87 kU/L (reference value ≤ 0.34 kU/L). The diagnosis of gelatin allergy was made and an epinephrine auto-injector was prescribed. This also confirmed the etiology of the patient's perioperative event as an anaphylactic reaction to Surgiflo®, a gelatin-based product. Education about strict avoidance of gelatin-based foods and products for future procedures was provided to the patient and family. Given that the allergy was to gelatin, it was determined that the sclerotherapy could be continued with bleomycin without the addition of Surgiflo®. The patient has recently returned for repeat sclerotherapy without incident using bleomycin without adding gelatin-containing products.

Discussion

Gelatin is a protein-containing compound derived from the enzymatic cleavage of cross-linkages between the polypeptide chains of the animal protein collagen [5]. This occurs through a process termed partial hydrolysis, whereby an enzyme facilitates the cleavage of bonds yielding smaller polypeptide chains. The result is a heterogeneous mixture of water-soluble proteins with gel-forming properties that can be used in the food and pharmaceutical industry to provide texture to foods (marshmallows, gummies, Jell-O™), as an ingredient in cosmetics, and in medical products. Gelatin is mostly composed of amino acid chains, primarily glycine, proline, and hydroxyproline as well as alanine, arginine, aspartate, and glutamate. This animal-derived protein comes from various sources including porcine skin, bovine hides, beef or porcine bones, and fish.

In clinical medical practice, gelatins are used as a binder to make materials more cohesive, as a gelling agent, and to increase the viscosity of solutions. For these reasons, it has been used as an ingredient in pill capsules and in vaccines including measles, mumps, rubella (MMR), varicella, herpes zoster, and diphtheria, pertussis, tetanus (DTP). When considering perioperative care, gelatins have been used in hemostatic agents which are used topically or as an injectable foam (FloSeal®, Surgiflo®). For this purpose, gelatin is used as a mixture of granules or in sponges that expands to compress the bleeding and as a matrix combined with thrombin to aid in clot formation (Gelfoam®, Gelfilm®, Surgifoam®).

FloSeal® is an FDA-approved sterile gel mixture composed of bovine gelatin, bovine thrombin, and glutaraldehyde

Articles © The authors | Journal compilation © J Med Cases and Elmer Press Inc™ | www.journalmc.org

[5]. Surgiflo® is a similar hemostatic agent composed of porcine gelatin, bovine thrombin, and glutaraldehyde. Gelatin-based sponges (Gelfoam® or Surgifoam®) can be used topically to pack wounds and promote thrombosis of open vessels, thereby providing local hemostasis in a variety of surgical settings. Gelfoam® pledgets may also be injected for hemostasis after solid organ or bone biopsies. Other commercially available hemostatic agents containing gelatin include Meropack®, Optisphere®, NovaShield®, Thrombi-Gel®, and Thrombostat®. Additionally, certain surgical devices such as vascular grafts, intravascular cannulas, and bone replacement materials may also contain gelatin [6].

As a biologically active agent derived from animal-based collagen, when gelatin is introduced into the body, it is recognized as a foreign antigen and may result in allergic reactions. As it may not be known as a primary ingredient in a medical product, its role as the inciting substance of a reaction may go unrecognized. Such was the case initially in our patient, as the primary agent injected was bleomycin and only after a thorough review of products used was it determined that the agent responsible was the gelatin in the Surgiflo®. The case demonstrates the importance of reviewing all products that have been administered when investigating an allergic reaction and looking for the etiologic agent.

During the intraoperative treatment of suspected allergic reactions, prompt identification of the provocative agent, immediate management according to fixed algorithms, and prevention of further exposure are essential. The clinical presentation of perioperative anaphylaxis can mimic other complications such as hypovolemia, myocardial depression related to general anesthetic agents, bronchospasm, or other conditions causing hypotension and altered respiratory compliance. When such events occur intraoperatively, the potential for an allergic reaction should be considered as early institution of appropriate treatment algorithms including the administration of epinephrine is necessary to ensure a successful outcome [7, 8].

Once the acute resuscitation has occurred, investigation into the primary etiology is indicated. Tryptase is a serine protease that is released by mast cell degranulation during an allergic reaction. As noted in our patient, an elevated serum tryptase level is consistent with a systemic anaphylactic reaction with mast cell degranulation [9]. Given its half-life of 120 min, a serum sample should be collected within 1 - 3 h after the onset of symptoms. While an elevated level can aid in the diagnosis, a normal serum tryptase does not rule out anaphylaxis.

During the postoperative course, referral to a pediatric allergist and immunologist is suggested to aid in definitively identifying the inciting agent. An in-depth review of the anesthesia and surgical records is performed and all potential allergens are identified. Based on the patient's past medical history and acute exposure history, skin testing may be pursued approximately 4 - 6 weeks after the acute event to identify the etiology of an IgE-mediated reaction [10]. Both skin-prick and confirmatory intradermal testing protocols are published for many medications. However, *in vitro* testing may have limited availability. These tests are designed to identify IgE antibodies against specific medications [8].

Historically, bleomycin has been used as chemotherapy to treat various types of cancers including germ cell tumors, lymphomas, gynecologic tumors, skin cancers, and squamous cell carcinomas of the head and neck [11]. It has also been found to be increasingly useful as a first-line sclerosant to treat vascular malformations. The most worrisome side-effect is pulmonary toxicity, which is less likely to occur in the doses used for sclerotherapy, occurring most commonly during its use in oncologic practice. However, anecdotal reports have noted this rare, non-immunologically mediated adverse effect after its use for sclerotherapy [12, 13]. There have also been anecdotal reports of acute adverse effects including hyperpyrexia, hypotension, altered mental status, and respiratory distress during the administration of bleomycin for chemotherapy in oncology patients [11, 14]. Although bleomycin was not determined to be the cause of the allergic reaction in our patient, other anecdotal reports have suggested its potential role in an allergic reaction known as flagellate erythema, a unique drug rash that appears as whip-like or linear streaks following local injection or application [15-17]. It may affect the face, trunk, or limbs.

Previous anecdotal reports have noted the potential for the occurrence of intraoperative anaphylactic reactions following the topical application of the gelatin-containing hemostatic agents (Floseal® and Surgiflo®) [18, 19]. Our patient and previous case reports demonstrate the potential utility of the preoperative evaluation in eliciting a history which may suggest the need to avoid gelatin-containing products. A higher incidence of intraoperative allergic reactions may be seen in patients with a history of previous allergic reactions or other atopic conditions. As was noted in our patient, the potential for gelatin allergy should be considered if history is consistent with reproducible IgE-mediated symptoms after eating gelatin-containing foods like marshmallows, Rice Krispies Treats™, or gummy-based products. There may also be a potential for allergic reactions after exposure to not only gelatin-containing products but also meat or milk, further emphasizing the importance of a detailed dietary history with milk or meat sensitivities [20].

Learning points

Intraoperative acute drug reactions are most commonly the result of exposure to antibiotics, neuromuscular blocking agents, opioids, chlorhexidine, and iodinated dyes for radiologic imaging. However, following an allergic reaction, a thorough investigation is required to identify the potential etiologic agent. Gelatin is a protein-containing compound derived from animal proteins. As a foreign protein, it may be the inciting agent in an allergic reaction. As it may not be known as a primary ingredient in a medical product, its role as the inciting substance of a reaction may go unrecognized. In our patient, gelatin was a component of the Surgiflo® hemostatic matrix used with bleomycin for sclerotherapy of a venous malformation. Perioperative anaphylaxis remains a rare but life-threatening event. During general anesthesia, the clinical presentation of an allergic reaction with hemodynamic and respiratory compromise can mimic other adverse intraoperative events including hypovolemia, myocardial depression related to general anesthetic agents, myocardial ischemia, and bronchospasm. The potential

for an allergic reaction should be considered as early institution of appropriate treatment including the administration of epinephrine is necessary to ensure a successful outcome.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Informed consent was obtained from a parent for anesthetic care and the use of de-identified data for educational and publication purposes.

Author Contributions

LR performed the initial case review and manuscript preparation, literature review, and editing of subsequent revisions. JT contributed to decision case review, literature review, and editing of the manuscript. GM, KS, LB, and MR cared for the patient and reviewed the final draft of the manuscript.

Data Availability

The data supporting the findings of this case report are available from the authors.

References

1. Fisher M, Baldo BA. Anaphylaxis during anaesthesia: current aspects of diagnosis and prevention. Eur J Anaesthesiol. 1994;11(4):263-284.
2. Laxenaire MC. Drugs and other agents involved in anaphylactic shock occurring during anaesthesia. A French multicenter epidemiological inquiry. Ann Fr Anesth Reanim. 1993;12(2):91-96.
3. Wakimoto M, Miller R, Kim SS, Uffman JC, Nafiu SO, Tobias JD, Beltran RJ. Perioperative anaphylaxis in children: A report from the Wake-Up Safe collaborative. Paediatr Anaesth. 2021;31(2):205-212.
4. Mertes PM, Lambert M, Gueant-Rodriguez RM, Aimone-Gastin I, Mouton-Faivre C, Moneret-Vautrin DA, Gueant JL, et al. Perioperative anaphylaxis. Immunol Allergy Clin North Am. 2009;29(3):429-451.
5. Liu D, Nikoo M, Boran G, Zhou P, Regenstein JM. Collagen and gelatin. Annu Rev Food Sci Technol. 2015;6:527-557.
6. Jiang Y, Yuan IH, Dutille EK, Bailey R, Shaker MS. Preventing iatrogenic gelatin anaphylaxis. Ann Allergy Asthma Immunol. 2019;123(4):366-374.
7. Girotra V, Lalkhen A. Anaphylaxis. Anaesth Intensive Care 2014;15:15-9.
8. Dewachter P, Savic L. Perioperative anaphylaxis: pathophysiology, clinical presentation and management. BJA Educ. 2019;19(10):313-320.
9. Ebo DG, Fisher MM, Hagendorens MM, Bridts CH, Stevens WJ. Anaphylaxis during anaesthesia: diagnostic approach. Allergy. 2007;62(5):471-487.
10. Garvey LH, Dewachter P, Hepner DL, Mertes PM, Voltolini S, Clarke R, Cooke P, et al. Management of suspected immediate perioperative allergic reactions: an international overview and consensus recommendations. Br J Anaesth. 2019;123(1):e50-e64.
11. Lam MS. The need for routine bleomycin test dosing in the 21st century. Ann Pharmacother. 2005;39(11):1897-1902.
12. Cho AL, Kiang SC, Lodenkamp J, Tritch WTH, Tomihama RT. Fatal lung toxicity after intralesional bleomycin sclerotherapy of a vascular malformation. Cardiovasc Intervent Radiol. 2020;43(4):648-651.
13. Mendez-Echevarria A, Fernandez-Prieto A, de la Serna O, Lopez-Gutierrez JC, Parron M, Marin-Aguilera B, Calvo C. Acute lung toxicity after intralesional bleomycin sclerotherapy. Pediatrics. 2018;141(1):1-5.
14. Rosello S, Blasco I, Garcia Fabregat L, Cervantes A, Jordan K, Committee EG. Management of infusion reactions to systemic anticancer therapy: ESMO Clinical Practice Guidelines. Ann Oncol. 2017;28(suppl_4):iv100-iv118.
15. Rubeiz NG, Salem Z, Dibbs R, Kibbi AG. Bleomycin-induced urticarial flagellate drug hypersensitivity reaction. Int J Dermatol. 1999;38(2):140-141.
16. Vennepureddy A, Siddique MN, Odaimi M, Terjanian T. Bleomycin-induced flagellate erythema in a patient with Hodgkin's lymphoma - A case report and review of literature. J Oncol Pharm Pract. 2016;22(3):556-560.
17. Pinto C, Lorca-Garcia C, Berenguer B, De Tomas Palacios ME. Bleomycin-induced flagellate erythema after venous malformation sclerosis-Case report and brief review. Pediatr Dermatol. 2018;35(1):e5-e8.
18. Spencer HT, Hsu JT, McDonald DR, Karlin LI. Intraoperative anaphylaxis to gelatin in topical hemostatic agents during anterior spinal fusion: a case report. Spine J. 2012;12(8):e1-6.
19. Lied GA, Lund KB, Storaas T. Intraoperative anaphylaxis to gelatin-based hemostatic agents: a case report. J Asthma Allergy. 2019;12:163-167.
20. Bogdanovic J, Halsey NA, Wood RA, Hamilton RG. Bovine and porcine gelatin sensitivity in children sensitized to milk and meat. J Allergy Clin Immunol. 2009;124(5):1108-1110.

 Articles © The authors | Journal compilation © J Med Cases and Elmer Press Inc™ | www.journalmc.org