OPEN

PRS GLOBAL OPEN

CASE REPORT
Breast

Recalcitrant Anaphylaxis Associated with Fibrin Sealant: Treatment with "TISSEEL-ectomy"

Mohammadali Saffarzadeh, BSc*
Anvith Mulpuri†
Jugpal S. Arneja, MD, MBA, FAAP, FACS, FRCSC*‡

Summary: Here, we present the case of an adolescent male who developed a severe allergic reaction 10 minutes after application of TISSEEL fibrin sealant to control bleeding during a gynecomastia revision surgery. Conventional treatments of acute hypersensitivity were ineffective. After a "tisseel-ectomy," the patient's condition improved and symptoms resolved. Besides oral tranexamic acid, and topical and local anaesthesia, no other medications besides TISSEEL were administered preceding the allergic reaction. After TISSEEL was identified as the allergen upon its removal, his clinical status improved. The patient had been exposed to TISEEL 15 months before the anaphylactic episode. This case can aid in decision-making for surgical re-exposure to fibrin sealants in the setting of acute anaphylaxis. *(Plast Reconstr Surg Glob Open 2021;9:e3382; doi: 10.1097/GOX.0000000000003382; Published online 22 January 2021.)*

CASE PRESENTATION

A healthy 16-year-old boy presented for bilateral gynecomastia excision. During the procedure, there was significant bleeding on the right side, for which hemostasis was assisted using tranexamic acid. TISSEEL (Baxter Inc., USA) (4 ml) was applied bilaterally before closure to further aid in hemostasis, with no further complications. The patient was sent to hematology for a work-up of any bleeding diatheses and none were found; oral tranexamic acid was suggested for any future surgical procedures.

After 15 months, the patient returned for a bilateral gynecomastia revision of redundant skin associated with the nipple–areolar complex. EMLA cream was applied and tranexamic acid (1500 mg PO) was given prophylactically 1 hour before the procedure. There were no immediate complications with the procedure. After several hours, the patient returned with significant bleeding on the left side, which was controlled with exploration, cauterization, and 1 ml of TISSEEL (Baxter Inc., USA) was placed to aid in hemostasis. Approximately 10 minutes after receiving TISSEEL, the patient developed respiratory tightness, pruritis in his throat and scalp, gastrointestinal discomfort, facial swelling, and disseminated urticaria (Figs. 1 and 2). The patient was transferred to the emergency department (ED) and over 8 hours in the ED was given 2 doses of diphenhydramine, 4 doses of 0.5 ml 1:1000 of epinephrine IM, 1 dose of dexamethasone (10 mg PO), 1 dose of methylprednisone (40 mg IV), and 5 doses of Salbutamol 100 mcg via MDI, with no sustained improvement of the anaphylaxis symptoms. The patient remained hemodynamically stable in the ED with no oxygen desaturation or drop in blood pressure. He was then transferred to the intensive care unit (ICU), given no sustained improvement, and a decision was made to explore the surgical site in the operating room (OR) and remove the TISSEEL. During the procedure, some mild airway erythema was noted in the epiglottis during intubation. A brief episode of hypotension also occurred that was successfully managed with phenylephrine in the OR. The patient was observed overnight and discharged directly from the ICU the following morning with no further symptoms or signs of anaphylaxis following the fibrin sealant removal.

DISCUSSION

Fibrin sealants are the largest set of biologically derived sealants, with great utility in a variety of surgical interventions, such as orthopedic, cardiovascular, and plastic surgeries.[1,2] As hemostatic agents, they are used to aid in leak and bleeding control, as well as wound closing.[2] The benefits of fibrin sealants in orthopedic surgeries include faster recovery, reduced blood loss and infection, shorter hospital stay, and enhanced range of movement in ruptured tendon and ligament repair.[2] In cardiovascular surgeries, fibrin sealants are used in a variety of interventions, including ventricular ruptures, aortic dissection repair, and coronary surgery.[2] In

*From the *Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada; †St. George's School, Vancouver, BC, Canada; and ‡Sauder School of Business, University of British Columbia, Vancouver, BC, Canada.*

Received for publication November 19, 2020; accepted December 2, 2020.

Copyright © 2021 The Authors. Published by Wolters Kluwer Health, Inc. on behalf of The American Society of Plastic Surgeons. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

DOI: 10.1097/GOX.0000000000003382

Disclosure: *The authors have no financial interest to declare in relation to the content of this article. No funding was received for this study.*

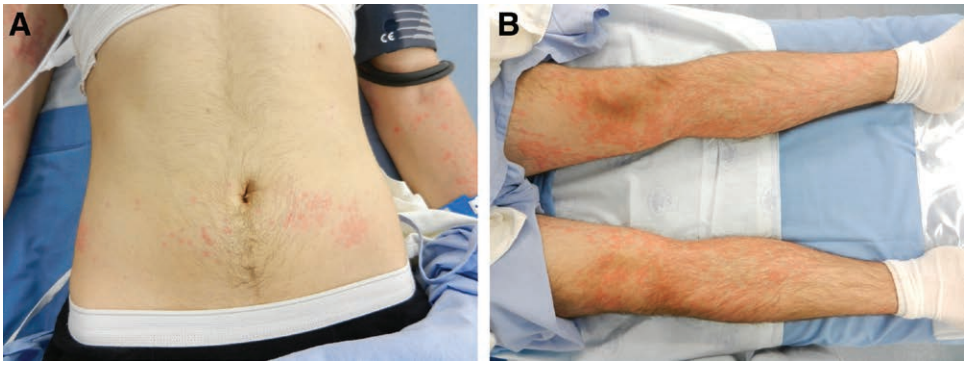

Fig. 1. Physical findings upon examination 10 hours post-TISSEEL placement – disseminated urticaria over the abdomen (A) and both legs (B).

plastic and reconstructive surgeries, the attachment of skin grafts can be facilitated by fibrin sealants as they not only act as adhesives to prevent slippage of grafts, but they also minimize scar formation.[2] Fibrin sealants have also been shown to be alternatives to conventional suture repair in coaptation of peripheral nerves.[3] Furthermore, the application of fibrin sealants under skin flaps control dead space, reduces seroma formation, facilitates neovascularization, and initiates hemostasis.[2]

Some disadvantages of fibrin sealants are their costly nature, in addition to poor ability to provide adequate mechanical strength to the tissues, which constitute their role as an adjunct to sutures or other conventional means of mechanical tissue stabilization.[2] Post-marketing experiences with fibrin sealants, such as TISSEEL, have identified adverse events, including hypotension, thromboembolism, angioedema, erythema, bradycardia, tachycardia, bronchospasm, and severe hypersensitivity reactions.[4]

Some of the common components of fibrin sealants are fibrinogen, thrombin, aprotinin, and calcium chloride.[5] Aprotinin, which was originally derived from cattle lungs and can be produced synthetically, is a serine protease inhibitor and prevents the normal process of fibrinolysis, leading to better blood clotting.[6,7] Previous research has identified aprotinin as an anaphylaxis-inducing agent, as it can be recognized as a foreign antigen and result in allergic reactions mediated by IgG and IgE antibodies, leading to rare but serious hypersensitivity reactions.[4,8,9]

Certain risk factors have been identified for aprotinin-associated hypersensitivity reactions, the most notable of which being prior exposure to aprotinin. A review of 124 aprotinin hypersensitivity reactions reported that 80% of patients had been previously exposed to aprotinin at some point in their lives.[10] Additionally, the time between aprotinin exposure appears to be a factor, as there is an accumulation of secondary hypersensitivity reactions during the first 3 months post-initial-exposure.[10] In an analysis of immune responses in 49 children to fibrin sealants containing aprotinin, 6 weeks after the initial exposure, 6% and 39% of the patients had aprotinin-specific IgE and IgG antibodies respectively.[11] In a retrospective analysis by Dietrich et al, the occurrence rate of allergic reactions to aprotinin with <6 months, 6–12 months, and >12 months between the exposures was 4.1%, 1.9%, and 0.4% respectively.[12] Interestingly, our patient's anaphylaxis was 15 months post-initial exposure.

TISSEEL (Baxter Inc., USA) is one of the best known topical fibrin sealants.[13] It is indicated as an adjunct for hemostasis

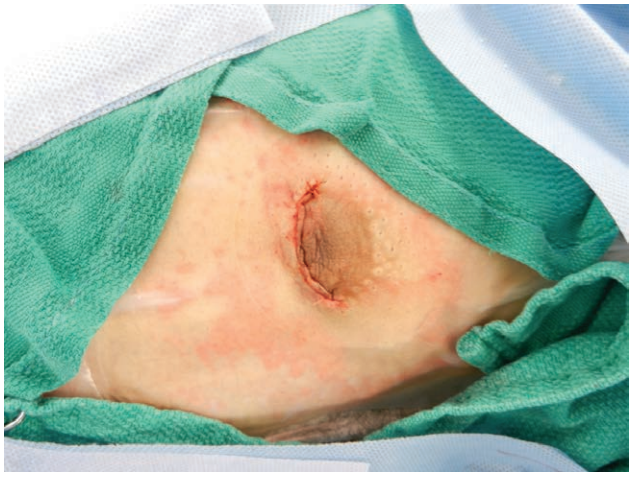

Fig. 2. Urticaria over the surgical site (nipple–areolar complex of the left chest).

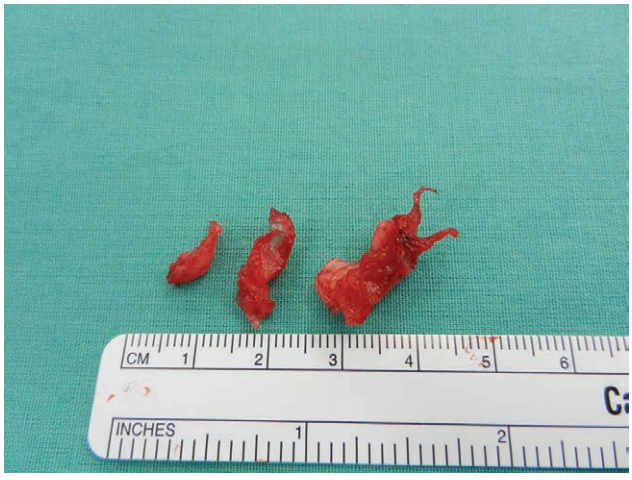

Fig. 3. The coagulated TISSEEL masses were removed from the surgical site at the left chest.

when conventional surgical practices for bleeding-control are ineffective.[4] According to the manufacturer, hypersensitivity reactions to TISSEEL rarely occur (<1/10,000)[4]; however, the incidence of allergic reactions seems to increase with repeated applications.[14] Schievink et al reported anaphylactic reactions in 2 of the 10 patients who received repeated injections of TISSEEL for the treatment of spontaneous CSF leaks within 3 months of initial fibrin sealant exposure.[14] Although the presence of aprotinin in fibrin sealants, such as TISSEEL, has been recognized for its anaphylaxis-inducing nature, aprotinin-free fibrin sealants, such as EVICEL (Ethicon Inc., USA), are available on the market that provide effective hemostasis and acceptable safety profiles.[15,16] Additionally, lower post-operative bleeding complications have been reported in patients receiving EVICEL compared with those receiving TISSEEL, providing further evidence to the advantages of an aprotinin-free fibrin sealant.[17]

In the presented case, the allergic reaction is thought to be a secondary immune response because the patient was most likely sensitized when he was exposed to TISSEEL 15 months before the anaphylactic episode. The patient had not been administered any medications in the hours preceding the development of hypersensitivity symptoms except for local anesthetic, tranexamic acid, and TISSEEL. Interestingly, the anaphylactic reaction was not able to be managed with traditional medical treatments, such as adrenergic agonists, H1 antihistamines, bronchodilators, and glucocorticoids, and a formal return to the operating room and TISSEEL removal were required (Fig. 3), suggesting a TISSEEL-induced anaphylaxis. Considering the reported cases of anaphylaxis to aprotinin in TISSEEL, we recommend the use of aprotinin-free fibrin sealants in patients who might undergo multiple procedures involving fibrin sealants. Additionally, we identify "TISSEEL-ectomy" as an effective treatment of anaphylaxis induced by TISSEEL that does not respond to conventional medical therapy.

Jugpal S. Arneja, MD, MBA, FAAP, FACS, FRCSC
Division of Plastic Surgery
Faculty of Medicine
Sauder School of Business
University of British Columbia
British Columbia Children's Hospital
K3-131 ACB, 4480 Oak St.
Vancouver, BC
Canada V6H 3V4
E-mail: jugpal.arneja@ubc.ca

REFERENCES

1. Shah NV, Meislin R. Current state and use of biological adhesives in orthopedic surgery. *Orthopedics*. 2013;36:945–956.
2. Jain R, Wairkar S. Recent developments and clinical applications of surgical glues: An overview. *Int J Biol Macromol*. 2019;137:95–106.
3. Biscola NP, Cartarozzi LP, Ulian-Benitez S, et al. Multiple uses of fibrin sealant for nervous system treatment following injury and disease. *J Venom Anim Toxins Incl Trop Dis*. 2017;23:13.
4. TISSEEL_PI. Highlights of prescribing information. Published December 2019. Accessed August 18, 2020. Available at https://baxterpi.com/pi-pdf/Tisseel_PI.pdf.
5. Wozniak G. Fibrin sealants in supporting surgical techniques: The importance of individual components. *Cardiovasc Surg*. 2003;11(suppl 1):17–21.
6. Royston D. The current place of aprotinin in the management of bleeding. *Anaesthesia*. 2015;70(suppl 1):46–49, e17.
7. Verstraete M. Clinical application of inhibitors of fibrinolysis. *Drugs*. 1985;29:236–261.
8. Dietrich W, Späth P, Ebell A, et al. Prevalence of anaphylactic reactions to aprotinin: Analysis of two hundred forty-eight reexposures to aprotinin in heart operations. *J Thorac Cardiovasc Surg*. 1997;113:194–201.
9. Laxenaire MC, Dewachter P, Pecquet C. [Allergic risk of aprotinin]. *Ann Fr Anesth Reanim*. 2000;19:96–104.
10. Beierlein W, Scheule AM, Dietrich W, et al. Forty years of clinical aprotinin use: A review of 124 hypersensitivity reactions. *Ann Thorac Surg*. 2005;79:741–748.
11. Scheule AM, Beierlein W, Wendel HP, et al. Fibrin sealant, aprotinin, and immune response in children undergoing operations for congenital heart disease. *J Thorac Cardiovasc Surg*. 1998;115:883–889.
12. Dietrich W, Ebell A, Busley R, et al. Aprotinin and anaphylaxis: Analysis of 12,403 exposures to aprotinin in cardiac surgery. *Ann Thorac Surg*. 2007;84:1144–1150.
13. Vyas KS, Saha SP. Comparison of hemostatic agents used in vascular surgery. *Expert Opin Biol Ther*. 2013;13:1663–1672.
14. Schievink WI, Georganos SA, Maya MM, et al. Anaphylactic reactions to fibrin sealant injection for spontaneous spinal CSF leaks. *Neurology*. 2008;70:885–887.
15. Alving BM, Weinstein MJ, Finlayson JS, et al. Fibrin sealant: Summary of a conference on characteristics and clinical uses. *Transfusion*. 1995;35:783–790.
16. Fischer CP, Wood CG, Shen J, et al. A randomized trial of aprotinin-free fibrin sealant versus absorbable hemostat. *Clin Appl Thromb Hemost*. 2011;17:572–577.
17. Wan Y, Lim S, Gao X, et al. Bleeding-related complications and readmission rates associated with fibrin sealant use in patients undergoing coronary artery bypass graft surgery in the United States. *J Cardiothorac Vasc Anesth*. 2017;31:876–882.