

A Case of Diffuse Desquamating Rash Following Exposure to Vancomycin-Impregnated Bone Cement

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Brett Williams, MD¹, Amy Hanson, PharmD¹, and Beverly Sha, MD¹

Abstract

Objective: To describe a case of systemic desquamating dermatitis following implantation of vancomycin antibiotic-laden cement (ABLC) in a patient with prior history of Stevens-Johnson (SJS) reaction to vancomycin. **Case Summary:** A 59-year-old man with a history of SJS reaction to systemic vancomycin and recurrent methicillin-susceptible *Staphylococcus aureus* prosthetic knee infection developed a painful, blistering rash after implantation of bone cement that had been mixed with 2 g of vancomycin. He was started empirically on steroids by his primary care provider and had desquamation about 1 week later. **Discussion:** Systemic absorption of antibiotics from ABLC has been well documented in the literature. Reports of systemic toxicity are rare, and none have described systemic allergic reactions to vancomycin. This patient's prior episode of SJS was diagnosed at another academic medical center 6 years ago, and records are unavailable. Following low-level reexposure to vancomycin, he developed a diffuse painful desquamating rash. Application of the Naranjo nomogram yielded a score of 8 (probable adverse reaction). Although he did not experience fever, sore throat, or mucous membrane involvement to fulfill classic features of SJS, we believe that his severe rash represented a less-severe form of a systemic hypersensitivity reaction to vancomycin. **Conclusion:** Antibiotics contained in ABLC are systemically absorbed, though at low levels, and have been associated with systemic toxicities. Antibiotics to which a patient has had a potentially life-threatening reaction should not be used in ABLC. Particular attention should be paid to an individual's antibiotic allergy history prior to implantation of any ABLC.

Keywords

vancomycin, cement, bone, arthroplasty, ABLC, Stevens-Johnson, systemic, rash

Introduction

According to the American Academy of Orthopedic Surgery, approximately 285 000 hip replacements and 600 000 knee replacements are performed per year, with approximately 1% to 2% of these complicated by infection.¹ Antibiotic laden cement (ABLC) spacers are frequently used in 2-stage treatment of prosthetic joint infections (PJIs), and antibiotics are often added to the fixing cement when the prosthesis is replaced.² Pharmacological studies have established that there is detectable systemic absorption of both aminoglycosides and vancomycin impregnated into bone cement. Vancomycin levels usually fall to undetectable within 10 days, but aminoglycoside levels are occasionally detectable more than a month after implantation.^{3–5} The addition of antibiotics to cement or spacers is generally considered safe, and one review found no reports of adverse reactions.⁶ To date, there are few reports of systemic toxicity from ABLC. We searched for published reports in MEDLINE, EMBASE, and Clin-Alert databases using the following keywords: *vancomycin*, *antibiotic*, *cement*, *allergy*, *toxicity*, and *Stevens-Johnson*. We were unable to

find any cases of systemic allergic reaction or Stevens-Johnson syndrome (SJS) related to vancomycin ABLC.

Adverse reactions to vancomycin are usually related to infusion or supratherapeutic levels; however, both SJS and linear IgA bullous dermatosis are well established reactions to systemically administered vancomycin.^{7–13} In addition, reports of exfoliative dermatitis and extensive fixed-drug reactions have been reported.^{14,15} We report the first case of a diffuse desquamating dermatitis following implantation of vancomycin-laden bone cement.

Case Summary

The patient was a 59-year-old man with hyperlipidemia, type II diabetes mellitus, and hypertension who had recurrent

¹Rush University Medical Center, Chicago, IL, USA

Corresponding Author:

Brett Williams, Rush University Medical Center, 600 S Paulina Suite #140 Chicago, IL 60612, USA.

Email: BrettWilliams0@gmail.com

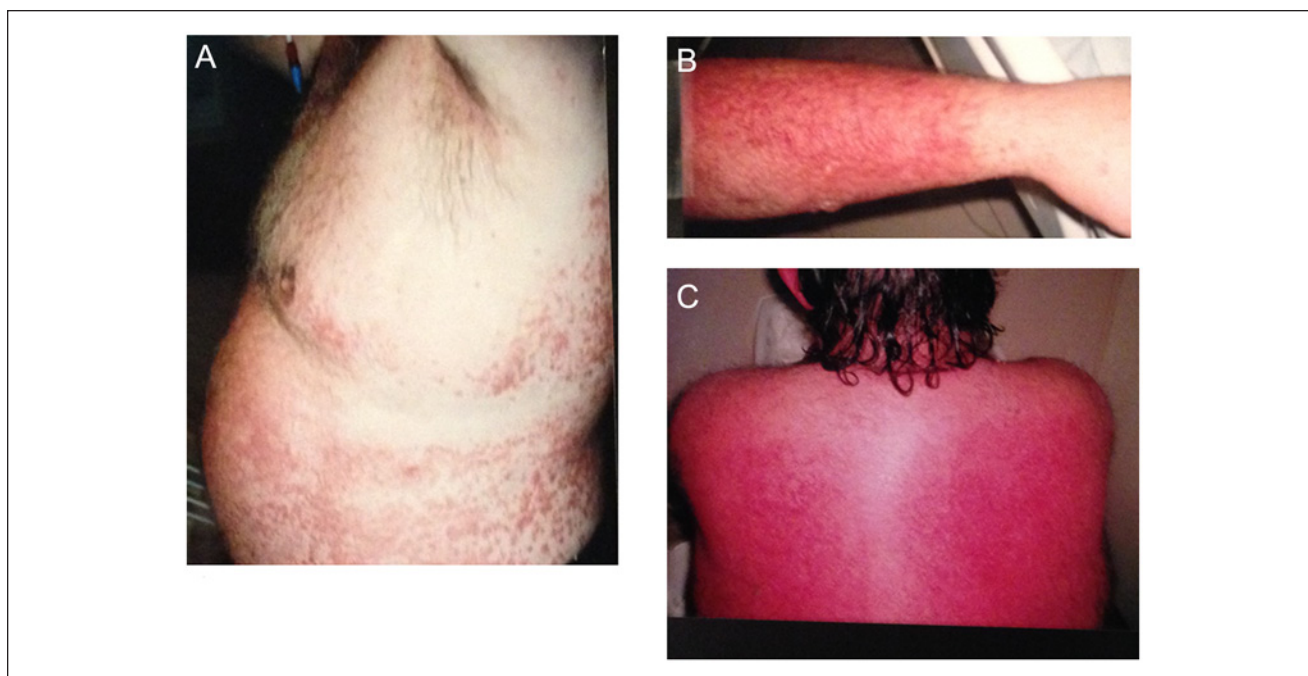


Figure 1. Initial reaction to systemic vancomycin; photos taken by patient's daughter.

infection of a left prosthetic knee joint with methicillin-susceptible *Staphylococcus aureus* (MSSA). He initially underwent left total knee arthroplasty (TKA) for osteoarthritis in December 2006, 7 years prior to his current presentation, and developed MSSA PJI in December 2007 at an outside facility. Because of a history of penicillin allergy, he was treated with systemic vancomycin and developed fever and a painful, blistering rash over most of his body, leading to intensive care unit admission at the outside facility (Figures 1A-1C). With the original reaction, he did not recall any mucous membrane involvement or pruritus but was febrile to 105°F. His skin peeled after several days, but he could not recall if this was before or after he was treated with steroids. He was diagnosed with SJS secondary to vancomycin, which was discontinued. He reported allergies to fish products (anaphylaxis), penicillin (hives), and quinolones (rash). He continued to have relapsing infection despite repeated incision and drainage, with exchange of hardware and eventual removal of his hardware and arthrodesis. Antibiotic treatment consisted of extended courses of intravenous daptomycin and then cefazolin after desensitization. After failing removal and reimplantation twice, he underwent knee fusion and was desensitized and treated with an extended course of cefazolin, followed by long-term suppressive cefadroxil. In May 2013, he developed mechanical loosening of his arthrodesis rod and had this replaced with a new arthroplasty in June 2013. He had no evidence of infection at the time of the surgery (pathology and cultures were negative, with cefadroxil discontinued 4 weeks prior to surgery). His new arthroplasty

was fixed with an unknown amount of cement, into which 2 g of vancomycin had been mixed. He received IV daptomycin for intraoperative prophylaxis. He started on celecoxib 200 mg daily for pain postoperatively, a medication that he had tolerated in the past. He was continued on chronic clonidine, lisinopril, labetalol, simvastatin, duloxetine, tamsulosin and hydrocodone-acetaminophen. He was treated postoperatively with as needed prochlorperazine, bisacodyl, senna, docusate, ondansetron, oxycodone, and intravenous morphine. He had previously tolerated all these medications. On the day of discharge (postoperative day 4), he began to notice a pruritic rash in his axillae. At discharge, new medications he was started on included rivaroxaban 10 mg orally daily for deep-vein thrombosis prophylaxis, hydrocodone-acetaminophen 10- 325 mg orally as needed for pain, and senna-docusate 8.6-50 mg orally twice a day for constipation. He denied any other new medications. Home medications continued at discharge included lisinopril 30 mg orally daily, tamsulosin 0.4 mg orally daily, clonidine 0.1 mg orally thrice a day, labetalol 200 mg orally twice a day, duloxetine 20 mg orally daily, and simvastatin 40 mg orally daily. Over the next 3 days, postoperative days 4 through 7, a painful blistering rash began, which was most intense on his operative leg but also involved his other leg, chest, and back and was not pruritic at any time. His axillary rash persisted but did not progress. He denied any mucous membrane involvement or objective fever, though he felt feverish at times during this episode (Figures 2A-2C). Pictures were taken by the patient's wife at home 6 days postoperatively. The patient stated that the rash

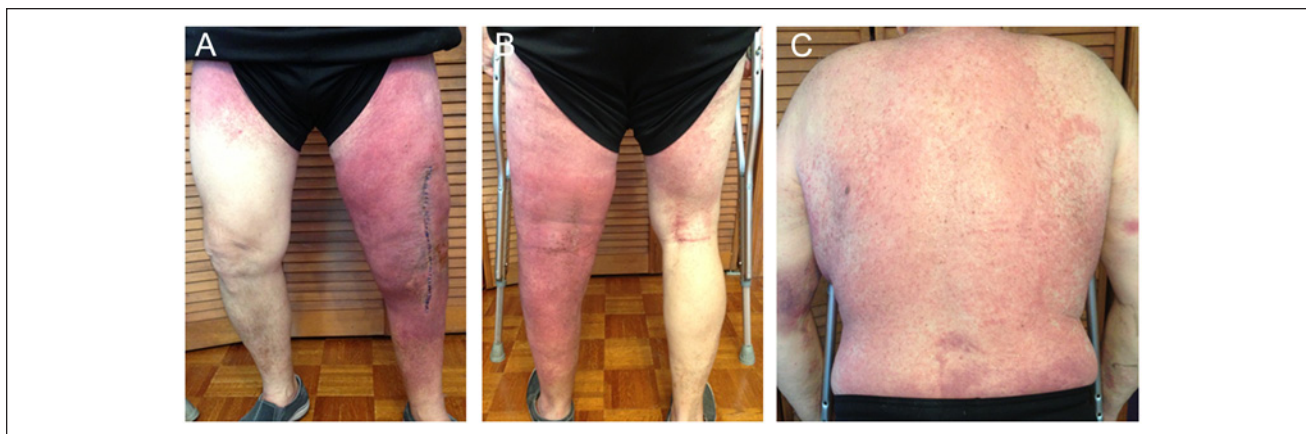


Figure 2. Photos taken by patient's wife on postoperative day 6.

was very similar to the rash he had with SJS 6 years before but less severe and that he had never had a similar reaction other than these 2 episodes. He called his orthopedist who advised him to stop the celecoxib, which he did. He visited his primary care physician who prescribed a short course of oral steroids, and several days later his rash, in his words, “peeled like a sunburn.” The total duration of his rash was 1 week, similar to his initial episode. No laboratory tests were performed to document systemic vancomycin levels, and he did not have a skin biopsy because our practice was not alerted to his rash until several weeks after resolution. He did not have any further recurrence of the rash. Unfortunately, he developed recurrent MSSA PJI requiring incision and drainage 1 month after the incident surgery, thought to be a complication of poor wound healing. He received intraoperative daptomycin for prophylaxis and was again discharged with celecoxib, rivaroxaban, hydrocodone-acetaminophen, and senna-docusate and did not develop any further rash. He is currently asymptomatic, and after completing 6 weeks of intravenous cefazolin remains on suppressive cefadroxil.

Discussion

Application of the Naranjo nomogram yielded a score of 8 (probable adverse drug reaction) to vancomycin. The Naranjo nomogram was scored positively for the following: previous conclusive reports for this reaction (1 point), reappearance of the reaction with readministration (2 points), lack of alternative causes for the reaction (2 points), less-severe reaction with decreased dose (1 point), similar reaction with the same drug on a previous exposure (1 point), and adverse reaction confirmed by objective evidence (1 point).¹⁶ Because the patient presented to our care after resolution of his symptoms and because his previous reaction occurred at another facility, there are data missing from the record. Ideally, we would

have liked to compare skin biopsy results from his initial reaction with his more recent one, but a skin biopsy was not done with this episode, and results are not available from his first episode. Given that his rash had features similar to his prior episode of SJS, timing after implantation of vancomycin-laden cement, the focus of severity being at the site of implantation, and lack of other plausible causes, we believe that a recurrent reaction to vancomycin is most likely. The spontaneous resolution of his rash is explained by the relatively rapid clearance of vancomycin from the blood after implantation of ABLC; treatment with corticosteroids may also have speeded resolution, though corticosteroids have not been proved to be effective in the treatment of SJS. Chohfi et al⁴ demonstrated that peak blood levels of vancomycin did not exceed 2.9 mg/L 6 to 24 hours after implantation of a total hip arthroplasty in 10 patients with a mean of 2.7 g of vancomycin-laden cement. This was minimal in comparison to peaks of 40 to 60 mg/L that are commonly achieved with IV vancomycin therapy. Vancomycin blood levels were 0 to 0.2 mg/L at day 3 postoperatively and undetectable in all patients at day 10. A search of the literature revealed no reported cases of systemic allergic response to vancomycin-laden cement. Three cases of acute renal failure (ARF) associated with vancomycin plus aminoglycoside-laden cement have been reported.¹⁷⁻¹⁹ A fourth case was reported by Patrick et al,¹⁸ though based on the description of the time course, the ARF was more likely related to intravenous vancomycin and piperacillin-tazobactam.¹⁸ These reports showed more delayed development of ARF than previous reports of systemic drug reactions caused by antibiotic-impregnated bone cement. A retrospective cohort study of 84 patients with TKA and implantation of ABLC found 14 cases of ARF.²⁰ In this study, 2 factors were significantly associated with ARF—ABLC with >4 g of vancomycin or >4.8 g of tobramycin; median creatinine peaked at day 30 in the ARF

cases. There are other case reports of isolated aminoglycoside-laden cement associated with ARF, ototoxicity, and allergic dermatitis.²¹⁻²³ The report of allergic dermatitis was in a 74-year-old woman, who developed a pruritic eczematous rash 3 days after gentamicin-impregnated bone cement was used in a left TKA procedure.²³ Similar to the current report, the rash extended to other areas of the body but remained most prominent in the left leg where the procedure was performed. The rash cleared in 2 weeks without any specific therapy. A potential similarity to our case is that the patient also reported a similar reaction after replacement of her opposite knee 2 years previously. Two reports from South Korea suggest an association of piperacillin-tazobactam-laden bone cement with systemic allergic reaction and drug fever.^{24,25} Although both piperacillin-tazobactam and vancomycin were used in the bone cement in both cases, a provocation challenge test with piperacillin-tazobactam IV administered at a reduced dose further confirmed that the reaction was caused by piperacillin-tazobactam-impregnated bone cement with repeat febrile episodes and worsening of rash. The vancomycin IV provocation challenge tests in both cases elicited no systemic response. In the first case, the patient denied prior exposure to piperacillin-tazobactam and developed fever and a pruritic maculopapular rash on her face, neck, and arms on postoperative day 16.²⁴ She developed an absolute eosinophil count of 425 cells/mm³. Because of continued fevers of unknown cause, she was rechallenged with piperacillin-tazobactam on postoperative day 26 and developed higher fever accompanied by red rash and diffuse itching for 2 days. She was rechallenged with several other medications, including vancomycin without response. Her spacer and antibiotic beads were removed, with resolution of her reaction. In the second case, the patient developed fever and eosinophilia on postoperative day 14, followed by a maculopapular rash on postoperative day 19.²⁵ The rash resolved on postoperative day 23, and the fever resolved spontaneously on postoperative day 32. An extensive infectious and autoimmune workup was negative. Drug provocation testing was negative for other antibiotics added to the bone cement but positive to piperacillin-tazobactam, which resulted in fever lasting 72 hours without rash. Reaction to ABLC may have been slower in these patients given their lack of prior exposure to the antibiotic, whereas our patient did have prior exposure. No other reports of systemic toxicity to vancomycin-laden bone cement were found during review of the literature as described above.

Conclusion

Though they appear to be rare, systemic toxicity and allergy to antibiotics in ABLC have been reported. As we discussed, antibiotic added to bone cement is systemically absorbed in

low levels, and in the case of life-threatening reactions such as anaphylaxis, SJS, and toxic epidermal necrolysis, even these low levels of systemic antibiotic can cause significant morbidity. When use of ABLC is being considered, a careful drug allergy history should be taken. A history of life-threatening allergic reaction to a specific antibiotic, as in our patient, should be considered an absolute contraindication to use of the said antibiotic in bone cement, unless the type of reaction is amenable to desensitization. In the case of this patient, we have recommended that he receive daptomycin ABLC as an alternative to vancomycin ABLC, should he need further ABLC.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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