CASE REPORT

Challenges in Managing Vancomycin Flushing Syndrome Following Vancomycin-Loaded Bone Cement for Periprosthetic Joint Infection: A Case Report

Mehdi Motififard, MD; Mehdi Teimouri, MD; Hossein Akbari Aghdam, MD; Hadi Ravanbod, MD; Mohammad Shahsavan, MD

Research performed at Isfahan University of Medical Sciences, Isfahan, Iran

Received: 31 March 2024 *Accepted: 26 June 2024*

Abstract

Periprosthetic joint infection (PJI) is a critical complication following arthroplasties, often treated with a two-stage revision using antibiotic-loaded bone cement spacers. Although these spacers can effectively manage infections, they occasionally cause severe adverse reactions. We reported the case of a 68-year-old female who developed vancomycin flushing syndrome (VFS), previously known as the red man syndrome, following the insertion of a vancomycin-loaded bone cement spacer during the first-stage revision surgery for PJI after undergoing total knee arthroplasty. Six hours postoperatively, she developed pruritus, diffuse rash, tachycardia, and hypotension. VFS was diagnosed based on clinical presentation after excluding other potential causes. She was treated with intravenous epinephrine, antihistamines, steroids, and fluid resuscitation without requiring spacer removal. The patient recovered uneventfully, underwent second-stage reimplantation after 6 weeks, and remained asymptomatic at 2-year follow-up. This highlights the importance of anticipating and managing this potentially severe reaction through a multidisciplinary approach, considering the risks and benefits of retaining versus removing antibiotic-loaded bone-cement spacers.

Level of evidence: IV

Keywords: Antibiotic cement, Periprosthetic joint infections, Total knee arthroplasty, Two-stage revision, Vancomycin, Vancomycin flushing syndrome

Introduction

Periprosthetic joint infection (PJI) is a common cause of revision arthroplasty, with rates of approximately 1-2% after primary arthroplasties.[1-3] Two-stage revision arthroplasty is a widely accepted method for the treatment of PJIs. This technique commonly utilizes antibiotic-loaded bone cement (ALBC) spacers, often containing vancomycin; however, it may also incorporate other antibiotics, such as gentamicin and tobramycin.[2,4,5]

The success rate of ALBC in two-stage revision surgery has been reported to be over 90%, making it the preferred method for treating subacute and chronic PJIs following total knee arthroplasty (TKA).[1,4] It is essential to acknowledge that while vancomycin spacers can be beneficial, there is a risk of adverse reactions. Although the literature infrequently mentions adverse effects from vancomycin-loaded bone cement (VLBC), acute kidney injury is the most commonly reported.[5] However, there have been some reports of dermatological reactions, such as drug reactions with eosinophilia and systemic symptoms, as well as linear IgA bullous dermatology following ALBC spacers.[6,7]

Furthermore, vancomycin flushing syndrome (VFS), previously known as red man syndrome, can occur, particularly with intravenous vancomycin therapy, and few cases have been reported after using vancomycin spacers.[3,8] VFS is a rare but significant adverse reaction. This case report contributes to the limited literature on VFS after using VLBC for PJI, emphasizing the importance of identifying and managing these rare but potentially severe reactions.

Corresponding Author: Mohammad Shahsavan, Department of Orthopedic Surgery, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Email: mohammad_shah69@yahoo.com

THE ONLINE VERSION OF THIS ARTICLE ABJS.MUMS.AC.IR

Arch Bone Jt Surg. 2024;12(9): 674-678 Doi: 10.22038/ABJS.2024.79046.3626 http://abjs.mums.ac.ir

Case Presentation

This study reports the case of a 68-year-old female patient who had undergone TKA two years ago at an alternative healthcare facility. The patient presented to our hospital with a three-month history of unexplained discomfort in the right knee. The patient had no history of drug allergy, hypersensitivity reactions, trauma, or fever. Metformin and lisinopril were administered to manage hypertension and diabetes mellitus, respectively. Upon physical examination, the patient's right knee appeared tender and swollen, with a limited range of motion and effusion. No instability, crepitation, or wound discharge was observed. The vital signs were within normal ranges. The heart rate was 89 beats/min, body temperature was 37.2°C, and respiratory rate was 14 breaths/min. However, the patient's white blood cell count was elevated, measuring 16.4 x 10^9/L, and her erythrocyte sedimentation rate was observed to be 60 mm/h. Additionally, her C-reactive protein level was 80 mg/L, which could indicate the presence of inflammation or infection.

An ultrasound-guided knee aspiration was performed, and joint fluid samples were collected for smears and cultures. Synovial fluid analysis revealed a white blood cell count of 4,006 cells/μL and 84% polymorphonuclear neutrophils. The presence of purulence in the synovial fluid was alarming, raising the suspicion of PJI based on accepted criteria.[9] Nonetheless, radiographs of the right knee showed no signs of infection, such as periosteal reaction, implant loosening, or fractures [Figure 1].

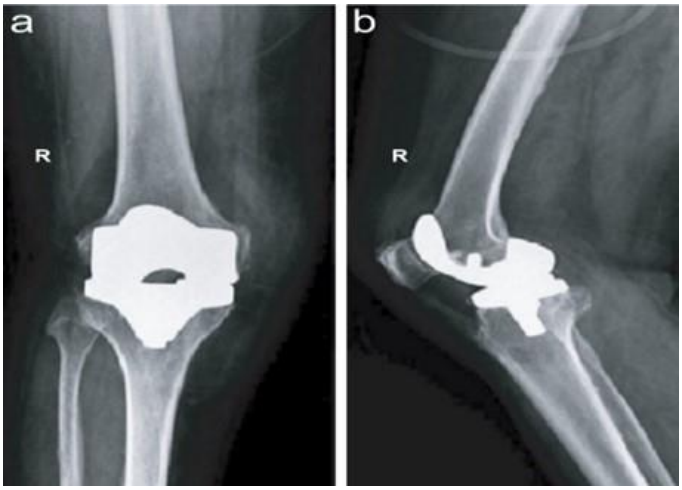

Figure 1. Anteroposterior (a) and lateral (b) radiographs of the right knee revealing no signs of loosening, displacement, bone loss, or osteolysis

The patient was deemed eligible for two-stage revision surgery, and cefazolin 2 g was administered as antibiotic prophylaxis within the first hour before the surgical incision. First-stage revision surgery was performed to remove the infected device, and a fixed VLBC containing 4 g of vancomycin per 40 g of cement was inserted following irrigation and debridement [Figure 2].

Six hours after the surgical procedure, the patient displayed signs and symptoms of an allergic reaction, including pruritus, skin redness, dermatitis, and erythematous papular eruptions, particularly in the abdominal and inguinal regions [Figure 3].

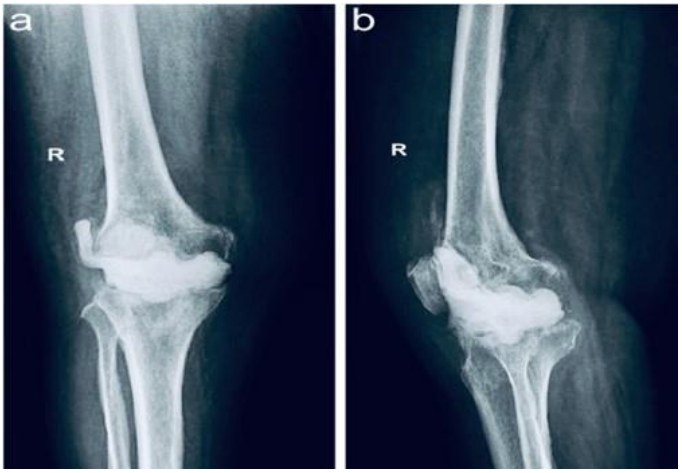

Figure 2. Anteroposterior (a) and lateral (b) radiographs of the right knee after removal of infected implants and replacement with a static spacer

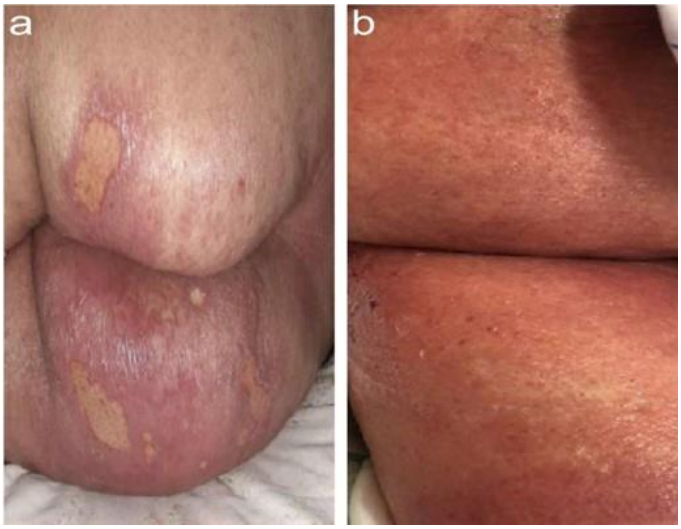

Figure 3. Patient's skin symptoms, such as maculopapular rashes on her buttocks (a) and annular erythematous plaques with centralized bullous formation on the inguinal region (b)

Her vital signs revealed a heart rate of 120 beats per minute and blood pressure of 85/55 mmHg, indicating tachycardia and hypotension. Upon observing these cutaneous symptoms and abnormal vital signs, consultation with infectious diseases and dermatology specialists was quickly initiated. These discussions resulted in a diagnosis of VFS based on the clinical manifestations and by excluding other possible causes. Accordingly, a personalized treatment strategy was decided based on the specialists' evaluation of the severity of the patient's symptoms and overall health status. This included the administration of intravenous epinephrine (0.5 mg), diphenhydramine (25 mg), methylprednisolone (80 mg), normal saline infusion, and cetirizine (10 mg twice daily).[10,11] The patient's response to this regimen was closely monitored. We had a contingency plan to remove the spacer if the patient's condition did not

improve or deteriorate. The decision to remove the cement was critical, considering the associated potential risks. However, the patient's vital signs stabilized shortly after the initiation of supportive care, negating the need to remove the VLBC. Methylprednisolone was later switched to oral prednisolone, and the dosage was gradually reduced as the patient's condition improved. During the patient's clinical treatment, microbiological culture examination revealed the presence of a negative culture in an aspirated synovial sample obtained on the day of admission, as well as in a histological examination of the periprosthetic tissue conducted intraoperatively. Following the surgical intervention, the patient was treated with intravenous cefazolin at a dose of 1 g every 6 h and prescribed oral antibiotics at the time of discharge.

Six weeks after the initial procedure, a second-stage revision surgery was conducted when the laboratory markers of infection normalized, and no clinical signs of infection were observed. Intraoperative pathological examination of the frozen section tissue specimens showed no evidence of infection. The spacers were replaced with revision knee arthroplasty using the NexGen Legacy Constrained Condylar Knee System [Figure 4].

Following surgical intervention, the patient exhibited prompt and uncomplicated recovery and was subjected to a comprehensive follow-up program spanning two years. No adverse events or complications occurred during follow-up.

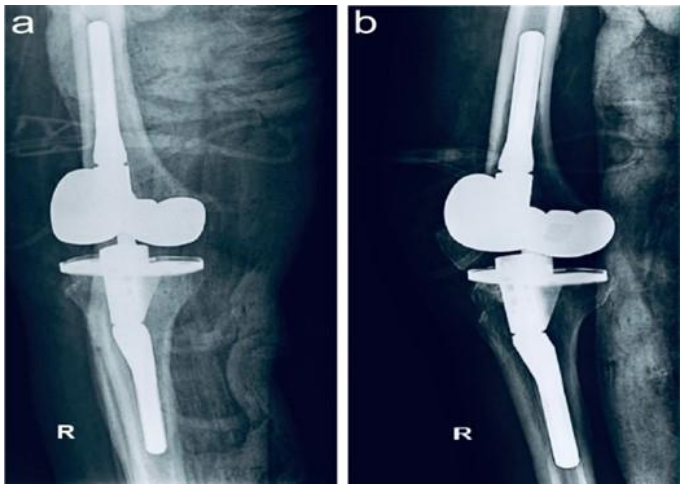

Figure 4. Prosthesis aligned and placed confidently, anteroposterior (a) and lateral view (b)

Discussion/ Conclusion

Vancomycin flushing syndrome, previously referred to as red man syndrome, is a rare but significant adverse reaction that is primarily related to intravenous vancomycin administration.[12] This report presents an unusual case of VFS following the use of VLBC in a two-stage revision surgery for PJI. The successful management of VFS without removing the VLBC spacer underscores the importance of prompt intervention and careful clinical judgment. The patient exhibited pruritus, erythema, tachycardia, and hypotension, which were effectively managed using intravenous epinephrine, antihistamines, steroids, and fluid resuscitation. Despite these severe symptoms, the decision to retain the VLBC spacer balances the need for infection control with the risk of hypersensitivity reactions. This approach highlighted the critical role of multidisciplinary collaboration in the management of complex clinical scenarios.

The proposed mechanism involves systemic absorption of vancomycin from the cement, triggering mast cell degranulation, leading to histamine release, and inducing VFS symptoms.[12-14] However, the exact mechanisms of VFS have not been fully elucidated, and further investigations are warranted to elucidate the precise pathophysiological mechanisms, identify risk factors, and establish optimal management protocols for VLBC-associated VFS.[14]

Chen et al.[14] described a case in which VFS occurred during primary TKA when VLBC was used for prophylactic purposes. In contrast, our patient developed VFS during first-stage revision surgery for treating an established PJI. This clinical setting presents a unique challenge, as it necessitates the simultaneous management of PJI and unexpected adverse drug reactions. Our approach, with intravenous epinephrine, antihistamines, steroids, and close monitoring, enabled successful resolution of VFS symptoms without requiring spacer removal.

Two other studies have reported cases in which VFS developed after vancomycin-impregnated beads were inserted to treat infected nonunion fractures and chronic osteomyelitis.[8,15] In contrast to our case, in which VFS was managed without removing the VLBC, these studies required the removal of vancomycin-impregnated beads to achieve symptom resolution. This divergence underscores the importance of a patient-specific, individualized approach to treatment that considers the severity of adverse reactions, clinical context, and potential risks associated with the removal or retention of antibiotic-impregnated spacers.

It is crucial to recognize the extensive array of adverse reactions that could result from ALBC, as they can go beyond the VFS. Although there have been a few cases of hypersensitivity reactions to ALBC with varying clinical presentations, it is vital to understand their diverse manifestations and potentially life-threatening consequences. This understanding is necessary for appropriate diagnosis and management strategies to effectively minimize adverse events.

Harper et al.[7] reported a case of drug reaction with eosinophilia and systemic symptoms syndrome following the use of an ALBC containing vancomycin and tobramycin during two-stage revision surgery for PJI. Although severe, the patient's symptoms resolved with medical management without requiring spacer removal.

In comparison, our case involved a distinct adverse reaction (i.e., VFS) and a different antibiotic combination (i.e., vancomycin alone), emphasizing the varying clinical manifestations and the impact of some factors, such as antibiotic selection and dosage, on the incidence of adverse reactions following ALBC. Therefore, it is imperative to evaluate these factors carefully to mitigate the likelihood of complications.

Riemenschneider et al.[6] reported a case of drug-induced linear IgA bullous dermatology that occurred after revision

knee arthroplasty using vancomycin and tobramycin-impregnated cement spacer. Despite the potential complications, the medical team initially chose to retain the spacer. After 4 months, the spacer was eventually removed, leading to remission, which was consistent with the approach used in our case. This decision exemplifies the intricate balance between managing infection risk and mitigating drug-induced adverse reactions, which requires a multidisciplinary evaluation of benefits and risks.

Adjusting the vancomycin infusion rate or administering H1 or H2 blockers prior to vancomycin administration is recommended to minimize the risk of such adverse reactions.[10,11,16] In addition, our case report supports investigations into antibiotic alternatives for patients with a history of adverse reactions to vancomycin. Williams et al.[17] reported a case of a patient who developed a systemic desquamating rash resembling Stevens - Johnson syndrome (SJS) after exposure to VLBC during the treatment of PJI despite a history of SJS induced by systemic vancomycin. In their study, the patient was treated with daptomycin instead of vancomycin in ALBC, highlighting the potential value of alternative antibiotics, as suggested by recent studies investigating low-dose teicoplanin-impregnated cement as a substitute for vancomycin.[18]

The findings highlight the importance of anticipating and managing VFS in patients receiving VLBC spacers, requiring a multidisciplinary approach to balance the benefits of infection control with the risks of adverse reactions. Although rare, VFS can occur with VLBC spacers during revision surgery for PJI. Immediate and appropriate management, including the use of intravenous epinephrine, antihistamines, and steroids, is crucial for patient recovery. Despite the adverse reactions, the decision to retain the spacer underscores the need for careful consideration of the risks and benefits. Regular monitoring, pretreatment with antihistamines or corticosteroids, and exploration of alternative antibiotics, such as teicoplanin, for patients with known hypersensitivity to vancomycin are recommended. The effective management of VFS requires timely intervention and a tailored approach to ensure patient safety and successful outcomes.

Acknowledgement

N/A

Authors Contribution:

Dr. Mehdi Motififard: Conceptualization, clinical management, and supervision.
Dr. Mehdi Teimouri: Writing—original draft preparation and literature review.
Dr. Hossein Akbari Aghdam: Contribution to manuscript preparation and final approval of the manuscript.
Dr. Hadi Ravanbod: Investigation and resources.
Dr. Mohammad Shahsavan: Writing—review, editing, and case details acquisition.

Declaration of Conflict of Interest: The authors do NOT have any potential conflicts of interest for this manuscript.

Declaration of Funding: The authors received NO financial support for the preparation, research, authorship, and publication of this manuscript.

Declaration of Ethical Approval for Study: The study adhered to the Declaration of Helsinki and was approved by the Institutional Review Board (IRB). Specifically, the Isfahan University of Medical Science Institutional Review Board (Approval ID: IR.ARI.MUI.REC.1401.281) approved the study.

Declaration of Informed Consent: The authors declare that there is no information (names, initials, hospital identification numbers, or photography) in the submitted manuscript that can be used to identify patients. We obtained informed consent from the patient who participated.

Mehdi Motififard MD [1]
Mehdi Teimouri MD [1]
Hossein Akbari Aghdam MD [1]
Hadi Ravanbod MD [1]
Mohammad Shahsavan MD [1]

1 Department of Orthopedic Surgery, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

References

1. Ucpunar H, Camurcu Y, Buyuk AF, Aydin A, Tas SK, Sahin V. Comparison of Contemporary Surgical Indications for Revision Total Knee Arthroplasty between 2005-2011 and 2012-2017 in a Referral Center. Arch Bone Jt Surg. 2022; 10(1):32-37. doi:10.22038/abjs.2021.47457.2326.
2. Lunz A, Schonhoff M, Omlor GW, et al. Enhanced antibiotic release from bone cement spacers utilizing dual antibiotic loading with elevated vancomycin concentrations in two-stage revision for periprosthetic joint infection. Int Orthop. 2023; 47(11):2655-2661. doi:10.1007/s00264-023-05922-7.
3. Nelson SB, Pinkney JA, Chen AF, Tande AJ. Periprosthetic Joint Infection: Current Clinical Challenges. Clin Infect Dis. 2023; 77(7):e34-e45. doi:10.1093/cid/ciad360.
4. Shahpari O, Mousavian A, Elahpour N, Malahias MA, Ebrahimzadeh MH, Moradi A. The Use of Antibiotic Impregnated Cement Spacers in the Treatment of Infected Total Joint Replacement: Challenges and Achievements. Arch Bone Jt Surg. 2020; 8(1):11-20. doi:10.22038/abjs.2019.42018.2141.
5. Anagnostakos K. Therapeutic Use of Antibiotic-loaded Bone Cement in the Treatment of Hip and Knee Joint Infections. J Bone Jt Infect. 2017; 2(1):29-37. doi:10.7150/jbji.16067.

6. Riemenschneider K, Diiorio DA, Zic JA, et al. Drug-induced linear IgA bullous dermatosis in a patient with a vancomycin-impregnated cement spacer. Cutis. 2018; 101(4):293-296.
7. Harper KD, Incavo SJ. Drug reaction with eosinophilia and systemic symptoms syndrome after total knee arthroplasty doi:10.3329/bjms.v14i3.17955.
9. Rodriguez-Merchan EC. The Function of Sonication in the Diagnosis of Periprosthetic Joint Infection after Total Knee Arthroplasty. Arch Bone Jt Surg. 2022; 10(9):735-740. doi:10.22038/abjs.2020.44329.2212.
10. Sivagnanam S, Deleu D. Red man syndrome. Crit Care. 2003; 7(2):119-20. doi:10.1186/cc1871.
11. M Shaju A, Panicker N, Chandni V, Lakshmi Prasanna VM, Nair G, Subeesh V. Drugs-associated with red man syndrome: An integrative approach using disproportionality analysis and Pharmip. J Clin Pharm Ther. 2022; 47(10):1650-1658. doi:10.1111/jcpt.13716.
12. Al-Anii FM, Sadat-Ali M, Al-Tabash KW, AlMulhim AI, AlMousa SA, AlHawas AM. Vancomycin flushing syndrome in orthopaedic practice: A case report. World J Orthop. 2023; 14(10):771-775. doi:10.5312/wjo.v14.i10.771.
13. Arthur JR, Bingham JS, Clarke HD, Spangehl MJ, Young SW. Intraosseous Regional Administration of Antibiotic Prophylaxis in Total Knee Arthroplasty. JBJS Essent Surg Tech. 2020; 10(4):e20.00001.doi:10.2106/jbjs.st.20.00001.
infection and placement of antibiotic spacer. Arthroplast Today. 2019; 5(2):148-151. doi:10.1016/j.artd.2019.04.005.
8. Juyal A, Khurana G, Maheshwari R. Red man syndrome: an unusual complication of vancomycin beads. Bangladesh Journal of Medical Science. 2015; 14(3):290.
14. Chen CT, Ng KJ, Lin Y, Kao MC. Red man syndrome following the use of vancomycin-loaded bone cement in the primary total knee replacement: A case report. Medicine (Baltimore). 2018; 97(51):e13371. doi:10.1097/md.0000000000013371.
15. Goh KL, Nazri MY, Ong CL. Allergic reaction following insertion of vancomycin loaded in bone cement. IIUM Medical Journal Malaysia. 2014; 13(1). doi:10.31436/imjm.v13i1.494.
16. Juyal AK, Khurana G, Maheshwari R. Red man syndrome: an unusual complication of vancomycin beads. Bangladesh Journal of Medical Science. 2015; 14:290-291.
17. Williams B, Hanson A, Sha B. Diffuse Desquamating Rash Following Exposure to Vancomycin-Impregnated Bone Cement. Ann Pharmacother. 2014; 48(8):1061-1065. doi:10.1177/1060028014529547.
18. Cimen O, Oner A, Koksal A, et al. A comparison of low-dose teicoplanin-loaded spacer application vs. high-dose vancomycin-and-gentamicin-loaded spacer application in the treatment of periprosthetic knee infection. JOTR. 2022; 29(1):22104917221082312. doi:10.1177/22104917221082312.