Clinical Case Report

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Red man syndrome following the use of vancomycin-loaded bone cement in the primary total knee replacement

A case report

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Abstract

Rationale: Red man syndrome (RMS) is the most common allergic reaction to vancomycin. It generally occurs during rapid infusion of vancomycin; only few cases have been reported as results of local vancomycin administration. We hereby report a rare case where RMS developed after insertion of vancomycin-loaded bone cement in a primary total knee replacement (TKR).

Patient concerns: A 74-year-old woman was admitted for a left TKR due to severe osteoarthritis. Erythematous changes over face, trunk, and extremities developed after the use of vancomycin-loaded bone cement.

Diagnoses: According to the clinical manifestations, the patient was diagnosed with vancomycin-induced RMS.

Interventions: She was treated with fluid challenge and intravenous ephedrine, followed by intravenous diphenhydramine and hydrocortisone.

Outcomes: The patient's symptoms and signs relieved within 1 h after treatment.

Lessons: Vancomycin-induced RMS may occur after the routine use of vancomycin-loaded bone cement in the primary TKR replacement.

Abbreviations: PACU = postanesthesia care unit, RMS = red man syndrome, TKR = total knee replacement.

Keywords: anaphylactoid reaction, perioperative complication, vancomycin hypersensitivity

1. Introduction

Vancomycin is a bactericidal antibiotic with activity against most gram-positive cocci, including methicillin-resistant *Staphylococcus aureus*.[1] Red man syndrome (RMS) is a common allergic reaction to vancomycin that typically presents with a rash on the face, neck, and upper torso after intravenous administration of vancomycin.[2,3] Less frequently, RMS may be accompanied by hypotension and angioedema. Although RMS is known to be a rapidly infusion-related reaction, it may also occur when infused in a slow rate.[4,5] Only few cases of RMS were reported to be associated with local uses of vancomycin.[6,7] Prophylactic use of antibiotic-loaded bone cement for the primary total knee replacement (TKR) is a common adjunctive treatment to prevent osteomyelitis in clinical setting.[8–10] We hereby reported a rare case where RMS developed after the use of vancomycin-loaded bone cement in a patient receiving a primary TKR. The patient has provided informed consent for publication of the case.

2. Case report

A 74-year-old woman underwent a primary left TKR due to severe knee osteoarthritis. She denied history of previous systemic diseases and had no remarkable findings during preoperative assessment. On arrival to the operating room, the standard monitors were applied and a prophylactic antibiotic cefazolin 1 g was administrated intravenously without noticeable adverse reaction throughout the operation. The operation was performed under spinal anesthesia. During operation, the patient received a knee prosthesis with bone cement loaded with vancomycin 1000 mg during implantation. With the use of tourniquet, there were no subjective complaints noticed and the vital signs remained stable throughout the procedure. The total operation time was 80 min and the tourniquet time was 55 min. The operation was uneventful. The intraoperative blood loss was 50 mL. The patient was sent to postanesthesia care unit (PACU) with stable vital signs. In the PACU, an erythematous rash on face, trunk, and extremities was noted 45 min after release of tourniquet (Fig. 1A and B). In the meantime, she complained of generalized discomfort and itchiness. She remained clear conscious and fine oxygen saturation read around 97%. However, a sudden drop in blood pressure to 47/34 mm Hg ensued. The surgical wound

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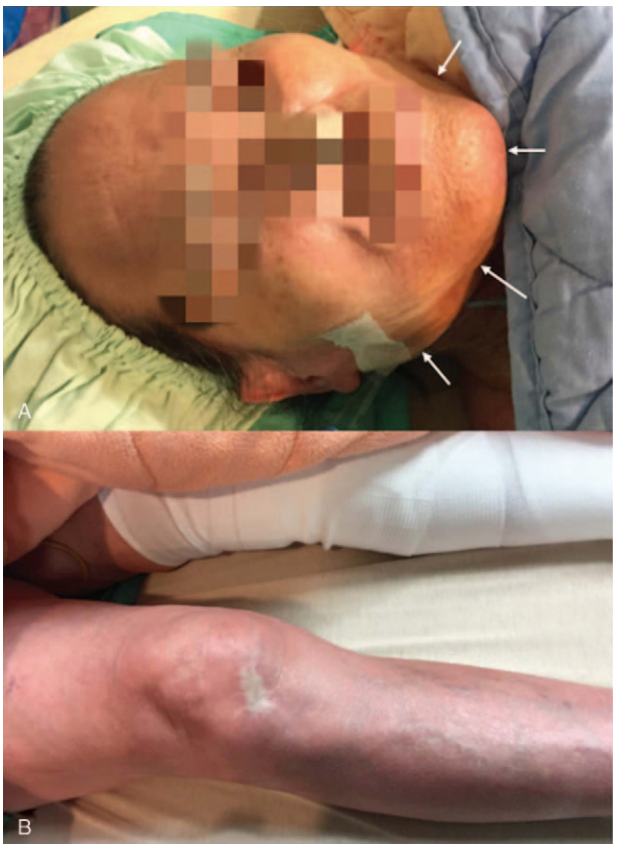

Figure 1. Representative images of red man syndrome induced by vancomycin-loaded bone cement in a 74-year-old woman after a primary left total knee replacement. (A) A rash on the face (white arrows). (B) A rash on the right lower extremity. Note the bleached spot is due to an unflushed old scar.

drainage of blood was less than 50 mL at that time. Under the tentative diagnosis of vancomycin-induced RMS, the patient was treated with fluid challenge and 8 mg of ephedrine intravenously, followed by administrating 30 mg of diphenhydramine and 100 mg of hydrocortisone intravenously. The patient's blood pressure was back to 95/55 mm Hg 15 min after treatment and remained stable during the 1-h monitoring in the PACU. Thereafter, she was transferred to the general ward. The erythematous rash and itching condition had improved around 1.5 h since the rash had first been discovered. She was discharged as scheduled.

3. Discussion

Hypersensitivity reactions to vancomycin include RMS and anaphylaxis.[2,3] RMS is the most common adverse reaction to vancomycin,[11] but it is rarely life-threatening. RMS is an anaphylactoid reaction caused by degranulation of mast cells and basophils after rapid infusion of vancomycin, resulting in the release of histamine.[12] It is characterized by flushing, erythema, and pruritis on face, neck, and trunk. However, more advanced responses, including fever, agitation, angioedema, tachycardia, hypotension, and even cardiovascular collapse, may occur in severe cases.[13] In this case report, the patient presented with flushing, erythema, and pruritis as well as transient hypotension following the use of vancomycin-loaded cement. She was thus diagnosed with vancomycin-induced RMS by excluding other possible causes. It should be noted that the patient also had an exaggerated skin reaction on the bilateral lower extremities, which is less seen in common vancomycin-induced RMS. We speculated that this exaggerated reaction in response to histamine could be attributed to the vasodilatory effect following spinal anesthesia.

The other vancomycin hypersensitivity is an anaphylactic reaction. Anaphylaxis is an immunologically mediated reaction involving drug-specific immunoglobulin E (IgE) antibodies and is independent of the infusion rate. Anaphylaxis in response to vancomycin administration is believed to be rare, although reactions involving angioedema, respiratory distress, and bronchospasm with evident drug-specific IgE have been described.[14] In cases of anaphylaxis, antihistamines are not thought to be useful.[15] Anaphylaxis can be severe, generalized allergic, or hypersensitivity reaction that is life-threatening; administration of epinephrine should be considered as rapidly as possible once anaphylaxis is recognized.[16] Moreover, a prior exposure to vancomycin is usually prerequisite for developing vancomycin-induced anaphylactic reaction. On the contrary, RMS is an anaphylactoid reaction that can occur during the first administration of vancomycin. Judging from the clinical manifestations as well as the absence of previous vancomycin exposure, anaphylaxis was not likely to be the cause in this case report.

In addition to vancomycin, antibiotics such as ciprofloxacin, amphotericin B, rifampin, and teicoplanin can potentially cause RMS.[17] More importantly, RMS can be aggravated in patients receiving opioid analgesics, muscle relaxants, or contrast dye because these drugs may induce histamine release from mast cells.[2] Fortunately, most RMS can be treated or prevented by slowing the medication infusion and administering a histamine-blocking agent.[18] In our case, vancomycin was the only potential antibiotic administered to induce RMS. Moreover, the patient underwent the operation under a pure spinal anesthesia technique, thus avoided the use of those drugs that predispose to the aggravated reaction of vancomycin-induced RMS. Therefore, the patient had a good response to our initial management without any sequelae.

There are still uncertainties regarding the rate and mechanism of vancomycin delivery from bone cement. Several factors including the type of cement used, the amount of vancomycin loaded, and the method of preparation may influence the delivery of vancomycin.[7] The use of vancomycin-loaded bone cement is considered to be safe in both animal and clinical studies.[8] The peak vancomycin concentrations in blood were achieved 6 to 24 h after implantation and were extremely low. In contrast, the concentrations of vancomycin in bone remain high throughout the first 6 months, which is an important characteristic for both curative and prophylactic treatment. There are very few case reports of adverse effects after the use of vancomycin-loaded bone cement. Goh et al[7] reported a 42-year-old army officer who developed RMS after vancomycin bead's insertion for chronic osteomyelitis. The symptoms persisted until the removal of vancomycin beads. Furthermore, Williams et al[19] reported a 59-year-old man with a history of Stevens–Johnson reaction to systemic vancomycin developed a painful, blistering rash after implantation of vancomycin-loaded bone cement for treating recurrent methicillin-susceptible *S. aureus* prosthetic knee infection. In our case, we speculated the cause of RMS might be attributed to the release of certain amount of vancomycin into local circulation during but not after implantation and polymerization process of the bone cement. The subsequent release of tourniquet might cause transient increases of systemic vancomycin and histamine levels that led to the development of

RMS. The good response to our initial treatment also supported our speculations and the removal of the vancomycin-loaded bone cement was thus avoided. Moreover, those previous cases were reported in patients with chronic osteomyelitis. To our knowledge, RMS has not been reported to occur after the routine use of vancomycin-loaded bone cement in the primary TKR in available literature.

4. Conclusion

Vancomycin-loaded bone cement is widely used in joint surgery for preventing or treating osteomyelitis. Although the development of RMS is mostly associated with intravenous administration of vancomycin, there are a few case reports of systemic toxicity and allergy reaction when vancomycin was loaded in bone cement for treating orthopedic-related infections. This case report further highlights the potential risk of RMS induced by the routine use of vancomycin-loaded bone cement in the primary TKR. Early detection and proper management of this potential risk in daily practice can thus prevent the unwanted outcomes.

Author contributions

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