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LETTER TO EDITOR

Serum Tryptase Cannot Differentiate Vancomycin-Induced Anaphylaxis From Red Man Syndrome

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To the Editor:

Perioperative anaphylaxis is a life-threatening event and requires prompt recognition and treatment to ensure a good outcome. Vancomycin can induce nonspecific direct stimulation of mast cells, resulting in histamine release and the anaphylactoid reaction known as "red man syndrome" [1]. Red man syndrome and anaphylaxis share a number of signs and symptoms, and thus differential diagnosis is difficult in some cases. Nonetheless, differential diagnosis between these conditions is crucial, since a diagnosis of anaphylaxis to vancomycin reduces the options for treatment of life-threatening infections such as infective endocarditis, severe pneumonia, and sepsis. Measurement of the serum tryptase concentration is considered useful to distinguish between red man syndrome and anaphylaxis [2]. However, we here report the case of a patient diagnosed as having anaphylaxis induced by intravenous vancomycin usage based on increased plasma tryptase concentration, despite a clinical presentation suggesting red man syndrome rather than anaphylaxis.

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Case Presentation

A 22-year-old male patient underwent a successful anterior cruciate ligament reconstruction under spinal anesthesia 7 days before presenting at our clinic with a complaint of redness and pain of the knee. At presentation, he had atopic dermatitis but was not being treated chronically with any drug and had no prior exposure to vancomycin. Because his symptoms were suggestive of pyogenic knee arthritis, microscope examination was performed. The results revealed Gram-positive cocci in the exudate fluid, confirming the diagnosis of pyogenic knee arthritis. An emergency lavage and debridement of the right knee was conducted under general anesthesia, and 2 g of vancomycin was selected as an empiric therapy.

Anesthesia was induced and maintained with propofol, ketamine, and remifentanil. Rocuronium was administered to facilitate placement of the laryngeal mask airway. In addition to the standard ASA monitoring, the bispectral index was monitored during anesthesia. No specific response occurred during induction of anesthesia. His vital signs were as follows: blood pressure, 123/78 mmHg; heart rate, 75 bpm; SpO_2, 100%; and pharyngeal temperature, 37.1 °C. Ultrasound-guided left femoral nerve block with 0.25% levobupivacaine was conducted by the attending anesthesiologist. After establishing the peripheral nerve block, the surgical procedure and intravenous administration of vancomycin 2 g were started. Nine minutes later, when the administration of vancomycin was almost finished, the patient's heart rate increased to 104 bpm and the tidal volume decreased from 500 mL to 150 mL. Because the administration of anesthetics, including rocuronium, did not increase the tidal volume, the laryngeal mask airway was displaced and the trachea was intubated. Even after tracheal intubation, the tidal volume did not increase and a capnogram showed an obstructive pattern. Shortly after intubation, his blood pressure decreased to 57/29 mmHg and his heart rate increased to 106 bpm. Due to his atopic dermatitis and hypotension, cutaneous signs such as flushing and swelling were obscured, if present.

Phenylephrine (0.2 mg) and ephedrine (4 mg) were given repeatedly but the hemodynamics and respiratory pattern did not change drastically. During the preparation of epinephrine administration, the hemodynamics and tidal volume returned to normal: blood pressure, 97/43 mmHg; heart rate, 110 bpm; and tidal volume, 500 mL. The duration of hemodynamic instability was only 10 min. An arterial line was inserted to the left radial artery and a blood sample was obtained for the measurement plasma histamine and tryptase 30 min after the increase in heart rate and airway resistance. To prevent a recurrence of anaphylactoid response, 6.6 mg of dexamethasone was administered during surgery. Salvage and debridement were conducted as scheduled. Emergence from general anesthesia was prompt. The patient was transferred to the intensive care unit. As anaphylaxis induced by vancomycin was undeniable, linezolid 1200 mg/day d.i.v was given instead of vancomycin. He was discharged from the intensive care unit on postoperative day 1 without recurrence of anaphylactoid response. On postoperative day 2, methicillin-sensitive *Staphylococcus aureus* was found in the exudate fluid and the antibiotic was changed to cefazolin.

As a result of the elevated plasma tryptase (11.2 ng/mL) and histamine (12.7 ng/mL) levels which were measured during anesthesia compared with the baseline tryptase and histamine levels of the patient (3.3 ng/mL and 0.99 ng/mL, respectively) which were measured on postoperative day 1, a diagnosis of vancomycin-induced anaphylaxis was made.

Discussion

The present patient was diagnosed as having anaphylaxis induced by vancomycin on the basis of his increased plasma tryptase concentration. Nonetheless, his lack of prior exposure to vancomycin, rapid infusion of vancomycin, and prompt recovery from hypotension and bronchospasm without administration of epinephrine all suggested red man syndrome rather than anaphylaxis. This case thus raises the question of whether an increased concentration of tryptase can distinguish between red man syndrome and anaphylaxis.

Although the significant association between increased tryptase concentration and anaphylaxis has been well established, tryptase is released by the nonimmunologic stimuli and increased tryptase does not always mean anaphylaxis [3, 4]. A retrospective study revealed a significant association between increased concentrations of tryptase and immunoglobulin E–mediated reactions, but the authors concluded that increased concentrations of tryptase did not always distinguish between anaphylactoid and anaphylaxis; in 33 of 155 patient with increased tryptase concentration, no immunoglobulin E antibodies were detected [3]. Moreover, one in vitro study revealed that vancomycin directly induced tryptase release from human foreskin mast cells, and the tryptase concentration was correlated with histamine concentration [4]. Vancomycin could induce mast cell activation and increase tryptase release in addition to histamine release. These results suggest that discrepancies between the clinical presentation and tryptase concentration after rapid infusion of vancomycin are possible. On the other hand, a clinical study revealed that rapid infusion of vancomycin (1 g/10 min) did not increase plasma tryptase concentrations, even though it did significantly increase plasma histamine concentrations [2]. In our case, the peak plasma concentration of vancomycin was 80×10^{-6} M, while patients in the previous study were exposed to 37×10^{-6} M vancomycin [5]. This difference in the plasma vancomycin concentration might have affected the tryptase concentration.

The present patient was diagnosed as having vancomycin-induced anaphylaxis on the basis of an increased tryptase concentration, and this case suggests that serum tryptase concentration does not clearly distinguish between anaphylaxis and red man syndrome.

Authors' Contribution All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent The authors have obtained written informed consent from the patient for publication.

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Capsule summary

- The patient was diagnosed with vancomycin-induced anaphylaxis based on increased plasma tryptase concentration.
- This case suggests that increased tryptase concentration might not distinguish between red man syndrome and anaphylaxis.