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Case Report

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Vancomycin Flushing Syndrome: Case Report

Adil Alharthi[1*], Eldawi Nawar[2], Sanaa Khedher[3], Hasan Aldosari[4], Hani Alkalaf[5], Asmaa A. Haseiba[6], Asif Kamran[7], Nabil Alkheir[8], Siddig Fadul[9]

[1]Consultant Internist, Waddi Addawasir hospital, Saudi Arabia

[2]Consultant surgeon, Waddi Addawasir hospital, Saudi Arabia

[3]Consultant Intensivist, Waddi Addawasir Hospital.

[4]Waddi Addawasir Hospital Director, Waddi Addawasir hospital, Saudi Arabia

[5]Waddi Addawasir Medical director, Waddi Addawasir hospital, Saudi Arabia

[6]Registrar Dermatology, Waddi Addawasir hospital, Saudi Arabia

[7]Registrar Medicine, Waddi Addawasir hospital, Saudi Arabia

[8]Registrar Medicine, Waddi Addawasir hospital, Saudi Arabia

[9]Registrar surgery, Waddi Addawasir hospital, Saudi Arabia

***Corresponding author**: Adil Alharthi, Consultant Internist, Waddi Addawasir hospital, Saudi Arabia

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Case Report

Our patient is a 74 years old male, presented with blackish discoloration of right big toe & infected ulceration of right shin, along with intermittent fever. He had multiple active medical problems including Diabetes Mellitus, Hypertension, Diabetic Nephropathy, & had a history of left mid-tarsal amputation in the past. On examination, he was febrile, and had raised blood glucose levels. Local Examination revealed gangrenous right big toe. There was a large foul smelling, tender ulcerated area on the lateral aspect of right shin, with dark edges. There was slight scattered pus on the ulcer. Peripheral pulses of the lower limbs were weak with absent dorsalis pedis & posterior tibial pulses on the right. Peripheral sensations were also markedly diminished. Based on the history as well as clinical evaluation, he was admitted as a case of Diabetic Foot/Necrotising Fasciitis, and was started on IV Meropenem & supportive treatment including IV Fluids & antipyretics. Daily wound dressing was also started.

The next day, patient got hemodynamically unstable with an episode of hypotension and was shifted to ICU. Due to persistently raised inflammatory markers and no significant clinical improvement, he was started on IV Vancomycin. After three days the hemodynamics improved and patient was shifted back to the ward. Sepsis markers improved but microbiology swaps from the non-improving wound grow Methicillin resistant Staph Aureus twice, so the vancomycin was continued. Six days after starting Vancomycin, patient complained of erythematous rash associated with itching of his whole body, especially around neck & trunk. Apart from mild fever & slightly low BP, there was no associated symptoms such as cough or respiratory distress and the patient wasn't receiving other medication known to cause such condition.

Based on the presentation as well as after consultation with dermatologist, a diagnosis of vancomycin Flushing Syndrome to IV Vancomycin was made. IV Vancomycin was immediately discontinued, and he was started on antihistamines. The patient made significant recovery over the next 1-2 days with settling of the rash as well as hemodynamic stability. The rash didn't appear again during the patient stay at the hospital.

Pathophysiology of the vancomycin flush syndrome:

The vancomycin flush syndrome (VFS) is the most common of the adverse reactions associated with vancomycin (VCM) administration. VCM can also cause anaphylaxis and the clinician

is thus faced with the challenge of differentiating between the two. VCM can still cause other rarer adverse reactions like severe cutaneous adverse reactions (SCAR) and drug reaction with eosinophilia and systemic symptoms (DRESS).

VFS is an anaphylactoid, NOT anaphylactic, reaction. Both reactions degranulate mast cells with the difference that in anaphylaxis IgE antibodies are involved while in an anaphylactoid reaction the mast cells are degranulated directly without IgE intermediation. As IgE is not necessary in anaphylactoid reactions, no prior exposure to antigen is needed (i.e. no sensitization), an anaphylactoid reaction can thus happen from first dose. The sensitization is necessary to prepare IgE for subsequent allergen exposures.

In anaphylaxis (and allergic diseases generally, also called immediate hypersensitivity reactions):

- Antigens (called allergens in the context of this type of immunologic reaction) are presented to the immune system inciting it to produce antigen-specific antibodies of the immunoglobulin E (IgE) type.

- This first encounter of the allergen (with resultant IgE production) with the immune system is called sensitization.

- The produced allergen-specific antibodies are then mounted onto mast cells surface waiting for the allergen to appear in subsequent encounters or exposures.

- These mast cells contain granules housing histamine and other vasoactive substances.

- When the allergen appears in subsequent exposures, it attaches to its specific immunoglobulins E (IgE) on mast cells surface.

- This allergen-IgE complex causes mast cells to degranulate releasing their preformed substances (like histamine and tryptase) then newly formed mediators (like prostaglandin D2, leukotrienes, thromboxane A2) into the circulation, causing the clinical picture of the reaction.

Horinouchi et al found in rats experiments that vancomycin DE granulates mast cells by mechanisms other than IgE [1]. Direct activation of mast cells (anaphylactoid) is known to be caused by various factors; host factors (stress, infection, etc.) and drug factors (rate of a drug injection, chemical properties and molecular weight. VFS was found to be related to the route of administration, infusion speed and drug concentration.It was clearly found linked to the VCM rate of infusion into the patient; the shorter the infusion period the more is the probability of developing VFS and the more is the probability of the reaction being severe (in contrast to moderate and mild). This is the basis why a one gram of VCM should be infused during more than one hour [2]. Furthermore, this action of VCM on mast cells was found to be potentiated by the concomitant administration of other drugs. Wong et al (1994) [3] reported a 'synergism' between VCM and narcotics in producing VCM hypersensitivity.

Management

The most effective way to manage acute VFS has not yet been assessed in controlled trials.In cases of mild to moderate reactions, such as patient discomfort because of flushing or pruritus but with steady hemodynamics and no chest pain or muscle spasms, the standard protocol involves discontinuing the infusion (Sivagnanam & Deleu, 2002) and administering diphenhydramine (50 mg orally or intravenously) and ranitidine (50 mg intravenously). In the typical scenario, symptoms tend to abate promptly. At this point, the infusion can be resumed at half the original rate or a maximum of 10 mg/min, whichever is slower [4].

In cases where the reaction is severe (such as those encompassing muscle spasms, chest pain, or hypotension), we discontinue the infusion and administer 50 mg of diphenhydramine and 50 mg of ranitidine intravenously, along with intravenous fluids if hypotension is present [5]. Differentiating severe VFS from anaphylaxis may be challenging or impossible, but both types of reactions may present with flushing and hypotension. If there is a suspicion of anaphylaxis, it is imperative that infusions not be resumed. This is because adjusting the rate of infusion and administering premedication's will not serve as preventive measures against IgE-mediated anaphylaxis [6,7]. Prevention: Empiric premedication to prevent Vancomycin Flushing Syndrome in patients receiving vancomycin for the first time at standard infusion rates (≤10 mg/min) is generally unnecessary [6] (Figure 1).

In contrast, the use of empiric premedication with antihistamines is often seen in cases where prompt infusions of vancomycin are needed in emergency or presurgical situations. The incidence and severity of VFS can be reduced through pre-treatment with antihistamines, although the best course of action has not yet been determined. An overwhelming 47 percent of the placebo group experienced reactions, while the diphenhydramine group experienced none [6,7].

It is recommended that patients receiving vancomycin at high infusion rates (exceeding 10 mg/min or 1 gram over one hour) be premedicated empirically. When feasible, oral therapy is the preferred option. While mildly increased infusion rates may only require H1 antihistamines, it is advisable to administer both H1 and H2 antihistamines to reduce the risk of a reaction when significantly faster rates are employed (such as 1 gram over 10 minutes) [8-11].

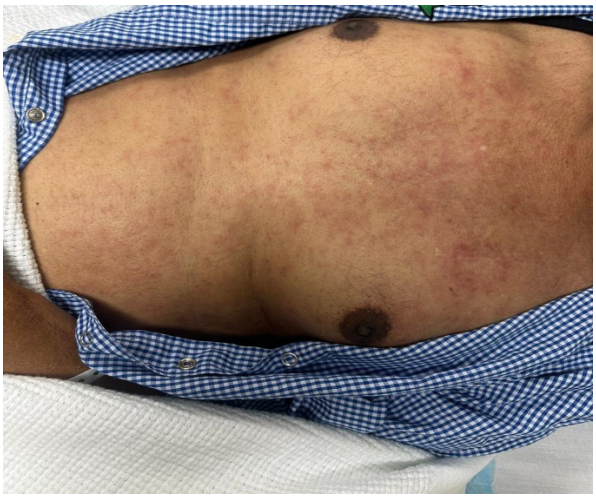

Figure 1: Vancomycin Flush Syndrome.

Conclusion

To optimize patient care and safety, it is crucial for the healthcare team to be able to:

1. Identify promptly if a patient requires pre-treatment for vancomycin - patients must be inquired about any previous complications with vancomycin infusion.

2. Ensure continuous monitoring of patient reaction to treatment and an adequate handover at swift modification to mitigate mistakes throughout current transfusion.

3. Consult with the supervisor, physician, or healthcare provider who prescribed the medication in case of any concerns regarding the patient's response to treatment or dosage.

4. Seek guidance from pharmacists regarding the medication and its recommencement procedure.

5. Acquaint themselves with the infusion protocols specific to the healthcare facility.

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