CASE HISTORY REPORT

ABSTRACT

Introduction: Thrombocytopenia is the reduction in the number of blood platelets, which may be caused by several different conditions such as sepsis, disseminated intravascular clotting, and large blood losses. Additionally, in rare situations, thrombocytopenia may also be induced by the use of medicaments. One of these drugs is the vancomycin, a glycopeptide presently used against serious infections involving Gram-positive bacteria such as the methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus*.

Objective: The objective of this study is to report on a case of serious vancomycin-induced thrombocytopenia in a patient infected with methicillin-resistant *S. aureus* after mandibular reconstruction with autogenous bone graft, and to draw attention to the importance of this clinically rare adverse effect.

Conclusion: Vancomycin-induced thrombocytopenia is a rare condition, which is also a significant disorder that demands attention and the rapid identification and replacement of the antimicrobial agent.

KEY WORDS: thrombocytopenia, vancomycin, antibacterial, bone graft

Vancomycin-induced thrombocytopenia: a rare adverse effect in a patient submitted to bone graft in the jaw

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Introduction

Vancomycin is a glycopeptide antimicrobial with bactericidal activity, which prevents the formation of peptidoglycans of the bacterial cellular wall. Without this protective layer, bacteria do not withstand the osmotic pressures, suffering rupture, and dying. The antimicrobial spectrum of vancomycin specifically comprehends Gram-positive bacteria and, pharmacologically, it has hydrophilic properties, being administered intravenously. It is excreted predominantly by the kidneys (80-90%), with the drug in its unaltered form. The pharmacodynamic characteristics of vancomycin consist of time-dependent bactericidal activity, i.e., it does not depend on its concentration.[1] Adequate serum concentration (25 μg/ml) may only be reached 72 h after the first intravenous application of the antimicrobial.[2]

Vancomycin was developed in 1956 and until around 1970, it was widely used for the treatment of different infections caused by Gram-positive microorganisms and in patients allergic to penicillin. In the 1980s, with the rapid expansion of antibiotic-resistant bacteria, it returned to the market where it remains until now for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant *Streptococcus*, the most serious types of infections.[3] Among the antimicrobials of choice for the treatment of serious infections by MRSA are linezolid, vancomycin, tigecycline, daptomycin, and ceftaroline.[4]

The most common adverse effect related to vancomycin is red man syndrome, which is a histaminergic reaction after rapid infusion of the drug. Ototoxicity and nephrotoxicity and thus renal function should be monitored appropriately. Less commonly, vancomycin has been associated with thrombocytopenia,[1,5] which is defined as a platelet counts below 100,000/mm^3.[6]

In this case report, vancomycin was the likely cause for thrombocytopenia in a patient submitted to a surgical procedure for the partial reconstruction of the mandible.

Case Report

A 57-year-old female patient presented herself at the Oral and Maxillofacial

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Surgery at the State University of Maringá in good general health, ambulating, oriented, and communicative. During anamneses, she reported a trauma in the face caused by gunshot one year previously, which resulted in the fracture of the right body and angle of the mandible, and the consequent loss of continuity of the mandibular contour. During the physical examination, she presented increased volume and erythema in the right chin region, and intrabuccally, she was completely edentulous with an important erythema in the region of the residual right mandibular ridge. On palpation, mobility of the right mandibular body and an area indicative of a fixation plate were observed. Radiographic image scans demonstrated an atrophic, fractured mandible and discontinuity of approximately 3 cm between the proximal and distal segments, as well as a failed rigid internal fixation system composed by a UniLock® angled reconstruction plate with 11 links and 9 self-drilling cruciform screws.

Antibiotic therapy with sodium cephalothin 1 g intravenously (6/6 h) associated with metronidazole 500 mg intravenously (8/8 h) was initiated. The patient evolved without pain complaints with the regression of the edema and the hyperemia. Five months later, she was submitted to a new surgical procedure under general anesthesia for the partial reconstruction of the mandible with iliac bone graft, conducted at the State University of Maringá Hospital (Brazil). Through an extrabuccal access in the right submandibular area extending to the medial region of the mandible, the osseous fragments were visualized, debrided, and prepared to receive the bone graft. The mandibular reconstruction was fixed with a UniLock® plate, 2.4 system, with 13 links and 9 titanium screws, previously adapted to the defect with the assistance of a template made by prototyping, and the use of an individualized titanium mesh, 1.5 system, to assist in the fixation and to form a scaffold for the graft. All the rigid internal fixation parts used in this, as well as in the previous surgery, were supplied by the same company (Synthes GmbH, Oberdorf, Switzerland).

Table 1. Naranjo's algorithm: determination of adverse drug reaction (ADR) probability.[5]

	Questions	YES	NO	DO NOT KNOW	SCORE
1.	Are there any previous conclusive reports in this reaction?	+1	0	0	+1
2.	Did the adverse event appear after the suspected drug was administered?	+2	–1	0	+2
3.	Did the adverse reaction improve when the drug was discontinued or a "specific" antagonist was administered?	+2	0	0	+2
4.*	Did the adverse reaction reappear when the drug was readministered?	+2	–1	0	0
5.	Are there alternative causes (other than the drug) that could, on their own, have caused the reaction?	–1	+2	0	+2
6.*	Did the reaction reappear when a placebo was given?	–1	+1	0	0
7.*	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8.	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9.	Did the resident have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10.	Was the adverse event confirmed by any objective evidence?	+1	0	0	0
**Score total that confirm the interaction					7

*Did not tested.
**(1) defined/highly probable >8 (2) Probable: 5–8 (3) Possible: 1–4 (4) Doubtful: <1.

Thirty days postoperatively, the patient evolved with signs of inflammation, suppuration, erythema, edema, and pain symptomatology. Bacterial culture revealed MRSA and, with the assessment and follow-up of an infectologist, antibiotic therapy with vancomycin 500 mg intravenously (IV) 6/6 h associated to rifampicin 300 mg orally 12/12 h, was prescribed for 20 days. Control complete blood count (CBC) conducted before administering the medicaments demonstrated parameters within normality, especially concerning platelet count (323,000/mm^3).

On day 11 of the antibiotic therapy, the patient evolved with platelet count at 9,000/mm^3, reporting discrete epistaxis episodes during the morning. On day 12, rifampicin was suspended. In the following day, platelet count rose discretely to 11,000/mm^3. On day 14, no significant improvement was observed concerning the thrombocytopenia (15,000/mm^3).

On that occasion, a detailed clinical evaluation was performed and applied the Naranjo's algorithm.[7] This instrument is recommended by the World Health Organization and the Ministry of Health, being perhaps the most used in the world to require an adverse drug reaction (ADR), which comes from a drug interaction. After completion of Naranjo's algorithm, we obtained a total score of 7 (Table 1) indicating, in conjunction with clinical assessment and laboratory tests of platelet count, the presence of a probable interaction. Therefore, the use

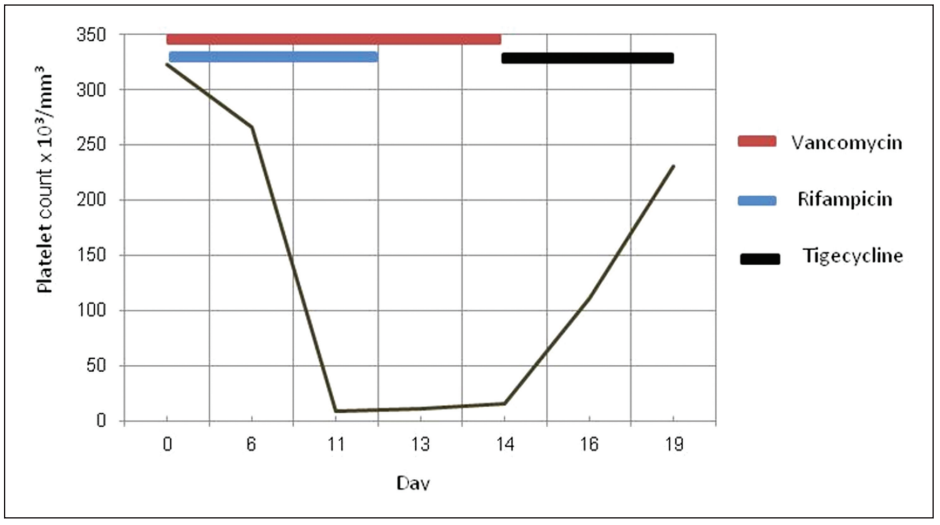

Figure 1. Platelet counts performed during the antibiotic therapy.

of vancomycin was replaced by tigecycline 50 mg IV 12/12 h. Platelet count was monitored daily. On the second day after vancomycin was suspended, platelet count increased sharply to 101,000/mm³, reaching 231,000/mm³ on the third day (Figure 1). In that moment, testing for vancomycin-dependent antiplatelet antibodies was requested. The results were nonreactive to both Immunoglobulin G (IgG) and Immunoglobulin M (IgM).

The antibiotic therapy was concluded on day 20. The patient was released from hospital, and requested to return for outpatient monitoring of the infection. At present she is in good general health without pain complaints and absence of suppuration. On palpation, osseous mobility is absent. A control cone beam computed tomography scan demonstrated continuity of the atrophic mandibular contour.

Discussion

Thrombocytopenia is defined as a platelet count below 100,000/mm³, which may occur due to the decelerated production of platelets, caused by bone marrow toxicity, or increased destruction of platelets mediated by the immune response.[8] Both may be induced by sepsis, disseminated intravascular clotting, large blood losses, immune thrombocytopenia, and drug-induced thrombocytopenia (heparin, linezolid, and piperacillin), which either increase bone marrow toxicity or the amount of immune mediators that cause the destructions of platelets.[6]

The differential diagnoses of the case being reported here were: (i) thrombocytopenia by sepsis and (ii) antibiotic therapy-induced thrombocytopenia. The first was excluded due to the regression in the signs of inflammation, absence of suppuration and hyperthermia, reduction of erythema, and the laboratorial protein C reactive (PCR) and erythrocyte sedimentation rate (ESR) exams showing no alterations. The second hypothesis was considered more adequate, and accepted. In patients with adequate production of platelets, as in this case, the time relation between the start of the therapy with vancomycin, the detection of thrombocytopenia, and the rapid reversal of platelet counts after the suspension of the antimicrobial agent suggested that thrombocytopenia was induced by the use of vancomycin.[9]

The drug-induced immune thrombocytopenia syndrome is an idiosyncratic reaction that only occurs with some medicaments. It is normally present 5 to 10 days after the initial exposition to the drug, or within hours after the secondary exposition to a drug that had been used in a previous occasion. Platelet counts are usually below 20,000/mm³, and spontaneous bleeding frequently occurs.[10] Three different mechanisms have been suggested for the occurrence of this syndrome: (i) the direct toxic effect, (ii) the "innocent bystander" immune response, and (iii) the formation of haptens. More widely accepted in the literature, the formation of haptens, resulting from the link between the drug (or its metabolites) and the platelets, leads to an immune response with the consequent formation of antiplatelet antibodies. These antibodies will eliminate the platelets, perceived by the body as antigens, from the circulation through the macrophages in the mononuclear phagocyte system, resulting in the reduction of platelet counts.[11]

Drug-induced thrombocytopenia diagnosis is more likely when the medicament has already had historical links with the condition. The recurrence of thrombocytopenia after reusing the drug may confirm the diagnosis.[10,12] Although drug-induced thrombocytopenia can be confirmed by demonstrating the presence of drug-dependent antiplatelet antibodies *in vitro*, laboratory testing is not readily accessible and test methods are not standardized.[13] Moreover, negative test results do not necessarily exclude the possibility of this cause-effect relationship.[5,10,12]

In the present case, in light of the possible destruction of platelets by vancomycin-induced antibodies, the testing for antiplatelet antibodies was conducted, but neither IgM nor IgG reagents were present. A possible explanation for these negative results is that vancomycin-dependent antiplatelet antibodies are only detectable after a minimum of 10 days from initiating the treatment. Thus, a more prolonged period of medicament use may be necessary for the antibodies to become reagent when laboratorial tests are performed.[14]

Vancomycin excretion is predominantly (80-90%) performed through hemofiltration (kidneys). Thus, the contribution of the total corporal clearance may be significant.[1] In patients with renal failure, i.e., deficiency to

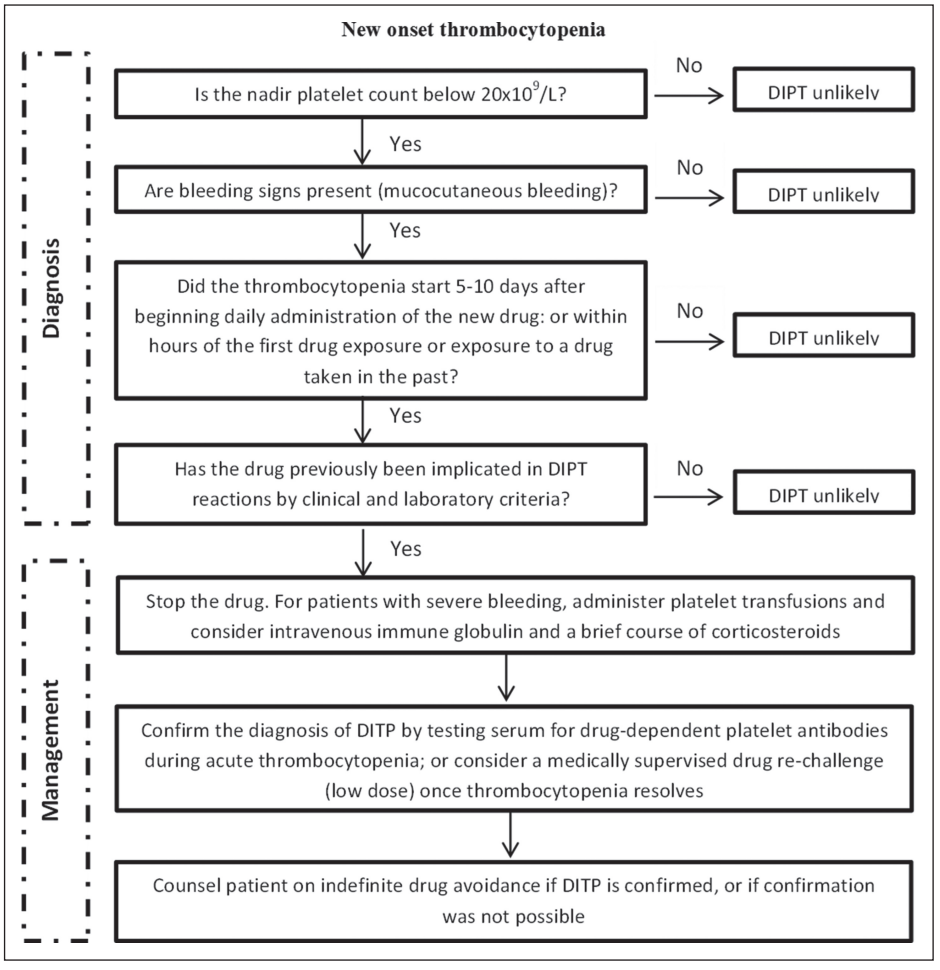

Figure 2. Approach to the diagnosis and management of a patient with new onset thrombocytopenia in whom drug-induced immune thrombocytopenia (DITP) is suspected.[12]

purify drugs, thrombocytopenia may persist for long periods of time after the administration of vancomycin is discontinued.[10] In the present case, laboratorial exams for renal function were conducted before starting the treatment, and daily after, to follow creatinine levels, with no alterations being found (ranging from 0.81 to 0.86 mg/dl), a fact that contributed to the considerably rapid return of platelet counts to levels above 150,000/mm^3.

A study performed in a university hospital in Brazil in 2011 assessed the prevalence of the adverse effects of vancomycin. By analyzing 350 medical records of patients that had made use vancomycin, and after excluding those whose laboratorial data were insufficient, adverse effects were found in 30 cases. Among these, thrombocytopenia was found in seven cases (2% of all patients treated with vancomycin), a surprising finding since such a response is considered historically rare.[3]

In 2013, guidelines for the treatment of drug-induced thrombocytopenia were established. Immediate interruption of drug use was defined as the most important action, based on the fact that platelet counts generally start to rise within 1 to 2 days after drug discontinuation.[10,12] In the present case, the patient made use of rifampicin associated with vancomycin. According to the study mentioned above,[10,12] rifampicin is one of the various drugs that can also induce thrombocytopenia. After being suspended, however, an insignificant elevation in the level of platelets, from 9,000/mm^3 to 15,000/mm^3, was observed in the second day. Then, after vancomycin was discontinued, platelet counts rose from 15,000/mm^3 to 101,000/mm^3 within only two days (Figure 1). The mean time to recovery of platelet counts to at least 150,000/µL after stopping vancomycin was 7.5 days, with a range of 4 to 17 days.[15]

The sequence for diagnosis and management of the drug-induced thrombocytopenia case described in this study was conducted based on the approach defined by Arnold *et al.* in 2013[12] (Figure 2).

The growth in the number of vancomycin-induced thrombocytopenia cases presently seen may be associated with the increased use of the drug, especially in multiresistant patients in ICU beds, and also to the advancement in laboratorial tests that can confirm the presence of vancomycin-induced antiplatelet antibodies. Nonetheless, no reports on vancomycin-induced thrombocytopenia associated with the treatment of patients by buccomaxillofacial surgeons have been found in the literature. This may be accounted for by the lack of adequate reporting of such cases by these professionals, despite the requirement from health surveillance agencies.

Final Considerations

Although vancomycin-induced thrombocytopenia is a rare condition, it is also a significant disorder that demands attention and the rapid identification and replacement of the antimicrobial agent. The increase in the number of reports of this condition is the result of the crescent use of vancomycin, especially in the fight against multiresistant microorganisms. Although testing for vancomycin-induced antiplatelet antibodies is the most elucidated diagnostic alternative, clinical findings cannot be underestimated in patients presenting thrombocytopenia and the associated use of vancomycin.

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