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Mini Review Article

Vancomycin-Induced Immune Thrombocytopenia: A Review Based On a Clinical Case

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Abstract

Thrombocytopenia is a common condition, particularly in a critical care setting. It can result from multiple conditions, including drug-related adverse effects. The link between vancomycin and thrombocytopenia was first described in 1985, with several case reports published ever since. The main goal of this article is to summarize the available knowledge about this condition.

We performed a review of available literature in PubMed and ISI Web of Knowledge, from which pertinent information on prevalence, natural history, clinical presentation, diagnosis and management was extracted.

Vancomycin-induced immune thrombocytopenia occurs after at least six days of exposure and platelet levels return to normal eight days after vancomycin discontinuation. The mechanism behind this phenomenon seems to be an immune mediated reaction involving vancomycin-directed antibody. Patients might present with no or mild symptoms, but one third have severe haemorrhagic manifestations requiring urgent management. The correct diagnosis of this condition is essential, since the most important therapeutic measure is stopping the culprit drug. Some other treatments have been proposed, namely steroids, but with no proven benefit.

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Introduction

Mrs. AP, a 79 year-old woman with cardiovascular risk factors, congestive heart failure, chronic atrial fibrillation and chronic venous insufficiency, presents to the emergency department (ED) with a four-day history of gum bleeding, wet purpura and diffuse petechiae. Patient was discharged from hospital four days earlier after a one-month hospitalization due to lower limb infected venous ulcers. She ran a 20-day course of antibiotics (vancomycin plus ceftazidime); vancomycin serum level at discharge was 60 (normal range: 15-20 µg/mL). At ED, patient was clinically stable; blood tests showed a platelet count below 10000/µL, with no aggregates or platelet anisocytosis. It also showed renal dysfunction, with creatinine 4.3 mg/dL (patient's usual value: 0,84 mg/dL), but no metabolic acidemia, electrolyte disturbances or symptoms suggestive of hypervolemia or uraemia. Although heparin was previously used, heparin-induced thrombocytopenia was clinically unlikely and there were no circulating anti-PF4/heparin antibodies; aPTT, PT, d-dimer and fibrinogen were within the range of normal: 32.5 seconds (normal range: 28-40 seconds), 12.3 seconds (normal range: 10-14), 0.2 (normal range: <0.5) and 302 mg/dL (normal range: 150-400 mg/dL), respectively. Vigorous fluid reposition was started and thrombocytopenia was regularly monitored. On day 3, patient presented with hematochezias; platelet count was still below 10000/µL. Methylprednisolone 1 g/day for three days was then begun. The remaining hospitalization was uneventful, with no further bleeding episodes, progressive decrease of serum vancomycin levels, renal function normalization and platelet count increment (**figure 1**). Vancomycin antibody search tests were not available at our hospital. Applying the Naranjo score(1) (**table 1**), there was a probable association between thrombocytopenia and vancomycin (8 out of 13 points).

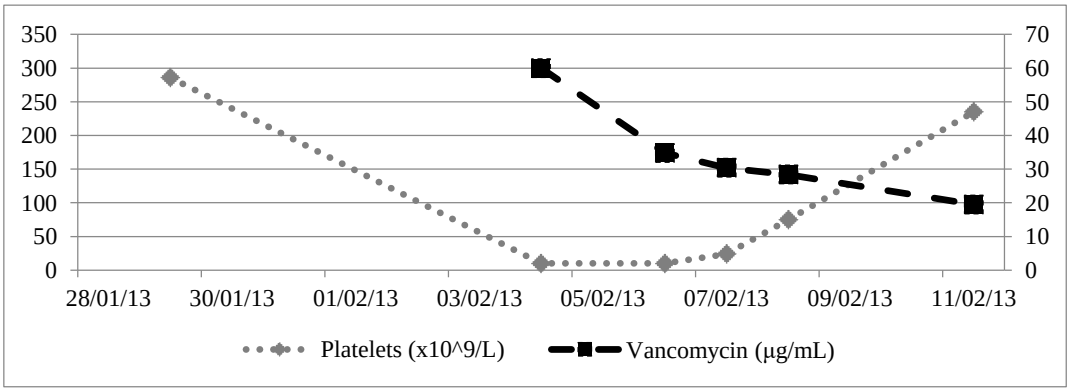

Figure 1. Evolution of vancomycin blood levels (µg/mL) and platelet count (x10^9/L) over a 15 day period of Mrs. AP hospitalization.

Table 1. The Naranjo score, as published in 1981 by Naranjo and colleagues

	Yes	No	Do not know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	

Thrombocytopenia is usually defined as a platelet count below 150000/μL(2), with further classification according to its severity: mild between 100000 and 150000/μL, moderate between 50000 and 99000/μL and severe below 50000/μL(3). Normal adult platelet count ranges from 150000 to 450000/μL, with mean values of 266000 and 237000/μL in females and males, respectively. A proportion of people has baseline platelet counts lower than 150000/μL, with no clinical manifestations. On the other hand, some individuals have absolute platelet counts in the range of normal, but a drop of at least 50% from baseline is enough for them to develop some form of haemorrhage. To the later, the rate of reduction is probably more relevant than the count itself.(4)

Prevalence of thrombocytopenia is best described in the intensive care unit (ICU) setting, where it occurs in 15-58% of patients.(5,6) Its occurrence has a negative impact on outcome, since it contributes to longer periods of mechanical ventilation, higher illness severity according to APACHE score, more organ failure development, longer hospital stays and higher mortality rates.(5–7)

The aetiology of thrombocytopenia is variable and depends on the clinical setting. It can be due to bone marrow or liver disease, nutrient deficiencies, infection, thrombotic microangiopathies, antiphospholipid syndrome, paroxysmal nocturnal hemoglobinuria, disseminated intravascular coagulation and drug related (drug induced thrombocytopenia – D-ITP).(8)

The first description of D-ITP was made in 1865 by Vipan and colleagues, and occurred after quinine use. Since then, around a hundred more drugs - among pain-killers, heparins, sedatives and anti-convulsants, chemotherapeutic agents, diuretics and antibiotics (penicillins, cephalosporins, sulfamide-derived and vancomycin) were deemed responsible for D-ITP.(9) This hard work of review has been done by James George and colleagues, with an updated list of culprit drugs published every two years and a resourceful website (www.ouhsc.edu/platelets) compiling comprehensive information about platelets and thrombocytopenia. The same author also proposed criteria for grading the association between a drug and thrombocytopenia.(10,11) Nevertheless, the incidence of this clinical entity is difficult to tell with certainty, as it ensues in settings where other aetiologies – either alone or combined – are possible and probable.(9)

D-ITP develops most commonly after seven to 14 days of continuous exposure, or after a prolonged but intermittent exposure to the culprit drug.(9,12,13) Rare case reports mention D-ITP after one or two days of exposure, presumably because the patient was immunized by previous drug usage.(14)

The mechanism of most D-ITP cases is immune-mediated platelet clearance, involving platelet-specific drug-dependent antibody formation and subsequent platelet destruction.(9) Taking quinine-induced thrombocytopenia as a model, the most frequently targeted platelet membrane epitopes are glycoprotein complexes GPIb/IX/V and GPIIb-IIIa. However, antibodies are not detected in all cases of D-ITP, even when clinical evidence is strong, which lead some authors to propose alternative mechanisms of platelet destruction: hapten-dependent antibodies; neo-epitopes generation, promptly recognized by patient antibodies; induction of auto-antibodies that react against autologous platelets even in the absence of the drug; drug binding to platelet factor 4; and immune complexes production, for which antibodies are specific.(14,15)

Thrombocytopenia tends to be clinically apparent with platelet counts of 20000/μL or less. Clinical manifestations of D-ITP vary from no symptoms to 9% of major bleeding. Some case reports suggest that 67% of patients present with mild or less than severe bleeding, such as ecchymoses and hemorrhages from nasal and buccal mucosae.

When D-ITP is suspected, all suspicious drugs must be stopped, dosage reduced or switched to a related drug with no cross-reactivity. Most signs and symptoms resume one or two days after drug discontinuation, but platelet count reaches normality usually only a week later.(14)

Vancomycin belongs to the glycopeptide antibiotic family, along with teicoplanin, telavancin, ramoplanin and decaplanin.(16) It is widely used against gram-positive bacteria, mainly methicillin-resistant *Staphylococcus aureus* (MRSA).(17) Its bactericidal activity results from preventing N-acetylmuramic acid and N-acetylglucosamine to incorporate into the peptidoglycan matrix – making cell wall permeable and fragile – and from selectively inhibiting bacterial RNA synthesis.(18,19)

Some adverse reactions have long been attributed to vancomycin, but were made evident by the more recent recrudescence of vancomycin use due to MRSA proliferation. The classically cited adverse effects are nephrotoxicity, ototoxicity and the red-man syndrome(20,21); thrombocytopenia and reversible neutropenia are usually considered rare side effects.(17,20,22)

The aim of this article is to locate, review and organize the available knowledge on thrombocytopenia induced by vancomycin when it comes to epidemiology, physiopathology, natural history, diagnostic work-up and treatment.

Material and methods

A search was performed in the PubMed and ISI Web of Knowledge databases using variable combinations of keywords *thrombocytopenia*, *vancomycin* and *side effects*. There were no restrictions concerning time of publication or article type, but the search was refined to locate articles about humans older than 18 years old. All articles written in languages other than English, Portuguese, Spanish or French were excluded.

Based on these search criteria, 76 articles in PubMed and 134 in ISI Web of Knowledge were found, totalizing 210 references. After a first triage based on title and abstract reading, 20 relevant references were selected from both databases.

Amongst the 190 other articles, three were excluded because of unavailability (not available online and no obtainable authors' address or e-mail) and 180 because they missed the scope (articles were either about vancomycin use or thrombocytopenia induced by drugs *latu sensu*).

In the end, 27 articles were analysed, 18 of which were case reports, six were retrospective studies, one was a basic science report, one was prospective and observational, and one was a matched cohort study (**figure 2**). Articles were fully read to extract the following information: vancomycin-induced thrombocytopenia (V-ITP) prevalence, time from vancomycin exposure to analytical thrombocytopenia, time from vancomycin discontinuation to thrombocytopenia resolution, risk factors, available diagnostic tools and management.

Discussion

Vancomycin was first associated with thrombocytopenia in 1985, by Walker and Heaton(23), after a case report of a 48-year-old female with end-stage renal disease due to Alport's syndrome, who was doing peritoneal dialysis and had several episodes of peritonitis. The patient was treated with vancomycin two times; the authors realized she developed spontaneous bruising and buccal bleeding after six to seven days of re-exposure to vancomycin. In that episode, her platelet count dropped to 9000/µL; after discontinuation of vancomycin it rose back to normal 18 days later.

The reported prevalence of vancomycin-associated thrombocytopenia ranges from 7,1% to 16,9%(4,18,24), but it is not clear how many cases are unequivocally due to vancomycin exposure.

The specific mechanism involved in V-ITP is still not clear, although the formation of antibodies seems to play a key role.(8,14,18,21) In fact, some case reports found anti-platelet antibodies of IgM and/or IgG classes in the serum of patients with vancomycin induced thrombocytopenia.(7,8,20,23–26) In 1990, Christie *et al*(29) showed that exposure to vancomycin elicited an immune response based on antibody production targeting glycoprotein IIb-IIIa. These findings were confirmed by Von Drygalski *et al*(30) – who managed to show no reaction when vancomycin-dependent antibodies were added to platelets' samples of a patient with type I Glanzmann's thrombasthenia (a disease characterized by the congenital absence of glycoprotein IIb-IIIa) -, and by Yamanouchi *et al*(21). Based on this theory, antibody-coated platelets were cleared from circulation by macrophages of the mononuclear-phagocytic system.

Only 20% of the samples referred for testing of platelet-reactive antibodies are positive.(30) Given this fact, either this mechanism of destruction isn't the only physiopathological explanation or diagnostic tools available are not sensitive enough.(2) In this regard, Towhid *et al*(31) purposed that vancomycin could also exert its destructive action over platelets by directly stimulating platelet apoptosis. This effect would be triggered by ceramide formation, caspase-3 activation, cell shrinkage and cell membrane scrambling.

Of note, Von Drygalski *et al*(30) described vancomycin-induced IgM antibodies in one of 451 subjects not exposed to the drug, raising the possibility that, in rare cases, naturally occurring antibodies may cause acute thrombocytopenia after a single dose of vancomycin.

Patients are usually exposed to vancomycin for at least six to eight days until thrombocytopenia ensues (range: 12 hours to 27 days).(12,30) Platelet count drops a mean of 93% from the pre-treatment value (range: 76-99%), with nadir averaging 13600/µL (range: 1000-60000/µL).(30) After vancomycin discontinuation, literature shows that all patients return to the baseline count, with the obvious exception of those who died.(30,32) The median time required for platelets to return to at least 150000/µL after vancomycin suspension was 7.5 days (range: 4-17 days).(24,30,33,34) Recovery may be delayed if there's concurrent renal failure.(30,33)

There is some debate on whether vancomycin doses are relevant to the development of V-ITP. Patel *et al*(4) described a linear exposure-response relationship between the highest vancomycin trough concentration in the first seven days and at least 50% decline in platelets from baseline. Other studies found an association between the duration of exposure to vancomycin and the extent of thrombocytopenia.(7) Marinho *et al*, on the other hand, showed that patients developing adverse reactions with vancomycin, whichever they were, received the same total dose as patients not developing them.(18)

When it comes to clinical presentation, most patients present no symptoms, 24-26% present with no clinically significant bleeding and 33% with serious bleeding, including haematuria and significant gastrointestinal haemorrhage.(30)

Diagnosis of V-ITP can be challenging, since most cases are detected in the context of critical illness and/or life threatening conditions.(9) It is considered a clinical diagnosis, demanding a high index of suspicion and a thorough pharmacological history. Using scores of probability – such as the generalist Naranjo score or the more specific George criteria, mentioned above – can be helpful.

There are some diagnostic tools for V-ITP diagnosis – staphylococcal protein A rosetting, monoclonal antibody immobilisation of platelet antibody (MAIPA), enzyme-linked immunosorbent assay (ELISA) and platelet immunofluorescence test (PIFT)(29,30) -, but they are either available only in reference laboratories or still not adequately standardised.(8) The lack of a specific diagnostic test may contribute to the underestimation of V-ITP prevalence.(21)

Treatment of this condition relies on the discontinuation of vancomycin. Some authors also propose using steroids (methylprednisolone 1 g/day IV for three days), intravenous immune globulin (IVIG, 1 g/Kg/day for two days), both high-dose steroids and IVIG, anti-Rh immune globulin and plasma exchange, the latter being reserved for critical care patients.(12,30) However, none of these approaches have proved to be of benefit so far.(2)

Platelets' transfusion can also be considered when there is risk of fatal intracranial or intrapulmonary haemorrhage. In fact, although literature describes failure of platelet transfusions on platelet count elevation(12,25,29), some authors have hypothesized that their effectiveness is compromised only in the presence of circulating vancomycin.(21)

Conclusion

Thrombocytopenia associated with vancomycin use is not uncommon, particularly in a critical care setting. However, the prevalence of cases directly attributable to the antibiotic exposure remains unknown.

The mechanism involved in platelets' destruction seems to be mainly antibody-mediated, but some authors propose alternative hypothesis, as antibodies are not always isolated.

Clinical manifestations of V-ITP are usually mild, but may be severe in a third of all cases, essentially due to gastrointestinal and/or urinary haemorrhage.

This review underlines that V-ITP is a clinical entity worth being considered, especially in critical care, since its occurrence worsens the global outcome and the management depends mostly on discontinuing vancomycin. Studies are needed to find more accurate diagnostic tools, measures to prevent this side effect and the role of steroids, IVIG and other immunosuppressive drugs.

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