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Vancomycin-Induced Thrombocytopenia as a Less Considered Contributing Cause in Differential Diagnosis of Thrombocytopenia: A Case Report

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ABSTRACT

Thrombocytopenia has been reported as an adverse effect of numerous medicines including vancomycin. Due to contribution of other suspected causes and lack of a standard diagnostic test, vancomycin-induced thrombocytopenia has been less addressed in clinical practice. In the current study, we present a suspected case initially diagnosed as heparin-induced thrombocytopenia but further workup proposed vancomycin as the offending medicine. Following discontinuation of vancomycin, the thrombocytopenia resolved which confirmed the diagnosis of vancomycin induced thrombocytopenia. We tended to highlight vancomycin-induced thrombocytopenia which is usually not considered in differential diagnosis of thrombocytopenia in comparison with heparin induced thrombocytopenia which is well known for clinicians; a scenario commonly encountered in clinical practice. This is important regard to high possibility of concomitant use of vancomycin and heparin in every day clinical practice. In accordance with educational aims of the current case, differential diagnosis of thrombocytopenia and clinical approach to thrombocytopenia is well documented in this patient.

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Introduction

Thrombocytopenia is a well-recognized adverse effect of many medicines including antibiotics (1-3). Although vancomycin is a safe and well-tolerated antibiotic, serious adverse events including hematologic side effects have rarely been reported (4, 5).Vancomycin is often overlooked as a causative agent in thrombocytopenia. Pathogenesis of vancomycin-induced thrombocytopenia (VIT) is not well understood and its diagnosis is often challenging because of concurrent contributing factors and lack of a definite diagnostic test. It seems that the final decision must be made based on clinical suspicion and ruling out all other possible causes. Besides a number of proposed modalities reported to date, discontinuation of vancomycin is the only effective approach in management of thrombocytopenia (6).

Case History

A 45-year woman with history of total abdominal hysterectomy due to uterine leiomyoma, which was performed two weeks ago, was admitted to general surgery ward with complaint of fever and wound secretions. The surgical site was debrided and empiric antibiotic therapy was started with regular daily irrigation of the wound. Vancomycin (1 g twice daily) and piperacillin/tazobactam (4.5 g three times a day) were prescribed for management of infection. Since the blood culture confirmed surgical site infection with methicillin-resistant staphylococcus aureus, piperacillin/tazobactam was discontinued. Due to reduced mobility, the patient received subcutaneous enoxaparin (40 mg daily) for prophylaxis of venous thromboembolic events (VTE) from the first day of hospitalization.

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After 7 days of antibiotic therapy, platelets count declined from 462 × 1000/mm^3 (baseline) to 4× 1000/mm^3 (Figure 1). The patient also showed signs of bleeding including hematuria, ecchymosis in hands, and petechia in legs and lips. The result of physical examination was negative for hepatosplenomegaly and lymphadenopathy. The patient did not have any history of coagulopathy or bleeding tendency in her medical records. With respect to normal WBC count and Hgb level (6040 /mm^3, 12.4 g/dl), low platelet count (25× 1000/mm^3), normal liver and renal functions, normal coagulation tests (PT: 14.2 sec, aPTT: 25 sec, INR: 1.1, D-dimer: 200 ng/ml, FDP: 2 mic/ml, fibrinogen: 100 mg/dl), and LDH level (232 u/l), hematology consultation proposed heparin-induced thrombocytopenia (HIT) and other possible differential diagnoses were ruled out (table 1). Enoxaparin was discontinued and rivaroxaban was replaced (20 mg daily) for management of HIT. Argatroban was not available due to resource limitations. However, the platelet count maintained the decreasing trend. The patient received multiple transfusions of platelet (20 units), packed red cells (5 units), and fresh frozen plasma (2 units). Given to worsening trend of platelet counts pharmacotherapy consultation was requested to rule out drug induced thrombocytopenia.

The pharmacotherapy consultation proposed low possibility of HIT after recalculation of 4T score (total score: 3). The high negative predictive value (99.8%) for patients stratified as "low probable" (based on 4tscore test), made HIT diagnosis questionable (7). Since thrombocytopenia worsened 6 days after discontinuation of enoxaparin and piperacillin/tazobactam, VIT remained the only potential cause of thrombocytopenia in this patient. Based on completion of antibiotic therapy, consecutive negative cultures, normal level of procalcitonin (0.06 ng/ml) and probability of VIT, the pharmacotherapy consultation recommended stopping vancomycin. Mildly elevated ESR (25 mm/h) and CRP (10 mg/l) could be justified by recent surgery and recent resolved infection. Noteworthy, the patient did not receive vancomycin during the previous hospitalization and the lifetime exposure was unknown. The patient did not declare history of any allergic reactions to drugs or non-drug substances. Finally, discontinuation of vancomycin led to the resolution of thrombocytopenia after three days and the patient was discharged with the platelet count of 150 × 1000/mm^3.

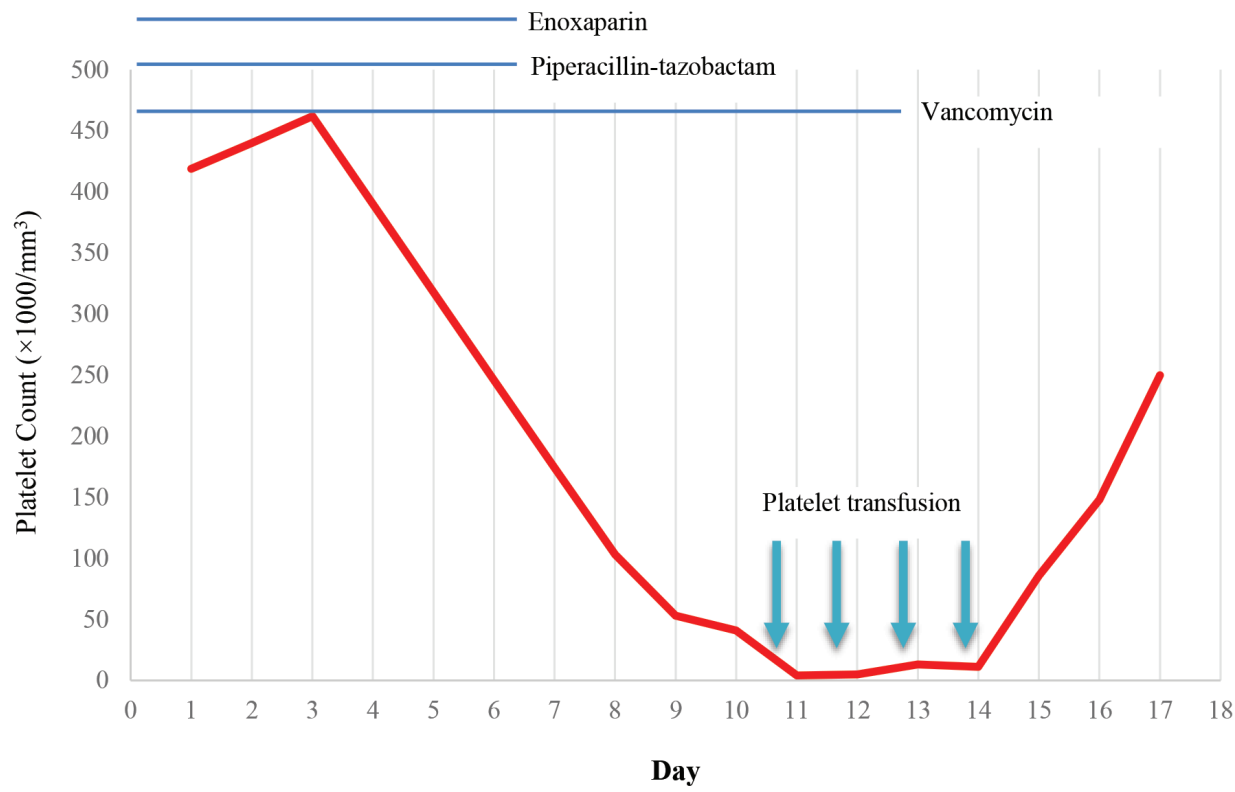

Figure 1. Platelet count trend, platelet transfusion, and antibiotic treatment during 17 days patient hospitalization

Table 1. Differential diagnosis of thrombocytopenia and the way in which these diagnoses are rejected in current case.

Differential diagnosis	Reasons to rule out
Pseudo thrombocytopenia Due to: • In-vitro platelet clumping caused by EDTA-dependent agglutinins • Insufficiently anticoagulated specimen • Presence of giant platelets (may be counted as white blood cells)	Examination of a peripheral smear prepared from a freshly-shed sample of non- anticoagulated blood
Acute Leukemia	Absence of Circulating blast cells and immature cells in peripheral blood smear and bone marrow aspiration
Marrow invasion with tumor, fibrosis, or granulomatous infection, such as tuberculosis	Absence of leukoerythroblastic blood feature (teardrop RBCs, nucleated RBCs, and early myeloid forms in the blood)
Myelodysplastic State	Absence of other cytopenias, no evidence of dysmaturation in myeloid series, erythroid or megakariositic series
Vitamin B12 or folic acid deficiency	No evidence of oval macrocytic RBCs along with hypersegmentation of neutrophils in peripheral blood smear and bone marrow aspiration/biopsy
Disseminated Intravascular Coagulation (DIC) or Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome	No evidence of microangiopathic hemolytic anemia in PBS, normal profile for hemostasis (PT, PTT and INR), and normal levels of LDH, FDP and D-dimer
Thrombocytopenia due to HIV or HCV infection	Seronegative for HIV and HCV infection
Distributional thrombocytopenia	Absence of massive transfusion
Alloimmunization	Absence of platelet transfusion history
Congenital thrombocytopenia	• Absence of bleeding and thrombocytopenia history • Absence of platelet with abnormal morphology (including platelet size, abnormal platelet granules, and/or neutrophilic inclusions)
Sepsis	Normal level of inflammatory markers, consecutive negative cultures, and no evidence of leukocytosis or leukopenia

Discussion

Thrombocytopenia is not a common adverse effect of vancomycin and its real incidence remains unclear. VIT seems to be under-diagnosed and under-reported in clinical practice and its true occurrence is higher than generally expected rates (2).

In general, a minimum period of 6 days after the first drug exposure is required to trigger an immune response and reach the platelet nadir count which can be considerably shorter on re-exposures. In our reported case, thrombocytopenia occurred 7 days after exposure which was consistent with the 5- to 10-day time frame described for classic drug induced thrombocytopenia. It is not yet clear which pharmacokinetic characteristic of vancomycin contributes to thrombocytopenia and can be considered as a predictive factor. Furthermore, it seems that duration of vancomycin utilization may play an important role in the occurrence of thrombocytopenia and VIT is not a function of cumulative doses (6).

In a study conducted by Von Drygalski et al., a mean time period of 7.2 days was reported for platelet count recovery to 150× 1000/mm^3 after vancomycin discontinuation (8). In patients with severe renal insufficiency, it may take several weeks to reach normal platelet counts since vancomycin circulates in the body for a longer time as a result of slow clearance (6). In our patient, recovery from thrombocytopenia was not achieved within 6 days of piperacillin/tazobactam and enoxaparin discontinuation and even worsening trend was observed. Platelet count returned to normal level within 3 days after stopping vancomycin.

A systematic approach combining clinical judgment and laboratory findings are required to identify the culprit medicine in drug induced thrombocytopenia. Quantification of clinical interpretation by using validated scores could be helpful to improve diagnosis and reduce diagnostic errors. Since the platelet counts were less than 10× 1000/mm3 on the day of pharmacotherapy consultation, and no evidence of erythematous/necrotic lesions at the site of injection or VTE on Doppler sonography, HIT diagnosis was rejected by consultant clinical pharmacist based on 4tscore. A causal association of vancomycin with thrombocytopenia was evaluated by the Naranjo Adverse Drug Reaction Probability Scale (9) and George et al., criteria (10). VIT was probable according to Naranjo score (score: 6) (table 2).In our patient treatment with vancomycin preceded thrombocytopenia, and complete and sustained recovery of thrombocytopenia was achieved by vancomycin discontinuation. So criterion 1 of George et al., Score which related level III evidence (possible) is met in our case (10).

Given to worsening of thrombocytopenia following

discontinuation of enoxaparin and piperacillin/tazobactam, lack of evidence for other alternative diagnoses, low probability of HIT based on pre-test 4T-score, possibility of VIT according to Naranjo and George causality assessment scales, and resolution of thrombocytopenia after vancomycin discontinuation, VIT was proposed as the final culprit in our patient.

Table 2. Assessment of causal relationship between vancomycin and thrombocytopenia in the current case based on Naranjo Adverse Drug Reaction Probability Scale (9).

Items	Yes	No	Unknown	Score
Previous conclusive reports on this reaction	+1	0	0	1
Appearance of adverse event after administrating of the suspected drug	+2	-1	0	2
Improvement of event when the drug was discontinued or administration of specific antagonist	+1	0	0	1
Reappearance of the adverse event when the drug was readministered	+2	-1	0	0
Presence of other alternative causes	-1	+2	0	2
Reappearance of the reaction when a placebo was given	-1	+1	0	0
Detection of drug in blood or other fluids in toxic concentrations	+1	0	0	0
Aggravation or alleviation of the event after increasing or decreasing dose	+1	0	0	0
positive history of similar reaction to the same or similar drugs in any previous exposure	+1	0	0	0
Confirmation of the adverse event by any objective evidence	+1	0	0	0
Total score	6			

Total score ≥ 9: definite association; 5 to 8: probable association; 1 to 4: possible association; and ≤0: doubtful association

Although discontinuation of vancomycin is the only effective approach in management of VIT, platelet transfusion may be suggested if severe thrombocytopenia and bleeding occurs. However, the survival time of transfused platelets is reduced significantly in drug induced thrombocytopenia and it does not always lead to expected enhancement in platelet counts in affected patients. Besides transfusion, other measures such as corticosteroids, intravenous immunoglobulins, rituximab, and plasma exchange have been recommended with variable benefits, but none has been reported to be consistently effective (6). Platelet level returned to normal level by discontinuation of vancomycin in our case and further intervention was not needed.

Detection of reactive antibodies is another tool which is used to confirm diagnosis of VIT. Although detection of reactive antibodies supports the diagnosis of VIT, the sensitivity of these tests is not clear and the test results may become falsely negative even in cases recognized as 'definite' according to the scoring tools (1). Despite all the limitations for antibody testing, performing these tests could enhance the likelihood of a correct diagnosis that was not carried out in our case due to access restrictions.

This case report could shed new light on the less considered culprit in drug-induced thrombocytopenia. In spite of published reports and reviews, VIT has been yet overlooked in clinical practice and its diagnosis may be overshadowed by other well-known contributing medicine in thrombocytopenia like heparin. Therefore, this report would raise awareness so this diagnosis may be made more readily in the future. Moreover, this case demonstrates the crucial role of clinical pharmacists in diagnosis and management of adverse drug-related side effects.

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