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Case Report

Vancomycin Induced Thrombocytopenia – Protracted Course in a Hemodialysis Patient

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Keywords
Vancomycin · Drug induced thrombocytopenia · End stage renal disease

Abstract
Vancomycin induced thrombocytopenia (VIT) is an uncommon side effect of vancomycin which can manifest from mild petechiae to life-threatening bleed. Decreased renal clearance of vancomycin results in prolonged thrombocytopenia by antibody-mediated platelet destruction in the presence of vancomycin. Improvement in thrombocytopenia is achieved with the elimination of vancomycin. We describe a patient with end stage renal disease who experienced a protracted course of thrombocytopenia from vancomycin. We illustrate the mechanism of thrombocytopenia and the treatment modalities used by us and those described in literature. VIT is an important differential in patients with thrombocytopenia admitted to the hospital.

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Introduction

Drug-induced thrombocytopenia is a well-recognized entity and a common hematology consult.

We present a case of protracted thrombocytopenia from vancomycin in a patient with end-stage renal disease. We also attempt to illustrate the relationship between serum vancomycin levels and platelet count, and thereby depict that immune mediated platelet destruction occurs in the presence of vancomycin. The use and utility of rituximab in persistent thrombocytopenia is also discussed.

Case Report

61-year-old male with a history of polycystic kidney disease, end stage renal disease and hepatitis C was admitted with a bleed in a right renal cyst which was treated with embolization. On admission the hemogram was normal other than hemoglobin of 11.6. He was started on antibiotics with vancomycin and Zosyn on Day 4 of hospitalization for fever. On Day 9 patient had drop in platelets to 15 (Fig. 1). As all infectious work up was negative antibiotics were stopped. Heparin induced thrombocytopenia panel was sent and was negative. Patient also had epistaxis from the nose, florid ecchymosis on the abdomen, thighs, chest wall, and upper extremities requiring platelets transfusions and nasal packing for the epistaxis. DIC panel was normal and peripheral smear showed decreased platelets with no schistocytes and normal WBC's. He was given Intravenous immunoglobulins on Day 11–13 at a dose of 1 g/kg/day. Patient was started on prednisone at 1 mg/kg/daily on Day 14. On Day 16, patient became severely hypotensive with BP 80/50 mm Hg and short of breath. CT abdomen and pelvis showed a new hemorrhage around the left kidney. Urology and IR deferred invasive procedures due to platelet count being <10 K/μL. A direct Coombs test done was positive, whereas on admission it had been negative, demonstrating hemolysis in addition to bleeding in the form of recurrent epistaxis, ecchymosis and melena causing severe anemia. Daily platelets and packed red blood cells were administered. Eltrombopag was started on Day 17 at a dose of 50 mg daily. He received hemodialysis every 48 h and darbepoetin weekly. Platelet count 1 h after transfusion showed no increase indicating platelet antibody-mediated destruction. Platelet drug dependent antibody panel was sent on Day 18 and flow cytometry demonstrated that IgG antibodies were positive in the patient sera without vancomycin; with introduction of vancomycin, both IgG and IgM antibodies to vancomycin became positive. On Day 24, 25 and 26, patient received plasma exchange in an effort to remove drug-induced antibodies. Patient also concurrently received CRRT for effecting greater vancomycin clearance. Vancomycin random levels drawn during the hospital course are depicted in Figure 1. On Day 31, patient was given Rituximab 375 mg/m^2 as platelets continued to be less than 10 K/μL. On Day 35, the platelet count doubled to 39 K/μL. On Day 37, patient became severely hypotensive with complaints of black stools and pain in the left flank. CT angiography found a recurrent bleed in the left kidney and he underwent IR guided embolization of the one of the segmental branches of the left renal artery. Platelet continued to improve and by Day 44 were within the normal range (245 u/L). On Day 47, patient was discharged with platelets of 322 K/μL and prednisone at tapering doses over 4 weeks.

Discussion

Vancomycin is bactericidal macrolide antibiotic used for suspected or confirmed gram-positive infections including methicillin resistant staph aureus [1]. Vancomycin-induced thrombocytopenia (VIT) while reported as early as 1985, is still a lesser known complication of the drug [2]. Patients had a wide spectrum of presentation, ranging from asymptomatic to florid petechial hemorrhages, ecchymoses, and oozing from the buccal mucosa, venipuncture sites to hematuria, lower gastrointestinal bleeding, and intrapulmonary hemorrhages [3–5]. In contrast to other drug-induced thrombocytopenia, bleeding is more severe and wet purpura have been commonly reported in the literature [6]. The mechanism of thrombocytopenia which has been largely proposed is a quinine type of antibody mediated destruction [7]. Vancomycin's interaction with platelet glycoprotein IIb/IIIa results in an antibody which weakly targets GP IIb/IIIa on the membrane; however, the presence of vancomycin provides the complementary electrostatic charges required to increase the binding affinity between the glycoprotein on the platelets and binding region of the antibody causing cell lysis [6–8]. Platelet destruction occurs only in the presence of vancomycin; hence, discontinuation of the drug followed by its renal clearance caused resolution of thrombocytopenia in most reports [3]. Testing for drug-dependent platelet antibody is recommended and is done in a reference lab (Blood Center of Wisconsin). The test uses O group platelets and incubates it with the patient's sera; after an hour of incubation, the platelets are washed with or without the implicated drug solution. Human IgG bound to the platelets is detected using anti Fc Ig derived from goats. These tests, though widely done are neither validated or standardized [9]. Poor responsiveness to platelet transfusions is a feature of this disease due to rapid destruction of platelets [4]. The median time for resolution of thrombocytopenia (platelet count of at least 150,000 per cubic millimeter) after vancomycin was stopped was 7.5 days [6]. In our patient, the duration of thrombocytopenia was 32 days from discontinuation of vancomycin. The prolonged duration was likely from decreased serum clearance of vancomycin due to end-stage renal disease and poor clearance of vancomycin with low flux hemodialysis [6]. Vancomycin is significantly dialyzable using high flux membranes for hemodialysis such as polysulfone, polyacrylonitrile, etc. and with continuous renal replacement therapy: hence, the rationale behind CRRT use in our patient. We used prednisone, IVIG, thrombo-mimetic agent eltrombopag and plasma exchange to treat the thrombocytopenia. The above modalities have all been used in published studies and did not show improvement in thrombocytopenia which was similar to our experience [3]. Our patient also had IVIG-mediated hemolysis in addition to bleeding, which complicated the clinical picture this was evidenced by a direct Coombs test done on admission which was negative, but which became positive after IVIG was given.

In patients with thrombocytopenia, the etiology is often unclear and the differential is broad, being comprised of sepsis, disseminated intravascular coagulation, TTP, atypical HUS, heparin- induced thrombocytopenia, other drug-induced thrombocytopenia, and post-transfusion purpura. In vancomycin induced thrombocytopenia, median time to development on thrombocytopenia varied ranging from 2–21 days after initiation of vancomycin [10–12]. In many reports, the thrombocytopenia developed with the first exposure to vancomycin, whereas in other occurrences it required two exposures. The time to nadir platelet count was on an average 8 days and the nadir varied from 100,000 to 2,000 K/mL [3, 6] In heparin-induced thrombocytopenia, the median time for development of thrombocytopenia is 7–10 days after exposure to heparin, a high 4T score and then later positive antibodies to heparin on the ELISA testing point to the diagnosis [13]. Post transfusion purpura is severe thrombocytopenia by antibodies to platelet HPA-1a antigen. These antibodies are generated by

alloimmunization from blood transfusions, multiparity, etc. These factors should be considered, in addition to testing for HPA genotyping and HPA-1a antibody in the patient's sera. Unlike VIT, PTP responds to intravenous immunoglobulin and plasma exchange [14]. Leukocytosis in sepsis, anemia from hemolysis and renal dysfunction seen in TTP and atypical HUS, schistocytes on peripheral smear, and coagulation derangements are other clues to delineate other possibilities. A careful history of both home and hospital-administered drugs is imperative.

Rituximab (375 mg/m^2, single dose), an anti-CD-20 monoclonal antibody was given to our patient, after which his platelet count doubled within 96 h and improved to normal thereafter. However, he had received 3 cycles of CRRT and his vancomycin serum levels were less than 0.8 mcg/mL, prior to the initiation of rituximab. As this is a single patient report, it is uncertain if the resolution of thrombocytopenia was directly a result of rituximab versus a gradual improvement secondary to elimination of serum vancomycin and thereby, decreased platelet destruction. We found only one reported case in which rituximab was used specifically for refractory VIT [15]. This case was an ESRD patient with VIT persisting for greater than 30 days; however, in contrast to our patient he was given weekly rituximab (375 mg/m^2) for a total for 4 doses before platelet count returned to normal. Rituximab, an anti-CD 20 monoclonal antibody, is hypothesized to bind to CD 20 on the memory B cells and block the synthesis of drug-induced antibodies to Gp IIb/IIIa [15]. In patients with persistent severe thrombocytopenia (platelet count <10,000 K/μL) and or major bleeding, the use of rituximab earlier, rather than later, in the hospital course is perhaps a more astute decision.

Drug sensitivity persists indefinitely once the patient develops DITP. In several reported cases on repeat exposure to vancomycin, the platelet count has plunged to critical levels [10, 16]. Patients should be educated and their chart labeled as having an allergy to the drug causing DITP, which should never be used. Drug-dependent antibodies typically do not cross-react with different drugs that have a similar molecular structure and so different drugs from the same class can be used [7].

In some reported cases, the thrombocytopenia developed only on the second exposure to vancomycin and it has been postulated that prior sensitization to vancomycin was present [6, 17]. In this case, the serum of the patient prior to vancomycin showed IgG antibodies to vancomycin and the post-exposure serum showed both IgG and IgM antibodies to the drug [17]. The thrombocytopenia in these reported cases developed within hours to a day of reintroduction to vancomycin; thus, it is an anamnestic antibody response. However, in the majority of cases, there is no history of prior vancomycin use reported. We hypothesize that the sensitization and the anamnestic response happens during the same single exposure such as occurred in our patient, when thrombocytopenia developed after a few days of treatment with vancomycin. Whereas if the development of thrombocytopenia is rapid, it might be worthwhile to explore if there was a history of vancomycin use. As per existing reports, there have been no risk factors identified that can predict which patients will develop severe thrombocytopenia in exposure to vancomycin. Thus, it is crucial to consider this etiology among our differentials of thrombocytopenia.

Conclusion

Vancomycin-induced thrombocytopenia, though well reported, is a less clinically recognized entity. It is important to be aware of this adverse effect as the thrombocytopenia is often severe, with significant bleeding. In an era where broad spectrum antibiotic coverage is

becoming the norm, it is important to consider if gram positive, specifically MRSA coverage, is required before starting vancomycin. It is equally critical never to administer vancomycin in patients who experienced thrombocytopenia from it.

Statement of Ethics

Patient is deceased. Patient's son has given verbal consent to publish the case report.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Nisha Ajit did the literature review, wrote and edited the manuscript. She was also involved in the patient management. Sindhu Priya Devarashetty reviewed the literature and wrote the manuscript. Samip Master supervised the patient management and reviewed the manuscript.

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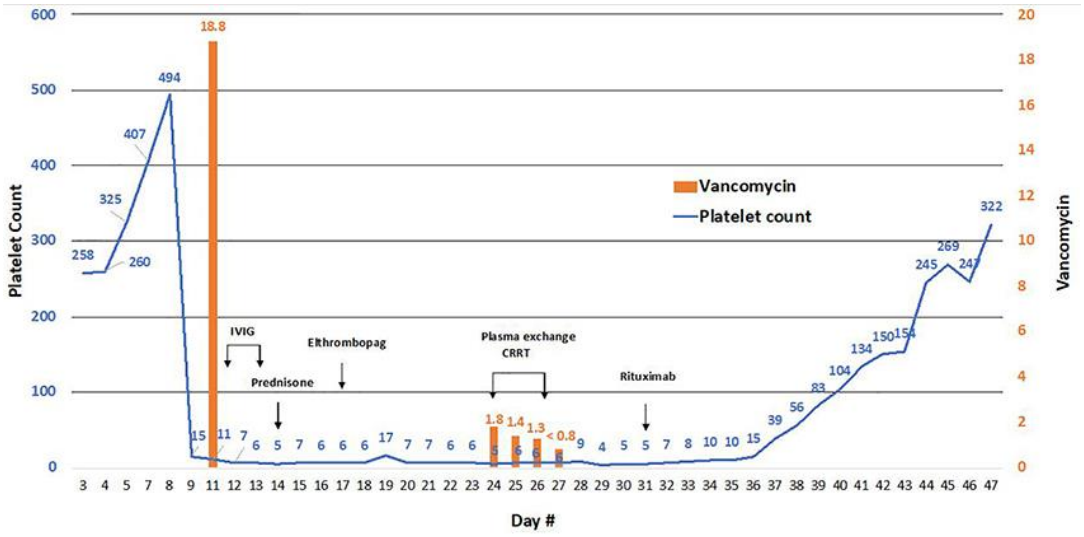

Fig. 1. Graph depicting the platelet counts and vancomycin random levels during hospitalization in reference to timing of treatment modalities.