Vancomycin: A Friend or a Foe- A Case of Life Threatening Thrombocytopenia Induced by Vancomycin

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Abstract

Thrombocytopenia is a rare side effect of vancomycin, an antibiotic that is widely used to treat Gram-positive bacterial infections particularly Methicillin-Resistant Staphylococcus Aureus (MRSA) infection. A 65-year-old male was treated with vancomycin for hospital-acquired pneumonia after an elective abdominal surgery. After only 7 doses of vancomycin, his platelet count dropped to a nadir of $1x\ 10^9$/L (baseline: platelet count 284 x 10^9/L) manifesting as visible mucosal bleeding, bleeding into colostomy bag and haemodynamic instability due to excessive blood loss. Vancomycin induced thrombocytopenia was diagnosed after exclusion of other causes and laboratory investigations supported the diagnosis. Reversal of the thrombocytopenia was achieved after stopping vancomycin and with intravenous immunoglobulin, methylprednisolone and multiple platelet transfusions. Vancomycin induced thrombocytopenia is an under recognized cause of thrombocytopenia in the hospitalised patients. Clinicians should be cognizant of this entity, and a definitive diagnosis should be sought if feasible by immunological testing and flow cytometry.

Keywords: Vancomycin; Thrombocytopenia; PIFT; MAIPA

Introduction

Vancomycin is a glycopeptide antibiotic used in the treatment of gram-positive infections particularly in Methicillin-Resistant Staphylococcus Aureus (MRSA) infection. The most common adverse reaction to vancomycin is red man syndrome, which is a histaminergic reaction causing a rash on the upper torso, neck, and face after rapid infusion of the drug. Rarely vancomycin has been associated with thrombocytopenia. In this entity, platelet destruction appears to be immune-mediated, often resulting in a precipitous drop in platelet count over a short period of time. Vancomycin is often clinically overlooked as a cause of thrombocytopenia, especially in a scenario of sepsis or when there is use of heparin. We report a proven but unusual case of vancomycin-induced thrombocytopenia and its reversal after discontinuation of vancomycin. The etiology is believed to be the induction of drug-dependent antibodies, which in turn cause immune-mediated destruction of platelets.

Case Presentation

65-year-old male was admitted for an elective bowel surgery to remove adenocarcinoma of ascending colon. The procedure was completed with no immediate post-operative complications. He was previously fit without any major co-morbidity and was on no regular medication. He reported allergies to penicillin. The patient was started on a prophylactic dose of Enoxaparin on the evening of surgery (8 hours Post-operatively). On day 2, he developed tachycardia with a heart rate of 120 bpm and he became hypoxic with oxygen saturations of 70% on room air. He remained normotensive and a febrile. Auscultation of the chest revealed reduced air entry at the bases as well as coarse crepitation over mid-zones bilaterally. A chest X-ray performed that showed bi-lateral consolidation. Intravenous vancomycin 1000 mg twice daily and gentamicin 300 mg once daily were started according to the hospital protocol for the treatment of penicillin allergic hospital-acquired pneumonia. However, his respiratory symptoms and signs did not improve despite antibiotic treatment. As a result a Computed Tomography Pulmonary Angiography (CTPA) was performed on day 3 post surgery that demonstrated bilateral Pulmonary Emboli (PE) along with bi-lateral lower lobes consolidation. He was started on rivaroxaban 15 mg twice daily for the PE. Blood culture was negative, wound swab was negative and Sputum culture grew *Pseudomonas aeruoginosa* sensitive to gentamicin. The patient's condition improved slowly following antibiotic treatment. His platelet count was 284 x 10^9/L and haemoglobin (Hb) 118 g/L before starting the antibiotic and rivaroxaban. on day 4 i.e. after 7 doses of vancomycin, 3 doses of gentamicin and 5 doses of

rivaroxaban the patient developed heavy mucosal bleeding, bleeding in colostomy bag. A repeat Full Blood Count (FBC) a platelet count of dropped to 35 x 10^9/L and Hb level of 85 g/L. Rivaroxaban was with held and all the clotting profile abnormalities were corrected with 4 units of Fresh Frozen Plasma (FFP) infusion. Despite that, bleeding worsened and the patient became haemodynamically unstable (blood pressure 83/50 mmHg, heart rate 120 bpm, O2 saturations 97% in room air) and a repeat FBC showed a platelet count of 2 x 10^9/L, Hb dropped to 69 g/L, INR 1.2, APTT 1.1, fibrinogen 3.9, renal profile were normal. Blood film showed marked thrombocytopenia without any platelet clump and no red cell fragments. He was resuscitated with 2 units of blood and 2 pools of platelets and he was transferred to Intensive Care Unit (ICU). Repeat platelet count after 2 pools of platelets was 1 x 10^9/L. The differential diagnoses considered were Disseminated Intravascular Coagulopathy (DIC), Heparin-Induced Thrombocytopenia (HIT), Immune Thrombocytopenia (ITP) or Vancomycin-Induced Thrombocytopenia (VITP). DIC was excluded clinically as apart from thrombocytopenia all other clinical and laboratory markers were not suggestive of the diagnosis. Although bleeding may be a side effect of oral anticoagulants, rivaroxaban is not a recognized cause of thrombocytopenia and, as such, was excluded as a cause of low platelet count. Although HIT is a recognized side-effect of enoxaparin, patient received only 2 prophylactic doses. And with a low Pre-test probability and negative High sensitivity HIT ELISA screen it was also excluded. Since it was thought to be the offending agent, Vancomycin was discontinued and gentamicin continued to cover *Pseudomonas aeuroginosa*. Despite multiple pools of platelet transfusion platelet increment remained poor. Therefore patient was started on 1000 mg of IV methylprednisolone and 70 g intravenous immunoglobulin infusion. Platelet count recovered fairly quickly thereafter reaching 165 x 10^9/L after 5 days. Blood sample was sent to National platelet immunology laboratory, Bristol, UK for platelet immunological assays which detected platelet directed IgG as well as IgM antibodies suggesting autoimmune thrombocytopenia due to vancomycin (Table 1-3).

Discussion

Vancomycin, a glycopeptide antibiotic originally derived from *Streptomyces* (Norcadia) *orientalis*. Thrombocytopenia is a rare complication of vancomycin. Antibiotic therapy with vancomycin is a rare and perhaps overlooked cause for new-onset thrombocytopenia in hospitalized patients. Only a limited number of published cases of thrombocytopenia induced by vancomycin have been found in the literature [1-4]. This report described a patient with VITP associated with life-threating bleeding. VITP was suspected from his clinical course and the diagnosis was made by the combination of exclusion of other causes as well as detection of vancomycin-dependent antiplatelet antibody by immunological assay [Table 1-3]. However, detection of vancomycin-dependent antiplatelet antibody with flow cytometry can also be used if available as this test can definitively diagnose vancomycin induced immune thrombocytopenia [5]. The mechanism of vancomycin-induced thrombocytopenia is considered to be immune-mediated, as suggested by its association with a specific drug-dependent anti-platelet antibody [1,4]. These antibodies bind to the platelet glycoprotein forming a complex that is then engulfed and cleared by macrophages in the phagocytic system [6]. This adverse reaction seems to be duration dependent with the mean time to platelet nadir count of 8 days (ranging 7 to 10 days) in reported cases [3,5,7]. The interval may be significantly shorter in re-exposure to the drug. Patients presenting with bleeding,

Table 1: Platelet HLA antibody Result.

Class	Method	Result
HLA Class I	Antibody Screening by Luminex	Negative
HLA Class II	Antibody Screen by Luminex	Negative

Comments: HLA Class I & Class II antibodies were not detected by Luminex in the serum from this patient.

Table 2: Indirect Platelet Immunofluorescence Test (PIFT).

Method	Result	Freq.	Specificity	Ab Class
Indirect PIFT	Positive	2/2	Unidentified	IgG+IgM

Comments: Platelet reactive antibodies were detected in the patient's plasma without the addition of the drug into the test system. However, the test was unable to identify the specificity of the antibodies detected in the indirect PIFT.

Table 3: Platelet Antibody Test Result.

Method	Result	Freq.	Specificity	Ab Class
Indirect PIFT	Positive	4/5	Unidentified	IgG
Indirect MAIPA (Gp IIb/ IIIA)	Negative	0/4	Negative	IgG
Indirect MAIPA (Gp Ia/IIa)	Negative	0/2	Negative	IgG
Indirect MAIPA(Gp Ib/Ix)	Negative	0/2	Negative	IgG
Indirect MAIPA (HLA)	Negative	0/1	Negative	IgG
Indirect MAIPA (CD109)	Negative	0/2	Negative	IgG
Indirect PIFT (additional)	Positive	5/5	Unidentified	IgM

Comments: Platelet reactive IgG & IgM antibodies were detected in the patient's serum in PIFT, antibodies to the major platelet glycoproteins (as above) were not detected in the same serum sample from this patient by MAIPA. These results support a diagnosis of Autoimmune Thrombocytopenia (AITP). Laboratory also mentioned that in their laboratory, serum auto antibodies are only found in about 20 to 40% of AITP. Determination of platelet associated immunoglobulin's is generally a better indicator of platelet autoantibody status but it is not possible to perform this investigation if the patient has received a platelet transfusion in the preceding 10 days as it was the case in our patient.

manifested as petechial haemorrhages or ecchymoses [4]. In our patient, only 7 doses of vancomycin were administered before platelet count fell. Previous studies have demonstrated an exposure-response relationship between vancomycin trough concentration and the severity of thrombocytopenia contrary to our patient as all the vancomycin blood levels in this patient were below therapeutic drug range [8]. VITP should be considered in any patient who develops severe thrombocytopenia (nadir platelet count less than 20 × 10^9/L) with bleeding complications that begins 7 to 10 days after starting daily administration of vancomycin. Positive laboratory testing demonstrating drug-dependent platelet reactive antibodies can confirm the diagnosis as in our patient but, a negative test does not rule it out [9]. To help establish the likelihood that a particular drug is the cause of the thrombocytopenia, several clinical scoring systems have been developed [10-12]. In 1982 Hackett et al. [10] proposed the following criteria: (1) Thrombocytopenia developed while the patient is taking the drug, resolved once the drug is stopped and did not recur while the patient was off the drug; (2) other causes of thrombocytopenia were excluded; (3) the thrombocytopenia recurred upon re-administration of the drug; and (4) an *invitro* test for drug-dependent platelet antibodies was positive. A positive re-challenge or positive laboratory test was sufficient to confirm the diagnosis. In our patient points 1, 2 & 4 were met to make a diagnosis of VITP. In the literature, drops in the platelet count of up to 93% have been reported [4]. This case showed almost total destruction of platelet (nadir platelet count 1 x 10^9/L). Vancomycin-induced antibodies have been shown to persist for months in the absence of exposure to vancomycin and several cases of recurrent thrombocytopenia after vancomycin

re-challenge have been reported [13-16]. VITP is drug-dependent, as discontinuation of Vancomycin frequently results in a timely return to baseline, pre-exposure platelet levels. Gradual recovery of platelet count usually occurs over a period of approximately 5-7 days after stopping vancomycin; however, recovery may be delayed in patients with renal failure presumably due to delayed excretion of vancomycin [9].

Conclusion

Vancomycin induced thrombocytopenia is an under recognized cause of thrombocytopenia in the hospitalized patients. Clinicians should be cognizant of this entity, and a definitive diagnosis should be sought if feasible.

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