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VANCOMYCIN-INDUCED THROMBOCYTOPENIA IN A COMPLEX HOSPITALIZED PATIENT.

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ABSTRACT

Vancomycin is a common antibiotic used in hospitalized patients with well-established side effects. Vancomycin induced thrombocytopenia is a lesser known adverse effect that is often overlooked and can complicate the recovery of hospitalized patients. The diagnosis is challenging as it requires a temporal relationship with the drug and exclusion of other causes. Testing for vancomycin-induced platelet antibodies can be useful when multiple causative drugs are suspected. The following case describes a rare case of a very severe although asymptomatic vancomycin-induced immune thrombocytopenia that resolved after discontinuation of the drug. It is hoped that this report will promote increased awareness amongst readers about the diagnosis and management of vancomycin induced thrombocytopenia.

Keywords: Drug-induced, Thrombocytopenia, Methicillin-resistant staphylococcus aureus, Vancomycin.

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Vancomycin is a common antibiotic used in hospitalized patients with well-established side effects. Vancomycin induced thrombocytopenia is a lesser known adverse effect that is often overlooked and can complicate the recovery of hospitalized patients. The diagnosis is challenging as it requires a temporal relationship with the drug and exclusion of other causes. Testing for vancomycin-induced platelet antibodies can be useful when multiple causative drugs are suspected. The following case describes a rare case of a very severe although asymptomatic vancomycin-induced immune thrombocytopenia that resolved after discontinuation of the drug. It is hoped that this report will promote increased awareness amongst readers about the diagnosis and management of vancomycin induced thrombocytopenia.

Keywords: Drug-induced, Thrombocytopenia, Methicillin-resistant staphylococcus aureus, Vancomycin.

INTRODUCTION

Vancomycin, a glycopeptide bactericidal antibiotic, is used primarily to treat resistant gram-positive pathogens and for prosthetic joint infections. Vancomycin use has increased in recent years due to an increased incidence of coagulase-negative staphylococcal (CNS) and methicillin resistant staphylococcus aureus (MRSA) infections.¹ Despite its effectiveness in the treatment of resistant gram-positive bacterial infections, vancomycin has a number of adverse effects including ototoxicity, nephrotoxicity, anaphylactoid reactions ('red-man syndrome'), neutropenia, and, rarely, thrombocytopenia.²

Vancomycin-induced thrombocytopenia (VIT) has increasingly been reported as a

cause of thrombocytopenia in the medical literature but the true incidence is not well defined. The estimated incidence of any drug-induced thrombocytopenia reported in literature is around 10 cases per million population/year, suggesting that VIT would be even rarer.³ However, this incidence is predicted to rise given reports of increased vancomycin prescribing of up to 10-25-fold in the last decade for treatment of an increasing number of resistant staphylococcal bacteremia related to implantation of foreign devices such as central lines and joint prostheses.⁴

We report here a case of VIT in a 58-years-old male patient who received vancomycin for a coagulase negative staphylococcal bacteremia complicating a central line insertion. Diagnosis of VIT was established based the temporal association of the development of thrombocytopenia 10 days after initiating intravenous vancomycin therapy, which resolved upon cessation of intravenous vancomycin and discussed the management of this

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condition.

CASE REPORT

A 58-year-old man was transferred from a peripheral district hospital for a non-healing diabetic foot ulcer, despite intravenous amoxicillin/ clavulanic acid antimicrobial therapy. This was in the setting of sub-optimally controlled diabetes mellitus (HbA1c 10.4%), treated hypertension, persistent microcytic anaemia, chronic atrial fibrillation, a pace-maker in-situ for sick sinus syndrome and a history of diverticular disease. His medications on admission were atorvastatin 20mg nocte, bisoprolol 5mg mane, furosemide 40mg mane, glicazide 80mg mane, losartan 50mg daily, omeprazole 20mg daily and basal bolus insulin totaling 24 units daily. There were no known drug allergies.

The patient's antimicrobial therapy was subsequently changed to piperacillin-tazobactam due to a growth of a resistant *Klebsiella pneumoniae* from the wound swab and he required drainage of a lower limb abscess found on imaging. Additionally, the patient's care was complicated by atrial fibrillation with rapid ventricular rate, electrolyte disturbances (Mg 0.4 mmol/L, K⁺ 2.8 mmol/L) due to proton pump inhibitor, diuretic use and inadequate oral intake, microcytic anaemia (Hb 7.1 g/dL), hypoglycemic episodes, mild acute hepatic injury, and widespread oedema due to hypoalbuminaemia (18g/L).

He gradually stabilized with on-going fluid resuscitation and blood transfusions via femoral central line, correction of his electrolyte disturbances, cessation of insulin and oral hypoglycemic agents and rate controlling his atrial fibrillation with transient use of digoxin therapy. However, on day 13 of admission, further investigations for persisting hypoglycemia and mild hyponatraemia revealed a blunted cortisol response to a short synacthen test. Glucocorticoid insufficiency due to exogenous steroid use was suspected based on

further questioning whilst a CT abdomen performed ruled out adrenal infarcts or haemorrhage. He was subsequently commenced on replacement hydrocortisone 60mg / day as per advice from the Endocrine team.

Blood cultures taken on day 14 of admission for a new onset febrile illness revealed a growth of multi-resistant coagulase negative staphylococcus (CONS) requiring commencement of vancomycin therapy via a pre-existing PICC line and removal of the femoral central line. The patient then improved in terms of symptoms and hemodynamic monitoring but subsequently, a petechial rash was noted in the patient's lower limbs corresponding with a dropping platelet count on day 23 of admission. The thrombocytopenia occurred 10 days after vancomycin was commenced (platelet nadir 6×10^3 /uL).

Vancomycin induced thrombocytopenia was suspected given the temporal association and the drug was stopped due to clinical recovery of the patient's sepsis. Two pooled units of platelets was transfused to maintain the platelets over 20×10^3 /uL with transient increment in his platelets. [Figure 1](#) illustrates the temporal relationships of vancomycin therapy to dropping platelet levels from admission to discharge.

Other differential diagnoses of other drug-induced thrombocytopenia, disseminated intravascular coagulation, consumption thrombocytopenia and microangiopathic thrombocytopenia were investigated and excluded. These differential diagnoses were excluded on the basis of a lack of temporal association of other drugs, normal coagulation studies, vitamin B12 level, non-reactive hepatitis panel, negative cytomegalovirus and Epstein Barr virus IgM by PCR, normal blood film, lack of bleeding and stable anaemia as well as normal auto-immune hemolysis screen. The patient was receiving subcutaneous

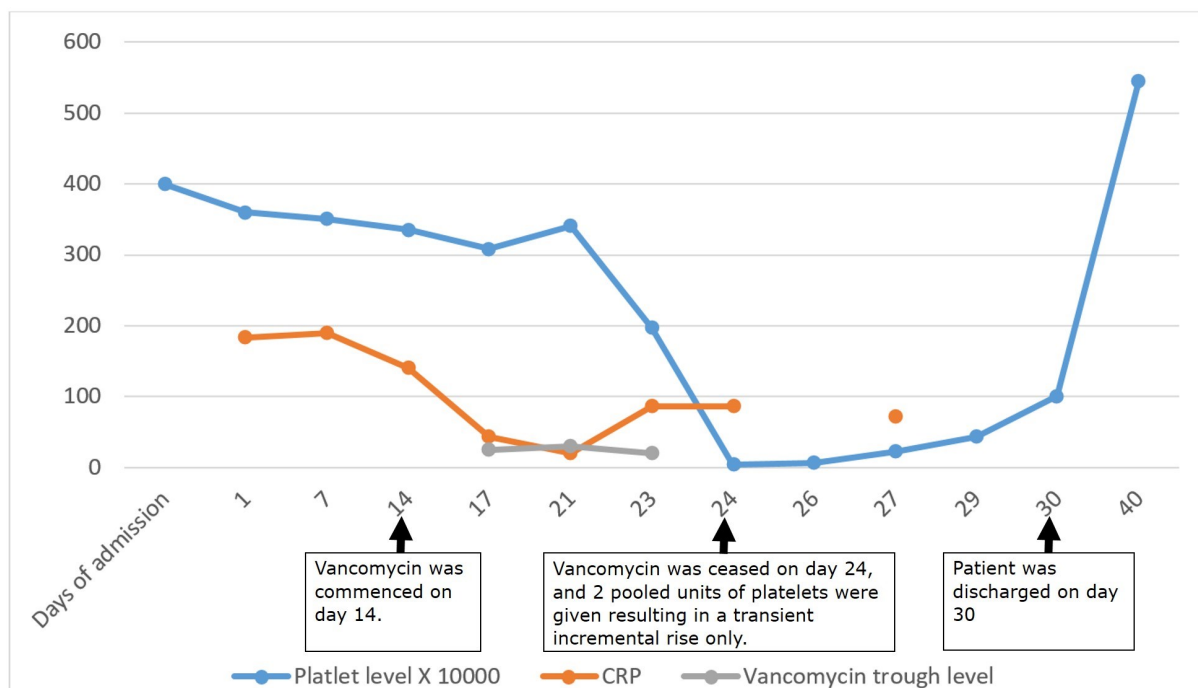


Figure 1: Graph of days since admission and platelet level, CRP and Vancomycin use.

ous fondaparinux 2.5 mg daily for prophylaxis of deep vein thrombosis therefore heparin induced thrombotic thrombocytopenia was also excluded. Fortunately, his platelet count recovered gradually 8 days after cessation of vancomycin to $101 \times 10^3/\mu\text{L}$ and had mild thrombocytosis (plt $544 \times 10^3/\mu\text{L}$) on follow up 10 days after discharge.

DISCUSSION

Drug induced thrombocytopenia can be categorized into three groups, a) antibody binding to a complex of drug or drug metabolite and platelet glycoprotein (e.g., quinine, vancomycin), b) antibody binding to a drug-exposed neoepitope in the GPIIb/IIIa complex (e.g., eptifibatide, tirofiban, abciximab) and c) antibody recognizing drug-bound platelet factor 4, resulting in platelet activation and thrombosis (e.g., heparin).^{5,6} Commonly drugs associated with drug induced thrombocytopenia include quinine, hydralazine, ampicillin and sulfonamides.^{7,8} Other agents implicated are listed in the table attached as [supplementary text](#).

Criterion and level of evidence for establishing a causative relationship of a drug-induced thrombocytopenia is available from the reviewed medical literature with our patient fulfilling criteria for level 2 evidence of VIT ([Table I](#)).⁹

Prominent features of VIT have been described in recent studies.¹⁰ Patients affected are usually exposed to vancomycin in a non-dosage dependent manner for at least six days with a subsequent drop in platelet counts by a mean of 93% from pre-treatment value. As seen in our patient, platelet nadir counts declined dramatically to an average of $13 \times 10^3/\mu\text{L}$ about 8 days after initiation vancomycin treatment (range of 1 to 27 days).

Recovery of platelet counts towards pre-treatment values occur by 6-8 days after discontinuation of vancomycin as seen in a case series whereby 90% (26/29) of patients had platelet recovery to normal counts after cessation of the drug.¹⁰ Other features of VIT which was present in our patient include the failure of platelet transfusion to elevate platelet levels in most patients (77% to 79%) but

Table 1: Criteria for drug induced thrombocytopenia (adapted from medical literature⁹).

Criteria	Description
a	Suspected drug preceded thrombocytopenia, and complete resolution of thrombocytopenia occurred after drug discontinuation
b	Suspected drug was the only drug used before the onset of thrombocytopenia, or other drugs were continued or reintroduced at a later stage with a sustained normal platelet count
c	Other causes of thrombocytopenia were ruled out
d	Re-exposure to the candidate drug resulted in recurrent thrombocytopenia
Level of Evidence	Description
1	Definite – criteria a, b, c and d are met
2	Probable- criteria a, b and c are met
3	Possible- criteria a is met
4	Unlikely- criteria a is not met

fortunately did not have severe bleeding (34% of patients).¹⁰

Vancomycin-induced platelet antibodies could be tested for confirmatory purposes when the diagnosis of VIT is not clear. However, these antibodies may occur even without isolation in-vitro of a drug dependent antibody.¹¹ These antibodies can also persist for months following exposure to vancomycin and even longer in patients with renal failure, presumably because of delayed clearance. It is postulated that on re-exposure to vancomycin, patients with VIT may have a more rapid decline in platelet counts due to amnesic immune response despite no detectable circulating antibodies to vancomycin. Thrombocytopenia in these subsets of patients can occur rapidly within 1 to 3 days.^{12,13}

The patient described above underlines an example of the complexities of managing multiple challenging and often inter-related issues in a hospitalized patient with multimorbidity with an isolated thrombocytopenia without microangiopathic haemolysis. After the exclusion of other causes of thrombocytopenia, VIT was diagnosed and vancomycin was stopped. The patient was monitored for any breakthrough infection and discharged after clinical recovery given the lack of alternative antibiotic options.

CONCLUSION

It is essential to be able to recognize drug-induced thrombocytopenia in hospitalized patients. The speed of the decline of platelets, a temporal association and the clinical status of the patient may give clues to the underlying aetiology. It is important for clinicians to understand the concept of VIT, have a high index of suspicion if thrombocytopenia occurs in patients on vancomycin. Regular monitoring of complete blood count and renal function is warranted. Prompt resolution of thrombocytopenia occurs if the diagnosis of VIT is made in a timely manner, and if vancomycin is discontinued. Once VIT is established, this drug sensitivity would persist permanently and patients should be advised to avoid vancomycin.

Financial disclosure or conflict of interest

The authors of this manuscript certify that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Consent

We have acquired consent from patient for all photographs of patients' body parts and imaging to be used in publication purpose.

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Supplementary Table: Drugs implicated in drug-induced thrombocytopenia on various medical specialties.

Drugs implicated in drug-induced thrombocytopenia on various medical specialties						
Cardiology	Neurology	Haematology & Oncology	Infectious Disease	General Medicine	Psychiatry	Miscellaneous
Aspirin/ Clopidogrel	Aspirin/ Clopidogrel	Bortezomib	Acyclovir	Acetamino-phen	Clonazepam	Methyldopa
Gp IIb/IIIa blockers (abcidimab, tirofi-ban, eptifibatide)	Butobarbital	Allopurinol/ colchicine Deferoxamine	Ampiillin/ Amoxycillin	Cimetidine/ Famotidine/ Pantoprazole/ Ranitidine	Haloperidol	Gold
Atorvastati/ Simvastatin	Carbamazepine	Ferrous Sulfate and Gluconate	Cephalosporins (Ceftriaxone , Cefotetan, Cefazolin)	Desmopressin	Amitriptyline	INF-alpha
Amlodipine	Diazepam	Filgastrim	Ciprofloxacin/ Levofloxacin	Diclofenac	Lithium	Danazol
Amiodarone	Lamotrigine	Oxaliplatin	Azithromycin/ Clarithromycin	Glucagon	Mirtazepine	Infliximab
Bumetanide/ Furosemide	Levetiracetam	Protamine sulfate	Fluconazole	Glyburide	Oxcarbezepine	Hepatitis B vaccine
Captopril/ Enalapril	Phenytoin	Rituxumab	Isoniazid/ Rifampicin/ Ethambutol	Ibuprofen/ Indomethacin/ Naproxen	Olanzapine	MMR vaccine
Carvedilol	Valproic acid	Transtuzomab	Linezolid	Lidocaine		Prednisolone
Chlorothiazide/ Hydrochlorothiazide	Acetazolamide	Bleomycin	Penicillin	Morphine		Sulfasalazine
Digoxin/Cardizem	Bromocriptine	Fludarabine	Piperacillin- Tazobactam	Indansetron		
Hydralazine			Quinidine/ Quinine			
Nadolol			Sulfamethox- azole- trimethoprim			
Procainamide			Vancomycin			

Drugs in bold letters are more commonly implicated.

Adapted from Ali N and Auerbach HE. New-onset acute thrombocytopenia in hospitalized patient: pathophysiology and diagnostic approach. *Journal of Community Hospital Internal Medicine Perspectives.* 2017;7(3):157-167.