Clinics in Surgery

Case Report
Published: 12 Jun, 2020

Unusual Combination of Polypharmacy Induced Thrombocytopenia in a Patient with Complex Diabetic Foot Disease

*Mariah Theresa Mwipatayi[1], Joseph Faraj[2], Jema Hua Xu[3], Donna Angel[2] and Bibombe P Mwipatayi[2,3,4]**

[1]University of Buckingham Medical School, Hunter Street, UK

[2]Department of Vascular Surgery, Royal Perth Hospital, Australia

[3]Department of Vascular Surgery, Hollywood Hospital, Australia

[4]Department of Surgery, University of Western Australia, Australia

Abstract

Background: Thrombocytopenia is a well-known complication of heparin and, to a lesser extent, vancomycin. Few case reports exist for thrombocytopenia induced by a combination of meropenem trihydrate, vancomycin and heparin. This report describes an interesting case of thrombocytopenia associated with the combined use of heparin, vancomycin and meropenem.

Case Presentation: A 68-year-old man presented for management of a chronic heel ulcer, complicated by osteomyelitis. On admission, the patient was currently on intravenous meropenem in consultation with an infectious disease physician vancomycin was added to his treatment regime. Heparin for Deep Vein Thrombosis (DVT) prophylaxis was also commenced. During hospitalisation, the patient developed purpura, and subsequent blood tests revealed a platelet count of 2,000 per microliter of blood. Meropenem, vancomycin and heparin were deemed to be the main culprits and were ceased. The Heparin-Induced Platelet Aggregation Assay (HIPAA) was negative, however the patient tested positive to heparin/PF4 antibodies.

Conclusion: Treated supportively, the patient recovered, and his platelet count returned to normal limits at time of hospital discharge.

Keywords: Diabetic ulcer; Peripheral vascular disease; Thrombocytopenia; Polypharmacy; HITTS

OPEN ACCESS

Correspondence:
Bibombe P Mwipatayi, Department of Vascular and Endovascular Surgery, Royal Perth Hospital, Level 2, MRF Building, Royal Perth Hospital, Perth, 6000, Australia, Tel: +61-8-9224 0228; Fax: +61-8-9224 0204; E-mail: bibombe@iinet.net.au

Received Date: *20 May 2020*
Accepted Date: *10 Jun 2020*
Published Date: *12 Jun 2020*

Citation:
Mwipatayi MT, Faraj J, Xu JH, Angel D, Mwipatayi BP. Unusual Combination of Polypharmacy Induced Thrombocytopenia in a Patient with Complex Diabetic Foot Disease. Clin Surg. 2020; 5: 2836.

Abbreviations

DVT: Deep Vein Thrombosis; HIPAA: Heparin-Induced Platelet Aggregation Assay; HIT: Heparin-Induced Thrombocytopenia; MRSA: Methicillin Resistant Staphylococcus Aureus; DITP: Drug Induced Thrombocytopenia; HITS: Heparin Induced Thrombocytopenia; IgM: Immunoglobulin M

Background

Drug-Induced Thrombocytopenia (DITP) is a rare but serious side effect associated with multiple drugs, such as penicillin, vancomycin, quinine, pantoprazole, abciximab and tirofiban [1]. Subcutaneous unfractionated heparin has become the routine standard therapy for DVT prophylaxis in most hospitals. An estimated 5% of adult patients who receive heparin will develop Heparin-Induced Thrombocytopenia (HIT) [2-4]. Vancomycin is a naturally occurring glycopeptide antibiotic traditionally indicated for treatment of *Methicillin-resistant Staphylococcus aureus* (MRSA). Thrombocytopenia is a recognised but extremely rare side effect of vancomycin therapy [5]. Sparse evidence exists describing acute onset thrombocytopenia with prolonged meropenem usage, with only one confirmed case report associating meropenem use with DITP. This case report demonstrates a case of combined therapy with heparin, vancomycin, and meropenem that led to the development of acute thrombocytopenia.

Case Presentation

A 68-year-old male was admitted to our institution for management of left calcaneal

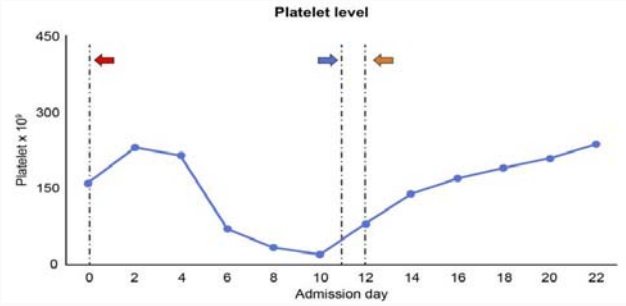

Figure 1: Platelet count over the course of the patient's admission.

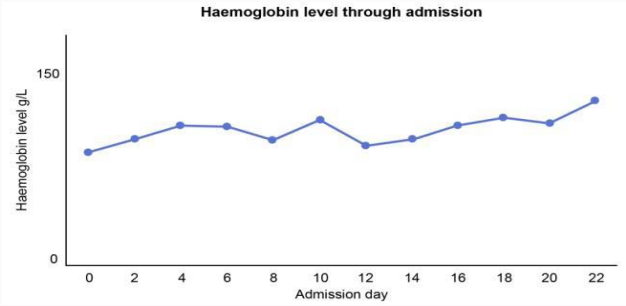

Figure 2: Haemoglobin level over the course of the patient's admission.

osteomyelitis. A tissue sample from the left heel grew *Streptococcus anginosus*, *Staphylococcus aureus*, *Proteus mirabilis* and *Enterobacter cloacae*. On admission, he was receiving three grams meropenem trihydrate daily, which was commenced during a previous admission. Due to his lack of clinical improvement and increased inflammatory markers, an infectious disease consultant assessed the patient and Intravenous (IV) vancomycin one gram twice daily was added to his treatment regime. He also received subcutaneous heparin 5,000 international-units twice daily for DVT prophylaxis. This is on a background where the patient in previous admissions had already received a combination of meropenem trihydrate or vancomycin with a second intravenous antibiotic, whilst receiving heparin prophylaxis, but never all three medications in the one sitting. On day three of admission, he developed a purpuric rash on both lower limbs with no change in his haematological parameters. The rash and laboratory haematological pattern were monitored daily. Ten days after his admission, there was progression of the purpuric rash, and his platelet count decreased from 231,000 platelets per microliter of blood (platelets/microL) to 35,000 platelets/microL and subsequently to 2,000 platelets micro/L (*ref. range 150,000 to 450,000 platelets/microL*) (Figure 1). The patient's haemoglobin level remained stable (Figure 2). HIT screening showed slightly increased Immunoglobulin M (IgM) on the platelet surface. The patient tested positive for heparin/PF4 antibodies. However, HIPAA was negative. After reviewing all medications administered to the patient, as well as excluding other causes of thrombocytopenia, vancomycin, meropenem, and heparin were suspected to be the most likely offending agents and were ceased. Despite receiving two units of platelets, the count remained at 2,000 platelets/microL. After consulting a haematologist, the patient was prescribed intravenous dexamethasone 40 grams once daily for five days, intravenous vitamin-K 10 mg once daily for two days and a single dose of intravenous immunoglobulin for presumptive immune-mediated thrombocytopenia. His platelet level slowly improved and gradually returned to 237,000 platelets/microLover a period of twelve-days. Once the platelet level improved, meropenem was reintroduced with careful monitoring. The patient was discharged home on IV meropenem with no further thrombocytopenic episodes.

Discussion

Thrombocytopenia is defined as a platelet count below 150,000 platelets/microL. There are numerous causes of thrombocytopenia, but DITP is a rare cause which must be identified early to cease the offending medication and commence supportive treatment. Aster et al. [6] provides six mechanisms with examples regarding the pathogenesis behind DITP (Table 1). Platelets are essential for wound healing, as they are an important trigger of the tissue repair process by releasing important growth factors [7]. In addition to thrombocytopenia potentially impairing wound healing, the cessation of the necessary antibiotics in this patient impacted on delivering the required treatment for his infective state and delayed wound healing. DITP occurs when exposure to a drug results in an antibody-mediated platelet destruction and subsequent thrombocytopenia. HIT is sometimes classified as a separate entity to DITP as the thrombocytopenia in HIT is associated with platelet activation. This platelet activation can cause life-threatening vessel thrombosis [8]. Heparin, vancomycin and meropenem were identified as potential causes of thrombocytopenia in this patient and subsequently ceased. Cessation of the offending drug is empirical treatment, with bleeding expected to cease within 2 days and the platelet count returning to normal within a week. Given previous exposures to heparin and not having developed HIT, the patient's diagnosis was attributed to DITP brought on by the combined use of meropenem, vancomycin and heparin. HIT is classified into two types. Type I, is non-immune mediated and results in a mild decrease in platelets (rarely <100,000 platelet/microL) within four days of heparin commencement. Thrombocytopenia is a result of heparin directly binding to PF4, resulting in mild platelet aggregation thrombocytopenia. Patients with type I tend to recover spontaneously without intervention. Type II is an immune-mediated thrombocytopenia and results in severe thrombocytopenia, with associated thrombosis. An immunoassay for PF4/heparin complex antibodies can be performed to biochemically diagnose type II HIT, however sensitivity and specificity for detection

Table 1: Six mechanisms of pathogenesis behind DITP.

Designation	Mechanism	Example
Hapten-dependent antibody	Drug (hapten) links covalently to membrane protein and induces a drug-specific immune response	Penicillin
Drug-dependent antibody	Drug induces antibody that binds to membrane protein only in the presence of soluble drug	Cephalosporins
Fiban-induced thrombocytopenia	Drug (ligand) reacts with membrane GPIIb-IIIa and induces a conformational change recognized by naturally occurring antibody?	Quinine, NSAIDs
Drug-specific antibody	Naturally occurring or induced antibody is specific for the murine component of a abciximab, a chimeric Fab fragment specific for GPIIIa	Abciximab
Autoantibody induction	Drug induces antibody that reacts with platelets in the absence of drug	Gold Salts
Immune complex	Drug binds to platelet factor 4 to produce a complex for which antibody is specific. The resulting immune complex activates platelets *via* Fc receptors	Heparin

is low [8]. Vancomycin is a bactericidal antibiotic that is being increasingly used in penicillin resistant infections such as *Methicillin-resistant Staphylococcus aureus*. The risk of thrombocytopenia secondary to vancomycin is cited as <0.1% and is believed to be immune mediated – with vancomycin dependent, platelet-derived antibodies being identified in patients who developed thrombocytopenia post-vancomycin administration [5]. Heparin is commonly used in hospitalised patients to prevent venous thromboembolism. It works by inactivating factors IIa and Xa in the clotting cascade. HIT is a well-known adverse effect, with mild reversible thrombocytopenia present in >1% of patients. Severe thrombocytopenia (type II) occurs in <1% patients, with catastrophic consequences. Type II HIT typically occurs day 5 to 10 post-commencement but can occur weeks after heparin cessation [4]. Meropenem is a broad-spectrum carbapenem which works by inhibiting bacterial wall synthesis. It is used empirically in multi-resistant gram-negative infections and in severe mixed aerobic/anaerobic infections. A common side effect of meropenem is thrombocytosis in >1% of patients. Conversely, thrombocytopenia occurs in <0.1% of patients [9]. Recently, Huang et al. [10] used enzyme immunoassays, flow cytometry and "monoclonal antibody immobilisation of platelet antigens" to determine meropenem was the causative agent in their patient with DITP– with antibodies being observed in a patients serum in the presence of meropenem. Huang article appears to describe the first confirmed case of meropenem-DITP.

Conclusion

Whilst there are laboratory tests available to aid the diagnosis of type II HIT and DITP, it must be stressed that any potential causative medications should be ceased immediately. Thus, any clinical suspicion of DITP or HITS should remain high in patients who develop thrombocytopenia within 10 days of commencing a new drug. Therapy involves immediate cessation of the suspected drug and close monitoring of the platelet count. Supportive measures such as platelet transfusions and corticosteroid therapy should be considered. Input from a hematologist may be warranted to help guide treatment. An improvement in the platelet count is expected within a week. The causative drug should not be restarted unless it is necessary, in which case small challenge doses may be given with careful monitoring under the direction of a hematologist.

References

1. Garbe E, Andersohn F, Bronder E, Salama A, Klimpel A, Thomae M, et al. Drug-induced immune thrombocytopenia: Results from the Berlin case-control surveillance study. Eur J Clin Pharmacol. 2012;68:821-32.
2. Davoren A, Aster RH. Heparin-induced thrombocytopenia and thrombosis. Am J Hematol. 2006;81:36-44.
3. Priziola JL, Smythe MA, Dager WE. Drug-induced thrombocytopenia in critically ill patients. Crit Care Med. 2010;38(6):S145-54.
4. Arepally GM, Ortel TL. Heparin-induced thrombocytopenia. Annu Rev Med. 2010;61:77-90.
5. Von Drygalski A, Curtis BR, Bougie DW, McFarland JG, Ahl S, Limbu I, et al. Vancomycin-induced immune thrombocytopenia. N Engl J Med. 2007;356:904-10.
6. Aster R, Curtis B, McFarland J, Bougie DW. Drug-induced immune thrombocytopenia: Pathogenesis, diagnosis, and management. J Thromb Haemost. 2009;7:911-8.
7. Szpaderska AM, Egozi EI, Gamelli RL, DiPietro LA. The effect of thrombocytopenia on dermal wound healing. J Invest Dermatol. 2003;120:1130-7.
8. George J, Arnold D. Drug-induced immune thrombocytopenia. 2019.
9. Nickson C. Heparin induced thrombotic thrombocytopenia syndrome. Life in the Fast Lane. 2014.
10. Huang R, Cai G, Zhang J, Liu F, Ma J, Liu H, et al. Meropenam-induced immune thrombocytopenia and the diagnostic process of laboratory testing. Transfusion 2017;57:2715-9.