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International Journal of Medical Case Reports and Medical Research

Case Report

Drug Induced Immune Thrombocytopenia Associated with Piperacillin/Tazobactam: A Clinical Challenge.

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Article Info

Received: May 17, 2024
Accepted: May 23, 2024
Published: May 27, 2024

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Citation: Henrique Atalaia Barbacena, Raquel Soares, Inês Matias Lopes and Patrícia Howell Monteiro. (2024) "Drug Induced Immune Thrombocytopenia Associated with Piperacillin/Tazobactam: A Clinical Challenge.", International Journal of Medical Case Reports and Medical Research, 2(5); DOI: 10.61148/2994-6905/IJMCRMR/042

Abstract:

Drug induced thrombocytopenia (DIT) is a rare side effect underrecognized in clinical practice, associated with multiple drugs. The diagnosis is difficult and mainly surpassed given the rarity of this entity and the lack of awareness of clinical teams. It requires a temporal relationship between drug use and thrombocytopenia, the complete resolution of thrombocytopenia once the drug is discontinued, and a recurrence of thrombocytopenia after drug re-exposure. Much is not known, but several etiological mechanisms are elicited, namely the structural drug conformational change, its interaction with platelet proteins and the designing of a neo-antigen able to sensitise the immune system. Piperacillin/tazobactam (P/T) is a beta-lactam antibiotic much in use in clinical practice. It has a known direct, however rare, myelosuppression side effect. DIT associated with P/T is a possible, although rarer side effect. Diagnostic evaluation is a challenge, since the relationship between drug and thrombocytopenia cannot always be confirmed. Nonetheless, there are clinical clues that suggest the diagnosis. In this case report, we present a case of DIT associated with P/T that features all the diagnostic clues besides the positivity of directed platelet antibodies.

Keywords: drug induced thrombocytopenia; piperacillin/tazobactam; beta-lactam antibiotics; antiplatelet antibodies.

Introduction:

Drug induced thrombocytopenia (DIT) is a recognisable idiosyncratic reaction clinically identified through the development of thrombocytopenia in the presence or exposure to a drug or other substances [1]. Mainly this picture contains an immune mediated background, in which drug exposure translates to sensitisation and the development of antibodies able to recognise secondarily epitopes of platelet proteins and thus resulting in platelet metabolization, thrombocytopenia and increased risk of clinically significant haemorrhage [1-3]. Drug dependent antibodies are an unusual class of antibodies, and it is well recognised that small molecules, such as drugs, cannot per se induce an immune response [3]. Therefore, drugs must combine with large protein molecules, such as transport proteins [1-3]. It is proposed that drugs able to produce such antibodies typically are charged or contain hydrophobic elements, able to connect to platelet proteins and to

antibodies, creating a "sandwich" model that facilitates the direct interaction between antibodies and platelet proteins, thus giving rise to sensitisation [1].

The prototypic example of DIT is the heparin-induced thrombocytopenia (HIT), in which interactions between heparin and platelet factor 4 (PFA) induces a conformational change of the latter, creating a neo-antigen [4]. When present, DIT has usually a benign course if the culprit drug is identified and removed, with complete recovery of platelet count and resolution of thrombocytopenia, only occasionally needing support therapy [2-3]. However, DIT diagnosis is not always straightforward. There are few cases published in the literature, but it is accepted that there must be a time relationship between drug exposure and thrombocytopenia. Other causes of thrombocytopenia must be excluded for DIT to be considered. Additionally, resolution of thrombocytopenia with drug discontinuation, and its recurrence after re-exposure are basilar criteria [1-3]. Although virtually all drugs can immune mediate thrombocytopenia, some are more frequently involved than others.

Piperacillin is a beta-lactam antibiotic frequently used in combination with the beta-lactamase inhibitor tazobactam. Their association results in the widest spectrum antibiotic of the beta-lactam class, able to act in a variety of gram-negative bacteria including *Pseudomonas spp* [5]. Its clinical use is mainly reserved for hospital acquired or nosocomial infections [5-7]. One of the adverse effects of this drug is myelosuppression, particularly neutropenia [6-8]. This effect is thought to be a direct toxic effect of the drug in myeloid progenitors, arresting the haematopoietic process and able to affect all cell lineages and develops slowly in time [6-8].

DIT associated with beta-lactam antibiotics, namely with piperacillin/tazobactam (P/T), is a known, however extremely rare side effect [6-8]. The exact molecular mechanism is not known; however, the most acceptable theory hypothesises that the beta lactam ring of the drug is able to open and interact with lysine residues of free amino groups of proteins [3]. Thus, P/T can interact with membrane platelet proteins, altering its conformation, creating a neo-antigen able to sensitise the immune-system and leading to the development of antibodies [9-11]. Alternatively, there are other theories, such as the bystander hypothesis. This model states that the drug binds primarily to unspecified antibodies previously existing in the plasma and secondarily to the platelet membrane, marking them and causing its destruction in the spleen and bone marrow [3, 8, 12]. However, we miss direct laboratory clues to support this hypothesis [13].

In the case presented, we describe an immune thrombocytopenia associated with P/T use.

Case Report:

An 85-year-old woman was admitted to the emergency department with a three-day history of anorexia and prostration. The patient had a history of hypertension, type 2 diabetes and chronic kidney disease stage 3b, with a baseline creatinine of 1,5 mg/dL. Three weeks before, the patient was admitted to the hospital with a diagnosis of urinary tract infection, with no agent identified in cultures, and was empirically treated with ceftriaxone.

Upon first observation, the patient was somnolent, apyretic, dehydrated and hypotensive, forcing volemic resuscitation, with no other significant findings. Laboratory evaluation (Table *1*) revealed a normocytic normochromic anaemia; normal white cell and platelet count; acute kidney injury AKIN 3; blood urea nitrogen of 177 mg/dL; and an elevated C-reactive protein of 29 mg/dL. Blood gas analysis showed a metabolic acidemia with a pH of 7.235, a bicarbonate level of 13.2 mmol/L. Urinalysis showed leukocyturia (500 cel/uL) and erythrocyturia (150 cel/uL). Renal ultrasonography with pielocalicial dilation of the left kidney with no pararenal collections; no valuable findings regarding the right kidney.

The diagnosis of nosocomial urosepsis with associated acute kidney injury was made, urine was collected for culture and P/T was initiated. An excellent clinical and laboratorial evolution was seen in the first days of antibiotic therapy, with clinical and laboratory improvement (Table *1*). Urine culture revealed an *Enterococcus faecium* sensitive to vancomycin and antibiotic therapy was shifted to daptomycin after four days of P/T.

After antibiotic shift, we watched a clinical worsening with new elevation of inflammatory markers, raising the possibility of antibiotic failure. New blood and urine cultures were collected, and P/T was readded to daptomycin on its fifth day.

Twenty-four hours after the reintroduction of P/T (day 10 of hospital stay), inflammatory markers showed a descending trend and the patient recovered, however, we noticed the development of a *de novo* thrombocytopenia reaching the minimum value of 4x10^9/uL (Table *1*). *Klebsiella pneumoniae* without a significant resistance profile was isolated in the second urine culture at the time. Suspecting a possible adverse effect related to P/T, antibiotic therapy was shifted to ceftriaxone. Transfusion of two platelet units was made and a dose of dexamethasone administered. In the following days platelet count raised progressively (Figure *1*). P/T was evicted, and the patient's platelet count remained stable during the rest of the stay. The presence of antiplatelet antibodies was positive.

Regarding the clinical improvement and stability, the patient was discharged at day 17 of hospital stay.

Discussion:

In the clinical case presented, the most exuberant effect noted is the abrupt and rapid fall of platelet count and its relationship with the reintroduction of the drug. Chronologically, we have a first five-day course of P/T, with a slight thrombocytopenia of 57x10^9/uL on the 6th day of admission. This probably relates to the time needed for drug sensitisation and formation of antibodies. With drug discontinuation, platelet count returns to normal. Later, with only 24h of drug reintroduction we observe a sudden and abrupt decrease of the platelet count. Following the second discontinuation, platelet count swiftly rose, returning to normal values in just 72h.

This temporal relationship functions, inadvertently, as a provocative test, and favours an immune-mediated mechanism, confirmed after the positivity of antiplatelet antibodies [1-3, 13]. Thus, the major criteria for DIT is fulfilled: there is a temporal relationship between drug exposure and thrombocytopenia; there is a recurrence of thrombocytopenia with re-exposure to the drug; and there is a complete recovery of platelet count with the drug's discontinuation.

Given the severely impaired platelet count on day 13 of hospital stay, although without signs of haemorrhage, the patient was given support therapy with platelet transfusion and intravenous corticoid administration. Both actions (drug discontinuation and support therapy) strengthen the immune-mediated hypothesis.

Together with this remark, we also cannot stop acknowledging a relative involvement of all cell lineages, with anaemia as well as leukopenia together with the thrombocytopenia. There are several mechanisms to explain such a phenomenon. First, we cannot exclude a myelosuppressive effect of the septic condition. The haematological compromise consistent with an inadequate hyperimmune response that characterises the septic picture is well known and established [14]. Second, a direct toxic effect of P/T may also be considered, arresting haematopoietic progenitors and thus resulting in pancytopenia [6, 8]. However, there are a few aspects that make this hypothesis less probable. For instance, the presence of anaemia from the first day of admission, and its stability through the hospital stay, disregards this drug's associated toxic effect, and hence other aetiologies for this finding.

In conclusion, the case presented is worth mentioning because of the time relationship established between platelet count and drug administration and discontinuation. It is a well brought example of DIT associated with P/T, and serves as a provocative test, unusual in clinical practice. There is a first five-to-six-day period of immune sensitisation with antibody formation, resulting in a first slight thrombocytopenia, followed by a drug discontinuation period, in which platelet count returns to normal and keeps stable, and a drug re-exposure with drastic and severe platelet count compromise. With the second time drug discontinuation, platelet count rises to normal. These findings go hand to hand with the described in the literature: a first exposure with rapid sensitisation to the drug, followed by recurrence of thrombocytopenia with re-exposure to the drug, and complete recovery of platelet count with the drug's discontinuation. Additionally, platelet directed antibodies were positive, strengthening the immune mediated mechanism, and supportive therapy with intravenous corticoid was given.

Additionally, we mustn't dodge the fact that P/T is one of the most used antibiotics in clinical practice, especially in the setting of hospital acquired or nosocomial infections. Despite rare, DIT associated with P/T is possible, clinicians must be aware of it, and suspicion must arise when a patient develops thrombocytopenia under P/T use.

Laboratory Parameter	Reference Value and Units	D1 HS	D6 HS	D7 HS	D9 HS	D10 HS	D13 HS	D14 HS	D15 HS	D17 HS (Discharge)
Haemoglobin	13-16g/dL	8.8	8.1	7.6	7.8	6.9	8.0	6.9	7.0	8.0
Leukocyte count	4,0 - 11,0 $\times 10^9$/uL	8.17	8.05	7.68	8.90	5.30	3.10	2.16	3.67	5.07
Platelet count	150 - 450 $\times 10^9$/uL	271	57	156	164	11	4	32	86	205
Urea	<30mg/dL	177	24	-	-	-	47	64	68	56
Creatinine	0.6-1.0mg/dL	5.23	1.02	-	-	-	2.09	1.89	1.91	1.89
C-reactive protein	< 0.5 mg/dL	29.2	7.02	8.58	11.3	-	7.96	7.10	3.06	6.85

Table 1: Blood work evolution during admission.

Legend: HS – hospital stay. We can observe retrospectively the evolution of platelet count from D1 to discharge: of note, P/T was initiated at D1, shifted at D5 and re-initiated at D9. There is an obvious and rapid decrease in platelet count after just 24h of drug re-exposure from D9 to D10 (164x10^9/uL to 11x10^9/uL), reaching a minimum severe value of 4x10^9/uL just 72h after drug re-exposure. After drug discontinuation (at D13), platelet count swiftly returns to normal.

Funding:

The authors declare that no fundings was used in this work.

Conflict of Interest:

The authors report there are no competing interests to declare.

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