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Piperacillin Induced Acute Severe Thrombocytopenia during VV ECMO in COVID19 Pneumonia: Case Report and Review of the Literature

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Authors' contributions

This work was carried out in collaboration among all authors. Author MKOQ write the first draft of case report, performed the literature review. Authors HARSAS and TRNM finalized the case report All authors read and approved the final manuscript.

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Case study

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ABSTRACT

Piperacillin-tazobactam is a frequently used antibiotic that has a broad spectrum of antibacterial activity and a wide safety profile. The development of thrombocytopenia following the use of piperacillin is usually a gradual phenomenon occurring several days following the first exposure, which is usually mild and passed unnoticed However, re-exposure can cause severe rapid thrombocytopenia secondary to pre-existing antibodies. Thrombocytopenia is relatively common during VV ECMO and multifactorial in nature. We present a case of acute severe thrombocytopenia after re-exposure to piperacillin during a prolonged VV ECMO run for COVID 19 respiratory failure leading to diagnostic challenge, after withdrawal of the piperacillin the acute severe

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thrombocytopenia improved dramatically, also we provide literature review for the similar cases available in the literature. Our case unique in that it had happened in ECMO patient with severe COVID ARDS, and we clinically confirmed that the piperacillin component of TZP is the culprit for the acute severe thrombocytopenia.

Keywords: Piperacillin-tazobactam; thrombocytopenia; VV ECMO.

ABBREVIATION

COVID : Coronavirus disease
TZP : Tazobactam and piperacillin.
DITP : Drug-induced thrombocytopenia.
DIC : Disseminated intravascular coagulation.
HIT : Heparin induced thrombocytopenia
ANA : Antinuclear antibody.
VEF : Von Willebrand factor.
MDR : Multi drug resistant.
OGD : Oesophago-Gastro-Duodenoscopy.
ITP : Idiopathic thrombocytopenia.

1. INTRODUCTION

Tazobactam and piperacillin (TZP) are antibiotics that are used to treat the majority of infections caused by β-lactamase-producing bacteria. Common adverse reactions associated with TZP treatment include neutropenia, leukopenia and thrombocytopenia, urticaria, allergic shock, exfoliative dermatitis, and adverse reactions of the nervous system [1].

Although drugs are a common cause of acute immune-mediated thrombocytopenia in adults, the drug etiology is often initially unrecognized. Most cases of drug-induced thrombocytopenia (DITP) are caused by drug-dependent antibodies that are specific for the drug structure and bind tightly to platelets by their Fab regions but only in the presence of the drug [2].

The development of thrombocytopenia following the use of piperacillin is usually a gradual phenomenon occurring several days following the first exposure, which is usually mild and passed unnoticed. However, re-exposure can cause severe rapid thrombocytopenia as low as $1x10^9$/L secondary to pre-existing antibodies, which usually recover after stopping the causative drug within 5 to 10 days, there is no obvious risk factor for developing DITP [3].

Thrombocytopenia is relatively common during VV ECMO and multifactorial in nature, the causes are usually related to destruction or consumption of the platelets because of the ECMO circuit itself, the underlying disease, and the medication that we are using can be a major contributing factor [4].

To our knowledge, none of the cases of Piperacillin induced thrombocytopenia have been reported in VV ECMO patients. We report a case of acute severe thrombocytopenia in VV ECMO patient with COVID ARDS after 3rd exposure to piperacillin.

2. CASE REPORT

A 57-year-old male patient was admitted to our medical intensive care unit (MICU) for severe COVID pneumonia. He received supportive care including noninvasive ventilation (NIV), antiviral therapy, and empiric Piperacillin tazobactam (PTZ) for 5 days (1st exposure). His condition did not improve requiring intubation for severe ARDS, on day 12 of admission and he was restarted again empirically on piperacillin/Tazobactam (2rd exposure) while awaiting bacterial culture results, at this time his platelets count was normal ($409x10^9$/L).

After the failure of rescue therapies for severe ARDS including lung-protective ventilation, optimized PEEP, and prone position, ECMO was initiated on day 13 of admission with Fem-Fem configuration.

He has first confirmed superimposed bacterial infection on day 15 of admission with an extended-spectrum Beta-lactamase (ESBL) producer Klebsiella pneumoniae isolated from tracheal aspirate, leading to a change in antibiotic therapy from Piperacillin/Tazobactam to Meropenem.

On day 18 of admission, his platelets reached a nadir of 67x109/L and then recovered to more than 100 x109/L after 7 days of PTZ discontinuation. His persistent mild thrombocytopenia was felt to be related to the ECMO circuit and sepsis. Repeated studies for heparin-induced thrombocytopenia were negative.

The patient continued to remain ECMO dependent due to poor lung recovery and had multiple courses of antibiotics for nosocomial sepsis, which did not include PTZ.

On day 55 of admission, he had another episode of pulmonary sepsis with carbapenem-resistant Pseudomonas aeruginosa and started on PTZ for the third time during this admission. At that time, his platelet count was 290 $x10^9$/L.

On day 56 of admission, one day post 3rd exposure his platelet count suddenly dropped to 12 $x10^9$/L and remained low to a nadir of 2 $x10^9$/L, despite multiple platelet transfusion. Multiple possible causes of thrombocytopenia were considered, including sepsis, bone marrow suppression, ECMO circuit, drug-induced, and DIC. However, consumption and the immunological cause was thought to be the most likely cause of thrombocytopenia considering the acute severe drop in platelets and no improvement with platelet transfusion. Alloimmunization was considered to be the most likely cause for antibody-mediated thrombocytopenia because of multiple blood product transfusions required during prolonged ECMO management. The course was complicated by severe GI bleeding requiring frequent PRBCs replacement.

Work up for thrombocytopenia included, review of the patient medications which could be a possible cause, DIC panel, HIT study, peripheral smear, hepatitis panel, ANA screen, VWF, reticulocyte count. All of the work-up was noncontributory to elucidate the cause of thrombocytopenia. Specific antibody testing for ITP and drug-related antibody testing was not available. Bone marrow biopsy was refused by the family.

Management strategy for severe thrombocytopenia included ECMO circuit change, regular single donor platelet transfusion, high dose steroids, IVIG, and Eltrombopag later changed to Romiplostim, As the CMV titer was high, the patient treated with extended gancyclovir course after consulting ID team, as foscarnet was not available in our institution. Ganciclovir was added as part of management plan after thrombocytopenia has established. Despite these interventions, platelet count remained low in the range of 2-5 $x10^9$/L, after 3 weeks post the 3rd exposure, PTZ was replaced with Ceftolozane/tazobactam based on MDR pseudomonal sensitivities. With this changes platelet count started to improve from the next day. reached up 60 $x10^9$/L 3 days later, after two weeks platelet count reached up to 126 $x10^9$/L. This dramatic improvement in the platelet count drive us to review the piperacillin exposure times and durations so we came out with conclusion that the piperacillin is a causative agent as the exposure frequency and duration is correlating strongly with the rapid drop in the platelet count as well as the recovery.

Patient VV ECMO support continued for 116 days, 4 membranes were changed during this period, we managed the severe thrombocytopenia period without heparin, no clot or significant change in trans-membrane pressure was noticed, when the platelet count starts to recover to more than $20x10^9$ we added pre-membrane heparin only, full heparinization resumed when platelet count reach more than 100 $x10^9$ and no other contraindications for heparin use.

3. DISCUSSION AND LITERATURE REVIEW

Piperacillin-tazobactam is a frequently used antibiotic in suspected severe sepsis due to its broad spectrum of antibacterial activity and wide safety profile. Thrombocytopenia is a well-known but rare adverse effect of PTZ. The development of thrombocytopenia following the use of piperacillin is usually a gradual phenomenon occurring several days following the first exposure, which is usually passed mild and unnoticed and attributed to sepsis. However, re-exposure may cause severe rapid thrombocytopenia secondary to pre-existing antibodies.

The pathogenesis of DITP is complex, in that, at least six different mechanisms Table 1 have been proposed by which drug-induced antibodies can promote platelet destruction [3].

We have 3 diagnostic option for diagnosis of DITP, clinical, laboratory, and test method that met laboratory criteria, In 1982 Hackett et al 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 in vitro test

for drug-dependent platelet antibodies was positive [4].

The detection of drug-dependent platelet antibodies in vitro can confirm the diagnosis. DITP testing has included a wide variety of techniques, with lack of standardization, Arnold et al proposed the following criteria for the assessment of the quality of DITP laboratory test methods and results from published reports, called the "DITP criteria": [1] Drug (or drug metabolite) was required for the reaction in vitro; [2] Immunoglobulin binding was demonstrated; [3] Two or more laboratories obtained positive results on separate occasions; and [4] Platelets were the target of immunoglobulin binding, Test methods that met validity criteria were flow cytometry, platelet suspension immune fluorescence test, enzyme immunoassays, radiolabeled anti-globulin-based assays and GP-specific assays [5].

To the best of our knowledge 21 cases of PTZ induced acute severe thrombocytopenia are reported in the literature. (Table 2). However, none of these cases has been reported in COVID19 pneumonia and ARDS requiring VV ECMO support, the mean age was 58 years. Most patients were male, with only 3 cases were female, 12 cases were treated in ICU sitting, 7 cases had confirmed pre-exposed to piperacillin-tazobactam. while 13 cases had a significant drop in platelets counts within the first 7 days, 8 out of these 13 had significant drop within the first 48 hours post-exposure.

Platelet nadir in most cases was less than 10 x109/L and sometimes reaching down to 1 to 2 $x10^9$/L. The mean recovery time to the baseline was 5 days. 7 cases out of 21 were confirmed with antibodies detection, 2 underwent rechallenge and the other 12 cases were diagnosed on clinical grounds.

Our patient developed mild thrombocytopenia initially following the second exposure and acute more severe thrombocytopenia following the 3rd exposure to piperacillin-tazobactam consistent with a possible immune sensitization with development of antibodies during initial exposure. The other possibility is the presence of preformed naturally occurring antibodies that react to platelets in the presence of piperacillin.

The case we are reporting has many unique aspects compared to prior reported cases. First of all it was during VV ECMO support. During ECMO, thrombocytopenia is a well-known complication related to an artificial circuit, in

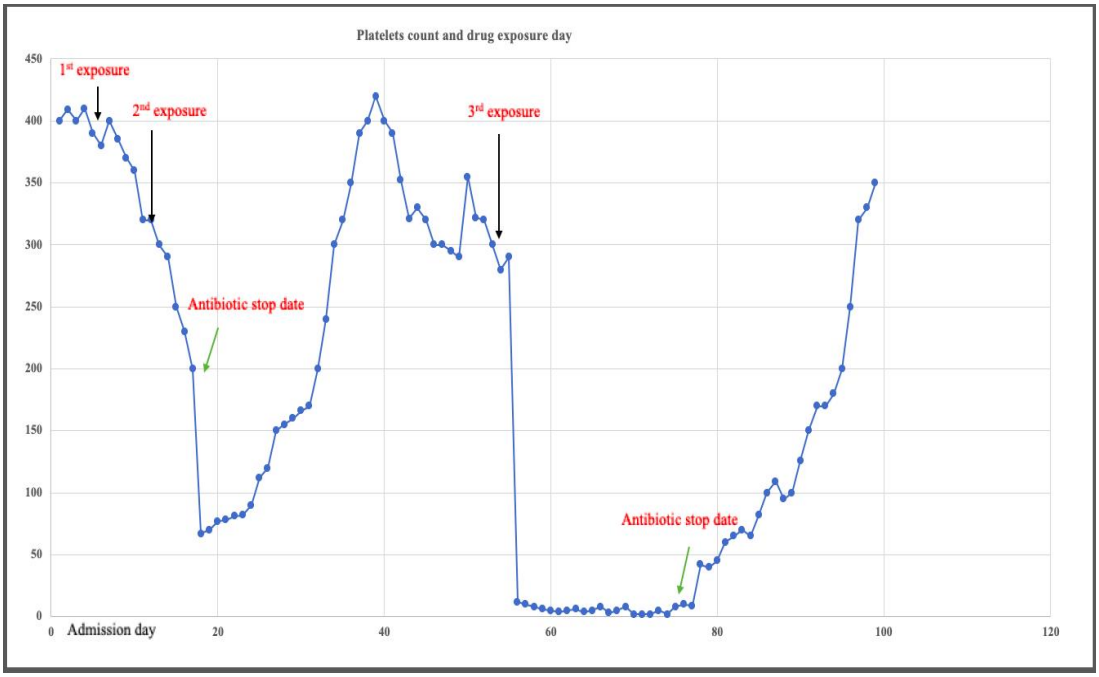

Fig. 1. Platelets count in relation to piperacillin exposure day

Table 1. Common drugs and the mechanism of DITP

Type of antibody	Mechanism	Example of drugs
Quinine type	Drug binds DDAbs and subsequently, platelet integrin	Quinine, sulfonamide antibiotics, nonsteroidal anti-inflammatory drugs
Hapten dependent	Drug links covalently to membrane protein and induces drug-specific binding by DDAbs	Penicillin, some cephalosporin antibiotics
Fiban type	Drug reacts with glycoprotein IIb/IIIa and induces neoepitope(s) for the DDAbs	Tirofiban, eptifibatide
Drug specific	DDAbs recognize the murine component of chimeric Fab fragment specific for glycoprotein IIIa	Abciximab
Autoantibody	Drug induces antibody that reacts with autologous platelets in the absence of drug	Gold salts, procainamide
Immune complexes	Antibodies form immune complexes with their target antigens	Heparin, protamine

Table 2. Cases of piperacillin induced thrombocytopenia available in the literature since 1992.

Case No.	Age/Gender	Pre- exposure	Platelet baseline × 10^9/L	Day of significant drop post exposure	Platelets Nadir level × 10^9/L	Platelet count × 10^9/L/days after stop	Diagnosis basis
1	71/M	Unknown	257	Day 12	5	261/ 3 days later	Re challenge with 2 g of piperacillin. [6]
2	69/F	Unknown	353	Day 11	15	208/ 3 days later	Antibody detection. [7]
3	78/M	Unknown	243	Day 8	3	215/ 3 days later	Clinical diagnosis. [8]
4	30/M	Yes	353	Day 12	18	300/3 days later	Clinical diagnosis. [9]
5	54/M	Unknown	193	Day 14	10	259/9 days later	Antibody detection. [10]
6	74/M	Unknown	99	Day 7	19	100/day3	Clinical diagnosis. [11]
7	48/F	Unknown	Not mentioned	Day 22	2	104/9 days later	Clinical diagnosis. [12]
8	67/M	Unknown	469	Day 16	1	109/7 day	Clinical diagnosis. [13]
9	47/M	Yes	198	Day 1	7	130/5 day	Clinical diagnosis. [14]
10	55/F	Unknown	325	Day 1	3	114/21 days	Clinical diagnosis. [14]
11	76/M	Yes	200	Day 1	13	190/2days	Re challenged with antibiotic.[1]
12	64/M	Yes	265	Day 1	5	Not mentioned	Clinical diagnosis. [15]
13	49/M	Unknown	216	Day 2	1	118/7 days	Antibody detection. [16]
14	81/M	Yes	470	Day 1	3	170/5 days	Clinical diagnosis. [17]
15	77/M	Yes	274	Day 5	7	95/ 3days later	Clinical diagnosis. [17]
16	20/M	Unknown	198	Day 1	1	198/10 days	Clinical diagnosis. [18]
17	40/M	Yes	295	Day 1	2	not mentioned	Clinical diagnosis. [19]
18	62/M	Unknown	not mentioned	Day 3	<20	not mentioned	Antibody against tazobactam only. [20]
19	50/M	Unknown	not mentioned	Day 5	2	3–5 days	Antibody detection. [21]
20	56/M	Unknown	not mentioned	Day 5	16	3–5 days	Antibody detection. [21]

Case No.	Age/Gender	Pre- exposure	Platelet baseline × 10^9/L	Day of significant drop post exposure	Platelets Nadir level × 10^9/L	Platelet count × 10^9/L/days after stop	Diagnosis basis
21	67/M	Unknown	not mentioned	Day 5	40	3–5 days	Antibody detection. [21]
Our case	57/M	Yes	290	Day 1	2	126/14 days	Clinical diagnosis. [21]

**Day of significant drop post exposure' is different from nadir day*

addition to other mechanisms due to severe illness. This complicates the management of ECMO patients as anticoagulation cannot be used due to severe thrombocytopenia and the risk of circuit thrombosis is high. Second point, we replaced Piperacillin/Tazobactam with ceftolozane/ tazobactam, confirming that thrombocytopenia was related to Piperacillin and not the antibiotic combination itself. In the published cases which diagnosed based on clinical criteria the authors blam the piperacillin and tazobactam combination as culprit but in antibody confirmed cases it was clear that piperacillin is the cause (cases 2,5,12 and18) except one case which identify antibodies against only tazobactam (case 6).

3 cases with profound thrombocytopenia were reported in uremic patients few days after staring piperacillin IV, they improved after the withdrawal of antibiotic as well as starting hemodialysis, denoting that uremia could be a contributing risk factor for developing such piperacillin induced sensitizing (cases 3,4 and 6), Interestingly one case was reported in a patient on multiple immunosuppressant (case12). Table (2) summarizes all the cases available in the literature.

4. CONCLUSION

Our case shows clearly how important to consider the second exposure of piperacillin as culprit for acute severe thrombocytopenia in patient with COVID pneumonia related ARDS requiring ECMO support, we confirm this according to clinical criteria of antibiotic exposure and withdrawal after ruling out other possible causes of thrombocytopenia like infectious, mechanical and hematological causes.

A physician who is taking care of critically ill patient requiring ECMO support should consider drugs (even if it is commonly used) as one of the possible causes for acute severe thrombocytopenia, especially if he found strong correlation between the starting time and the platelet count drop, especially if there is evidence of previous exposure to the same medicine, one example is Piperacillin.

CONSENT

All authors declare that 'written informed consent has been obtained for the publication of this case report A copy of written consent is available for review by the Editorial Office / Editor-in-Chief / Members of the Editorial Board of this magazine.

ETHICAL APPROVAL

The ethical aspect for publication approved by medical research committee in HMC.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Chen H, Fan Z, Guo F, Yang Y, Li J, Zhang J, et al. Tazobactam and piperacillin-induced thrombocytopenia: A case report. Exp Ther Med. 2016; 11(4):1223-1226.
2. George JN, Aster RH. Drug-induced thrombocytopenia: pathogenesis, evaluation, and management. Hematology Am Soc Hematol Educ Program. 2009; 153-158.
3. Aster RH, Curtis BR, McFarland JG, Bougie DW. Drug-induced immune thrombocytopenia: pathogenesis, diagnosis, and management. J Thromb Haemost. 2009;7(6):911-8.
4. Hackett T, Kelton JG, Powers P. Drug-induced platelet destruction. Semin Thromb Hemost. 1982;8(2):116-37.
5. Arnold DM, Nazi I, Warkentin TE, et al. Approach to the diagnosis and management of drug-induced immune thrombocytopenia. Transfus Med Rev. 2013;27(3):137-145.
6. Esteban Olivera, Prabhudas Lakhani & Chatrchai Watanakunakorn Isolated Severe Thrombocytopenia and Bleeding Caused by Piperacillin, Scandinavian Journal of Infectious Diseases. 1992;24 (6):815-817.
7. Perez-Vazquez A, Pastor JM, Riancho JA. Immune thrombocytopenia caused by piperacillin/tazobactam. Clin Infect Dis. 1998;27(3):650–651.
8. Yan MT, Chu HY, Chau T, Lin SH. Profound thrombocytopenia associated with piperacillin in a hemodialysis patient. Clin Nephrol. 2009;72(3):240-3.
9. Rousan TA, Aldoss IT, Cowley BD, Curtis BR, Bougie DW, Aster RH, et al. Recurrent acute thrombocytopenia in the hospitalized patient: Sepsis, DIC, HIT, or antibiotic-induced thrombocytopenia. American Journal of Hematology; 2009.

10. Anand A, Chauhan HK. Piperacillin and vancomycin induced severe thrombo cytopenia in a hospitalized patient. Platelets. 2011;22(4):294-301.
11. Lin SY, Huang JC, Shen MC, Chuang SH, Lee MH, Chen HC. Piperacillin-induced thrombocytopenia reversed by high-flux hemodialysis in an uremic patient. Hemodial Int. 2012 Oct;16 Suppl 1:S50-3.
12. Macwilliam JL, Mistry R, Floyd MS Jr, Baird AD. Piperacillin/tazobactam induced thrombocytopaenia--a delayed response. BMJ Case Rep. 2012;9;bcr0320125981.
13. Uzun G, Onem Y, Hatipoglu M, Turhan V, Mutluoglu M, Ay H. Piperacillin/ tazobactam-induced neutropenia, thrombocytopenia, and fever during treatment of a diabetic foot infection. Scand J Infect Dis. 2013;45 (1):73-6.
14. Shaik S, Kazi HA, Ender PT. Rapid-onset piperacillin-tazobactam induced thrombocytopenia. J Pharm Pract. 2015; 28(2):204-6.
15. Boyce K, Brar H, Stabler SN. Piperacillin/tazobactam-induced immune-mediated thrombocytopenia in the intensive care unit. J Clin Pharm Ther. 2016;41(6):730-732.
16. Patel S, Levin-Epstein R, Kobashigawa J. Piperacillin-induced Thrombocytopenia in a Dual Heart and Kidney Transplant Patient: A Case Report. Transplant Proc. 2017;49(7):1672-1674.
17. Alzahrani M, Alrumaih I, Alhamad F, Abdel Warith A. Rapid onset severe thrombocytopenia following reexposure to piperacillin-tazobactam: report of two cases and review of the literature. Platelets. 2018;29(6):628-631.
18. Masroujeh R, Bonder B, Mandviwala A, Haj Abdulkader A. Internal Medicine, Rapid Near-Fatal Piperacillin/Tazobactm-Induced Thrombocytopenia. American Journal of Respiratory and Critical Care Medicine. 2018;197:A6928.
19. Beaulieu C, Kurczewski L, Yajnik V. Cefepime challenge after piperacillin/tazobactam-induced thrombocytopenia. J Thromb Thrombolysis. 2019;48(1):167-170.
20. Minh-Tri H, Nguyen MD, Pavneet Kaur MD, Richard H. Aster, MD, Vidya Krishnan, MD MHS Blood; 2019.
21. Chen S, Cooper N, Müller M, Bein G, Sachs UJ. Piperacillin-dependent anti-platelet antibodies are a relevant, easy to confirm differential diagnosis in patients with rapid-onset thrombocytopenia. Br J Haematol. 2020;190(5):e320-e321.

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