Cross-reactivity of beta-lactam antibiotics in a patient with drug-induced immune thrombocytopenia

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Abstract

Beta-lactam antibiotics are a relatively common cause of immune thrombocytopenia. Cross-reactivity of them in patient with drug-induced immune thrombocytopenia is rarely reported. Here, we describe the case of a 79-year-old male patient experienced thrombocytopenia after receiving piperacillin-tazobactam for acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Fortunately, the patient was able to successfully challenge with meropenem and cefotiam. However, after the cefoperazone-sulbactam was administered, the patient experienced thrombocytopenia again. Therefore, there are cross-reactions of platelet-relative antibodies between piperacillin-tazobactam and cefoperazone-sulbactam. Although the exact responsible antibodies remain unknown and need further investigation, attention should be paid to the role of chemical structure similarities in determining the risk of immune thrombocytopenia among beta-lactams in the clinical setting.

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Running Title: Beta-lactam antibiotics-induced immune thrombocytopenia

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Abstract

Beta-lactam antibiotics are a relatively common cause of immune thrombocytopenia. Cross-reactivity of them in patient with drug-induced immune thrombocytopenia is rarely reported. Here, we describe the case of a 79-year-old male patient experienced thrombocytopenia after receiving piperacillin-tazobactam for acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Fortunately, the patient was able to successfully challenge with meropenem and cefotiam. However, after the cefoperazone-sulbactam was administered, the patient experienced thrombocytopenia again. Therefore, there are cross-reactions of platelet-relative antibodies between piperacillin-tazobactam and cefoperazone-sulbactam. Although the exact responsible antibodies remain unknown and need further investigation, attention should be paid to the role of chemical structure similarities in determining the risk of immune thrombocytopenia among beta-lactams in the clinical setting.

1. INTRODUCTION

Drug-induced thrombocytopenia (DIT) has been described as a sudden and severe hematologic complication. The diagnosis of DIT remains a challenge because its etiology is complex and multifactorial. It can have fatal outcomes when a platelet count nadir below 100,000/μL and a decrease in platelet count of [?]30%.[1] The incidence of DIT has been reported as 10 cases per million population per year, with a prevalence of approximately 25% in critically ill patients.[2]

Beta-lactam antibiotics are a relatively common cause of thrombocytopenia. Although beta-lactam antibiotics may decrease platelet production secondary to bone marrow suppression, drug-induced immune-mediated thrombocytopenia (DITP) is more common in this class.[3] Thus, cross-reactivity may exist between beta-lactam antibiotics because of the immunogenic nature of DITP and the structural similarities between them. To date, some studies focused on case reports or series suggested that there was no cross-reaction of DITP between the penam group and the cephem group.[4–6] However, these reports involved very few different beta-lactam antibiotics and did not identify responsible antibodies of DITP. Therefore, when a patient experiences DITP the question of whether an alternative member of beta-lactam antibiotics can safely be used often arises.

Here, we report a patient with piperacillin-tazobactam-induced immune thrombocytopenia can successfully challenge with meropenem and cefotiam, but cannot tolerant with cefoperazone-sulbactam.

2. CASE REPORT

A 79-year-old male patient with a 10-year history of chronic obstructive pulmonary disease (COPD) was admitted to the pneumology department of our hospital in July 2020 complaining of acute exacerbation of cough, dyspnea, wheezing. He also had a history of type 2 diabetes mellitus for 10 years, and hypertension for 6 years. He had no history of allergies reaction for drugs and food. His vitals on admission were temperature 36.5, blood pressure 112/82 mm Hg, pulse rate 84 beats/min and respiratory rate 18 breaths/min. Pulmonary examination revealed a "barrel-shaped" chest, a few moist rales at bilateral lungs. Laboratory examination revealed the white blood cell count (WBC) of 10.34×10^9/L, the neutrophils conut of 9.65×10^9/L, the platelets count of 150×10^9/L, the hemoglobin concentration of 145g/L, the serum C-reactive protein (CRP) concentration of 0.97 mg/L. A chest computed tomography (CT) scan showed chronic bronchitis, emphysema and a small amount of infection in bilateral lungs. The patient was diagnosed with acute exacerbation (AE) of COPD.

After admission, he was received losartan (100mg orally, once daily), gliclazide (60mg orally, once daily), doxofylline (0.3g intravenously guttae, once daily), bromhexine (4mg intravenously guttae, twice daily), piperacillin-tazobactam (4.5g intravenously guttae, every 8 hours), and methylprednisolone (40mg intravenously guttae, twice daily). On the fourth day following admission, the symptoms of cough and short-

ness of breath were improved. The repeat laboratory investigations showed WBC 8.3×10^9/L, neutrophils 7.08×10^9/L, platelet 76×10^9/L, haemoglobin 133g/L. On the eighth day following admission, the patient's general condition was good, and he asked to be discharged from the hospital, which was allowed.

In March 2021, the same patient was re-hospitalized for AECOPD and pulmonary infection. Laboratory examination revealed WBC 9.91×10^9/L, neutrophils 8.76×10^9/L, platelets 149×10^9/L. After admission, his medications were the same as the previous admission except the piperacillin-tazobactam (4.5g intravenously guttae, every 8 hours) and levofloxacin (0.5g intravenously guttae, once daily) were administered for pulmonary infection. However, on the third day, the repeat laboratory investigations showed the platelet levels of the patient rapidly drop to 25×10^9/L, but others normal. He had no neurological deficits, purpura or petechiae, mucosal bleeding, or epistaxis. The condition was considered thrombocytopenia associated with antibiotics. The severity of thrombocytopenia was assessed as grade 3, according to the grading criteria for bone marrow hypocellular.[7] Therefore, piperacillin-tazobactam and levofloxacin were discontinued. The meropenem 1g intravenously every 8 hours was administrated to complete treatment of his pulmonary infection. The platelet count gradually improved to 96×10^9/L 9 days after discontinuation of piperacillin-tazobactam without any other intervention (Figure 1). On the fourteenth day following admission, the patient was discharged for the cough and dyspnea improved. Seven days later, the patient was followed up in the outpatient, and the count of platelet returned to normal.

In May 2021, the patient was also admitted for AECOPD and pulmonary infection with an initial platelet count of 184×10^9/L. His medications were the same as the previous admission except the ceforiam 2g intravenously every 12 hours was administered for infection. The platelet count on the third and the ninth day of admission was 159×10^9 /L and 155×10^9 /L, respectively. On the eleventh day following admission, the patient reported that the cough and sputum improved, and was discharged.

In August 2021, the patient was re-admitted for AECOPD and pulmonary infection. Laboratory examination revealed WBC 7.71×10^9/L, haemoglobin 119g/L,platelets $122\text{x}10^9$ /L. The anti-infection regimen was switched to cefoperazone-sulbactam 4g intravenously every 12 hours. However, the platelet count fell to $22\text{x}10^9$ /L after seven days from time of administration, and the count of WBC was $5.68\text{x}10^9$/L, the hemoglobin was 118g/L. The condition was also considered thrombocytopenia associated with antibiotics. The severity of thrombocytopenia was assessed as grade 3, according to the grading criteria for bone marrow hypocellular.[7]Therefore, cefoperazone-sulbactam was discontinued. Recombinant Human Interleukin-11 3 mg was administered subcutaneously once daily. Over the next 4 days, the platelet count of the patient increased from $40\text{x}10^9$ /L to $64\text{x}10^9$ /L (Figure 1). The patient's symptoms of cough and shortness of breath were relieved and he was discharged. The platelets count returned to normal level after two weeks of follow-up. The depiction of the patient's time course of thrombocytopenia and exposure to potential antibiotics were presented in figure 1.

3. DISCUSSION

Here, we describe the case of a patient with a history of COPD, who required antimicrobial therapy for pulmonary bacterial infection, but the treatment was complicated by thrombocytopenia association with antibiotics. We found our patient with piperacillin-tazobactam-induced thrombocytopenia was able to successfully challenge meropenem and cefotiam, but cannot tolerant with cefoperazone-sulbactam for the treatment of pneumonia.

Due to the etiology of DIT still remains complex and multifactorial, its diagnosis remains a challenge. This case suggested that doctors should be aware of the risks of drug-induced thrombocytopenia, and that drugs should be discontinued following detection of drug-induced thrombocytopenia. The Naranjo scale was employed for assessing the causal relationship between the development of thrombocytopenia and piperacillin-tazobactam and cefoperazone-sulbactam treatment. This yielded a probability score of +9 for piperacillin-tazobactam, suggesting that it was the definite cause of thrombocytopenia, and a probability score of +7 for cefoperazone-sulbactam, suggesting that it was the probable cause of thrombocytopenia (Table 1).

Two mechanisms underlying beta-lactam antibiotics-induced thrombocytopenia have been proposed, includ-

ing drug-induced bone marrow suppression and DITP, but DITP is more common.[3] DITP is attributed to accelerated platelet destruction secondary to an immune response. Moreover, two different mechanisms have been elucidated for beta-lactam antibiotics DITP.[8] Thus, a limited number of case reports have previously documented confirmation of piperacillin-tazobactam DITP by identification of positive drug-induced antiplatelet antibodies.[5] Unfortunately, it was unfeasible to collect and test of piperacillin-tazobactam antiplatelet antibodies at our site. However, bone marrow suppression is often accompanied by a simultaneous decrease in leukocytes, hemoglobin, and platelets. In addition, given the nature of the mechanism, bone marrow suppression tends to develop more gradually over a few weeks, while DITP typically develops more quickly, often after 7 to 14 days of therapy, and even after 1 to 3 days of therapy in patients with prior exposure.[8]Therefore, due to the absence of decrease of white blood cells and hemoglobin and rapid platelet decline, DITP associated with piperacillin-tazobactam and cefoperazone-sulbactam was considered for our patient.

To date, previous reports have described the use of other beta-lactam antibiotics, such as carbapenems,[9–12]cefepime,[3,13,14] cefoperazone,[9]aztreonam,[10] in patients with piperacillin-tazobactam-induced thrombocytopenia. However, although our patient with piperacillin-tazobactam DITP was able to successfully challenge merropenem and cefatiam, cefoperazone-sulbactam was not tolerated. Thus, due to the immunogenic nature of DITP and the structural similarities between beta-lactam antibiotics, identifying the structural moiety of piperacillin-tazobactam responsible antibodies for this immunogenic response and evaluating the safety of other beta-lactam antibiotics in this clinical setting are of crucial importance. To the best of our knowledge, only three reports describing studies of drug cross-reactions in beta-lactam DITP have been reported. In one,[4] two ceftriaxone-dependent platelet-reactive antibodies failed to cross-react with any of five other cephalosporins. In two,[5] three piperacillin-induced antibodies failed to cross-react with two other penam and five cephem beta-lactam drugs. In three,[6]among 14 antibodies specific for penam drugs, five "strong" cross-reactions with other penam drugs were found; among 18 antibodies specific for cephem drugs, eight "strong" cross-reactions were identified. But antibodies induced by penam drugs did not cross-react strongly with cephem drugs and vice versa. These reports however covered very few different beta-lactam antibiotics, did not involve piperacillin and cefoperazone.

In our case, we hypothesized the possible platelet-reactive antibodies of beta-lactam antibiotics and presented in table 2. Firstly, previous reports observed a strong correlation between cross-reactions and similar or identical R1 side groups of the beta-lactams.[6] So we hypothesized that identical R1 side chains between piperacillin and cefoperazone maybe the underlying reason why our patient experienced thrombocytopenia during using piperacillin-tazobactam and cefoperazone-sulbactam. However, a case reported cefoperazone can successfully challenged in a patient with piperacillin-tazobactam DITP.[9] Therefore, R1 side chain considered as platelet-reactive antibodies was questioned. Secondly, we found sulbactam, like piperacillin, contains a beta-lactam structure, which may become the responsible of platelet-reactive antibodies. This may be similar to patients with an allergy to sulbactam will cross-react with other beta-lactams with the similar core.[15] And finally, previous study showed tazobactam-specific antibiotic had been obtained in a patient with piperacillin-tazobactam DITP.[16]Thus, tazobactam may be crucial drug in our case. In addition, the structural similarity between tazobactam and sulbactam provided the possibility of cross-reaction between piperacillin-tazobactam and cefoperazone-sulbactam. However, as multiple pathways may be involved in immune reaction, the exact responsible antibodies of beta-lactam antibiotics DITP have not been clearly defined and require further investigation in future research.

The proper treatment of DITP usually entails the withdrawal of the suspected drug, and supportive care with platelet transfusions as bleeding complications can be severe.[17] To data, there is no evidence that corticosteroids are efficacious in DITP,[17] which may be the reason why our patient still experienced DITP despite continuous methylprednisolone use. However, previous case reported where the drop in platelet count was minimized or mitigated when the patient was receiving higher doses of corticosteroids.[18]

4. CONCLUSION

Here, we reported the first case of piperacillin-tazobactam-induced immune thrombocytopenia successfully

challenged by the use of meropenem and cefotiam, but cannot tolerant with cefoperazone-sulbactam for the treatment of pneumonia. Although the exact responsible antibodies of piperacillin-tazobactam-induced immune thrombocytopenia remain unknown and need further investigation, attention should be paid to the role of chemical structure similarities in determining the risk of DITP among beta-lactams in the clinical setting.

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Conflict of interest statement

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Authors' contributions

XH and WH conceived the original idea and wrote the manuscript. XW and XL performed literature search and collected the clinical data. QC and LD revised and edited the manuscript. All authors contributed to manuscript revisions, read and approved the submitted version.

Data availability statement

All data generated or analysed during this study are included in this published article.

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Table 1 Naranjo scale for assessing the likelihood of piperacillin-tazobactam and cefoperazone-sulbactam induced thrombocy

Question
1. Are there previous conclusive reports on this reaction?
2. Did the adverse event appear after the suspected drug was administered?
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?
4. Did the adverse reaction reappear when the drug was re-administered?
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?
6. Did the reaction reappear when a placebo was given?
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?
10. Was the adverse event confirmed by any objective evidence?
Total Score

[a] **Score:** The probability score for piperacillin-tazobactam

[b]**Score:** The probability score for cefoperazone-sulbactam

Table 2 Cross-reactivity of possible platelet-reactive antibodies in our patient with immune thrombocytopenia

Platelet-reactive antibodies	**Immunizing drug**	**Cross-reacting drug**
R1 side chain	piperacillin	cefoperazone
Beta-lactam ring	piperacillin	sulbactam
Beta-lactam ring	tazobactam	sulbactam

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