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PIPERACILLIN/TAZOBACTAM INDUCED IMMUNE-MEDIATED ANAEMIA AND THROMBOCYTOPENIA

Agnes-Sophie Fritz, Marten Trendelenburg, Markus Mutke

Department of Internal Medicine, University Hospital of Basel, Basel, Switzerland

Corresponding author's e-mail: agnes-sophieluise.fritz@usb.ch

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ABSTRACT

Piperacillin/tazobactam (PTZ) is known to cause cytopenia but case reports on PTZ causing combined haemolytic anaemia and thrombocytopenia are scarce. We report on a 56-year-old male who developed severe, immune-mediated thrombocytopenia and anaemia during two treatment episodes with PTZ. After the first exposure, his blood count rapidly returned to normal after discontinuation of PTZ. One year later, in the context of an unintentional re-challenge with PTZ, the level of red blood cells and platelets dropped again causing acute haemolytic anaemia and immune thrombocytopenia. Recovery was delayed after discontinuation of PTZ. PTZ should be considered as a potential cause of immune-mediated bicytopenia.

KEYWORDS

Piperacillin/tazobactam, haemolytic anaemia, thrombocytopenia, bicytopenia, adverse drug effects

LEARNING POINTS

- Piperacillin/tazobactam can induce immune-mediated haemolytic anaemia and thrombocytopenia.
- Patients with underlying alteration of the immune system might be at higher risk for bicytopenia.

INTRODUCTION/BACKGROUND

Piperacillin/tazobactam (PTZ) is an antibiotic with a broad spectrum of antibacterial activity. It is used for a variety of bacterial infections such as intra-abdominal, lower respiratory tract, nosocomial pneumonia and skin infections. PTZ is commonly used as an empiric antibiotic regimen in immunocompromised patients, especially those presenting with febrile neutropenia[1]. In rare cases haematological toxicity caused by PTZ can lead to neutropenia, haemolytic anaemia or thrombocytopenia, 1.4%, ≤1%, and ≤1% of patients[2]. In this case report, we describe a patient who developed bicytopenia after exposure to PTZ.

CASE DESCRIPTION

Exposure to PTZ in July 2024: A 56-year-old male presented to the emergency room with dyspnoea and fever. His medical history included pontine stroke with persisting right motoric hemisyndrome and epileptic seizures,

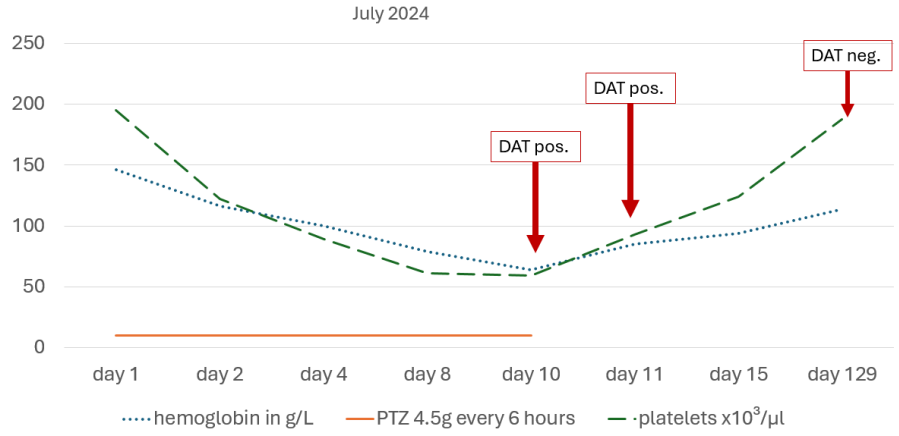
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repeated pneumoniae, suspected steroid-sensitive chronic inflammatory syndrome, paranoid schizophrenia and conatal solitary kidney. As the patient showed signs of global respiratory insufficiency at admission, he was intubated and put on intubation and vasopressor therapy in the intensive care unit for 3 days. On the day of admission, the patient met three out of four systemic inflammatory response syndrome (SIRS) criteria (temperature >38°C, heart rate >90 beats per minute (bpm), respiratory rate >20 breaths/minute). The working diagnosis was sepsis secondary to bilateral lower lobe bronchopneumonia. Pseudomonas aeruginosa was detected in the tracheal secretion leading to the initiation of resistance-adapted antimicrobial treatment with PTZ (4.5 g every 6 hours) on day 2 of hospitalization.

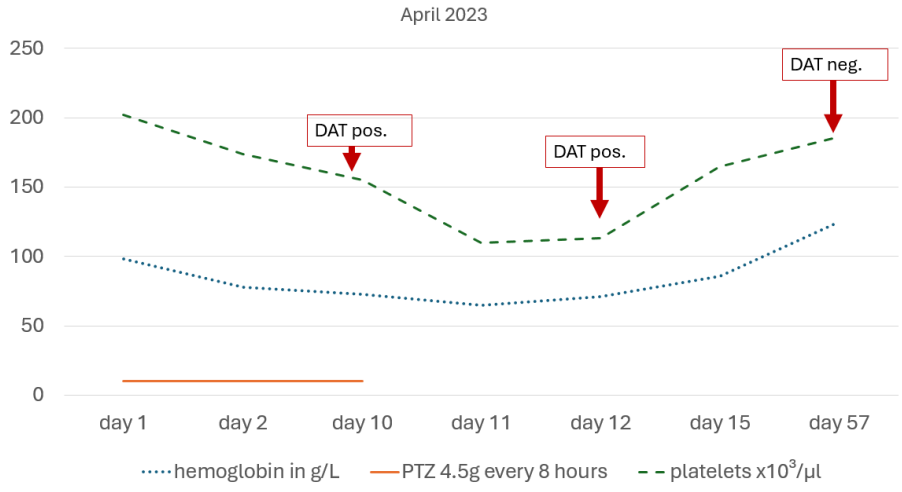
As shown in *Fig. 1*, the patient was admitted with normal levels of haemoglobin (146 g/l) and platelets (195,000 platelets/µl). A continuous decrease of both counts was detected, with a minimum count (haemoglobin 64 g/l, 59,000 platelets/µl) on day 10. Despite clinical improvement in terms of general condition and pneumonia, the patient remained subfebrile and showed a renewed slight increase in C-reactive protein (CRP), which is why PTZ was initially continued. However, the patients showed no clinical signs of a recurrence of the initial focus or other new infectious foci and PTZ was ultimately discontinued on day 10 due to suspected PTZ-induced bicytopenia. Two red blood cell (RBC) transfusions were given. The haemoglobin as well as the platelet counts recovered slowly after discontinuation of PTZ, reaching almost a normal value at the day of discharge. During the episode of bicytopenia in July 2024, the patient had a positive direct antiglobulin test (Coombs test) result on day 10 and 11 and a negative result 4 months after discharge. Regarding the anaemia, he had positive parameters for haemolysis on day 10 (lactate dehydrogenase 721 U/l, haptoglobin< 0.1 g/l) , not an appropriate response of reticulocytes to anaemia (haemoglobin 64 g/l, reticulocytes 11%), a normal titer of antinuclear antibodies (<1:80), absence of schistocytes, blast cells or other abnormalities in the peripheral blood smear and no relevant lack of substrates. He had no antibodies for heparin-induced thrombocytopenia normal coagulation parameters and no clinical signs of bleeding.

Previous exposure to PTZ in April 2023: Retrospectively, we discovered that the patient had already received a 10-day-long treatment with PTZ one year earlier. During this episode in April 2023, the patient met three out of four SIRS criteria (temperature >38°C, heart rate >90 bpm, respiratory rate >20 breaths/minute) and required 24 hours of vasopressor therapy in the intensive care unit. At that time, the working diagnosis was sepsis from



Abbreviations: PTZ, piperacillin/ tazobactam; DAT, direct antiglobulin test.

Figure 1. Exposure to PTZ in July 2024.



Abbreviations: PTZ, piperacillin/ tazobactam; DAT, direct antiglobulin test.

Figure 2. Exposure to PTZ in April 2023.

severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia with bacterial superinfection. No additional pathogens were identified beyond SARS-CoV-2. As shown in *Fig. 2*, the patient developed severe anaemia and thrombocytopenia during PTZ treatment, requiring a total of 5 RBC transfusions. The patient had a positive direct antiglobulin (Coombs) test during treatment with PTZ that became negative approximately 2 months after discontinuation of the treatment.

During the bicytopenia in April 2023, the coagulation status was unremarkable, and there were no clinical signs of bleeding. Haemolysis parameters were not assessed. The then-existing bicytopenia was considered a manifestation of the septic process.

DISCUSSION

We postulate that the patient developed PTZ-induced, combined, immune-mediated haemolytic anaemia and thrombocytopenia. This diagnosis is strongly supported by a Naranjo score— also known as the Adverse Drug Reaction Probability Scale — of 7, indicating that the reaction is likely related to the drug[3].

Beta-lactam antibiotics have been reported to induce the formation of drug-dependent antibodies that bind to RBCs in the presence of piperacillin, forming an immunogen that activates the complement system and leads to their destruction by haemolysis[4]. This assumed mechanism is well in line with the positive direct antiglobulin (Coombs) test results obtained during PTZ treatment. Similar pathophysiology is suggested for immune thrombocytopenia but no specific diagnostic test like the direct antiglobulin test is available in routine clinical practice[5].

A systematic review by Wang et al. investigated PTZ-induced hematologic adverse effects and found cytopenia among the 59 case reports in the following frequency: haemolytic anaemia (40%), thrombocytopenia (37%), and neutropenia (19.4%). Haemolytic anaemia or thrombocytopenia is generally believed to be immune-mediated, whereas neutropenia is thought to be related to bone marrow suppression[6]. However, while PTZ-induced cytopenias are a well-studied phenomenon, description of combined cytopenias are scarce, with varying compositions of the cytopenia[7,8].

One possible explanation for the patient's repeated bicytopenia after therapy with PTZ could be an underlying, undiagnosed immunological disorder. It is noteworthy that despite being 56 years old, the patient required intensive care several times, with 4 stays in the intensive care unit over the past 6 years and several episodes of invasive ventilation. A continuously elevated CRP led to the descriptive diagnosis of a 'steroid-sensitive inflammatory syndrome'.

We therefore also considered Evans syndrome, a rare autoimmune disorder characterized by the concurrent presence of autoimmune haemolytic anaemia and immune thrombocytopenia[9]. Evans syndrome often appears secondarily in immune diseases such as systemic lupus erythematosus, lymphoproliferative disorders, or primary immunodeficiencies. The multiple pre-existing serious conditions of our patient with repeated severe pneumonias would favour the hypothesis that the patient developed Evans syndrome due to PTZ therapy. However, Evans-syndrome is often associated with severe illness and the need for high dose immune modulating agents (steroids, immunoglobulins) whereas simply discontinuing the drug caused the blood counts in our patient to return to normal[10]. Further investigation is needed to see if the combined cytopenia of our patient represent an individual case or if underlying immunodeficiencies could facilitate the appearance and cluster of cytopenias when treated with PTZ.

CONCLUSION

PTZ-induced cytopenia can be easily overlooked but can affect several cell lines. Underlying immunodeficiency may facilitate the occurrence of bicytopenia in patients being treated with PTZ.

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