SAGE Open Medical Case Reports
Volume 12: 1–5

DOI: 10.1177/2050313X241285675
journals.sagepub.com/home/sco
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Fever and reversible laboratory abnormalities associated with prolonged use of piperacillin/tazobactam: A case report

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Abstract

Piperacillin/tazobactam is a widely used anti-infective agent. However, prolonged use can lead to adverse drug reactions, primarily presenting as fever and various abnormal laboratory test results. Certain abnormal test outcomes may mislead clinical assessments. We present a case of a 50-year-old Chinese woman who developed a fever and abnormal blood tests after receiving piperacillin/tazobactam for more than 2 weeks. These tests showed elevated levels of C-reactive protein, procalcitonin, transaminases, myocardial enzymes, and a significant increase in D-dimer. After stopping piperacillin/tazobactam, all relevant test results returned to normal within 10 days. It is imperative for clinicians to be vigilant of this adverse effect in patients undergoing extended piperacillin/tazobactam treatment, as early recognition can prevent unnecessary diagnostic tests and therapeutic interventions.

Keywords

Drug fever, D-dimer, piperacillin/tazobactam

Date received: 9 June 2024; accepted: 5 September 2024

Introduction

Drug fever is a common adverse reaction linked to many medications, especially antibiotics. Piperacillin/tazobactam, a commonly used antibiotic combination, has been reported to cause drug fever and reversible laboratory abnormalities in several studies.[1–5] However, current literature often does not provide comprehensive laboratory findings. Herein, we present a case study involving piperacillin/tazobactam (PTZ)-induced drug fever accompanied by several laboratory abnormalities, particularly D-dimer and lactate dehydrogenase (LDH) abnormalities. This report aims to improve understanding of the adverse reactions related to PTZ and to help ensure timely and accurate diagnosis.

Case report

A 50-year-old female patient with a 1-year history of recurrent cough presented to the first hospital on June 15, 2023. She was diagnosed with pulmonary tuberculosis 20 years ago but did not receive standard treatment. She denied any history of drug allergies or adverse drug reactions. Her medical, familial, and psychosocial histories were otherwise unremarkable. Chest computed tomography (CT) revealed left lower lobe atelectasis accompanied by a mass shadow in the same region.

The patient was diagnosed with pneumonia and was administered the PTZ therapy at a dosage of 4.5 g every 8 h. Her vital signs and hematological parameters were continuously monitored. They remained normal until day 15 of antibiotic administration. However, on day 16 of therapy, the patient developed a low-grade fever (37.8°C) accompanied by a decline in neutrophil count and fibrinogen levels compared to previous days. Over the following 2 days (days 17

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and 18), the fever escalated to 39.8°C, and her clinical condition deteriorated.

Upon discharge on hospital day 18 (July 8, 2023), the patient was admitted to our hospital that evening with complaints of fatigue. Upon admission, her vital signs were within normal limits: temperature 36.8°C, blood pressure 124/76 mmHg, respiratory rate 20 breaths/min, and pulse rate 76 beats/min. Auscultation revealed markedly decreased breath sounds in the left lower lung lobe. In addition, a significant ecchymosis was observed in the left groin region (Figure 1).

Blood tests revealed a white blood cell count of 5.5×10^9/L with 28.3% neutrophils, 45.6% lymphocytes, 6.4% eosinophils, 4.5% monocytes, and a hemoglobin level of 128 g/L. The erythrocyte sedimentation rate was 37 mm/h, the C-reactive protein level was 121.4 mg/L, and the procalcitonin (PCT) level was 6.44 ng/dl. In addition, an arterial blood gas obtained on room air indicated a pH of 7.37, a $PaCO_2$ of 34.8 mmHg, a PaO_2 of 80 mmHg, and a base excess of −4.7 mmol/L. Liver function tests showed elevated transaminases (alanine aminotransferase/aspartate aminotransferase: 48/487 U/L) and cholestatic enzymes (gamma-glutamyl transpeptidase/alkaline phosphatase: 103/144 U/L), with normal bilirubin levels. Blood creatinine and urea nitrogen levels were normal. LDH and D-dimer levels were significantly elevated at 6510 U/L (normal range: 120–250 U/L) and 230,620 μg/L (normal range: 0–500 μg/L), respectively. Additional tests indicated prolongation of prothrombin time (PT: 18.4 s, INR: 2.0) and activated partial thromboplastin time (APTT: 35 s), with a low fibrinogen level of 1.38 g/L. Immunoglobulin E was 37 IU/L (normal range: 0–87 IU/L). Routine urine and stool analyses showed no clinical abnormalities. Both blood cultures and T-SPOT.TB were negative. The changes in hematological parameters are presented in Table 1, and the trends in temperature and heart rate are shown in Figure 2. A repeat chest CT scan showed no progression of the lung lesion, and no pulmonary embolism was detected on pulmonary vascular enhancement CT (Figure 3).

The administration of PTZ was terminated, and her temperature normalized the following day. All abnormal laboratory test results also turned to normal within 10 days.

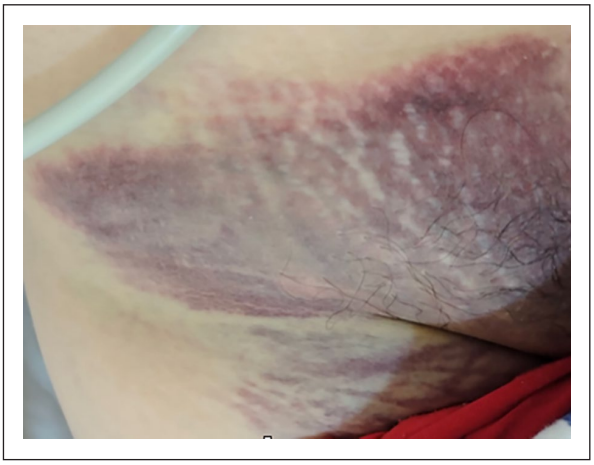

Figure 1. The patient had a large ecchymosis on the left groin.

Table 1. Pre-admission and post-admission laboratory profile.

Laboratory tests	Day-8	Day-1	Day 1	Day 2	Day 3	Day 4	Day 6	Day 10	Reference values
White blood cell	10.8	5.5	7.7	5.3	6	9.7	11.5	6.2	$3.5–9.5 \times 10^3$/μL
Neutrophils (%)	67.3	28.3	25.3	39.3	43.1	49	39.2	53.1	
Lymphocyte (%)	22.7	54.4	59.5	50.3	40.8	20.6	26.3	32.9	
Monocyte (%)	5.4	4.5	12.8	4.4	12.5	25.5	28.5	10.7	
Eosinophils (%)	3.9	6.4	4.2	5.5	3.3	4.7	5.7	2.9	
Platelet	240	98	161	172	170	143	143	291	$125–350 \times 10^3$/μL
CRP	0.8	121.4	124.2	72.8	30.6	9	9	7.4	0–8 mg/L
AST	15	426	487	461	585	415	81	49	7–40 U/L
ALT	10	29	48	79	129	144	82	30	13–35 U/L
ALP	71	98	144	192	250	178	105		50–135 U/L
GGT		80	103	180	376	471	316		7–45 U/L
LDH	245	2863	6510	7656	6448	3594	769	256	50–240 U/L
Procalcitonin	0.05	6.44				0.21			0–0.5 ng/ml
PT			18.4	13.2	12.2	11.5	11.2	11.7	10–14 s
APTT			35.2	30.1	28.3	25	26.4	28.3	25–31.3 s
Fibrinogen (g/L)	3.28	1.66	1.38	1.11	1.18	1.21	2.49	3.16	2.0–4.0 g/L
D-dimer	340	21,000	230,620	534,600	188,500	60,210	2360	820	0–500 μg/L

Day-1: the day before admission; Day-8: 8 days before admission. ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transpeptidase; LDH: lactate dehydrogenase.

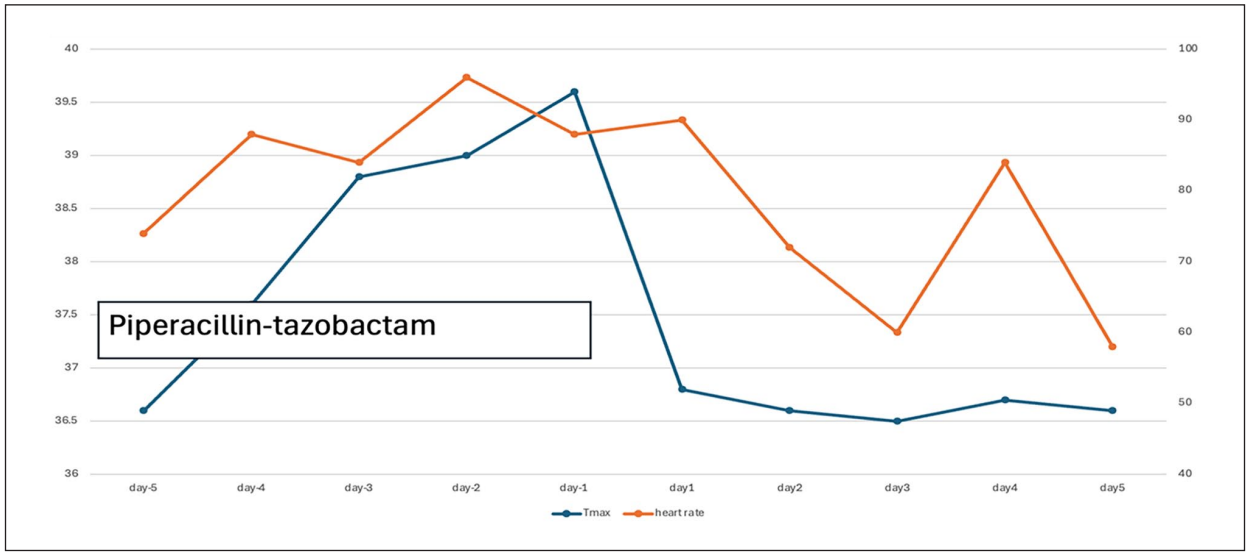

Figure 2. Trend of temperature and heart rate during the patient's last and this hospitalizations correlated with piperacillin–tazobactam.

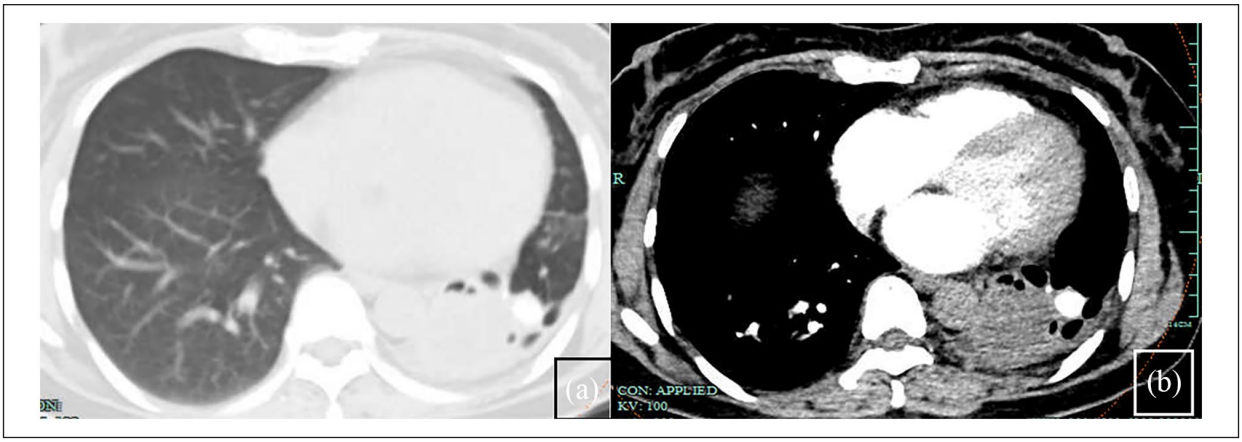

Figure 3. Chest computed tomography images acquired after admission, demonstrating atelectasis of the left lower lung, with consolidation, without enhancement after augmentation, shown in lung window (a) and Mediastinal window (b), respectively.

Discussion

Drug fever, an uncommon but significant contributor to the etiology of fever of unknown origin, is characterized by a transient febrile response to medication in the absence of an underlying disease that could cause fever.[2] In this case, the onset of fever occurred 12 days following intravenous PTZ administration. The fever quickly subsided after stopping the drug, indicating a strong link between PTZ cessation and fever resolution. Drug fever was diagnosed based on these criteria: (1) Fever over 37.5°C lasting more than 2 days during antibiotic treatment; (2) no other clinical signs or laboratory findings indicating an infection; (3) the fever was not linked to other treatments for infection; and (4) the fever quickly resolved after stopping the suspected antibiotic, known as "dechallenge."[6]

The incidence of drug fever among patients treated with PTZ was 17%, and it is often unrecognized and misdiagnosed.[6] Diagnosis of drug fever is typically made through a process of elimination when no alternative cause of fever can be identified. The occurrence of antibiotic-induced drug fever seems to depend partly on how long the treatment lasts. New-onset fever cases triggered by PTZ were observed between days 10 and 23 of treatment, with an average onset of 14.5 days. The mean duration of fever was 5.3 days (range: 3–12 days), with a mean temperature of 39.4°C (range 38.6–41.1°C). Fever typically resolved within a mean of 1.5 days (range: 1–3 days) upon drug discontinuation. Notably, the incidence of drug fever was higher in patients aged 69 years or younger, particularly those aged 49 or below, compared to those aged 70 years or older.[6]

A key indicator of drug fever is pulse-temperature dissociation, characterized by a heart rate that does not correspond with the degree of fever. Specifically, for a temperature of 39.5°C, an appropriate pulse response might be approximately 120 beats per minute, whereas a pulse rate of less than

110 beats per minute might indicate relative bradycardia.[7] In one case series of antibiotic-induced drug fever, the incidence of relative bradycardia in drug fever was reported to be 87.5%.[8] In addition, another clinical feature of drug fever is a "relative well" state despite the elevated temperature.

The mechanism of drug fever is complex and involves the formation of circulating immune complexes and cell-mediated immune responses. In addition, various other mechanisms have been identified, including the drug's influence on thermoregulation, its pharmacological action, idiosyncratic reactions, drug administration-related fever, and hypersensitivity reactions.[9] Since drug molecules are usually too small to act as antigens, they function as haptens by binding to larger molecules, which makes them recognizable as immunogenic substances. This drug–protein complex serves as an antigen against which antibodies are produced, leading to the formation of an antigen–antibody immune complex. The immune complex activates the complement system, resulting in neutrophil destruction. During this process, lymphocytes become sensitized. This sensitization may lead to the release of various pyrogenic substances, resulting in reactions such as fever.[10] The patient's relatively swift presentation of fever and alterations in laboratory parameters suggest a hypersensitivity reaction to PTZ.

The administration of PTZ can induce fever and lead to a spectrum of laboratory abnormalities, including reversible myelosuppression, hepatotoxicity, coagulation dysfunction, and elevated tumor markers and inflammatory markers. The neutropenia observed in patients treated with PTZ is believed to result from the arrest of myeloid cell proliferation, which is typically reversible. This adverse effect is often associated with high cumulative doses of PTZ and is infrequently observed when the treatment duration is less than 10 days.[11,12] Oizumi et al. also identified beta-lactam antibiotics as among the most prevalent causes of drug-induced fever. In this study, 51% of patients with drug fever experienced a transient increase in LDH, along with a 23% decrease in neutrophils and an 8% decrease in platelets.[6]

In terms of LDH levels, the elevation was observed in 51% of patients with drug fever, which is double the 20% observed in patients without drug fever. Conversely, no significant differences were observed in the incidence of elevated serum transaminases and alkaline phosphatase levels between the two groups.[6]

In this case, the PCT levels fluctuated in correlation with body temperature. PCT, a hormone of calcitonin, is known to be produced during bacterial infections. Despite the various mechanisms proposed for inducing PCT release, proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1, seem to play pivotal roles. Notably, TNF-α and IL-6 levels are also elevated in anaphylactic reactions.[13] Sifa et al.[14] investigated eight patients with severe cutaneous drug eruption, among whom two exhibited elevated PCT levels.

PTZ may induce coagulation abnormalities, such as elevated D-dimer levels, prolonged PT and APTT, and reduced fibrinogen concentrations and platelet counts. The prolongation of PT and APTT induced by PTZ may be attributed to decreased vitamin K absorption due to the suppression of intestinal flora.[15]

Thrombocytopenia induced by PDZ usually appears 1–31 days after treatment begins. The median exposure time before clinical onset is 10 days, while the mean is 6.5 days.[16] The main mechanism behind this thrombocytopenia is drug-induced immune thrombocytopenia, involving antibodies that lead to platelet destruction through the reticuloendothelial system.[17]

The significant elevation of D-dimer levels in this patient suggests two possible mechanisms. First, the elevation of D-dimer was accompanied by a corresponding decrease in fibrinogen levels, suggesting that PTZ may have induced fibrinogen consumption. Second, in the context of fibrinogen depletion, the patient experienced uncontrolled bleeding following arterial blood sampling, resulting in subcutaneous hematoma formation. This exacerbated coagulation dysfunction and further stimulated D-dimer production. Notably, a literature review revealed limited data on PTZ-associated drug fever and D-dimer elevation, and the underlying mechanisms remain unclear. One study reported anaphylaxis-induced coagulation disorders, including D-dimer elevation.[18] It is hypothesized that activated mast cells release tryptase, which may contribute to fibrinogen cleavage or facilitate this process by activating of plasminogen into plasmin, leading to hyperfibrinolysis.

Without bleeding or bacterial infection, these coagulative and inflammatory abnormalities usually resolve spontaneously after stopping PTZ, indicating a possible link to the drug.

Conclusion

Drug fever is a known complication of PTZ therapy that can lead to various laboratory test abnormalities. Clinicians should be aware of this potential adverse reaction in patients experiencing unexplained fever while receiving this antibiotic combination. Timely recognition and proper management are essential for achieving the best outcomes. In addition, research is needed to clarify the mechanisms behind PTZ-induced drug fever and to develop effective prevention strategies.

Acknowledgements

None.

Author contributions

L.S. contributed to contributed to conceptualization, investigation, data curation, resources, writing—original draft preparation, and review and editing.

Declaration of conflicting interests

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by a grant from the Health Commission of Zhejiang Province (No. 2022KY942).

Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patient for his anonymized information to be published in this article.

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