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Piperacillin-tazobactam caused post-trauma patient's postoperative leukopenia, hypokalemia, and periodic fever: a case report

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Abstract

Background Piperacillin-tazobactam (PT), a broad-spectrum β-lactam/β-lactamase inhibitor combination, is clinically used to treat infections caused by Gram-positive and Gram-negative aerobic and anaerobic bacteria. While gastrointestinal adverse effects, skin reactions, and fever have been previously reported during PT therapy, its association with periodic fever, leukopenia, and hypokalemia specifically in post-trauma surgical patients has not been documented.

Case presentation We report the case of a 55-year-old male trauma patient who received PT for 17 days pre-operatively for suspected infection. He then underwent surgical procedures including rib fracture open reduction and internal fixation, along with thoracic closed drainage. Post-operatively, on day 2, the patient developed periodic fever, occurring specifically between 20:00 and 23:00 hours each night, with normal daytime temperatures. Concurrently, during PT administration, the patient exhibited leukopenia and hypokalemia. Notably, cessation of PT led to an immediate resolution of the periodic fever, gradual normalization of leukocyte counts, and restoration of potassium levels. Although PT can cause fever, diagnosis can be challenging in the post-operative setting due to the potential for confounding factors.

Conclusions This case suggests that in surgical patients presenting with periodic fever, particularly when accompanied by leukopenia and hypokalemia after exposure to PT, the drug should be considered a potential causative agent, even if other post-operative complications are being investigated.

Keywords Piperacillin-tazobactam, Periodic fever, Leukopenia, Hypokalemia, Post-trauma surgery.

Introduction

Piperacillin-tazobactam (PT) is a combination of a ureidopenicillin and a β-lactamase inhibitor. Piperacillin is a semi-synthetic penicillin antibiotic with activity against many Gram-positive and Gram-negative bacteria. Tazobactam is a β-lactamase inhibitor that blocks bacteria producing β-lactamases, thereby enhancing the antibacterial effect of piperacillin. PT is a commonly used antibiotic with good safety profiles [1, 2]. However, several adverse reactions have been reported, including gastrointestinal reactions, skin reactions, fever, and hematological abnormalities. Among these, fever is a form of

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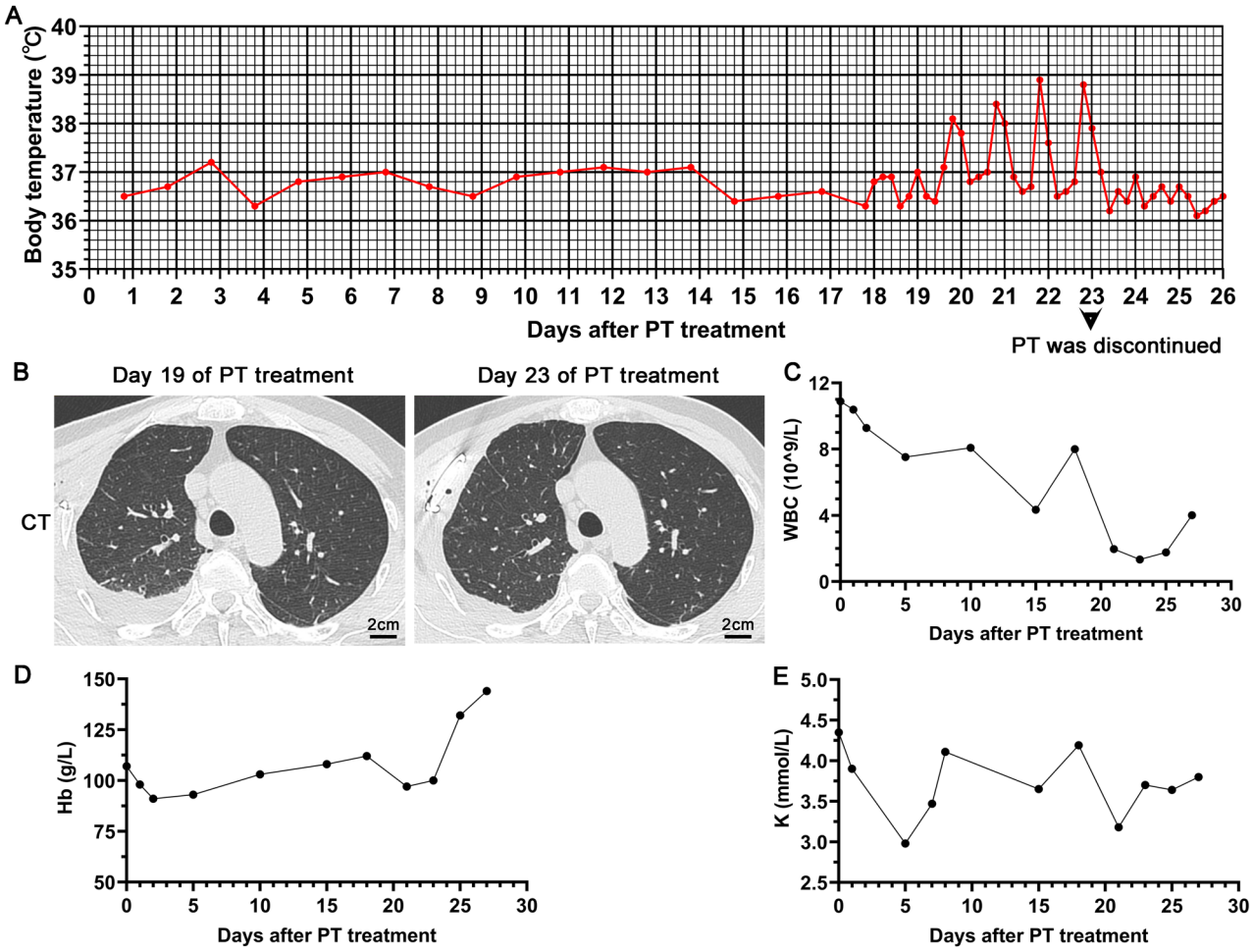

Fig. 1 Body temperature (**A**), chest CT (**B**), white blood cells (**C**), hemoglobin (**D**), and potassium (**E**) of patient during PT drug therapy

delayed drug hypersensitivity reaction, typically occurring in patients receiving PT for more than 10 days [3–6]. Here, we present a case of periodic postoperative fever associated with PT in a trauma patient.

Patient information

A 55-year-old male Han Chinese patient, a worker, with a history of diabetes (not previously on medication), was admitted to the hospital due to multiple injuries caused by a car accident. The patient had no significant medical history or history of hospitalization before admission, no known drug allergies, and no history of chemotherapy, radiation therapy, or immunosuppressive treatment. Family history was negative for significant genetic diseases or syndromes. The patient has a typical Eastern dietary habit and smokes an average of 20 cigarettes per day for 30 years.

Case presentation

In June 2025, a 55-year-old male with a history of type 2 diabetes presented to our hospital due to multiple injuries from a traffic accident. The diagnoses included left open calcaneal fracture, multiple right rib fractures, right pneumothorax, bilateral pulmonary contusion, and subarachnoid hemorrhage. Blood tests revealed: procalcitonin 0.166 ng/mL, C-reactive protein (CRP) 21.47 mg/L, and leukocytes 10.88 × 10^9/L. The patient was started on PT for empiric antibiotic therapy (4.5 g IV, every 8 h).

PT was continued for 17 days, after which the patient underwent open reduction and internal fixation of rib fractures and closed thoracostomy. On postoperative day 2(day 19 of PT treatment), the patient developed fever from 8 PM to 11 PM (temperature range 38.1–39.2 °C), with normal temperatures during the day (Fig. 1A). He had no cough or sputum production. Chest computed tomography (CT) showed right pleural effusion and bilateral pulmonary infiltrates (Fig. 1B). Blood tests revealed: CRP 80.09 mg/L, leukocytes 1.96 × 10^9/L (Fig. 1C). The wound showed mild redness, tenderness, and oozing, and the closed thoracostomy tube drained 150 mL of pale bloody fluid in 24 h. Suspecting wound infection, PT was continued.

Between 8 PM and 11 PM on post-operative day 6 (day 23 of PT treatment), the patient remained febrile.

However, the clinical condition had significantly improved at this point, with the absence of symptoms including cough, sputum production, dyspnea, and chest pain. Mental status and appetite were normal. Heart rate was within the normal range. Chest computed tomography (CT) imaging demonstrated a reduction in pleural effusion and decreased pulmonary inflammatory infiltrates (Fig. 1B). Color Doppler ultrasonography of both lower extremities was negative for deep vein thrombosis. Laboratory findings included a negative blood bacterial culture, reduced CRP and white blood cell levels, while liver enzymes and eosinophils were normal. Wound healing was uneventful, showing no signs of erythema, edema, warmth, or tenderness. Given these findings, although infection cannot be entirely excluded, the cyclical fever in this patient should be considered a possible consequence of PT induction.

Following PT discontinuation, the patient remained fever-free, and leukocyte counts began to gradually normalize (Fig. 1A and C). During PT treatment, we also noted that the patient had prolonged mild anemia and refractory hypokalemia. At this time, the patient's condition was stable, and there was no significant improvement in anemia despite the administration of iron supplementation and high-protein diet. Potassium supplementation was given after hypokalemia, and serum potassium returned to normal, followed by a fluctuating decrease. Both the anemia and hypokalemia gradually normalized after discontinuation of PT (Fig. 1D and E).

Discussion

In our case, fever developed 19 days after the initiation of PT and was cyclical. The onset of fever 2 days after open reduction and internal fixation with a plate for a fractured rib and closed thoracic drainage led us to initially consider common conditions such as postoperative absorbed fever or pulmonary infection, and therefore, PT antiviral therapy was continued. Reexamination of the blood on the fourth day after surgery showed that CRP levels decreased, white blood cell count further decreased, the wound healed well, and the patient's spirit and diet were good. Chest CT showed that right pleural effusion and bilateral lung exudative changes were better than before, but the patient's fever did not improve. Therefore, we considered the possibility of PT-induced fever and discontinued PT therapy; since then, the fever has not recurred. Previous studies have shown that PT-induced drug fever typically occurs within 10 to 23 days of treatment and resolves within 1 to 3 days after drug withdrawal, which is consistent with our findings [7–9]. However, previous reports on PT-induced drug fever did not mention a periodic phenomenon. Studies have shown that PT-induced drug fever is usually a delayed hypersensitivity reaction, in which TP acts as a hapten and combines with proteins in vivo to form a complete antigen, triggering an immune response involving immune complexes or T cells. These immune responses release endogenous pyrogens, leading to an elevated hypothalamic temperature set point [9, 10]. Regarding the periodicity of the fever, it may be related to the inherent circadian rhythm of the human body. The body's endogenous cortisol is secreted most actively during the day, exhibiting antipyretic and anti-inflammatory effects. However, cortisol levels are lowest at night, and its inhibitory effects on fever and inflammation are weakened [11, 12]. The secretion of pyrogens such as tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6) also follows a circadian rhythm, peaking at night, resulting in the phenomenon of elevated body temperature at night and normal body temperature during the day [13, 14].

In addition to periodic fever, during PT treatment, we also found that the patient experienced leukopenia, anemia, and hypokalemia. All these phenomena disappeared after PT treatment was stopped. Uzun et al. also reported fever, leukopenia, and a decrease in white blood cells and neutrophils during PT treatment for a diabetic foot infection, findings consistent with our case [15]. Among these effects, the leukopenia may be due to bone marrow suppression caused by PT. Similarly, we observed anemia in the patient, which may also be related to myelosuppression. However, Zanetti and Yong et al. suggested that immune hemolytic anemia is a main cause of anemia associated with PT [16, 17]. Furthermore, Tai Cheng et al. reported refractory hypokalemia in HIV-infected patients treated with PT combined with tenofovir alafenamide. This refractory hypokalemia was primarily attributed to the negative charge of PT, acting as a non-absorbed anion in the renal tubules. This affects sodium-potassium exchange, leading to increased renal potassium excretion [18, 19]. These observations indicate that although PT is used in different clinical contexts, it can share common side effects. It is also worth noting that case reports have described abnormal liver enzymes, eosinophilia, and thrombocytopenia during PT treatment [7]; however, in our case, liver enzymes, eosinophils, and platelet counts remained normal.

This patient was a post-trauma surgery patient, prone to pulmonary or wound infections, which presented as fever and leukocytosis. Anemia and hypokalemia were often accompanied by the trauma and poor diet. Therefore, when PT treatment overlaps with the periprosthetic infection process, anemia and hypokalemia are often difficult to recognize as evidence of PT-induced side effects, and infectious fever is frequently considered first, potentially leading to the overlook of drug fever. However, if the patient develops periodic fever, drug fever should be considered. Additionally, since the leukopenia induced by PT often shows an opposite trend compared to the

leukopenia caused by post-trauma surgical infection, this is also an important clue for identifying drug fever.

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Author contributions
Fei Zhang and Wuxun Peng drafted the title of the article, and Hong Luo and Xu Zhang consulted and read the literature and completed the literature writing.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare no competing interests.

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