

CASE REPORT

A puerperal patient with agranulocytosis during tazobactam/piperacillin administration : A case report

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Abstract : Tazobactam/piperacillin (TAZ/PIPC) is an injectable combination drug consisting of a broad-spectrum penicillin and a β -lactamase inhibitor. This antimicrobial has a wide spectrum of efficacy against both Gram-positive bacteria and anaerobes. Adverse events usually present as diarrhea or liver dysfunction ; agranulocytosis has not been reported in Japanese patients with puerperal disorders. However, we report a 32-year-old Japanese woman who received TAZ/PIPC to treat an intraperitoneal infection that developed after complications related to transvaginal delivery. Within 14 days of beginning TAZ/PIPC therapy, the patient developed agranulocytosis, indicated by a white blood cell count of 1900 cells/ μ L and a neutrophil count of 475 cells/ μ L. We discontinued TAZ/PIPC at this point and changed the antimicrobial to meropenem. Seven days later, her white blood cell count increased to 3700 cells/ μ L (neutrophil count : 1684 cells/ μ L), and the intraperitoneal infection resolved. Patients receiving TAZ/PIPC should be monitored periodically for agranulocytosis as well as for diarrhea and liver dysfunction. *J. Med. Invest.* 68 : 368-371, August, 2021

Keywords : piperacillin-tazobactam, agranulocytosis, neutropenia, puerperium

INTRODUCTION

Tazobactam/piperacillin (TAZ/PIPC) is a combination antibiotic preparation for injection consisting of a β -lactamase inhibitor, tazobactam (TAZ), and a penicillin antibiotic, piperacillin (PIPC), at a ratio of 1 : 8 (1). As TAZ/PIPC has a broad antimicrobial spectrum against Gram-positive bacteria, such as *Staphylococcus*, gram-negative bacteria, including *Pseudomonas aeruginosa*, and anaerobic bacteria (2), it is routinely used clinically to treat many infectious diseases (3). In Japan, the drug's indications for pneumonia, pyelonephritis, and peritonitis are covered by health insurance. In the Guidelines for the Treatment of Respiratory Infectious Diseases, TAZ/PIPC is recommended as a first-choice drug for hospital-acquired pneumonia (HAP), nursing- and healthcare-associated pneumonia (NHCA), and severe pneumonia (4). In the United States, TAZ/PIPC and carbapenem preparations are recommended as drugs for monotherapy in the guidelines for the management of intraperitoneal infectious diseases collaboratively announced by the Surgical Infection Society and Infectious Diseases Society of America in 2010. As primary adverse reactions, diarrhea and liver dysfunction have been reported, but no case report of agranulocytosis as a serious adverse event has been published in Japanese patients with puerperal disorders. We report a patient in whom the administration of TAZ/PIPC for intraperitoneal infection during puerperium may have induced agranulocytosis.

CASE PRESENTATION

Patient : A 32-year-old female patient.

Complaint : Delivery.

Medical history : Hypothyroidism.

Therapeutic drug : Levothyroxine sodium hydrate.

Family history : Not contributory.

Obstetric history : gravidity, 0 ; parity, 0.

Allergy : Not contributory.

Present illness : She was admitted due to premature rupture of the fetal membranes (Day 5 in Week 39 of pregnancy).

Laboratory data on admission : The laboratory data on admission are presented in the Table.

Physical examination on admission : The patient's height, body weight, body temperature, heart rate, and blood pressure

Table. Laboratory data on Day 4

WBC	98.40	$\times 10^9/\mu\text{L}$	TP	6.4	g/dL
Seg	83.2	%	ALB	3.0	g/dL
Eosin	0.0	%	AST	16	U/L
Baso	0.2	%	ALT	8	U/L
Lymph	11.7	%	LDH	184	U/L
Mono	4.9	%	BUN	5.6	mg/dL
RBC	40.4	$\times 10^5/\mu\text{L}$	Cr	0.37	mg/dL
HGB	10.8	g/dL	eGFR	157.3	mL/min
PLT	20.3	$\times 10^4/\mu\text{L}$	CRP	5.68	mg/dL

WBC : white blood cell count, Seg : segmented neutrophils, Eosin : eosinophils, Baso : basophils, Lymph : lymphocytes, Mono : monocytes, RBC : red blood cells, HGB : hemoglobin, PLT : platelets, TP : total protein, ALB : albumin, AST : aspartate aminotransferase, ALT : alanine aminotransferase, LDH : lactate dehydrogenase, BUN : blood urea nitrogen, Cr : creatinine, eGFR : estimated glomerular filtration rate, CRP : C-reactive protein

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were 155.8 cm, 54.5 kg, 37.2°C, 115 beats/min, and 130/87 mmHg, respectively.

Course after admission : After admission, delivery was induced using oxytocin, and on Day 4, a neonate was born by transvaginal delivery. After delivery, placental separation-related hemorrhage persisted, making management by ligation and blood transfusion difficult ; therefore, total hysterectomy was performed on the same day. From Day 8, fever ($\geq 38^{\circ}\text{C}$) persisted, and blood culture revealed *Bacterioides fragilis* on Day 9, suggesting intraperitoneal infection as an etiological factor. TAZ/PIPC therapy (4.5 g, every 8 hours) was started. Subsequently, the leukocyte count gradually decreased to $1900/\mu\text{L}$ on Day 23 (neutrophil count : $475/\mu\text{L}$), leading to a diagnosis of agranulocytosis. There was no change in the red blood cell count (RBC). There was a slight decrease in the platelet count (PLT), but the value did not meet the diagnostic criterion for thrombopenia. In addition, there were no changes in the eosinophil or basophil count in comparison with the values at admission.

Drug-induced agranulocytosis was suspected, and TAZ/PIPC administration was promptly discontinued. Considering the drug susceptibility of *Bacterioides fragilis* and breast milk transfer, TAZ/PIPC was changed to meropenem (MEPM) (1 g every 8 hours). Subsequently, granulocyte-colony stimulating factor (G-CSF) was not used, and the leukocyte count returned to $3920/\mu\text{L}$ on Day 27 (neutrophil count : $1784/\mu\text{L}$). Concerning the intraperitoneal infection, a reduction in the inflammatory response and fever resolution were noted 2 weeks after confirming a negative blood culture. MEPM therapy ended on Day 30. Subsequently, there was no recrudescence of agranulocytosis or intraperitoneal infection, and the patient was discharged on Day 38 (Fig).

DISCUSSION

We report a patient with agranulocytosis related to TAZ/PIPC administration during puerperium. Agranulocytosis related to

drugs, excluding anticancer drugs, is characterized by a neutrophil count of $\leq 500/\mu\text{L}$, and this adverse event is rare (5). Its incidence is 1–5 person-years per 1,000,000 persons (6). Drugs are involved in the etiology of agranulocytosis in approximately 70% of patients (7).

As drugs that frequently cause agranulocytosis, anti-thyroid drugs, antibiotics, and antipsychotics are known, but only a few patients with TAZ/PIPC-induced agranulocytosis have been reported (8-12) ; no puerperal patient has been reported. A definitive diagnosis of drug-induced agranulocytosis can be made if there is a decrease in the granulocyte count after drug administration in the absence of other factors causing granulocytopenia. However, a decrease in the granulocyte count is not rare in severe-status patients, especially those with infection. Conditions to be differentiated from acute agranulocytosis are viral/bacterial infection, bone marrow failure syndrome, hypersplenism, and drug-induced agranulocytosis (13). In the present case, we were unable to definitively conclude that TAZ/PIPC induced the granulocytopenia. However, considering the reduction in the abscess after the start of TAZ/PIPC therapy and the patient's recovery from protracted leukopenia to a leukocyte count of $5480/\mu\text{L}$ (neutrophil count : $3162/\mu\text{L}$) 12 days after discontinuing TAZ/PIPC administration despite few imaging findings suggestive of infection, TAZ/PIPC may have been etiologically involved in the protracted granulocytopenia in the present case. In addition to TAZ/PIPC, levothyroxine sodium was administered before admission to treat hypothyroidism ; however, no study has reported agranulocytosis related to levothyroxine sodium. Moreover, hematology on admission revealed no abnormalities in the leukocyte or neutrophil counts. Therefore, the possibility of levothyroxine sodium-induced agranulocytosis was excluded, and TAZ/PIPC may have induced the agranulocytosis. However, bone marrow examination was not conducted and a definitive diagnosis was not made, being a limitation.

Although the etiology of drug-induced agranulocytosis remains unclear, two mechanisms, direct toxicity and an immune mechanism, have been proposed (14).

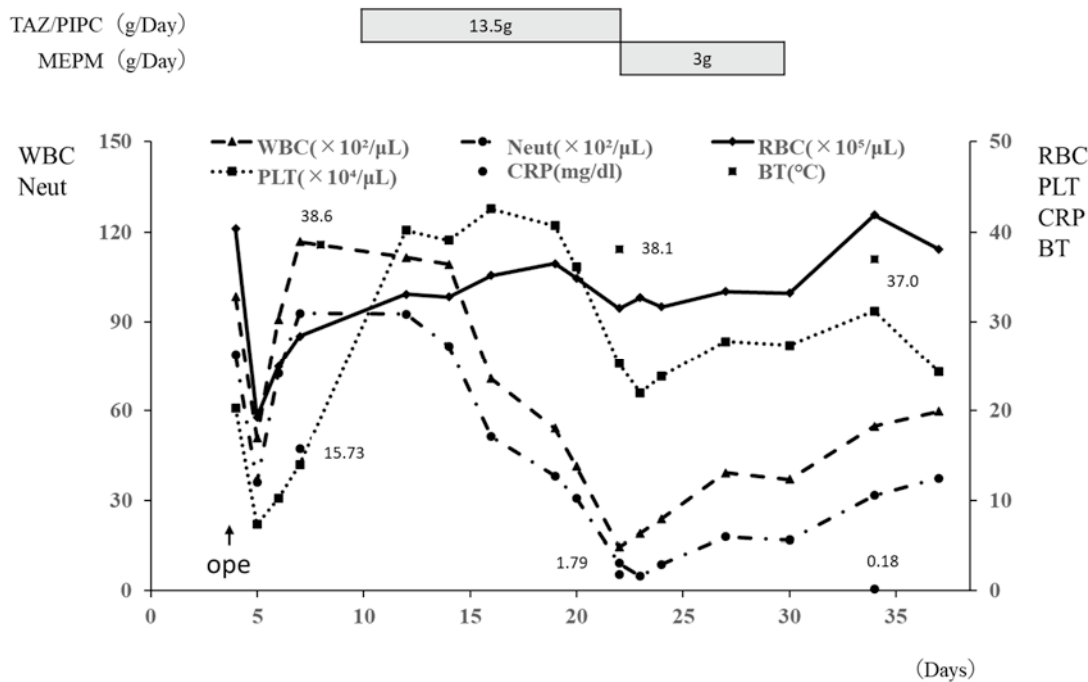


Figure. Leukocyte, neutrophil, red blood cell and platelet counts, C-reactive protein, and body temperature throughout the patient's hospitalization period

In Japan, the reported incidences of TAZ/PIPC- and PIPC-induced agranulocytosis are 0.1 to 5% and unclear, respectively, in the package inserts. We searched for “agranulocytosis” using a system to search for adverse reactions to drugs based on the “Japanese Adverse Drug Event Report database” announced on the Pharmaceuticals and Medical Devices Agency (PMDA) homepage, Drug Information Finding Outcomes (DRIFOs). For the respective drugs, 30 and 14 patients were found, respectively. There was no puerperal disorder in either series. TAZ/PIPC used in the present case is a combination drug that may induce adverse reactions. However, there is no commercially available product consisting of TAZ alone and no study has reported that the addition of TAZ to PIPC increases the risk of adverse reactions; therefore, comparison may be difficult. On the other hand, penicillin-induced agranulocytosis has been reported; therefore, in the present case, the adverse reaction may have been related to PIPC.

Regarding the cross-reactivity of TAZ/PIPC and MEPM, the probability of cross-reactions with carbapenems in patients with penicillin allergy was previously considered to be approximately 50%. However, this was based on a single study involving a small number of patients (15). A recent study reported that cross-reactions with carbapenems occurred in <1% of patients with penicillin allergy (16).

Concerning direct toxicity, antiepileptic and-psychotic drugs were reported to directly act on myeloid cells. The toxicity is induced by the drug itself, a toxic metabolite, or an accessory product. Leukopenia related to direct toxicity develops slowly. In comparison, an immune mechanism is termed a “drug allergy” in some cases, and drug adsorption/immune complex/auto-immune mechanisms are known to occur. The onset of a drug allergy is more rapid than a toxicity. Antibody is produced within 1 hour to 1 day in patients previously sensitized to the drug, and in 7–10 days in non-sensitized patients. Concerning penicillin antibiotics, an immune mechanism may be involved in the onset of agranulocytosis. In the present case, leukocytopenia and neutropenia were observed 14 days after the administration of TAZ/PIPC. This is consistent with the timing of agranulocytosis onset possibly related to an immune mechanism, which is supported by previous studies stating that adverse reactions developed 11–17 days after the use of TAZ/PIPC (11, 17). Furthermore, the risk factors for agranulocytosis are advanced age, female sex, renal hypofunction, and autoimmune diseases (18, 19). However, in the present case, the patient was 32 years old, and the creatinine clearance (Cr) (Cockcroft–Gault equation) was 165.58 mg/dL; there was no renal hypofunction. There was also no history of autoimmune disease.

The agranulocytosis-related mortality rate with TAZ/PIPC is approximately 10%, and agranulocytosis accounts for 20%–30% of drug-related deaths, and is the most frequent causative factor. As protracted/severe neutropenia increases the mortality rate, initial management is important. Therefore, when administering TAZ/PIPC to puerperal patients, neutrophil counts should be monitored to detect agranulocytosis, in addition to monitoring for diarrhea and evaluating liver function.

In the present case, bacteremia due to hospital-onset intraperitoneal infection was noted. To cover the Gram-positive bacteria suspected to be the causative bacteria in addition to *Bacterioides fragilis*, which was detected on blood culture, CFPM+CLDM or MNZ, a quinolone+CLDM or MNZ, or carbapenem antibiotics are considered options. In the present case, it was necessary to select a highly safe drug with low breast milk transfer, considering lactation. CLDM may affect the intestinal flora of children fed breast milk. The carcinogenicity of MNZ in animals and its mutagenicity in humans were previously demonstrated; therefore, healthy infants may be exposed to metronidazole via breast

milk (20). Considering the safety, according to these studies, MEPM with its low-level breast milk transfer was proposed as an alternative to TAZ/PIPC (21), preventing the unnecessary discontinuation of lactation.

In conclusion, we reported a patient with agranulocytosis related to TAZ/PIPC administered during the puerperal period. On the basis on the patient’s previous drug administration history, we considered that agranulocytosis was related to TAZ/PIPC and discontinued the drug, resulting in recovery. When administering TAZ/PIPC, neutrophil counts should be monitored to detect agranulocytosis, in addition to monitoring for diarrhea and evaluating liver function. Furthermore, drug administration should be discontinued at the onset of agranulocytosis, and TAZ/PIPC should be changed to other drugs, if necessary.

ETHICS APPROVAL

This study was performed according to the guidelines of the Declaration of Helsinki, and approved by the ethics committee of Kagawa University (Approval No. 2019-137). Written informed consent was received from the patient for publication of this case report.

CONFLICT OF INTEREST

None of the authors have any potential conflicts of interest associated with this research.

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