Piperacillin-tazobactam-induced myocardial injury with heart failure: A case report

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Abstract. Piperacillin-tazobactam is a clinically used antibiotic consisting of the semisynthetic penicillin piperacillin and the β-lactamase inhibitor tazobactam. Piperacillin-tazobactam is a broad-spectrum antibiotic used clinically to treat infections caused by gram-positive and gram-negative aerobic and anaerobic bacteria. The most common adverse reactions are gastrointestinal symptoms and skin reactions. There have been a few reported cases of possible drug hypersensitivity, with thrombocytopenia as the most commonly observed adverse event. The present article reported a rare case of myocardial injury with heart failure following treatment of pneumonia with piperacillin-tazobactam in a 75-year-old female patient. Specifically, this patient presented with fever, chills, flushing and tachypnea, in addition to elevated leukocyte, neutrophil, cardiac enzyme and brain natriuretic peptide levels. This patient also presented with a mild ST-segment elevation on the electrocardiogram following piperacillin-tazobactam treatment. Improvements in the aforementioned adverse reactions were observed and the underlying infection didn't come back following the discontinuation of piperacillin-tazobactam treatment. Therefore, the present observations suggest that piperacillin-tazobactam may have induced myocardial injury and heart failure. Possible occurrence of similar adverse reactions in the heart should be considered before choosing piperacillin-tazobactam as treatment in clinical practice.

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Introduction

Piperacillin-tazobactam is a broad-spectrum antibacterial drug consisting of the penicillin antibacterial drug piperacillin and the β-lactamase inhibitor tazobactam (1). Piperacillin-tazobactam is effective against gram-positive (such as Staphylococcus aureus, etc.), gram-negative aerobic (such as Escherichia coli, etc.) and anaerobic bacteria (bacteroides fragilis, etc.). It is typically used empirically for treating patients with pulmonary infections (staphylococcus aureus, haemophilus influenzae, pseudomonas aeruginosa, etc.) (2). As a commonly used clinical antibiotic, piperacillin-tazobactam is generally considered safe and well-tolerated (3).

Adverse reactions to piperacillin-tazobactam are rarely reported, with the most common commonly observed adverse reactions including gastrointestinal symptoms (0.9%) and skin reactions (including rashes and itching) (1.3%) (3). Renal dysfunction may increase the risk of adverse reactions. A previous case reported that a patient treated with piperacillin-tazobactam developed an allergic reaction (rash with pruritus) and drug-induced fever (despite negative penicillin skin tests (4). In addition, hematological adverse reactions associated with piperacillin-tazobactam treatment mainly include hemolytic anemia (<1%), thrombocytopenia (<1%) and neutropenia (<1%). Notably, both anemia and thrombocytopenia are associated with autoimmunity and neutropenia with bone marrow suppression (5). Another previous study reported that piperacillin-tazobactam treatment caused DRESS syndrome (an adverse reaction with eosinophilia and systemic symptoms, involving fever, rash, eosinophilia and multi-organ failure). H1 receptor antagonists and corticosteroids were used to treat the adverse reaction (6).

The present article describes the case of an elderly female patient with myocardial injury and heart failure induced by piperacillin-tazobactam treatment. However, this patient experienced a resolution of symptoms, return of blood indicators to normal levels and improvements on electrocardiogram (ECG) parameters following the discontinuation of piperacillin-tazobactam.

Case report

In April 2023, a 75-year-old female patient presented with an unexplained, irregular fever with a maximum temperature of

40˚C that had lasted for 11 days, accompanied by a generalized rash and joint pain. This patient possessed a history of hypertension for >10 years and was treated accordingly with irbesartan. The patient reported no history of coronary atherosclerotic heart disease, diabetes mellitus or hyperlipidemia. The patient was subsequently admitted to Shandong Provincial General Hospital in Jinan, China.

On admission, the patient presented with a body temperature of 38.5˚C, a heart rate (HR) of 78 beats/min and a blood pressure of 123/82 mmHg. The patient was conscious but fatigued, with a scattered rash on the skin of the chest and back. Respiratory sounds were clear in both lungs with no dry or wet rales. In addition, heart sounds were audible and rhythmical, with no heart murmurs. There was no presence of edema in the lower limbs. Results of laboratory tests demonstrated leukocyte levels of $15.58x10^9$/l, neutrophil levels of $13.89x10^9$/l, eosinophil levels of $0.10x10^9$/l, alanine aminotransferase levels of 57 U/l, glutamyl transpeptidase levels of 144 U/l, albumin levels of 26.6 g/l, glucose levels of 8.37 mmol/l, C-reactive protein (CRP) levels of 144.54 mg/l, D-dimer levels of 5.69 μg/ml, brain natriuretic peptide (BNP) levels of 1,655.34 pg/ml, ferritin levels of 4,523.31 ng/ml and positive anti-nuclear antibodies (Table I). The levels of leukocytes, neutrophil, alanine aminotransferase, glutamyl transpeptidase, glucose, CRP, D-dimer, BNP and ferritin were higher than the ref range. These suggested the presence of underlying infection, liver function impairment, hyperglycemia, heart failure, and blood hypercoagulability. Results of a chest CT scan (supplier: Siemens, imaging parameters: KV:120, ref.mAs:135, TI:0.5, SL 5.0/128.0x0.6/p1.5, W1200 C-600) demonstrated ground-glass opacity in both lungs, where patchy and corded shadows were observed in the middle and lower lobes of both right and left lungs (Fig. 1B-D). In addition, multiple small ground glass nodular shadows were observed in the upper and lower lobes of both lungs, where a large nodular shadow was observed in the upper lobe of the left lung, with a diameter of ~0.7 cm (Fig. 1A). There was calcification of the aorta and coronary arteries (Fig. 1E and F). Results of a coronavirus-19 (COVID-19) test, respiratory pathogen test, rheumatic series, Epstein-Barr virus test and blood, sputum and urine cultures all returned normal. Numerous clinical consultations and expert discussions led to the potential diagnoses of adult Still disease, pulmonary infection, hypoproteinemia, liver damage and hypertensive disease. Anti-infective piperacillin-tazobactam (4.5 g q12h iv.) and anti-inflammatory methylprednisolone sodium succinate (20 mg q12h i.v.) were administered to the patient, alongside symptomatic treatments, such as an anti-pyretic [ibuprofen (0.1 g prn po)] and liver function protection [glutathione (0.4 g qd po)]. Following 3 days of hospitalization, the body temperature of the patient returned to 37˚C, the rash cleared and the joint pain was relieved.

After nine of days, laboratory indicators were assessed again and the results demonstrated leukocyte levels of $11.84x10^9$/l, neutrophil levels of $9.81x10^9$/l, eosinophil levels of $0.15x10^9$/l, glutamyl transpeptidase levels of 97 U/l, albumin levels of 31.5 g/l, glucose levels of 3.82 mmol/l, CRP levels of 16.95 mg/l, sedimentation rate of 33 mm/h, D-dimer levels of 6.71 μg/ml and ferritin levels of 4,286.03 ng/ml (Table I). The levels of leukocytes, neutrophil, glutamyl transpeptidase, CRP, sedimentation rate, D-dimer, BNP and ferritin were higher than the ref range. These suggested the presence of underlying infection, liver function impairment, heart failure, and blood hypercoagulability. In addition, levels of alanine aminotransferase returned to normal (39 U/l, reference range: 9-50 U/l). However, the condition of the patient worsened at night. Specifically, the temperature of the patient increased to 40˚C, accompanied by chills, cold extremities and a loss of mental activity. Furthermore, the cause of the fever remained unknown and no improvements in the condition were observed. Transferal to a different hospital for treatment was recommended and the patient was discharged 2 days later and presented to outpatient clinic of the affiliated hospital of Shandong university of traditional Chinese medicine (Jinan, China).

The patient was admitted following a review of their medical history. On admission, her body temperature was 36.6˚C, with an HR of 57 beats/min and blood pressure of 166/84 mmHg. The patient's fever was paroxysmal. The patient would experience chills when the body temperature was >37.5˚C. Once the fever had subsided after ibuprofen (0.1 g prn po), the overall condition of the patient improved, with the rash cleared, wrist and knee pain being less severe compared with that reported 10 days prior. There was also no cough or presence of sputum and a 93% oxygen saturation recorded using a finger pulse. The ECG reading also appeared normal. Results of laboratory tests demonstrated potassium levels of 2.55 mmol/l, leukocyte levels of $16.47x10^9$/l, neutrophil levels of $13.51x10^9$/l, eosinophil levels of $0.38x10^9$/l, CRP levels of 43 mg/l, procalcitonin (PCT) levels of 2.13 ng/ml and D-dimer levels of 14.37 μg/ml (Table I). In addition, myocardial enzymes were increased, where results of further laboratory tests demonstrated creatine kinase isoenzyme levels of 1.75 ng/ml, creatine kinase levels of 195 U/l, lactate dehydrogenase levels of 275 U/l, α-hydroxybutyrate dehydrogenase levels of 193 U/l and BNP levels of 730 pg/ml. It was determined that the patient had been administered piperacillin-tazobactam at a previous hospital after a negative penicillin skin test result, based on reports from the patient family.

Although no bacterial infection was identified, the patient had pneumonia and both leukocyte and neutrophil levels were higher than the ref range. The patient was administered 4.5 g piperacillin-tazobactam as the treatment of pneumonia every 12 h on the day of admission, as recommended by American Thoracic Society/Infectious Diseases Society of America guidelines (7). In addition, the patient was fitted with a potassium chloride pump (30 mg st ivvp) and administered potassium citrate granules (2 g tid po) for potassium supplementation, ibuprofen (0.1 g prn po) for anti-inflammation and antipyretic, valsartan (80 mg qd po) and nifedipine (30 mg qd po) for blood pressure control, in addition to enoxaparin sodium (5000 U qd ih) for anticoagulation. At 7:00 p.m. on the first day of admission (11 days after initial admission), the patient developed chills, clenched hands, clenched teeth, fever with a temperature of 38˚C and irritability. The patient was subsequently intravenously administered with 40 mg methylprednisolone sodium succinate and low-flow oxygen. At 8:30 p.m, the chills subsided, though the patient was still experiencing flushing and tachypnea with a body temperature of 40˚C. Therefore, the patient was treated with physical cooling, ibuprofen (0.1 g prn po), dexamethasone sodium phosphate

Table I. Specific numbers of laboratory tests during the entire treatment process of the patient.

Laboratory tests	Normal value range	11 days before admission	2 days before admission	Day 1	Day 2	Day 3	Day 5	Day 7	Day 11	Day 13	Day 14	Day 16
Leukocyte, x10^9/l	3.5-9.5	15.58	11.84	16.47	N	21.27	15.49	11.94	7.62	11.1	21.95	7.53
Neutrophil, x10^9/l	1.80-6.30	13.89	9.81	13.51	N	18.82	10.48	8.36	6.18	10.64	21.08	6.38
Eosinophil, x10^9/l	0.02-0.52	N	N	0.38	N	0.15	0.32	0.10	N	0.05	0.12	0.02
Albumin, g/l	40-55	26.6	31.5	N	26.8	N	N	33.4	N	N	N	N
Glucose, mmol/l	3.9-6.1	8.37	3.82	N	7.73	N	N	N	N	N	N	N
C-reactive protein, mg/l	0-10	144.54	16.95	43	43	N	26	8.6	N	4.7	4.1	N
D-dimer, μg/ml	0-0.5	5.69	6.71	14.37	N	4.91	N	2.67	N	N	N	N
Brain natriuretic peptide, pg/ml	0-125	1655.34	N	730	7046	N	N	4922	2145	1621	6537	4888
Ferritin, ng/ml	13-150	4523.31	4286.03	N	4858	N	N	N	N	N	N	1145
Troponin I, ng/ml	0-0.1	N	N	1.995	3.378	1.29	0.39	0.114	N	N	0.037	N
Procalcitonin, ng/ml	0-0.1	N	N	2.13	N	N	N	1.81	N	0.35	15.28	3.41
Creatine kinase isoenzyme, ng/ml	0-5	N	N	1.75	10.31	5.99	N	2.14	N	2.1	4.77	1.71
Creatine kinase, U/l	50-310	N	N	195	366	174	N	10	N	19	355	50
Lactate dehydrogenase, U/l	120-250	N	N	275	568	519	N	248	N	293	276	209
α-hydroxybutyrate dehydrogenase, U/l	59-126.4	N	N	193	401	316	N	176	N	214	172	149

N, not measured.

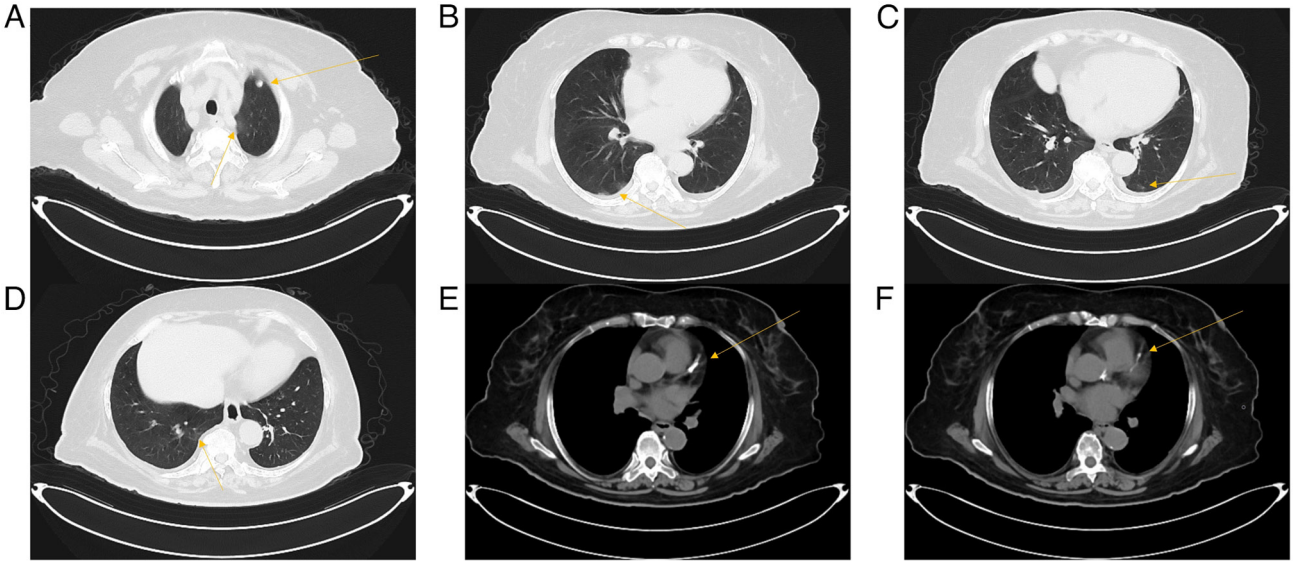

Figure 1. Chest CT demonstrating (A) a large nodular shadow in the upper lobe of the left lung, (B-D) an increased texture with patchy and corded shadows in different parts of both lungs and (E and F) different branches of coronary artery calcification.

(5 mg st iv) and lansoprazole (30 mg st iv.). Blood cultures were drawn and assessed, where ECG monitoring and finger pulse oxygen monitoring were also performed. At 11:20 p.m, the temperature of the patient had decreased to 37.5˚C and all other symptoms were resolved.

The following morning (1 day post-admission), the patient developed chills and a high fever on completion of a piperacillin-tazobactam infusion. Myocardial enzymes were increased and results of the laboratory tests demonstrated creatine kinase isoenzyme levels of 10.31 ng/ml, creatine kinase levels of 366 U/l, lactate dehydrogenase levels of 568 U/l, α-hydroxybutyrate dehydrogenase levels of 401 U/l, troponin I levels of 3.378 ng/ml, BNP levels of 7,046 pg/ml, ferritin levels of 4,858 ng/ml, albumin levels of 26.8 g/l, glucose levels of 7.73 mmol/l, glycosylated hemoglobin levels of 7% and CRP levels of 43 mg/l. In addition, liver function, lymphocyte subsets, rheumatic series and immunoglobulin levels were normal. ECG demonstrated mild ST-segment elevation. The patient did not exhibit any chest tightness, chest pain or dyspnea and had a blood pressure of 110/70 mmHg, an HR of 72 beats/min and no notable dry and wet rales or heart valve murmurs on auscultation of both lungs. Subsequent consultation with a cardiovascular specialist recommended that the patient should undergo a coronary angiography. However, the patient's family declined due to risks associated with old age and painful symptoms experienced by the patient. Following review of the patient's history of hypertension and other medical conditions, clinical symptoms and examination results, the cardiovascular specialist determined that the patient presented with myocardial injury with heart failure. In addition, the potential for acute coronary syndrome was suspected to be high. However, the cardiovascular specialist did not exclude the possibility of myocarditis and pericarditis. Subsequently, the patient was administered spironolactone (20 mg qd po), sacubitril valsartan sodium (100 mg qd po) and dapagliflozin (10 mg qd po) for the correction of heart failure, aspirin (0.1 g qd po) for antiplatelet aggregation, atorvastatin (20 mg qn po) and ezetimibe (10 mg qd po) to stabilize plaque formation. Following expert advice, the advanced antibiotic imipenem-cilastatin sodium hydrate was administered 0.5 g every 8 h to control the lung infection. At 9:00 p.m, troponin I levels were measured to be 2.003 ng/ml.

The next day (2 days post-admission, 13 days after initial admission), the body temperature of the patient was maintained at 37˚C. Results of a cardiac ultrasound suggested an aortic valve calcification and reduced left ventricular systolic function, with an ejection fraction of 49%. Results of the ECG demonstrated a decrease in ST-segment elevation from the levels previously observed. Results of the laboratory tests revealed leukocyte levels of $21.27x10^9$/l, neutrophil levels of $18.82x10^9$/l, eosinophil levels of $0.15x10^9$/l, D-dimer levels of 4.91 μg/ml and troponin I levels of 1.29 ng/ml. The levels of leukocytes, neutrophil, D-dimer, and troponin I were higher than the ref range. These suggested the presence of underlying infection, myocardial injury, and blood hypercoagulability. In addition, myocardial enzymes were increased and results of the laboratory tests demonstrated creatine kinase isoenzyme levels of 5.99 ng/ml, creatine kinase levels of 174 U/l, lactate dehydrogenase levels of 519 U/l and α-hydroxybutyrate dehydrogenase levels of 316 U/l.

At 4 days (15 days after initial admission) post-admission, results of laboratory tests demonstrated leukocyte levels of $15.49x10^9$/l, neutrophil levels of $10.48x10^9$/l, eosinophil levels of $0.32x10^9$/l, CRP levels of 26 mg/l and troponin I levels of 0.39 ng/ml. The levels of leukocyte, neutrophil, CRP, and troponin I were higher than the ref range. These suggested the presence of underlying infection, and myocardial injury. Results of the ECG demonstrated a T-wave inversion as compared with the results previously described. Results obtained following galactomannan and (1,3)-β-D-glucan detection, a COVID-19 test, and an influenza virus test were all negative. In addition, metagenome next-generation sequencing was performed externally (Kindstar Global) using blood samples. This is based on macro-genomics and high-throughput sequencing technology

that allows for the indiscriminate detection of all pathogens, including bacteria, fungi, viruses, parasites, mycoplasma and chlamydia in a variety of clinical specimens (8). However, results of the metagenome next-generation sequencing revealed that no pathogens were present. Since no definitive source of infection was identified, an expert opinion was obtained from a rheumatologist, who confirmed the potential for adult Still disease. Therefore, the patient was administered methylprednisolone sodium succinate (20 mg qd iv.) for anti-inflammation, methotrexate (10 mg qw po) and folic acid (10 mg qw po) for immunosuppression, calcium carbonate D3 (0.6 g qd po) for osteoporosis prevention and metoprolol tartrate (12.5 mg qd po) for ventricular rate control. Additional ECGs were performed the next day (5 days post-admission) and the results demonstrated progressive decrease in the ST-segment and an inverted T-wave. Subsequently, 1 day later (6 days post-admission), results of laboratory tests demonstrated leukocyte levels of $11.94x10^9$/l, neutrophil levels of $8.36x10^9$/l, eosinophil levels of $0.10x10^9$/l, CRP levels of 8.6 mg/l, D-dimer levels of 2.67 μg/ml, PCT levels of 1.81 ng/ml, troponin I levels of 0.114 ng/ml, BNP levels of 4,922 pg/ml and albumin levels of 33.4 g/l (reference range: 40-55 g/l). In addition, myocardial enzymes were decreased and results of laboratory tests demonstrated creatine kinase isoenzyme levels of 2.14 ng/ml, creatine kinase levels of 10 U/l, lactate dehydrogenase levels of 248 U/l and α-hydroxybutyrate dehydrogenase levels of 176 U/l. Of note, improvements were observed in the results of all laboratory tests. The condition of the patient was stable for the following 5 days (7-11 days post-admission) and there was no change in the treatment plan.

Since the condition of the patient stabilized, further laboratory tests were performed on day 12 post-admission (23 days after initial admission). Results of the laboratory tests demonstrated leukocyte levels of $11.1x10^9$/l, neutrophil levels of $10.64x10^9$/l, eosinophil levels of $0.05x10^9$/l, CRP levels of 4.7 mg/l, PCT levels of 0.35 ng/ml and BNP levels of 1,621 pg/ml. In addition, myocardial enzymes were stable; laboratory tests demonstrated creatine kinase isoenzyme levels of 2.1 ng/ml, creatine kinase levels of 19 U/l, lactate dehydrogenase levels of 293 U/l and α-hydroxybutyrate dehydrogenase levels of 214 U/l. Results of the ECG demonstrated a T-wave inversion. The patient's condition gradually stabilized, and experts suggested that antibiotics should be downgraded. Following expert advice, antibiotic step-down treatment was prescribed, where 4.5 g piperacillin-tazobactam was administered every 12 h to control infection following a negative penicillin skin test. Following infusion in the afternoon, the patient presented with a sore throat, chills, flushing, tachypnea, an elevated temperature of 38.8˚C and a 97% oxygen saturation. In addition, the blood pressure of the patient was 110/80 mmHg, the HR was 100 beats/min and the ECG demonstrated a mild ST-segment elevation. The patient was treated with physical cooling, dexamethasone sodium phosphate (5 mg st iv) and ibuprofen (0.1 g prn po), though the symptoms did not improve. Therefore, the presence of adverse reactions following treatment with piperacillin-tazobactam was considered. The patient was administered anti-allergy treatment with promethazine hydrochloride (25 mg st im) and calcium gluconate (1 g st iv), with piperacillin-tazobactam discontinued. This resulted in the gradual alleviation in the symptoms of the patient.

The following day (13 days post-admission), all laboratory parameters were reviewed. Results of the laboratory tests demonstrated leukocyte levels of $21.95x10^9$/l, neutrophil levels of $21.08x10^9$/l, eosinophil levels of $0.12x10^9$/l, CRP levels of 4.1 mg/l, PCT levels of 15.28 ng/ml, troponin I levels of 0.037 ng/ml and BNP levels of 6,537 pg/ml. In addition, myocardial enzymes were increased and results of the laboratory tests demonstrated creatine kinase isoenzyme levels of 4.77 ng/ml, creatine kinase levels of 355 U/l, lactate dehydrogenase levels of 276 U/l and α-hydroxybutyrate dehydrogenase levels of 172 U/l. Results of the ECG demonstrated ST-segment recovery close to baseline compared with the results observed the day prior, with T-wave inversion. Following the discontinuation of piperacillin-tazobactam, no additional antibiotics were administered.

All laboratory parameters were re-assessed 2 days later (15 days post-admission). Results of the laboratory tests demonstrated leukocyte levels of $7.53x10^9$/l, neutrophil levels of $6.38x10^9$/l, eosinophil levels of $0.02x10^9$/l, PCT levels of 3.41 ng/ml, BNP levels of 4,888 pg/ml and ferritin levels of 1,145 ng/ml. In addition, myocardial enzymes were decreased, and results of the laboratory tests demonstrated creatine kinase isoenzyme levels of 1.71 ng/ml, creatine kinase levels of 50 U/l, lactate dehydrogenase levels of 209 U/l and α-hydroxybutyrate dehydrogenase levels of 149 U/l. The next day (16 days post-admission), results of the ECG demonstrated T-wave inversion and the patient demonstrated no signs of fever since day 12 post-admission. By day 17 post-admission (28 days after initial admission), the condition of the patient was stable (joint pain and skin rash disappeared) and the patient was discharged from the hospital following expert advice. One month after discharge, myocardial injury and heart failure symptoms gradually improved and she did not develop fever.

The change curves of laboratory examination results during hospitalization were shown in Fig. 2. The changes in electrocardiogram results during hospitalization were presented in Fig. 3. The changes in body temperature and HR of the patient during hospitalization were presented in Fig. 4. The patient and the family of the patient approved the full treatment plan. Written informed consent was obtained from the patient. The present case was reported in accordance with the CARE guidelines (9).

Discussion

The present article reports the case of a rare adverse reaction, specifically myocardial injury with heart failure, caused by piperacillin-tazobactam. Previous studies reported that the majority of adverse reactions associated with piperacillin-tazobactam were gastrointestinal symptoms and skin reactions (including rashes and itching). Neutropenia and thrombocytopenia being the most common hematological adverse reactions (10,11). However, the presence of fever caused by an allergic reaction has also been reported (12), whereas a rare case of fever, eosinophilia and liver injury caused by piperacillin-tazobactam treatment has been documented in another case (13). Furthermore, Jafri *et al* (14) reported a case of induced hypersensitivity myocarditis, a rare complication of drug-related myocardial injury, following the use of

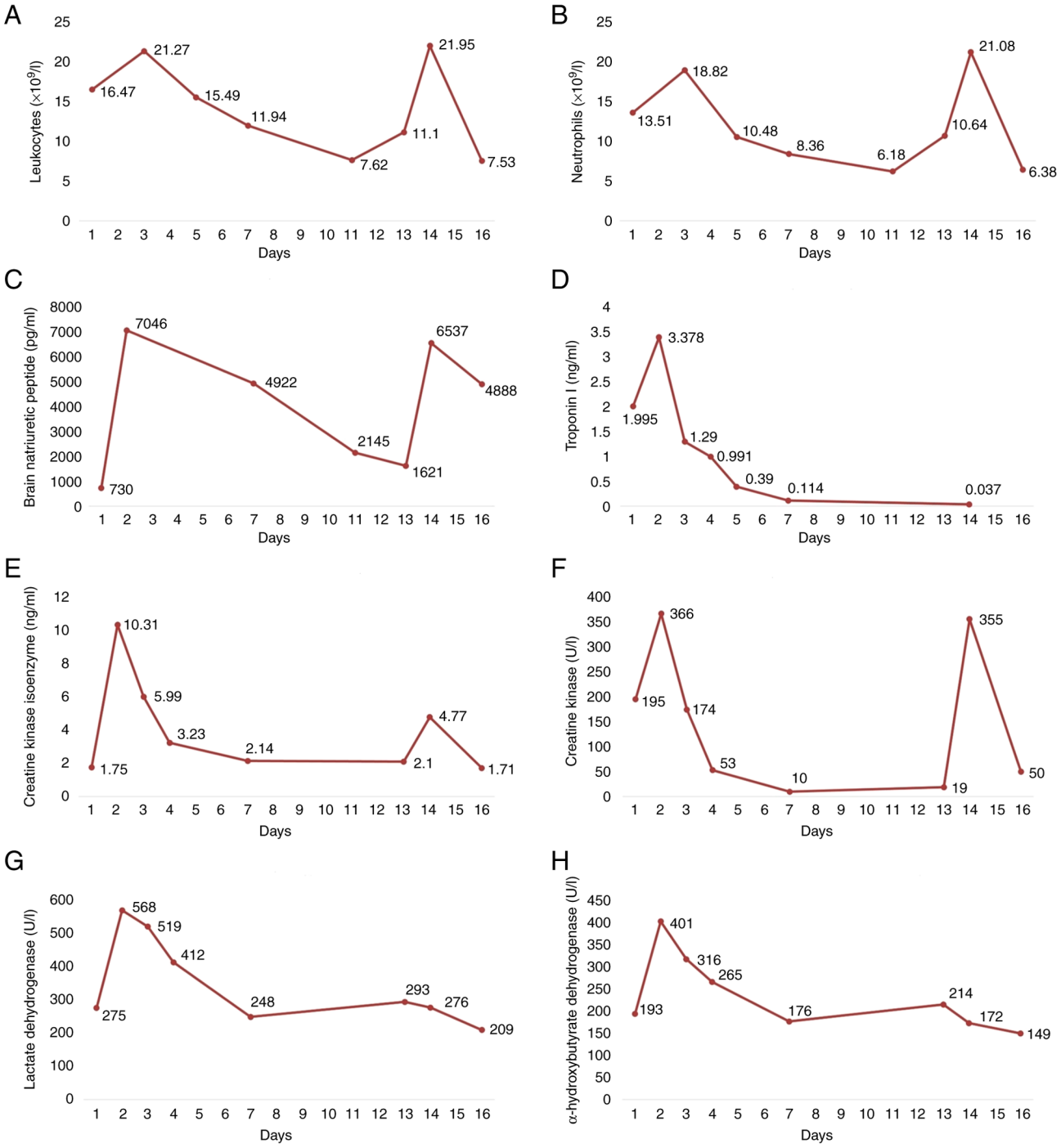

Figure 2. Changes during the patient's hospitalization in levels of (A) leukocytes, (B) neutrophils, (C) brain natriuretic peptide, (D) troponin I, (E) creatine kinase isoenzyme, (F) creatine kinase, (G) lactate dehydrogenase and (H) α-hydroxybutyrate dehydrogenase.

piperacillin-tazobactam. Calogiuri *et al* (15) reported a case of myocardial injury as a result of Kounis syndrome following the intravenous administration of piperacillin-tazobactam. Kounis syndrome is a rare allergic reaction that manifests as coronary vasospasm, which may lead to angina pectoris or anaphylactic myocardial infarction (16). Therefore, following the findings of the aforementioned studies, the present case report may further the current understanding of the association between piperacillin-tazobactam use and myocardial injury, which provide further evidence for guiding the use of piperacillin-tazobactam in clinical practice.

The present article details the case of an adverse reaction leading to myocardial injury with heart failure in a patient treated with piperacillin-tazobactam for an unexplained fever. The patient had a history of hypertension for >10 years. Following admission to hospital, coronary artery calcification was observed in the chest CT scan of the patient. Of note, it was considered that the patient may have a history of sub-clinical coronary atherosclerotic heart disease that the patient and family were unaware of, due to a lack of clinical symptoms. Prior to admission, fasting blood glucose levels were 8.37 mmol/l, indicating that the patient had a history of

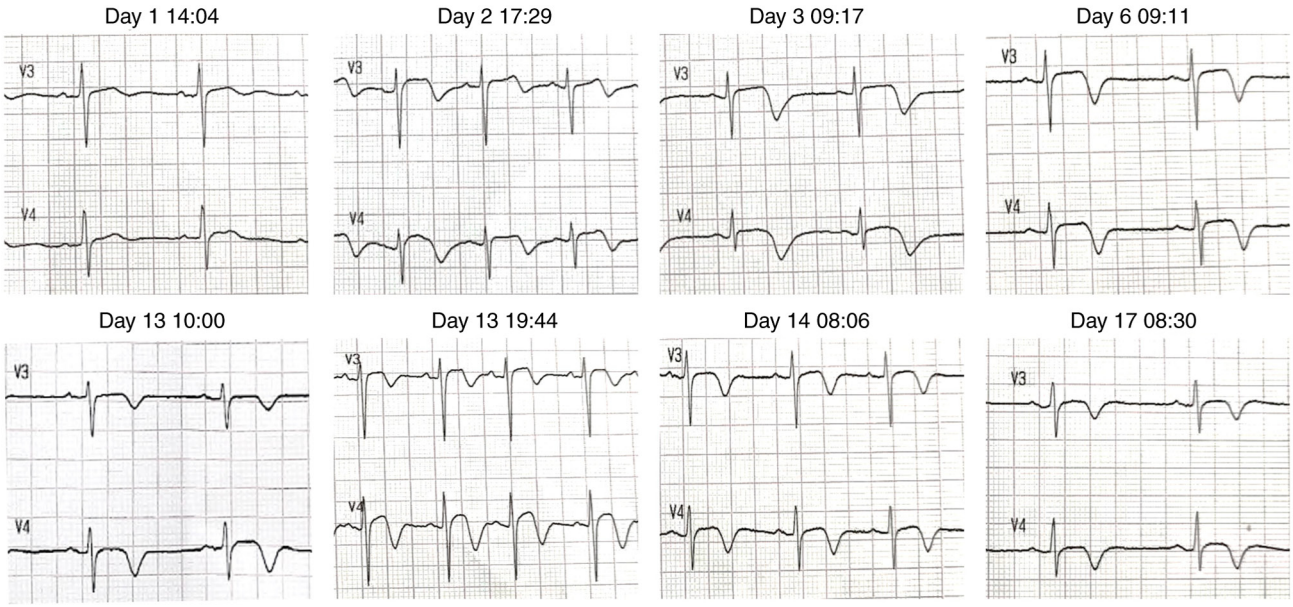

Figure 3. Changes in electrocardiogram results during the patient hospitalization.

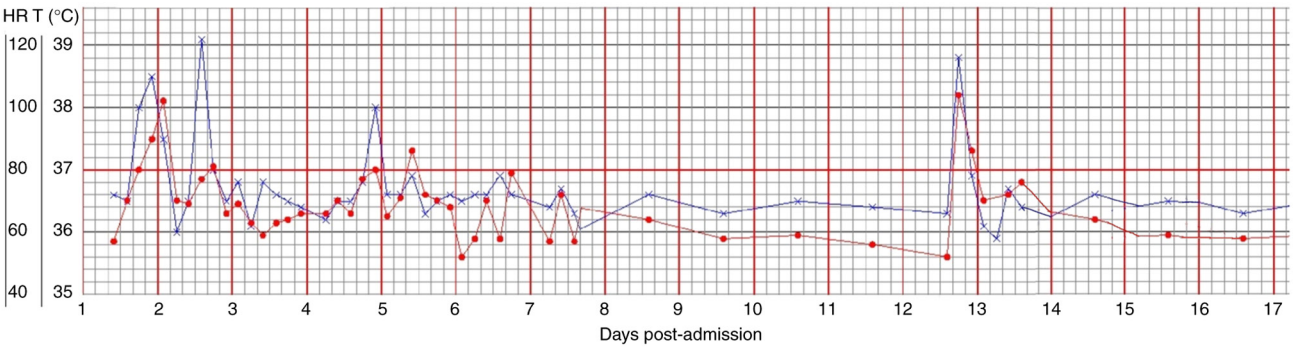

Figure 4. Changes in the patient body temperature and HR during hospitalization. This patient received piperacillin-tazobactam on day 1 and day 12 post-admission. HR, heart rate; T, temperature. Blue curves indicate temperature and red indicate HR.

hyperglycemia. As the patient had recently been treated with glucocorticoids, it was considered that the hyperglycemia may have been associated with the use of hormones. The patient developed fever, chills, clenched hands, clenched teeth, flushing and tachypnea following piperacillin-tazobactam treatment. Blood indicators, including leukocytes, neutrophils, creatine kinase isoenzyme, creatine kinase, lactate dehydrogenase, α-hydroxybutyrate dehydrogenase and BNP were all elevated, whereas the ECG demonstrated ST-segment elevation in certain leads, with myocardial injury and heart failure. Following the discontinuation of piperacillin-tazobactam, the body temperature of the patient returned to normal, systemic symptoms were resolved and all blood indicators returned to normal levels after 4 days. Therefore, results of the present study demonstrated a potential association between the aforementioned adverse reactions and piperacillin-tazobactam treatment.

The present case was suspected with adult Still disease before admission, which was also a suspected diagnosis in the previous hospitals the patient was admitted to. The patient was already prescribed methylprednisolone sodium succinate before admission, which was continued following admission. Levels of CRP and ferritin improved throughout the course of treatment without notable fluctuations, which may be associated with improvements in adult Still disease. The use of piperacillin-tazobactam again was associated with the exacerbation of the disease and was not linked to the dosage of steroids. Throughout the treatment course, symptoms were closely associated with piperacillin-tazobactam. The patient symptoms worsened and improved with the use and discontinuation of piperacillin-tazobactam. In addition, eosinophil levels remained within the normal range. PCT and troponin I levels were transiently elevated, but the potential association of these indicators with piperacillin-tazobactam treatment remains to be fully elucidated. Following the discontinuation of piperacillin-tazobactam treatment, PCT and troponin I levels returned to normal.

The event of myocardial injury with heart failure following piperacillin-tazobactam treatment is rare (14). The patient presented at Affiliated hospital of Shandong university of traditional Chinese medicine with an unexplained fever, where the underlying cause remained the key focus. Whilst aiming to

determine the underlying cause of the fever and any potential infections, adverse effects associated with piperacillin-tazobactam treatment were not acknowledged. Due to the elevated levels of leukocytes accompanied by lung inflammation observed on a CT scan, a penicillin skin test was performed. Notably, results of the penicillin skin test were negative and the patient had been administered piperacillin-tazobactam at a previous hospital with no history of a penicillin allergy. Therefore, piperacillin-tazobactam treatment was continued. However, following antibiotic step-down treatment, the results of the present study indicated that piperacillin-tazobactam was the direct cause of the induction of myocardial injury and heart failure. Following discontinuation of piperacillin-tazobactam, no additional antibiotics were administered to the patient and the condition of the patient improved. On admission to affiliated hospital of Shandong university of traditional Chinese medicine, the patient was only administered piperacillin-tazobactam twice, which did not cause any further harm to the patient. The medical history of the patient was then reviewed, where it was determined that underlying cardiovascular risk factors, such as hypertension, hyperglycemia and coronary artery calcification, may have resulted in piperacillin-tazobactam-induced myocardial injury. Therefore, clinicians should consider the use of piperacillin-tazobactam treatment in patients with a history of cardiovascular risk factors, such as hyperlipidemia, hyperglycemia and hypertension.

In addition, the patient exhibited liver dysfunction following piperacillin-tazobactam treatment at a previous hospital. Following treatment, liver function had returned to normal before discharge. Therefore, it was considered that liver dysfunction may have been associated with the prolonged use of piperacillin-tazobactam. Notably, a previous study reported the case of a patient with liver dysfunction [serum alanine aminotransferase levels exceeded the upper limit of reference range (50 U/l)] resulting from piperacillin-tazobactam treatment (16). However, the potential association with mortality or disease progression remains unclear. In a retrospective study, Saloojee *et al* (17) demonstrated that piperacillin-tazobactam treatment was associated with liver dysfunction in 225 critically ill patients. By contrast, McDonald *et al* (18) previously observed no significant difference in the levels of hepatotoxicity between high and licensed doses of piperacillin-tazobactam treatment. In the present case, the patient exhibited a normal ECG with a mild elevation of cardiac enzymes on admission to the affiliated hospital of Shandong University of traditional Chinese medicine, rendering mild myocarditis initially considered. Since the patient had been administered piperacillin-tazobactam several times prior to admission, drug-induced myocarditis and pericarditis could not be ruled out. It was considered that myocardial damage may have been associated with the accumulation of piperacillin-tazobactam in the body, specifically due to an allergic reaction induced by repeated treatment. The patient exhibited flushing, chills, tachypnea, tachycardia and decreased blood pressure, which are all symptoms of allergy (19). In addition, clenched hands, clenched teeth and muscle cramps may be signs of antibiotic encephalopathy comparable with epilepsy (20). Therefore, drug fever, allergic reactions and antibiotic encephalopathy, in addition to myocardial injury and heart failure, were considered to be associated with piperacillin-tazobactam treatment. However, the specific mechanisms underlying myocardial injury caused by piperacillin-tazobactam remain to be fully elucidated. It was hypothesized that myocardial injury was induced by cardiovascular risk factors in the patient, such as hypertension and hyperglycemia, whereby adverse reactions, such as drug fever and allergic reactions, were not directly caused by piperacillin-tazobactam treatment.

Adverse drug reactions may be considered if the source of fever cannot be determined following radiography, blood indicators or microbiological cultures. Notably, the patient in the present case exhibited numerous underlying diseases, including hypertension, hyperglycemia, coronary atherosclerotic heart disease, a history of cerebral infarction, pneumonia and a potential diagnosis of adult Still disease. Despite the involvement of multidisciplinary experts, the condition of the patient was complex and treatment designation was particularly difficult.

To conclude, the present article reports the case of myocardial injury and heart failure caused by a piperacillin-tazobactam-induced allergic reaction. Results of ECGs and the levels of cardiac enzymes highlighted the potential for myocardial injury due to drug-induced myocarditis. Therefore, myocardial injury and heart failure, though rare, should be considered adverse reactions of piperacillin-tazobactam treatment, suggesting that piperacillin-tazobactam may be cardiotoxic. Clinicians should cautiously consider the use of piperacillin-tazobactam treatment in patients with a history of cardiovascular risk factors, such as hyperlipidemia, hyperglycemia and hypertension.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YL contributed to conception and design. YL and LS collected data and drafted the manuscript. YL analyzed and interpreted data. CA and XA drew the figures and tables. YL and LS obtained medical images (e.g. CT scans). YL, XZ, LS and QZ advised on patient treatment. YL, CA, XA, XZ and LS confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of any images or data included in the present paper.

Competing interests

The authors declare that they have no competing interests.

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