CASE REPORT

Drug fever induced by piperacillin/tazobactam in an elderly patient with underlying human immunodeficiency virus (HIV) infection

Thein Swe, Mir Ali, Akari Thein Naing

Department of Internal Medicine, Interfaith Medical Center, Brooklyn, New York, USA

Correspondence to
Dr Thein, Swe,
mglay2004@gmail.com

Accepted 6 July 2016

SUMMARY

Our search of the literature revealed no detailed case reports about drug fever induced by piperacillin/tazobactam in a patient with HIV infection although there were a few case reports about drug fever due to piperacillin/tazobactam with other comorbidities. A 63-year-old male patient with HIV positive was admitted for acute cholecystitis. He was started on piperacillin/tazobactam. For the next 8 days, he had intermittent fever up to 103°F (39.4°C) with relative bradycardia although he showed clinical improvement. There was no laboratory or imaging findings suggestive of another infectious source and drug fever was suspected. The antibiotics were stopped and after 48 hours no fever was observed until the day of discharge. Piperacillin/tazobactam can induce fever in patients with cystic fibrosis and in patients with other conditions. Drug fever may be more prevalent in patients with HIV infection. It has no characteristic pattern and may not be associated with eosinophilia.

BACKGROUND

Drug fever alone is often underdiagnosed by clinicians. Fever can be the only manifestation of an adverse drug reaction in 3–5% of cases.^{1 2} It is most commonly found after 7–10 days of drug administration, persists as long as the drug is continued, disappears soon after stopping the drug and will rapidly reappear if the drug is restarted. The drugs most commonly associated with drug fever include the penicillins, cephalosporins, quinidine, procainamide, methylidopa and phenytoin.²

Early diagnosis and treatment of drug fevers are crucial in maintaining cost-effective, high-quality patient care. If drug fever is not recognised, patients may be subjected to prolonged hospitalisation and unnecessary testing or medications.³

Drug fever is associated with relative bradycardia in a minority of cases, shows no characteristic fever pattern, exhibits a highly variable lag time between the initiation of the offending agent and the onset of fever and only a few cases are associated with either rash or eosinophilia.⁴

Hypersensitivity is the most common cause of drug fever.^{1 3} The mechanism appears to be the formation of circulating antibody–antigen complexes and/or a T-cell immune response triggered by a drug or its metabolites.

CASE PRESENTATION

A 63-year-old male patient came to the emergency department and reported of non-bloody vomiting for 7 days and right upper quadrant abdominal pain for 2 days. He had been vomiting for 1 week, about once a day, non-bloody, not related to food, not associated with syncope, dizziness or headache. He started having abdominal pain 2 days prior, especially in the right upper quadrant, 9 of 10 in intensity, sharp in nature, no radiation, no specific aggravating or relieving factors and not associated with diarrhoea or constipation. However, he reported having fever (unrecorded) for 1 day. He denied chest pain, dyspnoea, palpitations, orthopnoea or urinary symptoms. Review of other systems was unrevealing. He has no known drug allergies. His other medical problems include hypertension, stage 3 chronic kidney disease, heart failure with preserved ejection fraction, dyslipidaemia, seizure disorder and HIV infection. He is on antiretroviral therapy (for 22 years). He was a former smoker and former alcoholic but quit more than 10 years ago. His home medications were aspirin, furosemide, labetalol, nifedipine, phenytoin, pravastatin, darunavir, emtricitabine, raltegravir and ritonavir. On physical examination, his temperature was 100.2°F (37.9°C), pulse rate was 95 bpm and blood pressure was 129/80 mm Hg without orthostasis. There was right upper quadrant tenderness with positive Murphy's sign; however, there were no signs of rebound tenderness, guarding or rigidity indicating acute peritonitis. All other system examinations were within normal limits except for dry mucous membranes.

INVESTIGATIONS

The initial laboratory reports revealed white cell count (WCC) of 13 900/μL with 74% neutrophils, absolute neutrophil count of 10.2k/μL, eosinophil count of 300 cells/μL, haemoglobin of 12.3 g/dL, platelet count of 297 000/μL, erythrocyte sedimentation rate of 50 mm/hour and C reactive protein level of 55 mg/L. The patient's electrolytes were within normal range except for an abnormal carbon dioxide of 20 mmol/L, blood urea nitrogen of 31 mg/dL, creatinine of 3.2 mg/dL and calculated glomerular filtration rate (GFR) of 30.50 mL/min. Liver function tests showed total bilirubin of 3.2 mg/dL, aspartate transaminase 40 IU/L, alanine transaminase 39 IU/L and alkaline phosphatase of 217 IU/L. Levels of amylase and lipase were normal. Urinalysis showed protein of 30 mg/dL,

CrossMark

To cite: Swe T, Ali M, Naing AT. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-215814

urobilinogen of >8 EU and all other measurements were normal. Coagulation profile was within normal limits. The patient's CD4 count during this admission was 260 cells/ μ L and HIV 1 RNA (PCR) was <20 days. Chest X-ray revealed no evidence of active lung disease and ECG was normal. CT scan of abdomen was significant for gallbladder distention with multiple gallstones and pericholecystic fluid. Hepatobiliary iminodiacetic acid scan confirmed the diagnosis of acute cholecystitis.

TREATMENT, OUTCOME AND FOLLOW-UP

The patient was started on conservative management with nothing orally, antiemetics, intravenous fluids and antibiotics after he refused surgery. He was started on the renal adjusted dose of piperacillin/tazobactam 2.25 g intravenous 6 hourly. On day 2, the WCC, neutrophil count, total bilirubin and temperature became normalised. However, during days 3 and 4, he had fever of 103°F (39.4°C), and on day 5, his fever subsided. He then had another bout of fever at 102.5°F (39.1°C) on day 6. His fever subsided again on the morning of day 7; however, he developed fever once again that afternoon which continued up to day 8. An antifebrile, acetaminophen, was given to the patient but this could not bring his temperature down. The patient denied any abdominal pain, abdominal tenderness, nausea, vomiting and diarrhoea on this day. He continued to improve clinically on day 8. From day 2 his diet was advanced to regular, and he tolerated this well. His pulse rate was around 80–90 bpm even during his fever spikes. His clinical condition continued to improve until the day he was discharged. Since after day 3, we repeated complete blood count with differentials, chest X-ray, urinalysis, lactic acid and procalcitonin and they were all within normal limits. A total of six sets of blood cultures and three sets of urine cultures were sent each time the patient developed fever and all were negative. CT scan of the chest revealed no active pulmonary disease. Throughout this period, there was no rash or eosinophilia. Drug fever was suspected and piperacillin/tazobactam was discontinued. Since then, the temperature normalised within 48 hours with no further fever spikes (figure 1) and the patient

was discharged. The patient refused to undergo drug provocation testing.

DISCUSSION

Drug fever is a diagnosis of exclusion and should be considered when no other cause of fever can be identified. In our case, the patient presented with intermittent fevers without any other source of infection and the stopping of antibiotics led to the resolution of fever within 48 hours. Therefore, the patient's fever was induced by piperacillin/tazobactam.

To the best of our knowledge there is no detailed case report about drug fever induced by piperacillin/tazobactam in a patient with HIV infection in the USA. There were few case reports about drug fever due to piperacillin/tazobactam with other comorbidities. One case was reported of a patient who underwent scoliosis correction surgery in China⁵ and another patient with antibiotic-loaded bone cement from Korea.⁶ In these cases, drug fever was associated with rash and/or eosinophilia. However, drug fever is only associated with rash in a minority of cases and fever may be the only manifestation in about 3–5% cases. Furthermore, absence of rash or eosinophilia should not deter the clinician to consider drug fever.⁴

Piperacillin has been reported to be associated with drug reactions including fever and rash in patients with cystic fibrosis. One chart review showed that out of the 31 patients given piperacillin, 11 patients had allergic reactions. The mean time to onset of drug-induced fever or of rash was 9.1 days.⁷ A study by Khettar *et al*⁸ has shown that out of a total of 116 patients with cystic fibrosis treated with piperacillin/tazobactam intravenously, 9 patients had developed fever higher than 101.3°F during treatment and the temperature normalised after stopping the antibiotics.

Our patient denied any exposure to β -lactams before and thus, it is unclear as to whether he can now be labelled as 'penicillin allergic'. Sensitivity testing might be worth considering since this patient is HIV positive and there is a high likelihood that he will require antibiotics in the future.

It is important to keep in mind that patients with HIV infection tend to have an increased risk of having drug reactions of

Figure 1 The development and disappearance of fever.

all types, including fever.⁹ Piperacillin/tazobactam can induce fever in patients with cystic fibrosis and in patients with other conditions. Drug fever may be more prevalent in patients with HIV infection. It has no characteristic pattern and may not be associated with eosinophilia.

Learning points

- ▶ Drug fever alone is often underdiagnosed by clinicians although it is not an uncommon condition.
- ▶ Piperacillin/tazobactam is a known drug that can cause fever in a minority of patients with cystic fibrosis and a few case reports also describe drug fever in patients with other conditions. However, it has never been reported in a patient with HIV infection.
- ▶ Patients with HIV infection appear to have an increased risk of having drug reactions of all types, including fever.
- ▶ Drug fever is associated with relative bradycardia in a minority of cases, no characteristic fever pattern, a highly variable lag time between the initiation of the offending agent and the onset of fever and is associated with either rash or eosinophilia.
- ▶ However, absence of rash or eosinophilia should not deter the clinician to consider drug fever.

Differential diagnoses were considered and excluded before making this diagnosis

1. Inadequate antibiotic coverage—it was unlikely because of normalisation of WCC and complete clinical improvement within 3–4 days after starting antibiotics.
2. Another infection—it was impossible due to normal results of repeated laboratory and imaging studies.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Roush MK, Nelson KM. Understanding drug-induced febrile reactions. *Am Pharm* 1993;33:39–42.
- 2 Tabor PA. Drug-induced fever. *Drug Intell Clin Pharm* 1986;20:413–20.
- 3 Johnson DH, Cunha BA. Drug fever. *Infect Dis Clin North Am* 1996;10:85–91.
- 4 Mackowiak PA, LeMaistre CF. Drug fever: a critical appraisal of conventional concepts. An analysis of 51 episodes in two Dallas hospitals and 97 episodes reported in the English literature. *Ann Intern Med* 1987;106:728–33.
- 5 Li Z, Shen J, Li Q, *et al*. Drug fever induced by piperacillin/tazobactam in a scoliosis patient. *Medicine (Baltimore)* 2015;94:e1875.
- 6 Park HB, Choi JS, Park SH, *et al*. Drug fever due to piperacillin/tazobactam loaded into bone cement. *J Korean Med Sci* 2011;26:301–3.
- 7 Pleasants RA, Walker TR, Samuelson WM. Allergic reactions to parenteral beta-lactam antibiotics in patients with cystic fibrosis. *Chest* 1994;106:1124–8.
- 8 Khettar S, Durupt S, Pages J, *et al* DI-050 Drug induced fever caused by piperacillin-tazobactam in adults with cystic fibrosis. *Eur J Hosp Pharm* 2014;21:A90.
- 9 Bayard PJ, Berger TG, Jacobson MA. Drug hypersensitivity reactions and human immunodeficiency virus disease. *J Acquir Immune Defic Syndr* 1992;5:1237–57.

Copyright 2016 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow