中文題目：Piperacillin/tazobactam 引起之急性間質性腎炎

英文題目：Piperacillin/tazobactam-induced acute interstitial nephritis

作　　者：劉家佑[1], 彭渝森[1,2]

服務單位：[1] 亞東紀念醫院內科部, [2] 亞東紀念醫院內科部腎臟內科

Case presentation

A 75-year-old man, had history of gastric ulcer and hypertension, was admitted to this hospital with right low back pain for 3 days. Regular medications included lansoprazole and irbesartan.

On examination, the temperature was 35.9°C, the pulse 69 beats per minute, the blood pressure 171/77 mm Hg, the respiratory rate 20 breaths per minute, and the oxygen saturation 99% while he was breathing ambient air. The general physical examinations were normal except for right back knocking tenderness. Blood levels of white-cell count was 29,670 per cubic millimeter (reference range, 3800 to 10,400) with neutrophil dominant (90%). Biochemical tests revealed hyponatremia (129 millimole per liter, reference range, 135 to 148), blood urea nitrogen (BUN) 52 milligrams per deciliter (mg/dl) (reference range, 7 to 22), and creatinine 6.47 mg/dl (reference range, 0.7 to 1.2). The patient's last creatinine level in this hospital was 1.25 mg/dl two weeks before admission. Urinalysis with sediments revealed yellow urine, with a pH of 5.5, a specific gravity higher 1.015, 2+ protein, and 2+ glucose, white blood cell 3.3 per high power field. The abdominal computed tomography without administration of contrast medium revealed mild peri-renal fat stranding in the right kidney. The patient was admitted to the hospital.

Empirical antibiotics with ceftriaxone was administered intravenously, and ibuprofen and irbesartan were discontinued. The urine output was fair. On the fifth hospital day, a new episode of fever up to 38.1°C was found, antibiotics was upgraded to piperacillin/tazobactam. Followed lab tests revealed white cell count 11,050 per cubic millimeter, BUN/creatinine 46/5.29 mg/dl. On the eighth hospital day (the third day of piperacillin/tazobactam using), sudden onset of oliguria, nausea and vomiting were noted. Repeated blood test revealed BUN/creatinine 28/8.41 mg/dl. Ultrasonography of the kidneys and bladder revealed no hydronephrosis or stone. Urinalysis revealed yellow urine, with a pH of 5.5, a specific gravity higher than 1.010, 2+ protein, 3+ occult blood. Lab tests of antinuclear antibodies was negative and no monoclonal gammopathy. The antibiotics was adjusted to ciprofloxacin. Renal biopsy was done and pathology examination revealed a few tubules were dilated with flattened epithelium and loss of nuclei. Drug-induced acute interstitial nephritis (AIN) was impressed. Systemic steroid with intravenous methylprednisolone (1mg/kg/day) was administered. The patient's urine output gradually increasing under bumetanide, and creatinine decreased to 3.76 mg/dl. He was discharged with

no diuretics and followed at out-patient department.

Discussion

The patient was admitted to this hospital due to infection disease, suspect acute pyelonephritis, and acute on chronic kidney disease, suspect infection and drug (ibuprofen and irbesartan) related. His renal function was improving with initial antibiotics treatment and discontinuation of culprit drug. However, a new episode of decline in renal function happened with sudden onset oliguria in less than 12 hours after piperacillin/tazobactam using for 3 days. Pre-renal acute kidney injury was less likely because patient had no evidence of hypoperfusion or heart failure signs. Ultrasonography of the kidneys with doppler scan also presented with color signal and vascular stenosis or occlusion were not favored. Ureter obstruction was also not found. Acute interstitial nephritis was diagnosed by renal biopsy.

Acute interstitial nephritis is presented with deterioration of renal function and inflammatory infiltrate in the kidney interstitium. Causes of AIN included drugs (70%), autoimmune diseases (20%), and infections (4%) [1]. The patient had no evidence of infection like systemic inflammatory response syndrome (SIRS) or other infection focus after antibiotics treatment, and antinuclear antibody was negative. Therefore, drug-induced AIN was most likely. Drug-induced AIN was mostly due to antibiotics in 49%, proton pump inhibitors (PPIs) in 14%, and nonsteroidal anti-inflammatory drugs (NSAIDs) in 11% [1]. It is not dose dependent, and recurrence or exacerbation can occur with a second exposure to the same or a related drug [2]. In this patient, PPI and antibiotics both could be the culprit drug of AIN. In PPIs, the interval between drug initiation and the onset of kidney abnormalities can oscillate between 1 week and 9 months, but a time frame of 10 to 11 weeks was the commonest [3]. The patient had used PPI as lansoprazole for about six months so it was less likely the culprit drug. In β-lactam antibiotic, the duration of exposure is usually relatively short, ranging from a few days to a few weeks [4]. The time course revealed that antibiotics with piperacillin/tazobactam was the most possible causative agent in our patient. However, fever, rash, eosinophilia, or eosinophiluria is seen in >75% of patients [4], and it was not typical in this patient.

Although piperacillin/tazobactam was rarely associated with AIN, there still were case reports revealed it was the causative drug [5][6]. The management for drug induced AIN included discontinuation of the potential culprit drug, and treat with glucocorticoid, as drug-induced AIN is an allergic, inflammatory process [4]. A retrospective, multicenter study suggested to start steroid immediately if the diagnosis of drug-induced AIN was established to avoid the progressive interstitial fibrosis and better recovery of renal function [7]. In conclusion, drug-induced acute

interstitial nephritis should always be considered in patient presented with acute kidney injury, identify and discontinuation of the culprit drug is the priority.

Reference

1. Biopsy-Proven Acute Interstitial Nephritis, 1993-2011: A Case Series. *Am J Kidney Dis.* 2014;64(4):558.
2. Acute tubulointerstitial nephritis related to antituberculous drug therapy. *Clin Nephrol.* 2010;73(6):413.
3. Changes in the aetiology, clinical presentation and management of acute interstitial nephritis, an increasingly common cause of acute kidney injury. *Nephrol Dial Transplant.* 2015 Sep;30(9):1472-9.
4. Drug-induced acute interstitial nephritis. *Nat Rev Nephrol.* 2010 Aug;6(8):461-70.
5. Piperacillin-Tazobactam Induced Interstitial Nephritis, Hepatitis and Serum Sckness-Like Illness. *J Ark Med Soc.* 2016 Jun;112(14):278-80.
6. Piperacillin–tazobactam-induced acute interstitial nephritis with possible meropenem cross-sensitivity in a patient with osteomyelitis. *Am J Health-Syst Pharm.* Vol 69 Jul 1, 2012.
7. Early steroid treatment improves the recovery of renal function in patients with drug-induced acute interstitial nephritis. *Kidney International.* (2008) 73, 940–946.