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Full Length Research Paper

Voriconazole therapy: Associated acute kidney injury

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Voriconazole is a good antifungal drug, which is often used to treat aspergillosis. Little is, however, known about its renal toxicity effect. A patient with microscopic polyangiitis (MPA) and pulmonary aspergillosis treated with Voriconazole suffered from acute renal failure, which was diagnosed Voriconazole therapy-associated acute kidney injury. Finally the patient recovered. This is a case report of Voriconazole therapy-associated acute kidney injury.

Key words: Voriconazole, aspergillosis, therapy-associated, acute kidney injury.

INTRODUCTION

Acute kidney injury (AKI) is a common disease characterized by a rapid decrease in kidney function, which is often fatal. About 2-5% of hospitalized patients will develop it. In recent years drug-associated AKI is more and more reported. So it should be paid more attention. A case of Voriconazole therapy-associated AKI is reported below.

CASE REPORT

The patient, 79 year old female, was hospitalized due to cough and expectoration with fever for 1 day. Eight months ago she began to feel fatigue and nausea and went to hospital and took relative examination. The results showed the level of serum creatinine (Scr) was 1260 μmol/L, urea protein 4.5 g/day, antinuclear antibody (ANA) negative, perinuclear anti-neutrophil cytoplasmic antibody (pANCA) 1: 420, myeloperoxidase-ANCA (MPO-ANCA) 1:60, and the patient was then diagnosed with microscopicpolyangiitis (MPA). The following therapies were applied: Methylprednisolone 40 mg qd PO, Mycophenlate Mofetil (MMF) 0.75 bid PO, and 12 times of plasma exchange combined with hemodialysis. ANCA became negative, and renal function was recovered with Scr level of 200 μmol/L. After discharge from hospital, were applied, and follow-up visit was performed once two weeks. The Scr level was stable at about 180 μmol/L. Methylprednisolone was reduced gradually. Urine volume was between 1500 ~ 2500 ml/day. The therapeutic regimen before hospitalization included Methylprednisolone 20 mg qd PO and MMF 0.75 bid PO.

Physical examination: T 39.9°C, Bp 150/90 mmHg

The patient was conscious, with slightly short breath, anemia appearance, as well as rough respiratory murmur and moistrale in both lungs. The heart rate was 150 bpm, and she had atrial fibrillation. The abdomen was soft and without tenderness. No pathologic reflex was found.

Laboratory examination

Blood routine examination: WBC 15.2× 10^9/L, N: 90%, Hb 51 g/L, PLT 120 × 10^9/L.

Hepatic and renal function

The levels of Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) were both normal. Scr was 225 μmol/L, blood urine nitrogen (BUN) was 6.9 mmol/L and urate (UA) was 620 μmol/L. Blood glucose was within normal range.

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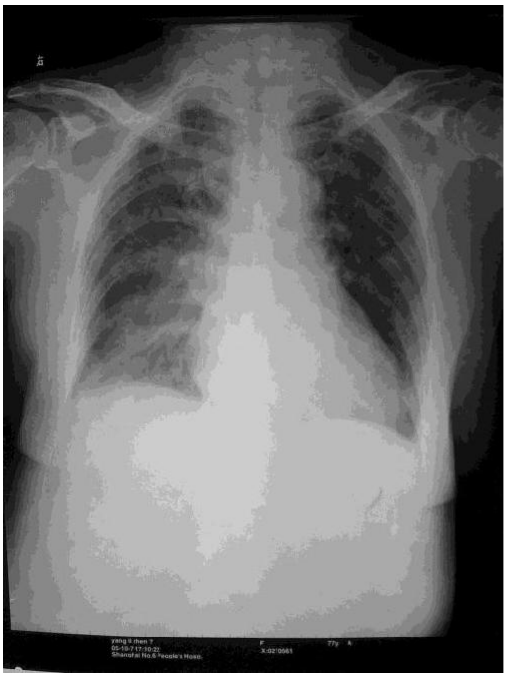

Figure 1. Thoracic X-ray. High-density shadows in right lower lung, expanded heart shadow.

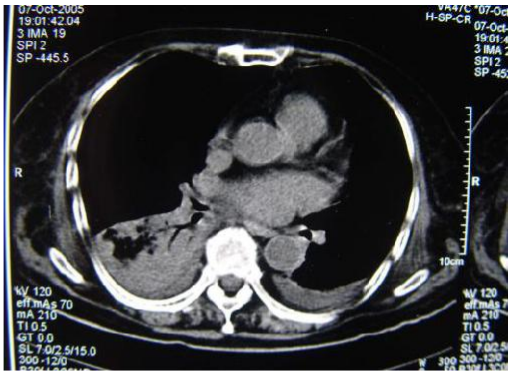

Figure 2. Pulmonary CT scan. Consolidation and atelectasis of right lower lung, bilateral pleural effusion.

Electrolytes

Sodium 132 mmol/L, potassium 3.8 mmol/L, chloride 102 mmol/L and carbon dioxide 19.8 mmol/L.

Immunology

Immunoglobulin G (IgG) 3.0g/L, C-reactive protein (CRP) 203 mg/dl, ANCA negative.

Sputum smear

Klebsiella pneumoniae could be detected.

Auxiliary examination

Thoracic X-ray showed a small piece of blur shadow in the right lower lung, increased streaks in both lungs, small amount of pleural effusion in both sides (Figure 1). Lung CT scan showed high-density shadow in right lower and left upper lungs, small amount of pleural effusion in both sides (Figure 2).

Echocardiogram

Increased left atrium and increased pulmonary artery pressure were observed. Abdomen ultrasonography scan showed medium volume of peritoneal fluid.

Diagnosis

MPA, chronic kidney disease (CKD) Stage 3 to 4, lung infection, secondary immune deficiency.

TREATMENT

Support treatment, heteropathy, transfusion and infusion of albumin were used. Anti-infection protocol was clindamycin 1.8 iv qd, cefoperazone and sulbactam (2:1) 3.0 iv bid, Imipenem 0.5 iv q8h, Fluconazole 0.1 iv bid. And intraveous Gamma globulin 10.0 g qd wes used. Two days later, the temperature became normal and general situation improved slightly, but there were still rales in lungs. WBC maintained within the range of WBC12-15×10^9/L and the percentage of N was higher than 85%. Refractory hyponatremia happened within the sodium level of 105 to 118 mmol/L, and epilepsia gravior happened several times. Blood gas analysis showed arterial pressure of oxygen 70 to 80 mmHg, normal pH and arterial pressure of carbon dioxide. Two weeks later, she had a bad hemoptysis with a volume of about 50ml. Emergency computed temography (CT) scan showed high-density images in left upper lung, high-density images associated with cavities in right lower lung (Figure 3). Sputum culture showed there was *Aspergillus fumigatus*. Pulmonary Aspergillosis was considered by experts from departments of pulmonary and infection of the hospital. Then intravenous Voriconazole 0.2 qd was used as well as cefoperazone and sulbactam 3.0 bid. Twenty-four hours after the administration of Voriconazole, the urine volume reduced from 1600 to 450 ml suddenly and Scr increased. A KI was diagnosed, and continuous renal replacement therapy (CRRT) was applied every two days in order to clear inflammatory

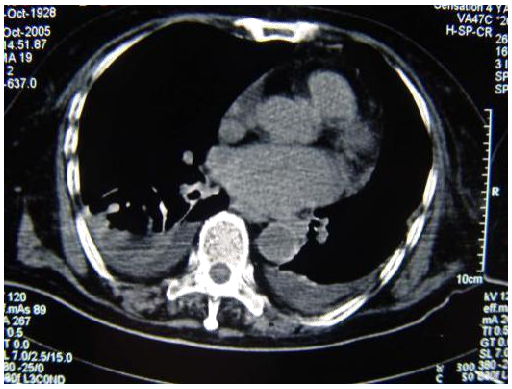

Figure 3. Pulmonary CT scan. Cavity formation of right lower lung, bilateral pleural effusion.

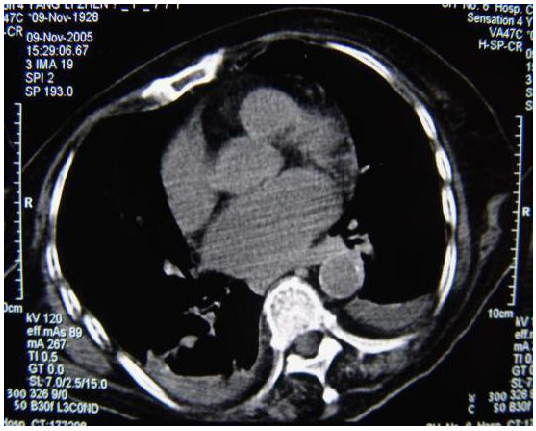

Figure 4. Pulmonary CT scanning. Decreased cavity, bilateral pleural effusion.

media and maintain acid-base equilibrium. Epileptic seizure never attack again after initial CRRT. Re-examination with CT after three weeks showed that the shadow in right lung was absorbed gradually and the size of cavities decreased (Figure 4). Then Voriconazole was applied with a level of 0.2 g/day PO, and other antibiotics were stopped gradually. After oral Voriconazole treatment, urine volume turned to be about 1500 ml/day. Then CRRT was stopped in the 4th week.

OUTCOME

The patient's general status turned out to be better. Body temperature became normal. Blood routine examination maintained normal. Signs in lungs vanished gradually. Rales nearly disappeared finally. She was discharged from hospital on 28th November, 2005. After the discharge, she maintained to take Voriconazole 0.2/day for a total duration of 8W. In January of 2007, the patient was treated with peritoneal dialysis because of end stage renal disease, and she died of chronic cardiac insufficiency in May of 2009.

DISCUSSION

MPA is a common systemic small-vessel vasculitis with a various clinical symptoms. It can be slight, or attacked acutely and progressed into renal failure rapidly, often associated with respiratory failure. Besides renal failure, secondary infection and lung lesions are major causes of death (Watts, 2010). Infection in lungs often happens in patients with MPA, not only because MPA can involve lungs directly, but also glucocorticoid and immunosuppressants are often used (Itabashi et al., 2010; Bosch, 2010). The patient reported here had a lung infection during MPA treatment, and was diagnosed as pulmonary aspergillosis. The infection could be related to the primary disease and administration of glucocorticoid and immunosuppressants (Silva et al., 2010; Wang et al., 2010). When the routine anti-infection therapy was not effective, she was treated with Voriconazole and cured finally.

Voriconazole has potential anti-fungus activity, and is of great use for severe fungal pneumonia. During treatment of severe pneumonia, purification of blood especially CRRT can clear inflammatory media, and modify resisting electrolyte imbalances rapidly and effectively. It can be used to treat electrolyte imbalances related with anti-infection, lower pulmonary exudate and pleural effusion, improve hypoxemia, and maintain homeostasis. It is likely to be decisive for prognosis. Support treatment is also very important. Once a patient was suspected with fungal infection, anti-fungus therapies should be applied as soon as possible. If general anti-fungus drugs (e.g. Diflucan) were not effective, non-sensitive fungi should be considered. Voriconazole should be applied to severe patients as early as possible, thus improving prognosis significantly.

The Chinese data about Voriconazole is limited currently. There is no report yet about apparent nephrotoxicity. Sulfobutylether-β-cyclodextrin (SBECD), the vehicle in vein of intravenous Voriconazole, can accumulate due to renal insufficiency, but the outcome is not clear. Therefore, intravenous Voriconazole should be applied with caution (Vfend® (voriconazole) Package Insert; FDA Antiviral Drugs Advisory Committee Briefing Document for Voriconazole, 2002). There were some pharmacokinetics studies about administration of Voriconazole in uremic patients for alternative treatment (Peng and Lien, 2005; Fuhrmann et al., 2007), but it is still unclear about dosage adjustment in patients with chronic renal disease (von Mach et al., 2006; Heinz et al., 2011). As the patient in this report had baseline chronic renal disease and oliguria happened after intravenous administration of Voriconazole, so dose reduction was

conducted based on experience. Thereafter oral Voriconazole was applied and her urine volume got normal, as proved Voriconazole could cause oliguria, especially for patients with chronic renal diseases. Of course it deserved further study whether it is a direct effect of Voriconazole or SBECD. The 0.2 g/day level of Voriconazole had a strong anti-fungal efficacy, and the clinical symptoms disappeared rapidly in this report. Therefore, oral Voriconazole is likely a good alternative for treatment of resisting fungal infection, and no obvious impairment to renal function was found (Figures 1 to 4).

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