Case Report

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Linezolid combined with trimethoprim–sulfamethoxazole therapy for the treatment of disseminated nocardiosis

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We describe a case of disseminated nocardiosis in a 45-year-old male with a history of chronic glomerular nephritis and allograft renal transplantation both treated with immunosuppressive drugs. Clinical symptoms included fever, chest distress, breathlessness, subcutaneous nodules and pustules. Pulmonary computed tomography scans revealed areas of consolidation in both lung fields, pleural effusion and massive pericardial effusion. Bacterial culture of the pus in the subcutaneous abscesses and pericardial effusion showed growth of *Nocardia asteroides* sensitive to linezolid and trimethoprim–sulfamethoxazole (TMP–SMZ) for both. Treatment with linezolid combined with TMP–SMZ resulted in a clear clinical improvement and bacterial clearance.

Introduction

Nocardia are Gram-positive aerobic bacteria of the order *Actinomycetales* and have become increasingly important opportunistic pathogens, mostly in immunosuppressed patients (Lerner, 1996). The most common species causing human infection is *Nocardia asteroides* (Martínez Tomás *et al.*, 2007). Nocardiosis is an infrequent disease that affects patients who display a cellular immunodeficiency, such as transplant recipients on immunosuppressive treatment. Disseminated nocardiosis affecting the central nervous system (CNS), abdomen, skin and lungs has been described in transplant recipients, such as those with bone marrow, lung or kidney transplants (Vinh & Rubinstein, 2009).

Trimethoprim–sulfamethoxazole (TMP–SMZ) is widely considered as the primary choice for the treatment of nocardiosis. Combination therapy with a carbapenem or a third-generation cephalosporin, with or without amikacin, is usually recommended for critically ill patients or for those with CNS involvement (Lerner, 1996). New antimicrobial agents are desirable because of the increasing resistance to sulfonamides and the lack of alternative highly active oral agents (Moylett *et al.*, 2003).

Linezolid is the first marketed antibiotic of the oxazolidinone class with demonstrated activity against antibiotic-susceptible and antibiotic-resistant aerobic Gram-positive cocci, including methicillin-resistant *Staphylococcus aureus*, glycopeptide

intermediate-susceptible *S. aureus*, vancomycin-resistant *S. aureus*, vancomycin-resistant enterococci and penicillin-resistant *Streptococcus pneumoniae*. Linezolid also has *in vitro* activity against some Gram-negative anaerobes as well as some atypical organisms (Diekema & Jones, 2001). Some case reports and susceptibility tests have been suggestive that linezolid is an effective choice for the treatment of nocardiosis (Vinh & Rubinstein, 2009).

Case report

In this study, we report a case of a 45-year-old male with a history of chronic glomerular nephritis and uraemia, who underwent allograft renal transplantation in January 2009. After the operation, the patient was discharged on a treatment regime of tacrolimus (1.5 mg twice daily), mycophenolic acid (CellCept) (0.5 g twice daily) and prednisone (10 mg daily, orally) as immunosuppressive agents. During the follow-up, we adjusted the dosage of tacrolimus constantly according to target blood drug concentrations (12–15 ng ml⁻¹ within 1 month after transplantation, 8–11 ng ml⁻¹ within 1–3 months and 5–8 ng ml⁻¹ after 3 months). The patient's serum creatinine level remained at a stable level between 170 and 180 µmol l⁻¹. On June 12 2009, the fifth month after his transplantation, he developed a fever (38.5 °C) and also felt pain in the left scapular region, but without coughing, expectoration, abdominal pain, diarrhoea, frequent micturition, urgency, odynuria and so on. Blood tests showed 15.8 × 10⁹ white blood cells l⁻¹, percentage neutrophilic

Abbreviations: CNS, central nervous system; CT, computed tomography; TMP–SMZ, trimethoprim–sulfamethoxazole.

granulocytes in white blood cells = 85.3 %, 103 g haemoglobin l^{-1} , 129×10^9 platelets l^{-1} ; and uroscopy revealed protein in the urine. Treatment with cefradine (1000 mg per day) and azithromycin (500 mg per day) was used. Twelve days later, the patient was admitted because there was no improvement and a poorer general status. Physical examination revealed low-grade fever (37.8 °C). Pulmonary computed tomography (CT) scans performed on June 25 2009 showed areas of consolidation in both his lung fields (Fig. 1a). Pulmonary mycosis was considered based on the information we had gathered. The patient's treatment schedule was adjusted to voriconazole (400 mg per day) combined with levofloxacin (500 mg per day). Unfortunately, the patient began to feel increasing chest distress and breathlessness, soreness in both legs and fatigue. What is more, his body temperature was as high as before. Physical examination revealed subcutaneous nodules in both his trunk and extremities, especially in the buttocks and lower limbs, and pustules of the scalp. Pulmonary CT scans on July 13 2009 showed increasing areas of consolidation, pleural effusion and massive pericardial effusion (Fig. 1b). Bacterial culture of the subcutaneous abscesses showed growth of *N. asteroides*, which was identified using API 20C AUX strips according to the literature (Kiska *et al.*, 2002). For the strain the MICs of gentamicin, erythromycin, ciprofloxacin, TMP-SMZ, imipenem, ceftriaxone and linezolid were determined by Etest strip according to the manufacturer's recommendations, giving the MICs as the following: 1.0, 256, >32,

0.125, 2, 1.0 and 0.25 $mg\ l^{-1}$, respectively. According to the Clinical and Laboratory Standards Institute recommendations for antimicrobial susceptibility testing of aerobic actinomycetes (CLSI, 2003), the strain was sensitive to TMP-SMZ, gentamicin, imipenem, ceftriaxone and linezolid, but resistant to ciprofloxacin and erythromycin. Biopsy of the subcutaneous abscesses in the patient's legs showed purulent inflammation of subcutaneous soft tissue. According to the clinical, radiological and aetiological findings, disseminated nocardiosis was definite. Then we changed the antibiotics to imipenem (1500 mg per day), voriconazole (400 mg per day) and TMP-SMZ (320–1600 mg per day). Six days later, the patient felt aggravated chest distress and breathlessness, orthopnoea, with a respiratory rate of 30 breath min^{-1} and heart rate of 130 beats min^{-1} . Since increased pericardial effusion was detected by Doppler ultrasonography, we performed paracentesis pericardii and placed a drainage tube. The symptoms of the patient were reduced to a great degree after drainage, but the fever and pain of both legs still existed. On the contrary, the subcutaneous nodules in the trunk and extremities, with pustules of the scalp, were growing. The third pulmonary CT scans still showed increasing areas of consolidation in both lung fields (Fig. 1c). We found growth of *N. asteroides* again in the pericardial effusion, which was a light yellow pus. Susceptibility testing using Etest resulted in a similar susceptible profile as previous isolates. Then, we adjusted the antibiotics immediately to intravenous linezolid

Fig. 1. Chest CT scans and an X-ray. (a) CT scan (25/6/2009) showing the presence of areas of consolidation in both lungs, pericardial effusion and pleural effusion. (b) CT scan (13/7/2009) showing increasing of the areas of consolidation in both lungs, pericardial effusion and pleural effusion. (c) CT scan (27/7/2009) showing extensive increasing of the areas of consolidation with air bronchogram. (d and e) CT scan (15/9/2009) and chest X-ray (24/11/2009) showing obvious improvement of the inflammation.

(1200 mg per day) and oral TMP-SMZ (320–1600 mg per day). The patient miraculously got better 1 week later, with no fever, reduced chest distress and breathlessness, less subcutaneous nodules, pustules and drainage pus of the pericardial effusion. Pulmonary CT scans 10 days after the adjustment also showed an obvious reduction of consolidation, pleural effusion and pericardial effusion. After 3 weeks of combined therapy of two antibiotics, the nodules were almost completely crusted, and no growth of *N. asteroides* was detected in pericardial effusion. Because of the reduction of haemoglobin (53 g l^{-1}) and platelets ($19 \times 10^9 \text{ platelets l}^{-1}$), we shifted the antibiotic therapy to oral TMP-SMZ only, with blood red cell infusion several times. The patient's blood count recovered gradually, and at the same time he had a definite clinical improvement (Fig. 1d, e). The course of treatment with TMP-SMZ was 6 months, and complete cure was achieved.

Discussion

Among opportunistic infections appearing in immunosuppressed patients, special consideration should be given to *Nocardia* species according to the subacute course, clinical variability and non-specific radiographic appearance. Disseminated nocardiosis may affect many organs of the patient, especially the lungs, CNS, skin and even the pericardium. In disseminated nocardiosis, early diagnosis by means of microbiological test is urgent, and getting appropriate samples is necessary for testing but is sometimes difficult. Septic body fluid or sometimes biopsy material should be gathered as far as possible, because it is

the best evidence for use in microbiological diagnosis. In this patient, we cultured *N. asteroides* from pus and pericardial effusion. As far as treatment is concerned, TMP-SMZ is still the first choice. This successful case confirmed that in some disseminated nocardiosis cases, linezolid may also be an important alternative that can give a better outcome. However, it should be emphasized that the risk of adverse effects might be increased if linezolid was combined with other antibiotics.

References

- CLSI (2003).** *Susceptibility Testing of Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes*, approved standard, M24-A. Wayne, PA: Clinical and Laboratory Standards Institute.
- Diekema, D. J. & Jones, R. N. (2001).** Oxazolidinone antibiotics. *Lancet* **358**, 1975–1982.
- Kiska, D. L., Hicks, K. & Pettit, D. J. (2002).** Identification of medically relevant *Nocardia* species with an abbreviated battery of tests. *J Clin Microbiol* **40**, 1346–1351.
- Lerner, P. I. (1996).** Nocardiosis. *Clin Infect Dis* **22**, 891–905.
- Martínez Tomás, R., Menéndez Villanueva, R., Reyes Calzada, S., Santos Durantez, M., Vallés Tarazona, J. M., Modesto Alapont, M. & Gobernado Serrano, M. (2007).** Pulmonary nocardiosis: risk factors and outcomes. *Respirology* **12**, 394–400.
- Moylett, E. H., Pacheco, S. E., Brown-Elliott, B. A., Perry, T. R., Buescher, E. S., Birmingham, M. C., Schentag, J. J., Gimbel, J. F., Apodaca, A. & other authors (2003).** Clinical experience with linezolid for the treatment of *Nocardia* infection. *Clin Infect Dis* **36**, 313–318.
- Vinh, D. C. & Rubinstein, E. (2009).** Linezolid: a review of safety and tolerability. *J Infect* **59** (Suppl. 1), S59–S74.