Successful Long-Term Treatment with Linezolid for Disseminated Infection with Multiresistant *Nocardia farcinica*

Nocardiosis is a common infection in organ transplant recipients and other immunosuppressed patients, caused by different *Nocardia* species. *Nocardia farcinica* is one of the most predominant *Nocardia* species isolated in these patients, frequently presenting resistance to multiple antibiotics used as first-line agents [1, 2]. Linezolid is an oxazolidinone agent apparently well designed for treating chronic osteomyelitis, but data on its effectiveness and tolerability in patients on prolonged therapy with linezolid are limited.

The authors present the case of an immunosuppressed patient who developed disseminated nocardiosis caused by a multiresistant *N. farcinica* strain requiring long-term treatment with linezolid.

The patient was a 42-year-old man who had undergone a heart transplant operation 6 months earlier due to dilated cardiomyopathy. On admission, the patient presented with fever and pleuritic chest pain present for the past 2 days. Basal immunosuppression had consisted of triple therapy with cyclosporin, deflazacort, and mofetil mycophenolate. On physical examination at admission he was conscious, with a heart rate of 126 bpm and a respiratory rate of 34 rpm. A bilateral hypoventilation was noticed. The blood count showed 23.48×10^3 leukocytes/μl and a hemoglobin level of 9.8 g/dl. Chest X-ray revealed a cardio-thoracic index increase and bilateral pleural effusions. The thoracic CT scan confirmed bilateral pleural effusions and showed a 9×7-cm intrapericardial collection. Drainage of the pleural effusion and the pericardial collection was performed. A Gram stain showed Gram-positive-branched filaments suggestive of *Nocardia* spp. The patient was treated with high-dose cotrimoxazole (25/5 mg/kg every 8 h). Mofetil mycophenolate was withdrawn and the cyclosporin dose was reduced. Nevertheless, the patient's level of consciousness became reduced and he developed headaches following the first week of treatment. A cranial CT scan (Figure 1) revealed multiple brain abscesses. Simultaneously, the patient developed a generalized cutaneous maculopapular rash interpreted as hypersensitivity to cotrimoxazole. Following this, cotrimoxazole was discontinued and treatment with imipenem plus amikacin was prescribed. At this point, the Gram-positive bacilli were identified as *N. farcinica* resistant to cotrimoxazole with a minimal inhibitory concentration (MIC) > 256 μg/ml, imipenem (MIC > 256 μg/ml), clindamycin (MIC > 256 μg/ml), vancomycin (MIC > 256 μg/ml), rifampicin (MIC > 256 μg/ml), and piperacillin/tazobactam (MIC > 256 μg/ml) and sensitive to amikacin (MIC: 1 μg/ml), amoxicillin/clavulanic acid (MIC: 3 μg/ml), linezolid (MIC: 1.5 μg/ml), and doxycycline (E-test method and disk diffusion for doxycycline susceptibility testing) [3, 4]. Imipenem was then withdrawn. The patient was treated intravenously with linezolid for 11 days (600 mg every 12 h) although amikacin was stopped due to a severe sensorial hearing loss after 10 days. The patient recovered progressively, presenting negative blood cultures, disappearance of the pleural effusion and the pericardial collection, and a dramatic, reduction in the size of the brain lesions. Mofetil mycophenolate was reintroduced and cyclosporin increased to previous levels. Linezolid treatment was maintained for 17 months, following the first 4 months during which a non-progressive mild distal sensorial polyneuropathy was observed in the lower limbs with axonal characteristics. At the end of this 17-month period, no hematologic toxicity was observed. Absence of brain abscesses at the end of treatment was confirmed by a cranial MRI scan (Figure 2).

The patient remained asymptomatic 8 months after the end of treatment and no secondary prophylaxis was required.

The authors believe this case report shows that disseminated infection caused by multiresistant *N. farcinica* in immunosuppressed patients may be successfully treated with long-term use of linezolid with only mild side effects, thus precluding treatment interruption.

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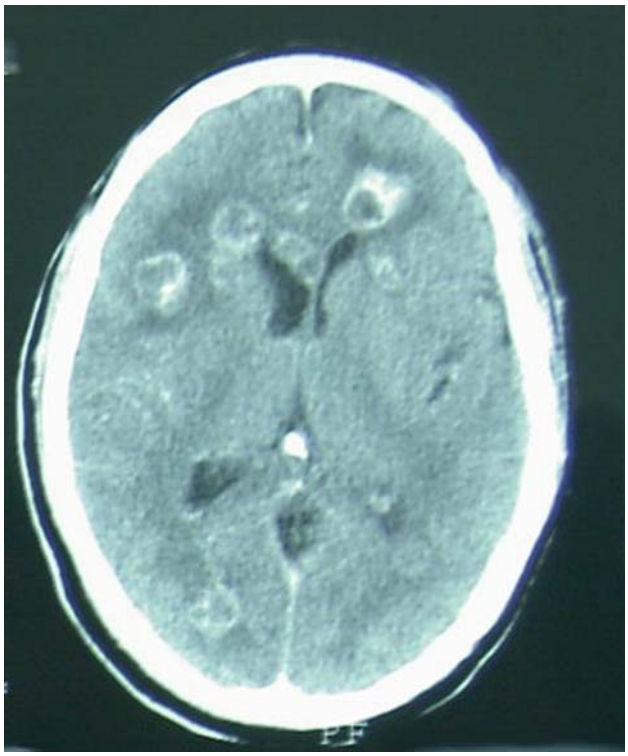

Figure 1. CNS involvement by *Nocardia farcinica* consistent with a disseminated infection.

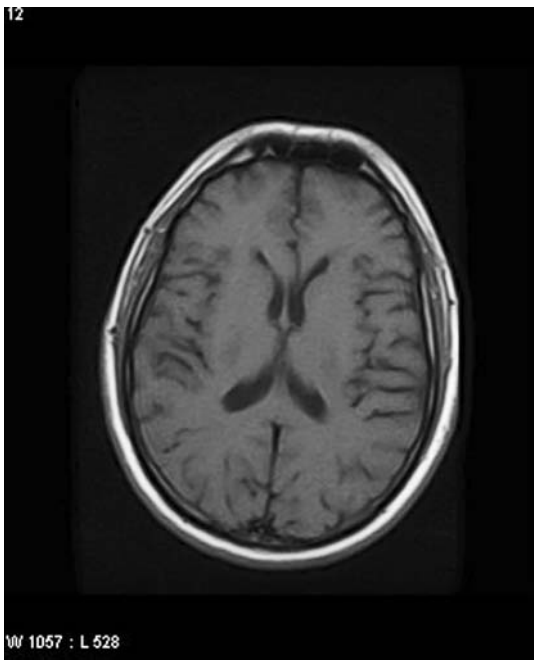

Figure 2. CNSl RMI at the end of linezolid treatment with no evidence of brain abscess.

As in other cases of nocardiosis described in the literature, our transplant patient received intense immunosuppressive treatment and showed a pleural, pericardial, and CNS involvement consistent with a disseminated infection [5, 6–9]. Treatment with high-dose steroids, a history of cytomegalovirus disease, and high levels of calcineurin inhibitors have all been identified as independent risk factors for *Nocardia* infection in organ transplant recipients [1]. The particular resistance profile of our *N. farcinica* strain led us to use a standard dose of linezolid for 17 months.

The prolonged use of linezolid has been studied in nocardiosis and other infections such as orthopedic implant infections, chronic osteomyelitis, and multidrug resistant tuberculosis [10–14]. Tolerance to prolonged use of linezolid has been variable. While in some cases treatment was interrupted after 2–4 months due to the development of severe side effects (myelotoxicity and lactic acidosis), in others prolonged treatment with linezolid was well tolerated. Most notable is the case of a patient who remained on linezolid treatment for more than 2 years [11].

Long-term linezolid administration complications include anemia and thrombocytopenia [15–17]. Severe anemia may occur in adult patients receiving prolonged linezolid therapy, making linezolid therapy cessation necessary [15, 18, 19]. One report suggests that pyridoxine may prevent myelosuppression [19]; however, a recent article concluded that treatment with pyridoxine is unlikely to benefit patients who have been receiving linezolid [16]. Our patient did not develop myelotoxicity during treatment with linezolid. Linezolid is reported to cause a progressive vision-impairing optic neuropathy and early discontinuation of this antibiotic may be associated with a gradual but not necessarily full recovery of visual function [20]. Our patient observed no impairment of vision during treatment. Peripheral neuropathy has been associated with prolonged courses of linezolid treatment by other authors [21, 22]. Although in our case report peripheral neuropathy was observed after 4 months of treatment, drug administration was not discontinued since peripheral neuropathy was mild and non-progressive. Furthermore, due to the resistance profile of the *N. farcinica* strain and the severe clinical course of this infection, long-term treatment with linezolid was needed. In conclusion, linezolid should be considered as an option for prolonged treatment of severe nocardiosis where treatment with other drugs is terminated due to the onset of important side effects. Its value as a first-line agent must be studied further.

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