Disseminated *Nocardia farcinica* infection in a patient with myasthenia gravis successfully treated by linezolid. a case report and literature review

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Abstract

Nocardiosis is increasingly being diagnosed due to a growing population of immunocompromised hosts and improvements in the detection of *Nocardia* species in clinical laboratories. Historically, sulphonamides have been the first-line therapy for the treatment of nocardiosis, but sulphonamides tend to have high rate of drug allergy in clinical settings. In this report, we described a disseminated *N. farcinica* infection occurred in a patient with myasthenia gravis, who suffered from multiple drug allergies and was successfully treated using linezolid. We undertook a review of literature of previously reported cases of nocardiosis treated with linezolid. To date, only 15 cases of nocardiosis treated with linezolid have been published. All cases exhibited long-term tolerance of linezolid and 14 out of 15 cases showed either an improvement in or complete clearance of the infection. According to the literature review, linezolid is an attractive alternative to trimethoprim-sulfamethoxazole for the treatment of disseminated nocardiosis, despite limited clinical evidence to support this claim.

Introduction

Nocardiosis is increasingly being diagnosed due to a growing population of immunocompromised hosts and improvements in the detection and identification of *Nocardia* species in clinical laboratories. However, none of the reported cases have been diagnosed concomitantly with myasthenia gravis (MG), making this the first reported case of its kind. Data regarding prognosis in nocardiosis are highly variable, with published mortality rates ranging from 14% to 40% [1-3]. In cases of disseminated infection, mortality rates may even approach 100%.

In this report, we describe a disseminated infection (with bacteraemia, multilobar pneumonia, and kidney and brain abscesses) caused by N. farcinica that occurred in a patient with MG. This patient suffered from multiple drug allergies and was successfully treated using linezolid. In addition reported cases of nocardiosis treated with linezolid were reviewed.

Case report

A 59-year-old woman was admitted to Kyoto University Hospital with malaise, cough and stomatitis in October 2010. She had been diagnosed

65 with myasthenia gravis (MG) one year prior to admission and had received
66 immunosuppressive treatment, including prednisolone (15mg once daily)
67 and tacrolimus. Upon admission, she appeared acutely ill and complained a
68 shortness of breath with body movement. Physical examination revealed a
69 body temperature of 36.5 °C, a respiratory rate of 24 breaths per minute,
70 blood pressure of 71/52 mm Hg, and a heart rate of 106 beats per minute.
71 Diffuse crackles were audible in both upper lungs. Laboratory tests
72 revealed hemoglobin of 8.0 mg/dL, a white blood cell count of 19,100/mm^3,
73 platelet count of 465 x 10^9/L, total protein of 4.4 g/dL, albumin of 2.4 g/dL,
74 C-reactive protein of 10.9 mg/dL, and IgG of 363 mg/dL. Chest radiographs
75 and computed tomography (CT) scanning showed extensive diffuse bilateral
76 reticulonodular infiltrates. An abdominal CT showed an abscess in the
77 right kidney, whereas a head CT did not reveal any abnormalities. Neither
78 vegetation nor valvular thickening was detected during transthoracic
79 echocardiography, which ruled out infective endocarditis. Two sets of blood
80 cultures and a sputum culture were obtained, and piperacillin-tazobactam
81 (TZP) 4.5g q8h and ciprofloxacin (CIP) 300mg q12h were started based on a
82 presumptive diagnosis of severe healthcare-associated, community-acquired

pneumonia and pyogenic kidney abscesses. Gram staining of the sputum showed Gram-positive filaments suggestive of *Nocardia* spp. or Actinomyces. TZP and CIP were changed to imipenem-cilastatin (IPM) 0.5g q6h and trimethoprim-sulphamethoxazole (TMP) 4 tablets orally q12h on the fourth day, due to a deterioration in respiratory function. On the seventh day, the blood and sputum cultures collected at admission grew a "*Corynebacterium* " species, based on identification using a VITEK 2 system (bioMérieux, Marcy l'Etoile, France). This culture was further identified as *N. farcinica* via sequencing analysis of the 16S rRNA gene of the isolates and the phenotype of the bacteria. The isolate was susceptible to cefotaxime (<= 2.0 ug ml^{-1}), AMK (< 1.0 ug ml^{-1}), CPFX (1.0 ug ml^{-1}), IPM (<= 0.5 ug ml^{-1}), minocycline (MINO) (1.0 ug ml^{-1}), and resistant to gentamicin (32 ug ml^{-1}), TZP (128.0 ug ml^{-1}). We changed IPM and TMP to MINO on the eighteenth day due to a generalised skin rash and a facial flushing that seemed to be caused by a drug allergy. Accordingly, we attempted desensitisation to TMP. Cyclosporine was started on the thirty-sixth day as a treatment for MG, as the physical signs of systemic illness were gradually improving.

On the fifty-seventh day, the patient's fever rose to 38 °C. She was free of

neurological symptoms, but multiple brain abscesses were detected by magnetic resonance imaging, and an abdominal CT showed enlargement of the abscess on the right kidney. We tried meropenem and amikacin, but infectious symptoms were not improved. Linezolid 600mg q12h was started, with subsequent improvement in the brain and right kidney abscesses. Mild thrombocytopenia developed on the ninety-seventh day (the platelet count decreased from 465 x 10^9/L to 121 x 10^9/L), and linezolid therapy was changed to TMP. Any side effect other than mild thrombocytopenia did not occur during 38-day course of linezolid therapy. The patient was discharged on the one hundred twentieth day and was followed up at an outpatient clinic without a worsening of infectious symptoms or a severe adverse reaction to TMP.

Disucussion

We reported herein a case of disseminated *N. farcinica* infection in which the causative organism was misidentified as a *Corynebacterium* spp. and a drug allergy to the first-line therapy for nocardiosis altered antibiotic selection.

Nocardia spp. can be cultured on most bacterial media, and thus a high

119 degree of suspicion is needed for diagnosis of nocardiosis. This includes
120 consideration of the patient's underlying illnesses and unique bacterial
121 characteristics identified via Gram and Ziehl-Neelsen staining. In the early
122 phase of growth on standard media, the organisms may resemble
123 'diphtheroid' bacilli, which commonly contaminate samples. This may lead
124 to an incorrect identification of patient cultures. In the case presented here,
125 an automatic identification system misidentified the bacilli as
126 *Corynebacterium* spp.; however, actinomycosis was strongly suspected due to
127 the patient's background and clinical progression. Therefore, we performed
128 sequencing analysis of the 16S rRNA gene of the isolates and made a
129 confirmatory diagnosis using the biological characteristics of the cultured
130 bacteria. Culture contaminants are commonplace, and invasive Nocardia
131 infections are rare. Therefore, close collaboration between clinicians and
132 clinical laboratories is necessary for the optimal diagnosis and treatment of
133 patients.

134 Historically, sulphonamides have been the first-line therapy for the
135 treatment of nocardiosis, with TMP being the most commonly used
136 treatment. Sulpha drugs may reduce the mortality rate when used alone or

in combination with other antimicrobials [1,2]. In an immunocompromised patient with severe, progressive infection or central nerve system involvement, treatment should involve a combined therapy of either TMP and a bactericidal agent or a combination of imipenem and amikacin [1-3]. In the current case, we decided to treat with amikacin (with close monitoring of neurological status) and IPM despite the patient's diagnosis of MG, due to the emergence of a drug allergy to TMP. Unfortunately, an allergic reaction to IPM also occurred, and the renal abscess worsened; therefore, we administered linezolid as a last line of defence.

Linezolid crosses the blood-brain barrier and has excellent bioavailability. In vitro activity of linezolid against *Nocardia* spp. was observed in several studies. Brown-Elliott et al. tested 140 clinical isolates by broth microdilution and demonstrated that linezolid concentrations of 4 ug/mL inhibited 90% isolates (90% minimum inhibitory concentration), which is in susceptible range according to the proposed Clinical and Laboratory Standard Institute MIC breakpoint. [4] In another study testing 93 *Nocardia* isolates by the Etest method, all isolates were susceptible to linezolid. [5] Thus, it is an attractive alternative treatment for central

155 nervous system nocardiosis, despite limited clinical evidence to support this
156 claim.
157 Fifteen cases of nocardiosis treated with linezolid have been published to
158 date.(Table)[6-15] Linezolid has a well-documented short-term adverse
159 effect profile, with headache and diarrhoea most commonly seen; however,
160 its long-term safety profile (>28 days) has not been extensively studied. In
161 9 of these cases, linezolid was selected due to a lack of tolerance to TMP or
162 beta-lactams, and 2 cases were due to multidrug resistant Nocardia spp.
163 All cases exhibited long-term tolerance of linezolid (median 120; range
164 30-720 days) and 14 out of 15 cases showed either an improvement in or
165 complete clearance of the infection. Whether linezolid treatment is superior
166 to TMP or beta-lactam treatment is still unknown; however, this agent may
167 be a last resort for nocardiosis. Information on efficacy and outcomes
168 similar to this report will be important in treating *Nocardia* spp. infections,
169 due to the need for an extended course of treatment and the relative lack of
170 available data.
171 Although reviews of therapy for Nocardia infections recommend TMP as the
172 therapeutic drug of choice, sulphonamide-resistant Nocardia infections have

been reported in many countries, including the United States, Japan, France and Britain[16,17]. TMP susceptibility varies geographically, and TMP resistance ranges from a low of 32% for *N. brevicatena* to 93% for *N. farcinica*. Multidrug resistance may also occur with *N. farcinica,* and thus susceptibility varies among *Nocardia* species as well. In addition, Tremblay et al. recently reported the high frequency of isolation of *N. farcinica* from specimens that indicated invasive disease (such as brain or lung biopsies and blood) [16]. Given the preponderance of invasive *N. farcinica* infection and the frequent non- susceptibility of isolates to TMP, this drug may no longer be the first choice in some regions.

Publication bias is an important consideration, as some authors hesitate to publish or present cases with poor outcomes. Another limitation is that the published evidence regarding the efficacy and safety of linezolid in patients with nocardiosis is derived solely from a small subset of case reports. Although the incidence of nocardiosis is thought to be on the rise, it remains a rare opportunistic infection. Thus, it is difficult to establish the use of linezolid in the therapeutic regimen for nocardiosis through randomised controlled trials.

Additional accumulation of case reports regarding the use of linezolid in Nocardia infections will be of use to clinicians and patients suffering from disseminated nocardiosis.

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Table Summary of cases of linezolid use for nocardiosis

No.	Age (y), Sex	Co-morbidities	Infection Site	Nocardia spp.	Indication	Outcome	Linezolid ADRs	Duration of Linezolid use (days)	Reference
1	NA/M	Trauma	Disseminated	*N. farcinica*	ADRs	Cure (followed by minocycline)	Myelosuppression, optic neuritis	150	[6]
2	29/F	SLE	Disseminated	*N. asteroides*	ADRs	Cure (followed by IPM and AMK)	Peripheral neuropathy	120	[7]
3	45/M	Silicosis/steroid	Disseminated	*N. asteroides*	ADRs	Cure	None	365	[8]
4	63/M	Silicosis/steroid	Disseminated	NA	Sulphona-mide allergy	Cure	Anemia	90	
5	54/F	None	Facial cellulitis	NA	Clinical failure	Cure (followed by TMP)	Anemia	60	

6	52/F	None	Disseminated	*N. otitidisca-varium*	ADRs	Cure	Anemia, thrombocytopenia, lactic acidosis, peripheral neuropathy	120	
7	6/M	CGD	Lung	*N. asteroides*	Clinical failure	Cure	None	790	
8	9/M	CGD	Disseminated	NA	ADRs	Cure	None	365	
9	58/M	NA/steroid	Brain abscesses	*N. farcinica*	NA	Improvement (followed by meropenem and amoxicillin/clavulanate)	None	49	[9]
10	12/M	Kidney transplant	Brain abscesses	*N. farcinica*	Clinical failure	Cure	Anemia	60	[10]
11	37/M	SLE	Brain abscesses	*N. asteroides*	Adjunctive therapy	Improvement	NA	NA	[11]
12	42/F	Heart transplant	Brain abscesses	*N. farcinica*	Multidrug resistance	Cure	Mild sensory neuropathy	510	[12]

13	51/M	Churg-Strauss syndrome	Lung	*N. asteroides*	ADRs	Improvement	None	36	[13]
14	66/F	Psoriasis	Disseminated	*N. farcinica*	Multidrug resistance	Unchanged	None	NA	[14]
15	45/M	Renal transplant	Lung, Subcutaneous abscess	*N. asteroides*	Clinical failure	Cure	Anemia, thrombocytopenia	NA	[15]
16	59/F	MG	Disseminated	*N. farcinica*	ADRs	Cure (followed by TMP)	Mild thrombocytopenia	30	Present case

NA = not available; ADR = adverse drug reaction; SLE = systemic lupus erythemtatotes; CGD = chronic granumatous disease; MG = myasthenia gravis