Clarithromycin As an Alternative and Prophylactic Agent in a Hematopoietic Stem Cell Transplantation Patient

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEFG 1 Katsushi Tajima
B 1 Shuhei Okuyama
B 1 Taichi Terada
BC 2 Daisuke Akaneya
D 3 Ryuichiro Hori
B 4 Shuichi Abe
D 5 Tsuguo Honma
B 1 Riko Tsumanuma
B 1 Eijiro Omoto
CD 6 Junko Ito
CD 6 Tohru Gonoi

1 Department of Hematology, Yamagata Prefectural Central Hospital, Yamagata, Japan
2 Department of Laboratory Medicine, Yamagata Prefectural Central Hospital, Yamagata, Japan
3 Department of Laboratory Medicine, Yamagata University School of Medicine, Yamagata, Japan
4 Department of Infectious Diseases, Yamagata Prefectural Central Hospital, Yamagata, Japan
5 Department of Radiology, Yamagata Prefectural Central Hospital, Yamagata, Japan
6 Medical Mycology Research Center, Chiba University, Chiba, Japan

Patient:	**Male, 34-year-old**
Final Diagnosis:	**Nocardia infection**
Symptoms:	**Chest pain**
Medication:	—
Clinical Procedure:	—
Specialty:	**Infectious Diseases**
Objective:	Rare disease

Background: Nocardia infections have rarely been reported in hematopoietic stem cell transplantation (HSCT) patients, who usually receive the prophylactic use of sulfamethoxazole/trimethoprim (ST) against *Pneumocystis jiroveci*. However, the ST prophylaxis, sensitive to Nocardia species, sometimes induces renal toxicities. Therefore, alternative prophylactic or therapeutic drugs are required for nocardiosis in HSCT patients.

Case Report: A 34-year-old Japanese man with acute mixed phenotypic leukemia with *t(9; 22)* received allogenic peripheral blood HSCT from a haplo-identical sibling donor. He developed graft versus host disease (GVHD) with grade II, and was treated with prednisolone and cyclosporine A with concurrent ciprofloxacin, fluconazole, valacyclovir, and ST. However, the prophylactic ST was ceased because of its renal toxicity. He developed a pulmonary nodular lesion with elevated β-D-glucan and Aspergillus galactomannan antigen. Repeated blood and sputum culture isolated no pathogens. Voriconazole treatment administered once improved these lesions and laboratory findings. One month later, he presented with right pleuritic chest pain and multiple ring-enhancing cavitation lesions along the ribs. A needle biopsy demonstrated *Nocardia elegans*, which is an extremely rare infection induced by *Nocardia* species, in the cavitation lesions, shown by 16S rRNA gene sequencing. He was started on doripenem and liposomal amphotericin B, and a subsequent treatment kept him free from *Nocardia elegans* infection, without any adverse effects, while continuing the cyclosporine A and prednisolone treatment for chronic GVHD.

Conclusions: Clarithromycin has fewer adverse effects than ST. This case suggests that clarithromycin is an appropriate alternative and prophylactic therapy for patients with nocardiosis and ST toxicities.

Keywords: Clarithromycin • Hematopoietic Stem Cell Transplantation • *Nocardia elegans* • Trimethoprim, Sulfamethoxazole Drug Combination

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/931731

📄 1770   ⊞ 1   📊 2   📚 18

Background

Nocardia infections have rarely been reported in hematopoietic stem cell transplantation (HSCT) patients, although these patients have numerous risk factors for *Nocardia* infection, including lymphopenia and steroid therapy for graft versus host disease (GVHD) [1-4]. The low incidence in HSCT patients may be due to not only the routine prophylactic use of sulfamethoxazole/trimethoprim (ST) against *Pneumocystis jiroveci,* but also the difficult isolation and identification of the genus *Nocardia* by routine microbiological methods [4,5]]. However, HSCT patients cannot always be treated with ST prophylaxis and/or therapy because of its various toxicities, including renal impairment [6]. Therefore, novel methods to precisely and rapidly identify *Nocardia* species, and safer alternative agents to ST, are required for HSCT patients. In the present study, we demonstrate that *N. elegans*, which is extremely rare in nocardiosis, was precisely and rapidly identified in subcostal abscesses in an HSCT patient by molecular methods, including matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) and 16S rRNA gene sequencing [5]. The present patient, who was the first HSCT patient with nocardiosis by *N. elegans*, was safely treated with long-term oral clarithromycin as an alternative to ST.

Case Report

The patient was a 34-year-old Japanese man with acute mixed phenotypic leukemia with *t(9;22),* which expressed myeloperoxidase and CD79a. He had no history of tobacco smoking, alcohol drinking, or substance abuse. After dasatinib and prednisolone chemotherapy, he achieved complete remission and subsequently underwent allogeneic peripheral blood HSCT from a haplo-identical female sibling donor, with a conditioning regimen comprising cyclophosphamide (60 mg/kg/day for 2 days) and busulfan (3.2 mg/kg/day for 4 days) in December 2015. The intersexual fluorescent in situ hybridization revealed complete chimerism on day 20.

The prophylactic treatment for acute GVHD comprised intravenous cyclosporine A (CyA) (3 mg/kg/day) and conventional short-term methotrexate. However, he developed acute stage 3 skin GVHD and stage 1 (grade II) gastrointestinal tract GVHD on day 22. He was initially treated with prednisolone (0.5 mg/kg) in addition to CyA, and the acute GVHD was relieved. However, upon tapering the prednisolone, he continued to have recurrent flares of GVHD, including the stage 3 skin and stage 3 gastrointestinal tract GVHD with diarrhea and weight loss and sicca syndrome. Finally, prednisolone (12.5 mg/day) and CyA (150 mg/day) were required, with concurrent ciprofloxacin, fluconazole, valacyclovir, and ST. However, renal impairment (creatinine, 1.83 mg/dL) occurred, and the prophylactic ST administration was ceased.

One month after the prednisolone treatment for chronic GVHD following acute GVHD on day 140, he developed a nodular lesion in segment 6 of the right lung (**Figure 1A**), and pleural effusion with elevated β-D-glucan (99.0 pg/mL: normal <20 pg/mL) and a positive reaction to *Aspergillus* galactomannan antigen. These findings suggested that he might have invasive pulmonary aspergillosis, although a bronchoalveolar lavage and biopsy were not performed. He was started on oral voriconazole, which suppressed the nodular lesions in the lung (**Supplementary Figure 1**). One month later, he presented with right pleuritic chest and back pain, non-productive cough, and fever without sputum. The laboratory findings were: hemoglobin level, 8.7 g/dL (13.7-16.8); white blood cell count, 15 000/mm^3 (3300-8600) (neutrophils, 90% (40-71); lymphocytes, 7% (27-46); platelet count, 19.2×10^4/mm^3 (15.8-34.8); and C-reactive protein concentration, 11.3 mg/dL (0.0-0.14). The serum liver enzyme levels were: glutamic-oxaloacetic transaminase, 47 IU/L (10-42); glutamate pyruvic transaminase, 101 IU/L (13-30); alkaline phosphatase, 2553 IU/L (38-113); gamma glutamic transpeptidase, 1097 IU/L (13-54); total bilirubin, 1.4 mg/dL (0.4-1.5); serum creatinine, 1.22 mg/dL (0.65-1.07); immunoglobulin (Ig) G, 113 g/dL (861-1747); IgA, 7 mg/dL (93-393); and IgM, 37 mg/dL (33-183). Assays for β-D glucan, *Candida* antigen, *Aspergillus* galactomannan antigen, cryptococcal antigen, and cytomegalovirus pp65 antigenemia were all negative. Repeated blood cultures isolated no pathogens. A contrast-enhancing computed tomography (CT) scan revealed slight growth of the previous lung nodule (**Figure 1B**) and new multiple ring-enhancing cavitation lesions along the tenth to twelfth ribs with pleural effusion (**Figure 1C, 1D**). The initial images of these lesions suggested mucormycosis as a possible breakthrough infection, despite the voriconzole administration. A CT scan of the brain was normal.

To determine the precise cause of the cavitation lesions in the subcostal muscle, a percutaneous CT-guided needle aspiration biopsy was performed, and a white, viscous specimen was obtained. Microscopic observation of the specimen revealed beaded or branching rods that were positive for modified Ziehl-Neelsen and Gram-staining, suggesting abscesses induced by the genus *Nocardia* (**Figure 1E**). We analyzed the isolated colonies by Bruker Biotype MALDI-TOF MS; the score for *N. nova* was 1.84 and that for *N. elegans* was 1.61. Finally, the 16S rRNA gene sequencing identified the isolated colonies as *N. elegans*.

The patient was started on intravenous doripenem (0.25 g every 6 h) and liposomal amphotericin B (5 mg/kg), and oral ST (320/1600 mg/day) was reattempted. However, the oral ST treatment was discontinued due to renal function deteriorating again. The continuing doripenem and amphotericin B treatments halted the cavitation lesions in the subcostal muscle for 2 weeks, and gradually relieved all of his symptoms and
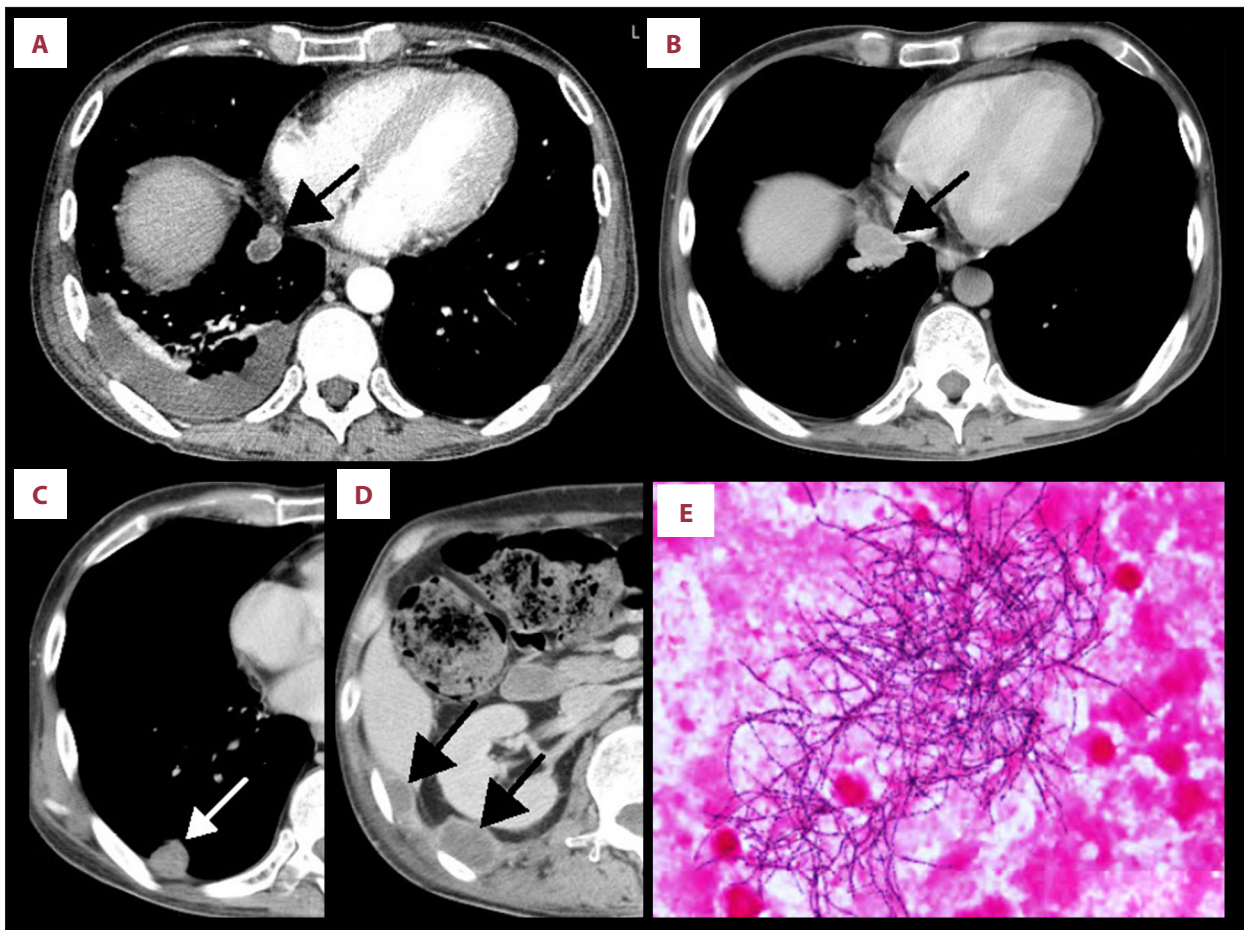
Figure 1. (**A**) A chest CT scan revealed a nodular lesion in the right lung (black arrow). (b)(c)(d) A CT scan revealed the previous lesion (**B**) (black arrow), (**C**) (white arrow), and ring-enhancing cavitation lesions in the subcostal muscle along with the ribs (**D**) (black arrows). (**E**) A microscopic analysis revealed beaded or branching rods (Gram staining).

improved his laboratory findings for 4 weeks. The isolated *N. elegans* strain was susceptible to ST, imipenem, amikacin, linezolid, and clarithromycin, based on antimicrobial susceptibility tests (**Table 1**). Thus, the patient was started on the clarithromycin treatment, with the subsequent withdrawal of doripenem and amphotericin B. Six months later, he remains well and free of *N. elegans* infection, while continuing the clarithromycin, the same dose of CyA, and the prednisolone treatment for the limited chronic GVHD, without any adverse effects.

Discussion

Nocardiosis occurs in less than 3% of HSCT patients due to the routine prophylactic use of ST [1]. However, breakthrough nocardiosis in some HSCT patients receiving ST prophylaxis has recently been noted [4,7]. A previous report showed that 42% of the *Nocardia* isolates in the United States during 1995 to 2004 were resistant to ST [8]. However, in other studies, *Nocardia* isolates in Spain and Taiwan remained susceptible to

ST [9,10]. The susceptibility to ST may depend on geographical *Nocardia* species variations and the history of antimicrobial use. A recent report revealed that the onset of nocardiosis in HSCT patients was related to either receiving steroids or not receiving ST prophylaxis at the time of diagnosis [7]. Our patient received prednisolone for chronic GVHD and no ST prophylaxis, and in addition, he had low levels of immunoglobulins and persistent lymphopenia, which have been suggested to be risk factors for *Nocardia* development [4]. These combined risk factors might have induced his nocardiosis.

In selecting antibiotics, the precise and rapid identification of the *Nocardia* species is critical for physicians to provide the most appropriate therapies. Advanced molecular methods, such as 16S rRNA sequencing and MALDI-TOF MS analysis, are useful and valuable tools in clinical laboratories to identify the taxonomy of *Nocardia* species. In this case, the presence of *N. elegans* was precisely identified by a combination of microbiological and molecular analysis for the subcostal abscess by needle biopsy. Therefore, we emphasize that vigorous

Table 1. Activities of antibiotics against *Nocardia elegans* in the current case.

Antibiotics	MIC (μg/ml)	Susceptibility
AMK	<0.5	S
ACV	>32/16	R
CTRX	16	I
CPFX	>4	R
IPM	<0.5	S
LZD	<1	S
MINO	2	I
ST	19/1	S
TOB	16	R
CTX	4	S
CFPM	2	S
DOXY	8	R
GM	16	R
CAM	<0.25	S

MIC – minimum inhibitory concentration; S – susceptible; I – intermediate; R – resistant; AMK – amikacin; ACV – potassium clavulanate; CTRX – ceftriaxone sodium; CPFX – ciprofloxacin hydrochloride; IPM – imipenem; LZD – linezolid; MINO – minocycline; ST – sulfamethoxazole/trimethoprim; TOB – tobramycin; CTX – cefotaxime; CFPM – cefepime dihydrochloride; DOXY – doxycycline hydrochloride; GM – gentamicin; CAM – clarithromycin.

examinations, including CT-guided needle aspiration, should be considered even in HSCT patients who have a bleeding risk [5].

In this case, the MALDI-TOF-MS analysis initially suggested *N. nova*, and not *N. elegans*, as the cause of the abscess lesions. This mistake was corrected by the 16S rRNA gene sequencing. The present MALDI-TOF-MS system may be improved by upgrading the analysis system, including an updated database, especially considering the molecular similarities of the *Nocardia* species and the insufficient depth of the database, which lacked extremely rare species, including *N. elegans* [11].

Only 8 cases of nocardiosis induced by *N. elegans* have been reported [12]. This is the first report of *N. elegans* nocardiosis in an HSCT patient; thus, the clinical characteristics remain to be fully elucidated. However, half of the cases of *N. elegans* had pulmonary or connective tissue lesions[12]. The present patient also had these lesions. There are only a few reports of antibiotic susceptibility and therapeutic experiences in *N. elegans* nocardiosis [9,12,13]. These reports showed that in addition to ST, imipenem, meropenem, amikacin, minocycline, and

clarithromycin are also active against *N. elegans*. ST has been the first-choice therapy in nocardiosis because of the sufficient tissue penetration with oral administration and the synergistic activities against nocardiosis in conjunction with other agents [3]. In the present patient, the antibiotic susceptibility of the isolated *N. elegans* was primary compatible with previous reports [8,10,14]. In our patient, treatment with oral clarithromycin maintained remission of his abscesses without any adverse effects [15,16]. In fact, clarithromycin has a higher concentration in connective tissue and better white blood cell penetration than in the plasma, and thus provides several other advantages in connective tissue lesions in terms of oral administration and fewer adverse effects that ST or injection agents. Therefore, we suggest that clarithromycin may be the most appropriate therapy, especially for nocardiosis caused by *N. elegans*. However, clarithromycin is also one of the drugs that inhibit drug metabolism in the liver, and the dose used should be monitored as it can lead to high levels of other concurrent medications utilizing the same pathway. There is a need for further studies to explore alternative prophylactic alternatives to ST.
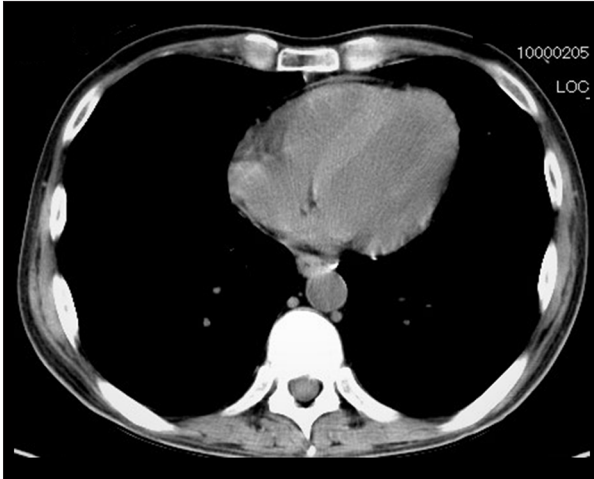
Our patient initially presented with a nodular lesion in the right lung, and the voriconazole treatment relieved the progression of this lesion and restored the levels of β-D-glucan and *Aspergillus* galactomannan antigen. These findings could not exclude the possibility that he might have had concurrent *N. elegans* nocardiosis and mycosis caused by unidentified fungal pathogens. Therefore, the surviving *N. elegans* might have directly extended to the subcostal muscle and formed abscesses from the primary nodular lesions. A previous study reported concurrent nocardiosis induced by *N. nova* and mucormycosis by the genus *Rhizopus* in an HSCT recipient, and emphasized that mucormycosis should still be suspected despite the use of prophylactic antifungal treatments [17]. However, the prevalence of nocardiosis and concomitant fungal infection remains unknown in HSCT patients. A recent report of a patient with disseminated nocardiosis caused by *N. farcinica* had elevated serum β-D-glucan, and suggested that the Nocardia genus may show cross-reactivity with the β-D-glucan assay [18], but this disagrees with our experience in the present case. The cross-reactivity with β-D-glucan may differ in each Nocardia species.

Conclusions

We precisely and rapidly identified *N. elegans* in the cavitation lesions in the subcostal muscle in an HSCT patient with GVHD and adverse effects from ST, using a combination of microbiological and molecular methods. Oral clarithromycin, as an alternative agent to ST, safely controlled the nocardiosis without any adverse effects for a long time. Oral clarithromycin treatment may be a promising alternative therapeutic agent, especially for some HSCT patients with GVHD and ST adverse effects.

Acknowledgements

Conflict of Interest

None.

Supplementary Figure 1. A chest CT scan revealed improvements of the nodular lesions in the lung.

References:

1. Schuster MG, Cleveland AA, Dubberke ER, et al. Infections in hematopoietic cell transplant recipients: Results from the organ transplant infection project, a multicenter, prospective, cohort study. Open Forum Infect Dis. 2017;4(2):ofx050

2. Lebeaux D, Morelon E, Suarez F, et al. Nocardiosis in transplant recipients. Eur J Clin Microbiol Infect Dis. 2014;33(5):689-702

3. Choucino C, Goodman SA, Greer JP, et al. Nocardial infections in bone marrow transplant recipients. Clin Infect Dis. 1996;23(5):1012-19

4. Cattaneo C, Antoniazzi F, Caira M, et al. *Nocardia* spp infections among hematological patients: Results of a retrospective multicenter study. Int J Infect Dis. 2013;17(8):e610-14

5. Ooi Y, Shiba H, Nagai K, et al. Lung *Nocardia elegans* infection diagnosed on matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS). Intern Med. 2014;53(18):2111-13

6. Nishida R, Mori Y, Iwasaki H, et al. Pulmonary nocardiosis developed in a hematopoietic stem cell transplant recipient with bronchiolitis obliterans. Intern Med. 2010;49(14):1441-44

7. Shannon K, Pasikhova Y, Ibekweh Q, et al. Nocardiosis following hematopoietic stem cell transplantation. Transpl Infect Dis. 2016;18(2):169-75

8. Uhde KB, Pathak S, McCullum I Jr. et al. Antimicrobial-resistant nocardia isolates, United States, 1995-2004. Clin Infect Dis. 2010;51(12):1445-48

9. Lai CC, Liu WL, Ko WC, et al. Multicenter study in Taiwan of the in vitro activities of nemonoxacin, tigecycline, doripenem, and other antimicrobial agents against clinical isolates of various Nocardia species. Antimicrob Agents Chemother. 2011;55(5):2084-91

10. Minero MV, Marin M, Cercenado E, et al. Nocardiosis at the turn of the century. Medicine (Baltimore). 2009;88(4):250-61

11. Pasciak M, Dacko W, Sikora J, et al. Creation of an in-house matrix-assisted laser desorption ionization-time of flight mass spectrometry corynebacterineae database overcomes difficulties in identification of *Nocardia farcinica* clinical isolates. J Clin Microbiol. 2015;53(8):2611-21

12. Nakamura I, Nagakura T, Fujita H, et al. *Nocardia elegans* infection: A case report and literature review. Int J Infect Dis. 2017;54:15-17

13. Masaki T, Ohkusu K, Ezaki T, Miyamoto H. *Nocardia elegans* infection involving purulent arthritis in humans. J Infect Chemother. 2012;18(3):386-89

14. Lai CC, Liu WL, Ko WC, et al. Antimicrobial-resistant nocardia isolates, Taiwan, 1998-2009. Clin Infect Dis. 2011;52(6):833-35

15. Liapakis IE, Light RW, Pitiakoudis MS, et al. Penetration of clarithromycin in experimental pleural empyema model fluid. Respiration. 2005;72(3):296-300

16. Yoshida H, Furuta T. [Tissue penetration properties of macrolide antibiotics – comparative tissue distribution of erythromycin-stearate, clarithromycin, roxithromycin and azithromycin in rats]. Jpn J Antibiot. 1999;52(7):497-503 [in Japanese]

17. Lim MY, Alker AP, Califano S, et al. Concurrent disseminated nocardiosis and GI mucormycosis in a stem-cell transplantation recipient. J Clin Oncol. 2016;34(10):e84-86

18. Sawai T, Nakao T, Yamaguchi S, et al. Detection of high serum levels of beta-D-Glucan in disseminated nocardial infection: A case report. BMC Infect Dis. 2017;17(1):272