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The emergence of rare nocardiosis following allogeneic hematopoietic stem cell transplantation in the era of molecular taxonomy

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ABSTRACT

Objective: The purpose of this study was to describe the clinical features of nocardiosis after allogeneic hematopoietic stem cell transplantation (allo-HSCT), focusing on new *Nocardia* species.
Methods: We retrospectively reviewed data from patients with nocardiosis after allo-HSCT treated at our hospital and documented cases in the medical literature.
Results: Fifty-seven cases were identified from our institution and the literature review. Although 51 patients (89.5%) responded to initial treatment, 28 (49.1%) patients were switched over to other treatment regimens due to the recurrence of nocardiosis or adverse events of antimicrobials. Nocardiosis-attributed mortality occurred in ten patients (17.5%). Antimicrobial susceptibilities varied among intra- and inter-species except linezolid (LZD). In the present study, five species were newly discovered after 2000, including *N. cyriacigeorgica*, *N. veterana*, *N. abscessus*, *N. aobensis*, and *N. mexicana*. All isolates of *N. cyriacigeorgica*, *N. veterana*, *N. abscessus*, and *N. aobensis* were sensitive to trimethoprim/sulfamethoxazole, amikacin (AMK), imipenem (IPM), and LZD; however, *N. mexicana* was resistant to AMK and IPM.
Conclusion: Newly identified *Nocardia* species have various antimicrobial susceptibility patterns. Long-term maintenance therapy could be challenging due to the adverse events of antimicrobials, especially in the allo-HSCT setting. Prudent evaluation is crucial for selecting a second-line or further treatment options.

Introduction

Nocardia species are aerobic, gram-positive, modified-acid-fast, branching filamentous bacilli that generally inhabit the soil, decaying vegetable matter, and aquatic environment (Brown-Elliott et al., 2006). Although *Nocardia* species infect immunocompetent persons, they most often infect immunocompromised patients, primarily those with abnormalities in cell-mediated immunity, and less often, those with leukocyte or humoral immunity disorders (Torres et al., 2002). In transplant patients, solid organ transplantation and allogeneic (allo-) or autologous hematopoietic stem cell transplantation (HSCT) account for up to 25% and 6% of nocardiosis cases, respectively (Minero et al., 2009). Patients after allo-HSCT are at much higher risk for nocardiosis than those with autologous HSCT due to the development of graft-versus-host disease (GVHD) and additional immunosuppressive treatments (Wilson, 2012). Although the occurrence of nocardiosis following allo-HSCT has already been

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described in the literature (Torres et al., 2002; Daly et al., 2003; Hardak et al., 2012; Cattaneo et al., 2013; Mansi et al., 2014; Shannon et al., 2016; Molina et al., 2018; Hemmersbach-Miller et al., 2018), its clinical significance and treatment strategies have not been established fully due to availability of few case series, and no comparative studies.

Nocardiosis occurrence after allo-HSCT is complicated to diagnose and manage for several reasons. First, the clinical features of nocardiosis, such as fever, cough, pleuritic chest pain, and headache, are non-specific findings (Minero et al., 2009). Second, the radiological findings of pulmonary nocardiosis are variable (Blackmon et al., 2011; Bargehr et al., 2013; Mehrian et al., 2015). Third, bacterial, fungal, and viral co-infections are present in 20 to 64% of nocardiosis cases (Lebeaux et al., 2014). Therefore, the risk of nocardiosis may be underestimated, and the disease is mistaken for other types of infection, thus causing a delay in treatment leading to poor prognosis in the allo-HSCT setting.

Molecular methods relying on 16S ribosomal RNA (rRNA) gene sequencing have resulted in the reclassification of *Nocardia* species and the identification of previously unknown species (Han et al., 2002; Roth et al., 2003; Cloud et al., 2004). However, data on the clinical features, such as baseline characteristics, susceptibilities, and treatment outcomes are not available for the new *Nocardia* species infections in patients after allo-HSCT. In this study, we described the clinical features and prognostic outcome of nocardiosis following allo-HSCT at our hospital and reviewed past reported cases, focusing on the *Nocardia* species discovered after 2000.

Methods

Case series

We reviewed nocardiosis cases after allo-HSCT treated at our hospital between January 2005 and March 2017 using the clinical laboratory database and medical records from a tertiary care cancer center in Japan in addition to our previous reports (Kakihana et al., 2007; Hino et al., 2016). Data on the baseline characteristics, underlying disease, computed tomography (CT) manifestations, species identification, susceptibility testing results, treatment modalities, and outcomes retrieved from the patients' electronic medical records. The institutional committee on research ethics at our hospital (approval number: 2114) approved this study and complied with the Declaration of Helsinki.

Transplant procedures at our institution

Transplant procedures at our institution are described in detail in the supplementary document. In the non-haploidentical allo-HSCT setting, patients received acute GVHD prophylaxis with cyclosporine or tacrolimus as well as short-term methotrexate. Tacrolimus was used in cases of unrelated or human leukocyte antigen-mismatched transplantation. In a few cases of CBT, mycophenolate mofetil was used for GVHD prophylaxis instead of short-term methotrexate. In the haploidentical allo-HSCT setting, patients received the combination of a low dose of rabbit antithymocyte globulin (thymoglobulin, Thy; 2–2.5 mg/kg) and GVHD prophylaxis consisting of tacrolimus and methylprednisolone. Methylprednisolone dose reduction was initiated on day 15 and tapered until day 30 in the absence of acute GVHD. Acute and chronic GVHD were diagnosed and graded according to previously established criteria (Rowlings et al., 1997). Standard initial therapy for acute GVHD (grade II or more) was methylprednisolone 1–2 mg/kg/day (Ruutu et al., 1997). Mycophenolate mofetil, mesenchymal stromal cells, or Thy were used as a treatment for steroid-refractory acute GVHD.

Levofloxacin or tosufloxacin, and fluconazole or itraconazole were started orally 14 days before allo-HSCT as prophylaxis for bacterial and fungal infection, respectively. Trimethoprim/sulfamethoxazole (TMP/SMX) was administered to prevent pneumocystis pneumonia (PCP) after engraftment. Pentamidine or atovaquone was alternatively used in patients with cytopenia or adverse events to TMP/SMX. As a rule, acyclovir was administered seven days before allo-HSCT until the end of immunosuppressive drug administration to prevent herpes virus or varicella-zoster virus infection. A diagnosis of invasive pulmonary aspergillosis (IPA) was done by the EORTC/MSG criteria (De Pauw et al., 2008).

Literature review

We identified single case reports and retrospective case series of nocardiosis cases after allo-HSCT published in the English language after January 2000 by searching the PubMed database using the terms ("*Nocardia*" or "nocardiosis"), ("bone marrow" or "cord blood" or "stem cell"), and "transplantation". Case reports in languages other than English, and pediatric cases ($\leq$5 years-old) were excluded. Retrospective case series irrespective of the underlying disease (Torres et al., 2002; Hardak et al., 2012; Cattaneo et al., 2013; Hemmersbach-Miller et al., 2018) were also excluded due to insufficient individual data in allo-HSCT recipients. Furthermore, we focused on new *Nocardia* species proposed since 2000 and identified single case reports of *Nocardia abscessus*, *N. aobensis*, *N. veterana*, and *N. mexicana* infections irrespective of the underlying disease by searching the PubMed database. We retrieved data on the baseline characteristics, underlying disease, coexisting infections, species identification, susceptibility profiles, treatment modalities, and outcomes.

Definition and microbiology

Nocardiosis was identified by the presence of *Nocardia* species in culture or on histopathologic examination of a clinical specimen obtained from a normally sterile site (including subcutaneous lesions) and a compatible clinical presentation (van Burik et al., 1997). Disseminated infection is an infection in two noncontiguous organs, in the bloodstream, or the central nervous system (Menéndez et al., 1997). The isolates were identified using 16S rRNA gene sequence analysis and antimicrobial susceptibility testing using the broth microdilution method following the recommendations of the Clinical and Laboratory Standards Institute M24-A2 (Clinical and Laboratory Standards Institute, 2011).

Results

Case series from our institution

The clinical charts of 935 allo-HSCT recipients (575 men, 360 women; median age, 46 years; range, 15–73 years) were reviewed retrospectively for nocardiosis, and we identified seven episodes (0.75%) of nocardiosis, including those in our previous case reports (Kakihana et al., 2007; Hino et al., 2016), with a median interval of 7 months (range, 3 to 39 months) from allo-HSCT to onset. The patients' clinical features are summarized in Table 1. The patients' median age was 59 years (range, 18 to 66 years); four were male and three were female. The underlying diseases were acute myeloid leukemia (AML, n = 2), myelodysplastic syndrome (MDS, n = 2), acute lymphoblastic leukemia (ALL, n = 1), chronic myelomonocytic leukemia (n = 1), and mixed-phenotype acute leukemia (n = 1). One patient received matched-related donor allografts, 3 received matched-unrelated donor allografts, and 3 received mismatched-unrelated donor allografts. No patients received

Table 1
Clinical characteristics of nocardiosis in patients at our institution.

Case No.	Age/sex	Primary disease	Stem cell source	Donor type	Conditioning regimen	MAC or RIC	GVHD prophylaxis	Acute GVHD	Chronic GVHD	Immunosuppressive drugs at the nocardiosis onset			PCP prophylaxis at the nocardiosis onset	Interval until the nocardiosis onset after allo-HSCT	Initial symptoms			Affected organs	Diagnostic specimens	Species	Chest CT at the nocardiosis onset				Pulmonary co-infection at the nocardiosis onset
								Overall grade (affected organs)	Type (affected organs)	PSL	Calcineurin inhibitor	MMF			Fever	Cough	Chest pain				Consolidation	GGO	Nodules	Cavity	
1 (Kakihana et al., 2007)	18/M	MPAL	PBSC	MRD	AraC, CY, 12Gy-TBI	MAC	CyA, sMTX	I (skin)	Extensive (skin, mouth, liver, lung)	20 mg/day	+	–	None	13 months	+	–	+	Lung	Sputum, TBLB	*N. farcinica*	–	–	+	+	None
2	60/M	MDS	BM	MUD	FLU, BU, 4Gy-TBI	RIC	Tac, sMTX	II (skin)	Extensive (skin, eye, gut, lung)	12.5 mg/day	+	+	Pentamidine	3 months	+	–	–	Lung	Sputum	*N. abscessus*	–	–	+	–	None
3	59/M	CMML	BM	MUD	CY, 12Gy-TBI	MAC	Tac, sMTX	I (skin)	Extensive (skin, mouse, eye, gut, liver, lung, muscle)	15 mg/day	+	+	Pentamidine	39 months	+	+	–	Lung	Sputum	*N. aobensis*	+	–	+	–	None
4 (Hino et al., 2016)	50/F	AML	BM	MUD	BU, CY	MAC	Tac, sMTX	II (skin, liver)	Extensive (skin, eye, gut, lung)	10 mg/day	+	+	TMP/SMX	23 months	–	+	–	Brain, liver, lung, SST	Sputum, TBLB, SST	*N. abscessus*	–	–	+	+	Proven IPA
5	66/F	ALL	BM	MMUD	FLU, BU, 4Gy-TBI	RIC	Tac, sMTX	I (skin)	Extensive (skin, gut)	–	+	–	Pentamidine	6 months	+	+	–	Lung	Sputum	*N. farcinica*	+	+	+	–	Probable IPA
6	65/M	MDS	BM	MMUD	FLU, BU, 4Gy-TBI	RIC	Tac, sMTX	II (skin)	Extensive (skin, gut)	5 mg/day	+	–	Pentamidine	7 months	+	+	–	Lung	Sputum	*N. veterana*	+	–	+	+	Probable IPA
7	48/F	AML	BM	MMUD	BU, CY	MAC	Tac, sMTX	II (skin, gut)	Extensive (skin, gut, liver)	30 mg/day	+	–	Pentamidine	6 months	+	+	+	Lung	Sputum	*N. farcinica*	+	–	+	–	None

Abbreviations: ALL, acute lymphoblastic leukemia; allo-HSCT, allogeneic hematopoietic stem cell transplantation; AML, acute myeloid leukemia; AraC, cytarabine; BM, bone marrow; BU, busulfan; CMML, chronic myelomonocytic leukemia; CT, computed tomography; CY, cyclophosphamide; CyA, cyclosporine; F, female; FLU, fludarabine; GGO, ground-glass opacity; GVHD, graft-versus-host disease; Gy, gray; IPA, invasive pulmonary aspergillosis; M, male; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; MPAL, mixed-phenotype acute leukemia; MMF, mycophenolate mofetil; MMUD, mismatched-unrelated donor; MRD, matched-related donor; MUD, matched-unrelated donor; PBSC, peripheral blood stem cell; PCP, pneumocystis pneumonia; PSL, prednisolone; RIC, reduced-intensity conditioning; sMTX, short-term methotrexate; SST, skin and soft tissue; Tac, tacrolimus; TBI, total body irradiation; TBLB, transbronchial lung biopsy; TMP/SMX, trimethoprim/sulfamethoxazole.

haploidentical transplantation. All the patients developed extensive chronic GVHD at the onset of nocardiosis and received calcineurin inhibitor with or without mycophenolate mofetil. All but one patient also received oral prednisolone with a median daily dose of 13.8 mg (range, 5–30 mg). No patients received Thy as part of their GVHD prophylaxis or treatment. Six patients were not administered TMP/SMX prophylaxis for PCP at the onset of nocardiosis due to myelotoxicity. Co-infection with proven or probable IPA was present in three patients. All patients developed pulmonary nocardiosis, and one progressed to disseminated infection with subcutaneous lesions, liver, and central nervous system involvement (Case 4). A chest CT was performed in all the patients, and the findings are presented in Supplementary Figure S1. All the patients presented with nodules in the bilateral lungs. Four patients presented with patchy consolidation with or without ground-glass opacity. Three patients presented with cavity lesions. The isolated species were *N. farcinica* (n = 3), *N. abscessus* (n = 2), *N. aobensis* (n = 1), and *N. veterana* (n = 1).

The treatment and outcome data are summarized in Table 2. Initial treatment in six patients was using combination therapy. In three patients, the treatment regimen consisted of imipenem/cilastatin (IPM/CS) and amikacin (AMK). Antimicrobial regimens of definitive treatment were classified as monotherapy with TMP/SMX (n = 5) or minocycline (MINO) (n = 1), and combination therapy with ciprofloxacin (CPFX) and MINO (n = 1). However, three patients were switched over to other treatment regimens due to adverse drug events from TMP/SMX therapy (Case 2, 3, and 6). All the patients showed a favorable response to initial treatment, but recurrence was observed in one patient during definitive treatment (Case 1). At the last follow-up on December 30, 2018 (data cutoff), two patients had survived for 1,095 and 467 days, respectively, after the onset of nocardiosis (Case 4 and 7). Nocardiosis-attributed mortality occurred in one patient (Case 1). Deaths occurred in four other patients, with the causes of death being pneumonia with an unknown pathogen (n = 2), encephalitis with an unknown etiology (n = 1), or acute heart failure (n = 1). These patients had no exacerbation of nocardiosis.

Literature review of allo-HSCT recipients

Fifty episodes of nocardiosis following allo-HSCT were identified from 14 single case reports (Supplementary Table S1) and four case series (Supplementary Table S2) published after 2000. Thirty-seven patients were male and 13 female, with a median age of 48 years (range, 15–72 years). The time interval between transplantation and onset of nocardiosis from our case series and literature review is summarized in Supplementary Figure S2. Nocardiosis occurred at a median interval of 9 months (range, 1–93 months) after allo-HSCT. The underlying diseases with available data (n = 48) were AML (n = 16, 33.3%), chronic myeloid leukemia (n = 7, 14.6%), malignant lymphoma (n = 7, 14.6%), MDS (n = 5, 10.4%), ALL (n = 4, 8.3%), and others (n = 9, 18.8%). Prophylaxes for PCP at the onset of nocardiosis with available data (n = 44) were pentamidine (n = 18, 40.9%), atovaquone (n = 12, 27.3%), TMP/SMX (n = 10, 22.7%), or none (n = 4, 9.1%). All the patients with available data (n = 42) received immunosuppressive drugs for acute or chronic GVHD at the onset of nocardiosis.

Affected organs identified by cultures or histopathology were lungs (n = 40, 80.0%), central nervous system (n = 18, 36.0%), skin and soft tissues (n = 8, 16.0%), eyes (n = 7, 14.0%), blood (n = 6, 12.0%), and others (pleura, bone, genitals, and bowel). Twenty-five patients (50.0%) progressed to disseminated infection. Initial treatment in 25 patients (51.0%) with available data (n = 49) was a combination therapy. The initial treatment mainly included TMP/SMX (n = 30, 61.2%), IPM (n = 11, 22.4%), meropenem (n = 9, 18.4%), and AMK (n = 7, 14.3%). Although 44 patients (88.0%) responded to initial treatment, 23 (46.0%) were switched over to definitive treatments due to the recurrence of nocardiosis or adverse events associated with the use of antimicrobials. Death occurred in 21 patients (42.0%) and nocardiosis-attributed mortality occurred in nine patients (18.0%). Seven (28.0%) of 25 patients with disseminated infection succumbed to nocardiosis.

Figure 1 lists the isolated species in combination with our cases (n = 57). The isolated species were *N. asteroides* (n = 14, 24.6%), *N. farcinica* (n = 12, 21.1%), *N. nova* (n = 7, 12.3%), *N. cyriacigeorgica* (n = 6, 10.5%), *N. veterana* (n = 3, 5.3%), *N. abscessus* (n = 2, 3.5%), *N.*

Table 2
Treatment and outcomes of nocardiosis in patients at our institution.

Case No.	Initial treatment		Definitive treatment			Outcome		
	Drugs	Initial treatment length (days)	Drugs	Reason for change in management	Definitive treatment length (days)	Response	Current status	Cause of death
1 (Kakihana et al., 2007)	MEPM	14	MINO → MEPM → AMPC/CVA → MEPM → LVFX → MEPM → LZD	Recurrence of nocardiosis	1,324	Recurrence	Death under definitive treatment	BO, pulmonary nocardiosis
2	MEPM + AMK	28	TMP/SMX→MINO	Liver and renal damage	450	Resolved	Death after treatment completed	BO, pneumonia with unknown etiology
3	MEPM + TMP/SMX	16	TMP/SMX→DOXY	Renal damage	452	Resolved	Death under definitive treatment	Sepsis, aspiration pneumonia
4 (Hino et al., 2016)	IPM/CS + TMP/SMX	42	TMP/SMX	N/A	400	Resolved	Alive after treatment completed	N/A
5	IPM/CS + AMK	56	CPFX + MINO → AMPC/CVA + MINO	Myelosuppression	276	Resolved	Death under definitive treatment	Acute heart failure
6	IPM/CS + AMK	56	TMP/SMX → CAM	Liver damage	666	Resolved	Death under definitive treatment	Encephalitis with unknown etiology
7	IPM/CS + AMK	42	TMP/SMX	N/A	391	Resolved	Alive after treatment completed	N/A

Abbreviations: AMK, amikacin; AMPC/CVA, amoxicillin/clavulanate; BO, bronchiolitis obliterans; CAM, clarithromycin; CPFX, ciprofloxacin; DOXY, doxycycline; IPM/CS, imipenem/cilastatin; LVFX, levofloxacin; LZD, linezolid; MEPM, meropenem; MINO, minocycline; N/A, not assessed; TMP/SMX, trimethoprim/sulfamethoxazole.

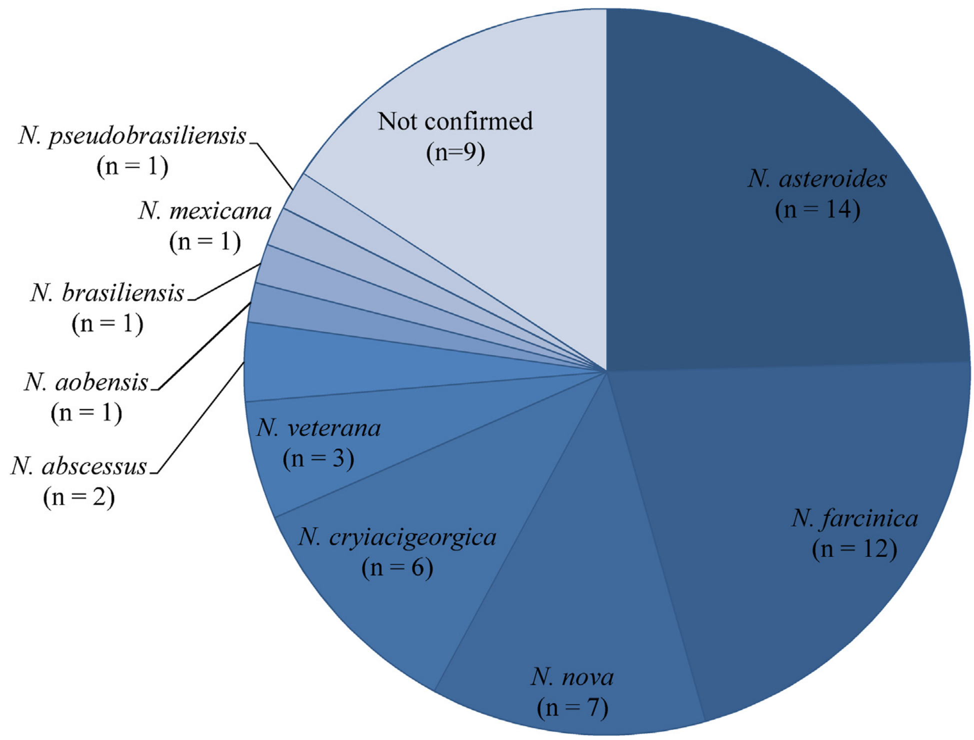

Figure 1. *Nocardia* species detected in allogeneic hematopoietic stem cell transplant recipients from our case series and literature review.

aobensis (n = 1, 1.8%), *N. brasiliensis* (n = 1, 1.8%), *N. mexicana* (n = 1, 1.8%), and *N. pseudobrasiliensis* (n = 1, 1.8%), and not confirmed (n = 7, 15.8%). The results of antimicrobial susceptibilities were available for 29 *Nocardia* isolates (50.9%) in our case series and literature review (Table 3). Susceptibility results for each antimicrobial were as follows: 28 of 29 isolates (96.6%) to TMP/SMX, 21 of 22 (95.5%) to AMK, 18 of 22 (81.8%) to IPM, 15 of 15 (100%) to linezolid (LZD), 10 of 15 (66.7%) to amoxicillin/clavulanate, 3 of 8 (37.5%) to CPFX, 5 of 11 (45.5%) to clarithromycin, 7 of 9 (77.8%) to MINO, and 3 of 7 (42.9%) to doxycycline. Available data for all five isolates identified in patients receiving TMP/SMX prophylaxis for PCP at the onset of nocardiosis show sensitivity to TMP/SMX (Hino et al, 2016; Shannon et al., 2016; Molina et al., 2018).

In our cases and literature review of allo-HSCT recipients, five species *N. cyriacigeorgica*, *N. veterana*, *N. abscessus*, *N. aobensis*, and *N. mexicana* were identified after 2000 (Yassin et al., 2000; Gurtler et al., 2001; Yassin et al., 2001; Kageyama et al., 2004; Rodríguez-Nava et al., 2004). Antimicrobial susceptibilities to oral agents varied among intra- and inter-species, except for LZD. All isolates classified as *N. cyriacigeorgica*, *N. veterana*, *N. abscessus*, and *N. aobensis* were sensitive to the most commonly used first-line drugs, including TMP/SMX, AMK, and IPM. Notably, *N. mexicana* was resistant to AMK and IPM.

Discussion

We describe extensive clinical characteristics, coexisting infections, susceptibility profiles, CT findings, treatment, and outcomes in seven patients with nocardiosis treated at our hospital. Furthermore, we reviewed 50 cases described earlier in single case reports and retrospective case series since 2000 and focused on the newly identified species, *N. cyriacigeorgica*, *N. abscessus*, *N. aobensis*, *N. veterana*, and *N. mexicana*. This report is the first literature review of new *Nocardia* species infections following allo-HSCT. Our case series and literature review showed the isolation of a variety of *Nocardia* species, and widely different antimicrobial susceptibility patterns among intra- and inter-species. Most patients responded to the first-line treatment, and nocardiosis-attributed mortality was relatively low despite a high dissemination rate. However, maintenance therapy was difficult to continue due to the adverse events of antimicrobials.

Of the five newly identified *Nocardia* species after 2000, *N. abscessus*, *N. aobensis*, *N. veterana*, and *N. mexicana* isolates were rare in our case series and literature review (Figure 1). Notably, our case series is the first report of *N. abscessus* and *N. aobensis* infections in allo-HSCT recipients. In Japan, Mikami et al. performed speciation in 536 *Nocardia* species from 1999 to 2008 and reported that the three most prevalent species were *N. farcinica* (29.9%), *N. nova* (15.1%), and *N. brasiliensis* (13.2%), while *N. abscessus* (4.1%), *N. aobensis* (0.9%), and *N. veterana* (0.6%), isolated in our case series, were rare (Mikami, 2010). The present study adds to the expanding spectrum of diseases attributable to the newly identified *Nocardia* species.

For further assessment of these four species, we identified eight case reports of *N. abscessus* infection, two of *N. aobensis*, nine of *N. veterana*, and two of *N. mexicana* in non-allo-HSCT recipients. The clinical characteristics of these infections in our case series and previous single case reports irrespective of underlying diseases are summarized in Table 4. In terms of clinical manifestations, *N. abscessus* infections included brain abscesses (n = 6) as the most common form followed by pneumonia (n = 4), and skin and soft tissue infection (n = 4); in *N. aobensis* infections, skin and soft tissue infections (n = 2), and pneumonia (n = 1) were observed; in *N. veterana* infections, pneumonia (n = 4), abscesses (n = 2), endophthalmitis (n = 1), nodular lymphangitis (n = 1), ascites fluid infection (n = 1), mycetoma (n = 1), and disseminated infection (n = 1) were observed; and in *N. mexicana* infections, disseminated infection (n = 2), and pneumonia (n = 1) were observed. The available susceptibility data shows resistance to TMP/SMX in two of seven *N. abscessus* isolates (28.6%) and two of three *N. mexicana* isolates (66.7%). Susceptibility to other key antibiotics,

Table 3
Antimicrobial susceptibilities for *Nocardia* species detected in allo-HSCT recipients from our case series and literature review.

Species	First identified year	Author, year	Case No.	Susceptibility to antibiotics								
				TMP/SMX	AMK	IPM	LZD	AMPC/CVA	CPFX	CAM	MINO	DOXY
N. farcinica	1889	Lakosha et al., 2000	N/A	S	S	R	N/A	R	N/A	N/A	N/A	N/A
		Mansi et al., 2014	2	S	N/A	N/A	N/A	S	N/A	N/A	N/A	N/A
		Mansi et al., 2014	3	R	N/A	N/A	N/A	S	N/A	N/A	N/A	N/A
		Shannon et al., 2016	9	S	S	S	S	S	S	N/A	N/A	N/A
		Shannon et al., 2016	13	S	S	S	S	S	N/A	N/A	N/A	N/A
		Molina et al., 2018	2	S	S	S	N/A	N/A	N/A	N/A	N/A	N/A
		Molina et al., 2018	10	S	S	S	N/A	N/A	N/A	N/A	N/A	N/A
		Present case (Kakihana et al., 2007)	1	S	N/A	S	N/A	S	N/A	I	S	N/A
		Present case	5	S	S	S	S	S	S	R	S	I
		Present case	7	S	S	I	S	S	R	R	S	I
N. asteroides	1891	Kumar and Jimenez, 2001	N/A	S	N/A	S	N/A	N/A	N/A	N/A	N/A	N/A
N. nova	1982	Yamakawa et al., 2014	N/A	S	N/A	S	S	S	N/A	S	S	N/A
		Mansi et al., 2014	4	S	N/A	N/A	N/A	S	N/A	N/A	N/A	N/A
		Shannon et al., 2016	3	S	S	S	S	N/A	N/A	S	N/A	N/A
		Shannon et al., 2016	14	S	S	N/A	S	N/A	N/A	S	N/A	N/A
N. pseudobrasiliensis	1996	Lebeaux et al., 2010	15	S	S	R	S	R	S	N/A	S	N/A
N. abscessus	2000	Present case	2	S	S	S	S	S	R	R	S	S
		Present case (Hino et al., 2016)	4	S	S	S	S	S	R	R	S	S
N. cyriacigeorgica	2001	Mansi et al., 2014	1	S	N/A	N/A	N/A	S	N/A	N/A	N/A	N/A
		Shannon et al., 2016	11	S	S	N/A	S	N/A	N/A	N/A	N/A	N/A
		Shannon et al., 2016	15	S	S	N/A	S	N/A	N/A	N/A	N/A	N/A
		Molina et al., 2018	1	S	S	S	N/A	N/A	N/A	N/A	N/A	N/A
		Molina et al., 2018	7	S	S	S	N/A	N/A	N/A	N/A	N/A	N/A
		Molina et al., 2018	9	S	S	S	N/A	N/A	N/A	N/A	N/A	N/A
N. veterana	2001	Molina et al., 2018	3	S	S	S	N/A	N/A	N/A	N/A	N/A	N/A
		Molina et al., 2018	4	S	S	S	N/A	N/A	N/A	N/A	N/A	N/A
		Present case	6	S	S	S	S	R	R	S	I	I
N. aobensis	2004	Present case	3	S	S	S	S	R	R	S	S	S
N. mexicana	2004	Majeed et al., 2017	N/A	S	R	R	S	R	N/A	R	R	R

Abbreviations: allo-HSCT, allogeneic hematopoietic stem cell transplantation; AMK, amikacin; AMPC/CVA, amoxicillin/clavulanate; CAM, clarithromycin; CPFX, ciprofloxacin; DOXY, doxycycline; I, intermediate; IPM, imipenem; LZD, linezolid; MINO, minocycline; N/A, not assessed; R, resistant; S, sensitive; TMP/SMX, trimethoprim/sulfamethoxazole.

such as AMK, IPM, and LZD was present in all the *N. abscessus*, *N. aobensis*, and *N. veterana* isolates. However, two of the three *N. mexicana* isolates (66.7%) showed resistance to two or more key antibiotics.

Previous studies showed that *N. abscessus*, *N. aobensis*, and *N. mexicana* are sensitive to TMP/SMX (Larruskain et al., 2011; Schlaberg et al., 2014); however, we detected resistant isolates in our case series and single case reports irrespective of underlying diseases (Table 4). Additionally, antimicrobial susceptibilities of *N. mexicana* were consistent with an unusual feature of resistance to multiple key antibiotics. On the contrary, although 25.0% (one of four isolates) of *N. veterana* showed TMP/SMX resistance in an earlier study (Larruskain et al., 2011), all of our isolates were susceptible to key antimicrobials. Such a diversity emphasizes again that individual susceptibility testing should be performed in clinical practice for uncommon *Nocardia* species.

The efficacy of TMP/SMX prophylaxis for nocardiosis is still controversial in allo-HSCT patients (Daly et al., 2003; Shannon et al., 2016; Molina et al., 2018; Hemmersbach-Miller et al., 2018). From our case series and literature review of available data (n = 51), 11 patients (21.6%) developed nocardiosis despite TMP/SMX prophylaxis (Table 1, Supplementary Tables S1 and S2). Interestingly, all five isolates from patients who received TMP/SMX prophylaxis were sensitive to TMP/SMX. The breakthrough nocardiosis under low-dose TMP/SMZ is also reported among solid organ transplant recipients (Peleg et al., 2007). Peleg et al. reported that 69% of the 35 solid organ transplant recipients with nocardiosis received prophylactic doses of TMP/SMZ at the onset of nocardiosis. The majority were prescribed a single-strength tablet (80 mg/400 mg) administered twice or three times per week. Similar to our study, all but one breakthrough *Nocardia* isolate were susceptible to TMP/SMX. These data indicate that low-dose TMP-SMX prophylaxis for PCP is unreliable in preventing nocardiosis despite favorable antimicrobial susceptibility. The possibility of nocardiosis might be considered even if the patients receive TMP/SMX prophylaxis after allo-HSCT.

Risk factors for nocardiosis are non-specific and overlap with other infectious complications following allo-HSCT. Some studies showed that patients with nocardiosis after allo-HSCT tended to have prolonged neutropenia, active GVHD, concomitant opportunistic infections, low CD4 positive T cells, and low CD19 positive B cells (Cattaneo et al., 2013; Mansi et al., 2014). However, these risk factors could be applied to other pulmonary infections (Tomblyn et al., 2009), such as aspergillosis (Patterson et al., 2016). In our case series, three patients developed co-infection with proven or probable IPA, which made the diagnosis of nocardiosis difficult. The possibility of co-infection also should be kept in mind while assessing at-risk patients.

Considering the slow growth of *Nocardia* species, growth periods longer than one week are necessary to obtain reliable susceptibility data (Lebeaux et al., 2014), which underscores the importance of the selected empirical antimicrobial treatment. In general, the treatment of nocardiosis involves use of TMP/SMX as the first-line drug, and use of other antimicrobials, such as IPM, MINO, and AMK (Brown-Elliott et al., 2006). However, the current information is sometimes contradictory on the frequency of

Table 4
Clinical characteristics of new *Nocardia* species infections irrespective of underlying disease.

Species	Author, year	Country	Age/Sex	Underlying condition or disease	Affected organs	Susceptibility to key antibiotics				First line treatment	Surgical treatment	Outcome
						TMP/SMX	AMK	IPM	LZD			
N. abscessus	Horré et al., 2002	Germany	24/M	Immunocompetent	SST (muscle)	N/A	N/A	N/A	N/A	N/A	N/A	Resolved
	Marchandin et al., 2006	France	34/N/A	Immunocompetent	Brain	N/A	N/A	N/A	N/A	CTRX + DOXY + TMP/SMX	–	Resolved
	Daeschlein et al., 2011	Germany	49/N/A	LC	SST	R	N/A	N/A	N/A	PIPC/TAZ	+	Resolved
	Al Tawfiq et al., 2013	Saudi Arabia	37/M	Immunocompetent	Brain	S	S	S	S	CTRX + LZD + TMP/SMX	+	Resolved
	Lai et al., 2015	Taiwan	54/M	Angiosarcoma	Lung	R	N/A	R	N/A	CTRX	–	Death
	Farran and Antony, 2016	United States	60/M	Immunocompetent	Brain	S	S	S	N/A	CTRX + TMP/SMX	+	Resolved
	Sherbuk et al., 2016	United States	40/M	AIDS	Brain, lung, SST	S	S	S	S	MEPM + TMP/SMX	–	Resolved
	Boccardi et al., 2016	Italy	75/F	Rheumatoid arthritis	Brain, liver, SST	N/A	N/A	N/A	N/A	CTRX + TMP/SMX	–	N/A
	Present case 2	Japan	60/M	Allo-HSCT recipient	Lung	S	S	S	S	AMK + MEPM	–	Resolved
	Present case 4 (Hino et al., 2016)	Japan	50/F	Allo-HSCT recipient	Brain, liver, lung, SST	S	S	S	S	IPM/CS + TMP/SMX	–	Resolved
N. aobensis	Vongphoumy et al., 2015	Laos	30/M	Immunocompetent	SST	N/A	N/A	N/A	N/A	AMK + TMP/SMX	–	Resolved
	Yong et al., 2015	Australia	27/M	Immunocompetent	SST	S	S	S	S	TMP/SMX	–	Resolved
	Present case 3	Japan	59/M	Allo-HSCT recipient	Lung	S	S	S	S	MEPM + TMP/SMX	–	Resolved
N. veterana	Godreuil et al., 2003	France	40/M	AIDS	Pleura	S	S	S	N/A	None	–	Death
	Kashima et al., 2005	Japan	42/F	SLE	SST	S	S	S	N/A	MINO	+	Resolved
	Ansari et al., 2006	United States	58/M	CLL, LC	Blood, lung	S	S	S	N/A	AZM + PIPC/TAZ + TMP/SMX	–	Resolved
	Schlebusch et al., 2010	Australia	83/F	Ischaemic heart disease	Bowel	S	S	S	N/A	CTRX + GM + MNZ	+	Resolved
	Liu et al., 2011	Taiwan	30/M	AIDS	Blood, lung	S	N/A	S	N/A	CAM + MFLX + TMP/SMX	–	Death
	Arends et al., 2011	Netherlands	73/M	DM	Brain	S	S	S	N/A	TMP/SMX	+	Resolved
	Scott et al., 2013	United States	66/M	Cardiac transplant recipient	Eye	N/A	N/A	N/A	N/A	LZD + MEPM	–	Resolved
	Dua and Clayton, 2014	United Kingdom	72/N/A	NHL	SST	N/A	N/A	N/A	N/A	TMP/SMX	–	Resolved
	Poisnel et al., 2015	France	51/M	Glioblastma	Lung, urinary tract	S	N/A	S	S	CTRX + TMP/SMX	–	Death
	Present case 6	Japan	65/M	Allo-HSCT recipient	Lung	S	S	S	S	AMK + IPM/CS	–	Resolved
N. mexicana	Raby et al., 2016	Australia	81/M	DM, GC, MALT lymphoma, PMR	Brain, lung, SST	R	R	R	S	TMP/SMX	+	Death
	Kuchibiro et al., 2016	Japan	61/F	Immunocompetent	Lung	R	S	S	S	TMP/SMX + MINO	–	Resolved
	Majeed et al., 2017	United States	48/M	Allo-HSCT recipient	Brain, eye, lung, SST	S	R	R	S	TMP/SMX	–	Resolved

Abbreviations: AIDS, acquired immunodeficiency syndrome; allo-HSCT, allogeneic hematopoietic stem cell transplantation; AMK, amikacin; AZM, azithromycin; CAM, clarithromycin; CLL, chronic lymphocytic leukemia; CTRX, ceftriaxone; DM, diabetes mellitus; DOXY, doxycycline; F, female; GC, gastric cancer; GM, gentamicin; IPM, imipenem; IPM/CS, imipenem/cilastatin; LC, lung cancer; LZD, linezolid; M, male; MEPM, meropenem; MFLX, moxifloxacin; MINO, minocycline; MNZ, metronidazole; N/A, not assessed; NHL, non-Hodgkin's lymphoma; PIPC/TAZ, piperacillin/tazobactam; PMR, polymyalgia rheumatica; R, resistant; S, sensitive; SLE, systemic lupus erythematosus; SST, skin and soft tissue; TMP/SMX, trimethoprim/sulfamethoxazole.

sulfonamide resistance among *Nocardia* species (Uhde et al., 2010; Brown-Elliott et al., 2012). Moreover, a recent study showed resistance of several species to more than one commonly used drug, including TMP/SMX, AMK, IPM, and ceftriaxone (Brown-Elliott et al., 2012). Thus, empirical treatment may warrant a combination therapy until the susceptibility results are available, and a combination of IPM and AMK can be recommended based on their broad spectrum of activity in both *in vitro* and *in vivo* models of pulmonary or cerebral nocardiosis (Lebeaux et al., 2014), although no established guidelines have been published. In our case series and literature review, combination therapy was chosen as the empirical treatment in 32 patients (Table 2 and Supplementary Tables S1 and S2).

Antimicrobial therapy for nocardiosis should be prescribed for 6 to 12 months duration due to high recurrence rates (Wilson, 2012). However, long-term antimicrobial treatment after allo-HSCT is challenging due to cumulative toxicities. The long-term use of TMP/SMX is often limited because of its frequent side-effects such as nephrotoxicity, digestive disturbance, and bone marrow suppression (Lebeaux et al., 2014). In our case series and literature review, 28 patients (50.0%) were compelled to change definitive treatments due to the recurrence of nocardiosis or adverse events of antimicrobials (Table 2 and Supplementary Tables S1 and S2). Antimicrobial susceptibility testing is also essential in the context of selecting the second-line or further treatment options. In our patients, all but one patient experienced no further disease aggravation after switching to the maintenance therapy based on a careful assessment of antimicrobial susceptibility profiles.

This study has some limitations due to the retrospective observational case series. First, our study may have underestimated the incidence of nocardiosis for the reasons stated in the introduction. Second, the reliable data between in vitro antimicrobial susceptibility and clinical outcome is still lacking. Therefore, the results of antimicrobial susceptibility testing should be interpreted with caution. However, a rigorous study design for the treatment of nocardiosis was challenging because of the low incidence of nocardiosis after allo-HSCT. Therefore, this first report and review of rare nocardiosis after allo-HSCT, including the information of clinical manifestations and susceptibility profiles can provide useful insights into this complication.

In conclusion, *Nocardia* species isolated from allo-HSCT patients had various intra-species as well as inter-species antimicrobial susceptibility patterns. A similar feature was observed in the new *Nocardia* species proposed after 2000. Although nocardiosis-attributed mortality is relatively low, long-term maintenance therapy for nocardiosis could be challenging due to the adverse events of antimicrobials, especially in the allo-HSCT setting. Careful evaluation of antimicrobial susceptibility testing is crucial for the management of nocardiosis in the context of selecting the second-line or further treatment options.

Ethical approval

The institutional committee on research ethics at our hospital (approval number: 2114) approved this study.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare no conflicts of interest.

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Author contributions

SK, NS, and ND designed this study, collected clinical information, and wrote the manuscript. NS, ND, TY, YK, AN, YY, TK, SK, KY, SS, TU, KI, TT, AI, YN, HM, TK, KK, HS, and KO contributed to the clinical care of the patient and reviewed the manuscript. All authors read and approved the final manuscript.

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Appendix A. Supplementary data

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