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FULL PAPER

An eight-year experience of *Nocardia* infection in Italy: does immunosuppression matter?

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SUMMARY

Nocardia has always been considered a pathogen of the immunocompromised host, but recent evidence has also highlighted its role as a pathogen in the immunocompetent. We aim to assess the role of immunosuppression in the disease. We reviewed all the cases of infections due to *Nocardia* spp. in our center that occurred from 1 January 2012 to 30 September 2019. Patients were divided into three groups: typical immunocompromised (PLWHIV, solid organ or hematopoietic cell transplant recipients, individuals under immunosuppressive drugs), atypical immunocompromised (ongoing chronic diseases involving the lung, kidney, liver and diabetes) and immunocompetent.

We identified 53 patients with an infection by *Nocardia* spp. Thirty-four (60.4%) of them were immunocompromised, 22 (64.7%) typical and 12 (35.3%) atypical immunocompromised. Nineteen (35.8%) were immunocompetent. The two conditions most frequently associated with infection were chronic lung disease (41.5%) and ongoing treatment with immunosuppressive drugs (33.9%).

In our cohort a remarkable prevalence of nocardiosis in immunocompetent and atypical immunosuppressed patients was observed.

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INTRODUCTION

Nocardiosis is a localized or disseminated infection caused by the soil-borne aerobic actinomycetes *Nocardia* spp. (Lerner *et al*., 1996). Nocardiosis has always been considered an uncommon infection of the immunocompromised host with impaired cell-mediated immunity (Filice *et al*., 2005). The principal known risk factors identified in the immunocompromised are: being the recipient of solid organ or hematopoietic stem cell transplantation, ongoing treatment with high-dose glucocorticoid, concurrent malignancy, and concomitant human immunodeficiency virus (HIV) infection (Coussement *et al*., 2017; Torres *et al*., 2002; Peleg *et al*., 2007). However, other clinical conditions have been associated with nocardiosis, such as autoimmune diseases, chronic obstructive pulmonary disease (COPD), bronchiectasis, inflammatory bowel disease and diabetes mellitus (Lederman et al., 2004; Abreu *et al*., 2015) emphasizing its role as a pathogen in non-immunocompromised hosts as well (Paige *et al*., 2019; Rivière *et al*., 2011; Riviera *et al.*, 2017). Moreover, the prevalence of different *Nocardia* spp. is strictly related to the geographical area in which the patients have acquired the infection (Uhde *et al*., 2010; Valdezate *et al*., 2017; McGuinness *et al*., 2016). Unfortunately, currently available epidemiological and antimicrobial susceptibility results of *Nocardia* spp. in Italy are limited to case series and small observational studies (Mazzaferri *et al*., 2018; Cattaneo *et al*., 2013).

To assess the prevalence and the role of risk factors associated with the disease and to provide a more detailed depiction of the Italian scenario, we performed a retrospective analysis of all the cases of confirmed infections by *Nocardia* spp. in an Italian referral hospital.

Key words:
Nocardia spp.; pulmonary infection; typical immunocompromised patients; atypical immunocompromised patients.

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MATERIALS AND METHODS

Patients and case definition

This is a retrospective study conducted at the Foundation IRCCS Policlinico San Matteo of Pavia, Italy, a large tertiary-care teaching hospital. Laboratory and clinical records of patients with a confirmed infection by *Nocardia* spp. from 1 January 2012 to 30 September 2019 were collected. Nocardiosis was diagnosed with the isolation of a *Nocardia* spp. from any biological specimen in a patient presenting compatible clinical symptoms and radiological findings. Specifically, pulmonary infection was diagnosed by the isolation of *Nocardia* spp. from respiratory samples such as sputum, bronchoalveolar lavage or lung tissue. Central nervous system (CNS) infection was ascertained by the isolation of *Nocardia* spp. from brain abscess. Finally, the microbiological identification of *Nocardia* spp. in at least two different sites or in blood cultures (*Nocardia* bacteremia) was defined as systemic infection.

Demographics and clinical features (including comorbidities and coinfections) were collected, together with the *Nocardia* spp. identification (when available), antimicrobial susceptibility tests and outcome, in terms of intrahospital mortality. Concomitant microbiological isolates, collected within 1 month after the diagnosis of nocardiosis, either bacterial, viral or fungal, were recorded.

Patients were divided into three groups: typical and atypical immunocompromised host and immunocompetent host (Steinbrink *et al*., 2018). The typical immunocompromised host group included people living with HIV (PLHIV) and solid organ or hematopoietic cell transplant recipient patients, as well as those receiving immunosuppressive drugs such as chemotherapeutic agents, interleukin-2 inhibitors, disease-modifying antirheumatic drug and high-dose corticosteroids (more than 20 mg of prednisone or equivalent per day) given for at least 4 weeks before the diagnosis of *Nocardia* infection. The atypical immunocompromised host group included patients with ongoing chronic diseases such as chronic lung disease (collectively including refractory asthma, COPD or bronchiectasis), diabetes mellitus, chronic kidney disease (CKD) and chronic liver disease (CLD) (Woodworth *et al*., 2017). When atypical and typical characteristics concurred, the typical one was considered prevailing in classifying the patient.

Microbiological analysis

Nocardia samples were stained on blood, chocolate and Buffered Charcoal Yeast Extract (BCYE) agar plates. Blood agar plates were incubated at 35-37°C in aerobic atmosphere for 3-5 days, chocolate and BCYE agar plates in CO_2 atmosphere (5-10%) for 3-5 days, and for up to 10 days, respectively. When mycobacterial culture was requested by the physician ordering the exam, all the specimens underwent decontamination with N-acetyl-L-cysteine sodium hydroxide and were then inoculated into Lowenstein Jensen soil as well as into Mycobacteria Growth Indicator Tube, a liquid culture system, for a maximum of 8 weeks. Positive samples were identified by staining of modified Kinyoun, morphologic evaluation and, since 2014, with Matrix-Assisted Laser Desorption Ionization Time-Of-Flight (MALDI-TOF) mass spectrometry (Microflex LT/SH Bruker Daltonik GmbH, Bremen, Germany), equipped with Bruker biotyper 3.1 software. Before 2014 and when not assessed by MALDI-TOF, identification of *Nocardia* spp. was based on microscopic observation, evaluation of the colonial morphology and growth in lysozyme broth (Murray *et al*., 2003). Sensitivity tests were performed according to Kirby Bauer and E-test diffusion agar and, since 2018, with Microdilution by the Sensititre System (TREK Diagnostic Systems Waltham, USA). Minimum inhibitory concentration (MIC) interpretation was performed using breakpoints from Clinical and Laboratory Standards Institute (CLSI), which recommends employing the broth microdilution method (CLSI, 2011). The tested antibiotics were chosen based on drugs used routinely for *Nocardia* provided in CLSI, including amikacin (AMK), trimethoprim-sulfamethoxazole (TMP-SMX), gentamicin, ciprofloxacin (CIP), imipenem (IMP), ceftriaxone (CRO), amoxicillin-clavulanate, linezolid (LNZ), and cefotaxime.

Statistical analysis

Descriptive statistics were obtained for all variables assessed in the study population (median and interquartile range for continuous variables, proportions for categorical variables). Fisher exact test was applied to compare extra-pulmonary distribution among immunocompetent and immunosuppressed hosts. Data were analyzed using Microsoft Excel (Microsoft Corporation, USA). The study was approved by the IRCCS Policlinico San Matteo Ethic Committee (P-20190024992). All patients had signed an informed consent at admission to the Hospital.

RESULTS

Demographics, immunodepression and underlying diseases

Fifty-three patients met the inclusion criteria. Their median age was 66.7 years (IQR 59-75) and 28 (52.8%) were men. Thirty-four (64.1%) patients were immunocompromised. Among them 22/34 (64.7%) were typical and 12/34 (35.3%) atypical immunocompromised with median age 66.5 years (IQR 16.5). Immunocompetent patients were 19/53 (35.8%) with median age 64 years (IQR 15.5). Immunocompetent patients did not have any underlying disease. Overall, the two most common underlying conditions were chronic lung disease and treatment with high-

Table 1 - *Demographic data, underlying conditions, and distribution by site of infection (n=53).*

	Overall (n=53)		Immunocompetent (n=19)		*Immunocompromised (n=34)*			
					Typical (n=22)		*Atypical (n=12)*	
	n	%	n	%	n	%	n	%
Median age (range) (years)	65 (IQR 16)		64 (IQR 15.5)		70.5 (IQR 19.5)		61.5 (IQR 10)	
Male sex	28	52.8	8	42.1	15	68.2	5	41.6
Immunosuppres- sive drug	18	33.9			18	81.8	0	
HIV/AIDS	4	7.5			4	18.2	0	
Malignancy	3	5.6			3	13.6	0	
Chronic lung dis- ease	22	41.5			10	45.4	12	100
Diabetes	7	13.2			5	22.7	2	16.6
CKD	3	5.6			3	13.6	0	
CLD	3	5.6			3	13.6	0	

IQR: interquartile range; HIV: Human Human Immunodeficiency Virus; AIDS: Acquired immuno-deficiency syndrome; CDK: chronic kidney diseases; CLD: Chronic liver disease; CNS: central nervous system.

dose immunosuppressive drugs, recorded in 22/53 (41.5%) and 18/53 (33.9%) patients, respectively. HIV infection was present in 4/53 (7.5%) cases. Some patients presented more than one risk factor (10/53, 18.8 %). *Table 1* summarizes the characteristic of the patients enrolled. Overall, the incidence of isolates per year did not vary significantly during the study period (data not shown).

Sites of infection

The lung was the most common site of infection, being involved in 47/53 patients (88.7%). Six patients out of 53 had a CNS infection (11.3%) and 2/53 (3.7%) had systemic nocardiosis (1 case of concomitant pulmonary and brain infection and 1 case with a pulmonary focus). In one case each (1.8%) *Nocardia* was isolated from skin and from a lymph node by biopsy. Among the 47 patients with pulmonary nocardiosis, 19 were typical and 12 atypical immunocompromised. Twenty-two (46.8%) had a chronic lung disease. Three of the 6 patients with a CNS involvement (50%) were typical immunocompromised while the remaining 3 (50%) were immunocompetent. Finally, the two patients affected by diffuse nocardial disease were both immunocompetent.

Concomitant infections

Bacterial, fungal or viral infections were found in 9/53 patients. Among them, 6 were immunocompromised and 3 immunocompetent. *Stenotrophomonas maltophilia* was isolated in one case, *Aspergillus fumigatus* in 2, *Aspergillus terreus* in 2, *Mycobacterium avium* in 1, *Mycobacterium phlei* in 1 and *Rhodotorula mucilaginosa* in 1. All patients were treated for these concomitant infections, except for the one with *Rhodoturola mucilaginosa* isolates, which was deemed a contaminant microorganism.

Hospital associated mortality

Three out of 53 (5.6%) patients died during hospitalization. One had brain, another lung and the last both lung and brain infection. All three were typical immunocompromised patients. *Nocardia species*. Among the 53 *Nocardia* isolates, species identification was possible in 27 patients (52.8%). The most frequently identified species were *N. abscessus* (57.1%) and *N. farcinica* (21.4%). *Nocardia* spp. isolated in our cohort are summarized in *table 2*.

Table 2 - *Species of Nocardia identified with their relative frequencies (n=27).*

Species	*N*	*%*
N. farcinica	16	59.2
N. abscessus	6	22.2
N. wallacei	1	3.7
N. brasiliensis	1	3.7
N. nova	1	3.7

Antimicrobial susceptibilities

Forty-two strains were tested for TMP-SMX susceptibility; 7 (16.6%) were resistant. Susceptibility to carbapenems was tested for imipenem in 38 species; 23 were resistant (58.9%). Among the 37 species for which ceftriaxone susceptibility was tested, 10 were resistant (27%), while among the 38 *Nocardia species* tested for ciprofloxacin susceptibility, 27 were resistant (71%). Finally, susceptibility to AMK was checked in 43 species and only 1 was resistant. When stratified according to the species, 1/14 (7.1%) of the *Nocardia abscessus* isolates were resistant to TMP-SMX, 13/14 (71.4%) to IMP, 4/14 (28.5%) to CRO, 13/15 (86%) to CIPRO, whereas no doxycycline-resistant and linezolid (LNZ)-resistant isolates were found. *N. farcinica* was resistant to TMP-SMX in 1 out of 5 (20%), to IMP in 3/5 (60%), 1/2 to CRO (50%), 2/5 to CIP (40%), whereas no isolates were LNZ-resistant and none was tested for doxycycline. AMK was tested in 4 and LNZ in 6 isolates of *Nocardia farcinica* and all of them were susceptible to both these drugs. In the same way, all of the tested isolates of *Nocardia abscessus* were susceptible to AMK and LNZ (16 and

Table 3 - *Antimicrobial susceptibilities of the isolated Nocardia spp. (Number of sensitive specimens/total number of tested specimens).*

	AMK	*TMP/SMX*	*IMP*	*CRO*	*CLR*	*CIP*	*DOX*	*LNZ*
N. farcinica	4/4	5/6	1/3	1/2	0/3	3/5	Not tested	6/6
N. abscessus	16/16	13/14	1/4	10/14	2/11	2/15	11/11	10/10
N. wallacei	0/1	0/1	0/1	0/1	0/1	1/1	0/1	1/1
N. brasiliensis	1/1	1/1	0/1	0/1	Not tested	Not tested	Not tested	Not tested
N. nova	1/1	1/1	1/1	1/1	1/1	0/1	Not tested	1/1

AMK: amikacin; TMP/SMX: trimethoprim/sulfamethoxazole; IMP: imipenem; CRO: ceftriaxone; CLR: clarithromycin; CIP: ciprofloxacin; LNZ: linezolid.

10, respectively). *Nocardia wallacei* was resistant to all the antibiotics apart from fluoroquinolones and linezolid (LNZ). Only one *Nocardia brasiliensis* strain was susceptible to AMK and TMP/SMX and resistant to IMP and CRO. LNZ, CIPRO, clarithromycin (CLR) and DOX were not tested. Differently, *Nocardia nova* was susceptible to all the antibiotics apart from CIPRO. *Table 2* summarizes the results of the susceptibility tests. Antimicrobial susceptibilities of the isolated *Nocardia* spp are summarized in *Table 3*.

DISCUSSION

To our knowledge, this is the largest single-center study of *Nocardia* infection ever conducted in Italy. As well-documented in other series, in our cohort the most common predisposing factor for nocardiosis was the presence of chronic lung disease, which must be considered an immunocompromising factor, even in the absence of typical immunosuppressive conditions (Steinbrink *et al*., 2018).

The administration of high doses of immunosuppressive drugs was the second most frequently encountered risk factor. Indeed, as clearly described in the literature, the administration of corticosteroids has been associated with the risk of developing infection by *Nocardia* spp. (Johnson *et al*., 1993; Clark *et al*., 2013). Other common predisposing factors are HIV infection (Pintado et al., 2013), malignancy (Torres *et al*., 2002), organ and hematopoietic stem cell transplantation (Coussement *et al*., 2017), which are all conditions associated with abnormalities of cell- mediated immunity (Johnson *et al*., 1993; Clark *et al*., 2013;) These classic risk factors were poorly represented in our cohort, with only 3 cases occurring in transplanted patients and 3 cases in HIV-positive patients. Although *Nocardia* was traditionally regarded as an opportunistic pathogen (Minero et al., 2009), in our cohort immunocompetent patients represented almost 40% of the population. This datum is supported in the literature, even though our numbers are particularly high (Paige *et al*., 2019). Interestingly, the rate of extra-pulmonary infections was not different between immunocompromised and immunocompetent individuals. A possible explanation for disseminated and extra-pulmonary nocardial infection in previously healthy adults has been provided by Rosen *et al.* (Rosen *et al*., 2015), who documented in these subjects the presence of circulating antibodies against granulocyte macrophage colony-stimulating factor. Another explanation for these data can be a selection bias. Indeed, all the samples were analyzed in a single microbiology laboratory at our Institution with extensive experience in *Nocardia* spp. identification, in patients previously evaluated by an infectious disease specialist. This close collaboration between specialists might have had a synergistic effect on *Nocardia* spp. isolation in non-typical immunocompromised patients as well, prompting uncommon microbiological researches. Indeed, *Nocardia* spp. is not routinely identified in respiratory specimens or in other samples, therefore infection rates are probably underestimated. Clinicians should be aware of microbiological issues related to *Nocardia* culture, which is often challenging, with slow growth rates occurring even on enriched media (McTaggart *et al*., 2018). Therefore, it might be useful to extend the duration of incubation of agar plates from the routine 2 days to 7 days and also inoculate a BCYE plate for each sample if mycobacterial culture is not ordered. Close contact between the laboratory and the clinical personnel is therefore required to avoid a late or under-diagnosis. In the literature, 54 different Nocardia species have been described as causing disease in humans, 23 of them in immunocompetent individuals (Martìnez-Barricarte 2020). A retrospective evaluation of *Nocardia* epidemiology was conducted on 765 isolates submitted to the Centers for Disease Control and Prevention in the United States from 1995 to 2004 (Uhde *et al*., 2010). The most common species identified were *N. nova* complex (28%), *N. brasiliensis* (14%), and *N. farcinica* (14%). On the other hand, a Spanish review of 1,119 *Nocardia* isolates collected from 2005 to 2014 showed a different distribution of *Nocardia* species, since 25.3% belonged to the *N. cyriacigeorgica* species, 15% were *N. nova,* 12.7% were *N. abscessus* and 11.4% were *N. farcinica* (Valdezate *et al*., 2017). In a Chinese study conducted on 53 *Nocardia* isolates, *N. farcinica* was the most common species (24.5%), followed by *N. cyriacigeorgica* (20.8%) (Huang L. *et al*., 2019).

In our series the most isolated species was *N. abscessus* (59.2%) followed by *N. farcinica* (22.2%). Our study contributes to the Italian scenario of nocardiosis, which is poorly described, at least in the English literature. In their retrospective survey of nocardiosis in nine tertiary hospitals in northern Italy, Farina et al. identified *N. asteroides* and *N. farcinica* as the predominant species. Of note, *N. asteroides* complex has been now renamed to other and new species, including *N. abscessus* (Farina *et al*., 1995). In a more recent report of 26 cases from northern, central and southern Italy, *N. asteroides* and *N. farcinica* remained the most common species, while *N. nova* and *N. brasiliensis* were rarely encountered (Farina *et al*., 2007). Furthermore, in a nine-year experience only 4 cases of *N. brasiliensis* were described (Cercenado *et al*., 2007). Finally, *N. abscessus* and *N. farcinica* have recently been confirmed as the most frequent isolates in another Italian series (Mazzaferri, 2018). These results are fully consistent with ours, thereby suggesting that these species are predominant in Italy.

Regarding antibiotic therapy, TMP-SMX has always been considered the drug of choice for nocardiosis, but combination therapy is warranted in severe infections (seriously ill patients, with CNS involvement or with disseminated disease) (Clark *et al*., 1993). Other active agents include AMK, IMP, third-generation cephalosporins like CRO, extended spectrum fluoroquinolones (e.g., moxifloxacin), minocycline, LNZ, tigecycline, and dapsone (Gomez-Flores *et al*., 2004; Cercenado *et al*., 2007). Data extracted from different studies demonstrated that *N. farcinica* has an unfavorable susceptibility profile when compared to *N. nova* and *N. abscessus* (Farina *et al*., 2007; Coussement *et al*., 2017). Specifically, *N. farcinica* is usually resistant to third-generation cephalosporins (ceftriaxone and cefotaxime), extended spectrum fluoroquinolones (e.g., CIP), minocycline and IMP, while AMK and TMP/SMX usually retain activity (Schlaberg *et al*., 2014). *N. abscessus* is frequently resistant only to fluoroquinolones (Lebeaux *et al*., 2019). According to the literature, most *Nocardia* species are susceptible to TMP-SMX and AMK, while susceptibility varies among the carbapenems (Farina *et al*., 2007). Considering the limited size of our cohort, our results partially agree with those above, with *N. farcinica* isolates being largely resistant to carbapenems (75%). These data may be helpful to support Italian clinicians in their choice of empiric antimicrobial therapy before the availability of susceptibility tests. Identification of *Nocardia* isolates to species level is important to ensure that the appropriate treatment is correctly given to patients (Conville *et al*., 2018).

Our study has several limitations. It is a single-center study, which can limit the ability to generalize the results to other institutions and populations. In addition, the fact of being a referral center for solid and hematologic transplant patients, with clinicians experienced in recognizing the diseases, associated with the per-protocol execution of bronchoalveolar lavage with *Nocardia* spp. culture, could have enhanced the diagnosis rate of nocardiosis in non-immunocompromised patients as well. Moreover, due to the retrospective nature of this study, information regarding type and duration of treatment are lacking, as the majority of patients were lost to follow-up. Another limit related to the retrospective nature of the study is the fact that our strains are no longer available and therefore we cannot further clarify the involved species. Unfortunately, this is a major limitation that restricts the epidemiological conclusions. Finally, according to the case definition provided by Ott and colleagues (Ott *et al*., 2019), which applied European Organization for Research and Treatment of Cancer (EORTC) criteria for invasive aspergillosis to nocardiosis, the majority of our cases should be classified as "probable" infections.

Nevertheless, to the best of our knowledge, this is the largest cohort of patients with infection by *Nocardia* spp. in Italy. It demonstrates a remarkable prevalence of nocardiosis in immunocompetent and atypical immunosuppressed patients, thereby stressing the importance of suspecting this infection, particularly in the presence of known chronic pulmonary disease. Moreover, half of the brain infections affected immunocompetent individuals in our series, and this leads us to consider the need for more thorough diagnostic investigation if lung involvement is identified. Finally, it highlights the microbiological characteristics of the Italian scenario, showing *N. abscessus* and *N. farcinica* as the leading cause of nocardiosis and suggesting a prudent use of carbapenems as an empiric treatment.

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