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Review Article

Nocardiosis in Solid Organ Transplant

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Abstract

Nocardiosis is the infection produced by a group of aerobic actinomycetes belonging to the Nocardiaceae family. It is an infrequent infection, but with an associated mortality of more than 60% produced by the different species of genus *Nocardia*. *Nocardia sp* is an opportunistic microorganism that affects between 0.04% and 3.5% of patients with solid organ transplantation (SOT), causing local infections that mainly affect the lung. It is capable of producing invasive infection which requires long antimicrobial therapy. Its diagnosis is complex due to the non-specific symptoms that it produces. It is based on the isolation and identification of the microorganism in the affected tissues such as bronchoalveolar lavage, pleural fluid, abscesses or blood. The objective of this review is to vet the incidence of nocardiosis in patients with SOT and to guide in the empiric antimicrobial treatment.

ABBREVIATION

SOT: Solid Organ Transplantation

INTRODUCTION

Nocardia is a genus of aerobic actinomycetes belonging to the Nocardiaceae family that causes localized or disseminated infections in animals and humans [1].

The genus *Nocardia* includes more than 80 known species, with at least 33 of them related to human pathology [2,3]. It is an opportunistic pathogen, causing infection generally in immunosuppressed, mainly with long exposure to corticosteroids, transplanted or HIV positive patients. It has worldwide distribution and is very ubiquitous, being found in terrestrial and aquatic environments as well as in vegetal material in decomposition and in suspension in the air.

Inhalation is the most frequent mechanism of acquisition, although there are other ways such as direct cutaneous inoculation of the microorganism after trauma, surgery, through a vascular catheter or by stings or scratches of animals.

A feature of nocardiosis is its great capacityof dissemination through the blood to any organ and its trend to relapse. Invasive nocardiosis often developed as a complication of an underlying disease, such as chronic lung disease or altered cell-mediated immunity, affecting between 0.04% and 3.5% [2] of patients with solid organ transplantation (SOT). In addition, it is associated with a global mortality of 60% [4,5].

Antibiotic treatment should combine different broad spectrum antibiotics with duration of 6 to 12 months [1]. In transplant patients this therapy is difficult to manage due to cumulative toxicity and interactions with immunosuppressive drugs.

EPIDEMIOLOGY

About 25% of cases of nocardiosis in the literature are described in SOT [4].

The frequency of nocardiosis varies according to the type of SOT, appearing in 3.5% of patients with lung transplantation, 2.5% cardiac, 1.5% intestinal, 0.2% renal and 0.1 % hepatic [6].

The first described case of death associated with nocardiosis in patient with renal transplantation was documented in 1967 [7]. Subsequently similar cases of patients with liver, heart or lung transplantation were reported [8,9,10].

In the last years a decrease in number of cases described has been observed. Table 1 summarizes the incidence (number of cases and percentages) of nocardiosis in SOT patients found in the literature from 1990 to January 2017. The first series published in patients with heart transplantation date back to the 1970s, where the incidence reached 13% (21/160 patients) [20], while currently is 0.42 (1/236) to 2.5% (10/392) [2,6]. That is possibly due to the introduction of trimethoprim-sulfamethoxazole as prophylaxis [1]. The incidence in patients with lung transplantation ranges between 0.8% (1/122) [14] and 3.5% (18/521) [6,8,21]. On the other hand, the incidence of nocardiosis in renal transplantation is lower than in the other kind of transplant, varying from 0.04% (1/2527) [14,15] to 0.7% (9/1255) [1,18,21]. This divergence between kinds of graft may be due to the fact that inhalation is the main route of entry.

Table 1: Incidence of nocardiosis in SOT patients from 1990 to January 2017 [nºcases/patients (%)].

	Trasplantedorgan					
Year /autor/reference	**Heart**	**Lung**	**Liver**	**Kidney**	**Pancreas**	**Intestine**
2017, Haussaire et al [2]	1/236 (0.42)	4/263 (1.52)	1/520 (0.19)	8/1144 (0.69)		
2011 Tripodi et al [11]	12/508 (2.36)					
2011, Santos et al [12]	4/612 (0.65)	7/392 (1.78)	3/1654 (0.18)	5/1900 (0.26)	0/42 (0)	
2008, Poonyagaruyagorn et al [13]		11/577 (1.90)				
2007, Peleg et al [6]	10/392 (2.50)	18/521 (3.50)	2/1840 (0.10)	3/1717 (0.20)		2/155 (1.30)
2007, Virgil et al [5]				8/760 (1.00)		
2005, Wiesmayr S [14]	0/241 (0)	1/122 (0.80)	1/746 (0.10)	1/2527 (0.04)	0/368 (0)	2/24 (8.00)
2004, Queipo-Zaragoza et al [15]				5/1239 (0.04)		
2003, Peraira et al [16]	5/560 (0.90)					
2002, Husain et al [17]		10/473 (2.10)				
1993, Ardunio et al [18]				9/1255 (0.70)		
1990, Forbes et al [19]			7/191 (3.70)			

Nocardiosis in the first trimester after SOT is exceptional, while in 63% of cases it is diagnosed within the first year after transplantation and in 14% of cases after 5 years [1,6]. On the other hand, the sequential association between *Nocardia sp* infection and graft rejection has been described [8,21,22].

There are a few data to assess the risk factors associated with post-transplant nocardiosis. Peleg et al. [6], evaluated these risk factors using a case-control study. Authors observed that transplant rejection 6 months before infection, high doses of prednisone (defined as 20 mg of prednisone for 1 month or 12 pulses of 1 g intravenous methylprednisolone) 6 months prior nocardiosis and receiving previous antifungal prophylaxis were found to be statistically significant. Conversely, elevated levels of calcineurin inhibitor (tacrolimus or cyclosporine) up to 30 days prior infection or previous cytomegalovirus infection in the preceding 6 months were independent.

CLINICAL MANIFESTATIONS

N. farcinica, *N. cyriacigeorgica*, *N. nova*, *N. brasiliensis*, *N. otitidiscaviarum*, *N. veterana* and *N. abscessus* are responsable for most human nocardiosis [1].

Primary cutaneous nocardiosis appearing about 10% of transplants, being acquired by direct inoculation. Its symptoms are cutaneous nodules, pustules or abscesses that may progress to soft tissue infections [23,24]. In the general population *N. brasiliensis* is the most frequently involved species, whereas in SOT the main species are *N. nova* or *N. otitidiscaviarum* [25,26].

Invasive nocardiosis, also called pulmonary nocardiosis, appears in 80-90% of the cases, being pneumonia its main source. *N. cyriacigeorgica*, *N. brasiliensis* and *N. farcinica* are the most frequent species isolated in invasive Nocardiosis [2,4]. They are disseminated through the blood to other organs, including the CNS, with sub-acute or chronic manifestations, asthenia or moderate fever. In lung, nodules may appear in more than 60% of patients with SOT, cavitation in more than 30% and pleural effusion in about 20%. The extra-pulmonary localization is described in 20-71% of the cases, being the most frequent the CNS and occurring as cerebral abscesses [25,26]. Due to the slow evolution of the infection, patients may not present neurological signs until they reach advanced stages, including intracranial pressure, convulsion or coma [1,3,12,27]. Other extra-pulmonary locations have been described, such as renal, hepatic, ocular, soft-tissue or heart valve infections [1,12,24,27,28].

DIAGNOSIS

Microbiological diagnosis plays a fundamental role in the specificity of clinical signs. This is based on the isolation of the microorganism in infected material and subsequent identification by phenotypic methods based on biochemical reactions or tests of hydrolysis. Because they have a very limited ability to differentiate species, confirmation by molecular methods (sequencing of the 16S rRNA, hsp65, secA1 or sodA genes) is required [8,28,29,30,31].

Nocardia spp. is a slow-growing (1 to 3 weeks) microorganism with a hard identification. In fact, until the late 1980s, only *N. asteroides* was known as a human pathogen. In 1988, Wallace et al. [32], knowing the great diversity of antimicrobial susceptibility of the *N. asteroides* strains studied, suggested the existence of other species. They confirmed this hypothesis by sequencing the 16S rRNA gene. In fact, *N. farcinica*, *N. cyriacigeorgica*, *N. nova*, *N. brasiliensis*, *N. otitidiscaviarum*, *N. asteroides* and *N. abscessus* are the most involved species in human pathology, whereas *N. asteroides*is actually an unusual pathogen in humans [4].

It is important to emphasize the important role of Gram stain to guide the diagnosis and to start an early but targeted treatment [1,33]. On the other hand, advances in microbiological diagnosis using mass spectrometry seem to be a promising method for a rapid and effective identification [33,34,35,36].

TREATMENT

The choice of an empiric treatment in case of suspected nocardiosis is a therapeutic challenge since: i) each species of *Nocardia* has its own antimicrobial susceptibility pattern (Table 2), ii) the high frequency of co-infections, 20% in patients with SOT, by filamentous fungi, cytomegalovirus and other bacteria [6], iii) the technical difficulty found in the preparation

Table 2: Antimicrobial sensitivity of more frequent *Nocardia spp.* in human pathology [1,37].

Antimicrobial	*N. cyriacigeorgica*	*N. farcinica*	*N. nova*	*N. brasiliensis*	*N. transvalensis*	*N. otitidiscaviarum*
Trimethoprim-sulfamethoxazole	S	S	S	S	S	S
Amoxicillin	R	R	S	R	-	R
Amoxicillin-clavulanicacid	R	S	R	S	R	R
Ceftriaxone	S	R	S	R	S	R
Imipenem	S	S	S	R	R	R
Amikacin	S	S	S	S	R	S
Doxycycline	R	R	R	-	-	-
Minocycline	R	R	R	S	R	R
Ciprofloxacin	R	R	R	R	S	R
Erythromycin	R	R	S	R	R	-
Clarithromycin	R	R	S	R	R	R
Linezolid	S	S	S	S	S	S

S: Susceptible. R: Intermediate or Resistant.

of the antibiotic susceptibility testing, iv) interactions with immunosuppressive drugs.

Classically, trimethoprim-sulfamethoxazole has been considered the treatment of choice because it is a drug with good bioavailability in all tissues, including the worst irrigated ones such as bones, and to be active against almost all *Nocardia* species except *N. otitidiscaviarum* [38,39]. However, it is a bacteriostatic drug that needs long treatments, being ineffective in immunosuppressed patients. In addition, its interaction with cyclosporine leading to an increased risk of nephrotoxicity, as well as its frequent adverse effects such as allergy, digestive disorders, nephrotoxicity or bone marrow suppression, cause withdrawal between 20-50% of the cases [39,40].

Therefore, combination therapy with a bactericidal antibiotic such as amikacin, imipenem or third generation cephalosporins should be considered.

Amikacin has a good *in vitro* activity against all *Nocardia* species except *N. transvalensis*, but in the case of renal transplant patients, its nephrotoxic effect must be taken into account. On the other hand, imipenem is not active *in vitro* against *N. brasiliensis* nor 10% of *N. farcinica*, *N. transvalensis* and *N. asteroids* strains [41,42,43].

Meropenen may be considered as a therapeutic alternative to imipenem in cerebral nocardiosis because it has a good cerebrospinal fluid penetration and it is associated with a lower incidence of seizures. However, it was found to be less active than imipenem with *N. farcinica* and *N. nova*, whereas ertapenem appears to be inactive versus *Nocardia spp*. [28].

The main advantage of cephalosporins is their low toxicity. They show good *in vitro* activity for all *Nocardia* species except *N. farcinica*, *N. transvalensis* and *N. otitidiscaviarum*. In addition, there are studies demonstrating synergistic *in vitro* activity of cefotaxime and imipenem or cefuroxime and amikacin [41,43].

Linezolid is an oral therapeutic alternative to imipenem, amikacin or trimethoprim-sulfamethoxazole because it is active against all *Nocardia* species with clinical relevance. No resistant strains have been described to date because they have an oral bioavailability close to 100%. Also it reaches adequate levels in serum and it has good diffusion to tissues. However it must be considered that adverse effects such as hematologic toxicity, lactic acidosis, optic neuritis or peripheral neuropathy may occur in long treatments [44].

For the use of further alternative drugs such as macrolides, fluoroquinolones or tigecycline, with a few data in the literature, it is recommended to do *in vitro* studies on the sensitivity previously.

CONCLUSIONS

Post-transplant nocardiosis is a rare disease, being isolated mainly in patients with lung transplantation. A prospective multicenter study would provide important data to clarify the associated risk factors. Empiric antibiotic treatment remains a therapeutic challenge because of the diversity of sensitivity in the different species of *Nocardia* although linezolid seems to be a good alternative as an empirical treatment.

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