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REVIEW

Nocardiosis: a case series and a mini review of clinical and microbiological features

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ABSTRACT

Infections caused by *Nocardia* species are uncommon and have a wide variety of clinical manifestations in immunocompetent and immunocompromised patients. The diagnosis of nocardiosis can easily be missed because there are no characteristic symptoms.

We present one case of a *Nocardia* infection in detail and give a brief description of eight other cases, including a relatively unique type of *Nocardia veterana*, diagnosed in our hospital during a five-year period. The diversity of clinical manifestations, microbiological identification and general principles of treatment of nocardiosis are reviewed.

KEYWORDS

Immunocompromised, *Nocardia, Nocardia veterana,* nocardiosis, sulphonamide, trimethoprim

INTRODUCTION

Nocardiosis is an uncommon bacterial infection with a wide variety of clinical manifestations in immunocompetent and immunocompromised patients. The incidence of nocardiosis in the United States has been estimated to be 500 to 1000 cases per year.[1] The number of cases reported in the literature is increasing. This might be due to an absolute increase in the number of immunocompromised patients but also to improvement in laboratory techniques to detect nocardiosis. Most patients with nocardiosis have an immune dysfunction due to haematological malignancies, other malignancies, organ transplantation, AIDS, liver cirrhosis, diabetes, alcoholism or corticosteroid use.

CASE REPORT

A 76-year-old man presented with painful upper legs, proximal muscle weakness, morning stiffness in the pelvic girdle and headache. On suspicion of polymyalgia rheumatica or giant-cell arteritis (biopsy of the temporal artery was negative), he was treated with 60 mg prednisolone daily, without any effect.

Three months later, he was admitted because of severe pain in the left upper leg for one week. There was no trauma or fever. Physical examination revealed erythema at the medial side of the left upper leg (10 x 20 cm). Laboratory investigation showed an increase in the erythrocyte sedimentation rate (ESR, 38 mm/h), high C-reactive protein level (CRP, 116 mg/l) and leucocytosis (15.9 x 10^9/l). The serum creatinine kinase was normal; lactate dehydrokinase (LDH) was slightly elevated (593 U/l). Ultrasound investigations indicated an elongated collection of fluid at the medial side of the upper leg (4.9 cm x 10 cm). A computerised tomography (CT) showed an abscess in the adductor compartment with indurations of the gracilis muscle and the subcutaneous fat. The abscess was evacuated surgically. In the gram stain, branching gram-positive rods were observed. The culture yielded *Nocardia farcinica*.

Treatment with trimethoprim-sulphamethoxazole (TMP-SMX) 1920 mg twice daily for three months was successful. After three weeks, the CRP was <5 mg/l with normal leucocyte counts. The ESR was still slightly elevated (31 mm/h).

Eighteen months after cessation of the antibiotics, the patient developed renal insufficiency, due to a Wegener's granulomatosis. He was treated successfully with high-dose prednisolone and cyclophosphamide. There were no signs of reactivation of the *Nocardia* infection.

DISCUSSION

During the period from January 2000 to July 2004 nine cases of nocardiosis were diagnosed in our general 600-bed teaching hospital with facilities for autologous stem cell transplantation, rheumatic diseases and follow-up after lung transplantation (*table 1*).

Most patients were infected with *Nocardia farcinica* or *Nocardia asteroides* complex. We found one case of *Nocardia veterana* (case 5). Little is known about *Nocardia veterana* because it is infrequently reported as a pathogen.[2-7] It is named after the veterans hospital, where it was first isolated. The first report of *N. veterana* isolated from human samples was by Gurtler in 2001.[2] Pulmonary nocardiosis was observed in seven patients, primary cutaneous nocardiosis in one patient and systemic nocardiosis in one patient. The time to diagnosis varied from two to seven days.

Eight patients could be considered to be immunocompromised as part of their underlying disease or treatment. Most patients (cases 1, 2, 4, 6 and 8) were treated with various kinds of chemotherapy and immunotherapy, because of cancer. Three patients were on immunosuppressive medication because of lung transplantation (case 5), polymyalgia rheumatica (case 3) or COPD (case 9). Most patients were treated with TMP-SMX. The duration of therapy varied from 1 to 630 days. One patient died within one day and one patient was not treated. Of the remaining seven patients, six patients recovered. One patient was treated for two years, the other four patients for 14 to 90 days.

DIAGNOSIS

Nocardia species are found worldwide in soil, decaying vegetable matter and aquatic environments.[8] The main route of acquisition is through direct inhalation of contaminated particles or by direct inoculation through the skin. The manifestations of nocardiosis can be solely pulmonary, but *Nocardia* species can also disseminate from a pulmonary or cutaneous focus to virtually any organ. The onset of pulmonary nocardiosis may be acute, subacute or chronic. Due to its nontypical manifestations nocardiosis is frequently misdiagnosed.

The initial diagnoses are pneumonia, tuberculosis and carcinoma or lung abscesses. Fatigue, fever, chills, productive cough, dyspnoea, pleural chest pain and loss of weight can occur in patients with nocardiosis. Cutaneous nocardiosis leads to cellulitis, pustules, pyoderma, paronychia, ulcerations or localised abscesses.

Table 1. *Characteristics of nine Nocardia infections*

Case	Species	Localisation	Time to diagnosis (days)	Disease	Antibiotic treatment	Duration of therapy (days)	Outcome
1	*Nocardia farcinica*	Disseminated: lung, gluteal region, iliac fossa, kidney, cerebrum	6	NHL	TMP-SMX and imipenem, followed by amikacin and TMP-SMX, followed by TMP-SMX	630	Recovered
2	*Nocardia farcinica*	Lung	6	MM	TMP-SMX 2 x 1920 mg iv	60	Recovered
3	*Nocardia farcinica*	Upper leg abscess	2	PMR	TMP-SMX 2 x 1920 mg iv	90	Recovered
4	*Nocardia asteroides* complex	Lung	4	CLL	TMP-SMX 2 x 1920 mg iv, followed by amikacin 2 x 375 mg iv and meropenem 3 x 1 g iv	20	Death
5	*Nocardia veterana*	Lung	1	LTX, because of interstitial fibrotic lung disease	TMP-SMX 3 x 1920 mg iv, followed by imipenem and amikacin iv followed by minocycline orally	30	Recovered
6	*Nocardia asteroides* complex	Pneumo-nectomy cave	2	Metastatic NSCLC, chemotherapy	TMP-SMX 2 x 960 mg iv	14	Recovered
7	*Nocardia asteroides* complex	Lung	7	Bronchogenic cyst	Ciprofloxacin 2 x 500 mg	60	Recovered
8	*Nocardia* spp.	Lung	2	Metastatic prostate carcinoma	Imipenem 4 x 500 mg, amikacin 15 mg/kg iv	1	Death
9	*Nocardia* spp.	Lung	-	Bronchiectasis	No treatment	-	Death due to COPD and heart failure

NHL = non-Hodgkin lymphoma; TMP-SMX = trimethoprim-sulphamethoxazole; MM = multiple myeloma; PMR = polymyalgia rheumatica; CLL = chronic lymphocytic leukaemia; LTX = lung transplantation; NSCLC = non-small-cell lung carcinoma; COPD = chronic obstructive pulmonary disease.

Figure 1. *CT scan shows an abscess in the left iliac fossa due to disseminated nocardiosis*

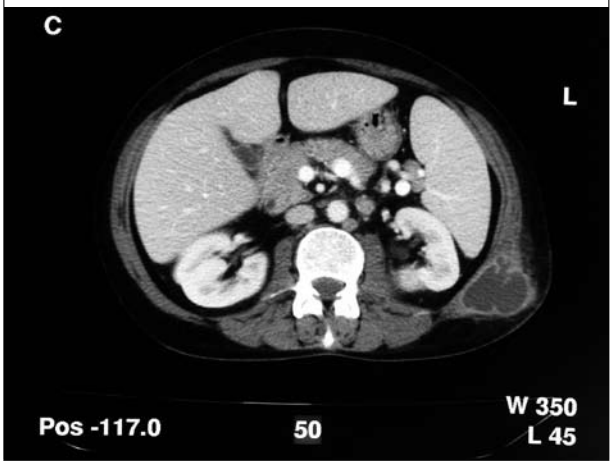


Figure 2. *CT scan reveals pulmonary infiltrates in a patient with disseminated nocardiosis*

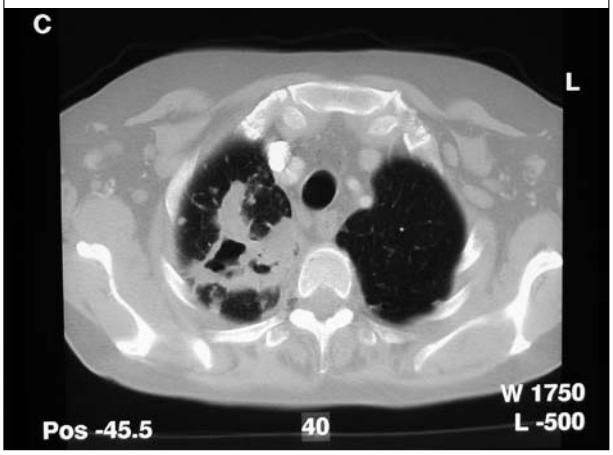
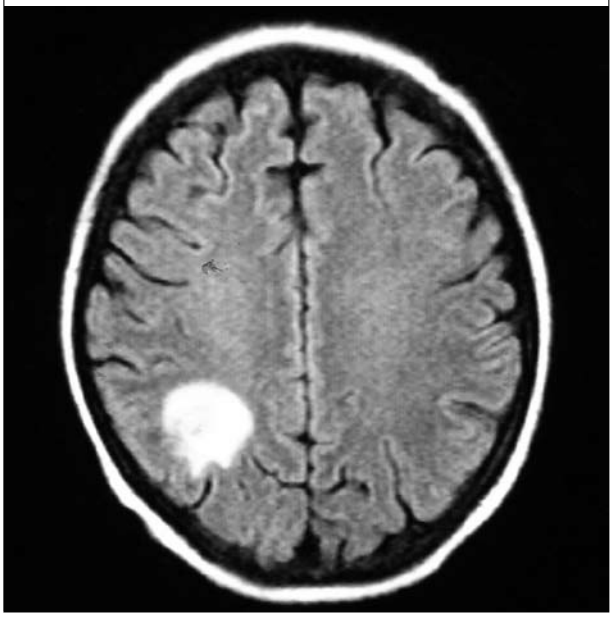


Figure 3. *Magnetic resonance imaging shows signs of an abscess in the right occipital cerebrum*



Haematogenous spread most commonly involves the central nervous system, bone, retina, heart, joints and kidneys. The presence of lesions in two or more organs of the body defines systemic or disseminated disease.[9-11]

The genus of *Nocardia* is rapidly expanding and consists of at least 22 species. The most frequently isolated species belong to the *N. asteroides* complex, which is a heterogeneous group that includes *N. asteroides* sensu strictu, *N. farcinica, N. nova* and *N. abscessus.*[12] Other medically important species are *N. brasiliensis, N. otitidis-caviarum, N. africana, N. brevicatena* complex, *N. carnea, N. paucivorans, N. pseudobrasiliensis, N. transvalensis* and *N. veterana.* Identification of clinical isolates beyond the genus level is important since *Nocardia* species differ in the clinical spectrum of the disease they cause and their susceptibility to antibiotics. In particular, *N. farcinica* is much more resistant than other *Nocardia* species.[13]

The genus of *Nocardia* belongs to the family of aerobic actinomycetes characterised as gram-positive branching filamentous rods producing fungus-like colonies in culture.[12] *Nocardia* species can be recovered on isolation media for bacteria, fungi or mycobacteria, but growth is slow and incubation should be continued for at least two weeks. They can grow at high temperatures (37° to 45°C) and growth is accelerated by CO_2. Premature discontinuation of culture will decrease the sensitivity of recovery and may contribute to underestimation of the true incidence of nocardiosis. Typically, colonies are chalky white, but they can also be yellow, pink or orange. A characteristic smell is produced, vividly described as a musty basement odour or earthy smell. Further characteristics that help to identify *Nocardia* in the laboratory are its partial acid-fastness, lysozyme resistance and hydrolysis of casein, tyrosine, xanthine and hypoxanthine. After presumptive identification, final determination is nowadays accomplished in reference labs by molecular techniques, such as 16S rRNA sequence analysis, restriction fragment length polymorphism (RFLP) or polymerase chain reaction (PCR).

TREATMENT

Management of nocardiosis involves antimicrobial therapy in conjunction, where appropriate, with surgical debridement/drainage and improvement of immune function if feasible. Therefore, the choice of therapy depends on the severity and localisation of the infection, the host immune status, potential drug interactions and toxicity and the *Nocardia* species involved. In general, nocardiosis has been treated successfully with sulphonamides since the early years of antimicrobial therapy.[14,15] Combined with TMP synergy occurs, and TMP-SMX has been the mainstay treatment of *Nocardia* infections. Probably due

to the low prevalence of nocardiosis, studies prospectively comparing TMP-SMX with sulphonamide monotherapy or other antibiotic regimens have not been performed. Duration of therapy has not been systematically evaluated either, but it is generally advised to treat cutaneous forms of *Nocardia* infection for one to three months, patients with pulmonary or systemic nocardiosis for six months and those with involvement of the central nervous system for 12 months.[13,15] All immunocompromised patients should be treated for at least one year.[13,15] In the present series, we observed resolution in six of nine patients. In five patients the therapy was three months or less. In some cases it might be possible to give shorter treatment than recommended in the literature. For adults with normal renal function, the recommended daily dose is 5 to 10 mg/kg TMP and 25 to 50 mg/kg SMX, divided over two to four doses. For the treatment of cerebral abscesses, severe disseminated disease and AIDS patients, a higher initial daily dose can be considered: 15 mg/kg TMP and 75 mg/kg SMX.[15] After three to six weeks, dosage can generally be reduced and treatment can be continued orally.

In general, TMP-SMX is well tolerated, but side effects may occur. These include gastrointestinal symptoms, skin disorders, renal impairment, hepatotoxicity and bone marrow failure.[16] During the prolonged treatment regimens required for nocardiosis, side effects occur more frequently, especially in AIDS patients. In these patients, a high incidence of rash, fever and neutropenia has been noted.[17,18] In addition, 20% of AIDS patients develop hepatotoxicity upon treatment with TMP-SMX.[17] One of the most serious side effects is bone marrow suppression related to folate deficiency. Patients may develop pancytopenia, or more rarely and less well understood agranulocytosis, anaemia or thrombocytopenia.[18] Supplementation of folinic acid could prevent folate depletion and the related side effects. Serious side effects such as neutropenia may necessitate a switch to alternative antimicrobial agents, belonging to the carbapenems, cephalosporins, aminoglycosides, quinolones, macrolides or tetracyclines.

The use of TMP-SMX may be further complicated by the occurrence of resistance. Reports on resistance are sporadic and hampered by the fact that no universally accepted antimicrobial susceptibility testing method has been established for *Nocardia* species.[14] In general, *Nocardia* species are still considered susceptible to most antimicrobial agents, except *N. farcinica* and *N. otitidiscaviarum*. *N. farcinica* is resistant towards ampicillin, third-generation cephalosporins, erythromycin, gentamicin and tobramycin.[13] *N. farcinica* remains susceptible to amikacin, imipenem, ciprofloxacin and TMP-SMX. The clinical outcome of therapy depends on the site of infection, the comorbidity and underlying host factors. Mortality is high among immunocompromised patients and those with multiple brain abscesses (75 to 90%). Disseminated nocardiosis has a poor prognosis with a mortality rate >85% in immunocompromised hosts.[9,13,14]

CONCLUSION

Due to its low incidence and nontypical manifestations, nocardiosis is frequently misdiagnosed while recognition of this infection is important for the choice of appropriate antibiotic treatment. Treatment duration has to be at least months. Despite prolonged treatment, mortality remains high, especially in immunocompromised patients.

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