ORIGINAL ARTICLE

Secular trends of nocardia infection over 15 years in a tertiary care hospital

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Aims: To assess the incidence of nocardia infection over 15 years in a tertiary care hospital.
Methods: Over a 15 year period, *Nocardia* spp were isolated from 20 patients hospitalised at the Geneva University Hospitals, Switzerland.
Results: Sixteen patients had one or more underlying conditions. The median time between symptom onset and diagnosis was 30 days. The most common initial unconfirmed diagnosis was pulmonary tuberculosis (four). The lung was involved in 16 cases, followed by the central nervous system (two) and skin (two); one patient had disseminated infection. The most common species identified was *N asteroides*. In vitro susceptibility testing was performed on 14 of 20 strains. All strains were susceptible to imipenem and amikacin. Initial treatment with trimethoprim/sulfamethoxazole (TMP/SMX) was started in 14 patients, although five patients had to be switched to another treatment because of side effects or lack of efficacy. A cure was observed in 15 patients, death in three, and relapse or complications in two.
Conclusions: Nocardiosis can become a severe infection and mainly affects profoundly immunocompromised patients. Differential diagnosis often delays the time to diagnosis, which worsens the outcome. New diagnostic tools, such as the polymerase chain reaction, could provide more rapid and reliable results. TMT/SMX was the most commonly prescribed treatment, but needed to be changed for another treatment because of side effects or lack of efficacy in a considerable proportion of patients. Imipenem should be used as an alternative treatment for severely ill patients, and the sulfa combination for less severe infections.

Nocardiosis is a localised or disseminated infection caused by ubiquitous, soil borne, aerobic, and saprophytic actinomycetes. Although nocardia species can infect immunocompetent individuals, they most often affect immunocompromised patients.[1 2] Earlier reports estimated that 500 to 1000 cases/year occur in the USA, and probably 150 to 250 in France.[3 4] The current incidence of nocardiosis in Europe is still unknown because of the lack of comprehensive reporting systems.[5] Reports in the literature are limited to case reports and case series that include only a small number of patients. Moreover, nocardial infections can be difficult to recognise, which leads to misdiagnosis and consequently underestimation of its incidence.[5–7] For the same reason clinical experience remains limited.

> ''Nocardial infections can be difficult to recognise, which leads to misdiagnosis and consequently underestimation of its incidence''

In this study, we review the epidemiology, clinical, and microbiological characteristics, treatment, and outcome of nocardial infections diagnosed in 20 patients at the Geneva University Hospitals, Switzerland over a 15 year period.

PATIENTS AND METHODS

Patients

Our retrospective study was conducted at the 2200 bed Geneva University Hospitals, Switzerland. Cases of nocardiosis were identified with a computerised query of the clinical microbiology laboratory database for specimens collected between January 1989 and December 2003. Thereafter, the medical records for all patients with *Nocardia* spp were reviewed. Information on demographic characteristics, underlying conditions, immunosuppressive treatment, nocardiosis clinical, radiological manifestations and diagnostic methods, concomitant infections, treatment, and outcome were assessed.

Definitions

Nocardiosis was considered a definite diagnosis when *Nocardia* sp. was identified in a clinical specimen of a symptomatic patient. Disseminated nocardiosis was defined as nocardia infection in two or more non-contiguous sites and nocardaemia when *Nocardia* sp. could be isolated from blood cultures. Colonisation was defined as a positive culture of a specimen from a non-sterile site without clinical evidence of infection. Breakthrough nocardiosis was identified when a recurrent nocardial infection occurred in a patient receiving systemic antibacterials with known in vitro activity against *Nocardia* spp for at least four days before the onset of nocardial infection. Lymphopenia was defined as $< 1000 \times 10^6$ lymphocytes/litre, neutropenia as $< 500 \times 10^6$ neutrophils/litre, hypoproteinaemia as a serum concentration of protein$<$ 60 g/litre, hypoalbuminaemia as a serum concentration of albumin $<$ 35 g/litre, and raised lactate dehydrogenase (LDH) as $>$ 240 U/litre.

Effective antimicrobial treatment was defined as when patients were cured or their clinical signs and symptoms of nocardiosis improved, including microbiological and radiographical findings. Failure was identified when patients died or deteriorated as a result of nocardial infection. Relapse was noted when an initial improvement was followed by the reappearance of clinical symptoms, radiographical findings, and the isolation of *Nocardia* sp.

Abbreviations: BMT, bone marrow transplantation; CNS, central nervous system; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; TMP/SMX, trimethoprim/sulfamethoxazole

Microbiological methods

Nocardia spp were cultured on different media such as sheep blood agar (Columbia base), CNA, and chocolate agar incubated aerobically at 35°C, in an atmosphere enriched with 5% CO_2.[8] Identification was based on microscopical morphology after Gram stain and modified Kinyoun stain, on strictly aerobic growth, and on physiological tests (casein, tyrosine, xanthine, starch, gelatin, urea, susceptibility to lysozyme, and growth at 45°). Since 2001, species identification has been determined by the amplification and sequencing of 16S rDNA.[9 10] Susceptibility to antimicrobial agents was determined with E-test strips (AB Biodisk, Solna, Sweden) on Mueller-Hinton blood agar.

RESULTS

Over the 15 year study period *Nocardia* spp were isolated from 20 patients. In 16 patients, the infection was community acquired. The remaining four nosocomial cases were not clustered, because the patients developed the infection at different times and were hospitalised in different wards. Fourteen patients were male. The mean age was 51.8 years (range, 4–88).

Sixteen patients had at least one underlying condition responsible for a certain degree of immunodeficiency (table 1). One patient with chronic obstructive pulmonary disease was treated with longterm inhalational corticosteroids, and another 88 year old patient had a previous respiratory syncitial virus infection. No underlying disease could be identified in two children presenting with cutaneous nocardiosis. Pulmonary aspergillosis was diagnosed in two patients before nocardiosis; one of them had concomitant pulmonary tuberculosis and one a concomitant pulmonary paecilomyces infection. Breakthrough nocardiosis occurred in one patient with chronic granulomatous disease after prophylactic treatment with trimethoprim/sulfamethoxazole (TMP/SMX), 400/80 mg twice daily.

The median time interval between onset of symptoms and diagnosis was 30 days (mean, 24.9; range, 3–50 days). The most common initial diagnosis instead of nocardiosis was pulmonary tuberculosis in four patients, followed by bacterial sinusitis in two, and legionellosis, pulmonary embolism, and Wegener's disease in one patient each.

The most frequent abnormality identified by laboratory analysis was lymphopenia, which was seen in 15 patients. None of the patients had neutropenia. In three patients with human immunodeficiency virus infection, the CD4 counts ranged from 2 to 17 $\times$ 10^6 cells/litre. Raised LDH was seen in 10 of 11 patients, hypoproteinaemia in six of 13, and hypoalbuminaemia in eight of nine patients for whom laboratory results were available.

Table 1 Nocardiosis characteristics in the 20 patients

Characteristic	No of episodes (%)
Underlying condition	
Solid organ malignancy*	4 (20)
HIV infection	3 (15)
Diabetes mellitus	3 (15)
Solid organ transplantation†	3 (15)
Idiopathic lymphopenia	1 (5)
Chronic granulomatous disease	1 (5)
Common variable immunodeficiency	1 (5)
Chronic lung disease	
Cystic fibrosis	1 (5)
Sarcoidosis	1 (5)
Corticosteroids administered one month before nocardiosis‡	6 (30)
Immunosuppressive chemotherapy administered one month before nocardiosis	4 (20)
Radiotherapy received during the previous year	1 (5)
Coinfection ¶	4 (20)
Nocardia spp	
N asteroides	13 (65)
N asteroides complex	4 (20)
N farcinica	1 (5)
N nova	1 (5)
N brasiliensis	1 (5)
Site of infection	
Pulmonary§	16 (80)
CNS	2 (10)
Cutaneous	2 (10)
Disseminated**	1 (5)
Outcome	
Cure/improvement	15 (75)
Failure	1 (5)
Relapse	1 (5)
Death	3 (15)

*Breast in 2 patients; prostate and tongue in 1 patient each. †Cardiac in 2 patients and renal in 1 patient. ‡In combination with other immunosuppressive treatment (azathioprine, cyclosporine, OKT-3) in 3 patients. ¶*Pneumocystis carinii* pneumonia in one HIV positive patient; *Mycobacterium tuberculosis* infection in one patient with cancer; cytomegalovirus infection in one cardiac transplant recipient; *Mycobacterium intracellulare*, cytomegalovirus, and *Toxoplasma* sp. infection in one cardiac transplant recipient. §Presented as primary infection or as part of disseminated infection. **Lung, peritoneum, and blood involvement.
CNS, central nervous system; HIV, human immunodeficiency virus.

Clinical characteristics

The body site most frequently involved was the lung, followed by the skin and the brain. Disseminated infection was seen in one patient. Three patients with nocardaemia carried intravenous catheters. Two of them developed pulmonary nocardiosis and one developed disseminated nocardiosis.

All but one of the 16 patients with pulmonary involvement were symptomatic. Three patients presented an acute form of infection and 12 a subacute form. Three patients were hospitalised at the intensive care unit as a result of severe respiratory distress syndrome (n = 1) or septic shock (n = 2). Table 2 presents the clinical manifestations and radiographical features. Pulmonary nocardiosis was caused by *N asteroides* sensu stricto in 12 patients, *N asteroides* complex in 2, *N nova* in one, and *N farcinica* in one. Diagnostic cultures were obtained from at least one of the following clinical specimens: sputum in 10 patients, bronchoalveolar lavage in six, empyema drainage in three, and lung biopsy, abscess puncture fluid, and gastric fluid in one each. In 15 of 22

Table 2 Clinical manifestations and radiographical features in 16 patients with pulmonary nocardiosis

Finding	No (%) of patients
Clinical manifestations	
Fever	10 (62.5)
Cough	10 (62.5)
Worsening asthenia	9 (56.3)
Weight loss	8 (50.0)
Pleuritic pain	3 (18.8)
Severe headache	2 (12.5)
Haemoptysis	1 (6.3)
Radiographical features	
Infiltration	
Lobar	5 (31.3)
Multilobar	5 (31.3)
Nodules	
Multiples	5 (31.3)
Solitary	2 (12.5)
Pleural effusion	4 (25.0)
Empyema	3 (18.8)
Cavitation	3 (18.8)
Abscess	1 (6.3)
Bronchiectasis	1 (6.3)

pulmonary specimens *Nocardia* spp were visible on Gram stain.

The patient with disseminated nocardiosis as a result of *N asteroides* had pneumonia with pleural effusion, perigastric abscess, peritonitis, and nocardaemia. The patient was a heart transplant recipient who had received prolonged immunosuppressive treatment. He was transferred to our hospital because of pneumonia of unknown aetiology, which had been treated with ciprofloxacin and clarithromycin for 21 days. At admission, he presented with sepsis, which rapidly progressed to septic shock as a result of concomitant cytomegalovirus infection.

Central nervous system (CNS) nocardiosis was diagnosed in the two patients with cerebral abscesses. The neurological features in one patient were aphasia, right central facial paresis, and right hemiparesis. The abscess was 3 cm in diameter in the left parietal anterior lobe. The second patient had an abscess of 2 cm diameter in the left cerebellum. He suffered from headache, nausea, and instability, and the computed tomography scan showed a solitary ring enhancing lesion with central necrosis and surrounding oedema within the corresponding localisation. Nocardial infection was limited to the CNS in both cases; *Nocardia* spp were suspected after examination of the Gram stain, and *N asteroides* complex and *N asteroides* sensu stricto grew from bacteriological cultures from the abscess specimens.

Nocardia brasiliensis and *N asteroides* complex were identified in the cases of cutaneous nocardiosis.

Treatment and outcome

In vitro testing for the principal antibacterial agents was performed for 14 of 20 strains (table 3). Resistance to either imipenem or amikacin was not detected among the *N asteroides* sensu stricto or *N asteroides* complex strains. TMP/SMX and ceftriaxone showed high activity against the isolates, whereas ciprofloxacine, tobramycin, and gentamicin showed less anti-nocardial activity. The lowest activity against *N asteroides* was noted for penicillin, amoxicillin, and amoxicillin-clavulanic acid.

Treatment targeting *Nocardia* spp was given to 17 of 19 patients (information was not available for one patient). Antibacterial agents with known anti-nocardial activity used in monotherapy or in combination included TMP/SMX in 14 patients, imipenem in seven, ciprofloxacin in four, and minocyclin, amikacin, and sulfadiazine in three each. The most common initial treatment consisted of TMP/SMX, oral (n = 7) and parenteral (n = 4). TMP/SMX had to be switched to another treatment because of side effects in three patients and because of a lack of efficacy in two other patients. The median treatment duration in surviving patients was 90 days (mean, 117; range, 10–360). In two patients with CNS involvement, a craniotomy with abscess evacuation was performed. Abscess debridement was carried out for the two patients with the cutaneous nocardiosis. For the patient with disseminated nocardiosis, a perigastric abscess was drained and a peritoneal rinse with drainage was performed.

A cure was obtained in 15 patients. One patient with chronic granulomatous disease experienced three relapses during the four month period after the pulmonary nocardiosis. The primary pulmonary infection and the relapse episodes occurred during prophylactic and curative treatment with TMP/SMX, and were caused by *N nova*, which was susceptible in vitro to TMP/SMX. During the first episode, the patient was treated with parenteral TMP/SMX for three days, but was then switched to oral treatment. He was definitely cured after a six week treatment with imipenem in combination with amikacin for two weeks. A human immunodeficiency (HIV) positive patient with pulmonary nocardiosis who was treated with oral TMP/SMX had a cerebral infection one month later (identified radiologically as an appearance of multiple focal lesions in Virchov Robin and lenticular nucleus regions). Clinical improvement was achieved after a two week treatment with imipenem.

Death as a result of nocardial infection occurred in three patients. Among the patients who died, one patient with cancer had not been treated for the nocardia infection because the clinical manifestations had been attributed to tuberculosis. A second patient with cancer had been treated with oral TMP/SMX. In both patients, nocardia targeted treatment was introduced late—23 and 50 days after the onset of clinical manifestation, respectively. The third patient, a cardiac transplant recipient, was treated with oral sulfadiazine.

DISCUSSION

Previous reports indicate a possible increased incidence of nocardia infection.[1 4] Our present study revealed that nocardiosis remains infrequent in our institution. The incidence over the 15 year study period stayed constantly low, with one to two new cases each year. The same findings have also been reported in other European countries.[6 11]

Table 3 *Nocardia* spp antimicrobial susceptibility

	Susceptible strains/Tested strains				
Antibiotic	***N asteroides***	***N asteroides* complex**	***N nova***	***N farcinica***	***N brasiliensis***
Penicillin	0/3	–	–	–	–
Amoxicillin	1/7	–	–	–	–
Amoxicillin-clavulanate	1/4	–	–	–	–
Piperacillin	1/3	–	–	–	–
Cefuroxime	4/4	–	–	–	–
Ceftriaxone	6/6	–	–	0/1	–
Imipenem	9/9	2/2	1/1	1/1	0/1
TMP/SMX	8/9	2/2	1/1	1/1	1/1
Amikacin	9/9	2/2	–	1/1	–
Gentamicin	4/6	–	–	0/1	–
Tobramycin	2/3	–	–	–	–
Ciprofloxacin	5/8	–	–	1/1	–
Minocycline	1/1	2/2	–	–	–
Tetracycline	1/2	–	–	0/1	–
Vancomycin	1/2	–	–	–	–
Erythromycin	0/3	–	–	–	–

TMP/SMX, trimethoprim/sulfamethoxazole.

Most patients were male, similar to most of the published reports.[6 11–16] The reason for this distribution is unclear and may be related to hormonal effects on the virulence or growth of nocardia.[17] However, the predominance in men shifted to equal proportions in the groups of patients with cancer[18] or lung transplant recipients.[19]

Although rare, nocardial infection can occur in immunocompetent patients. A study, in which 253 cases of nocardiosis were reviewed, found no evidence of underlying illness or immunosuppressive treatment in 15% of patients,[3] and this figure ranges from 10% to 25% in other reports.[1 6 12 17] In general, Most patients presenting with nocardiosis have a certain degree of immune deficiency. Activated macrophages and T cells constitute the major defence mechanism for nocardial infection, whereas B cells and humoral immunity do not appear as important in protecting the host.[2] An incidence of 2.3% of nocardial infection was found in renal transplant recipients,[20] 0.06% in patients with cancer,[18] 0.3% in bone marrow transplant (BMT) recipients,[13] and 0.38–1.8% in HIV positive patients.[7 11 21] Impaired local pulmonary defences seen in chronic obstructive pulmonary disease or other chronic pulmonary diseases predispose to pulmonary nocardiosis, particularly in patients requiring longterm corticosteroid treatment.[1 5] Systemic immunosuppression predisposes to invasive pulmonary and disseminated infections, which is often the case in organ transplant recipients.[15 19 22] Colagenous vascular diseases, chronic granulomatous diseases, dysgammaglobulinaemia, alcoholism, and diabetes mellitus all enhance susceptibility to nocardiosis. Although some reports have indicated a surprisingly low incidence of nocardiosis among HIV infected patients, nocardiosis remains an important cause of morbidity and mortality in HIV positive patients with advanced infection, particularly in those not receiving TMP/SMX prophylaxis.[7 21 23]

''The most common site of infection was the lung, which was involved in 13 patients''

In our present study, 16 of the 20 the patients had at least one known underlying condition responsible for immunodeficiency. In addition, two patients had other predisposing factors such as longterm corticosteroid inhalation and transient immunosuppression secondary to respiratory syncitial virus infection. The most common underlying disease was solid organ malignancy, followed by solid organ transplantation, diabetes mellitus, and HIV infection. Surprisingly, none of our patients had a haematological malignancy or was a BMT recipient. Lymphocytopenia was seen in 15 of the 20 the patients, and the HIV positive patients were in a late stage of the disease. None of the patients in our study was neutropenic. Elsewhere, neutropenia was reported in only 10% of patients with cancer who had nocardiosis,[18] and was not considered to be a significant risk factor in BMT recipients.[13]

The most common site of infection was the lung, which was involved in 13 patients; the subacute lung form, which is known as the typical manifestation of nocardiosis,[5] was particularly prevalent. However, acute forms are common, especially in severely compromised hosts,[1 18] and this form seems to be correlated with a poor prognosis.[17] In our present study, all three patients with nocardaemia had central venous catheters. Such endovascular devices and prosthetic valves appear to be a main risk factor associated with bacteraemia.[17] One of our patients with cystic fibrosis was colonised with *N asteroids*. This confirms previous reports that the isolation of *Nocardia* spp from patients with cystic fibrosis does not necessarily imply active infection, but treatment is recommended to protect against potential dissemination.[24]

CNS involvement may be present in up to 20% of patients with nocardiosis.[6 11–15] The two patients who we identified survived after neurosurgery in conjunction with antibiotic treatment. Nocardial brain abscesses can be life threatening and may cause diagnostic and therapeutic difficulties, particularly in patients with cancer.[18 25] A high mortality rate was reported in a Swiss study of cerebral nocardiosis as a result of underlying diseases or complications.[25] A lower mortality rate was published in an Australian report, but only two of the 11 patients in that study were severely immunocompromised.[26] Disseminated infection was uncommon in our present study, as reported by others,[18 21] although in some other studies the prevalence was reported to be higher.[3 6 12 14] The cutaneous form of nocardiosis may be underdiagnosed in our region because Gram stain and cultures are not routinely performed for superficial skin lesions.

Clinical recognition of nocardial infection is difficult because of its relatively low incidence and a lack of pathognomic symptoms.. The chronic debilitating course of this infection often mimics tuberculosis, pneumocystosis, invasive fungal disease, or malignancy.[20 27] Pleomorphic and non-specific radiological manifestations further complicate the diagnosis. In our present study, the median time between the onset of symptoms and diagnosis was long, with a mean of 30 days, a delay also reported elsewhere.[21 27] The most common initial diagnosis instead of nocardiosis was pulmonary tuberculosis, which was suspected in four patients in our present study; this is because of the clinical similarity of these infections, particularly in HIV positive patients.[21 28–30] In one case, Wegener's granulomatosis had been misdiagnosed when pulmonary nodules surrounded with ground glass attenuations and a pleural effusion were seen on the chest computed tomography scan in the presence of an abnormal urinary sediment. An analogous differential problem was described before.[31] Moreover, in some cases, the diagnosis has been established only after death.[3 12 18]

In our present study, four patients had concomitant infections related to their immunosuppressive state, as was largely reported in previous studies.[18 21 23] Almost one third of the patients with bacteraemic nocardiosis had a positive blood culture for other pathogens, most notably Gram negative bacteria.[17] Cytomegalovirus was the most frequent viral copathogen, and was even found to be associated with poor prognosis in patients with cancer and nocardiosis.[18] This shows that *Nocardia* spp should not be considered only as a colonising microorganism, especially in severely immunocompromised patients.

Most of the isolates in our study were *N asteroides*. This predominance has been reported in other European and non-European studies.[3 4 6 12 16 17 21 32] However, the prevalence of *N farcinica* in our present study was lower than in certain European series (Germany, 60%; France, 24%; Italy, 19%),[27 4 6] or in certain patient groups (chronic granulomatous disease, 14%; lung transplant recipients, 30%; patients with nocardaemia, 14.3%).[14 17 19] Usually, high antibiotic resistance of *N farcinica*, including third generation cephalosporins, emphasises the importance of its identification.[27]

Because the incubation time of the cultures must be prolonged and decontamination techniques adequately selected, the microbiology laboratory should be informed when nocardiosis is clinically suspected. The observation of thin Gram positive, irregularly stained or beaded branching filaments is important in the recognition of *Nocardia* spp.[1] In our present study, nocardia were suspected after Gram stain examination in 65% of specimens from which *Nocardia* spp could be cultured. Therefore, direct microscopy may provide rapid and useful information that could influences the choice of initial antimicrobial treatment. However, multiple clinical

Take home messages

- Nocardiosis mainly affects immunocompromised patients and can become a severe infection
- Differential diagnosis, especially with tuberculosis, often delays the time to diagnosis, which worsens the outcome
- New diagnostic tools, such as the polymerase chain reaction, could provide more rapid and reliable results
- Trimethoprim/sulfamethoxazole was the most commonly prescribed treatment, although it had to be changed in a considerable proportion of our patients because of side effects, and its oral form was not sufficiently efficient in patients with severe infection
- Imipenem should be used as an alternative treatment for severely ill patients, and the sulfa combination for less severe infections

specimens must be examined; in other reports microscopy and cultures were simultaneously positive in only one third of cases.[1]

All *N asteroides* sensu stricto and *N asteroides* complex strains identified in our study were susceptible to imipenem, amikacin, TMP/SMX, and ceftriaxone. A sulfonamide containing regimen, particularly TMP/SMX, was the most commonly administered treatment in our study, and is still considered as the treatment of choice.[16 17 20 21] However, for a considerable number of our patients, TMP/SMX had to be switched to an alternative treatment because of side effects or a lack of efficacy. Moreover, in four patients receiving oral treatment, the treatment was considered to be a therapeutical failure, and two of these patients died. In vitro and animal model data showed that imipenem and amikacin were the most effective anti-nocardial agents and were superior to TMP/SMX.[33–35] In this study, imipenem alone, or in combination with amikacin proved more effective. Because of its higher bactericidal activity, most authors now propose imipenem monotherapy, or imipenem in combination with amikacin, particularly in severely immunocompromised patients, and in cases of CNS, disseminated, or advanced infection.[4 6 12 16 18 32] As shown recently, linezolid is another potential second line agent. Because of its high activity against all clinically important *Nocardia* spp,[36] excellent bioavailability, and positive pilot clinical results, this drug may be particularly useful for patients already undergoing complex medical regimens, such as HIV infected patients or organ transplant recipients.[37 38] However, the longterm toxicity of linezolid still needs to be determined.

The optimal duration of treatment is unknown. Mostly, authors recommend a prolonged course of medication because of the relapsing nature of the infection. In our present study, the median duration of treatment in surviving patients was 90 days. All our patients with the CNS and the cutaneous forms of nocardiosis received a combined medical–surgical treatment, with a satisfactory clinical outcome.

The observed mortality rate (15%) in our study was relatively low. In certain studies concerning the general population,[4 11] patients with cancer,[18] organ transplant recipients,[15 19 20] HIV infected patients,[21 22] and patients presenting with bacteraemia,[17] the observed mortality rate was higher, ranging from 26% to 63%. The three patients who died in our present study had severe underlying diseases, and the infection was diagnosed late or even after death. Most authors have suggested that mortality is related to the severity of the underlying disease, late diagnosis, and an advanced or disseminated form of nocardial infection.[11 17 20 21] The clinical course of two patients in our present study was very complicated. One patient showed a metastatic spread to the CNS. The second patient with chronic granulomatous disease experienced the primary infection during TMP/SMX prophylaxis and had several relapses when receiving TMP/SMX treatment. This clinical case supports a previous suggestion that neither prophylaxis with interferon γ nor prophylaxis with a sulfonamide prevents nocardial infection, but may protect against dissemination. Most patients in our study were treated with at least two parenteral antibiotics, including a sulfonamide, and showed good resolution.[14]

> ''The three patients who died in our present study had severe underlying diseases, and the infection was diagnosed late or even after death''

In conclusion, nocardiosis may become a severe infection and mainly affects profoundly immunocompromised patients. Differential diagnosis, especially with tuberculosis, often delays the time to diagnosis, which worsens the outcome. New diagnostic tools, such as the polymerase chain reaction, could provide more rapid and reliable results. TMT/SMX was the most commonly prescribed treatment; however in a considerable proportion of our patients it had to be changed for another treatment because of side effects, and its oral form was not sufficiently efficient in patients with severe infection. Imipenem should be used as an alternative treatment for severely ill patients, and the sulfa combination for less severe infections.

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