Nocardiosis in Srinagarind Hospital, Thailand: review of 70 cases from 1996—2001

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Summary

Objective: Nocardiosis is a common opportunistic infection found in both immunocompromised and immunocompetent patients. The clinical manifestations, underlying diseases, radiologic findings, antimicrobial susceptibility and treatment of nocardial infection are presented here.

Method: A retrospective study at Srinagarind Hospital, Khon Kaen in Thailand was performed. Medical records from 1996—2001 were reviewed.

Results: There were 81 cases of nocardiosis during the study period but data of only 70 cases were available. 80% of cases were male. The mean age was 39.7 ± 14.9 years. Underlying diseases were found in 80%, of which HIV infection was the most common (34.3%). The common clinical findings were fever, cough, and cutaneous abscess. The most common clinical syndrome was pleuropulmonary infection (44.3%), followed by skin and soft tissue infection (22.8%). Multorgan dissemination was found in 11.4% of cases. The chest X-rays were abnormal in 46 cases (65.7%); alveolar and reticulonodular infiltration was common. Only 70% had positive cultures for Nocardia spp. The resistance rate of Nocardia isolates to trimethoprim-sulfamethoxazole (TMP-SMX) was very high (57.9%) in this study. Most of the patients (85.7%) were treated with antimicrobials, of which TMP-SMX was commonly used. In-hospital mortality was 20%. Most of the cases who died had dissemination, brain abscesses or infection with TMP-SMX-resistant strains. The long-term prognosis was good, with a treatment success rate of 93.75%.

Conclusion: Nocardiosis is a common opportunistic infection in many immunocompromised conditions. It can present with various clinical syndromes, especially pleuropulmonary infection. Culture may not yield the organism but modified acid-fast staining is very helpful in diagnosis. Drug susceptibility testing should be performed due to increasing resistance to TMP-SMX.

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Introduction

Nocardiosis, an infection caused by Nocardia species, is a common opportunistic infection in immunocompromised patients, especially those with acquired immunodeficiency syndrome (AIDS) or those using corticosteroids or immunosuppressive agents.1—5 Although there are many reports about nocardiosis in the literature there are few large series from Thailand6,7 where the AIDS epidemic continues.

This study reviews nocardiosis at Srinagarind Hospital, Thailand, over a six-year period to emphasise its importance as a common pathogen that still causes significant morbidity and mortality.

Materials and methods

The medical records of patients with a diagnosis of nocardiosis coded by the ICD-10 diagnostic coding system at Srinagarind hospital, Khon Kaen University teaching hospital from 1996–2001 were retrospectively reviewed. Cases were included in the study if either a clinical specimen showed positive modified acid-fast stained filamentous bead-branching organisms or a positive culture, or both. Epidemiologic data, clinical, chest X-ray, microbiologic and treatment data were collected and analysed.

Culture, identification and antimicrobial susceptibility testing methods

The specimens from the patients were usually inoculated in routine non-selective media for bacteria, fungi and mycobacteria. Nocardia isolates were identified and tested for antimicrobial susceptibility using a disk diffusion method using Mueller Hilton agar.8

Results

Epidemiographic data

Over the study period, there were 81 cases of nocardiosis at Srinagarind Hospital. Eleven cases were excluded: two cases were less than 15 years old and the medical records of nine cases were lost. Therefore, data of 70 cases were collected. The age, sex distribution and underlying diseases (found in 80% of cases) are shown in Table 1. Immunosuppressive agents (either corticosteroids or chemotherapeutic agents) were concurrently used in 24.3% of cases. Only two cases with HIV infection received antiretroviral treatment due to limited availability in Thailand during the study period. The two treated patients had received dual therapy (zidovudine plus didanosine) about one year before developing nocardiosis.

Clinical features

The common clinical findings were fever, cough, and cutaneous abscess (Table 2). Only 17.1% of patients had fever less than one week before presentation. Septic shock was documented at initial presentation in three cases. When clinical presentations were stratified in relation to organ involvement (Table 3) the most common clinical syndrome was pleuropulmonary infection (44.3%), followed by skin and soft tissue infection (22.8%). Multiorgan dissemination was found in 11.4% of total cases. Brain abscess occurred in a patient with systemic lupus erythematosus as a result of hematogenous seeding.
from pneumonia. Bacteremia was found in four cases, one each with mitral stenosis, diabetes mellitus, and AIDS and one without underlying disease. Concurrent infections were found in eight cases, all of whom were AIDS patients: four with pulmonary tuberculosis, three with cryptococcosis and one with histoplasmosis.

The complete blood count of 44 cases was analysed; mean hemoglobin was 9.7 ± 2.9 (range 2.5 ± 16.2) g/dL, mean white blood cell count 13.4 ± 0.9 (range 0.4–41.4) × 10^9/L, and mean polymorphonuclear cell count 78.7 ± 15.73%. Only one case showed pancytopenia.

**Radiographic findings**

Chest radiographs of all 70 cases were reviewed with a radiologist. They were abnormal in 46 cases (65.7%). The abnormal findings are summarised in Table 4. The common abnormalities were alveolar and reticulonodular infiltration, which accounted for 56.5% of cases. Cavitation and pleural effusion were found either alone or concurrently with infiltration.

**Microbiologic findings**

All 70 patients had evidence of nocardial infection by positive modified acid-fast staining or culture of *Nocardia* spp. Forty-nine patients (70%) had positive cultures of *Nocardia* spp. of which 28 (40%) cases had negative modified acid-fast staining of the organism. Twenty-one cases had only a positive smear as evidence of Nocardia infection but negative cultures. Seventy-eight isolates of *Nocardia* were recovered from cultures of specimens, (pus 30, biopsied tissue from mycetoma 2, tissue from bone biopsy 1, tissue from pleural biopsy 3, ascites fluid 9, synovial fluid 3, pleural fluid 12, sputum 11, blood 7), of which most were reported as *Nocardia* spp. but ten were identified as *Nocardia asteroides*.

The susceptibility testing was carried out by the disk diffusion method and the results are shown in Table 5. The susceptibility rate of *Nocardia* spp. isolates to trimethoprim-sulfamethoxazole (TMP-SMX) was only 42.1%.

**Treatment**

Sixty cases received treatment with antimicrobials, 50 with TMP-SMX. The usual dosage of TMP-SMX used in the treatment of nocardiosis in Srinagarind Hospital was 15 mg of trimethoprim/kg/day. The other ten cases did not receive treatment due to initially negative modified acid-fast staining of the sputum or pus and were referred to another hospital. Five patients with a previous history of adverse events from TMP-SMX were treated with other regimens; one with azithromycin due to pancytopenia, one each with amoxicillin/clavulanate, doxycycline plus

<table>
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<th>Table 3</th>
<th>Clinical manifestation of 70 cases of nocardiosis.</th>
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<td>Clinical syndrome</td>
<td>Number of patients (%)</td>
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<tr>
<td>Pleuropulmonary infection</td>
<td>31 (44.3)</td>
</tr>
<tr>
<td>Skin and soft tissue infection</td>
<td>16 (22.9)</td>
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<tr>
<td>Musculoskeletal infection</td>
<td>4 (5.7)</td>
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<tr>
<td>Lymphadentitis</td>
<td>4 (5.7)</td>
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<tr>
<td>Intraabdominal infection</td>
<td>4 (5.7)</td>
</tr>
<tr>
<td>Eye infection</td>
<td>3 (4.3)</td>
</tr>
<tr>
<td>Dissemination</td>
<td>8 (11.4)</td>
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</tbody>
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<tr>
<th>Table 4</th>
<th>Chest X-ray findings.</th>
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<tr>
<td>Findings</td>
<td>Number of patients (%)</td>
</tr>
<tr>
<td>Alveolar infiltration</td>
<td>18 (39.1)</td>
</tr>
<tr>
<td>Patchy</td>
<td>17 (36.9)</td>
</tr>
<tr>
<td>Lobar</td>
<td>1 (2.2)</td>
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<tr>
<td>Interstitial infiltration</td>
<td>6 (13.0)</td>
</tr>
<tr>
<td>Diffuse</td>
<td>4 (8.7)</td>
</tr>
<tr>
<td>Perihilar</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Reticulonodular infiltration</td>
<td>8 (17.4)</td>
</tr>
<tr>
<td>Pulmonary nodules</td>
<td>5 (10.7)</td>
</tr>
<tr>
<td>Pulmonary mass</td>
<td>4 (8.7)</td>
</tr>
<tr>
<td>Cavitary lesion</td>
<td>10 (21.7)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>7 (15.2)</td>
</tr>
<tr>
<td>Hilar adenopathy</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>1 (2.2)</td>
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cefuroxime axetil, ofloxacin, and ciprofloxacin plus cefuroxime axetil due to allergy to TMP-SMX. There were also five patients receiving other medications, including two cases given amoxicillin due to a missed diagnosis as actinomycotic mycetoma, one given ceftriaxone plus metronidazole for peritonitis and two given imipenem due to suspected concurrent Gram-negative septicemia.

Outcome

Twelve cases died during admission in the hospital, accounting for 20.0% of the 60 cases who received treatment. Eight of these had severe pneumonia, one had a brain abscess, and three had no initial diagnosis. There were 18 cases lost to follow up. Thus 32 cases were evaluated for long-term outcome. One HIV-positive patient who had treatment with oral doxycycline and cefuroxime axetil due to sulfa allergy had a recurrence of Nocardia abscess of the neck and was later lost to follow up. Another case had mycetoma of the foot treated with amoxycillin for three months without improvement, followed by amputation. For the remaining 30 patients, the treatment was successful, with resolution of clinical symptoms and signs as well as pleuropulmonary abnormalities and treatment was therefore discontinued. The median time of treatment was four months (two weeks—16 months).

There were 13 cases infected with TMP-SMX-resistant strains of Nocardia but still treated with TMP-SMX. Data of only five cases were available, all of whom died. The remainder were lost to follow up.

Discussion

Nocardiosis is a common opportunistic infection in immunocompromised hosts that can cause serious or disseminated disease. More than 60% of all reported cases of nocardiosis are associated with pre-existing immune compromise ranging from alcoholism and diabetes to organ transplantation and AIDS. Persons requiring long-term corticosteroid treatment are also at risk. Although the overall incidence in AIDS is low, in this study AIDS cases comprised 34% of the total cases or 42.8% of cases with underlying diseases. None of the AIDS patients with nocardiosis received TMP-SMX prophylaxis for Pneumocystis carinii pneumonia, either because their HIV status was unknown or they were intolerant to sulfonamides. This may signify the importance of TMP-SMX for prophylaxis of opportunistic infections in HIV-positive patients.

Pulmonary disease is the predominant clinical finding (44.3%) in this series, which is similar to other reports. The most common pulmonary manifestation was pneumonia but lung abscess and empyema were also seen. No difference between alveolar and reticulonodular or interstitial pattern of pulmonary infiltration was found. Although cavitation was common in pulmonary nocardiosis (21% found in this study) no radiologic patterns are pathognomonic.

Skin and soft tissue infection was the second most common manifestation in this study, found in 22.8% of cases, especially cutaneous or subcutaneous abscess. This may be explained by the fact that the most common occupation of most of the patients in the series was farming, which exposes to environmental reservoirs of Nocardia.

Disseminated infection is characterised by widespread abscess formation in multiple organs including brain, skin and soft tissue, and lung. Disseminated nocardiosis occurred in 11.4% of cases. Only one case had metastatic brain abscess despite one large survey in which over 44% of systemic nocardiosis had central nervous system involvement. Nocardia bacteremia was reported in a minority of patients with nocardiosis but four cases, with one suspected endocarditis in a mitral stenosis patient were found.

In this study, most Nocardia were not specified. In the literature, Nocardia asteroides is responsible for about 80% of invasive infections whereas N. brasiliensis is the most frequent cause of cutaneous disease.

Clinical experience has shown that successful therapy requires the use of antimicrobial drug(s) in combination with appropriate surgical drainage or débridement. Trimethoprim-sulfamethoxazole (TMP-SMX) is the recommended antimicrobial for the treatment of nocardiosis although optimal antimicrobial regimens have not been established.

Fifty of 60 cases (83.3%) in this study who received antimicrobials were treated with TMP-SMX.
Antimicrobial susceptibility testing by disk diffusion was performed in most isolates. Only 42.1% of isolates were sensitive to TMP-SMX. There are conflicting opinions about the treatment of TMP-SMX resistant nocardiosis because there is still no accepted and validated reference and there are discrepancies between in vitro data and clinical outcome. In this series, five cases of nocardiosis resistant to TMP-SMX did not respond to TMP-SMX and all died. Antimicrobial susceptibility testing of Nocardia may be indicated in patients with a lack of response or relapse after treatment with TMP-SMX. In this study, the proportion of Nocardia isolates sensitive to ceftriaxone, amikacin and imipenem were 73.3%, 96.2%, and 98.1%, respectively. Clinical experience with amikacin and imipenem has been encouraging. Ceftriaxone-containing regimens have been used successfully in several case reports.

In-hospital mortality was 20% and related to severe disease, missed diagnosis and TMP-SMX-resistant strains. The long-term prognosis was good. The success rate of treatment was 93.75%.

In conclusion, nocardiosis is not uncommon and is still a major problem in immunocompromised hosts. Pulmonary infection was the predominant manifestation. Positive smears of Nocardia were seen in only 60% of cases, which may have resulted in missed or delayed diagnosis in the remainder. Therefore, nocardiosis should be suspected in immunocompromised patients who are at risk.

References