

Case Reports of Nocardiosis in Patients with Human Immunodeficiency Virus (HIV) Infection

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Abstract

Introduction: We present 4 local cases of nocardiosis in HIV-infected patients and discuss the diagnosis, clinical syndromes and therapy of nocardiosis. **Clinical Picture:** Two cases presented with pulmonary nocardiosis, one had a cervical lymph node abscess and one had disseminated nocardiosis with pulmonary, cerebral and soft tissue involvement. **Treatment:** Combination therapy is often employed. Sulphonamides or co-trimoxazole, amikacin, imipenem, minocycline and ceftriaxone are some of the drugs that could be used. **Outcome:** Outcome hinges on the early recognition and optimal treatment of this infection. **Conclusions:** Clinical presentations vary and diagnosis is difficult and frequently delayed. Nocardiosis should be suspected in patients who present with pulmonary lesions with soft tissue and/or cerebral abscesses.

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Key words: Abscess, AIDS, Antibiotics, Brain, Nocardia, pulmonary

Introduction

Nocardiosis is an infection caused by a soil-borne aerobic filamentous bacterium in the genus *Nocardia* and the order *Actinomycetales*. Within the genus *Nocardia*, *N. asteroides*, *N. brasiliensis* and *N. caviae* are responsible for nearly all nocardial infections in man. *N. asteroides* is by far the most common and accounts for the majority of nocardial infections of lung, skin and other tissues. It is most commonly introduced through the respiratory tract and the pulmonary event may be self-limiting or progress to an acute, subacute or chronic infection, mimicking tuberculosis, mycotic infection or a malignancy. The nervous system and skeletal soft tissues are frequent sites of dissemination.

Nocardia species are recognised as opportunistic pathogens for patients with impaired host mechanisms and has been described in patients with malignancies,^{1,2} organ transplantation,³ steroids or other immunosuppressive therapy⁴ as well as those with underlying pulmonary diseases.⁵ Nocardiosis in HIV-infected patients has also been well-described.⁶⁻⁸ Although it is not a frequent opportunistic infection complicating HIV infection, cases are being increasingly recognised.⁹⁻¹¹ Diagnosis of this infection is frequently delayed and thus associated with considerable mortality and morbidity.^{5,11} We present four

local cases of nocardiosis in HIV-infected patients and highlight pertinent points in its presentation, diagnosis and management. Since successful therapy hinges on early recognition of this infection and initiation of specific therapy, it is crucial for physicians caring for immunocompromised and HIV-infected patients to maintain a high level of suspicion regarding this potentially fatal infection.

Case Reports

Case 1 (Figs. 1 & 2)

A 34-year-old Indian male working as a boilerman in a shipyard was first diagnosed to be HIV-seropositive when he presented with cough and fever for 1 month. Absolute CD4 lymphocyte count then was 28 cells/mm³. He was noted to have oral thrush and also gave a history of 2 recent episodes of cutaneous herpes zoster infection in the past 6 months. His risk factor was unprotected sexual exposure with commercial sex workers. His chest X-ray (CXR) on admission showed left lower lobe consolidation. Sputum sent for acid fast bacilli smear and pyogenic culture were negative and he was started on empirical treatment with intravenous (IV) ceftriaxone for bacterial pneumonia.

However, he did not respond and continued to have

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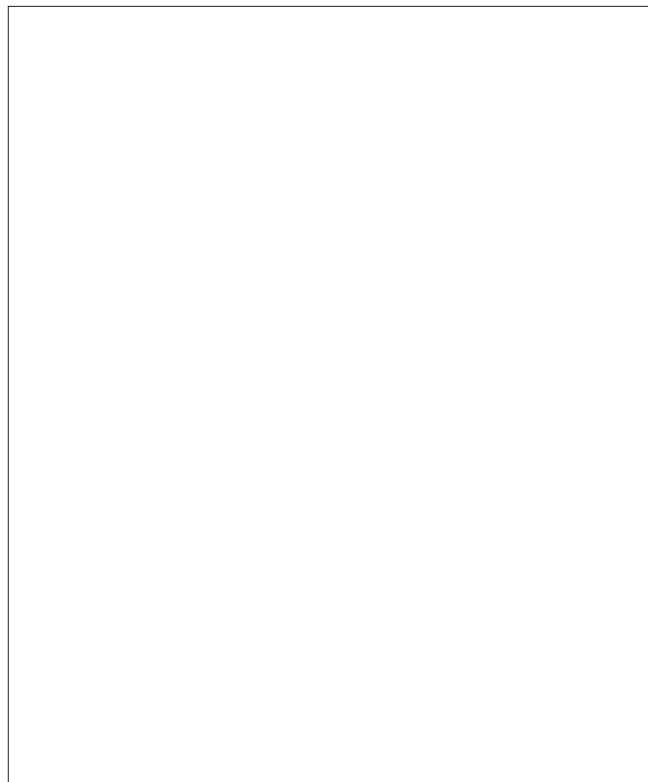


Fig. 1. Left lower zone consolidation in Case 1.

cough and fever. A diagnostic bronchoscopy was carried out and no bronchial obstruction was seen. Bronchoalveolar lavage (BAL) did not show any acid-fast bacilli (AFB), *Pneumocystis carinii* or fungus. Culture for pyogenic organism was also negative from the BAL. Bronchial biopsy showed necrotising granulomata. The impression then was possible pulmonary tuberculosis. He was started on empirical anti-tuberculous therapy with isoniazid, rifampicin and pyrazinamide. His symptoms improved after 1 week of medication and he was discharged.

However, 2 days after discharge, his fever and cough recurred. This time he also experienced mild shortness of breath with production of purulent sputum. A small left pleural effusion was noted. A pleural aspiration performed did not yield any bacteria, mycobacterium or fungus. A repeat bronchoscopy was subsequently carried out and BAL this time was positive for aerobic actinomycetes. A sputum specimen taken 1 day before the second bronchoscopy also yielded the same organism. Culture subsequently grew *N. asteroides* which was sensitive to amikacin, minocycline but resistant to co-trimoxazole, ceftriaxone, cefuroxime, imipenem and erythromycin. He was then started on IV ceftriaxone, amikacin and co-trimoxazole for pulmonary nocardiosis and his fever and respiratory symptoms improved.

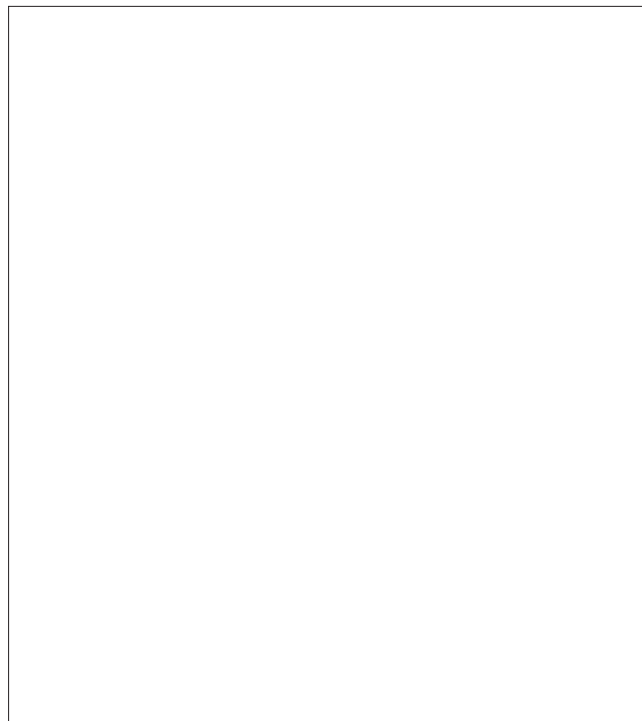


Fig. 2. Case 1: Nocardial cerebral abscesses are often multiple, multi-loculated with thick walls.

One month later, he developed generalised seizures without focal neurological deficit. Urgent magnetic resonance imaging (MRI) of the brain showed multiple small ring enhancing nodules scattered in different parts of the brain, including the right frontal, right parietal lobes, the right insula, the left temporal lobe and the left cerebella hemisphere. Most of these lesions showed enhancement with a fairly thick wall. Adjacent white matter oedema was also present. These lesions were located at the grey-white matter interface compatible with haematogenous process of spread. The imaging features were consistent with the presence of multiple nocardial abscesses. He was started on phenytoin for control of the seizures. He was continued on IV ceftriaxone, amikacin and oral co-trimoxazole.

Incidentally, he also developed a 3-cm left chest wall abscess about 6 weeks after the initial presentation and few days after starting therapy for nocardiosis. Incision and drainage of the abscess was done. There was no connection with the underlying lung lesions and a bone scan showed no evidence of osteomyelitis. Culture did not yield any organism. The clinical impression was that of cutaneous nocardiosis and the sterile culture was attributed to pre-treatment with antibiotics.

This patient continued to improve but developed ototoxicity secondary to IV amikacin after 2 months of therapy. The trough level for amikacin was 0.2 mg/L that was within the recommended range. A repeat MRI of the

brain showed marked reduction in size of the cerebral abscesses. He was then continued on oral co-trimoxazole and minocycline and was discharged well. However, the patient defaulted follow-up after discharge. We managed to contact the patient 10 months after discharge at his residence. He has remained well during this period with no clinical evidence of relapse. Follow-up CXR and CT-scans could not be performed in this patient as he had defaulted outpatient clinic review/attendance since his discharge. The primary physician based the follow-up at 10 months on a phone interview. The patient was later seen and examined at the clinic but he had refused radiological investigations because of financial considerations.

Case 2 (Fig. 3)

A 36-year-old Chinese male food seller first presented with a right cervical swelling of 1-month duration. It was associated with intermittent pain and fever. It did not respond to empirical therapy of ampicillin and cloxacillin given by a general practitioner. The patient consulted an ENT specialist who identified a tender 5-cm non-fluctuant cervical mass. Nares endoscopy was normal and a diagnostic aspiration carried out on the cervical mass was non-revealing.

Two weeks later, the patient was warded in the hospital with severe headache, neck stiffness and fever. He had loss of weight and appetite associated with lethargy over the past 2 months and also gave a history of unprotected sexual exposure with commercial sex workers. Computerised tomography (CT) scan of the brain with IV contrast did not show any focal mass or hydrocephalus. A lumbar puncture performed revealed that he has cryptococcal meningitis. His HIV serology was also positive with a viral load of 149,778 copies/mL plasma and the absolute CD4 lymphocyte count was 19 cells/mm³. CXR showed no pulmonary infiltrates.

During this admission, his right cervical mass enlarged and became inflamed. A CT scan of the neck revealed a 2.5-cm right cervical lymph node abscess. An incision and drainage was carried out subsequently. The preliminary microbiological report of the pus culture was that of aerobic actinomycetes. The final culture yielded *N. asteroides* that was sensitive to amikacin, erythromycin, minocycline and co-trimoxazole but resistant to cefuroxime. He was initially treated with IV co-trimoxazole. However, he developed severe neutropenia and the antibiotic regimen was changed to IV ceftriaxone and oral minocycline for 2 weeks. The patient was subsequently discharged with oral co-trimoxazole and fluconazole for chronic suppression of his nocardiosis and cryptococcosis, respectively. He was also started on dual antiretroviral therapy consisting of d4t (stavudine) and 3TC (lamivudine). There was no clinical

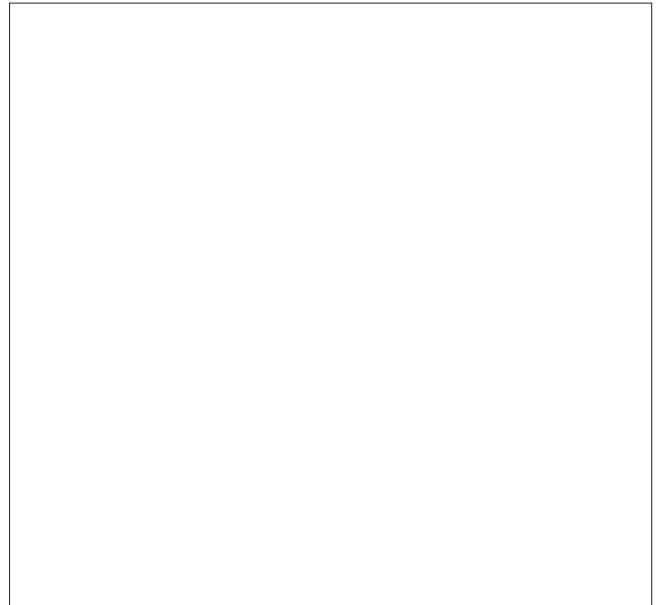


Fig. 3. Cervical lymph node abscess seen in Case 2.

evidence of relapse of the nocardiosis at 1-year follow-up.

Case 3

A 35-year-old carpenter presented to a general hospital in Thailand with fever and altered consciousness for 2 days. He was noted to be cachectic with oral thrush. His HIV serology was positive and his CD4 cell count was 22 cells/mm³ then. AFB smears were positive from his sputum and cervical lymph node aspiration. The biochemistry and microscopy of the cerebral spinal fluid (CSF) examination was suggestive of tuberculous meningitis although the AFB smear was negative. Indian ink stain for *Cryptococcus* in the CSF was negative. He was diagnosed to have disseminated tuberculosis (TB) and was treated with rifampicin, isoniazid, ethambutol and pyrazinamide.

He subsequently returned to Singapore for further management. After 6 weeks of anti-TB treatment, he improved clinically. His sputum smear was negative for AFB and CXR showed clear lung fields.

Two weeks later (after 2 months of anti-TB treatment), the patient was re-admitted to the hospital with worsening cough, right chest pain and fever. CXR revealed consolidation at the right middle lobe of the lung. Bronchoscopy found thick purulent secretions from the right middle lobe and culture of the secretions isolated *N. asteroides* 3 days later, the organism having definite sensitivity to ceftriaxone, cefuroxime, amikacin and imipenem; and with intermediate sensitivity to co-trimoxazole. He was treated with IV ceftriaxone and oral co-trimoxazole for a month. His CXR improved and he was subsequently maintained on oral cefuroxime and co-trimoxazole for pulmonary nocardiosis.

In the course of this admission, he also developed a left dense hemiplegia. Two non-ring-enhancing hypodensities (suggestive of old infarcts), at the right internal capsule and the right thalamus respectively, were seen on the CT scan of the head. Over the next 1 week, his mental state deteriorated. A repeat CT scan of the head showed thick meningeal enhancement (suggesting TB meningitis), an enhancing nodule in the left temporal lobe compatible with a tuberculoma, as well as several cerebral infarcts of the right and left internal capsule and basal ganglia, suggesting TB-associated cerebral vasculitis. CSF findings were consistent with that of TB meningitis (WBC 170, glucose 1.3, chloride 102, and total protein 162). This diagnosis was further supported when mycobacterial blood culture isolated multi-resistant *Mycobacterium tuberculosis complex* during this admission. The isolate was resistant to rifampicin and isoniazid and the anti-TB regimen was changed to pyrazinamide, ethambutol, PAS, kanamycin and ofloxacin. Prednisolone was continued for TB meningitis and vasculitis. Culture and sensitivity of the initial AFB in Thailand when the patient first presented was unavailable.

Nosocomial methicillin-resistant *Staphylococcus aureus* and multidrug-resistant *Pseudomonas aeruginosa* pneumonia further complicated the patient's clinical course and he finally succumbed to these infections and disseminated multidrug-resistant tuberculosis.

Case 4 (Fig. 4)

A 43-year-old Chinese male lorry driver with a 6-year history of non-insulin dependent diabetes mellitus and recurrent herpes zoster presented with fever, dry cough and shortness of breath over a 3-month period. Chest X-ray showed bilateral perihilar infiltrates suggestive of *Pneumocystis carinii* pneumonia (PCP). Due to co-trimoxazole allergy, he was treated with IV pentamidine. His HIV serology was positive and his absolute CD4 lymphocyte count was 13 cells/mm³. His risk factor was multiple exposure to commercial sex workers.

He responded to initial treatment of the PCP. However, less than a week after completing treatment, he was readmitted for worsening cough and fever. The CXR this time showed bilateral reticulo-nodular infiltrates. A diagnostic bronchoscopy with lung biopsy revealed cytomegalovirus (CMV) pneumonitis. The diagnosis was further supported by concomitant CMV retinitis. IV ganciclovir induction followed by maintenance therapy was prescribed. However, after three weeks of ganciclovir, he continued to have fever and cough. His CXR this time showed right upper lobe cavitation.

The differential diagnosis at that point included *Mycobacterium tuberculosis* infection, atypical myco-

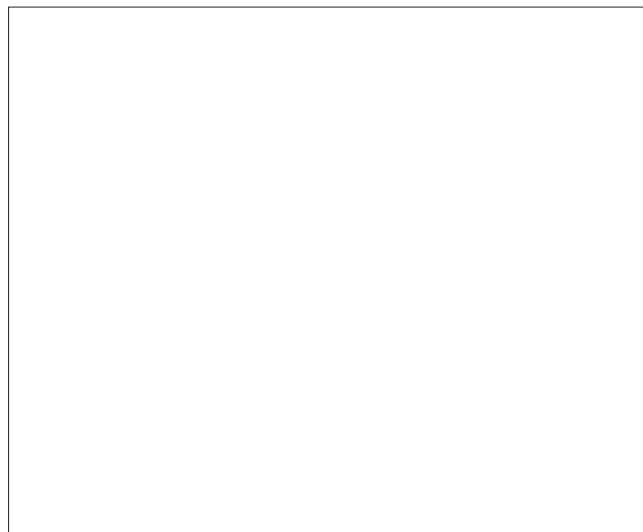


Fig. 4. Upper zone pulmonary infiltrates with cavities mimicking tuberculosis in Case 4.

bacterial infection or cavitating *Pneumocystis carinii* pneumonia. He was put on a therapeutic trial of anti-TB treatment to which he did not respond. Sputum smears and culture were also negative for AFB. There was subsequent worsening of both clinical and radiological pictures. A subsequent CXR showed multiple cavities and right middle zone consolidation. Finally, a transbronchial lung biopsy showed granulomatous infiltrate. Gram stain of the BAL showed branched gram-positive bacilli. Culture results of sputum and BAL subsequently isolated *N. asteroides*. He was treated with oral minocycline 100 mg bd and IV ceftriaxone 2 gm om for 10 weeks with good clinical response. He was then maintained on life-long oral minocycline and cefuroxime.

Patient was started on zidovudine (AZT) for his HIV infection but this was soon discontinued due to intolerance. Six months after the diagnosis of nocardiosis, he developed disseminated *Mycobacterium avium complex* (MAC) infection. This was followed by 3 episodes of recurrent pneumonia within the same year. CT scan of the thorax showed evidence of bronchiectasis. *N. asteroides* was not isolated from the respiratory secretions in any of these 3 episodes although relapse cannot be completely excluded. The patient's clinical condition improved with IV ceftriaxone in 2 of the episodes though *Pseudomonas aeruginosa* was isolated from the BAL in one of the episodes. Fourteen months after the diagnosis of nocardiosis, the patient finally succumbed to a relapse of PCP (BAL was positive for *Pneumocystis carinii*) while he was on dapsone for anti-PCP prophylaxis.

Discussion

Clinical Syndromes (Table I)

Nocardial infections give rise to a broad spectrum of

TABLE I: CLINICAL SUMMARY OF THE 4 PATIENTS

Case	Biodata	Presenting symptoms of nocardiosis	Organ involvement	Absolute CD4 cells/mm ³ at diagnosis	Treatment	Outcome of nocardiosis (as of December 1998)
1	34-year-old Indian male	Persistent cough and fever. Subsequently developed generalised seizure and cutaneous abscess.	Lung, brain, skin	28	IV ceftriaxone, amikacin and oral bactrim for 2 months. Followed by oral bactrim, minocycline indefinitely.	Discharged well. Defaulted follow-up. No clinical relapse after 10 months of default.
2	36-year-old Chinese male	Single cervical swelling.	Cervical lymph node	19	I&D, IV ceftriaxone, oral minocycline for 2 weeks, followed by oral bactrim indefinitely.	Developed cryptococcal meningitis. Presently stable.
3	35-year-old Chinese male	Persistent cough and fever	Lung?Brain	22	IV ceftriaxone, bactrim for 1 month. Oral cefuroxime and bactrim indefinitely.	Developed multi-drug resistant TB. Died.
4	44-year-old Chinese male	Persistent cough and fever	Lung	13	IV ceftriaxone and oral minocycline for 1 month followed by oral cefuroxime and minocycline indefinitely.	Succumbed to PCP relapse 1 year later.

I&D: incision and drainage; TB: tuberculosis; PCP: *pneumocystis carinii* pneumonia

diseases and range from self-limited subclinical infection to an aggressive, disseminated disease resulting in death. The clinical syndromes are not vastly dissimilar in immunocompetent or immunocompromised patients and in patients with or without HIV infection.

The clinical and pathological features are wide and non-specific, mimicking other disease processes; such as tuberculosis (Cases 1, 2, 4), mycotic infection or malignancy.⁶ It can also be the first manifestation of HIV infection (Cases 1, 2) but it usually occurs in those in the advanced stages of infection.^{7,11} The mean CD4 was 109 cells/mm³ in one series with 30 patients¹¹ and in our 4 cases, all were severely immunocompromised with CD4 <50 cells/mm³. Similar to the series by Uttamchandani et al,¹¹ the majority of our cases (Cases 2, 3, 4) also had an AIDS-defining infection before or concurrently with nocardiosis. Nocardiosis in the same organ system can undergo remission as well as exacerbation even while on treatment. New manifestations may also appear while the patient is on effective treatment. This is thought to be due to the progression of previously seeded abscesses that evolve despite effective antimicrobial activity. This scenario is best exemplified in Case 1 where cerebral and soft tissue abscesses evolved while the patient was on antibiotics. In the absence of other pathogens, the management is to continue the antibiotics (unless antibiotic resistance is suspected). Surgical drainage of the abscesses that appeared may also be necessary especially if there is no clinical improvement or the patient remains febrile.

Nocardial organisms are notorious for evoking a pyogenic response with abscess formation. The regions of the body affected most are (in descending order of prevalence) lung, brain and skin. Eyes, muscles, bones, lymph nodes, kidneys, joints, bone marrow, spinal cord, peritoneum, inner ears and liver can also be infected.¹⁰ Our patients presented with lung, brain, lymph node and cutaneous involvement. With the exception of mycetoma, cutaneous, subcutaneous and lymphocutaneous infection, other forms of nocardial infection are frequently seen in individuals who have some underlying debilitation.

In most cases, nocardial infection can be classified as either pulmonary with or without dissemination or cutaneous. Pulmonary nocardiosis can be chronic or subacute, but can be acute with rapid dissemination especially in severely immunocompromised patients. The initial production of small amount of thick purulent sputum, fever, anorexia, weight loss and malaise are common. Dyspnoea, pleuritic pain and hemoptysis are less common. Pulmonary nocardiosis itself produces a wide range of radiological appearances that are variable and non-specific. Lobar or multilobar consolidation was the most frequent radiological pattern.^{5,12} In one big series, 77% of the infiltrates were in the upper lobe, mimicking tuberculosis.¹¹ Infiltrates may be alveolar, interstitial, reticular or reticulonodular. Nodules and cavitations are common in patients with AIDS.^{12,13} Empyema is evident in 25% of the case.¹⁰ Nocardial infection should be entertained in the differential diagnosis of an unexplained lung nodule or

progressive lung cavitation in HIV-infected persons. In half of all cases of pulmonary nocardiosis, extrapulmonary involvement is present.¹¹ The central nervous system (CNS) is the most common site for disseminated disease;^{9,10} about 45% of patients with systemic nocardiosis have CNS infection.¹⁰ Usually there is one or more supratentorial abscesses. They are often multi-loculated. These abscesses tend to burrow into ventricles or the subarachnoid space. The signs and symptoms of brain nocardiosis are more indolent than abscesses due to other bacteria. Patients usually present with fever, headache and occasionally seizures. Focal neurological signs are few. Meningitis without abscess is rare. *Nocardia* is also not easily detected in the CSF. In Case 1, the cerebral abscesses are most likely due to nocardiosis since it responded well to anti-nocardial treatment although diagnostic confirmation would be ideal. In Case 3, the cerebral process may be either due to nocardiosis or tuberculosis although the presence of cerebral infarcts and isolation of *Mycobacterium tuberculosis complex* from the blood favour the diagnosis of tuberculosis. In radiological and pathological correlation studies of HIV-infected patients with enhancing parenchymal lesions, the finding of subependymal nodules or enhancement is suggestive of nocardiosis.¹⁴ An associated pulmonary infiltrate may provide a clue to diagnosis and serve as a more accessible site for biopsy and culture. However, stereotactic biopsy or even open brain biopsy (if the lesion is large) may be indicated for definitive diagnosis especially in HIV-infected patients where it becomes important to establish an aetiological diagnosis in view of the long term treatment and the potential for coexisting infection and/or tumour (lymphoma).

Microbiology and Laboratory Diagnosis

Nocardia is a genus belonging to the order *Actinomycetales*. They are distinctive gram-positive, variably acid-fast, strictly aerobic bacteria, which form branched filaments that fragment into rod or coccoid elements. The first step in laboratory diagnosis of nocardiosis is the examination of sputum, pus or tissue for crooked, branching, beaded gram-positive filaments. However, these characteristics are very difficult to detect in routine haematoxylin and eosin (H&L)-stained tissue sections. Thus, the pathologist must be alerted for appropriate special stains such as modified Gram stain to be used. *Nocardia* is acid-fast in direct smears from specimens if weak acid is used for decolourisation (e.g. in modified Kinyoun or Ziehl-Neelson stains). The above characteristics are sufficient to distinguish the nocardial organisms from most other bacteria, fungi and mycobacteria. However, the most reliable approach to identification is isolation of the organism and biochemical testing on the colonies obtained to confirm the diagnosis. *Nocardia* species grow readily over a wide

temperature range on simple media e.g. Sabouraud's glucose agar, blood agar and Lowenstein-Jensen agar. Since therapy will be quite different for nocardial organisms and other actinomycetes (*Nocardia* is usually resistant to penicillins *in vivo*), the distinction is an important one. Antimicrobial susceptibility testing of *Nocardia* species is currently not standardised or validated, as there is no *in vitro* with *in vivo* correlation. Nevertheless, such tests are still useful, as resistance of *Nocardia* species to drugs can be variable. Such tests are best done at a specialised or reference laboratory.

Nocardial infections are difficult to diagnose, and invasive techniques such as bronchoalveolar lavage, lung and brain biopsies are often required for isolation and identification in culture.^{10,11} The use of invasive diagnostic methods to diagnose nocardial infection was required in 77% of the patients in one series.¹¹ Sometimes, such procedures may have to be repeated if the clinical suspicion is strong. In Cases 1 and 2, the cultures were positive only from the specimens obtained from a second invasive procedure. It is also noteworthy that in Cases 1 and 4, the bacteria was also isolated from the sputum, but bronchoscopy was already performed for both cases before the results were available.

Nocardia species are slow growers in mixed cultures and identification of the colonies may take 2 to 4 weeks. The laboratory must be alerted when nocardial infection is suspected so that the culture plates are not disposed off prematurely and selective media can be used to enhance the recovery of the bacteria. Colonies from pure culture can grow after only 48 hours incubation. Even when appropriate cultures are initiated, 1 to 2 weeks are often required to obtain definitive results. Multiple specimens should be submitted for culture since smear and cultures are simultaneously positive in only one-third of the case.¹⁰ Routine blood cultures are usually not positive but occasionally *Nocardia* can be isolated from blood if blood cultures are inoculated and incubated aerobically for up to 30 days with frequent subcultures performed. A single *Nocardia* colony isolated from pleural fluid or other normally sterile site with an appropriate clinical picture cannot be ignored since *Nocardia* species are seldom laboratory contaminants or part of body's normal flora.¹⁰

Currently, no serological test is available to help identify patients with active nocardiosis quickly and with acceptable sensitivity and specificity. A recently recognised 55/54 - KD glycoprotein antigen (secreted into culture medium during nocardial growth) is being evaluated for a more specific antibody marker of active infection by *Nocardia*.¹⁵ Polymerase chain reaction (PCR) has been used in combination with restriction endonuclease analysis of amplified products from culture to distinguish mycobacterial from nocardial infections and to identify the different

species of *Nocardia*.¹⁶ At present, however, molecular techniques have yet to contribute to rapid, routine pathologic diagnosis of nocardiosis.

Therapy

The mainstay of therapy up to the present is sulphonamides¹⁷⁻¹⁹ to which the disease shows excellent response despite poor *in vitro* correlation.¹⁷ In retrospect, the initial clinical improvement seen in Case 1 is likely secondary to the ceftriaxone (although the isolate was resistant to this drug *in vitro*) that was given for 5 days rather than the anti-TB medications. Combination therapy should be employed in such instances when the pathogen is suspected to have resistance to one of the drugs used. In Cases 1 and 3, we have chosen to use co-trimoxazole in combination with other drugs although the isolate shows intermediate sensitivity or resistance to co-trimoxazole.

Sulphonamides have been successfully used as monotherapy to treat nocardiosis.¹⁷ However, co-trimoxazole is more easily available and is now frequently used to treat this infection despite the lack of conclusive data supporting the theoretical advantage of co-trimoxazole over sulphonamides alone. Some authors recommend that sulphonamides should be in sufficient dosages (from 4 to 12 gm/day) to achieve serum levels of 120 to 150 µ/mL, especially for the first 6 weeks of therapy, or until clinical improvement occurs.^{20,21} Similarly, anti-PCP doses of co-trimoxazole at 15 mg/kg/day or 2 double strength tablets of co-trimoxazole orally at 4 times a day are recommended for nocardiosis.¹⁰ Unfortunately, due to adverse reactions in up to 50% of HIV-infected patients treated with sulpha-containing drugs, alternative therapies are often needed in this population.^{7,22} It is thought that patients with AIDS who are taking co-trimoxazole prophylactically against PCP and eventually develop nocardiosis are more likely to develop sulpha-resistant strains of *Nocardia* though there are insufficient data to support this view. Primary resistance of *Nocardia* to sulphonamides and late relapse after treatment with sulphonamide monotherapy do occur even in the immunocompetent population.^{19,23} Thus, combination or alternative therapy is needed. This is especially so when *in vitro* resistance coupled with poor clinical responses are encountered.

In the acutely ill patients or patients who are severely immunocompromised, combination therapy is useful. Combination of amikacin with imipenem is thought to be the parenteral drugs of choice in the very ill patient.¹⁰ Synergy is displayed *in vitro* with the combination of imipenem and cefotaxime, amikacin and co-trimoxazole, as well as imipenem and co-trimoxazole.²⁴ For *N. asteroides*, the isolates are uniformly susceptible to amikacin although resistance to imipenem can be as high as 23% (as in Case 1 where the isolate is only sensitive to amikacin and

minocycline).¹⁰

Minocycline is a potent tetracycline analogue with excellent *in vitro* efficacy against many strains of *Nocardia*. It has been shown to be clinically effective as an alternative form of treatment for nocardiosis.¹⁹ Both oral and IV routes achieve good serum and CSF levels. Side effects include giddiness or vertigo as a result of vestibular toxicity. Other potential drugs used for treatment in *N. asteroides* infections are ceftriaxone, cefuroxime, amoxycillin / clavulanic acid, doxycycline, ciprofloxacin, erythromycin and dapsone.¹⁰

Cerebral nocardiosis is associated with a high mortality (30% in immunocompromised patients).¹⁸ Mamelak et al¹⁸ recommended stereotactic aspiration followed by antibiotic therapy for immunocompetent patients with solitary cerebral lesion. In the immunocompromised or those with multiple abscesses, craniotomy with excision of cerebral abscesses may be indicated. Other authors also recommended such aggressive modes of therapy for nocardial brain abscess.²⁵ However, there are also case reports of successful treatment of nocardial brain abscess with combination antibiotics alone without surgery²⁶ (as illustrated in Case 1 here). Nonetheless, regardless of surgical management, combination regimens containing two or more drugs like imipenem, amikacin, minocycline, co-trimoxazole or a third generation cephalosporin should be considered for cerebral nocardiosis.

Optimal duration of treatment is unknown but prolonged therapy is advised, as there is the potential for the infection to relapse or worsen while on therapy. In the study by Wallace et al,¹⁹ relapse rarely occurs if co-trimoxazole was given for more than 3 months. It was recommended that immunocompetent patients with pulmonary or systemic non-CNS nocardiosis should be treated for a minimum of 6 to 12 months while those with CNS involvement should receive at least 12 months of treatment. On the other hand, all immunocompromised patients should have at least a year of therapy regardless of their clinical presentation. There is no study to address whether HIV-infected patients with nocardiosis would need lifelong suppressive therapy because of the small number of cases. But life-long suppression was suggested as with the case of HIV-infected patients with PCP. In the largest series comprising 30 patients with nocardiosis,¹¹ relapse was not universal in those who stopped suppressive therapy after initial response to treatment. Fourteen out of the 22 patients relapsed after stopping therapy in this series. We can only conclude that our patient (Case 1) has no suggestion of relapse at 10 months follow-up although relapse is still a possibility with longer follow-up.

Conclusion

Nocardiosis is not a common opportunistic infection associated with HIV infection. This may be due to the

widespread use of co-trimoxazole as anti-PCP prophylaxis in advanced HIV infection, which also protects against nocardiosis.¹¹ The diagnosis of nocardial infection is frequently delayed or missed because the clinical presentations mimics that of many other more common opportunistic infections in immunocompromised patients e.g. TB, atypical mycobacterial lung infections, fungal infections, etc. These infections need to be excluded actively before we can consider less frequent infections like nocardiosis. Some believe that the perceived low incidence among HIV-infected patients is largely due to lack of recognition of the disease. However, the treatment of nocardiosis is different from that of the diseases it mimics, it is important to establish a firm diagnosis, preferably by culture. The isolation of aerobic actinomycetes in clinical specimens should alert the physician to this diagnosis, as *Nocardia* is rarely a contaminant. Sensitivity testing is useful especially in refractory cases of nocardiosis but generally, the sulphur drugs, amikacin, imipenem, minocycline and ceftriaxone are highly active therapeutic agents.

Nocardiosis should always be included in the list of differential diagnosis in patients who present with a syndrome of lung, brain and/or skin abscesses.

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