

NOCARDIOSIS : REPORT OF THREE CASES AND REVIEW OF THE ARTICLES

กฤษณา วรางพงษ์ศรี

รพ. บ้านโป่ง

ABSTRACT :

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Department of Medicine , Banpong Hospital, Rachaburi, Thailand.

Three cases with different clinical manifestations of nocardiosis were reported. Suppurative lymphadenitis at right groin and pulmonary nocardiosis were presented in the first and second cases who also had symptomatic human immunodeficiency virus (HIV) infection. Left subdiaphragmatic abscess was diagnosed in the third case with active systemic lupus erythematosus (SLE) during corticosteroid therapy. The diagnosis of nocardiosis was simply made by Gram and acid-fast or modified acid-fast stains in all cases. Cotrimoxazole, in the dosage of 15 mg/kg/day of trimethoprim, and 75 mg/kg/day of sulfamethoxazole in three divided doses, were given intravenously or orally every eight hours. The therapeutic response was excellent and satisfactorily in two but grave in one case. However, deaths finally ensued in the first and third cases, primarily due to their overwhelming infections and underlying diseases. In the era of AIDS epidemic and rising immuno-suppression conditions due to other causes, initial and accurate diagnosis of nocardiosis can be reached using Gram and modified acid-fast staining of appropriate clinical specimens in any hospitals where laboratory facility for microbiological culture and identification is limited.

บทคัดย่อ :

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กลุ่มงานอายุรกรรม,
รพ. บ้านโป่ง, ราชบุรี.

รายงานผู้ป่วย ในคาร์ดิโอสิส 3 ราย รายแรกเป็นฝีที่ต่อมน้ำเหลืองบริเวณขาหนีบข้างขวา, รายที่สองเป็นปอดอักเสบ ส่วนรายที่สามเป็นฝีที่ไตทะลุถึงด้านซ้าย ผู้ป่วยทั้งสามรายมีภาวะภูมิคุ้มกันบกพร่องร่วมด้วยโดยมีโรคเอดส์ 2 ราย อีก 1 รายเป็นผู้ป่วย systemic lupus erythematosus ที่กินคอร์ติโคสเตียรอยด์ในขนาดค่อนข้างสูงมานานเพื่อควบคุมภาวะชักที่เกิดบ่อย ๆ ผู้ป่วยทั้งหมดได้รับการวินิจฉัยว่าเป็นในคาร์ดิโอสิส ค่อนข้างช้ากว่าจะได้รับการรักษาด้วย Cotrimoxazole ในขนาด 15 มก./กก./วัน ของ trimethoprim และ 75 มก./กก./วัน ของ sulfamethoxazole ผู้ป่วยตอบสนองดีมากต่อการรักษาเพียง 1 ราย และตอบสนองบ้างในระยะแรกอีก 1 ราย แต่รายนี้ก็เสียชีวิตเหมือนกับอีก 1 ราย ที่เสียชีวิตจากโรคเดิมและการติดเชื้อที่ควบคุมไม่ได้ รายงานนี้มีจุดประสงค์ที่จะให้แพทย์ทั่วไปนึกถึงโรคนี้ไว้ เนื่องจากปัจจุบันมีผู้ป่วยที่มีภูมิคุ้มกันเสื่อมและโรคเอดส์มากขึ้นเรื่อย ๆ การเพาะเชื้อโนคาร์เดียมีความลำบากและต้องใช้เวลา การวินิจฉัยทางห้องปฏิบัติการในโรงพยาบาลต่างจังหวัดยังเป็นปัญหา การย้อมสิ่งส่งตรวจโดยวิธีแกรม, acid-fast, modified acid-fast จะช่วยให้ได้การวินิจฉัยเบื้องต้นสำหรับโรคนี้รวดเร็วขึ้น

Introduction

Nocardiosis is the disease caused by *Nocardia* species,¹ the higher bacteria.¹⁻³ It can be found worldwide⁴ and most patients are men in their third to fifth decade.⁴ The micro-organisms usually occur as saprophytic soil dwellers^{2,4} which favour environmental rich in organic matter. The organism can also be isolated from healthy pets and farm animals. *Nocardia* species are aerobic, gram-positive branching filamentous rods,² belong to Family Nocardiaceae, Order Actinomycetales which were mistakenly referred to as fungus.^{3,4} Its filaments are easily fragile,² yielding coccid and bacillary forms. Many *Nocardia* species are partially⁴ acid-fast and thus are better microscopically visualized by modified acid-fast technique using 1-3 percent of H₂ SO₄ or HCl for decolorization⁵ instead of acid-alcohol. Upon culture, they grow very slowly on many simple medias and may take 2-4 weeks³ for colonial appearance on the plate. Pathogenic strains in human are *N. asteroides*, *N. brasiliensis* and *N. otitidiscaviarum* (*syn. caviae*). All strains are capable to cause primary cutaneous nocardiosis, lymphocutaneous syndrome as well as systemic infection which usually manifest initially as pulmonary nocardiosis. However, some type of infection is predominantly associated with certain species for example, *N. brasiliensis* is primarily recovered from mycetoma while *N. asteroides*, the predominant^{1,3,5-9} human pathogen is almost always responsible for pulmonary infection^{3,4,9,10} the most common⁵⁻⁸ nocardiosis which dissemination can occur. Routes of transmission³ are well known to be inhalation, transdermal inoculation and through injured gastro-

intestinal tract. In Thailand, reported cases of systemic nocardiosis is quite rare before 1958 because the infection was initially misdiagnosed until Leelarasamee et al. Reported numerous cases of systemic nocardiosis. Recently, the first three cases of nocardiosis with different clinical manifestations and underlying immunocompromised illnesses were diagnosed at this hospital. We wish to report these cases with emphasis on early diagnosis and we anticipate that more cases will be found if simple diagnostic technique is practiced in the era of rising immunocompromised condition.

Case Report

Case I

A Thai alcoholic house-wife, aged 21 years was admitted to Banpong Hospital on 16 th November 1995 due to chronic diarrhea, fever, anorexia, lethargy and a painful swelling mass at right groin for five months. Five months ago, she complained of fever and right inguinal mass. She was seen at out-patient clinic of this hospital and was told to have right inguinal abscess. The abscess was aspirated and empiric antibiotic was given. Oral candidiasis was also noted at that time. However, she lost to follow-up until she returned with the same symptom to this hospital five months later. Physical examination on admission revealed that she was febrile with body temperature of 38.8°C, pulse rate of 80 per minute, blood pressure of 80/50 mm.Hg. and respiratory rate of 20 per minute. She was anemic and cachectic with body weight of 39 kg. Generalized darkish erythematous papules with excoriation were seen on the skin

over the body and all extremities. Oral candidiasis was again detected. Right inguinal lymph nodes were enlarged, tender and fluctuate. Other systems were unremarkable. Routine investigations showed hematocrit 29 percent, white blood cell 7.6×10^9 cell per litre ; neutrophil 75 per cent, lymphocyte 14 percent, monocyte 8 percent and eosinophil 3 percent. Stool culture was negative for pathogenic bacteria. Chest roentgenogram was normal. Anti-HIV test was reactive. TPHA was positive and VDRL was reactive at titre of 1 : 4.

The abscess was aspirated three times, each yielded 3-5 ml. of frank pus. Gram stain was performed and disclosed gram-positive, branching, long and short filaments together with many white blood cells. Acid-fast staining was subsequently done and revealed acid-fast filaments with branching. (Figure 1) The result of pus culture on blood agar yielded few colonies characteristically compatible with *Nocardia* spp. at 48 hours later. The microscopic examination of the colony was confirmed to be gram-positive branching filaments. She was then treated with six tablets of cotrimoxazole daily in 3 divided doses. Unfortunately, she died 9 days later after the initiation of cotrimoxazole.

Case II

A Thai male, married, aged 23 years was admitted at Banpong Hospital on the 18 th September, 1996 because of fever, cough, weight loss, weakness, tachypnea and sweating for more than one month. One month prior to the admission, he was treated at a private hospital for fever, cough and fatigue which had developed for one week.

The chest X-ray was taken and showed parenchymal infiltration in the right upper lobe. (Figure 3) Pulmonary tuberculosis was diagnosed and he was treated accordingly. Since no clinical improvement was achieved after 2 weeks of therapy, he went to another private clinic. Again the diagnosis of pulmonary tuberculosis was reassured based on the same finding from the chest X-ray. The same anti-tuberculous (HRZE) drugs consisted of isoniazid, rifampicin, pyrazinamide and ethambutol were prescribed for two more weeks. Then his condition definitely deteriorated as hemoptysis, rapid breathing and mild dyspnea began to intervene. So he came to seek medication at this hospital. Physical examination on admission revealed body temperature of 38.7°C , pulse rate of 92 per minute and blood pressure of 130/80 mm.Hg. and respiratory rate of 22 per minute. He looked anemic and tachypneic with body weight of 41 kg. Seborrheic dermatitis appeared over face and trunk and all extremities together with generalized darkish erythematous papules with excoriation. Oral thrush was seen. Breath sound was diminished and medium crepitation were ausculted over the right upper lung. Other systems were unremarkable. Complete blood count showed hematocrit 17 per cent, white blood cell 7.6×10^9 cell per litre ; neutrophil 86 per cent, lymphocyte 11 per cent, eosinophil 2 per cent and basophil 1 per cent. Blood chemistry was within normal limit with the exception of serum albumin and globulin which were 2.5 and 4.4 gm. per litre respectively. Chest roentgenogram showed right upper lobe consolidation with air bronchogram. Anti-HIV test was reactive. TPHA and VDRL were non-reactive. Blood culture

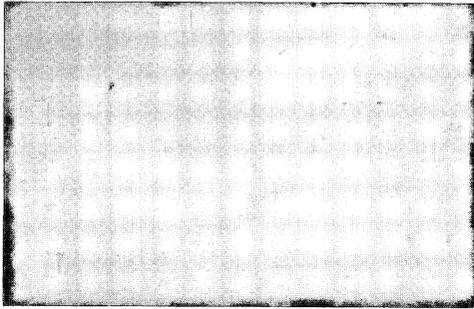


Figure 1

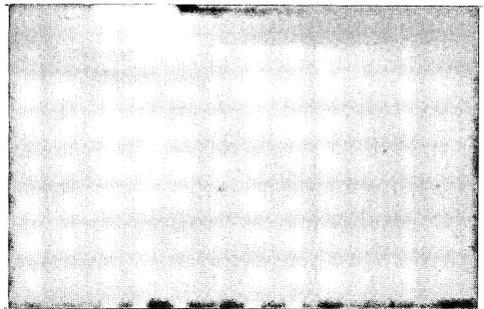


Figure 2

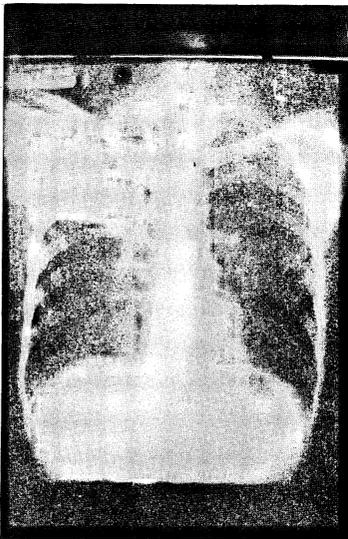


Figure 3

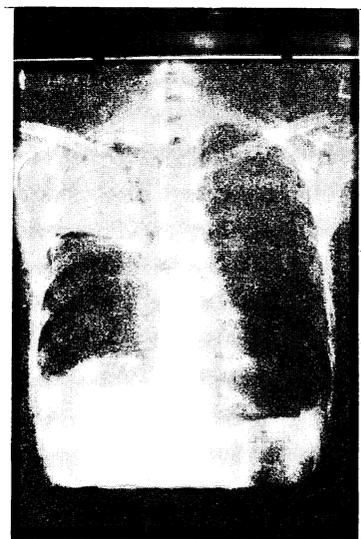


Figure 4

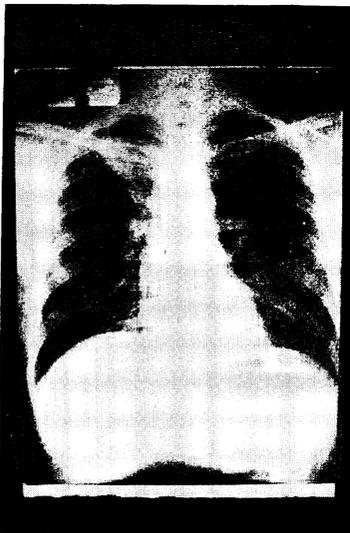


Figure 5

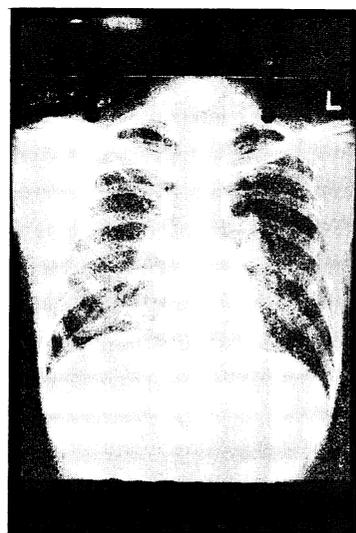


Figure 6

for pathogenic bacteria and sputum smear for acid-fast bacilli were negative. Sputum culture grew out *Klebsiella pneumoniae*. The CD4, CD8 and CD4 : CD8 ratio were 20 cell/mm³, 490 cell/mm³ and 0.04 respectively four months later.

The anti-tuberculous drugs (HRZE) were further continued for the first week in the hospital. Since the follow-up chest film showed multiple tiny cavities within right upper lobe consolidation with minimal right pleural effusion (Figure 4) and repeated sputum staining for acid-fast bacilli (AFB) was negative, the HRZE were changed to ceftriaxone given intravenously 2 gm per day in accordance to the result of sputum culture and susceptibility test. He showed no response after 3 days treatment with ceftriaxone. At the meantime, repeated sputum examination for AFB were requested and positive for acid-fast branching bacilli. (Figure 2) Thus cotrimoxazole was prescribed alone and given parenterally for the first five days when his condition began to improve thus oral cotrimoxazole was subsequently given in the dosage of 15 mg. per kg per day of trimethoprim and 75 mg per kg per day of sulfamethoxazole in 3 divided doses. Later on, AZT and DDI were also prescribed in this patient. The same dosage of cotrimoxazole was continued for three months then it was tapered to ordinary dosage at the time reported. The therapeutic result in this case was considered excellent.

Case III

A Thai female, single, aged 23 years was admitted to Banpong Hospital several times during April-November 1996. She was a known case of

systemic lupus erythematosus (SLE) according to the criteria of the American Rheumatology, with central nervous system and renal involvement. Reasons for those admissions were recurrent convulsions, infection included pneumonia. She had presented with generalized edema, fever, dyspnea, ascites and pleural effusion as a result of hypoalbuminemia, and serositis. She was treated with prolonged course of corticosteroid and consequently developed cushingnoid appearance. Recurrent pulmonary infections were evidenced by repeated chest X-ray findings of pulmonary infiltration and pleural effusion of both lungs, leukocytosis with predominant neutrophil and positive sputum culture. Anti-HIV was non-reactive. On the last admission, all septic work-up procedures were made including hemocultures, urine examinations and cultures, repeated thoracocentesis, an abdominocentesis and a lumbar puncture. Various antimicrobials were prescribed at different times according to the result of bacterial cultures. If the result of culture was not available, antimicrobial was given empirically using epidemiological data on the likely micro-organism. Later on intercostal drainages were done to drain pleural fluid. The dosage of corticosteroid was adjusted accordingly to the severity of the underlying disease.

On the last admission, she had pain at the left upper quadrant flank for a few days. Physical examination revealed warmth, erythematous, firm with slightly bulging of the skin overlying the left costal margin with marked tenderness. Sonogram of upper abdomen showed a subdiaphragmatic abscess. Pus was aspirated through the point of

maximal tenderness. Local incision and drainage were repeated twice. Evacuation of pus and excision biopsy of the wall of the abscess for histopathological examination were done. This yielded moderate amount of pus which by Gram and modified acid-fast stains were positive for branching filamentous rods. Pus culture for other bacteria was negative. Histopathological examination of the abscess wall also showed gram-positive, partially acid-fast, thin beaded branched filamentous rods of *Nocardia* species.

Cotrimoxazole in the recommended dosage was then added to the regimen with satisfactory response of the subdiaphragmatic abscess. However, the patient died subsequently of the overwhelming pneumonia.

Discussion

The clinical spectrum of pulmonary nocardiosis ranges from subclinical to severe and fatal, can be either transitory or chronic, depend on the hosts immune status. There are no specific symptoms. In its protean manifestations, these consist of high fever, dry coughing initially which becomes productive later on, chest pain, tachypnea, dyspnea, anorexia, weight loss, sweating, all of which occur rather insidious and progressive if left untreated. Thus the course of the disease usually is chronic or subacute as compared to the commonly found bacterial pneumonia^{2,6} but may be acute and afebrile in immuno-compromised host. It has to be emphasized that the organism eventually causes suppurative process so that exudative specimen is always available at certain time of the course before

the illness reach its final stage. Nocardiosis is unlikely if suppuration does not occur after 1-2 month^{2,6} of onset of the disease. Because most laboratory personnels in Thailand are not familiar with the micro-organism and there are no selective culture media for nocardiosis, thus the micro-organism is also often missed to show up when appropriate specimen is collected for culture. Fortunately, some simple criterias exist to help clinicians accurately diagnose the infection.

Our cases were good examples of the delayed diagnosis. The first case had history of an aspiration from inguinal abscess since last five months before final diagnosis could be made. The primary site of infection was unknown. Although she did not have mycetoma, a prior cutaneous infection might take place in the right leg long before the appearance of the abscess. The abscess could not be the consequence of distant dissemination because she survived for five to six months without appropriate therapy. If it was the result of dissemination, she should rather have a stormy course once dissemination occurred and the primary site should have been apparent since plenty of time elapsed before the last admission. The second case was a typical demonstration of how pulmonary nocardiosis was finally diagnosed in area where pulmonary tuberculosis was also prevalent. Since the chest radiographic pictures of nocardiosis are pleomorphic and not specific,^{1-3,5,6,8,10,11} and largely depend on duration and severity of the disease and underlying disease, it can mimic acute or chronic pneumonia due to other causes. However, lobar infiltration, consolidation, mass or nodule, single or

multiple, often cavitory,^{7,11,12} are most common. Later, pleural effusion, empyema, abscess are frequent findings. Involvement may be unilateral or bilateral. Lower lobe lesions are seen frequently as compared to tuberculosis. Lymph node may be enlarged. Calcification⁷ was not seen in pulmonary nocardial lesion. Radiological differential diagnosis⁷ included pulmonary tuberculosis, cavitory neoplasm, bacterial pneumonia such as Staphylococcal and Klebsiella pneumonia, fungal pneumonia such as histoplasmosis, actinomycosis and blastomycosis. Nocardiosis should be a differential diagnosis in any patient whose pneumonic process does not respond to ordinary antibiotics used for treatment of common bacterial pneumonia especially in immunocompromised host. The diagnosis is also no exception for immunocompetent host, especially when cavitory pulmonary lesions associated with metastatic abscess, particularly brain abscess. Since abnormal shadow in the second case was found in the upper lobe, tuberculosis had to be ruled out first before nocardiosis is considered. The clue to the diagnosis of nocardiosis in this case should rely on sputum smear for acid-fast bacilli. If acid-fast bacilli compatible with mycobacterium is not found in three consecutive specimens in spite of cavitory lesion and careful microscopic search for the mycobacterium, then mycobacterial infection is unlikely and other micro-organism should be looked for including nocardia. In addition, in any tuberculous patient with or without positive sputum smear-stain for acid-fast bacilli, who have adequate anti-tuberculous treatment without satisfactory response, pulmonary nocardiosis must be suspected though in this

scenario, it may be too late to diagnose nocardiosis. In the third case, pneumonia firstly developed and followed by pleural effusion. Then both primary lesions could extend directly through diaphragm to form subdiaphragmatic abscess or by dissemination. Nocardiosis of the third case reached far advanced stage before accurate diagnosis was given. What we learned from our three cases with respect to the method of diagnosis are good examples for other clinicians not to miss nocardiosis. Leelarasamee A. et al reported their experience with the very first cases of nocardiosis that the crucial point to the diagnosis is to do Gram staining of pus or sputum. If only branching gram-positive filaments surrounded with necrotic cellular debris and neutrophils or monocytes are found, nocardiosis can be the likely diagnosis. It can be distinguished from Actinomyces which in the smear, contains bacteria of various morphology and sulfur granule. The later is anaerobic bacteria and not acid-fast. With this simple step, systemic nocardiosis began to be reported frequently at Siriraj Hospital and finally from other hospitals as well. Visible colonies on blood agar plate may take one to three weeks and laboratory personnel should be notified for clinicians suspicion of nocardiosis because nocardias are frequently obscured by other organisms when contaminated specimens such as sputum, were sent for culture. There is no reliable serologic^{1,3,5,11,13-15} test and thus early diagnosis must rely on Gram stain and modified acid-fast stain of the appropriate clinical specimens by a skillful clinician or laboratory personnel.

Therapy with cotrimoxazole resulted in cure

in only one of our three cases and initial improvement was seen in another though death ensued in this case. Our second case with underlying AIDS responded quite well to cotrimoxazole therapy. Hence response to therapy is directly related to extent of the lesion rather than severity of underlying disease. If the lesion is still confined to one organ when the diagnosis is made, then certain level of response up to cure can be achieved. Our third case had far advanced stage when cotrimoxazole was initiated and resembled the second case reported by Leelarasamee A, et al. Who also had extensive pneumonia and right empyema. The diagnosis of nocardiosis in their second case was almost instant after hospitalization but the initiation of cotrimoxazole therapy also induced respiratory failure. Tissue damage is not only caused by the invasion of micro-organism but also due to the cytotoxic substance released from the cells during their death. Accordingly early diagnosis of nocardiosis can not be over-emphasized if good response to cotrimoxazole therapy is anticipated. Dissemination to various organs may occur by hematogenous^{3,13} or lymphatic³ routes and the organism has organ tropism.³ Metastatic abscess can occur in any organ with frequent involvement of brain, skin and soft tissue, kidney, liver, spleen, pancreas, suprarenal gland, lymph node. Result of treatment could be poor under these circumstances. Mortality is increased in patients³ (1) with acute infection i.e. symptomatic for less than 3 weeks, (2) being treated with corticosteroids or antineoplastic agents, (3) with Cushing's disease and (4) with disseminated disease involving two or more noncontiguous

organs or the CNS. Patients with cell-mediated immunity defects such as lymphoreticular malignancy, HIV Infection, those with immunosuppressive therapy for their underlying diseases such as nephrotic syndrome, systemic lupus erythematosus, pemphigus vulgaris, or organ transplantation, renal or cardiac, etc, are prone to acquire nocardiosis, included patients receiving anti-neoplastic treatment for their malignancies. Other predisposing conditions are chronic granulomatous diseases, i.e. pulmonary tuberculosis and sarcoidosis, chronic lung disease, i.e. chronic obstructive pulmonary disease, silicosis, and alveolar proteinosis. Others are diabetes mellitus, chronic alcoholism, chronic renal failure, etc. Three-quarters⁴ of the affected patients are immunocompromised, occasionally it can occur in normal host.^{1,5,6,11-13} Sulfonamides^{3,5,7,8,12} are drugs of choice for nocardiosis. Sulfadiazine given 6-8 gm per day in four divided doses used to be the drug of choice. Currently, cotrimoxazole is preferred¹⁶ to sulfadiazine and is the only available parenteral sulfonamide with proven efficacy in the dosage of 15 mg per kg per day of TMP and 75 mg per kg per day of SMX given 8 hourly.³ The combination of TMX and SMX apparently achieves significant level in the cerebrospinal fluid and brain tissue.^{16,8} The duration of treatment is uncertain,^{15,16} at least 6¹⁵⁻⁸ weeks, usually 3-6 months up to a year^{12,13,15-17} in the severe cases, in order to prevent relapse. Some authors recommend continued therapy for 6 weeks after clinical cure while others advise low ordinary dosage cotrimoxazole after 6 week period of full-dosage. Other antibiotics may be used in combination^{9,13,16} with cotrimoxazole or follow

cotrimoxazole.

Long term follow up after cessation of treatment is necessary.⁹ Leelarasamee, et al. Could demonstrate branching filaments in smear-stain of expectorated sputum in most patients in contrast to reports from the western countries which seldom demonstrated the organisms by smear-stain techniques. To my opinion it is due to the difference of the two groups of patient that our patients usually come lately to the hospital thus the infection had developed to advanced stage. Aggressive diagnostic approaches i.e. bronchoscopy with bronchial lavage, transbronchial biopsy, percutaneous needle aspiration, open lung biopsy to obtain clinical material closed to the pathology are worthwhile in many cases. In case of sulfonamide hypersensitivity, intolerance or failure, the alternative drugs^{4,15} are minocycline, amikacin, macrolides, or quinolones. Anyhow, data are not large enough and susceptibility must be confirmed. Surgical drainage of abscess and excision of necrotic material are adjuvant measures.^{4,8,13}

In conclusion, nocardiosis is expected to be encountered more widely in the era of epidemic of various illnesses that lead to immunosuppression state. Our reported cases should re-emphasize from time to time the importance of early recognition of nocardiosis and prompt treatment with cotrimoxazole should be practically achievable if one follows those simple steps of diagnosis as mentioned in our report. Prognosis in nocardiosis is not always worse, even in immuno-compromised patients,¹⁵ if the diagnosis made early and prompt, appropriate treatment be given before the spread of primary lesion

as illustrated in our second case.

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