รายงานผู้ป่วย Case Report

Nontuberculous Mycobacterial Skin Infection: Cases Report and Problems in Diagnosis and Treatment

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Abstract Nontuberculous mycobacteria (NTM) are infrequently harmful to humans but their incidence increases in immunocompromised host. There are 4 subtypes of NTM; among them *M. marinum* is the most common pathogen to human. Clinical manifestation of NTM infection can mimic tuberculosis of skin. Therefore, supportive evidences such as positive acid-fast bacilli smear, characteristic histopathological finding and isolation of organism from special method of culture can help to make the definite diagnosis.

Cases of NTM skin infection were reported with varying skin manifestations. Even patients responsed well with many antimicrobial agents and antituberculous drug, some difficult and recalcitrant cases have partial response especially in *M. chelonae* infected-cases.

Kay words: nontuberculous mycobacteria, M. chelonae, skin infection, treatment

Introduction

Nontuberculous mycobacteria (NTM) are infrequently harmful to humans but their incidence increases in immunocompromised host. There are 4 subtypes of NTM; and the subtype *M. marinum* is the most common pathogen to human⁽¹⁾. Clinical manifestation of NTM infection can mimic tuberculosis of skin, and thus supportive evidences such as positive acid–fast bacilli smear, characteristic histopathological findings and isolation of organism from special method of culture can help to make the definite diagnosis.

The genus Mycobacterium is well-known as the cause of two serious diseases – tuberculosis and leprosy. Mycobacteria other than typical tubercle and leprae bacilli or nontuberculous mycobactria (NTM)

were once termed as anonymous, atypical, tuberculoid, or opportunistic mycobacteria that are infrequently harmful to humans⁽¹⁻⁴⁾. Until recently, there were increasing coincidences of NTM infections with a number of immunocompromised and AIDS cases.

The diagnosis of NTM infection requires a high index of suspicion. A history of exposure to the source of infection and an immunocompromised host are suggestive. Finding acid-fast bacilli in a smear from the lesion and characteristic histopathological features with or without organisms are helpful for making relative diagnosis. A definite diagnosis is confirmed by isolation and identification of the organism⁽⁵⁾.

The objective of this study was to demonstrate the problem cases of NTM with vary clinical manifestations, clinical course and their recalcitrant history to treatment and line of management.

Case Report

Case 1

A 41-year-old Thai food vender man had developed a small reddish nodule on his right knee area for 3 years. The lesion extended gradually and peripherally to be a large thick curve shape mass with scaly irregular surface size around 5x6 cm². He felt no pain and no itch. He had never gone to see any doctor.

The physical examination showed a single well-defined large curve scaly erythematous granulomatous plaque with verrucous surface size around 5x6 cm² on right knee (Figure 1). The provisional diag-

Figure 1 Large scaly erythematous granulomatous plaque on right knee



nosis was tuberculosis verrucosa cutis (TVC) and the differential diagnoses were atypical mycobacterial infection and deep fungal infection.

Skin biopsy was taken for Gram stain, acid-fast bacillus (AFB) stain, bacterial culture, AFB culture, fungal culture and atypical mycobacterial culture. Tuberculin test was done with negative result. The histopathological finding was compatible with pseudocarcinomatous epidermal hyperplasia with foci of suppurative granuloma in upper dermis; and microscopic diagnosis was chronic infection with AFB stain negative result. Gram stain, AFB stain as well as bacterial and fungal cultures were all negative. The atypical mycobacterial culture gained positive culture for *Mycobacterium marinum* which was sensitive to rifampin, doxycycline, streptomycin, minocycline and resistant to co-trimoxazole, gentamicin, tetracycline, ciprofloxacin, ofloxacin, isoniazid, and clarithromycin.

Doxycycline (100 mg) was given twice daily with good response. His lesion was nearly 80% clear within 3 months before he was lost to follow up.

Case 2

A 41-year-old Thai woman had developed an eryhtematous flat plaque on the distal part of dorsal aspect of the right middle finger for 1 year. She was a housewife, so she had to cook and launder every day. The lesion started as a small papule on right middle finger that she tried to use a needle to remove it out, but failed. The lesion became thicker and expanded to cover distal part of the finger. It was itching with no pain. She went to see doctor at many hospitals; and was treated as dermatitis with minimal improvement. Two months ago mild edema was developed at the lesion. She took itraconazole (100 mg) twice daily for 2 months without improvement,

then she came to the Institute of Dermatology for treatment.

The physical examination showed solitary ill defined erythematous scaly plaque on the dorsal aspect of the right middle finger (Figure 2).

The skin biopsy was taken for histopathology study, AFB stain, culture for bacteria, fungus, mycobacteria and atypical mycobacteria. The histopathologic diagnosis was tuberculoid granuloma dermatitis with negative AFB stain. All cultures had negative results except positive culture of atypical mycobacteria, *M. marinum*, *which was* sensitive to amikin, clarithromycin, doxycycline, rifampin and resist to minocycline.

She was treated by clarithromycin (250 mg) twice daily combined with doxycycline (100 mg) twice daily. The lesion responded well to the treatment and disappeared within 3 month. Six-week follow up after stopping the medication the lesion was stilled clear.

Case 3

A 16-year-old Thai young man had developed a raised, large annular plaque (10 cm in diameter) on the buttocks, with ulcers and verrucous lesion at the center for 8 years (Figure 3). There was no history

Figure 2 Solitary ill define scaly erythematous plaque on dorsal aspect of right middle finger



of trauma; but he admitted sitting on the ground. His family occupation was selling fresh chicken meat. He had irregular treatments. The lesion was improved after several courses of treatment; but there was relapse when the treatment was discontinued.

A biopsy specimen for bacterial culture and polymerase chain reaction (PCR) yielded *M. fortuitum*; and thus the diagnosis was *M. fortuitum* cutaneous infection.

Chemotherapy with the combination of amikacin, intramuscular, 750 mg/d and clarithromycin 1 gm/d showed a good response within 1 month. But he was lost to follow-up after 2 months of treatment.

Case 4

A 25-year-old Thai housewife developed papules and pustules that gradually progressed into large plaques on the abdomen, chest, back, cheeks, arms, chin, and pinnae. They were associated with mild pain for 6 months.

The plaques were brownish red in color, mild oozing, crusting with discrete and groups of umbilicated papules, pustules and granuloma. Some plaques

Figure 3 *M. fortuitum*, large granulomatous plaque on the buttock with ulcer and verrucous at the center



showed telangiectasia on the surface (Figure 4). Regional lymphadenopathy were noted; otherwise there were no other systemic symptoms.

Chest X-ray was normal. Tests for VDRL and HIV were negative, and the skin test for cell-mediated immunity showed some impairment. Histopathological section of the skin showed mixed cell granuloma with no organism. Inguinal lymph node biopsy showed mixed cell granuloma with caseation necrosis. Bacterial culture of the skin biopsy specimen yielded *M. chelonae*. The antimicrobial sensitivity test showed that the organism was resistant to antituberculous drugs, ciprofloxacin, doxycyclin, erythromycin, and azithromycin; and that it was sensitive to clarithromycin and amikacin (MIC 2 μg/ml and 6 μg/ml). The diagnosis was *M. chelonae* cutaneous infection.

The patient was treated with the combination of clarithromycin 1 mg/d and amikacin 750 mg/d for 4 months with partial response. Heat therapy with hot patch 16 hours/d and cryotherapy were used on some areas, but some lesions remained active. After

6 months, the chemotherapy was changed to clofazimine 300 mg/d and kanamycin 1 gm/d. Most of lesions on the body healed with hypertrophic scars; but some lesions, especially on her face and pinnae, still persisted despite continuous treatment for over one year.

Case 5

A 40-year-old Thai woman whose occupation was selling construction equipments developed subcutaneous nodules on the left thigh and the right leg for a period of 6 months. A history of trauma was not indicated, but she noticed that the lesions looked like insect bites at the beginning.

The lesion on the thigh was a nodule, 4.8 cm in diameter, with pus oozing from the center and two small satellite papules (Figure 5). The lesion on her right leg was a solitary, 1-cm. diameter, bluish-red, firm nodule. Pus smear from the lesion showed acid-fast bacilli. Bacterial culture yielded *M. chelonae*, sensitive to streptomycin, amikacin, and clarithromycin; but resistant to isoniazid (INH),

Figure 4 M. chelonae, annular granulomatous lesion on the shoulder



rifampin, and ethambutol. Diagnosis was *M. chelonae* cutaneous infection.

Before the sensitivity testing, she was treated with rifampin 600 mg/d and ethambutol 800 mg/d for 2

months, with partial response. Then the treatment was changed to streptomycin 1 gm/d and clarithromycin 500 mg/d, according to sensitivity test. Lesions healed within 4 months of treatment.

Figure 5 M. chelonae, bluish red granulomatous lesion on the thigh, lesion began like an insect bites



Case 6

A 52-year-old Thai male presented with skin lesions on the face for 3 months (Figure 6). He had no history of trauma or contact to any chemical substances. 2 years ago he had a wide spread lesions on his chest which was diagnosed as disseminated herpes zoster. He noticed his significant weight loss within a year. He also had pulmonary tuberculosis and chronic renal insufficiency.

On examination, his skin showed multiple pruritic erythematous plaques, papules and pustules with yellowish crust on both cheeks, neck, nasal cavity.

Laboratory investigation found increased level of BUN and creatinine. Anti HIV antibody was negative. Chest X-Ray suggested pulmonary tuberculo-

Figure 6 *M. chelonae*, widespread granulomatous papules and pustules and plaque on the face



sis. Regional lymph node smear for AFB showed 1+, histopathology of lymph node showed non-ceseation granoloma. Skin biopsy from the face showed mixed cell granuloma, suggested mycobacterium granuloma. Tissue culture yielded *Mycobacterium Chelonae*. Bacterial culture showed the organism was sensitive to gentamycin, amikacin, kanamycin, netilmycin, doxycycline, minocycline, ciprofloxacin and clarithromycin.

He was treated with clarithromycin 1 gram daily, combined with doxycycline 200mg/day. The lesions healed within 6 months. He still suffered from his underlining obstructive nephropathy, and passed away within one year from chronic renal failure.

Case 7

A 56-year-old Thai woman who was a farmer developed skin lesions on her face with painful granulomatous plaque studded with pustules and crusts on the bridge of the nose and butterfly area of the cheek, with sinus tracts and serosanguinous fluid oozing from

the left cheek and left side of chin with frequent lacrimation that persisted for a year (Figure 7). There were no signs of lymph-node and systemic involvement. The provisional diagnosis was lupus vulgaris.

A smear of purulent discharge from the lesion demonstrated acid-fast bacilli. Histopathological evaluation of the lesion revealed mixed cell granuloma. Her serum showed negative HIV; and CD4 count was decreased. Chest X-ray showed no active or chronic lung lesion. Bacteriological culture of the lesion yielded *M. avium complex* (MAC).

During admission, she developed an abnormal bleeding in the vagina. After examination and full investigations, she was diagnosed carcinoma of cervix stage II. Physicians believed that CA cervix had induced an immune-compromised state in this patient. Diagnosis was primary cutaneous infection of *MAC*. She was treated with streptomycin 1 gm/d for 3 months combined with INH 300 mg/d and rifampin 600 mg/d for 9 months. The lesion cleared completely with scar formation.

Figure 7 M. avium intracellulare, painful granulomatous plaque, pustules and sinuses on the chin



Discussion

Nontuberculous mycobacteria were isolated by Pinner in 1931⁽⁶⁾. He found that these organisms were different from Mycobacterium tuberculosis in their lack of virulence for guinea pig and poor response to antituberculous drugs. The organisms are widely distributed in water, wet, soil, house dust, dairy products, cold-blooded animals, and plants. The portals of entry are by inhalation, mucosa, and percutaneous penetration, which would result in pulmonary, lymph node, or skin lesions. Generalized infections also occurred, mainly in immunocompromised subjects. Lesions on skin may vary from pustules, hyperkeratotic plaques, nodules with or without suppuration, sporotricoid pattern, or ulcers with draining sinuses. Bacteriological culture for identification of the causative organism is necessary in order to establish the definite diagnosis.

In 1959, the classification of NTM into 4 groups on the basis of growth rate and colony pigment on Lowenstein–Jensen media was introduced⁽³⁻⁴⁾ (Table 1). This classification had advanced the understanding and recognition of these bacteria. However, it has become less useful nowadays because growth rates and pigment productions vary; also many organisms

do not fit into this category. An appropriate temperature was important in determining growth rate and pigment. Biochemical tests can help to achieve an accurate identification.

M. marinum belong to Runyon group I, a slow growing photochromogen, with an optimum temperature at 30–32°C, failure to hydrolyze Tween 80 in 7 days, negative for nitrate reductase, niacin test negative, and catalase positive.

M. marinum was isolated in $1926^{(7)}$. A large outbreak of cutaneous lesions involving swimming pool in Colorado occurred in 1961; and since then the disease has been called swimming pool granuloma⁽⁸⁾. Later, a number of other aquatic environments had been found to be the sources of infection, including fresh water, salt water, brackish water, and household aquariums⁽⁹⁾. Fishtank granuloma is another name for this infection. Diagnosis was made by clinical appearance, history of trauma, and exposure to water, which is confirmed by a positive culture for mycobacteria. M. marinum is the most common cutaneous infection among NTM. It is possible that many cases diagnosed earlier as tuberculosis were, in fact, M. marinum infection. A definite diagnosis should be considered and confirmed by demonstration of the

Table 1 Mycobacterial Runyon Classification

Group	Pigment Growth	Growth Rate	Organism
Ι	Photochromogen	2-3 wks	M. marinum, M. kansasii
II	Scotochromogen	2-3 wks	M. scrofulaceum, M. szulgai
III	Nonchromogen	2-3 wks	M. avium, M. xenopi
IV	Rapid growth	3-5 days	M. fortuitum, M. chelonae

Remark: According to Grange, the common pathogens of skin are *M. ulcerans*, *M. marinum*, *M. fortuitum*, *M. chelonae*; of lungs: *M. avium intracellulare*, *M. kansasii*; and of lymph nodes: *M. avium intracellulare*, and *M. scrofulaceum*. ⁽⁵⁾

organisms.

In general *M. marinum* infection is localized primarily on the skin at the site of inoculation. It commonly appears as a solitary papulo-nodular, granulomatous nodule with central ulceration or verrucous plaque with central clearing or sporotrichoid form on areas predisposed to trauma, for example, fingers, hands, and knees with a history of water exposure⁽¹⁰⁻¹²⁾. Disseminated lesions or deep infection involving tendon sheath and bone in the hand were reported⁽¹³⁻¹⁷⁾. Small superficial lesions may heal spontaneously, while large and deeper lesions may remain for months to several years⁽¹⁸⁻¹⁹⁾.

The organism is usually sensitive to tetracycline, minocycline, doxycycline, trimethoprim-sulfamethoxazole, rifampin, and ethambutol (20-21). Recommended duration for treatment is 3-6 months or until the lesion is healed. Surgery is an alternative treatment for a small lesion. In this paper, two cases of M. marinum are reported as scaly erythematous plaque on knee and finger. First case had never been treated before came to the Institute of Dermatology then by clinical manifestation it was classified in granuloma group that line of management and investigation is well established. But for general practitioners or even some dermatologists misdiagnosis and wrong treatment could be occurred, as in the second case that lesion was treated as dermatitis or infection for long time and modified clinical picture made it more difficult to recognize. Culture from biopsy specimen can give definite diagnosis. In general, M. marinum respond well with doxycycline but combined treatment as in second case give more effective result; and follow up should be recommended.

M. fortuitum and M. chelonae are organisms in group IV of Runyon classification. They showed rapid

growth rate with no pigment production. The time of growth is 3-7 days at 25-40°C.

M. chelonae, or a turtle tubercle bacillus, was isolated by Friedmann BF in 1903⁽²²⁾, and it was used as a vaccine for immunotherapy against tuberculosis. *M. fortuitum* was isolated from frogs. Both organisms exist as saprophytes; and they are found in water, soil, dust, and animals. The infection usually occurs after trauma, contact with animals, surgery, injection, or contact with contaminated medical instruments⁽²³⁾. However, cutaneous infection may also follow dissemination from an endogenous source. These two organisms were often grouped together as fortuitum complex. Immunocompromised patients are susceptible to infection with the rapid growers and make it more difficult to treat. The prevalence of cutaneous infection is low.

From our cases report, we could conclude that without adequate treatment *M. fortuitum* cutaneous infection may persist as long as 8 years. *M. chelonae* showed variation in clinical appearance; and a difficulties in treatment may occur, as shown in case 4, in which a cell-mediated immunity impairment was detected.

Rapid growers can induce a wide spectrum of clinical diseases including noncavitary pneumonia, endocarditis, lymphadenitis, osteomyelitis, and skin infections. Skin lesions may present as cellulitis, abscess, nodules, sinuses, and ulcers with serosanguinous or purulent discharge. They may induce extensive subcutaneous necrosis and exude thick pus. Regional lymphadenitis is usually present.

Excision and debridement may be necessary for abscess and ulcer. The organisms are often resistant to antituberculous drugs and antimicrobial agents. Sensitivity test for susceptible drug is necessary. Drugs

recommended for M. fortuitum are amikacin, defoxifin and sulphonaminde; and those recommended for M.chelonae are amikacin, erythromycin, or doxycycline^(24–26).

M. avium (the avian tubercle bacilli) and M. intracellulare are closely related and difficult to differentiate, so it was common to refer to them as M. avium intracellulare (MAI) or M. avium complex (MAC). It is a slow growing nonphotochromogen with optimal temperature at 37°C. The organism was found in fresh and salt water, soil, dairy products, and domestic animals. MAC infection has increased due to association with AIDS. It often occurs in the terminal stage and may cause disseminated disease in 15 - 40% of AIDS patients (27-31).

An immunocompromise condition induced by malignancy of cervix had played a role in case number 7. Despite high incidence of AIDS, we have not found a case of cutaneous mycobacteria associated with AIDS.

Studies found that *MAC* usually induced lung disease, followed in frequency of occurrence by cervical and inguinal adenitis. Skin lesions showed abscess, ulcerations, sinus formation, granuloma, or erythematous plaque with yellow crusted base. Cutaneous lesion may be primary or secondary to a disseminated infection (32-37). A papulonecrotic tuberculid to disseminated *MAI* was reported in AIDS (38). Combination of antituberculous drugs, for example, refampin, clofazimine, or ciprofloxacin, has been recommended.

Conclusions

Nontuberculous mycobacterial skin infections are often overlooked because of their unremarkable presentations combined with a low index of suspicion and/or inadequate culture techniques. When definite

criteria for diagnosis were not fulfilled they were often diagnosed as tuberculosis. Fortunately, some of them also responded to antituberculous drugs. Nowadays they have received more recognition; and, with the improvement of laboratory skills and the number of immunocompromised and AIDS patients, the diagnosis of NTM infections had increased. Even though NTM showed susceptibility to many antimicrobial agents, recalcitrant organisms, especially *M. chelonae* could occur and induce problems in controlling the disease.

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บทคัดย่อ: การติดเชื้อ Nontuberculous Mycobacteria ที่ผิวหนัง: รายงานผู้ป่วยและปัญหาในการวินิจฉัยและรักษา

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เชื้อ nontuberculous mycobacteria (NTM) เป็นเชื้อที่มักไม่ก่ออันตรายในคนทั่วไป แต่จะ พบในผู้ป่วยที่มีความบกพร่องในระบบภูมิคุ้มกันร่างกาย เชื้อ NTM มีแยกเป็น 4 กลุ่มย่อย ซึ่ง ชนิดที่พบก่อโรคในคนมากที่สุดคือเชื้อ M. marinum ลักษณะการติดเชื้อ NTM ทางคลินิกอาจ คล้ายคลึงกับการติดเชื้อวัณโรคที่ผิวหนัง ดังนั้น จึงต้องอาศัยหลักฐานเชิงประจักษ์อื่น ๆ เพื่อช่วยการวินิจฉัยเช่น การตรวจพบ acid-fast bacilli จากการทำสเมียร์ การตรวจพบลักษณะเฉพาะจากการตรวจทาง พยาธิวิทยาและการตรวจพบเชื้อจากการเพาะเชื้อด้วยวิธีพิเศษ ในรายงานนี้ รายงานผู้ป่วยติดเชื้อ NTM หลายรายที่มีลักษณะทางคลินิกแตกต่างกันซึ่งต้องใช้การยืนยันการติดเชื้อจากหลายวิธี แม้ว่าผู้ป่วยจะ ตอบสนองต่อการรักษาด้วยยาปฏิชีวนะและยาต้านวัณโรคหลายชนิดแต่พบผู้ป่วยบางรายที่ดี้อต่อการรักษา หรือยากต่อการรักษา โดยเฉพาะรายที่ติดเชื้อ M. chelonae

คำสำคัญ: การติดเชื้อ nontuberculous mycobacteria, เชื้อ M.chelonae, โรคผิวหนัง, การรักษา