

Infection Due to Nontuberculous Mycobacterium Other than MAC in AIDS Patients at Siriraj Hospital During 1998-2000 : Saprophyte vs Pathogen

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Abstract

HIV is a major health problem in Thailand. These patients are vulnerable to opportunistic infections, especially *Mycobacterium tuberculosis* and MAC infection. However, NTM was considered a rare disease in Thailand before the AIDS era. In this study, there were 38 HIV seropositive patients with NTM (other than MAC) identified from clinical specimens during the 3 year period 1998-2000 at Siriraj Hospital, which has a higher prevalence than the previous report. Among these patients, 29 cases were likely to have had definite infection from NTM, 5 cases possibly had NTM as a pathogen, and 4 cases had NTM as colonization. The most common site of infection was the lung (87%) and most common symptoms were cough (62.2%), fever (34.2%), weight loss (42.1%), and lymphadenopathy (5.3%). The outcome was poor because many NTM are not susceptible to standard medication for tuberculosis which is the empirical treatment for the majority of HIV seropositive patients with a clinical finding suspected of mycobacterial infection. The fatality rate was as high as 58.6 per cent. Awareness of NTM as a potential pathogen in HIV seropositive patients and adjustment of medications even before the availability of culture results may improve the outcome of treatment of NTM infection in HIV seropositive patients.

Key word : Non-Tuberculous Mycobacterial Infection, Acquired Immunodeficiency Syndrome, Thailand

**RATANASUWAN W,
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J Med Assoc Thai 2002; 85: 886-893**

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Although nontuberculous mycobacterium (NTM) was discovered nearly a century ago, it was rarely associated with clinical diseases before the AIDS era⁽¹⁾. Many NTM have been classified as saprophytes⁽²⁾. NTM differs from *M. tuberculosis* which is always considered as a pathogen when it is isolated from clinical specimens. When NTM are isolated from clinical specimens, they are not always acting as pathogen. Usually the existence of a predisposing condition is required for NTM to be pathogen⁽³⁾. Because of low virulence and pathogenicity, most NTM infections were found in patients with underlying lung diseases, such as chronic obstructive lung diseases, chronic interstitial lung diseases, bronchiectasis etc⁽⁴⁾. Immunosuppression from diseases and drugs is recognized as a predisposing factor for the development of mycobacterial diseases⁽⁵⁾. Patients with acquired immunodeficiency syndrome (AIDS) are especially vulnerable to mycobacterial infection. *M. tuberculosis* and MAC are well recognized as common opportunistic infections in AIDS patients, however, the significance of NTM (other than MAC) as opportunistic infections in AIDS patients is still not well defined⁽⁶⁾. Mycobacterial infection is a common opportunistic infection of HIV patients in Thailand but mostly due to *M. tuberculosis* and MAC (7,8). NTM infection was considered a rare disease in Thailand. There were 24 cases reported from the Central Chest Hospital which is the biggest mycobacteriosis center in Thailand during the 10 year period from 1969 to 1978⁽⁹⁾. Because of the ubiquity of NTM (other than MAC) in the environment, the difference in susceptibility patterns among species which cause difficulty in treatment, and the high prevalence of HIV infection in Thailand, these NTM can be an important health problem in Thailand. To explore the problem of these NTM in HIV seropositive patients in Thailand, this study was performed to evaluate the clinical significance of NTM (other than MAC) in Thai AIDS patients at Siriraj Hospital from January 1998 to December 2000.

PATIENTS AND METHOD

This retrospective/prospective study was conducted at Siriraj Hospital from January 1998 to December 2000. The inclusion criteria were: HIV-positive patients proved by two different serologic tests, patients with signs and symptoms suspected of mycobacterial infection including fever, chronic cough, weight loss, lymphadenopathy, diarrhea, and chronic

skin ulcers. Clinical specimens from these patients were sent for mycobacterial culture. Mycobacterial culture was performed in both systems, conventional culture with L-J media for sputum or pus specimens, and BACTEC 9240 system for blood culture. For blood culture, 5 millilitres of venous blood were drawn and injected into a BACTEC 9240 bottle under aseptic techniques. Whenever mycobacteria grew on media, the organisms were speciated by Gen-probe for *M. tuberculosis* and *Mycobacterium avium complex*, and conventional biochemical methods for other mycobacteria by using the scheme of identification of CDC, Atlanta USA. Once NTM (other than MAC) were identified, the treatment was modified if the patients did not respond well to the standard treatment of tuberculosis including INH (isoniazid), RFP (rifampicin), EMB (ethambutol), and PZA (pyrazinamide).

In this study, patients with NTM identified from patients' specimens were classified into three groups including definite infection, probable infection, and likely colonization. Patients were classified as definite NTM infection if they had symptoms compatible with NTM infection such as fever, cough, lymphadenopathy and they had no other infections or conditions that could explain their symptoms. Patients were classified as probable infection if NTM were identified from non-sterile sites such as sputum and patients had symptoms compatible with NTM infection such as fever, cough, lymphadenopathy, but these patients also had other infections or conditions that could explain their symptoms. Patients were classified as likely colonization if small number of NTM were identified from non-sterile sites such as sputum without symptoms and patients were still doing well without any specific treatment for NTM.

RESULTS

Information of 38 patients who had NTM (other than MAC) identified from clinical specimens including sputum, blood, and tissue biopsy from January 1998 to December 2000 at Siriraj Hospital is shown in Table 1. The mean patient age was 32.87 years (range 21-58 years). Twenty five cases (65.8%) were male and 13 cases (34.2%) were female. Twenty nine cases (76.3%) were classified as definite NTM infection, 5 cases (13.2%) classified as probable NTM infection and 4 cases (10.5%) as likely colonization. Among these 38 patients, NTM were identified from sputum in 34 cases (89.5%), from blood in 3 cases (7.9%) and 1 case from skin biopsy (2.6%).

Table 1. Clinical characteristics of NTM (other than MAC) in AIDS patients at Siriraj Hospital.

Case #	Sex	Age	Symptoms	CXR Finding	CD4 Cell/mm ³	Species of NTM	Treatment	Associated illness	Outcomes
1	M	43	Fever, cough, wt. loss	RUL, LLL infiltrate	NA	<i>M. vaccae</i> 3/3	INH, RFP, PZA, EMB	OC, sinusitis	Loss FU
2	F	29	Fever, productive cough, wt. loss	Miliary infiltration	3	<i>M. chelonae</i> 3/3	INH, RFP, PZA, EMB 3 mo. not improved	OC, PPE	Improved after azithro+ofox+EMB
3	M	47	wt. loss	Diffuse reticulo nodular infiltration	10	<i>M. flavescens</i>	None	PPE, stroygoloidiasis	Death
4	F	28	Fever, productive cough, lymphadenopathy	RUL infiltration	200	<i>M. vaccae</i>	INH, RFP, PZA, EMB	OHL, HSV genitalis	Death
5	M	21	Fever, cough	Perihilar infiltration	NA	<i>M. flavescens</i> 2/3	INH, RFP, PZA, EMB	PPE, HSV OHL, OC	Death
6	M	34	Fever, cough	Miliary infiltration	NA	<i>M. fortuitum</i>	INH, RFP, PZA, EMB	OC, PPE	Death
7	M	27	Fever, productive cough	RLL reticulo nodular infiltration	10	<i>M. vaccae</i>	INH, RFP, PZA, EMB	OC, PPE	Death
8	M	39	Fever, productive cough, wt. Loss	RUL infiltration	NA	<i>M. kansasi</i> 2/4	INH, RFP, PZA, EMB	OC, HSV CMV retinitis	Death
9	M	29	Fever, cough, wt. Loss 2 wk.	Both LL infiltration	19	<i>M. scrofulaceum</i>	None	Penicilliosis	Death
10	M	27	cough, wt. Loss	reticulo nodular infiltration	76	<i>M. fortuitum</i> 4/4	INH, RFP, PZA, EMB	PPE, OHL	Loss FU
11	M	58	Skin papules	Normal	22	<i>M. marinum</i>	Clarithro, cipro, TMP/SMX	OC, PPE	Improved
12	M	36	Fever, wt. Loss, Lymphadenopathy	Perihilar infiltration	2	<i>M. kansasi</i> 2/3	INH, RFP, PZA, EMB	AWS, CMV retinitis	Death
13	M	37	Cough, wt. Loss	R middle lobe infiltration	4	<i>M. chelonae</i> 3/3	INH, RFP, PZA, EMB	CMV retinitis, PPE	Loss FU
14	F	36	Fever, cough, wt. Loss	Reticulo nodular infiltration	6	<i>M. scrofulaceum</i> H/C	INH, RFP, PZA, EMB	PPE, OC, HZV	Death
15	F	28	Productive cough 4 mo.	Reticulo nodular infiltration	NA	<i>M. scrofulaceum</i> H/C	INH, RFP, PZA, EMB	OC, OHL	Death
16	M	25	Productive cough 2 mo.	Interstitial infiltration	22	<i>M. scrofulaceum</i> 3/3	INH, RFP, PZA, EMB not improve but improve when add clarithro	OC, PPE, OHL	Alive
17	M	30	Fever 2 wk, weight loss	Interstitial infiltration	NA	<i>M. scrofulaceum</i> H/C	INH, RFP, PZA, EMB	Salmonella B bacteremia	Death
18	M	39	Cough, weight loss, fatigue	Reticulo nodular infiltration	NA	<i>M. chelonae</i> 2/3	INH, RFP, PZA, EMB not improve	Alive improve after cipro, clarithro, EMB	

Table 1. Clinical characteristics of NTM (other than MAC) in AIDS patients at Siriraj Hospital (Continue).

Case #	Sex	Age	Symptoms	CXR Finding	CD4 Cell/mm ³	Species of NTM	Treatment	Associated illness	Outcomes
19	M	39	Cough, fever, weight loss Productive cough, weight loss	Hilar infiltration LUL infiltrate Reticulo nodular infiltration	5 45 8	<i>M. fortuitum</i> 2/3 <i>M. cheloneae</i> 2/3	INH, RFP, PZA, EMB INH, RFP, PZA, EMB INH, RFP, PZA, EMB	OC, CMV retinitis PPE OC, PPE	Death Death Death
20	M	46	Productive cough						
21	F	31							
22	M	30	Productive cough, weight loss	RUL infiltrate	138	<i>M. fortuitum</i> 2/3	INH, RFP, PZA, EMB	OHL	Loss F/U
23	M	30	Fever, cough, dyspnea	Military infiltration	NA	<i>M. kansassii</i> 3/3	INH, RFP, PZA, EMB	PPE, OHL	Alive
24	F	39	Fever, malaise, cough, weight loss	Hilar infiltration	NA	<i>M. gordonae</i> 2/3	INH, RFP, PZA, EMB	OHL, PPE	Death
25	F	27	Fever, cough	LUL infiltrate	NA	<i>M. kansassii</i> 2/3	None	HSV	Death
26	M	33	Cough	Reticulo nodular infiltration	68	<i>M. fortuitum</i> 4/4	INH, RFP, PZA, EMB	OC, OHL	Alive
27	F	32	Productive cough, weight loss	Reticulo nodular infiltration	25	<i>M. fortuitum</i> 3/3	INH, RFP, PZA, EMB	OHL, PPE	Alive
28	F	45	Cough, dyspnea	Nodeular infiltration	9	<i>M. cheloneae</i> 2/3	None		
29	F	28	Productive cough, dyspnea	Reticulo nodular infiltration	31	<i>M. scrofulaceum</i> 2/3	INH, RFP, PZA, EMB not improve then Doxy, TMP/AMX, improve	OC, PPE OC, PPE	Death Alive
30	M	24	Productive cough		183	<i>M. fortuitum</i> 2/3	None	OHL	Loss F/U
31	F	22	Fever, malaise 2 wk.	Normal	NA	<i>M. cheloneae</i>	None	OHL	Loss F/U
32	M	28	Fever, cough 2 wk.	Normal	158	<i>M. kansassii</i> 1/5	None	OC	Loss F/U
33	M	24	Fever, productive cough, diarrhea	Normal	1	<i>M. gordonae</i> 1/2	None	CMV, CMV	Death
34	M	25	Fever, cough, wt. Loss	Normal	31	<i>M. cheloneae</i>	None	retinitis	Loss F/U
35	F	52	Cough off and on	Normal	94	<i>M. cheloneae</i> 2/5	None	CMV, AWS	Alive
36	M	36	Cough off and on	Normal	3	<i>M. fortuitum</i> 2/3	None	PPE	Alive
37	F	20	cough	Normal	218	<i>M. cheloneae</i> 1/3	None	OC, CM	Alive
38	M	25	Cough	Fibrotic infiltration	23	<i>M. avianum</i>	None	None	Alive

NA = not available, INH = isoniacid, RFP = rifampicin, PZA = pyrazinamide, EMB = ethambutol, OC = oral candidiasis, PPE = papulo pruritic eruption, OHL = oral hairy leukoplakia, HSV = Herpes simplex virus, CMV = cytomegalovirus, CM = cryptococcal meningitis, AWS = AIDS wasting syndrome, clarithro = clarithromycin, cipro = ciprofloxacin, TMP/SMX = Trimethoprim / sulfamethoxazole, HZV = Herpes zoster virus, Cefox = cefoxitin, Amik = amikacin

Table 2. Species of NTM* and sources of specimens.

Species	Sputum	Blood culture	Tissue biopsy
<i>M. kansasii</i>	5	1	-
<i>M. scrofulaceum</i>	3	3	-
<i>M. chelonae</i>	9	-	-
<i>M. fortuitum</i>	8	-	-
<i>M. marinum</i>	-	-	1
<i>M. gordonae</i>	2	-	-
<i>M. vaccae</i>	3	-	-
<i>M. flavescens</i>	2	-	-
<i>M. asiaticum</i>	1		

* does not include DMAC

Definite infection

Patients number 1 to 29 were classified as definite cases of NTM infection because they had symptoms compatible with NTM infection, heavy growth of NTM from culture, and had no alternative diagnosis to explain their symptoms. Among these patients, 28 cases had pulmonary infection, 3 cases had disseminated infection, and 1 case had skin and soft tissue infection. The three cases of disseminated NTM infection also had evidence of pulmonary infection.

The most common symptom of patients with pulmonary infection was coughing (62.2%). Other symptoms were fever (34.2%), weight loss (42.1%), and lymphadenopathy (5.3%). Chest radiographs of these patients revealed various patterns of abnormalities including, reticulonodular infiltration 9 cases (32.1%), patchy infiltration 8 cases (28.6%), perihilar infiltration 5 cases (17.9%), miliary infiltration 3 cases (10.7%), interstitial infiltration 3 cases (10.7%). Twenty two patients received anti-tuberculous drugs as empirical treatment with isoniazid, rifampicin, ethambutol, and pyrazinamide. Only one patient responded to this combination because the patient had *M. kansasii* infection. Thirteen patients of this group died while they were taking isoniazid, rifampicin, ethambutol, and pyrazinamide. Six patients survived because their treatments were modified after their culture results were available. Rapid grower mycobacteria, *M. fortuitum* and *M. chelonae*, were the most common pathogens of pulmonary infection.

Three patients had disseminated infection. All of them also had chest X-ray abnormalities (2 patients had reticulonodular infiltration and 1 patient had interstitial infiltration). These patients had NTM identified from blood culture, all of them died before

the culture results were available. They died while they were taking empirical treatment with isoniazid, rifampicin, ethambutol, and pyrazinamide. These three patients had the same causative organism which was *M. scrofulaceum*.

One patient presented with chronic skin papules and ulcer. Because of mild symptoms, the patient received no treatment until *M. marinum* was identified from the culture. The skin ulcer responded well to clarithromycin, ciprofloxacin and TMP/SMX.

Probable infection

Patients number 30-34 were classified as probable NTM infection. All of the patients in this category had pulmonary symptoms including fever, cough, however, CXR showed no infiltration. The authors could not follow the progression of these patients because 1 patient died from other opportunistic infections (cryptococcal meningitis, CMV retinitis) and the other four patients were lost to follow-up.

Colonization

Patients number 35-38 were classified as likely NTM colonization because they had occasional cough, normal chest X-ray and are still doing well without any specific treatment.

DISCUSSION

After 1981, there have been an increasing number of case reports of NTM (other than MAC) in the medical literature(10,11). *M. gordonae*, once classified as a common contaminant, was reported as a pathogen(12). *M. smegmatis*, once believed almost never pathogenic, was also reported as a pathogen in AIDS patients. The prevalence of NTM (other

than MAC) infection has clearly increased since the AIDS epidemic worldwide(13-18). From this study, there were many NTM species identified from HIV seropositive patients' clinical specimens including *M. kansasii*, *M. scrofulaceum*, *M. chelonae*, *M. fortuitum*, *M. marinum*, *M. gordonaiae*, *M. vaccae*, *M. flavescens*, *M. asiaticum*. Most NTM (other than MAC) discovered were definite or probable infection in Thai AIDS patients at Siriraj Hospital. The most common site of NTM (other than MAC) infection in this study was the lung which was the same as other studies (4,19). The chest X-ray findings in this study were different from other studies which reported the finding in non-HIV patients(20-22). Those studies found around 70 per cent cavitary lesions(20-22). The present study found no case of cavitary lesion.

The most common species causing diseases in this study was *M. chelonae* (23.7%), and *M. fortuitum* was the second most common (21.1%). This finding is different from other studies(16,23-26). Those studies found *M. kansasii* and *M. xenopi* to be the common causative agents among NTM (other than MAC) infection. This difference may be due to the difference in geographical distribution of non-tuberculous mycobacteria.

The present study also found that the prevalence of NTM (other than MAC) infection in men was twice the prevalence in women. This finding had the same trend as another study(27). This finding may be explained by chance exposure to NTM (other than MAC) in the environment (soil, natural source of water) because men tend to do more outdoor activities than women(28,29).

Nearly all patients who received empirical treatment with standard antituberculous drugs including INH (isoniazid), RFP (rifampicin), EMB (ethambutol), and PZA (pyrazinamide) showed no response and patients died within months, and some of them died before the culture results were available. All three patients who had NTM identified from blood cultures died before the culture results were available, even though all of these patients had fever and abnormal chest X-ray, and were treated with standard antituberculous drugs (INH, RFP, PZA and EMB). Interestingly, these three patients had *M. scrofulaceum* bacteremia. *M. scrofulaceum* is usually *in vitro* resistant to INH, RFP, PZA and EMB but sensitive

to clarithromycin. If the treatment for these patients had been modified to include clarithromycin when the patients did not respond to INH, RFP, PZA and EMB after 2 weeks of treatment, they might have benefited and survived until the culture results became available.

The fatality rate was as high as 58.6 per cent. Thirteen patients who had pulmonary infection died before receiving appropriate treatment. Nine of these 13 patients died while they were on standard treatment for tuberculosis with INH, RFP, PZA and EMB. Five patients were lost to follow-up. Six patients who initially showed no response to standard antituberculous drugs (INH, RFP, PZA and EMB), improved when the cultured results were available and treatment was modified to appropriate drugs.

Currently, drug sensitivity testing is not routinely performed in all mycobacteria isolated from clinical specimens. Because of the difference in susceptibility patterns among species which cause difficulty in treatment, the authors may need to culture all specimens suspected of mycobacterial infection, and then do the sensitivity for all mycobacteria isolated from clinical specimens from HIV-positive patients. As the process of culture and susceptibility tests for mycobacteria take time, it may be useful to add new macrolides (clarithromycin or azithromycin) to the standard empirical antituberculous regimen in HIV-positive patients who have clinically suspected mycobacterial infections but show no response after 4 weeks of standard empirical antituberculous treatment as mentioned above while waiting for the results of culture and susceptibility tests. This suggestion is based on experience in the treatment of MAC infection(30,31). By this measure, it may be possible to decrease the mortality of HIV-positive patients from these NTM infections.

In conclusion, any NTM identified from clinical specimens should be considered as a potential causative agent of HIV patients' illness. Mycobacterial culture, identification and sensitivity test of all clinical specimens from HIV patients with clinical suspicion of mycobacterial infection should be performed and adjustment of medications even before the availability of culture results may improve outcome of treatment NTM infection in HIV seropositive patients.

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การติดเชื้อมัยโคแบคทีเรียม ที่ไม่ใช้วัณโรค และไม่ใช่ เอวีญม คอมเพล็กซ์ ในผู้ป่วย โรคเอดส์ ที่โรงพยาบาลศิริราช ระหว่างปี พ.ศ. 2541-2543: เชื้อก่อโรคหรือเชื้อ ไม่ก่อโรค

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โรคเอดส์ยังเป็นปัญหาสาธารณสุขที่สำคัญ ของประเทศไทย ผู้ป่วยเหล่านี้มีความเสี่ยงสูงที่จะมีเชื้อโรคฉวยโอกาส แทรกซ้อน โดยเฉพาะการเป็นวัณโรคและการติดเชื้อมัยโคแบคทีเรียม เอวีญม คอมเพล็กซ์ ถึงแม้การติดเชื้อมัยโคแบคทีเรียม ที่ไม่ใช้วัณโรคยังถือว่า เป็นโรคที่พบน้อยในประเทศไทย แต่กำลังมีแนวโน้มสูงขึ้น จากการศึกษานี้พบผู้ป่วยเอดส์ ที่มีเชื้อมัยโค-แบคทีเรียม ที่ไม่ใช้วัณโรคและไม่ใช่ เอวีญม คอมเพล็กซ์ จำนวน 38 ราย ที่โรงพยาบาลศิริราช ในช่วงเวลา 3 ปี 2541-2543 ซึ่งเป็นจำนวนที่มากกว่าในอดีตมาก ในจำนวนนี้ผู้ป่วยจำนวน 29 รายซึ่งมัยโคแบคทีเรียนนั่นจะเป็นสาเหตุของการเจ็บป่วยแน่ ผู้ป่วย 5 รายเชื้อมัยโคแบคทีเรียนนั่นอาจจะเป็นสาเหตุของการเจ็บป่วย ส่วนผู้ป่วยจำนวน 4 ราย เชื้อมัยโคแบคทีเรียนนั่นไม่น่าจะเป็นสาเหตุของการเจ็บป่วย เป็นการพบเชื้อโดยบังเอิญ และพบว่าปอดเป็นอวัยวะที่พบรอยโรคมากที่สุด ประมาณ 87% ของผู้ป่วย และอาการของผู้ป่วยที่พบบ่อยตามลำดับคือ ไอ (62.2%) ไข้ (34.2%) น้ำหนักตัวลดลง (42.1%) และตื่อน-น้ำเหลือง (5.3%) ผลการรักษาได้ผลไม่ต้องการตายสูงถึง 58.6% เมื่อจากเชื้อมัยโคแบคทีเรียม ที่ไม่ใช้วัณโรคและไม่ใช่ เอวีญม คอมเพล็กซ์ เหล่านี้มักดื้อต่อยาต้านรูปแบบที่ใช้รักษาวัณโรคที่ผู้ป่วยนักจะได้รับในระหว่างการรับผิดชอบทางห้องปฏิบัติการ การเพาะเชื้อ ดังนั้นการตื่นตัวว่าเชื้อมัยโคแบคทีเรียม ที่ไม่ใช้วัณโรคและไม่ใช่ เอวีญม คอมเพล็กซ์ เหล่านี้อาจเป็นเชื้อก่อโรคได้ โดยเฉพาะผู้ป่วยที่มีภูมิคุ้มกันทางภานุคิดปกติ เช่นผู้ป่วยเอดส์ การรับยาให้เหมาะสมสมถ้วนด้วยต้องทำก่อนที่จะได้ผลการตรวจทางห้องปฏิบัติการอาจมีความจำเป็น เพื่อช่วยให้ผู้ป่วยรอดชีวิตมากขึ้น

คำสำคัญ : การติดเชื้อมัยโคแบคทีเรียมที่ไม่ใช้วัณโรค และไม่ใช่เอวีญม คอมเพล็กซ์, ผู้ป่วยโรคเอดส์, ประเทศไทย

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จตุมหาภัยแพทย์ฯ 2545; 85: 886-893

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