Prevalence of Disseminated *Mycobacterium Avium* Complex Infection in Thai AIDS Patients

CHAROEN CHUCHOTTAWORN, M.D.*, BOONMEE SATHAPATAYAWONGS, M.D.**,
SOMSIT TANSUPHSAWADIKUL, M.D.***, SURAPOL SUWANAGOOL, M.D.****,
PACHAREE KANTIPONG, M.D.*****, SOPA PORNCHAIPOONTHAVEE, Cert. Med.Sci.*

Abstract

Infections caused by nontuberculous mycobacteria (NTM), although rare in immuno-competent individuals, can potentially produce problems in immunocompromised patients such as those with acquired immunodeficiency syndrome (AIDS). In this study, hemocultures for mycobacteria using radiometric BACTEC 13A media were taken from 334 patients with known human immunodeficiency virus infection admitted to four referral hospitals with fever of unknown site of infection and negative blood cultures for pathogenic bacteria. The mycobacterial hemocultures were positive for *Mycobacterium avium* complex (MAC) in 58 patients (17.4%) and positive for *Mycobacterium tuberculosis* in 34 patients (10.2%). The results of this study have proved that MAC infection, indeed, exists among Thai AIDS patients. The prevalence of MAC infection in Thailand is very high and comparable to that in the western countries. Physicians taking care of AIDS patients in Thailand should be aware of potential MAC infection, particularly in advanced cases. Considering the high prevalence of infection, primary prophylaxis against MAC infection in advanced AIDS patients is recommended.

Key word : *Mycobacterium Avium* Complex Infection, Acquired Immunodeficiency Syndrome, Human Immunodeficiency Virus, Thailand

* Department of Medicine, Central Chest Hospital, Ministry of Public Health, Nonthaburi 11000,
** Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400,
*** Department of Medicine, Bamrasnaradura Hospital, Ministry of Public Health, Nonthaburi 11000,
**** Department of Preventive and Social Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700,
***** Department of Medicine, Chiang Rai Hospital, Ministry of Public Health, Chiang Rai 50000, Thailand.

Bacteria in the genus Mycobacterium are composed of three major groups. Two of them are organisms which cause important health problems, *Mycobacterium tuberculosis* for tuberculosis and *Mycobacterium leprae* for leprosy[1]. The third group of mycobacteria which consists of more than 50 species is collectively called nontuberculous mycobacteria (NTM)[2]. By and large, NTM have low virulency and pathogenicity compared to *M. tuberculosis* and *M. leprae*. The prevalence of NTM infection in immunocompetent individuals is very low. Most of the infections are found in immunocompromised patients or in patients with underlying lung diseases[3]. Consequent to the human immunodeficiency virus (HIV) pandemic, which causes acquired immunodeficiency syndrome (AIDS), NTM infections have become a significant health problem.

Owing to the decline in self immunity, HIV-infected patients are susceptible to infections with unusual organisms especially from an environment. *Mycobacterium avium* complex (MAC), a common NTM in natural environment, has been reported to be a major opportunistic infection in advanced AIDS patients in western industrialized countries[4]. However, there had been no report of MAC infection in Thai AIDS patients prior to the start of this study. This is surprising bearing in mind the high number of AIDS patients in Thailand.

Therefore, the aims of this study were to determine the prevalence rate of MAC infection in Thai AIDS patients and to explore if MAC infection really exists in Thai AIDS patients. This study was not designed to delineate the clinical features or risk factors which predispose patients to MAC infections and not designed to determine the optimal treatment or the outcome of MAC infections in Thai AIDS patients.

MATERIAL AND METHOD

This study is a multicenter, prospective study with the collaboration of 5 hospitals. Two university hospitals, Ramathibodi Hospital and Siriraj Hospital, collaborated in this study. The other two hospitals were Bamrasnaradura Infectious Hospital, which is a tertiary referral hospital for AIDS patient in Bangkok and nearby provinces and Chiang Rai Regional Hospital, which is situated in Chiang Rai province with the highest HIV prevalence in Thailand. The fifth hospital, Central Chest Hospital, served as a laboratory center for the study since the automated radiometric culture system for mycobacteria was only available therein. The inclusion criteria for patients in this study were patients who had HIV infection proved by two different serologic tests. Patients who had a history of fever longer than two weeks with a documented temperature higher than 38°C on two occasions at least 3 days apart. Patients who did not have an obvious localizing sign of infections and serum cryptococcal antigen was negative or cerebral spinal fluid study was negative. Patients who had negative blood culture for pathogenic bacteria.

Patient who fulfilled criteria for the study received hemoculture for mycobacteria by using BACTEC 13A bottle (Becton Dickinson Diagnostic Instrument System, Sparks, Maryland), which is a radiometric culture system[5]. Five millilitres of venous blood were drawn from a cubital vein and injected into BACTEC 13A hemoculture bottle under aseptic technique. Half a millilitre of the culture enrichment was immediately injected into the bottle after being inoculated with blood. At least one sample of hemoculture was taken from each patient but in some patients two or more samples were taken. The inoculated BACTEC 13A bottles were kept in an incubator at 37°C until sent to the laboratory at the Central Chest Hospital. For Chiang Rai Hospital, the inoculated BACTEC 13A bottles were sent by an evening bus twice a week on Monday and Thursday night. At the Division of Microbiology, Central Chest Hospital, all the received bottles were placed in an incubator at 37°C and brought out for reading with automated BACTEC 460 TB instrument (Johnston Laboratories, Inc., Cockeysville, Maryland) three times a week. The bottles which had Growth Index (GI) of more than 20 were read daily until GI was more than 100. A small amount of medium was drawn from the bottle and smeared, stained with Ziehl -Neelsen method to demonstrate mycobacterial acid fast bacilli. For the identification of mycobacterial species, DNA probe hybridization with species specific probe was done from pure primary isolates (AccuProbe, Gen-Probe, San Diego, California). The results of cultures and identifications were sent back to each hospital and treatment was judged by responsible physicians.

RESULTS

The study period was from December 1995 to December 1996. Three hundred and thirty four patients from the four collaborating hospitals were

Table 1. Prevalence of disseminated MAC infections and tuberculosis in this study.

Hospital	No. patients	Positive MAC	%	Positive *M.tuberculosis*	%
Bamrasnaradura	219	42	19.2	27	12.3
Ramathibodi	50	12	24.0	4	8.0
Siriraj	20	3	15.0	-	-
Chiang Rai	45	1	2.2	3	6.7
Total	334	58	17.4	34	10.2

enrolled into the study. 288 patients were male and 46 patients were female. There were 50 patients from Ramathibodi Hospital and 20 patients from Siriraj Hospital. The highest number of patients, 219, were enrolled from Bamrasnaradura Hospital. In Chiang Rai Hospital, 45 patients were enrolled into the study. The number and prevalence rate of positive blood cultures for MAC and *M. tuberculosis* according to hospitals are shown in Table 1. Disseminated MAC (DMAC) infection which is defined as positive blood culture for MAC could be found in every hospital with the highest rate in Ramathibodi Hospital. The average of DMAC infection rate was 17.4 per cent in this study. Disseminated tuberculosis (DTB) infection which is defined as positive blood culture for *M. tuberculosis* was also seen in this study. Only Siriraj Hospital did not have any case of DTB infection. The average prevalence rate of DTB was 10.2 per cent in this study.

DISCUSSION

Mycobacterial infection is a very common opportunistic infection and causes a major morbidity and mortality in HIV infected or AIDS patients. Early epidemiological studies have shown that the type of mycobacterial infection in eastern developing countries was different from that in western industrialized countries. For developing countries in Asia or Africa, tuberculosis caused by *M. tuberculosis* is the most common opportunistic infection with the prevalence rate of 30-60 per cent in Thailand(6). Moreover, tuberculosis could be found in HIV / AIDS patients at any stage of immune status from early immunodeficient to advanced immunodeficient stage. The major postulation of this high prevalence of tuberculosis is that tuberculosis remains highly prevalent in developing countries, therefore, most of the population had already been infected with *M. tuberculosis* from natural infections.

In contrast, MAC infection was the most common opportunistic infection in HIV/AIDS in western industrialized countries such as the United States(7). Tuberculosis is an uncommon disease in these countries. Many explanations have been postulated. Firstly, tuberculosis has been under control in these countries for the last few decades therefore the general population was naive of natural infection. Furthermore, most HIV/AIDS patients have been treated and prophylaxis for most opportunistic infections under a better system of medical care. Thus, HIV/ AIDS patients could survive until their immunity deteriorated to a very low level to contract an infection from environmental microorganisms such as MAC. Moreover, MAC is a common environmental mycobacteria and exists abundantly in the environment in those countries(8).

It is noteworthy that many epidemiological surveys from African countries have shown that MAC was also frequently isolated from the environment in Africa. Up to the current study, however, only two reports which were designed to determine DMAC infection in African AIDS patient failed to demonstrate any case of DMAC infection(9,10). Both studies were undertaken in Uganda and comprised 205 AIDS patients, 50 of whom were severely ill. In one study, six of seven soil samples and four of seven water samples yielded MAC isolate of 420-3900 CFU (colony forming unit/millilitre). No MAC or DMAC infection in AIDS patients was reported from Asian countries before this study was conducted.

The results of this study have confirmed that DMAC infection truly exists in Thai AIDS patients and the distribution of infection could be found in every hospital. Recently, Suwanagool et al reported prevalence of DMAC infection in 24 per cent of advanced AIDS patients from Siriraj Hospi-

tal[11]. The prevalence of DMAC infection in both studies was rather high and comparable to that in the United states. Nightingale reported the prevalence rate of 20 per cent per year in American AIDS patients[12]. Unfortunately, there has been no good epidemiological survey of NTM in the environment in Thailand. Some cases of pulmonary infections with MAC in non HIV/AIDS patients have been reported in Thailand[13,14]. Given the high prevalence rate of DMAC infections in this study, primary prophylaxis against DMAC infection is recommended in advanced Thai AIDS patients[15].

An other important finding from the results of this study is that 10.2 per cent of patients had disseminated tuberculosis. This finding implies that an occult infection with tuberculosis is very common in the patients. According to the literature, disseminated tuberculosis is an unusual disease with a prevalence rate of 0-2 per cent in patients with pulmonary tuberculosis[16]. Owing to the fact that blood cultures for mycobacteria are not taken routinely in pulmonary tuberculosis in Thailand, the actual prevalence of disseminated tuberculosis is unknown. Three out of the four hospitals in the present study had DMAC infection rates higher than DTB infection rates except in Chiang Rai Hospital. This difference likely arises from the dual epidemic of HIV infection and tuberculosis in the past decade in Chiang Rai, where the total number of tuberculosis has markedly increased[17]. This reflects that etiologies of opportunistic infection in AIDS patients in various geographic locations are different. Therefore, empiric treatment of HIV/AIDS patients with unknown etiology of infection should depend specifically on the prevalence of diseases in each geographic area.

ACKNOWLEDGMENTS

This study was supported by Abbott laboratories (Thailand) Ltd.

(Received for publication on November 17, 1998)

REFERENCES

1. Nolte FS, Mycobacterium. In: Murray PR, ed. Manual of clinical microbiology. Washington D.C.: ASM press, 1995: 400-4.
2. The official statement of the American Thoracic Society. Diagnosis and treatment of disease caused by nontuberculous mycobacteria. Am Rev Respir Dis 1990; 142: 940-53.
3. Wolinsky E. Nontuberculous mycobacteria and disease. Am Rev Respir Dis 1979; 119: 107-37.
4. Benson CA, Ellner J. Mycobacterium avium complex infection and AIDS: Advances in theory and practice. Clin Infect Dis 1993; 17: 7-20.
5. Witebsky FG. Evaluation of new BACTEC medium for culture of blood for mycobacteria. Abstract U70. American Society of Microbiology annual meeting, Atlanta, GA, 1987.
6. Payanandana V, Kladphuang B, Talkitkul N, et al. Information in preparation for an external review of the national tuberculosis programe, Thailand 1995. The second edition. Tuberculosis Division, Ministry of Public Health, 1995.
7. Jones JL, Hanson DL, Dworkin MS, et al. Trends in AIDS related opportunistic infection among men who have sex with men and among injected drug users, 1991-1996. J Infect Dis 1998; 178: 114-20.
8. Falkinham JO, Pasker BC, Gruft H. Epidemiology of infection by nontuberculous mycobacteria. Am Rev Respir Dis 1980; 121: 931-7.
9. Okello DO, Sewankambo N, Goodgame R, et al. Absence of bacteremia with Mycobacterium avium-intracellulare in Uganda patients with AIDS. J Infect Dis 1990; 162: 208-10.
10. Morrissey AB, Aisu TO, Falkinham JO, et al. Absence of Mycobacterium avium complex disease in patients with AIDS in Uganda. J Acquir Immune Def Syn 1992; 5: 477-8.
11. Suwanagool S, Leelarasamee A, Jearanaisilavong J, et al. Prolonged fever due to Mycobacterium avium complex (MAC) disease in advanced HIV infection: a public health concern. J Med Assoc Thai 1998; 81: 893-905.
12. Nightingale SD, Byrd LT, Souyhern PM, et al. Incidence of Mycobacterium avium-intracellulare complex bacteremia in human immunodeficiency virus-positive patients. J Infect Dis 1992; 185: 1082-5.
13. Sriyabhaya N, Wongwatana S. Pulmonary infection caused by atypical mycobacteria: A report of 24 cases in Thailand. Rev Infect Dis 1981; 3: 1081-9.
14. Wongwatana S, Sriyabhaya N. Nontuberculous mycobacterial infection of the lung in a Chest Hospital in Thailand. J Med Assoc Thai 1992; 75: 1-10.

15. Guidelines for the clinical management of HIV infection in children / adults. The fifth edition. Ministry of Public Health, April 1997: 134-5.
16. Shapiro L. The frequency of bacillemia in tuberculosis. Am Rev Tuberc 1932; 26: 418-23.
17. Yanai H, Uthaivoravit W, Panich V, et al. Rapid increase in HIV-Related tuberculosis in Chiang Rai. Thailand, 1990-1994. AIDS 1996; 10: 527-31.

ความชุกของการติดเชื้อ*มัยโคแบคทีเรียม เอเวียม* คอมเพล็กซ์ ในโรคเอดส์ในประเทศไทย

เจริญ ชูโชติถาวร, พ.บ., บุญมี สถาปัตยวงศ์, พ.บ.**,*
*สมสิทธิ์ ตันสุภสวัสดิ์กุล, พ.บ.***, สุรพล สุวรรณกูล, พ.บ.****,*
*พัชรี ขันติพงศ์, พ.บ.*****, โสภา พรชัยพูลทวี, ป.วิทยาศาสตร์การแพทย์**

โรคที่เกิดจากการติดเชื้อมัยโคแบคทีเรียที่ไม่ใช่วัณโรคนั้นเป็นโรคที่พบได้ไม่บ่อยในผู้ป่วยที่ภูมิต้านทานปกติ แต่จะพบได้และเป็นปัญหาในผู้ป่วยที่มีภูมิต้านทานผิดปกติหรือบกพร่อง เช่น ผู้ป่วยที่ป่วยเป็นโรคเอดส์ ในการศึกษาครั้งนี้จากผู้ป่วย 334 ราย ที่มีการติดเชื้อเอ็ชไอวีจากโรงพยาบาล 4 แห่งที่ร่วมศึกษา ผู้ป่วยทุกรายมีไข้มากกว่า 2 สัปดาห์ โดยไม่ทราบอวัยวะที่ติดเชื้อและผลการเพาะเชื้อไม่พบแบคทีเรียก่อโรค ผู้ป่วยได้รับการเจาะเลือดเพาะเชื้อมัยโคแบคทีเรียโดยใช้อาหารเพาะเชื้อชนิดพิเศษ BACTEC 13A ที่มีกัมมันตภาพรังสีอยู่ ผู้ป่วย 58 รายหรือร้อยละ 17.4 มีเชื้อ *Mycobacterium avium* complex (MAC) ในเลือดและผู้ป่วย 34 ราย หรือร้อยละ 10.2 มีเชื้อวัณโรคอยู่ในเลือด การศึกษาได้พิสูจน์ว่าการติดเชื้อ MAC ในผู้ป่วยโรคเอดส์ไทยมีอยู่จริงและมีอัตราที่สูงเช่นเดียวกับที่พบในประเทศตะวันตก แพทย์ผู้ดูแลผู้ป่วยในประเทศไทยควรจะคำนึงถึงโรคนี้ในผู้ป่วยโรคเอดส์ระยะสุดท้ายและควรให้การป้องกันการติดเชื้อ MAC ในผู้ป่วยโรคเอดส์ระยะท้าย ๆ

คำสำคัญ : *ภาวะติดเชื้อมัยโคแบคทีเรียม เอเวียม* คอมเพล็กซ์, โรคเอดส์, เอ็ชไอวี, ประเทศไทย

* กลุ่มงานอายุรกรรม, โรงพยาบาลโรคทรวงอก, กระทรวงสาธารณสุข, นนทบุรี 11000
** ภาควิชาอายุรศาสตร์, คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10400
*** กลุ่มงานอายุรกรรม, โรงพยาบาลบำราศนราดูร, กระทรวงสาธารณสุข, นนทบุรี 11000
**** ภาควิชาเวชศาสตร์ป้องกันและสังคม, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10700
***** กลุ่มงานอายุรกรรม, โรงพยาบาลเชียงรายประชานุเคราะห์, กระทรวงสาธารณสุข, จ.เชียงราย 50000