Pulmonary *Mycobacterium avium* Complex (MAC)-Analysis of 124 Cases in a Medical Center in Taiwan

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One hundred twenty-four cases with positive sputum *Mycobacterium avium* complex (MAC) cultures at a medical center in Taiwan were reviewed retrospectively. Seventeen of the caases fulfilled the criteria of pulmonary MAC, according to the guidelines published in 1997 by the American Thoracic Society (ATS). These patients were analyzed on the basis of: (1) age and sex distribution; (2) underlying co-morbidity; (3) radiographic pattern and location of the lesions; (4) the hospital sections that the patients visited and the treatment rate in each section; and (5) treatment regimens, duration of therapy, and treatment results. The pulmonary MAC patients in this hospital were predominantly males.

Most of the patients in the male group were elderly and had underlying chronic lung disease or other systemic diseases, while those in the elderly female group denied any underlying lung or systemic disease. The cases of 2 elderly female patients reviewed for analysis revealed an atypical presentation of pulmonary MAC disease that fulfilled the criteria of "Lady Windermere's syndrome", which include: (1) middle or lingular lobes infiltrates; (2) no underlying lung disease or history of smoking; and (3) elderly women exclusively. The treatment rate of these patients was low, whether in the chest medicine or other sections, and the treatment outcome was poor. This result indicates that hospitals should pay much more attention to the education of doctors and patients regarding pulmonary MAC disease, in order to improve disease management and patient compliance. With a greater awareness of this disease, an earlier correct diagnosis can be achieved and proper therapy initiated. ***(Thorac Med 2006; 21: 133-140)***

Key words: *mycobacterium avium* complex

Introduction

Pulmonary *Mycobacterium avium* complex (MAC) disease is the most common non-tuberculous mycobacterial infection, and its incidence has been increasing. However, this disease is often ignored; pathogen is indistinguishable from traditional *M. tuberculosis* under microscopic examination, which increases the difficulty in diagnosis. In this report, we investigated the characteristics of pulmonary MAC disease in a hospital in Taiwan. The radiographic pictures of these patients were carefully reviewed, and the treatment rate in each section that the patients

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visited was analyzed and compared. We were also very interested in the treatment regimens used and the outcome.

Patients and Methods

Patients

The cases of 124 patients with a positive sputum culture for MAC were retrospectively reviewed between January 2001 and July 2003, at Taichung Veterans General Hospital. The symptoms, radiological changes, and sputum mycobacterium culture results of 17 patients (14 men, 3 women) fulfilled the criteria of pulmonary MAC disease that were proposed by the American Thoracic Society (ATS) in 1997 [1].

The following criteria apply to symptomatic patents with infiltrates, nodular or cavitary disease, or high resolution computed tomography scans showing multifocal bronchiectasis and/or multiple small nodules

A. If 3 sputum/bronchial wash results are available from the previous 12 months:

1. 3 positive cultures with negative AFB smear results or
2. 2 positive cultures and 1 positive AFB smear;

B. If only 1 bronchial wash is available:

1. a positive culture with a 2+, 3+, 4+ growth on solid media

C. If sputum/bronchial wash evaluations are non-diagnostic or another disease cannot be excluded:

1. transbronchial or lung biopsy yielding a MAC or
2. biopsy showing mycobacterial histopathologic features (granulomatous inflammation and/or AFB), and 1 or more sputum or bronchial washings that are positive for MAC, even in low numbers.

The 17 patients presented herein met the criteria symptomatically, and had typical chest radiographic changes and 3 positive sputum cultures for MAC.

Date analysis

We compared the differences in the chest radiography lesion locations between the male and female groups, and the differences in sputum conversion and chest radiography response between the treatment group and the non-treatment group. The chi-square method was used, and all analyses were performed with SPSS 10.0 for Windows software.

General data and co-morbidity

Age, sex, occupational exposure to dust, previous pulmonary diseases, and conditions that may have impaired immune defenses, e.g., diabetes mellitus, rheumatoid arthritis, lymphoma, leukemia, use of corticosteroids and/or immunosuppressive drugs, were recorded. In addition, chronic CNS disorders (old CVA, dementia, seizure, hypoxic encephalopathy), cardiovascular diseases (old MI, CAD s/p PTCA), and a post-gastrectomy history were all on the list of co-morbidities.

Radiography

The pre-treatment and subsequent radiographs and computed tomography were read by co-ordinating physicians, including 1 chest physician and 1 radiologist. The radiographic patterns were classified into 3 groups: fibrous/interstitial, cavitied, and nodular. The distributions of lesions were classified into the upper lung lobes, middle or lingular lobes, and diffused locations.

Treatment regimens, bacteriology and treatment results

The culture medium for Mycobacterium used in our hospital was the BACTEC MIGIT culture medium. We used the BD probeTEC system, following the manufacture's recommended procedures, to confirm the diagnosis of MAC infection. The treatment regimen data for each patient were collected from the medical records. Sputum conversion was defined as 3 consecutive negative sputum cultures within 6 months [2].

Results

Clinical demographic data

Of the 17 patients that fulfilled the diagnostic criteria, 14 (82.4%) were male, and 3 (17.6%) were female. Elderly patients (≥60 years-old) outnumbered younger patients, among both males and females. Ten (71%) males and 2 (67%) females were older than 60 years.

Of the total group, 14.2% of the males and 66.7% of the females were without underlying diseases (Table 1). The most common co-morbidity of the males was chronic lung disease, and the next most common was a past history of pulmonary tuberculosis. Only 1 woman had an underlying disease, which was a case of SLE with chronic steroid use.

Table 1. Age distribution and sex of patients with pulmonary MAC disease.

Age (years)	Male	Female	Total
30-39	1	1	2 (11.8%)
40-49	2	0	2 (11.8%)
50-59	1	0	1 (5.9%)
60-69	2	2	4 (23.5%)
70-79	6	0	6 (35.3%)
80-89	2	0	2 (11.8%)
Total	14 (82.4%)	3 (17.6%)	17

MAC, *Mycobacterium-avium complex*

Radiographic features

As for the radiographic evidence (Table 2), most male patients (50%) presented with fibrous interstitial patterns, and the remainder presented with cavitary (14.2%) and nodular (35.5%) patterns. Interestingly, the female patients showed pure (100%) nodular patterns. The most common distribution sites of lesions for the male patients were diffused locations (42.6%) and the upper lung fields (35.5%), and the least common sites were the middle or lingular lobes (21.3%).

The lesion location and distribution sites for the women, as revealed by chest radiography were all within the middle or lingular lobes (100%; p=0.01). The relationship between gender

Table 2. Co-morbidity of patients with pulmonary MAC disease.

Underlying disease	Male (n=14)	Female (n=3)
DM	1 (7.1%)	0 (0%)
Chronic lung disease	6 (42.6%)	0 (0%)
Malignancy	1 (7.1%)	0 (0%)
Chronic CNS disorder	2 (14.2%)	0 (0%)
Cardiac vascular disease	1 (7.1%)	0 (0%)
Immunocompromised or use of steroid	1 (7.1%)	1 (33.3%)
History of pulmonary TB with or without TX 6 months before admission	5 (35.5%)	0 (0%)
Post-gastrectomy	2 (14.2%)	0 (0%)
No underlying disease	2 (14.2%)	2 (66.6%)

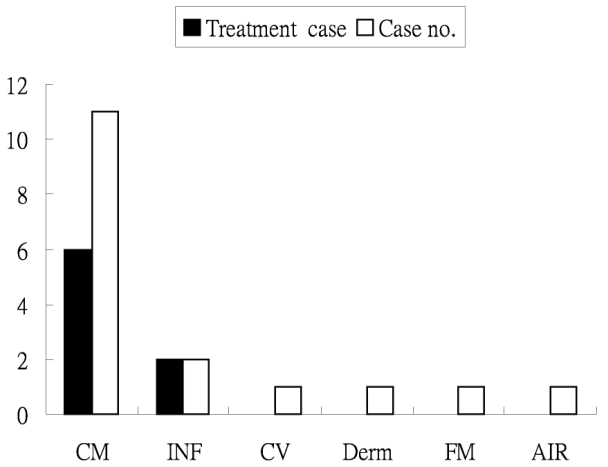

Fig. 1. The distribution of pulmonary MAC patients among the different sections and the treatment case number in each section.

and this disease will be discussed later in this report.

Treatment regimens and outcome

All the patients diagnosed with pulmonary MAC disease were classified according to the hospital sections that they visited (Figure 1). Eleven patients (65%) followed up at the chest medicine section, and 6 (54%) of them received treatment. Two patients (12%) visited the infection section initially, and all of them (100%) received anti-MAC therapy. There was only 1 patient each in the cardiovascular (6%), dermatology (6%), family medicine(6%), and rheumatology (6%) sections. None of the patients in these sections took anti-MAC medication. Eight patients (47%) received therapy (Table 3). The treatment regimen, as well as the treatment duration varied from patient to patient. One doctor (13%) treated the pulmonary MAC patients with traditional anti-tuberculosis regimens (INH, EMB, RIF, PZA) as soon as the initial sputum smear showed positive results for acid-fast stain, and continued the regimen even after the culture results revealed MAC infection. The other 7 doctors (87%) initiated therapy with traditional anti-mycobacterium medication plus klaricid or erythromycin. None of the 8 patients completed the whole course of therapy laid out in the ATS guidelines. Three of the the 8 patients (38%) showed bacteriologic conversion; the other 5 (62%) had persistent positive cultures for MAC.

As for the radiographic status, 2 patients (25%) showed a resolution of the lesion, 1 (12.5%) was in stable condition, and the other 5 (63%) revealed a progressive status in the radiographic pattern.

Nine patients (53%) received no treatment (Table 4). Of this group, only 1 patient (11%) showed bacteriologic conversion; the other 8 (89%) showed none. Radiologically, 1 patient (11%) showed improvement, 3 (3%) were in stable condition, and the other 5 (56%) showed progressive disease. There was no obvious difference in the bacteriological conversion (p= 0.081) and radiological response (p=0.132) between the treatment and no treatment groups.

Table 3. Radiographic findings of patients with pulmonary MAC disease.

		Male (n=14)	Female (n=3)
Pattern	Fibrous/interstitial	7 (50%)	0 (0%)
	Cavity	2 (14.2%)	0 (0%)
	Nodular	5 (35.5%)	3 (100%)
Distribution	Upper lung lobes	5 (35.5%)	0 (0%)
	Middle or lingular lobe	3 (21.3%)	3 (100%)
	Diffused	6 (42.6%)	0 (0%)

Table 4. Bacteriological results and radiographic status in 8 patients with several combinations of chemotherapy.

Patient	Regimens	TX duration	Results				
			Bacteriological conversion		Radiographic status		
			Yes	No	Improved	stable	Progression
1	RF+EM+Kla	1 year	V		V		
2	INH+EM++RF+Kla	4 months	V		V		
3	RF+EM+Ofl+Kla	10 months		V			V
4	RF+INH+PZA+EM	1 year	V			V	
5	RF+EM+Ery	1 month		V			V
6	RF+EM+PZA+Kla	4 month		V			V
7	Ofl+Kla	1 month		V			V
8	EM+Sin+Kla	1 month		V			V
Total: 8			3 (38%)	5 (62%)	2 (25%)	1(13%)	5(63%)

RF: Rifampin; EM: Embutamol; INH: Isonizid; Kla: Klaricid; Ofl: Ofloxacin; Sin: Sinflo

Discussion

Those patients that were diagnosed with pulmonary MAC disease in the hospital under study were predominately males. A review of the literature has revealed no definite evidence of sexual predominance for this disease, so this characteristic may be due to the fact that this hospital is a veterans' hospital. As for the distribution of age, most of the patients in the male and female groups were older than 60 years. In comparing the elderly male and female patients, it was interesting to find that almost all the male patients had underlying lung diseases, such as chronic obstructive lung disease, bronchiectasis, and pneumoconiosis, and a pulmonary tuberculosis history, while the elderly female patients did not . It seems reasonable that patients with chronic lung disease could suffer from poor sputum expectoration, to some extent, due to destroyed lung anatomy. This condition might lead to chronic inflammation and predispose the patients to MAC infection.

When reviewing the radiographic patterns of the patients, and classifying them according to the pattern and distribution of the lesions, most of the male patients showed a fibrous interstitial pattern with a diffused distribution. In contrast to the male patients, we found that the radiographic pattern and distribution of lesions in the female group were purely nodular; the involved fields were limited to the middle or lingular lobes. The symptoms of these elderly female patients fulfilled the criteria of "Lady Windermere's syndrome"[3].

The term "Lady Windermere's syndrome" was first used in 1992 to describe a symptom complex of elderly women without preexisting lung disease, who developed MAC pulmonary infection limited to the middle lobe or lingual [4-5]. The middle lobe and lingula have long, narrow, dependent bronchi and an absence of collateral ventilation that predisposes them to inflammation [6]. Since women are more likely to regard expectoration as socially unacceptable behavior, their voluntary cough suppression leads to an inability to clear secretions, which results in a chronic nidus for inflammation that favors subsequent infection by MAC. Two elderly female

pulmonary MAC patients in this study had the typical presentations of Lady Windermere's syndrome, and the chest CT scan proved the infiltrates in the middle or lingular lobe to be bronchiectasis. A greater awareness of the syndrome by clinicians should provide an earlier diagnosis and initiation of therapy.

As we classified all the patients according to the hospital they visited initially, it was surprising to find that only about 55% of patients in the chest medicine section had received therapy, and that none of the patients in sections other than the chest and infection sections received therapy. The reasons why most of the doctors in the chest medicine and other sections did not initiate therapy requires further investigation. The revelation of so many patients (53%) who did not receive correct treatment and who saw their disease eventually progress, reminded us how important it is to educate doctors regarding pulmonary MAC disease.

When we reviewed the treatment regimens and treatment duration, as shown in Table 3, we found there was great deviation in the choice of drugs and treatment duration from patient to patient. Historically, the medical treatment of MAC infectious disease in HIV-negative patients has been disappointing. Before the introduction of macrolides in the 1990s, multi-drug regimens, including isonized, rifampine, ethambutol, and streptomycin had been recommended. The long-term success rate was less than 50%, mainly due to treatment failure and relapse [7-9]. The newer macrolides, clarithromycin and azithromycin, have shown excellent in vitro and clinical results in recent studies. For the treatment of adults without HIV infection, the ATS recommends a regimen of clarithromycin or azithromycin, rifampin or rifabutin, and ethambutol, to be taken daily. This therapy must continue for at least 12 months after sputum conversion. Streptomycin should also be considered, especially for patients who have radiographically extensive or cavitary disease, and particularly when this is accompanied by strongly positive sputum smears [1]. However, it was surprising to find that none of the patients reviewed had undergone an adequate duration of treatment , as set forth by the ATS guidelines.

Thelower bacteriological conversion rate and high incidence of radiographic status progression in this hospital could be due to incorrect treatment and an inadequate treatment duration.

Table 5. Bacteriological results and radiographic status in 9 patients without treatment

Patient	Results				
	Bacteriological conversion		Radiographic status		
	Yes	No	Improved	stable	Progression
1		V			V
2		V		V	
3		V		V	
4		V			V
5		V			V
6	V		V		
7		V		V	
8		V			V
9		V			V
Total: 9	1 (11%)	8 (89%)	1 (11%)	3 (33%)	5 (56%)

There were 9 patients in the no-treatment group (Table 5). One patient was accidentally found to have shown sputum conversion and improvement in the chest lesions. This finding of sputum conversion could be due to a false negative result in the sputum microbiology or a laboratory error. And the initial chest film presentation could be the result of MAC infection with a bacterial co-infection. That the follow-up chest film showed improvement may be the result of a remission of the bacterial infection. However, the above are only hypotheses. If we had had a longer observation period for this patient, we might have found the answer.

In conclusion, most of the pulmonary MAC patients in this hospital were males. The elderly were predominant among both male and female patients. Most of the elderly male patients had underlying lung disease, while all the elderly female patients fulfilled the criteria of Lady Windermere's syndrome, with middle or lingular lobe involvement. The treatment rate was low, both in the chest medicine and other sections, and the treatment outcome was poor. A greater awareness of the diagnostic criteria and treatment of this disease may lead to a prompt diagnosis and better outcome.

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肺部鳥型分枝桿菌感染—台灣一醫學中心之病例分析

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我們以回朔的方式，回顧124位痰液培養為鳥型分枝桿菌的病人，發現其中有17位病人符合1997年美國胸腔醫學會診斷肺部鳥型分枝桿菌感染之條件。我們將這17位病患依照年齡及性別之分佈、本身原來之疾病、肺部X光之型態及分佈、病患看診之科別及各科治療率、治療之藥物及治療療程和結果來做分析。結果發現本院之病患大部份為男性，且大部份為老年有肺部或全身性之疾病之病人，而老年女性病患則無其它疾病且符合“Lady Windermere”症候群之診斷要件。在本院不管是胸腔科或其他科別對於此疾病之治療律都偏低且預後都不佳。所以，我們要注意來教育醫師及病患有關肺部鳥型分枝桿菌感染之知識，以增加此病之治癒率及病患之治療耐受性。及早查覺此疾病，就可及早得到正確之診斷和治療。*(胸腔醫學* ***2006; 21: 133-140)***

關鍵詞：肺部鳥型分枝桿菌疾病

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