

# *Mycobacterium avium* Pulmonary Disease with Non-Specific Chest Imaging Findings

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## Abstract

A 20-year-old female without immune-compromise was referred to our clinic complaining of cough with hemoptysis. Chest radiology showed multiple small lung nodules at the upper lobe of bilateral lung. After received regular anti-tuberculosis therapy and experiential anti-fungal therapy, the lesions in lung get worse. The biopsy was pursued and the diagnosis was made through lung tissue-based mycobacterial culture. It is difficult to differentiate *Mycobacterium avium* pulmonary disease with non-specific imaging findings from lung fungal infection and pulmonary tuberculosis.

**Keywords:** *Mycobacterium avium*; Non-tuberculous mycobacterial pulmonary disease; Herxheimer-like reaction; Non-immunocompromise; Lung biopsy

## Introduction

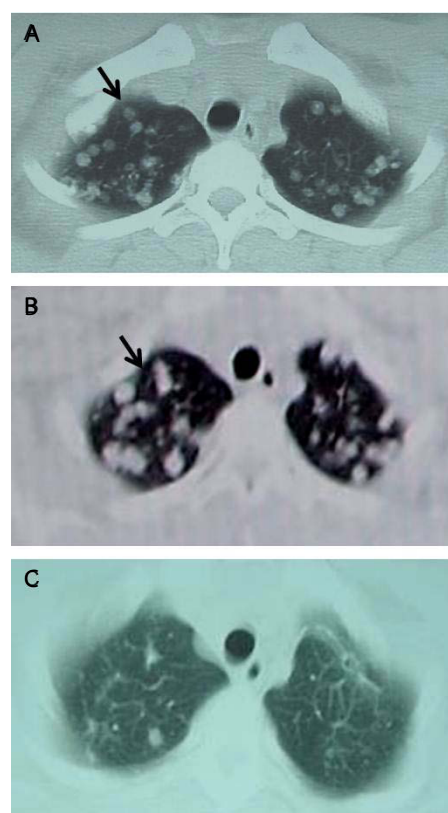
Although the epidemiology of pulmonary Tuberculosis (TB) is well described, the prevalence and epidemiology of Non-Tuberculous Mycobacterial (NTM) lung disease is largely unknown. The incidence of NTM is increasing in the non-HIV population [1-3]. The Official Statement of the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) on NTM [4] described that the minimum evaluation of a patient suspected of NTM lung disease should include the following: (1) chest radiograph or, in the absence of cavitation, chest High-Resolution Computed Tomography (HRCT) scan; (2) three or more sputum specimens for Acid-Fast Bacilli (AFB) analysis; and (3) exclusion of other disorders, such as TB. Confirmed diagnosis should include further specific characters such as clinical, radiologic, and microbiologic criteria. Here we report a case of pulmonary NTM disease proved by lung biopsy with non-specific imaging findings in a non-immunocompromised patient.

## Case Report

A 20-year-old female student was admitted to hospital for cough with hemoptysis one month. One month ago, the patient developed intermittent cough with no obvious incentive. The cough was paroxysmal intensified at day time and accompanied with hemoptysis. It was bright red blood and blood clots could be seen sometimes. It was approximately 200ml per day, without stomach contents, no fever, no chest and abdominal pain, no diarrhea, no chest tightness, no shortness of breath and no heart palpitations.

She was diagnosed with community acquired pneumonia but she was still bleeding after repeated antibiotics treatment. A chest CT scanning (Figure 1A) showed multiple small lung nodules in lung, mainly at the upper area of bilateral sides, with minor bronchiectasis in the middle lobe of right lung. The medical history showed that she had no any accompanied disease. No immunocompromised state existed. No superficial lymph node enlargement; no fever, coarse breath sounds in bilateral lungs, no wet and dry rales. Regular experimental tests were shown at Table 1. The diagnosis was supposed to be pulmonary tuberculosis. She began to receive experiential short-course chemotherapy strategy for tuberculosis, which includes regular dosages of isoniazid, rifampin, streptomycin and pyrazinamide. On the second day, the hemoptysis decreased and seldom occurred thereafter.

However, after about two months' therapy, she still had intermittent



**Figure 1:** A to C showed the changes of main lesions of the lung by chest CT scan. A, CT showed small nodules in the upper lobes of lung before treatment; B, nodules enlarged after anti-tuberculosis therapy; C, nodules were dissipation after anti-*M. avium* therapy.

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Item	Results
<b>Peripheral blood</b>	
Blood Routine	Normal
ESR	89 mm / h
Anti-tuberculosis IgG	POS
Cryptococcal latex agglutination test	NEG
Anti-HIV antibody	NEG
CD4+ T cell/CD8+ T cell	1.87
Galactomannan test	POS
Beta-D-glucan test	POS
<b>Sputum culture</b>	
Bacteria	NEG
Fungi	NEG
Tuberculosis	NEG
Sputum smear for acid fast stain	NEG
Tuberculin purified protein derivative skin test	10 × 10mm

POS, positive; NEG, negative

**Table 1:** Initial laboratory finding of the patient.

cough with occasional hemoptysis. She received the second chest CT scan and it showed that the nodules were not dissipated but increased, with a film-like plaques, nodules, irregular shape, uneven density within the boundary not very clear (Figure 1B). She received more tests for the diagnosis. Chest X-ray showed multiple small lung nodules in lung, with density uneven. For differential diagnose of fungal infection, blood fungal antigens were detected. The Galactomannan test (GM test) and beta-D-glucan (G test) were performed as manufactory suggested. The GM tests in blood were positive twice and G test in bronchoalveolar lavage fluid was positive also. Based on the results of antigen detections, the diagnosis of pulmonary fungal disease especially aspergillus can not exclude according to the guideline of ATS/IDSA [5]. She received experiential anti-aspergillus therapy due to probable diagnosis of pulmonary aspergillosis without stop the anti-tuberculosis drugs.

Two weeks later, she got a recurrence of hemoptysis. To identify the diagnosis, the patient received Video-Assisted Thoracoscopic Surgery (VATS) for lung biopsy. Her lung pathology showed pathological granulomatous lesions with non-specific central necrosis in HE stained slides (Figure 2A). The PAS staining and methenamine silver staining of biopsied tissue were negative. Pathologist found the acid-fast positive bacilli in the tissue using acid-fast stain (Figure 2B). But the lesions of patient still couldn't get better after the active anti-tuberculosis therapy. Finally what we suspected was proved by the tissue culture and identified by 16s RNA gene sequencing. The results showed it was *M. avium*. She received continuous anti-NTM treatment based on the drug susceptibility test. The duration was suggested to 18 months but she was followed up for only 9 months. Drugs include Rifapentine, Ethambutol, Azithromycin and Isoniazid. The lesions were dissipation finally (Figure 1C).

## Discussion

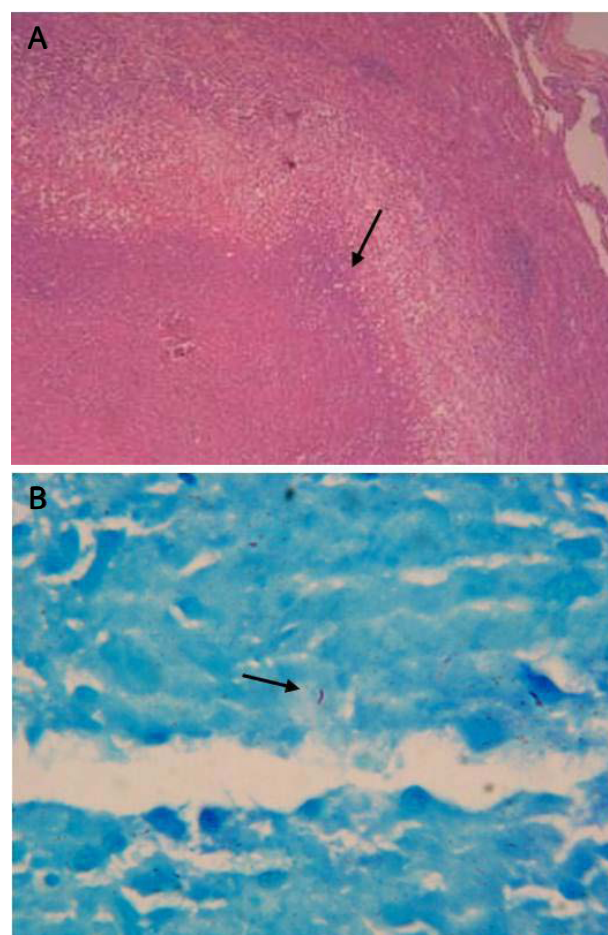
This case illustrates several difficulties in the diagnosis of pulmonary NTM. Recent report showed that *M. avium* pulmonary disease is not rare, particularly among females [2]. In most patients, we could not make a right diagnosis based on sputum smear and culture, because sputum smear and culture usually were negative. Several methods such as serological antibody detection and Polymerase Chain Reaction (PCR) etc. were developed to improve the diagnosis possibility [6-8]. But it is still remain unsatisfactory in the early diagnosis of NTM. When the diagnosis can not be determined and the patient's situation

begins to get worse, the lung biopsy is needed somehow. Early diagnosis is crucial for providing the patient right treatment and good prognosis.

Secondly, the positive result of acid-fast stain could not be regarded as mycobacterium tuberculosis infection only. Non-tuberculosis, *M. leprae* and *Nocardia* bacteria are also stain positive by acid-fast stain. As we know, granulomatous lung diseases are a special kind of proliferative lesions. The etiologies are various, in which mycobacterium, sarcoidosis and fungal infections are the common causes of them. If we combined pathological Hematoxylin-Eosin (H.E.) staining with specific staining such as acid-fast stain, PAS stain and methenamine silver staining, etc. for differentiating the diagnoses, the positive rates can be improved.

Meanwhile, it is important to send samples acquired from biopsy to bacterial culture and identify the type of bacterium. Sometimes it is difficult to identify the pathogen only by pathology and methods of special stains. In this case it is difficult to make the diagnosis of pulmonary NTM if we didn't get the result of bacterium culture and identification from her lung biopsy samples. NTM has a higher rate of drugs resistance. Results of bacteria-type identification and drug susceptibility are the guidance for treatment options. The effectiveness of anti-NTM treatment in patients with NTM was relatively slow [9].

Sometimes in the follow-up of the treatments of pulmonary



**Figure 2:** A, HE stain of lung biopsy sample showed the granulomatous lesions with non-specific central necrosis, H.E. stain, ×100; B, acid-fast staining with lung biopsy sample, ×400. Arrow showed acid-fast staining positive bacilli in the tissue.

mycobacterial diseases, the lesions become larger than before. This phenomenon can be observed in various kinds of mycobacterial infections, which named paradoxical expansion, or Herxheimer-like reaction, due to increase lesions after the anti-mycobacterial therapy. In this case, we can not decide that it was the paradoxical expansion or not, because the treatment was not exactly the right one at that time. But by upholding anti-*M. avium* treatment, the lesions absorbed finally.

Fungal antigens tests have prospects in the diagnosis of fungal infections. Several guidelines suggest a good sensitivity and specificity of G test and GM test for diagnosing pulmonary fungal infection [5,10]. However, factors such as albumin or globulin injection, hemodialysis, perioperative period, specimens contact with gauze, allogeneic bone marrow transplantation and the use of semi-synthetic penicillin, etc. would cause G test or GM test prone to false positive [11]. In this case, the patient was tested positive in both G test and GM test, probably resulted from previously piperacillin use, provided a possible diagnosis of invasive pulmonary aspergillosis with clinical microbiology evidence. But the PAS staining and methenamine silver staining of biopsied tissue were negative. She was pathologically proved that it was not aspergillus infection but *M. avium* infection. Kobashi et al. [12] had reported 9 cases of Chronic Necrotizing Pulmonary Aspergillosis (CNPA) as a complication of *M. avium* pulmonary disease. The two diseases need to be differentiated carefully.

In short, we have described a case of lung biopsy proved *M. avium* pulmonary disease without specific imaging findings in non-immunocompromised patient. NTM is not rare even in patients with normal immune states. If biopsy was pursued, tissue-based pathogen cultures are helpful to identify the pathogen, especially for the diagnosis of NTM with non-specific imaging findings.

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