CLINICAL VIGNETTE

Pulmonary Nontuberculous Mycobacterial Infection Could Be a Misdiagnosis: A Case Report

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Case Report

A 25-year-old female with no significant past medical history presented to Infectious Disease for hemoptysis after 3-month coughing. CT chest found a right upper lobe cavitary mass, 4.5 x 3.8 x 3.7 cm, with a thick wall and adjacent satellite airway distributed nodules. She was admitted for Tuberculosis evaluation and underwent bronchoscopy. Her quantiferon was negative. One of the bronchoalveolar lavage (BAL) sample cultures grew Mycobacterium phocaicum and there were no other pathogens identified. The biopsy showed benign bronchial mucosa and focal alveolar parenchyma, with negative specific stains for Acid-Fast Bacilli (AFB) and modified Gomori Methenamine-Silver Nitrate (GMS), and no evidence of malignancy. Given her symptoms, imaging findings and BAL culture, she was diagnosed with pulmonary nontuberculous mycobacteria (NTM) infection. She was started on Trimethoprim/sulfamethoxazole and Azithromycin based on the susceptibility of the M. phocaicum. In the first month of treatment, her hemoptysis resolved, though the productive cough persisted. After starting antibiotics, she also developed severe diffuse skin itching, without rash. She discontinued the treatment because she presumed that her pruritus was caused by the antibiotics. She was also lost to follow-up for several months due to personal reasons. After stopping antibiotics, her symptoms worsened, with sustained coughing, night sweats, weight loss and recurrent intermittent hemoptysis. Her skin itching did not improve.

She returned after 3 months. Labs were remarkable for significant leukocytosis and thrombocytosis, with white blood cell (WBC) 16.65 x 10^3/uL and platelet 603 x 10^3/uL. Repeated CT chest found new and increased nodular and mass-like consolidations, some with cavities. She resumed antibiotic treatment with Trimethoprim/sulfamethoxazole and Azithromycin, and started Amikacin inhalation after collecting three sputum samples for cultures. All these sputum cultures for bacteria, Nocardia, AFB and fungus showed no growth. Amikacin inhalation induced worsening hemoptysis, forcing discontinuation after several doses. Her symptoms did not improve significantly, WBC ranged between 9x10^3/uL to 16x10^3/uL. After 4 months, repeat CT scan showed interval increase in size and progression of multifocal consolidation, which were compatible with her history of atypical infection.

Given her progressing lung disease on antibiotic treatment, CT guided biopsy of the lung mass was performed. Pathology reported eosinophilic pneumonia with necrosis. The AFB and GMS tissue stains were negative. The cultures of the biopsy for bacteria, Nocardia, AFB and fungus all showed no growth. With the results of the second lung biopsy, we considered that pulmonary NTM infection was not the real cause of her lung disease and she started steroid treatment by pulmonology.

Despite oral steroids, her symptoms progressed and raised concern about the diagnosis of eosinophilic pneumonia. Repeat CT chest found increased size of the cavitary mass and additional new nodular lesions. She underwent open lung biopsy by wedge resection which revealed stage IVB Hodgkin lymphoma. Tissue cultures for bacteria, Nocardia, AFB and fungus showed no growth. She was referred to oncology and diagnosed with stage IVB Hodgkin lymphoma. She was treated with combination chemotherapy with doxorubicin, bleomycin, Vinblastine and Dacarbazine. Her symptoms improved and her WBC count normalized.

Discussion

NTM are the mycobacterial species other than those belonging to Mycobacterium leprae and Mycobacterium tuberculosis com-plex. They are widely distributed in the environment with high isolation rates worldwide, especially in soil and water, including both natural and treated water sources.[1] Most NTM species are non-pathogenic, but some can cause human disease. Mycobacterial avium complex (MAC), M. abscessus, M. kansasii, M. malmoense, and M. xenopi are reported as the most important species of human infection with increasing incidence worldwide.[2-9]

There are four different clinical syndromes caused by NTM, including pulmonary disease, superficial lymphadenitis, skin and soft tissue infection and disseminated disease. Over 90% of NTM infections present as lung disease.[1] Though the prevalence of NTM infection is higher among patients with cystic fibrosis (CF) and non-cystic fibrosis bronchiectasis, as well as chronic obstructive pulmonary disease (COPD), there are still many patients with no apparent risk factors.[10-11] The manifestations of pulmonary NTM infection are variable and not specific, including dry or productive cough, fatigue, dyspnea, chest discomfort, and occasional hemoptysis. The symptoms and signs are also influenced by the presence of pre-existing symptomatic lung disease. Presence of symptoms

along with microbiologic evidence and imaging findings are the diagnostic criteria for pulmonary NTM infection.[1]

MAC is the most common NTM pulmonary infection. Other than MAC, M. abscessus and M. kansasii are other major causes of pulmonary NTM infection. Other species of NTM infection in lung are rarely reported.

M. phocaicum is a rapidly growing mycobacterium which was first described in 2006.[12] It is very similar to M. mucogenicum, but can be distinguished by rpoB gene or HSP 65 gene sequence analysis. Since it was discovered, nine cases of catheter-related bacteremia have been reported.[13-15] Lung disease caused by M. phocaicum is very rare. Wethasinghe, et al. reported a case of hypersensitivity pneumonitis-like granulomatous lung disease associated with both M. phocaicum and MAC cultured from respiratory tract samples. Although the development of pneumonitis may have been caused by either or possible both organisms, M. phocaicum was believed to be causal because (1) it was isolated from sputum and pool water from the spa, (2) sputum smears had high numbers of mycobacteria, and BAL specimen cultures identified only M. phocaicum and no MAC.[16] Adekambi, et al also isolated M. phocaicum from respiratory secretions of a patient and considered that it was associated with the development of chronic pneumonia, but the clinical details were not formally reported.[12]

Diagnosing pulmonary NTM infection is still difficult, given the symptoms are non-specific and the differential diagnoses are usually very broad.[2] In the early 1980s, Emaneul Wolinsky, a pioneer in the field of NTM disease, proposed 5 criteria to distinguish clinically relevant NTM disease from presence of NTM without relevant clinical correlates, including (1) medium-to-heavy growth of NTM in culture, (2) repeated isolation, (3) positive specimens from sites with little or no contact with the environment, (4) a medium-to-high probability that the isolated NTM species causes disease, and (5) the presence of risk factors predisposing to NTM disease.[17] The American and British Thoracic Societies proposed 3 similar though simplified criteria to establish diagnosis of NTM disease: (1) compatible correlates in a radiograph or CT scan of the thorax, including bronchiectasis, infiltrates, multiple nodules, multifocal bronchial disease, and cavities, plus (2) compatible clinical symptoms and exclusion of other diseases with similar symptoms and radiological signs, including TB, plus (3) at least 2 positive sputum samples from 2 separate expectorated samplings or 1 positive culture from at least 1 bronchial wash or lavage (both of which are only relevant for patients with nodular bronchiectasis disease, who do not expectorate sputum) or isolation of mycobacteria from a sterile site, including lung tissue obtained by transbronchial or open lung biopsy.[1,18] These diagnostic criteria were developed with respect to the diseases caused by MAC, M. kansasii, or M. abscessus. Currently the evidence supporting diagnosis of NTM infection with the species other than these three is very limited. There is not enough known about most other NTM to be confident that these diagnostic criteria are universally applicable for all NTM respiratory pathogens.

Our patient had progressing cavitary lung disease, and initial evaluation which only identified M. phocaicum in a BAL culture without other etiology. This met the clinical and microbiologic criteria for the diagnosis of pulmonary NTM infection based on the evidence of her symptoms, cavitary opacities on chest radiograph, positive culture result of BAL sample, and no other diagnoses. However, the lack of risk factors for NTM infection, absence of NTB findings on tissue pathology, progressive lung disease despite appropriate antibiotic treatment, and absence of subsequent positive AFB cultures, the diagnosis of pulmonary NTM infection became very questionable. The open lung biopsy by wedge resection proved that pulmonary NTM infection was not responsible for her symptoms and established the correct diagnosis.

Because NTM exists in environment, they can contaminate the respiratory samples. When an uncommon NTM species is identified in a respiratory sample, it is very important to decide whether it is a true pathogen. Risk evaluation for NTM infection, researching published case reports of the identified NTM specie, repeating the cultures of the respiratory or biopsy samples combined with the tissue pathology findings may be helpful to reduce misdiagnoses.

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