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Mycobacterium Avium Complex Presenting as a Lung Mass, Broncho-pleural Fistula and Empyema in an Immunocompetent Patient-A Case Report and Review of Literature

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Authors' contributions

This work was carried out in collaboration among all authors. Authors SC and SKN did substantial contributions to conception and design, acquisition of data, drafting the article, performed analysis of the study and formulated the protocol. Author SC wrote the first draft of the manuscript. Author SKN revised it critically for important intellectual content and for final approval of the version to be published. Authors SC, SP and SKN equally managed the analyses of the study and equally contributed the literature searches. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Mycobacterium avium complex (MAC) is a non-tuberculous mycobacteria (NTM) that causes subacute or chronic nodular bronchiectasis, cavitary or fibro-cavitary pneumonia in patients with chronic structural lung pathology including emphysema, chronic bronchitis, and bronchiectasis. It is also known to cause pulmonary and extrapulmonary infections in patients with impaired cell mediated immunity such as transplant recipients, (Acquired Immune Deficiency Syndrome) AIDS where it can cause disseminated infections. Empyema from MAC has been reported in immunocompromised patients and is a rare phenomenon. Here we report a patient who presented with chronic left pleural effusion and a left lower lobe lung mass that went undiagnosed for 2 years, despite extensive work-up. Later in his course, he presented with a large effusion complicated by a

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bronchopleural fistula and was diagnosed as MAC empyema. To our knowledge, this is the first case of MAC empyema, that presented as a chronic lung mass, complicated by a bronchopleural fistula. In this article, we present the clinical, laboratory, and radiological features, with emphasis on a combined medical and surgical approach in the management of MAC empyema. We also provide a brief overview of cases of MAC associated pleurisy and empyema that have been reported in literature.

Keywords: Chronic pleural effusion; empyema; lung mass; Chronic Obstructive Pulmonary Disease (COPD); Mycobacterium Avium Complex (MAC); broncho-pleural fistula.

1. INTRODUCTION

Non-tuberculous mycobacteria are ubiquitous in the environment, frequently isolated from soil and water. Unlike Mycobacterium tuberculosis, infections are not transmitted from person to person, and are acquired from the environment. Pulmonary infection with NTM presents as a mild nodular bronchiectasis or a more severe cavitary pneumonia. Risk factors include underlying structural airway disease such as bronchiectasis, chronic obstructive pulmonary disease (COPD), or cystic fibrosis. In recent years, there has been a gradual increase in the incidence and prevalence of NTM pulmonary disease around the world [1-3]. The reasons for this increase is presumed to be multifactorial, and is attributed to alterations in the environment, host, and microbes [4-7].

Based on the in *vitro* growth rate of different species of NTM, they are classified as slow growers or rapid growers. The most common slow- growing NTM belong to the Mycobacterium avium complex (MAC) that consists of 12 different species. The most common group isolated from patients with pneumonia are *M. avium*, *M. intracellulare*, and *M. chimaera*. Other slow-growing NTM that cause pulmonary disease are *M. kansasii* and *M. xenopi* [8]. Rapidly growing NTM include *M. abscessus, M. chelonae* and *M. fortuitum* that cause lung abscess [9,10]. Unlike *M. tuberculosis*, NTM have not been associated with pleural involvement, bronchopleural fistula, or empyema.

In clinical practice, pathogens frequently isolated from patients with pulmonary empyema include Streptococcal species, *Staphylococcus aureus*, Enterobacteriaciae or anaerobes. Among mycobacteria, *M. tuberculosis* is likely to cause cavitary pneumonia, pleurisy, chronic pleural effusion, broncho-pleural fistula, and empyema. Unlike *M. tuberculosis*, pleural involvement with pleurisy pleural effusion, and empyema is rarely seen with pulmonary MAC infection [11]. Reports of pulmonary MAC presenting as a lung mass, pleural effusion or empyema are scarce in literature. Prior studies have reported that 3.5-6% patients with pulmonary MAC present with pleurisy and pleural effusion, with a mortality rate of 37-66% at 1 year [12-15].

To our knowledge, this is the first case of MAC empyema, that presented as a chronic lung mass, complicated by a bronchopleural fistula and empyema. In this article, we present the clinical, laboratory, radiological features, and management of MAC empyema in an elderly patient. We also provide a brief overview of cases of MAC associated pleurisy and empyema that have been reported in literature.

2. CASE REPORT

A 72 yr old caucasian male with past medical history of chronic obstructive pulmonary disease (COPD), atrial fibrillation, gastroesophageal reflux disease, arterio-venous malformation of ascending colon, abdominal aortic aneurysm, stable left lower lobe lung mass (noticed on imaging 2 years ago) was admitted with chief complaints of progressively worsening shortness of breath associated with left sided pleuritic chest pain and productive cough with yellowish sputum for 2-3 weeks. He also stated that he has had the lung mass for 2 years, has had a lung biopsy that was negative for cancer. He also had sputum tested for tuberculosis in the past and was reported negative. His only travel outside the country was to South Korea in 1960s. He denied any sick contacts or exposure to tuberculosis in the past. He has had TB skin test (purified protein derivative-PPD) test done twice over prior 3 years that was reported negative. He denied any fevers, chills, abdominal pain, loss of appetite, loss of weight, night sweats, exposure to birds or animals. He also denied being homeless or incarcerated that would place him under a high risk for pulmonary tuberculosis.

A chest X-ray done 3 months prior to this admission revealed a left lower lobe consolidation, with left upper lobe cavitary changes. A computerized tomographic scan (CT scan) of thorax at that time showed the left upper lobe cavity, a left lower lobe 6 cm mass lesion, and a small pleural effusion. He underwent extensive work up at that time including positron emission tomography scan (PET scan), a core biopsy of the lung mass by intervention radiologist, sputum cultures for acid fast bacilli, cytology and pathology all of which came back negative for infection and malignancy.

2.1 Imaging

This admission he had a chest X-ray that showed a significant increase in the left pleural effusion (Fig. 1). A CT scan of thorax was performed for better delineation of the left lower lobe, which revealed a complex loculated left pleural effusion, air in pleural space suggestive of a broncho-pleural fistula, significant mediastinal/para-aortic lymphadenopathy and a left lower lobe mass (Fig. 2).

2.2 Initial Management

He was evaluated by the medicine team and started on levofloxacin for possible community acquired bacterial pneumonia. Given a high index of suspicion for pulmonary tuberculosis, he was placed under air borne isolation and infectious disease team was consulted. With progressive shortness of breath, fever and peripheral leucocytosis, antimicrobial coverage was broadened with intravenous vancomycin and moxifloxacin to include coverage for methicillin resistant *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Hemophilus influenza, Legionella pneumophila* and other atypical pathogens.

2.3 Work up

Following tests were done: sputum for bacterial Gram stain and cultures, fungal stain and cultures, acid fast bacilli (AFB) stain and cultures, histoplasma urine antigen, and serum galactomannan antigen. A diagnostic and therapeutic thoracentesis was performed that showed turbid and purulent pleural fluid but all cultures were negative. Histoplasma urine antigen and pleural fluid galactomannan antigen test (for possible Aspergillosis) were negative.

2.4 Surgical Management

Thoracic surgery team was consulted and patient underwent video-assisted thoracoscopic surgery (VATS) with left thoracotomy, lysis of extensive adhesions in the left pleural space, disruption of multiple loculated pockets of gelatinous fluid and fibrin debris. This was followed by decortication of the lung around the pleural peel. The left lower lobe mass that was visualized on CT scan of thorax, adjacent to the diaphragm was found to be a phlegmon/inflammatory tissue.

Fig. 1. Left lower lobe consolidation/mass with pleural effusion

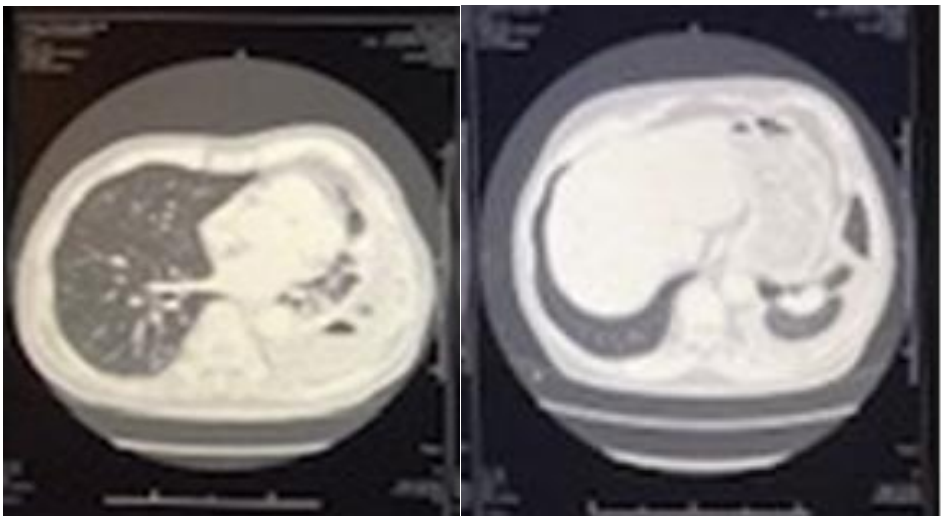

Fig. 2. Left lower lobe mass, bronchopleural fistula and loculated pleural effusion

Table 1. Clinical, laboratory and radiological features of case patient

Serum WBC	12.4
Hemoglobin	10.2
Platelets	358
Serum BUN	24
Creatinine	0.9
Liver function tests	Normal
Pleural fluid appearance	Turbid and purulent
WBC	17035 (76% PMNs, 19% M, 5% L)
RBC	5000
Pleural fluid Protein	4.1
Pleural fluid LDH	2362
Pleural fluid Glucose	1
Sputum and Pleural Fluid Microbiology	Bacterial, Fungal cultures negative MAC culture positive *M. tuberculosis* DNA probe negative
Pleural Fluid Antigen	Galactomannan, β- D glucan negative
Pleural Tissue Pathology	Fibrin, granulation tissue, fibrosis, inflamed fibroid tissue interspersed with granulomatous inflammation, and fibrinopurulent exudate. AFB, Fungal stains negative
Serum Galactomannan Antigen	Negative
Urine Histoplasma Antigen	Negative
Serum TB Quantiferon	Negative
Medical management	Azithromycin, Rifampin & Ethambutol for 12 months post negative sputum culture.
Surgical Management	VATS, drainage, decortication

2.5 Diagnosis

AFB stain performed on tissue was positive, *Mycobacterium tuberculosis* nucleic acid amplification test was negative, tissue and sputum cultures turned positive 2 weeks later for Mycobacterium avium intra-cellulare complex (MAC). Tissue sent for pathology showed Fibrin, granulation tissue, fibrosis, inflamed fibroid tissue interspersed with granulomatous inflammation, and fibrinopurulent exudate.

2.6 Medical Management

Patient was taken off airborne isolation, all antibiotics were discontinued, and patient was started on oral 3-drug therapy for MAC with

Table 2. Clinical, radiological and pulmonary function test changes pre and post MAC treatment

Changes	Pre- Treatment	Post-Treatment
Clinical features	Shortness of breath, productive cough with yellow sputum, left chest pain, Loss of weight from 200 pounds to 165.5 pounds in 3 months	Resolution of all symptoms. Weight gain from 165.5 to 194 pounds in 8 months
Pulmonary Function Tests	FEV1: 3.27 FVC: 4.75 DLCO: 60	3.2 4.49 53
CT Scan of Thorax	Left lower lobe mass, bronchopleural fistula, complex loculated left pleural effusion, emphysematous changes, fibronodular changes.	Resolution of left lower lobe mass, bronchopleural fistula. loculated effusion with band like atelectasis and scarring in LLL. Persistent emphysematous changes.

FEV: Forced Expiratory Volume
FVC: Forced Vital Capacity
DLCO: Diffusing Capacity for Carbon Monoxide

azithromycin 500 mg once daily, ethambutol 1.3 gm once daily, and rifampin 600 mg once daily. His baseline liver function tests were normal, he was advised to have visual acuity and color discrimination exams every 2 months and was discharged home in stable condition. He tolerated all his medications, was adherent, and was treated for a total of 12 months from the day of negative AFB sputum culture. At the end of anti- MAC therapy, he had clinically improved with resolution of shortness of breath, cough and sputum production. He had completely recovered at the time of follow-up clinic appointment, 3 months after completing therapy for pulmonary MAC. His pulmonary function tests were stable with no worsening. A CT scan of thorax was repeated that showed complete resolution of the left pleural effusion and the left lower lobe mass. Area of left upper lobe cavity had resolved and showed scarring, with a band of fibrosis and atelectasis.

3. DISCUSSION

Pulmonary infection with MAC causes subacute or chronic nodular bronchiectasis, cavitary or fibro-cavitary pneumonia in patients with chronic structural lung pathology including emphysema, chronic bronchitis, and bronchiectasis [2-4].

Although frequently seen in patients infected with *M. tuberculosis*, chronic pleural effusion, bronchopleural fistula, and empyema secondary to MAC is a rare phenomenon. Several cases of pneumothorax with pulmonary MAC infection have been reported in literature, likely related to ruptured bulla [13,14]. Disseminated MAC infection presents as an indolent infection with fever, loss of appetite, splenomegaly, pancytopenia due to bone marrow involvement, and has been reported in patients with acquired immune-deficiency syndrome (AIDS), not on antiretroviral therapy, and in other immunocompromised patients [15].

Literature review suggests that another rare, but unique risk factor for MAC empyema is the presence of autoantibodies to gamma interferon. It is a late-onset adult gamma interferon-deficiency disorder where patients are unable to mount a specific immune response to mycobacterial antigens. Patients present with either multifocal pneumonia with pleurisy/empyema or disseminated MAC and is associated with prolonged morbidity and relatively high mortality [16].

To date, very few cases of MAC empyema have been reported in literature. Most infections are chronic and indolent in nature where symptoms and signs progress gradually for months or years before a diagnosis is made, as in this case [17].

One of the largest collection of cases of NTM related pleurisy in literature, was recently published by Ando et al. It was a retrospective chart review that spanned a 10-year period.

Authors identified 1,044 cases with pulmonary NTM, the mean age of study patients was 69 years, NTM pleuritis occurred in 15 cases (1.4%), 6 cases (40.0%) were complicated by pneumothorax, subpleural cavities were radiologically detected in 11 cases (73.3%), and extrapulmonary air-fluid level was detected in 14 cases (93.3%). Eleven patients were treated with combinations of 2–4 antimycobacterial drugs, including clarithromycin, and 2 patients were treated with isoniazid, rifampicin, and ethambutol. A total of 11 patients had chest tube drainage and 6 patients underwent surgical intervention. Two patients treated with only antimycobacterial medications without surgical intervention. Two patients died from NTM pleuritis, and 1 patient died from pneumonitis during a mean of 1.8 years of follow-up [12].

Appropriate diagnosis is a crucial first step in evaluation. Given the long duration of treatment, ~6 to 12 months, based on clinical and radiological criteria, decision to treat pulmonary MAC needs to be done judiciously, in consultation with infectious disease and pulmonary teams. As MAC is known to colonize airways of patients with chronic structural lung diseases, it is important to understand that isolation of MAC from respiratory specimens, by itself, is not diagnostic for pulmonary MAC. According to guidelines published by the American Thoracic society (ATS) and Infectious Disease Society of America (IDSA), diagnosis of pulmonary MAC infection requires the presence of clinical, laboratory (culture) and radiological criteria. Patients who have evidence of colonization alone, need to be closely followed for any pulmonary symptoms or new radiographic abnormalities. Authors recommend that clinicians need to perform a careful assessment of the pathogenicity of the organism, risks and benefits of therapy, and detailed discussion with patients regarding their wish to adhere to long term therapy prior to initiating combination drug treatment. In some instances, if all criteria for treatment are not met, "watchful waiting" with close follow up for clinical or radiological deterioration may be the preferred course of action. [18].

Although the clinical, radiological features may resemble M. *tuberculosis*, pulmonary MAC rarely presents with pleural effusion, mass, bronchopleural fistula, or empyema. Interestingly our patient presented with all the above unique and rare features. The initial presentation was a mass 2 years prior to his diagnosis during which time malignancy was suspected, but lung biopsy showed benign lung with chronic inflammation. Subsequently patient developed left sided chronic pleural effusion, thoracentesis revealed an exudate but mycobacterial, fungal, and bacterial cultures were negative a year ago. Diagnosis was finally made when patient presented with an empyema and broncho-pleural fistula requiring both medical management and surgical intervention [19, 20].

The pathophysiology of pleural involvement in our patient is likely from disruption of the sub-pleural inflammatory left lower lobe mass into the left pleural space causing empyema and progressive worsening of symptoms and signs. As stated earlier the left lower lobe mass was inflammatory tissue that had significantly decreased in size at the time of thoracotomy and was not clearly visualized. The mass/ inflammatory tissue was likely bridging one of the terminal bronchioles and the pleura. Necrosis and spontaneous disruption of the inflammatory mass is likely to have resulted in the broncho-pleural fistula and empyema. Performance of video-assisted thoracoscopic surgery (VATS) with debridement, drainage, and decortication followed by triple drug combination treatment with azithromycin, ethambutol and rifampin resulted in a successful outcome in our patient [19,20].

4. CONCLUSION

This case emphasizes the fact that pulmonary MAC could masquerade as a lung mass, and have a chronic indolent presentation. Undiagnosed and untreated, it could linger on for years prior to presenting with complications such as pleural effusion, bronchopleural fistula, and empyema. Medical treatment alone for empyema and bronchopleural fistula has been associated with clinical failure and poor prognosis. Combined medical and surgical approach in a timely fashion is essential for a successful outcome [27-29]. A high index of clinical suspicion, appropriate testing for NTM and a timely medical and surgical interventions are keys to successful management that would result in improved morbidity and mortality in complicated cases.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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