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Case report

Characteristics of *Mycobacterium avium complex* (MAC) pulmonary disease in previously treated lung cancer patients☆

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ABSTRACT

Introduction: *Mycobacterium avium complex* (MAC) is responsible for a large portion of non-tuberculous mycobacterial (NTM) infections worldwide. Host factors such as active malignancy, immunosuppression, chronic obstructive pulmonary disease (COPD) and bronchiectasis increase the risk of MAC infection. However, the relationship between previously treated lung cancer with subsequent development of MAC pulmonary disease and treatment outcomes have not been previously studied.

Methods: We retrospectively identified all patients with lung cancer and MAC pulmonary disease documented in medical records at Mayo Clinic between January 2005 and October 2016. Patients who were diagnosed with MAC pulmonary disease before or at the time of lung cancer diagnosis were excluded. Patients meeting all inclusion criteria underwent chart review for prior oncologic treatments, clinical characteristics, and MAC treatment response.

Results: We identified 13 patients with MAC pulmonary disease and prior lung cancer, including 4 men and 9 women. Eight patients had structural lung disease that can predispose to MAC pulmonary disease, including bronchiectasis (23.0%) and COPD (46.2%). Four (30.8%) had no apparent immunosuppression or other risk factor(s) for MAC pulmonary disease. Primary pulmonary malignancies included pulmonary carcinoid, adenocarcinoma, and squamous cell carcinoma. Ten (76.9%) patients were started on antimicrobial treatment for MAC, and 8 (61.5%) patients completed MAC treatment with 6 (46.1%) patients achieving symptomatic improvement.

Conclusion: MAC pulmonary disease in previously treated lung cancer can occur without apparent risk factors for this NTM infection. Symptomatic improvement with MAC antimicrobial therapy appears to be lower than expected but comorbidities might influence outcomes in this patient population.

1. Introduction

Non-tuberculous mycobacterium (NTM) represents a diverse group of mycobacterium (e.g. Mycobacterium avium complex, Mycobacterium kansasii, Mycobacterium marinum, Mycobacterium abscessus complex, and many others) that are found in soil and water systems [1]. When inhaled into the airway, these microbes can colonize the bronchial mucosa and cause pulmonary infections in susceptible hosts. The prevalence of NTM pulmonary infections is increasing worldwide with Mycobacterium avium complex (MAC) constituting 80% of all NTM infections [2–5].

Distinguishing between airway colonization with mild infections and infections associated with progressive disease can be challenging. The symptoms of MAC infection are non-specific and include malaise, cough, weakness, dyspnea, and occasional hemoptysis [6]. Standard MAC treatment for non-cavitary MAC disease usually requires a prolonged course of triple antimicrobial therapy including a macrolide, ethambutol, and rifamycin. Despite therapy, treatment outcomes for MAC pulmonary disease can be suboptimal and organism eradication without relapse was achieved in only about 55% in one series [7], but in about 84% of patients in more recent study [8]. The treatment failure rates have been thought to be a result of the prolonged treatment requirements, medication side effects/intolerance, and re-infection in an already susceptible host.

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Host factors such as malignancy, including lung cancer, immunosuppression, as well as structural pulmonary disease such as chronic obstructive pulmonary disease (COPD) and bronchiectasis, increase the risk of MAC colonization and infection [2,9]. Up to 25% of patients with active lung cancer have MAC positive respiratory cultures [10], and up to 7% of patients with MAC positive cultures have underlying lung cancer [11,12]. However, the relationship between prior or treated lung cancer and subsequent development of MAC pulmonary disease has not been clearly delineated. We have observed several patients in our practice with MAC pulmonary disease and history of lung cancer in the absence of obvious host risk factors for this NTM infection. To further characterize the clinical features and treatment outcomes of this unique patient population, we conducted a retrospective case series evaluating all patients with a history of MAC pulmonary disease and prior diagnosis of lung cancer treated at Mayo Clinic Rochester between January 2005 and October 2016.

2. Methods

The study was reviewed and approved by the Mayo Clinic Institutional Review Board (IRB number 16-006845). We utilized an advance cohort explorer (ACE) system to retrospectively identify all patients with diagnosis of lung cancer and MAC pulmonary disease or suspected infection documented in a clinical note and/or in ICD9/ICD10 coding between January 1, 2005 and October 20, 2016. MAC pulmonary disease was defined utilizing the American Thoracic Society and Infectious Disease Society of America (ATS/IDSA) guidelines: Pulmonary symptoms including malaise, cough, weakness, dyspnea, with or without hemoptysis; nodular or cavitary opacities on chest radiograph; or multiple small nodules surrounded by multifocal bronchiectasis on high resolution computed tomography [6,13]. Microbiologic criteria for MAC pulmonary disease diagnosis included two positive sputum cultures, one positive bronchial wash or lavage, or a lung biopsy with the histological features of granulomatous inflammation with presence of positive acid fast bacilli (AFB). Patients not meeting these criteria or who had alternate explanations for their pulmonary symptoms based on chart review were excluded. Patients who were diagnosed with MAC pulmonary disease before or at the time of lung cancer diagnosis were also excluded. Patients diagnosed with prior small cell carcinoma, squamous cell carcinoma, adenocarcinoma, malignant carcinoid tumors, and metastatic lung cancer treated with chemotherapy, radiation, or surgery were included. Patients meeting all inclusion criteria underwent chart review for type of oncologic treatment, clinical outcome, and MAC treatment regimen. Additionally, chest imaging from initial lung cancer diagnosis was reviewed, when available, and tumors were classified as central if they were within 2 cm of the proximal bronchial tree or other mediastinal structures [14].

3. Results

We identified 31 patients with prior diagnosis of lung cancer and MAC pulmonary disease based on clinical documentation and/or ICD coding. Eighteen patients were excluded secondary to concurrent lung cancer and/or not meeting ATS/IDSA criteria for MAC pulmonary disease. The remaining 13 patients were comprised of 4 men (30.7%) and 9 (69.2%) women (Table 1). They ranged from 48 to 82 years of age. Prior lung cancer history included pulmonary carcinoid in 2 patients, pulmonary adenocarcinoma in 7 (53.8%) patients, squamous cell carcinoma in 2 (15.4%) patients, a remote history of small cell carcinoma and subsequent squamous cell carcinoma in 1 (7.6%) patient, and prior history of carcinoid and subsequent development of adenocarcinoma in 1 (7.6%) patient. No patients had a prior history of isolated small cell carcinoma. Of these 13 patients, 3 had image documented peripherally located lung cancers and 3 had centrally located lung cancers. The remaining 7 patients had the initial lung cancer imaging completed at an outside facility. The imaging studies were not available for our review. Treatment regimens for prior lung cancer included platinum based chemotherapy (38.5%), radiation therapy (38.5%), and surgical resection (76.9%). Seven (53.8%) patients were diagnosed with non-cavitary pulmonary disease, and six (46.2%) patients had cavitary pulmonary involvement (Table 1).

Table 1
Characteristics of patients diagnosed with *Mycobacterium avium complex* pulmonary disease following treatment for lung cancer.

	Subject, No. (%)
Demographics	
Male Sex	4 (30.8)
Age, years	
Mean	69.8
Range	48–82
MAC Pulmonary Involvement	
Non-cavitary	7 (53.8)
Cavitary	6 (46.2)
Underlying Pulmonary Disease	
COPD	6 (46.2)[a,b]
Bronchiectasis	3 (23.1)[a,c]
None	5 (38.5)[d]
Pulmonary Cancer Type	
Adenocarcinoma	8 (61.5)[e]
SCC	3 (23.1)
Carcinoid	3 (23.1)[e]
Cancer Treatment	
Systemic Chemotherapy	5 (38.5)
Targeted Radiation	5 (38.5)
Surgical Resection	10 (76.9)

Abbreviations: COPD=Chronic obstructive Pulmonary Disease, SCC = Squamous cell carcinoma, MAC = *Mycobacterium avium complex*.
[a] One patient had both COPD and bronchiectasis.
[b] One patient with COPD was also treated with etanercept prior to the diagnosis of MAC pulmonary disease.
[c] One patient with bronchiectasis was diagnosed with lymphoma soon after diagnosis of MAC pulmonary disease.
[d] One patient without underlying pulmonary disease was also treated with everolimus for metastatic renal cell carcinoma.
[e] One patient was diagnosed with both pulmonary adenocarcinoma and pulmonary carcinoid.

Ten (76.9%) patients were started on MAC treatment, and 8 (61.5%) patients completed MAC antimicrobials with 6 (46.1%) having symptomatic improvement with MAC treatment. One patient discontinued therapy after less than 1 week secondary to side effects, and one patient discontinued therapy after approximately 1 month secondary to a terminal diagnosis of metastatic renal cell carcinoma. Overall, 5 patients died during the study period. Within 1 year of diagnosis with MAC pulmonary disease, 2 (15.3%) patients died (one from metastatic renal cell carcinoma and one from an unknown cause). Of the remaining 3 patients who died during the study period, one died from squamous cell carcinoma of the lung 4 years after MAC treatment, one died from severe COPD/respiratory failure 5 years after MAC treatment, and one died in a motor vehicle accident 2 years after MAC treatment.

Among the host factors associated with MAC pulmonary disease, 8 out of 13 patients had structural lung disease that can predispose to MAC pulmonary disease, including bronchiectasis (23.0%) and COPD (46.2%) (Table 1). None of these 13 patients had a prior history of pulmonary tuberculosis, but two patients were likely immunosuppressed at the time of the initial MAC pulmonary diagnosis. One patient with bronchiectasis was diagnosed with lymphoma after the initial MAC infection diagnosis. Another patient with COPD also was treated with etanercept. Among the 5

(38.5%) patients who had no structural lung disease, one patient was treated with everolimus for metastatic renal cell carcinoma but the other four (30.8%) had no apparent immunosuppression or other risk factor(s) for MAC pulmonary disease. Of these 5 patients, 4 (80.0%) had a prior pulmonary adenocarcinoma and 1 (20.0%) had a prior pulmonary carcinoid. Four of these 5 patients had a surgical resection and 2 of them radiation therapy for their pulmonary malignancy. Three out of these 5 patients received chemotherapy several years prior to the diagnosis of MAC pulmonary disease (Table 2). Two (40.0%) of these patients symptomatically improved with MAC treatment. Of the remaining patients, 1 stopped MAC treatment early due to progressive metastatic renal cell carcinoma, and 2 others did not undergo MAC treatment secondary to concerns regarding treatment side effects.

4. Discussion

Most research regarding lung cancer and MAC infections focuses on concurrent diagnoses. This retrospective study was conducted because of observations of increasing number of MAC infections in patients who had previously been treated for lung cancer. The increased awareness of infection may be due to more specific diagnostics that have developed over the last 20 years allowing identification with greater ease than before [15]. Other contributing factors include increased use of CT scans, and recognizing MAC infections among women aged greater than or equal to 60 who have no underlying risk factors [16]. The risk factors of our study patients varied between having bronchiectasis, chronic obstructive pulmonary disease (COPD), immunosuppression and a combination of those factors, but no other apparent underlying risk factors for NTM was seen in 4 out of 13 (30.8%) of study patients. In fact, a large series from Taiwan also found a high prevalence of NTM disease in patients with cancer, including 50% of patients with lung cancer, and without apparent underlying lung disease [17]. The presence of underlying pulmonary diseases and/or immunosuppression in the majority of our study patients suggests that prior tissue damage to airway and/or lung parenchyma and defects in patient immunity may be a possible inciting factor for development of MAC pulmonary disease. Moreover, many patients with non-small cell lung cancer have peripherally located lesions. Pulmonary MAC disease also tends affects the small bronchi and bronchioles in peripheral lung distribution [10]. Thus, we could speculate that structural distortion of the distal airways associated with previously treated lung cancer could predispose these patients to MAC airway colonization and subsequent development of MAC disease.

Another interesting observation is that none of the patients identified in our study had a previous history of small cell lung cancer. This is likely secondary to the fact that treatment for small cell lung cancer is usually associated with higher mortality rate and lower survival than other types of lung cancer. In patients with limited small cell lung cancer, survivals range from 15 to 20 months, with a reported five-year survival rate of 10–13%. For patients who have extensive disease, survival is 8–13 months, with a five-year survival of 1–2% [18]. The smallest duration between the initial lung cancer diagnosis and MAC pulmonary disease diagnosis in our study was 3 years, surpassing the average survival for a patient with small cell lung cancer.

Our population did not share a common cancer treatment. Majority of the patients received various combinations of platinum based chemotherapy, radiation therapy, and surgical resection. Although patients receiving cancer treatments tend to be immunosuppressed, our study patients had completed treatment primary lung malignancies before the diagnosis of MAC infection was established with the exception of the three patient who were immunosuppressed for other conditions.

In a study performed by Lande et al., it was discovered that, although some positive MAC cultures were obtained before the diagnosis of lung cancer, most of their diagnoses were made simultaneously [10]. This was likely because many of the positive MAC cultures were obtained by bronchoscopy from the same location that biopsy-proven tumors were obtained. It is plausible that tumors in the lung create a microenvironment in some patients that allows for the establishment of infection. The ensuing

Table 2
Characteristics of patients with MAC pulmonary disease following lung cancer treatment.

Case	Gender	Age	Pulmonary risk factors for NTM	Cancer diagnosis	Cancer type	Cancer treatment	MAC diagnosis	Method of diagnosis	Date of death (mon/day/year)
1	F	48	None	2000	ADCA	Radiation therapy and Chemotherapy	2011	Bronchoscopy	Living
2	F	74	COPD	2001 2008	Carcinoid ADCA	Surgery	2009	Bronchoscopy	Living
3	F	74	COPD/ Bronchiectasis	2008	Squamous	Surgery	2011	+ Sputum Microbiology (×2)	Living
4	F	75	COPD[a]	2001	ADCA	Surgery and Radiation therapy	2005	BAL + Sputum Microbiology (×3)	Living
5	F	48	None[b]	2003	ADCA	Surgery, Radiation therapy and Chemotherapy	2012	BAL	12/7/2012
6	F	74	Bronchiectasis	2003 2014	Small cell Squamous	Radiation therapy and Chemotherapy	2011	BAL	05/31/2015
7	F	76	COPD	1977	ADCA	Surgery	2006	+ Sputum Microbiology (×2)	04/05/2011
8	F	75	COPD	1991	ADCA	Surgery	2012	+ Sputum Microbiology (×3) Lung tissue	Living
9	F	73	COPD	2006	Squamous	Radiation therapy and Chemotherapy	2009	Bronchial Washing	Living
10	M	82	None	2001	Carcinoid	Surgery	2007	Bronchoscopy	10/24/2009
11	M	82	None	2011	ADCA	Surgery	2014	Lung tissue	09/26/2015
12	M	78	None	2011	ADCA	Surgery and Chemotherapy	2015	BAL	Living
13	M	49	Bronchiectasis[c]	1997	Carcinoid	Surgery	2015	Outside + Microbiology	Living

Abbreviations: F = female; M = male; NTM=Non-tuberculous mycobacteria; MAC = *Mycobacterium avium complex*; ADCA = Adenocarcinoma; BAL= Bronchoalveolar lavage; COPD= Chronic obstructive pulmonary disease; N/A = Not available.

[a] Patient was also previously treated with etanercept.

[b] Patient was also treated with everolimus for metastatic renal cell carcinoma.

[c] Patient was also diagnosed with lymphoma soon after the initial diagnosis of MAC pulmonary disease.

inflammatory response initiated by immune system detection of tumor cells is accompanied by localized immune suppression driven by the tumor cells in an attempt to escape immune surveillance. This suppressed immune microenvironment not only promotes tumor progression, but may also provide a permissive environment for pulmonary NTM infections to thrive [10]. Patients found to have concurrent lung cancer at the time they were diagnosed with MAC infection were excluded from our study, but it is possible other unknown factors associated lung cancer patients that could have predispose to develop MAC pulmonary disease in some of our study patients. In a large series from a referral cancer center, men with lung cancer had a higher prevalence of MAC pulmonary disease (1.37%) than men without lung cancer (0.34%) (4.0-fold; $P < 0.001$), but this rate was similar to that in women, suggesting that some other non-apparent factors may also play a pathogenic role for these NTM infections to progress in this population [19].

A large clinical trial in the United Kingdom showed that, out of the 47 MAC pulmonary disease patients with mostly cavitary features (i.e. 70%) who received treatment with the recommended macrolide-based regimen, 23% were reported as “cured” after 5 years [20]. However, an overall high all-cause mortality was observed in this study subpopulation over 5 years (i.e. 48%). Among the patients in our cohort, 46.1% had symptomatic improvement with MAC treatment, which is below the rate of successful treatment response of 84% described in a recent study from a referral center in Texas [8]. Our patient population had a low percentage of improvement, which could be in part related to a high prevalence of cavitary lung disease (i.e. 46.2%), which is usually more difficult to treat, especially in patients with significant comorbidities such as emphysematous COPD and immunosuppression. Along these lines, this suboptimal treatment response finding may be also due to the small sample size of our study or other confounding variables in this complex patient population with prior malignancies.

The limitations of this study include the retrospective nature of collection and the small sample size of 13 patients. Our study had no comparison group and only included patients treated at the Mayo Clinic. Future studies looking at the association between peripherally treat lung cancers, the effect of new treatment modalities for lung cancer and development of MAC pulmonary diseases are warranted.

Competing interests

All authors have reviewed and contributed to this manuscript. No authors have any financial disclosures or competing interests.

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