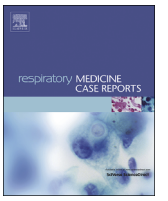
Respiratory Medicine Case Reports 40 (2022) 101751

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr



Case Report

Association between non-tuberculous mycobacterial infection and aerodigestive cancers: A case series highlighting different features, sequence and association

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A B S T R A C T

Non-tuberculous mycobacterial lung disease (NTM-LD) is increasingly recognized as an important cause of chronic respiratory infections. Diagnosing NTM infection in patients with a history of cancer can be delayed, or overlooked, due to potential overlapping symptomatology and similarities among radiographic features, including lung masses, cavities, and nodules. This retrospective case series aims to demonstrate the variable association of NTM-LD and aerodigestive cancers and how in some cases the diagnosis of NTM-LD can be delayed in patients with malignancy. Six patients with biopsy proven aerodigestive malignancy (either lung or head & neck cancer) and culture positive NTM infection were identified through a retrospective review of medical records between 1/1/2013 and 9/20/2020. Their demographic characteristics and clinical course are described to help elucidate both similarities and differences in presentation and diagnosis. Awareness of the association of NTM-LD and lung malignancy may help in early identification of these potential comorbidities and hence influence proactive diagnosis and management.

1. Background

Increased prevalence, morbidity and mortality associated with NTM infection has been recognized worldwide [1,2]. Moreover, lung cancer has emerged as a major comorbidity in these patients with 2–8.5% of patients with respiratory NTM also having lung cancer [3,4]. Clinically, both lung cancer and mycobacterial infection can present similarly with weight loss, cough, and hemoptysis as well as nonspecific constitutional symptoms. Despite the availability of contemporary diagnostic tools differentiating between these two medical conditions remains a challenge due to these similarities in presentation and some common, and shared radiographic features including lung masses and nodules. It is also important to recognize that malignancy and its treatment can lead to immunosuppression with resultant increased burden of co-existing infection. In addition, the architectural distortion due to the primary cancer, or its resection, may also increase vulnerability to NTM infection and colonization [5]. Computed tomography (CT) and positron emission tomography (PET) imaging findings cannot reliably differentiate between the two conditions [6] as both can present with a similar array of heterogenous features. Pathologically, previous case reports have even described the co-existence of NTM and carcinoma in the same lung mass [7]. In this limited case-series review, we analyzed the characteristics of six patients diagnosed with NTM-LD associated with aerodigestive malignancy (see Table 1).

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https://doi.org/10.1016/j.rmcr.2022.101751
Received 19 June 2022; Received in revised form 28 September 2022; Accepted 30 September 2022
Available online 7 October 2022

Table 1
Patient characteristics based on initial diagnosis.

1st diagnosis	Cancer	NTM
n	3	3
Age (median [IQR])	62.00 [61.00, 64.50]	74.00 [65.50, 79.00]
Sex = Male (%)	3 (100.0)	0 (0.0)
Race = White (%)	2 (66.7)	3 (100.0)
Smoking Hx (median [IQR])	30.00 [30.00, 55.00]	10.00 [8.75, 59.00]
Stage (%)		
II	1 (33.3)	0 (0.0)
IIB	0 (0.0)	1 (33.3)
III	2 (66.7)	0 (0.0)
IV	0 (0.0)	1 (33.3)
Unknown	0 (0.0)	1 (33.3)

2. Case presentations

2.1. Case 1

67-year-old African American man with a past medical history of poorly controlled diabetes mellitus type II, hypertension, and former tobacco use with 30-pack years of smoking who initially presented to the emergency department (ED) for facial redness and swelling and was subsequently admitted for facial cellulitis. He denied respiratory symptoms at the time, but a chest X-ray (CXR) obtained in the ED demonstrated a right upper lobe mass confirmed as an 8 cm mass on chest CT (Fig. 1a). Cytology from bronchial brushing was positive for squamous cell carcinoma. He was initiated on neoadjuvant carboplatin/paclitaxel chemotherapy and radiation. He subsequently underwent right upper and middle lobectomies, with resection of the parietal pleural and mediastinal lymph nodes, for a post-neoadjuvant stage II tumor. Following completion of cancer therapy, he developed a chronic, productive cough with intermittent hemoptysis. Three years later, chest CT showed areas of nodularity within the right upper lung zone as well as increasing nodularity and consolidative changes within the right lower lobe (Fig. 1b). Due to overall stability of his clinical state after nearly a year of chemotherapy and non-response to additional anti-PDL-1 antibody therapy, a biopsy of the new nodules was performed and revealed granulomatous inflammation with three sputum cultures positive for *mycobacterium avium intracellulare complex* (MAC). He was treated for MAC-lung disease (MAC-LD) as per guideline based standard therapy [8]. Sputum cultures three years since diagnosis remain positive despite treatment.

2.2. Case 2

62-year-old white man with a past medical history of chronic bronchitis, former tobacco use with 80 pack years of smoking, alcohol use, and incompletely treated pulmonary aspergillosis initially presented with throat pain and odynophagia. He was ultimately diagnosed with stage III moderately differentiated squamous cell carcinoma of the glottis based on a neck CT and subsequent panendoscopy with biopsy. Initial chest CT demonstrated multiple subcentimeter lung nodules with subsequent PET scan showing a new 3.2 × 3.1 cm confluent opacity with surrounding ground-glass attenuation at the posterior right lower lobe. He was treated with radiation and 6 weeks of weekly cisplatin therapy. Imaging surveillance was planned for the pulmonary lesions as there was concern for possible metastatic disease. A year later a new irregular, pleural based hypermetabolic right middle lobe nodule was discovered, but not biopsied due to resolution on imaging performed at the time of planned biopsy. Three years later CT acquired for persistent cough demonstrated a stable right upper lung opacity with areas of cavitation and bronchiectasis as well as areas of tree-in-bud nodularity (Fig. 2a). Two of three sputum samples resulted positive for *mycobacterium (m.) kansasii*. He was treated with guideline-based therapy including rifampin, ethambutol, and isoniazid daily with clearance of sputum cultures. Two years later a repeat CT scan demonstrated

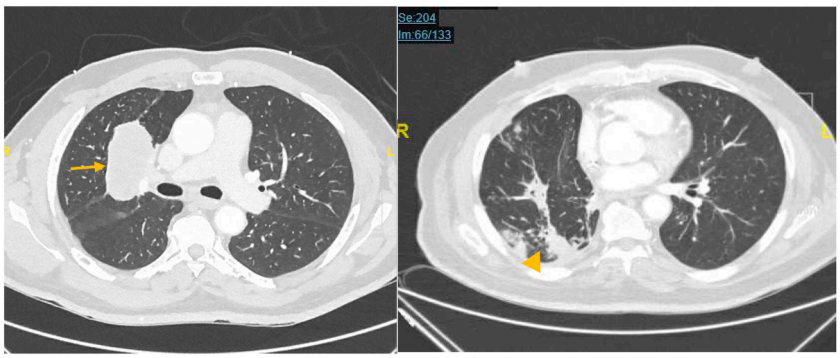

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Fig. 1. a demonstrates the initial 8 cm right upper lobe mass (yellow arrow). Fig. 1b (yellow arrowhead) demonstrates the repeat scan 3 years later with new consolidative changes in the right lower lobe leading to a diagnosis of MAC. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

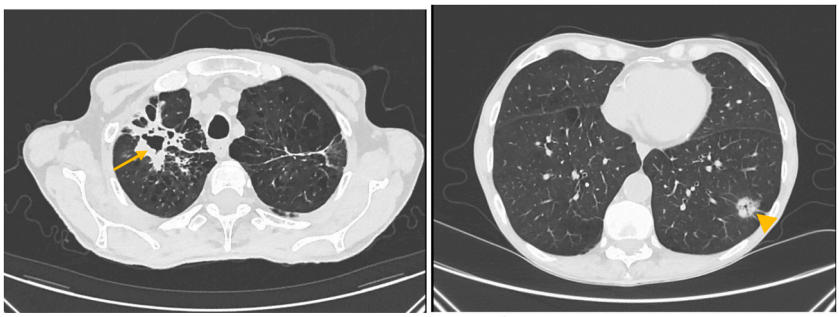

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Fig. 2. a demonstrates right upper lung opacity with areas of cavitation and bronchiectasis as well as areas of tree-in-bud nodularity (arrow). Fig. 2b demonstrates opacity in the lateral basilar segment of the left lower lobe (yellow arrowhead). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

increase in opacity in the lateral basilar segment of the left lower lobe (Fig. 2b). He had complained of a productive morning cough and weight loss, but no night sweats, hemoptysis, or fatigue. Biopsy was pursued and revealed adenocarcinoma of lung origin.

2.3. Case 3

60-year-old white man with a past medical history of COPD, current tobacco use with 30 pack years history of smoking and hypothyroidism who was diagnosed with T3N0M0 squamous cell laryngeal cancer of the right glottis, when he presented with dysphonia, dysphagia and wight loss of 5 pounds in 1 month. He was treated with cisplatin and radiation. Initial CT scan acquired for chronic cough demonstrated multiple predominately small nodular densities and a more focal opacity in the left lower lobe anteriorly (Fig. 3a). Repeat CT scan approximately a year later revealed a new pulmonary nodule (Fig. 3b). Surgical pathology revealed necrotizing granuloma and was positive for acid-fast bacilli. Sputum culture demonstrated MAC from broth only. Before treatment for MAC could be initiated the patient died of an undetermined cause.

2.4. Case 4

57-year-old white woman with a past medical history of hypertension, COPD treated with albuterol, tiotropium, and fluticasone, and former tobacco use with 108 pack years history of smoking presented with dyspnea on exertion, sputum productive of green phlegm and periodic hemoptysis. CT scan of the lung showed a thick-walled cavitary lesion in the right upper lobe (Fig. 4a) with surrounding nodularities and associated bronchiectasis. Two of three sputum cultures were positive for MAC. Despite guideline-based treatment for MAC-LD with azithromycin, rifampin, and ethambutol her sputum samples remained positive for 3 years with worsening shortness of breath, nonproductive cough, and chills without fevers. Repeat CT of the lung revealed collapse of the left lower lobe with associated cavitation (Fig. 4b) and bronchoscopic biopsy of the left upper lung demonstrated lung adenocarcinoma. The patient elected for hospice care for her adenocarcinoma due to poor functional status secondary to COPD.

2.5. Case 5

84-year-old white woman with a past medical history of hyperlipidemia, melanoma in situ and former tobacco use with 10 pack years history of smoking presented with a pleural based 1.4 cm nodule in the right upper lobe noted as an incidental finding (Fig. 5a). Additionally, bronchiectatic changes and ground glass attenuation were noted in the posterior basal segment of the left lower lobe (Fig. 5b). Three sputum cultures were positive for MAC. She denied any cough, shortness of breath or weight loss at that time. She declined treatment for MAC given her lack of symptoms and follow-up CT scan in 1 year was recommended. CT scan a year later demonstrated that the previously described pleural based right upper lobe nodule had increased in size (Fig. 5c). Biopsy of the mass revealed poorly differentiated squamous cell carcinoma.

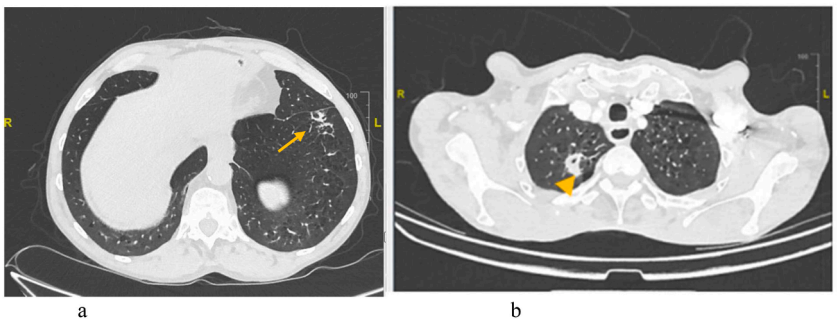

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Fig. 3. a demonstrates focal opacity in the left lower lobe anteriorly (yellow arrow). Fig. 3b demonstrates a new partially cavitary lesion in the right upper lobe (yellow arrowhead). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

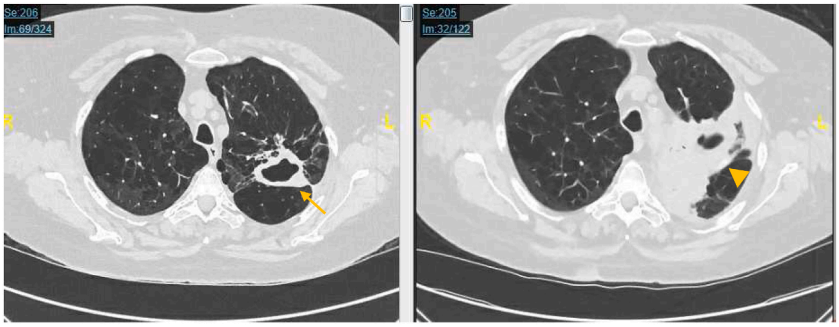


Fig. 4. a demonstrates extensive emphysematous changes throughout the bilateral lungs and a thick-walled cavitation of the left lung (yellow arrow). Fig. 4b is a CT scan obtained three years later demonstrating collapse of the left upper lobe with areas of necrosis (yellow arrowhead). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

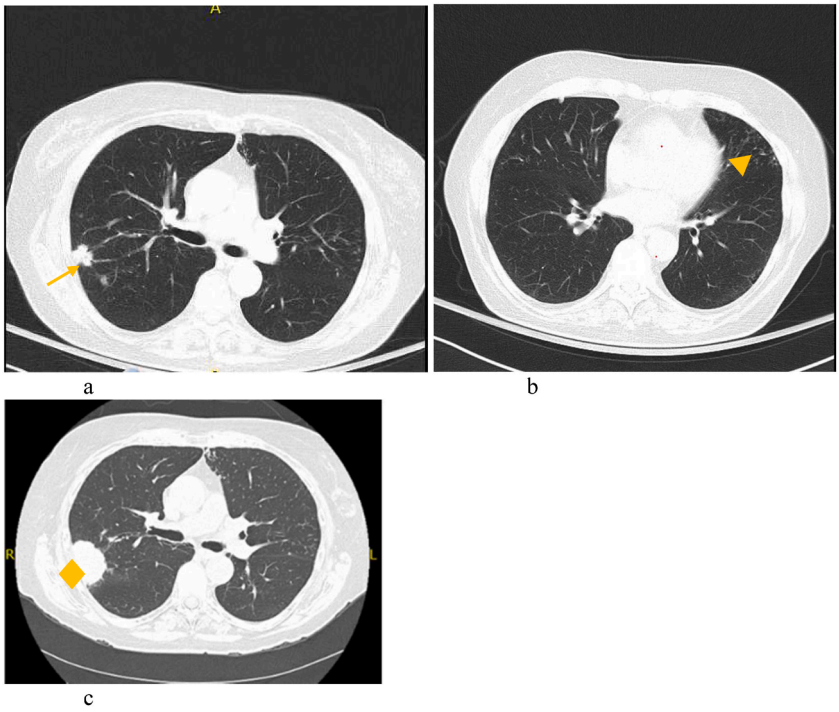


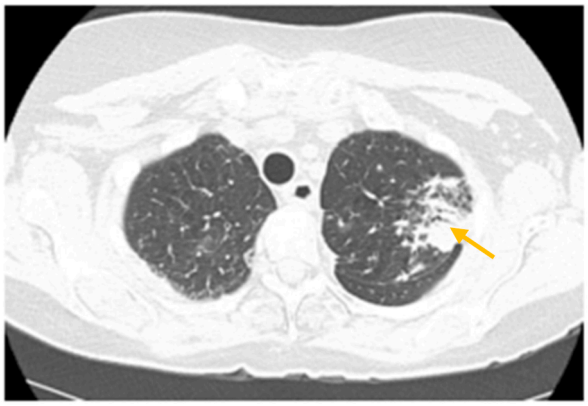
Fig. 5. a demonstrates a spiculated subpleural nodule in the right upper lobe (yellow arrow). Fig. 5b demonstrates ground glass attenuation in the posterior basal segment of the left lower lobe on the same CT scan (yellow arrowhead). Fig. 5c demonstrates increased pleural-based soft tissue density on a repeat CT scan 1 year later (yellow diamond). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2.6. Case 6

74-year-old white woman with a past medical history of atherosclerotic vascular disease, obstructive sleep apnea, hypothyroidism, former tobacco use with a 7.5 pack year history of smoking and family history of breast cancer in two aunts presented with a left upper lobe mass on chest CT scan. She had been previously followed for asymptomatic MAC-LD based on sputum cultures with a non-specific left apical lesion (images not available for review) for 4 years. Fine needle aspiration of the lesion failed to reveal any specific diagnosis. New sputum studies revealed *m. kansasii.* The patient responded well to her NTM treatment and was placed on surveillance. Her therapy was discontinued after three years as CT scans and symptoms remained stable. However, surveillance CT six years demonstrated a partially pleural based mass like consolidation with indistinct and irregular boarders in the left upper lobe with associated volume loss (Fig. 6a). Biopsy of the increasing left upper lobe mass revealed poorly differentiated adenocarcinoma.

3. Discussion

This case series presents three patients initially diagnosed with malignancy and three patients first diagnosed with NTM-LD. MAC was the most represented nontuberculous mycobacteria with 4 patients having at least two sputum cultures positive for MAC. One patient had sputum positive for *m. kansasii* and one patient had sputum initially positive for MAC and later for *m. kansasii,* both prior to



a

Fig. 6. a demonstrates a mass like consolidation with indistinct and irregular borders in the left upper lobe (yellow arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

being diagnosed with lung malignancy. Our study did not make the distinction between *m.avium* and *m.intracellulare* of MAC. The median age at diagnosis in the initial cancer group was 63 (IQR 61–64.50) compared to 72 (IQR 65.50 to 79.00) in the group that received the diagnosis of NTM first. The initial cancer diagnosis group was all males with a median smoking history of 30 pack years (IQR 30–55) while those with an initial diagnosis of NTM had a median smoking history of 10 pack years (IQR 8.75–59). All patients had at least two comorbidities, the most common of which were hypertension and COPD with one patient using inhaled corticosteroids. Only one patient had a documented family history of cancer (breast cancer in two aunts). One patient with an initial diagnosis of NTM-LD was African American and the rest of the patients were white. Squamous cell carcinoma was diagnosed in four patients, adenocarcinoma was diagnosed in one patient, and both adenocarcinoma and squamous cell carcinoma was diagnosed in one patient. Patients initially diagnosed with malignancy were younger, more often male and had fewer pack-years of smoking. Symptoms among the patients were diverse. Symptoms for both lung cancer and NTM included shortness of breath, weight loss and worsening cough. Masses, nodules and cavitary lesions were the most frequently encountered lesions on CT imaging while other imaging findings included bronchiectasis and ground glass opacities. Bronchiectasis and ground glass opacities favored the diagnosis of NTM, while masses and cavitary lesions were less specific for the initial diagnosis obtained.

NTM were once considered non-pathogenic but are now increasingly recognized as an important cause of chronic respiratory infections, with MAC and *m. absecuss complex* being the most common. Immunosuppression, both congenital and acquired, has emerged as an important risk factor for the development of NTM-LD. For example, inhaled and oral steroids are frequently prescribed for COPD, asthma as well as several autoimmune conditions. This phenomenon has increased the odds ratio for development of NTM-LD from 7.6 to 19.6 in one Danish study [9]. Lung structure abnormalities, as occurs with COPD and bronchiectasis, have also emerged as important risk factors in the development of NTM-LD [10]. Lung parenchyma abnormalities were an important characteristic observed in our limited cohort of patients.

It has been hypothesized that inflammation and scarring from NTM serves as a risk factor for development of lung cancer [3]. But just how lung cancer would lead to mycobacterial infection is less clear. Proposed mechanisms point to a suppressed immune tumor microenvironment [3]. The association of NTM-LD and lung malignancy is further strengthened by the observation that NTM-LD is often isolated from bronchoscopic culture samples from the same location as the malignancy and has even been documented in the same lung lesion pathologically [3,7]. The symptomatology and imaging findings of MAC and lung cancer can often overlap making it difficult to distinguish one from the other based on these characteristics alone, leading to delayed or missed diagnosis. It is possible that the association between lung cancer and NTM is underestimated as patients who undergo bronchoscopic biopsy for suspected cancer often do not have samples sent for mycobacterial testing. Thus, resulting in a lost opportunity to simultaneous diagnose both conditions and detect subclinical and low-grade infections [3].

4. Conclusion

NTM are increasingly recognized as pathogenic organisms in immunocompromised patients and those with structural lung disease. The association between mycobacterial lung disease and malignancy is well established, although the underlying factors leading to this association are unclear. Symptoms and imaging findings of malignancy and NTM can overlap and therefore an appropriate evaluation should include consideration for both diseases Patients can be diagnosed with either a malignancy or NTM at any point in the disease continuum, and therefore suspicion for either is important while a patient is undergoing post-treatment surveillance. In our six patient case series, common shared symptoms included cough, shortness of breath, hemoptysis, and weight loss. Radiographically, ground glass opacities and bronchiectasis were more often associated with NTM, whereas masses and cavitation could represent both NTM and lung cancer. The clinician should be aware of these shared associations throughout diagnosis and management of aerodigestive malignancies.

Declaration of competing interest

On behalf of all authors, there are no conflicts of interest to report for all authors. The study was not funded.

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