Case Report

Nontuberculous mycobacterial lung infections in patients with eating disorders: plausible mechanistic links in a case series

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Abstract: Nontuberculous mycobacteria (NTM) are widely distributed in the environment and are almost always acquired into the lungs by bioaerosol inhalation or aspiration of NTM-contaminated water, biofilms, and soil. NTM are increasingly recognized as causes of lung diseases in immunocompetent hosts, a not insignificant number of whom have a life-long or nearly life-long slender body habitus as well as thoracic cage abnormalities such as scoliosis and pectus excavatum. While several hypotheses have been offered to explain the purported increase in susceptibility to NTM lung disease in such individuals, the precise explanation remains unknown. We described three patients with eating disorders associated with severe malnutrition and either purging behaviors or other risks for aspiration who were diagnosed with NTM lung infections—the largest number of such patients to date in a single report. We discuss the clinical and experimental evidence that low body weight and chronic vomiting with attendant jeopardy for aspiration, as seen in patients with eating disorders, may represent risk factors for NTM lung disease. We also speculate the possibility of occult and undiagnosed eating disorders in some of the slender NTM lung disease patients with no known risk factors for the opportunistic infection other than their low body weight.

Keywords: Anorexia nervosa (AN); case series; nontuberculous mycobacterial lung infections; severe malnutrition; purging behaviors; leptin

Received: 22 May 2020; Accepted: 02 December 2020; Published: 25 January 2021.
doi: 10.21037/acr-20-101

View this article at: http://dx.doi.org/10.21037/acr-20-101

Introduction

Anorexia nervosa (AN) is a mental disorder characterized by severe restriction of food intake (AN-R) with or without binging and purging behaviors (AN-BP), resulting in dramatic weight loss, and a myriad of medical complications. Nontuberculous mycobacterial (NTM) lung infections in five women (ages 20–53 years old) with AN have been reported, with all as single case reports (1-6). Since NTM lung disease occurs much more commonly in elderly individuals, these cases in relatively younger individuals presented herein suggest that patients with very thin body habitus as seen in those with AN and other eating disorders are more vulnerable to NTM lung disease.

In the United States, NTM lung infection is caused primarily by *Mycobacterium avium* complex (MAC), *Mycobacterium abscessus* complex, and *Mycobacterium kansasii* (7). Lung disease due to NTM can be differentiated into two distinct forms although both may occur simultaneously in any person: the fibrocavitary form, most commonly occurring in older male smokers with emphysema, and the nodular bronchiectatic form, which appears most frequently in nonsmoking, thin, white, middle-aged to elderly women without a known history of underlying lung disease, but who invariably have bronchiectasis at the time NTM lung disease diagnosis is made (8).

We present three patients with AN-R or AN-BP associated with severe malnutrition, each of whom also
manifested NTM lung disease. To the best of our knowledge, this is the largest series of such cases to date. All three were evaluated at “ACUTE”, an inpatient medical stabilization unit dedicated to the acute care of those with extreme forms of eating disorders. We also speculate whether occult and perhaps mild eating disorders may be present in a number of NTM lung disease patients—who are mostly women—since many have a life-long or nearly life-long thin body habitus with no other apparent risk factors for NTM lung disease.

We present the following case in accordance with the AME Case Series reporting checklist (available at http://dx.doi.org/10.21037/acr-20-101).

Case presentation

Case report #1

A 54-year-old woman with a longstanding history of AN-BP was admitted to ACUTE at Denver Health Medical Center at 72% of her ideal body weight (IBW) with a body mass index (BMI) of 15 kg/m². She has a history of self-induced vomiting with progressive escalation the past several years, gastroparesis, mild esophageal dysmotility, dysphagia, and gastroesophageal reflux disease (GERD). While she had maintained her weight at approximately 75% of her IBW for a period of time, she developed more weight loss in the setting of new-onset respiratory symptoms found to be due to *Mycobacterium abscessus* lung disease. Antibiotics prescribed for the NTM lung disease were poorly tolerated, with side effects of nausea, vomiting and further weight loss. The patient was referred to our unit for weight restoration in anticipation of a planned right upper lobectomy. Outside hospital work up revealed an esophageal pH monitoring showing severe distal esophageal acid exposure; a swallow study demonstrating moderate pharyngeal dysphagia and aspiration; and an esophagram revealing mild esophageal dysmotility. A chest computed tomography (CT) demonstrated a right apical cavity, right upper lobe nodularity, and bronchiectasis (Figure 1). A bronchoscopy was performed, and the bronchial washings were positive for *M. abscessus*. Initial laboratory studies were normal other than mild lymphopenia.

The patient received nutritional rehabilitation, medical stabilization, and behavioral therapy as well as speech therapy for her dysphagia. Based on drug susceptibility testing of her *M. abscessus*, she received clofazimine, inhaled amikacin, and intravenous imipenem-cilastatin. She was initiated on more aggressive treatment for the GERD with omeprazole 40 mg BID and famotidine 40 mg BID as well as mechanical measures to prevent reflux.

The patient required supplemental enteral nutrition.
through a nasogastric tube due to her catabolic state and high caloric requirements for weight gain. Her nutrition plan at discharge was based on a 5,400-kcal/day diet to sustain her ongoing weight restoration. Upon discharge, she was at 85% of her IBW. She was transferred to a residential eating disorder center for further weight restoration before her planned partial lung resection, which was ultimately successfully performed when she was fully weight restored.

**Case report #2**

A 41-year-old woman with known MAC lung disease presented with a BMI of 11.1 kg/m$^2$ (53% of IBW) for weight restoration in preparation for a planned left pneumonectomy. Her past medical history was also significant for remote Hodgkin’s lymphoma stage 4B with pulmonary involvement, treated with chemotherapy, local radiotherapy, and autologous stem cell transplantation. At age 33, she was diagnosed with NTM lung disease and was begun on daily azithromycin, ethambutol, and rifampin with later addition of moxifloxacin and streptomycin. She underwent left lower lobectomy at age 34, and all antibiotics were stopped at age 35. Barrett’s esophagus was diagnosed at age 36. However, she was noted to have a recurrence of pulmonary MAC with cavitary disease at age 39 associated with worsening malnutrition (Figure 2). Therefore, azithromycin, ethambutol, and rifampin were resumed, although she was frequently non-adherent.

While she denied any eating disorder symptoms including a drive for weight loss, body dysmorphia, or purging behaviors, she experienced emesis with increased oral intake. Upon admission to ACUTE, she was treated for presumed gastroparesis secondary to her malnutrition, and she underwent percutaneous endoscopic gastrostomy placement to supplement her oral intake given the high caloric diet required for her weight restoration. While it was the opinion of her providers that the emesis had a volitional component consistent with AN-BP, she was ultimately diagnosed with avoidant restrictive food intake disorder (ARFID), an eating disorder characterized by highly selective eating habits, disturbed feeding patterns, or both resulting in significant nutrition and energy deficiencies similar to what is observed in AN patients. The patient was discharged at 83.1% of her IBW with a 5,700-kcal/day nutritional plan.

**Case report #3**

A 41-year-old man with a past medical history of severe protein-caloric malnutrition, generalized anxiety disorder, and obsessive-compulsive disorder, was admitted to ACUTE for severe protein-caloric malnutrition complicated by hypoglycemia, various electrolyte and liver function test abnormalities, anemia and mild leukopenia. On

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**Figure 2** Images of Case 2 showing severe NTM lung disease of the left lung 7 years after a left lower lobectomy. (A) Chest X-ray demonstrating volume loss of the left lung with shift of the mediastinum to the left, opacification of the bottom two-thirds of the left hemithorax, and a possible air-fluid level. There is also increased reticular-nodular opacities of the hyperinflated right lung. (B) Axial CT scan near the carina shows evidence of necrotic left lung with severe upper lobe cavitary formation (black arrow). The right lung shows bronchiectasis (white arrow), mosaic attenuation, and patchy areas of consolidation (arrowhead). CT, computed tomography; NTM, nontuberculous mycobacterial.
presentation, his BMI was 16 kg/m² (73% of his IBW); however, this was likely overestimated due to the presence of severe anasarca. He reported a 2-year history of weight loss that was not explained by any condition other than self-starvation. The patient ascribed his caloric restriction to his desire to stay healthy but also to symptoms of esophagitis and subjective dysphagia. Several weeks before admission, he developed progressive lower extremity edema unresponsive to increasing doses of furosemide. Three months before, the patient presented with odynophagia and oral leukoplakia and was diagnosed with oropharyngeal candidiasis and presumed *Candida* esophagitis for which he received a full course of fluconazole. Over the past several years, he had been noted to have pancytopenia occasionally requiring red blood cell transfusions. A bone marrow biopsy in January 2017 revealed a normocellular bone marrow with severe fat atrophy possibly related to severe malnutrition.

A chest X-ray obtained during his admission to ACUTE revealed multiple right upper lobe nodular lesions, some of which appeared cavitary. A chest CT scan confirmed thick-walled cavitary lesions in the right upper lobe as well as bronchiectasis and severe panacinar emphysema (Figure 3). Acid-fast bacillus (AFB) staining of the sputum was positive, and cultures were positive for MAC. Since he had no history of purging, aspiration as a cause of bronchiectasis was not suspected. The white blood cell count, IgG levels, alpha-1 antitrypsin level and phenotype, rheumatoid factor, cyclic citrullinated peptide, Sjogren’s antibodies (anti-SS-A/anti-SS-B), *Aspergillus* antibodies, sweat chloride, urine histoplasma antigen, and serum *Coccidioides* antibody tests were all negative or within normal limits. An echocardiogram revealed a normal left ventricular systolic function, mild tricuspid regurgitation, normal pulmonary artery systolic pressures, and a small pericardial effusion. The cause of the patient’s anasarca was ultimately attributed to hypoalbuminemia and severe malnutrition. The patient’s MAC infection was initially treated with azithromycin, ethambutol, and rifampin. A repeat chest CT before

**Figure 3** Images of Case 3 showing unilateral nodular and cavitary densities. (A) Chest X-ray demonstrating nodular densities in the right upper lung field and a single, linear plate-like atelectasis in the left upper lung field. (B) Coronal CT scan showing complex cavitary lesions (arrow) with surrounding bronchiectasis in the right upper lobe. (C) Axial CT at the level of the aortic arch reveals an irregularly shaped density in the anterior segment of the right upper lobe suggestive of a mucous plug (arrow). There are smaller nodules in the peripheral right lower lobe. CT, computed tomography.
discharge revealed that the cavitary nodules in the right upper lobe and superior segment of the right lower lobe had almost entirely resolved.

He was ultimately diagnosed with AN-R and received supportive psychotherapy, psychiatric consultation, and nutritional rehabilitation. He was able to reach 85% of his IBW by the time he was discharged from the hospital.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients.

Discussion

These three relatively young patients with caloric-restrictive eating disorders demonstrate that low body weight is a plausible risk factor for NTM lung disease since, except for the cystic fibrosis population, lung diseases attributed to these environmental organisms typically occur in older individuals. Nodular bronchiectasis due to NTM infection was first described predominately in older women without a preexisting illness (9).

Pre-existing bronchiectasis and emphysema are the most prevalent predisposing conditions for NTM lung disease. Bronchiectasis may be due to prior suboptimal treated infections such as tuberculosis but may also be seen in the setting of cystic fibrosis, alpha-1-antitrypsin deficiency, primary ciliary dyskinesia, and connective tissue disorders like Sjogren's syndrome. Furthermore, occult or symptomatic GERD—shown to be increased in patients with NTM lung disease—may exacerbate bronchiectasis as well as provide a mechanism by which NTM inoculate the lungs (Figure 4) (10-13). Interestingly, all our patients had various gastrointestinal disorders including dysphagia, GERD, emesis (volitional or non-volitional), and/or gastroparesis.

It has been observed that not an insignificant number of patients with NTM lung disease without known underlying host risk factors possess Marfanoid features such as life-long slender body habitus and thoracic cage abnormalities such as pectus excavatum and scoliosis (14-20). This observation has been substantiated by the documentation of reduced baseline BMI or body fat in pulmonary NTM patients (14,21-23). Two of the three patients with NTM lung disease in this case series are middle-aged white women with AN-R or AN-BP, and BMI between 10 and 16 kg/m².

One mechanism by which slender individuals with low body fat content may be predisposed to NTM infections is their relative deficiency of leptin, an adipokine produced by fat cells whose canonical function is that of a satiety hormone (24). However, leptin has a number of immunomodulatory functions that can enhance host-immunity against NTM, including the differentiation of uncommitted T0 cells toward

Figure 4 Diagram of the possible mechanisms by which individuals with anorexia nervosa may be predisposed to NTM lung disease. Please see text for discussion. NTM, nontuberculous mycobacteria; FSH, follicle stimulating hormone; LH, luteinizing hormone; IL, interleukin; TNF, tumor necrosis factor; NF-κB, nuclear factor-kappa B.
the T_h1 interferon-gamma (IFN-γ)-producing phenotype (Figure 4) (19). Indeed, leptin-deficient mice are more susceptible to experimental \textit{M. abscessus} lung infection (25). In addition, pulmonary NTM patients have been found to have reduced serum leptin levels (26) or a loss in the normal direct relationship between percent body fat and serum leptin concentration (27).

Very thin individuals with secondary leptin deficiency are prone to develop hypothalamic amenorrhea. The reason is that normally leptin induces the expression of follicle stimulating hormone (FSH) and luteinizing hormone (LH). Could disruption of this FSH/LH-estrogen axis due to leptin deficiency also help explain why such thin individuals are predisposed to NTM infections? Indeed, the nodular bronchiectasis form of NTM lung disease are disproportionately more common in post-menopausal women, accounting for 65–85% of the cases (11,28-31), suggesting that estrogen in women (and possibly androgen in men) may play a host-protective role. This notion is supported by reports of MAC infections in those with untreated panhypopituitarism (32).

Experimentally, binding of estrogen to estrogen receptors on macrophages has been shown to augment both phagocytic function and Fcγ receptor expression (33). Furthermore, estrogen is known to activate endothelial nitric oxide synthase (eNOS) (34), an enzyme that is also present on airway epithelial cells and that catalyzes the production of nitric oxide (NO), a free radical known to have anti-mycobacterial properties. While still early in its development as an anti-mycobacterial agent, inhalation of exogenous NO holds some promise as adjunctive treatment for NTM lung disease (35-37). This “estrogen-deficient hypothesis” of NTM susceptibility is corroborated by an in vivo study showing that oophorectomized mice were more susceptible to pulmonary MAC than mice with intact ovaries; furthermore, reconstitution with exogenous estrogen increased NO production and restored the ability of the oophorectomized mice to control the infection better, similar to that seen in the control mice (38).

Another plausible mechanism by which estrogen protects against NTM is the ability of estradiol to inhibit activation of nuclear factor-kappa B (NF-κB) in macrophages (34), and we have shown that NF-κB inhibition augments autophagy in macrophages, a known killing mechanism against mycobacteria (Figure 4) (39).

Thus, we believe that our three subjects with eating disorders have at least two clinical conditions that left them vulnerable to NTM lung disease: gastroesophageal disorders ± volitional or non-volitional emesis and very thin body habitus. The gastroesophageal emesis and very thin body habitus likely impaired their immunity against the opportunistic environmental organisms with relative low virulence through reduction in leptin and possibly other mechanisms such as secondary estrogen deficiency. All three patients presented with nodular bronchiectasis with cavitary disease, the latter a sign of more severe NTM lung disease. Further prospective investigation is needed to determine whether there exists any causation effect between the purging behaviors of eating disorders and NTM lung infections, and whether reversing the complications of eating disorders improves or prevents the NTM lung infections.

Conclusions

The recognition of factors potentially associated with the increased susceptibility to developing NTM lung infections in patients with eating disorders is important to ensure earlier diagnosis and more rapid intervention to prevent disease progression and to exhort treatment of a covert or overt eating disorder. The well-described unique body habitus in some patients with NTM lung disease may indeed be a surrogate for an occult and underlying eating disorder. Whether the thin body habitus in patients with NTM lung disease is contributed by an underlying eating disorder or not, it remains to be determined whether effective nutritional repletion can positively affect the outcome of NTM lung disease and/or reduce the high rate of recurrence.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the AME Case Series reporting checklist. Available at http://dx.doi.org/10.21037/acr-20-101

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/acr-20-101). The authors have no conflicts of interest to declare.
**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Ethic Approval and Consent to Participate: GM/Cayuse# 19-0165, COMIRB# 19-0455. P.I. Daniela E. Grayeb, MD, P.I. institution DHHA. Written informed consent was obtained from the patients.

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