Non-tuberculous mycobacterial lung disease due to multiple "minor" risk factors: an illustrative case and a review of these "lesser elements"

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Introduction

Non-tuberculous mycobacterial (NTM) lung disease typically occurs in those with structural lung diseases such as pre-existing bronchiectasis and chronic obstructive pulmonary disease (COPD, typically emphysema). Prototypical causes of bronchiectasis include cystic fibrosis (CF), alpha-1-antitrypsin (AAT) deficiency, primary ciliary dyskinesia (PCD), Sjogren's syndrome, and sequela of prior tuberculosis or other bacterial pneumonia, as well as several other uncommon disorders. However, it is well acknowledged that NTM can also cause lung disease in otherwise healthy subjects. We encountered an individual with mild but *bona fide* NTM lung disease who appeared to have multiple "minor" risk factors for it. Since these factors are often not discussed in the context of NTM, we have taken this opportunity to review their role in the acquisition of NTM lung disease.

Illustrative case

A 66-year-old woman is referred for evaluation and management of *Mycobacterium avium* complex (MAC) lung infection, manifested by a chronic cough and blood-streaked sputa, the latter occurring 2 months prior to the referral. Eight years before, at age 58 years, a chest CT scan to evaluate a mild chronic productive cough—present for 3 months—revealed mild bronchiectasis and peripheral nodularity in the left upper lobe, but no interventions were made.

Pertinent medical and surgical history include hypothyroidism and uterine sarcoma, the latter treated with a total hysterectomy and bilateral salpingo-oophorectomy and adjunctive cis-platinum and ifosfamide 14 years ago. Gastroesophageal reflux (GER) was also present for many years with the patient preferring to sleep on her left side with no head-of-bed elevation. Family history is notable for father with lung cancer and a maternal grandfather with pulmonary tuberculosis. She is a never smoker and drinks half a glass of wine a day. She has a horse that she visits on a farm with consequent exposures to soil and dust. Medications included levothyroxine, dexlansoprazole, zolpidem, celecoxib, and various over-the-counter vitamins, minerals, and supplements.

On examination, the temperature is 36.9 ℃, heart rate 82 per minute, blood pressure 123/62 mmHg, respiratory rate 18 per minute, SpO_2 98% on room air, and body mass index (BMI) of 19 kg/m^2. Physical examination is unremarkable with normal breath sounds.

The complete blood count, electrolytes, renal and hepatic functions, immunoglobulin levels, IgG subclass levels, and antibody responses to diphtheria, tetanus and pneumococcus are within normal limits. The blood T and B cell subsets, natural killer cell function, and interferon gamma (IFNγ) level are also normal. The *cystic fibrosis conductance regulator* (*CFTR*) genotype is heterozygous for delta F508. The AAT protease inhibitor (Pi) phenotype is PiMS and the level is 106 mg/dL (normal range, 72 to
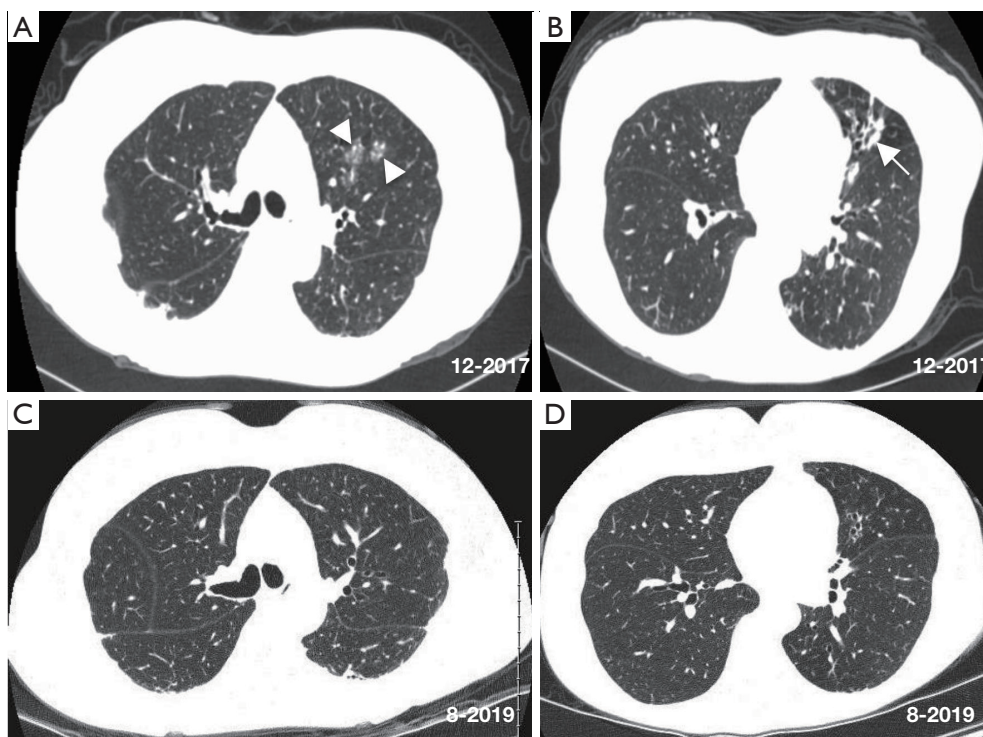
Figure 1 Axial chest CT scan images at the time of referral show relatively mild centrilobular nodules/ground glass opacities (arrowheads) and bronchiectasis (arrow) affecting the left lung more than the right lung (A,B). Chest CT scan nearly 2 years later (C,D) show modest radiographic improvement with resolution of the left upper lobe ground glass opacity, decrease in subpleural densities, and minimal to modest improvement of the lingula following antibiotic treatment for NTM, use of airway clearance measures, implementation of head-of-bed elevation and other anti-reflux measures, and reduction of soil aerosol exposures. CT, computed tomography; NTM, Non-tuberculous mycobacterial.

192 mg/dL). Six sputum cultures within the past 2 months were all positive for *M. avium*, sensitive to clarithromycin, rifampin, rifampin-ethambutol combination, rifabutin, and clofazimine; the minimal inhibitory concentration to amikacin was 8 to 32 µg/mL.

A CT scan 2 months before referral and compared to a CT scan 8 years prior revealed increased nodular ground glass opacities and development of bronchiectasis in the left upper lobe, progression of bronchiectasis in the lingula with associated mucus plugging and scarring, bilateral subpleural densities, and nodules in the posterior left lower lobe (*Figure 1A,B*). Spirometry, lung volumes, and diffusion capacity for carbon monoxide are within normal limits. A tailored barium swallow revealed decreased and delayed hyolaryngeal elevation with delayed epiglottic inversion, and moderately deep, non-transient laryngeal penetration of thin barium. The esophagram is unremarkable.

She was eventually begun on daily azithromycin,

rifampin and ethambutol as well as airway clearance and anti-reflux measures that included dietary precautions and head-of-bed elevation using an adjustable bed. After 1 month of treatment, her sputum converted to negative. She was treated for 12 consecutive months with the triple antibiotics with subsequent improvement in chest CT abnormalities (*Figure 1C,D*).

Discussion

NTM are ubiquitous in the environment—in soil, water, and biofilms—and thus most individuals are likely exposed to NTM by inhalation, ingestion, and/or aspiration. A study from Germany found that the most abundant NTM in soil and dust was *M. avium*—the same species found in our patient—present in 33% of dust samples and 22% of soil samples but interestingly, no *M. avium* was isolated from water sources or biofilms (1). However, because

there are regional variations in the NTM species isolated from environmental sources (2), it does not rule out the possibility that our patient acquired the *M. avium* from a water or biofilm source despite her periodic exposures to aerosolized dust and soil. As NTM is so prevalent in the environment, exposures to them are likely widespread; but since NTM lung disease is relatively uncommon, it suggests that those with such a disorder are likely to possess one or more host susceptibility factors.

Isolated NTM lung disease may occur *de novo* in normal lungs but is more likely to develop in those with pre-existing bronchiectasis or COPD. The three most common genetic disorders associated with bronchiectasis are CF, AAT deficiency, and PCD (3,4). Other disorders known to be associated with bronchiectasis include Williams-Campbell syndrome (cartilage defect), Mounier-Kuhn syndrome (elastin defect resulting in marked airway dilatation), and Sjogren's syndrome (dry, inspissated mucus leading to bronchiectasis) as well as sequelae from suboptimally treated pyogenic bacterial pneumonia or tuberculosis. Other predisposing conditions for NTM lung disease include pulmonary alveolar proteinosis, use of antagonists to tumor necrosis factor-alpha (TNFα), and aspiration due to swallowing dysfunction or laryngopharyngeal reflux.

While our patient does not have the prototypical major risk factors for NTM lung disease (e.g., CF or COPD), we posit that the presence of several "minor" host risk factors—in addition to environmental exposure to NTM-containing soil and dust—may have worked in concert to significantly increase her predisposition. Thus, in the context of our patient, we will discuss the possible role that the following may play in the predisposition to NTM lung disease: (I) CFTR heterozygosity, (II) AAT heterozygosity, (III) GER, (IV) low BMI, (V) post-menopausal status, and (VI) exposure to silica/dust (*Figure 2*).

CFTR anomalies and susceptibility to NTM

CF is an autosomal recessive disorder caused by mutation of the *CFTR* gene. The prevalence of a *CFTR* gene mutation in the Caucasian population is estimated to be 1 in 20 individuals, resulting in the occurrence of CF in 1 in 2,000–2,500 live births (5). CF patients, even those with milder forms of *CFTR* mutations (e.g., various compound heterozygosity), are particularly susceptible to recurrent and chronic bacterial infections including those due to *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Burkholderia cepacia* complex, fungi, and NTM (6-8). The mechanisms

for this susceptibility are likely protean including inspissated mucus with reduced ability to clear bacteria-laden mucus, secondary ciliary dysfunction due to chronic bronchial infection, and reduced human beta-defensin-2 function and level (9). Macrophage dysfunction due to CFTR dysfunction has also been demonstrated and embraces impaired phagocytosis, increased apoptosis, decreased autophagy, impaired clearance of apoptotic neutrophils (i.e., reduced efferocytosis), and excessive production of inflammatory mediators to microbial stimuli (10-12). In simplistic terms, macrophages may be divided into the M1 ("pro-inflammatory") and M2 ("anti-inflammatory") phenotypes. Whether the M1 or the M2 population predominates in the CF lung is controversial but there is evidence that CF macrophages are defective in switching between these two phenotypes (13).

While our patient is only heterozygous for the delta F508 *CFTR* gene mutation, it is increasingly recognized that individuals who are heterozygous carriers of a single *CFTR* mutation may also be more susceptible to NTM lung infection, resulting in bronchiectasis (14,15). Whether the one defective *CFTR* gene increases the susceptibility to NTM, bronchiectasis, or both is not known. Because one study showed that family members not affected with NTM infection have greater frequency of *CFTR* gene mutation than their relatives with NTM lung disease, it suggests that bronchiectasis in CF patients may be the predisposing factor to NTM infection and not necessarily the CFTR mutation *per se* although each possibility is not mutually exclusive of the other (16).

AAT anomalies and susceptibility to NTM

Whether AAT deficiency is associated with bronchiectasis is controversial, although there is increasing evidence of at least an association. In a study of over 200 bronchiectatics, the frequency of abnormal AAT genotypes was not significantly different than those without bronchiectasis (17). In contrast, others found an association between frank AAT deficiency and bronchiectasis (18-21). Guest and Hansell (18) examined the CT scans in 17 patients with proven AAT deficiency and found that seven had bronchial wall thickening and/or dilatation and one had gross cystic bronchiectasis. Similarly, Parr *et al.* (19) examined 74 patients with the PiZZ phenotype—the most common anomalous AAT that results in frank AAT deficiency— and found that 70 (95%) had bronchiectatic changes on CT scan involving an average of 3.7 lobes and 20 (27%)
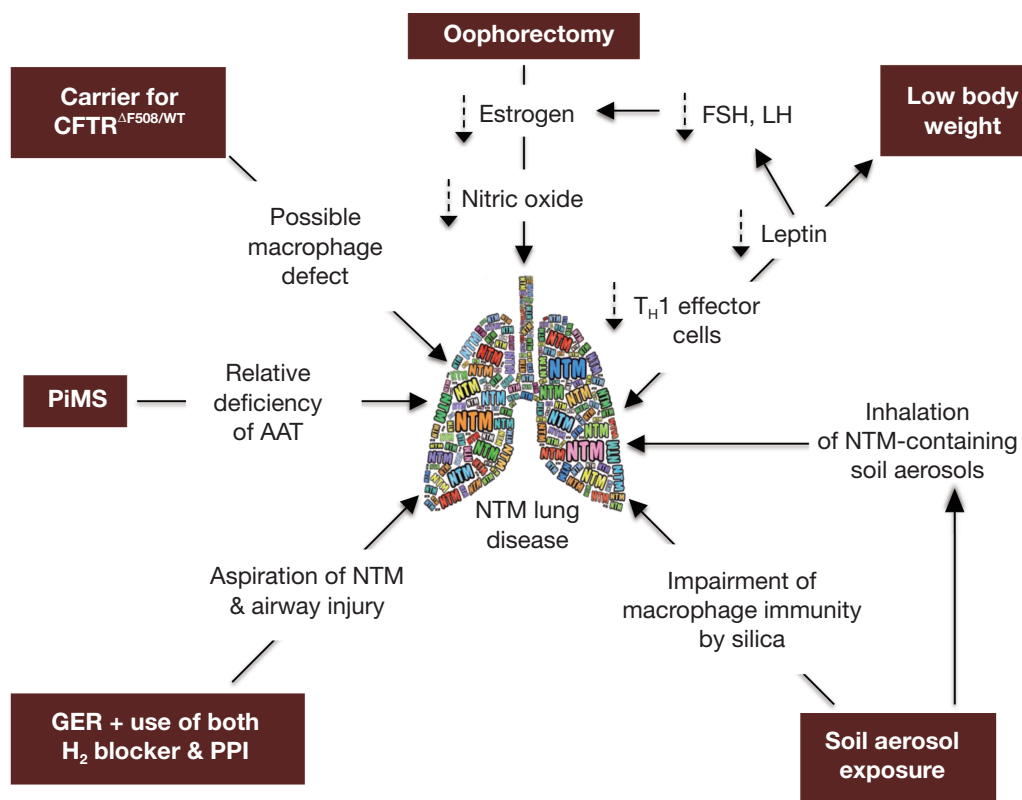
Figure 2 Diagram of the conditions that likely predisposed our subject to NTM lung infection. The texts within the maroon-colored background are the conditions, with the purported mechanisms located "downstream" in the direction of the arrows. The double-ended arrow connecting "NTM lung disease" and "low body weight" is used to denote that low body weight predisposes to NTM lung disease and vice versa. AAT, alpha-1-antitrypsin; FSH, follicle stimulating hormone; GER, gastroesophageal reflux; LH, luteinizing hormone; NTM, non-tuberculous mycobacteria; PiMS, protease inhibitor phenotype "MS"; PPI, proton pump inhibitor.

had "clinically significant bronchiectasis", defined as bronchiectasis affecting ≥ four lobes and "regular sputum production". Thus, based on these studies, it is likely that AAT anomalies are uncommon when examining unselected group of bronchiectatics whereas bronchiectasis is commonly seen when analyzing patients with frank AAT deficiency (22). Since the "Z" isoform of AAT may polymerize in the lung and act as a chemoattractant for neutrophils, which are then able to release inflammatory mediators and elastase that incite airway damage, this is a plausible mechanism by which an abnormal AAT protein may predispose to bronchiectasis (23). However, one potential confounder is that COPD itself may be associated with bronchiectasis (24-26).

NTM lung disease has been reported in a patient with frank AAT deficiency with both bronchiectasis and COPD (27). Whether the susceptibility is due to the structural lung disease, AAT deficiency itself, or both is unclear. We

and others previously reported that the presence of AAT anomalies—mostly heterozygous PiMS—were more common in patients with NTM lung disease compared to the general U.S. population, suggesting that anomalous AAT may predispose to NTM infection, which can secondarily cause bronchiectasis (28,29). This paradigm is supported by an *ex vivo* study showing that monocyte-derived macrophages (MDM) from PiZZ subjects incubated in autologous plasma—both obtained immediately after a session of intravenous AAT augmentation—were better able to control *M. intracellulare* infection than MDM incubated in plasma that were obtained before AAT infusion (30). One mechanism by which AAT augmented macrophage control of *M. intracellulare* was through inhibition of nuclear factor-kappa B (NF-κB), stimulating autophagy (30). Thus, vulnerability of AAT-deficient individuals to NTM lung disease may occur as a result of impaired innate immune function against NTM as well as alterations in lung

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architecture (bronchiectasis and COPD).

Our patient has a PiMS phenotype with a serum AAT that is within normal limits. The S allele of AAT differs from the normal M-AAT protein by a single amino acid substitution in which glutamic acid on position 264 is substituted by valine but is considered to function normally (31). The mildly reduced serum AAT level associated with S-AAT is due to increased intracellular degradation of newly synthesized S-AAT, decreased secretion from hepatocytes, increased turnover in plasma, and decreased thermal stability of S-AAT; whereas Z-AAT forms polymers and aggregates in the endoplasmic reticulum of the liver, such hepatic accumulation does not occur with the S-AAT protein (31,32). On the surface, it may appear unlikely that the PiMS phenotype of our patient is playing a significant role in susceptibility to NTM since her AAT level was within normal limits and the S-AAT protein is considered to be functional (33). However, since AAT is an acute-phase reactant and its plasma level is known to increase two- to four-fold in inflammatory states, perhaps her AAT level of 106 mg/dL—which is in the lower half of the normal range—is a relative deficiency; i.e., at a time when her NTM infection was not under control—as evinced by six sputum cultures that were positive—a supranormal AAT level may be the more appropriate response.

GER and susceptibility to NTM

GER occurs when the normal anti-reflux barrier between the stomach and the esophagus is compromised, such as lower esophageal sphincter incompetence, transient lower esophageal sphincter relaxation, and hiatal hernias. In this regard, severe GER, especially in the supine position as during sleep, is likely the most common cause of aspiration. While it may be difficult to prove definitively whether aspiration is the cause of the bronchiectasis, the prevalence of bronchiectasis in two-thirds of children with chronic pulmonary aspiration strongly indicates that chronic aspiration itself may induce bronchiectasis (34).

There is increasing evidence that aspiration—"from above" due to spillage of oropharyngeal secretions as a result of swallowing dysfunction or "from below" due to GER of contents from the esophagus or stomach—may predispose to NTM lung infection. In three separate studies, GER was present in 26–44% of pulmonary NTM subjects and 12–28% in non-NTM infected controls (35-37). However, another study found no difference in GER disease in 184 patients who met criteria for NTM lung disease *vs.* those who had

respiratory NTM isolated but did not meet criteria (38). Those with GER were more likely to be acid-fast smear positive and display more diffuse bronchiolitis and bronchiectasis (35). Use of acid suppression was associated with the presence of consolidation and lung nodules in the setting of NTM lung infection, suggesting greater burden of disease (36). With preferential lateral decubitus position during sleep, aspiration is more likely to occur into the lung that is dependent, as supported by a study demonstrating that the predominant lung affected in asymmetric idiopathic pulmonary fibrosis matched with the preferential (dependent) side to fall asleep in 94% of the cases (39).

Absence of ingested drink or food, the gastric mucosa normally has a pH <2.0; but with full strength proton pump inhibitor, it increases to pH of 4–5 range or even higher (40,41). For slow-growing mycobacteria and *M. chelonae*, the optimal pH for replication is ~6.0 whereas for rapidly-growing mycobacteria, the optimal growth pH is higher at ~7–7.4 (42-44). Thus, acid suppression is likely to enhance the growth of NTM in the stomach. Similarly, mixing of food material with gastric secretions could potentially improve gastric NTM survival by raising the pH to a mid-acidic range with subsequent aspiration of viable NTM into the lungs if there is severe GER.

Other than aspiration of NTM into the lungs, could GER of other contents in the stomach predispose to airway injury and subsequent NTM infection? In addition to the acid which can injure airway epithelial cells, aspiration of various gastric and pancreatic enzymes—proteases, lipases, and amylase—has the potential to cause airway mucosal disruption, providing a portal for NTM to initiate and establish residence in the airways. The protease secreted by the stomach is pepsinogen, which is activated by stomach acid to pepsin. The pancreas secretes an array of digestive enzymes including trypsinogen, chymotrypsinogen, and carboxypeptidase, with the first two being converted to their active isozymes in the duodenum in the presence of pancreatic-derived bicarbonate. But perhaps more germane to the pathogenesis of bronchiectasis and impairment of host defense is that the pancreas also secretes several elastases that degrade elastin and other proteins. Besides its key role in the pathogenesis of bronchiectasis, elastase also impairs host immunity against pathogens, by cleaving Fcγ receptors and complement receptor 1 from neutrophil surfaces as well as digesting immunoglobulins and complement components from bacterial surfaces (4). These activities impair opsonization of bacteria and reduce recognition of bacteria by neutrophils, leading to decreased

phagocytosis and killing of pathogens, culminating in exacerbation of bronchiectasis. Thus, if there were pyloric incompetence and esophageal reflux, these pancreatic proteases and elastases may be aspirated, inducing airway damage and host immunosuppression.

Our subject with GER preferred to lie on her left side without use of head-of-bed elevation initially; and, interestingly, her initial abnormal chest CT and subsequent progression of *M. avium* lung disease were worse in the left lung. Perhaps her lung disease is relatively mild because reflux is less likely to occur with left lateral decubitus than right lateral decubitus (45-47) although this paradigm has been challenged (48). While lying on the left side may be more likely to reduce GER than the right decubitus position, it must be combined with head-of-bed elevation to allow gravitational forces to limit GER in the first place (49).

Low body weight and susceptibility to NTM

Reduced BMI or subcutaneous fat has been documented in the pulmonary NTM patients and appears to be presently basally and not necessarily caused by the NTM infection itself (50-52). It has been hypothesized that low body weight in itself is a risk factor for NTM lung disease (50,51,53). This concept is supported by very large epidemiological studies (combined >2.5 million subjects) showing that thin individuals are much more likely to develop active tuberculosis (54-56). Furthermore, low BMI (<18.5 kg/m^2) has been associated with greater likelihood of both NTM lung disease progression and mortality (57,58). Interestingly, NTM lung disease has been reported in relatively younger women (ages 20–53 years old) with anorexia nervosa (59-64). Since NTM lung disease is much less common in younger individuals than in the elderly, the relatively younger age of those with anorexia nervosa and NTM lung disease would lend credence to the possibility that their thin body habitus is a risk factor. A possible mechanism by which slender individuals with low body fat content may be predisposed to NTM infections is relative deficiency of leptin, an adipokine whose canonical function is that of a satiety hormone (53). However, leptin has a number of immunomodulatory functions that can potentially enhance host-immunity against NTM, including the differentiation of uncommitted T_0 cells toward the T_H1 IFNγ-producing phenotype (65). Indeed, leptin-deficient mice are more susceptible to experimental *M. abscessus* lung infection (66). Pulmonary NTM patients have been found to have reduced serum leptin levels (67), or a loss in the normal direct relationship between percent

body fat and serum leptin concentration (50). Thin, pre-menopausal women with secondary leptin deficiency may also be more vulnerable to NTM infection because of estrogen deficiency—described below—since another function of leptin is to induce the expression of follicle stimulating hormone (FSH) and luteinizing hormone (LH). Parenthetically, disruption of this leptin-FSH/LH-estrogen axis is why very thin individuals—even if young—are prone to develop hypothalamic amenorrhea.

The occurrence of NTM lung disease in individuals without any known predisposing condition is well recognized; a number of these patients possess Marfanoid features such as life-long slender body habitus and thoracic cage abnormalities such as pectus excavatum and scoliosis (50,51,53,67-71). We and others have postulated that the aforementioned thoracic cage abnormalities may be a marker for an underlying and yet-to-be identified genetic predisposition, perhaps related to a minor variant of Marfan syndrome or ciliary dysfunction (16,50,51,69,70,72-74).

Our patient's BMI reflects her thin body habitus and possibly low body fat. Intuitively, low BMI is more likely to be predictive of low body fat whereas high BMI does not necessarily indicate high body fat as evinced by individuals who may have high BMI with low percentage body fat; e.g., body builders. Nevertheless, in certain groups of individuals, even high BMI may predict increased body fat percentage and obesity (75). According to the National Health and Nutrition Examination Survey (Centers for Disease Control), the average BMI for an adult woman in the U.S. is 26.5 kg/m^2. While our patient's BMI (19 kg/m^2) is within the healthy range of 18.5–24.9 kg/m^2, it is at the lower end and far lower than the average American woman. We reasoned that perhaps the relative deficiency of adipose tissue may have contributed to the susceptibility to NTM in the presence of other "minor" risk factors.

Post-menopausal status and susceptibility to NTM

Clinical observations accumulated over the past several decades indicate that NTM-associated bronchiectasis without an underlying predisposing condition like CF or PCD is disproportionately more common in post-menopausal women, a demographic group that accounts for 65–85% of NTM lung disease cases (28,70,76-80), 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 (81). Experimentally, binding

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of estrogen to estrogen receptors on macrophages has been shown to augment both phagocytic function and Fcγ receptor expression (82). This "estrogen-deficiency hypothesis" is corroborated by a study showing that oophorectomized mice were more susceptible to experimental MAC lung infection than mice with intact ovaries (83). Furthermore, reconstitution with exogenous estrogen in the oophorectomized mice reduced the burden of bacilli back to the level seen in the control mice through enhanced production of reactive nitrogen intermediates (83).

Another plausible mechanism by which estrogen protects against NTM is the ability of estradiol to inhibit NF-κB activation (84) because we have shown that such inhibition augments autophagy in macrophages, a known killing mechanism against mycobacteria (85). Furthermore, estrogen is known to activate endothelial nitric oxide synthase (eNOS) (86), an enzyme that is also present on airway epithelial cells and that catalyzes the production of nitric oxide (NO), the prototypical reactive nitrogen intermediate. While it is still too early to know whether inhaled NO will be an effective anti-mycobacterial agent, preliminary studies with inhaled NO show promise as adjunctive treatment for NTM lung disease (87-90). Perhaps the lack of estrogen may predispose to NTM due, in part, to decreased NO production. However, other studies do not support a host-protective role for estrogen against mycobacterial infections—as evinced by two studies showing that estrogen receptor-deficient mice infected with *M. avium* have increased production of host-protective TNFα and IFNγ, and a trend toward reduced *M. avium* load in the liver as well as significantly greater control of an *ex vivo M. avium* infection in peritoneal macrophages from estrogen receptor-deficient mice (91,92). Thus, the role estrogen plays in host defense against NTM infections remains to be clarified.

The average age at menopause for the American woman is estimated to be 51 years. The age of onset is due to a number of factors including the BMI, where a higher BMI is associated with a relative delay in menopause (93). Our patient was menopausal at age 47 years and had hysterectomy and bilateral oophorectomy at age 52 years. Perhaps this earlier period of natural and then surgical menopause predisposed her to NTM lung infection, symptoms of which began when she was 58 years old.

Dust exposure and susceptibility to NTM

There is convincing evidence that soil is a source of

NTM infections in humans (94-96). In a retrospective cross-sectional study of 1,392 patients with a history of "occupational dust exposure" who had sputum analysis for acid-fast bacilli, NTM were isolated in 82 (97). Multivariate analysis demonstrated that prior tuberculosis, greater number of small opacities, and high-grade of large opacities (>10 mm on longest axis)—with the latter two being potential markers of pneumoconiosis—are significantly associated with NTM culture positivity (97). In a case-control study from South Korea to identify risk factors for *M. kansasii* lung disease, 86 such patients were matched with 172 respiratory-healthy controls. Multivariate analysis showed that work in "heavy industries"—occupation considered to have greater dust exposure (e.g., grinding of metals, welding, shipyard work, etc.)—and low BMI were independent risk factors for *M. kansasii* lung disease (98). Similarly, in Japan, pulmonary MAC disease was more likely to be associated in individuals who live in an area with significantly greater number of primary industries (e.g., agriculture, forestry, and fisheries) or secondary industries (e.g., construction, mining, and processing of materials produced by the primary industries) but not tertiary industries (that provide customer services) (99).

It is well known that silica exposure—even in the absence of radiographic evidence of silicosis—is a strong risk factor for tuberculosis (100). Additionally, silicosis and other forms of pneumoconiosis are also risk factors for NTM lung disease (101,102). Studies of gold miners from South Africa showed that pulmonary silicosis was highly associated with NTM lung disease, with an odds ratio of 12.6 (101). The most common NTM in the South African gold miners was *M. kansasii*, responsible for two-thirds of the cases (101,102). Furthermore, the incidence of *M. kansasii* lung disease was estimated to be 66 per 10^5 person-years in the gold miners (103). Morita and colleagues (104) examined the sputa of 155 subjects with pneumoconiosis and isolated NTM in 60 (39%) of them. However, only two met criteria for having NTM lung disease as set forth by the American Thoracic Society and Infectious Diseases Society of America (104,105). Nevertheless, this study would support the notion that dust exposure increases infection to NTM and, in the presence of other risk factors, is an initial step in the increased vulnerability to NTM lung disease. *M. malmoense* is an NTM that disproportionately occurs in Northern Europe. Of an unspecified number of patients with coal miner's pneumoconiosis in the United Kingdom, four had sputum positivity for *M. malmoense* and three of them met

criteria for NTM lung disease (106). Other case reports have linked NTM lung disease with silicosis or other forms of soil or dust exposures (94,107).

The aforementioned epidemiologic studies are supported experimentally. Gangadharam and co-workers (108) administered silica intravenously to Swiss Webster mouse strain, infected them with *M. intracellulare*, and showed that they had a greater burden of bacilli in the lungs than control mice without silica exposure. Coal and quartz given to guinea pigs by inhalation increased the burden of *M. kansasii* lung disease even though the NTM was given intravenously (109). An often-cited mechanism for silica-induced susceptibility to mycobacterial infections is that following macrophage ingestion of silica particles, these phagocytes are impaired in their effector functions. Two such mechanisms include reducing expression of pattern-recognition receptors and inducing premature death of macrophages that have ingested silica particles (110,111).

Our patient owned a horse, which she visited regularly and likely had frequent exposure to aerosolized organic matter and soil that are pervasive in barns and riding corrals, respectively. She did not wear a mask during these visits. Not only are soil and dust exposure a potential source for NTM infection (99,112-116), but, as noted above, inhalation of silica present may potentially compromise host immunity.

Summary

Our patient with NTM lung disease did not have an identifiable, dominant predisposing condition such as frank CF or COPD. Clinicians should consider the presence of multiple subtle risk factors, perhaps insufficient if acting alone, that predispose to NTM lung disease in those without a prime risk factor.

Acknowledgments

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-986). EDC serves as an unpaid editorial board member of *Journal of Thoracic Disease* from Dec 2018 to Nov 2020. The other author has 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).

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