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Similar characteristics of nontuberculous mycobacterial pulmonary disease in men and women

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Title

Similar characteristics of nontuberculous mycobacterial pulmonary disease in men and women

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To the Editor:

The characteristics of nontuberculous mycobacterial pulmonary disease (NTM-PD) in individuals without clinically apparent predisposing factors have been described in female-predominant cohorts. Phenotypic characteristics are advanced age, tall stature, slender body habitus, right middle lobe (RML)- and/or lingula-predominant nodular bronchiectasis and increased frequencies of scoliosis, pectus excavatum (PEX) and mitral valve prolapse.[1-3] Increased rates of cystic fibrosis transmembrane conductance regulator (CFTR), immune, ciliary and connective tissue gene mutations and abnormal alpha-1-antitrypsin (AAT) phenotypes have also been reported.[4,5] The phenotypic archetype of NTM-PD in men is upper lobe cavitation in a middle-aged smoker. We hypothesized that the characteristics of male patients without pre-existing structural lung disease and immunocompromise resemble those of female patients.

We conducted a retrospective study of patients evaluated at National Jewish Health (NJH) from the inception of the Electronic Medical Record in 2008 through September 2017. Inclusion criteria were NTM-PD as defined by American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines[6], never-smoker status, available chest computed tomography (CT), and available mycobacterial identification. Exclusion criteria were structural lung disease other than bronchiectasis, immunocompromise and inherited predisposition to bronchiectasis. Data were extracted by manual review of electronic records. Two investigators (MH and TK) independently evaluated CT chest images and resolved discordant findings by consensus review. Lobar disease predominance was determined qualitatively. PEX was defined by a Haller Index (HI) > 2.5 or a Correction Index (CI) > 10.0.[7] The CI controls for false positive results in normal subjects with narrow anteroposterior or wide transverse thoracic dimensions. Both indices were measured on axial CT reconstruction at the point of greatest posterior sternal deformity, usually in the lower third of the sternum. Thoracic scoliosis was defined by a Cobb angle > 10° on posteroanterior chest radiograph or coronal CT topogram. Thoracic kyphosis was quantitated by the Cobb angle on lateral chest radiograph or sagittal CT topogram. Non-parametric statistical analysis was performed using "R", version 3.5.1. Continuous data are presented as: mean [95% confidence interval]. Statistical comparisons utilized permutation testing for continuous data and Fisher's Exact Test for proportions.

An ICD-10-based search of the NJH Research Database found records for 103 men and 865 women. One hundred women were randomly selected for further evaluation. Reasons for exclusion were failure to satisfy the ATS/IDSA NTM-PD criteria (33 males, 8 females), pre-existing structural lung disease or immunocompromise (12 males, 17 females), (ex-)smoker status (6 males, 4 females) and insufficient data (6 females). Ultimately, 52 men and 65 women were included in the study.

Results are summarized in Table 1. In keeping with other US studies, patients were of advanced age and predominantly white race. Sexual dimorphism likely accounts for the greater height and weight of male than female patients. The BMI of male patients (23.5 kg/m^2 [22.7, 24.4]) was lower than that of men aged 60-69 years in the general population (mean: 29.4 kg/m^2, SEM: 0.41).[8] Nodular bronchiectasis was present in almost all patients. RML-predominant disease was statistically significantly more common in women and there were trends toward upper lobe predominance being more common in men. Only one male patient had isolated upper lobe cavitation, suggesting

that smoking and structural lung disease are more important risk factors for this pattern of disease than male sex.

Frequencies of PEX in men and women were not statistically significantly different and demonstrated greater congruence when determined with the CI (19% vs. 18%) than the HI (19% vs. 28%), suggesting relatively narrower anteroposterior chest dimensions in female patients. Kim et al. reported PEX in 11% of a predominantly female cohort with NTM-PD.[2] Kartalija et al. reported a much higher rate of 87%, perhaps due to differing measurement technique.[3] Scoliosis was present in 35% of women in the present study, a rate comparable to that reported by Kartalija et al. (31%) and Kim et al. (51%). In keeping with population sex differences, male patients exhibited statistically significantly lower posteroanterior Cobb angles and a trend toward lower scoliosis frequency (19%). Nonetheless, the rate of scoliosis in men was higher than the general population of white males aged 65-74 years (approximately 7%).[9]

Comorbidities were similar between male and female patients. The higher frequency of osteopenia or osteoporosis in women ($p<0.001$) is expected. Esophageal dysmotility, oropharyngeal dysphagia and gastroesophageal reflux disease (GERD) were prevalent. Aspiration is a plausible route of infection and GERD has been associated with NTM-PD by other studies.[10] A history of rhinitis or sinusitis was reported by almost half the patients and CT sinus was abnormal in 9 (90%, n=10) men and 7 (50%, n=14) women. These findings support possible impairment of respiratory mucociliary clearance in individuals with NTM-PD, who exhibit decreased nasal nitric oxide production and ciliary beat frequency.[11]

Results of screening for hypogammaglobulinemia, connective tissue diseases, cystic fibrosis, AAT deficiency and vitamin D deficiency were similar between men and women. No patient was diagnosed with clinically significant hypogammaglobulinemia. CFTR gene mutation screening by DNA probe analysis or whole gene sequencing detected a clinically significant mutation in 4 men and 3 women. These patients were of white, non-Hispanic, non-Ashkenazi-Jewish ethnicity and represented 12% of screened men (n=33) and women (n=26) of this racial/ethnic background. In contrast, the CFTR mutation carriage rate in the general Caucasian population is approximately 4%.[12] Abnormal AAT phenotypes were detected in 11% of men (3 MS, 2 MZ) and 16% of women (5 MS, 4 MZ, 1 SS), frequencies exceeding the North American population rate of approximately 7%.[13] Increased frequencies of CFTR mutation carriage and abnormal AAT phenotypes in patients with NTM-PD have been reported by other studies and implicated in disease susceptibility.[2,5]

A novel finding was more severe disease in women, evidenced by more frequent pulmonary cavitation, lower BMI, more extensive treatment history and a trend toward more marked ventilatory impairment. This finding was not due to differing causative species. *M. avium* complex (MAC) and *M. abscessus* accounted for 69% and 25% of isolates from men and 77% and 21% of isolates from women, respectively. Although women with MAC tended to have macrolide-resistant isolates more frequently than men (15% vs. 3%, $p=0.07$), this likely reflects more common prior ineffective therapy in the female cohort due to referral bias. The observed difference in disease severity may be due to selection bias but is consistent with the possibility that the female sex-bias of NTM-PD reflects the influence of female-specific disease susceptibility factors. Data supporting this possibility are limited and equivocal. In a French retrospective study of patients with at least one respiratory nontuberculous mycobacterial isolate, male sex was an independent predictor of a

composite endpoint of symptom resolution, radiological improvement and culture negativity after 12 months (OR: 2.34 [1.26-8.16]).[14] However, this association was absent in the subset of patients meeting ATS/IDSA diagnostic criteria and mortality was higher in men than women. A population-based cohort study in Oregon found that women were more likely than men to have persistent radiological and microbiological findings of NTM-PD on unadjusted but not multivariate analysis.[15]

Limitations of the present study include its retrospective design and inclusion of cohorts from a single, referral institution for NTM-PD. Within these limitations, the data support similar characteristics in men and women with NTM-PD in the absence of pre-disposing structural lung disease and immunocompromise. The lesser disease severity observed in male patients requires prospective evaluation.

Table 1: Baseline characteristics, comorbidities and investigation results

	Men (N = 52)	Women (N = 65)	p-value
Baseline Characteristics			
Non-Hispanic white ethnicity	47 (90%)	53 (82%)	0.2
Age (years)	67 [63, 69]	65 [63, 68]	0.61
Height (m)	1.77 [1.75, 1.79]	1.62 [1.61, 1.64]	< 0.001
Weight (kg)	74.05 [71.33, 77.29]	56.37 [54.39, 58.51]	< 0.001
BMI (kg/m^2)	23.54 [22.70, 24.37]	21.42 [20.74, 22.13]	< 0.001
FEV1 (% predicted)	79.9 [73.9, 85.5]	73.6 [69.2, 77.8]	0.09
Prior/ongoing medical treatment	29 (56%)	49 (75%)	0.03
Prior surgical resection	1 (2%)	4 (6%)	0.38
Selected Comorbidities*			
Rhinitis or sinusitis	25 (48%)	29 (45%)	0.71
Gastroesophageal reflux	26 (50%)	30 (46%)	0.71
Chronic inhaled steroid use	11 (21%)	11 (17%)	0.64
Osteopenia or osteoporosis	1 (2%)	34 (52%)	< 0.001
Gastrointestinal Investigations†			
Esophageal dysmotility	28 (68%, n = 41)	38 (60%, n = 63)	0.53
Gastroesophageal reflux	22 (55%, n = 40)	28 (45%, n = 62)	0.42
Oropharyngeal dysphagia	27 (69%, n = 39)	32 (52%, n = 62)	0.1
Selected Laboratory Results			
CFTR gene mutation carriage‡	4 (11%, n = 36)	3 (8%, n = 36)	1
Abnormal AAT phenotype	5 (11%, n = 46)	10 (16%, n = 62)	0.58
Serum vitamin D < 30 ng/mL	17 (36%, n = 47)	16 (27%, n = 59)	0.4
Chest Imaging			
Nodular bronchiectasis	50 (96%)	65 (100%)	0.2
Cavitation	10 (19%)	25 (38%)	0.03
Lobar predominance			
Right Upper Lobe	24 (46%)	19 (29%)	0.08
Right Middle Lobe	25 (48%)	47 (72%)	0.01
Right Lower Lobe	16 (31%)	22 (34%)	0.84
Left Upper Lobe	11 (21%)	5 (8%)	0.06
Lingula	21 (40%)	36 (55%)	0.14
Left Lower Lobe	8 (15%)	11 (17%)	1
Pectus Excavatum			
Haller Index	2.17 [2.09, 2.27]	2.27 [2.18, 2.38]	0.15
Haller Index > 2.5	10 (19%)	18 (28%)	0.38
Correction Index	6.58 [5.42, 8.11]	6.95 [5.99, 8.15]	0.68
Correction Index > 10	10 (19%)	12 (18%)	1
Scoliosis and Kyphosis			
PA Cobb Angle (°)	6.01 [4.86, 7.53]	8.20 [6.90, 9.80]	0.04
PA Cobb Angle > 10°	10 (19%)	23 (35%)	0.06
Lateral Cobb Angle (°)	47.34 [44.64, 50.31]	45.14 [42.44, 48.36]	0.31

Abbreviations: BMI = body mass index, FEV1 = forced expiratory volume in 1 second, CFTR = cystic fibrosis transmembrane conductance regular, AAT = alpha-1-antritrypsin, PA = posteroanterior

*Comorbidities were extracted from clinical notes or routine patient questionnaires

†Esophageal dysmotility and gastroesophageal reflux were evaluated with an esophagram protocol that included 2 minutes of supine positioning. Oropharyngeal dysphagia was evaluated with tailored barium swallow.

‡Patients with clinically significant CFTR mutations are reported and all were heterozygotes. Denominators comprise all patients screened by DNA probe mutation analysis or whole gene sequencing. Mutations were as follows: p.F508del (2 men, 2 women), p.W1282X (1 man), c.2657+5G>A splice site mutation (1 man), p.G85E (1 woman).

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