Lady Windermere Dissected: More Form Than Fastidious

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In the opening scene of Oscar Wilde's satirical commentary on late-nineteenth-century societal norms, Lady Windermere refuses to shake hands with Lord Darlington because it would not be proper, as her hands were "wet with roses" (1). This portrayal of fastidious behavior as an analogy for voluntary cough suppression because of societal norms was proposed by Dr. Reich and Dr. Johnson in 1992 to explain the development of a syndrome of lingular and right middle lobe nodular bronchiectasis in women without obvious predisposing pulmonary disease (2).

Although this theatrical eponym has become engrained in the medical vernacular, the analogy is more problematic than just the fact that Wilde used Lady Windermere's fastidiousness as a mask for flaws in moral character. To begin with, Lady Windermere's estranged mother (a.k.a. Mrs. Erlynne) would have been a better match for the typical age at presentation. In this month's issue of *AnnalsATS,* the study by Daniels and colleagues (pp. 1712–1720) provides yet another piece of an evolving phenotype that further supports a susceptible host model of disease pathogenesis for development of pulmonary disease associated with the ubiquitous environmental mycobacteria (3).

Since Prince and colleagues first described the occurrence of slowly progressive nodular disease predominantly found in older women, there have been multiple reports describing a unique phenotype for many of these patients (4–6). This tall, asthenic body morphotype with a high prevalence of features such as scoliosis, joint hypermobility, chest wall pectus abnormalities, and mitral valve prolapse overlaps considerably with known heritable connective tissue disorders such as Marfan or Beall syndromes.

The clustering of these disease manifestations in families has further strengthened the hypothesis of a susceptible host model with potential associated genetic risk variants that may not have protein alterations severe enough to result in the typical gene-associated disease phenotype, but may alter the phenotype enough to predispose to late-onset progressive airway disease and predisposition to nontuberculous mycobacteria (NTM) (7–9).

Indeed, there has been considerable overlap in both directions between these patients with "idiopathic" bronchiectasis and NTM and known heritable connective tissue disorders, genetic disorders affecting mucociliary clearance such as cystic fibrosis (CF) and primary ciliary dyskinesia (PCD), and certain primary immune deficiencies such as STAT3 mutated hyper-IgE or Job's syndrome (Figure 1).

All these genetic disorders have been associated with a high prevalence of NTM lung infection, and genetic or phenotypic features of these disorders have been described in association with idiopathic
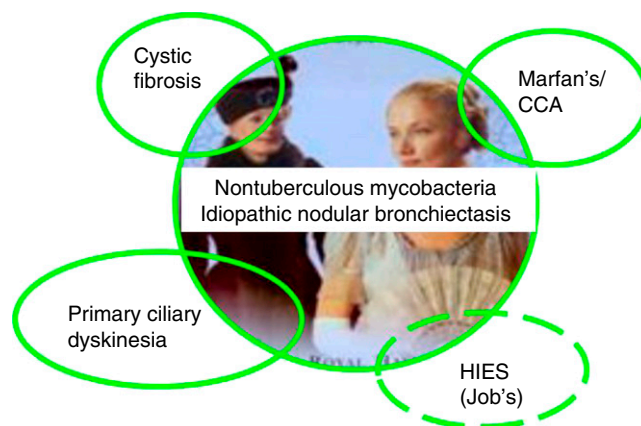

Figure 1. Overlap with known genetic diseases. Lady Windermere Syndrome, characterized by idiopathic nodular bronchiectasis and nontuberculous mycobacteria, has overlapping features with several known Mendelian transmitted genetic diseases. The *inner circle* depicts Lady Windermere and Mrs. Erlynne (Lady Windermere's estranged mother) from the 2002 Theater Royal production (https://www.londontheater.co.uk/reviews/lady-windermeres-fan). *Overlapping circles* indicate bidirectional relationships, with each of these genetic diseases having an associated high prevalence of nontuberculous mycobacteria and, in turn, Lady Windermere syndrome, having associated genetic or phenotype features from these conditions.

bronchiectasis or NTM lung infection (10–14). Early studies of these patients noted mono-allelic mutations in *CFTR* (CF gene) in one-third to one-half of these patients (5, 15). Similarly, we found a significant reduction in ciliary beat frequency in nasal and bronchial epithelial cells obtained from patients with NTM lung infections compared with healthy individuals and CF control subjects (16).

A recent study by our group looked for associated genetic risk loci via whole-exomic sequencing in familial and sporadic cohorts of patients with NTM infection. There was a high prevalence of rare, protein-altering, monoallelic variants in genes associated with each of these 4 areas of overlap, and most patients had variants in more than one gene, and often more than one category of genes (9). In fact, several patients had indels or known deleterious variants in genes such as *FBN2*, *TGFBR1*, and *COL5A1* associated with congenital contractural arachnodactyly (Beall syndrome), Loeys-Dietz syndrome, and Ehlers Danlos syndrome, respectively.

In the familial cohort, the frequency of variants in heritable connective tissue disorder genes, *CFTR*, and cilia-related genes was similarly elevated for "affected" and "unaffected" family members, when "affected" was defined as having bronchiectasis and NTM. However, more than 75% of the unaffected family members had one or more of the body morphotype features described here, so they weren't truly unaffected. Because many of these other individual features, such as joint hypermobility, low body mass index, mitral valve prolapse, pectus abnormalities, and even scoliosis, either affected a relatively small proportion of the patients or were also seen in the background population, it was difficult to correlate them with exomic variants.

Dural ectasia also occurs at a very high frequency in Marfan and Loeys-Dietz syndromes, but has not been described in the general population (17, 18). The defining measurements can be easily obtained from lumbar magnetic resonance imaging scans and are reproducible. In the article by Daniels and coworkers, the average lumbar dural sac diameter in patients with idiopathic bronchiectasis was larger than in both healthy and disease (CF) controls, but not as large as seen in Marfan syndrome. Further, patients with positive respiratory tract cultures for NTM had significantly larger dural sac diameters than patients with bronchiectasis without NTM. A correlation was also seen between increased dural sac diameter and anatomic involvement of bronchiectasis in the anterior regions (right middle lobe and lingula) of the lung, as described in Lady Windermere Syndrome.

In the Wilde play, Lady Windermere is in her early 20s. If she had the syndrome that bears her name, she likely would have had little in the way of associated symptoms or lung findings. One of the limitations of assessing genetic linkage in pedigrees of familial cohorts with idiopathic bronchiectasis and NTM has been the late age of onset of disease and the inability to distinguish family members in younger generations who are likely to develop the disease from those who are not.

If preliminary data from Daniels and coauthors showing a correlation between T10–L1 dural sac diameter assessed by chest computed tomographic (CT) imaging in patients with idiopathic bronchiectasis and the magnetic resonance imaging L1–L5 dural sac diameter is verified in a larger cohort, it may be possible to better segregate family members using readily available bronchiectasis screening CT images in future genetic correlation studies and, as noted, monitor younger family members with dural ectasia for subsequent development of bronchiectasis and chronic NTM infection (19).

In summary, the findings of an association between dural ectasia and patients with idiopathic bronchiectasis and NTM infection provide another important phenotypic link in the pathogenesis of this disease. These findings help better complete the picture of a unique susceptible host with, relative to known genetic diseases such as cystic fibrosis or primary ciliary dyskinesia, delayed onset of respiratory symptoms and detection of disease. Future expanded genotype/phenotype correlative studies that include dural ectasia as part of the phenotype will hopefully have a greater likelihood of elucidating the genetic and biologic pathway origins of this disease. ■

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