Pulmonary Sarcoidosis: Beyond Restriction and Forced Vital Capacity

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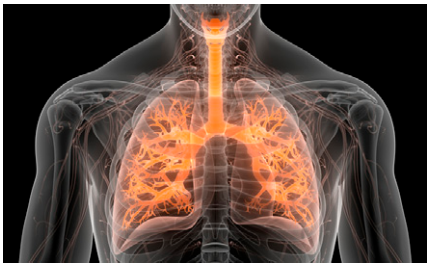

Pulmonary sarcoidosis has historically been considered a restrictive lung disease (1) however, several studies indicate that this is not always so (2–4). Up to 30% of patients have normal pulmonary function (3), and among those with abnormal lung function, other phenotypic pulmonary function impairments (obstructive phenotype [2, 5], a mixed obstructive and restrictive phenotype [3, 6], and a phenotype with an isolated diffusion defect [3, 7]) have been described. The presence of a mixed obstructive and restrictive phenotype has been associated with increased mortality (3), and the presence of more severe impairment in pulmonary function, a marker of more severe disease (8, 9), has been associated with Black race and lower socioeconomic status (2, 10). Variations in pulmonary function patterns in sarcoidosis by race, gender, and other sociodemographic variables have hitherto not been studied.

In this issue of *AnnalsATS*, Sharp and colleagues (pp. 30–37) report on an important study that showed for the first time that among patients with sarcoidosis and pulmonary involvement, phenotypic impairments in pulmonary function vary by race, gender, disease duration, and tobacco use (11). In their study, 44% of patients with established pulmonary sarcoidosis had normal lung function, and this was more likely to be so in White than Black patients (66% vs. 26%) (11). Furthermore, among patients with abnormal lung function, Black patients were more likely to have a restrictive phenotype (41% vs. 9%) and isolated diffusion defects (12% vs. 4%), whereas White patients were more likely to have an obstructive phenotype (17% vs. 9%). Men were more likely to have an obstructive phenotype (19% vs. 9%), whereas women more commonly had a restrictive phenotype (30% vs. 21%). Unexpectedly, current and past smokers were more likely to have a combined obstructive and restrictive phenotype or an isolated diffusion defect than they were to have an isolated obstructive or restrictive phenotype. As in prior studies, Black subjects had worse lung function, and this was true for all phenotypes except for the combined phenotype, for which pulmonary function was worse in White subjects (11). Sharp and colleagues have eloquently explored some of the reasons for these variations in lung function impairments, and their surmising is clearly elaborated in their paper.

One of the most important findings of this study is that although restriction was the most common pulmonary functional abnormality observed, fewer than half (41%) of those with abnormal lung function, and only a quarter (27%) of the entire cohort, had a restrictive phenotype. These findings are noteworthy for numerous reasons. Sarcoidosis is a disease of unknown etiology for which drug treatments and management algorithms continue to be refined (12). Central to this refinement process are clinical trials, many of which have struggled to identify appropriate clinical endpoints for evaluating patient response to therapy (13). A significant number of trials have adopted forced vital capacity (FVC), the marker of restrictive lung disease (14), as the best outcome measure of patient response (15). Indeed, over the past several years, some drugs/interventions have been judged "not efficacious" on the basis of failure to reach an arbitrary threshold change in FVC (16). Although FVC is certainly an important clinical endpoint that should be incorporated into clinical trials, the findings of Sharpe and colleagues (11) reinforce that it is not representative of all (or even most) patients with pulmonary sarcoidosis (irrespective of radiographic pattern) and therefore should not be the sole criterion or focal point by which the success or failure of an intervention is determined. In fact, these data suggest that continuing to focus on FVC as the sole or most significant primary endpoint in clinical trials evaluating therapies in pulmonary sarcoidosis may inadvertently misclassify potentially efficacious drugs/interventions as not effective for the majority of patients for whom a demonstrable change in FVC may not be feasible by virtue of their disease phenotype. Furthermore, as FVC has also been used as a study eligibility/inclusion criterion (13), there is also a concern that potential study subjects (with legitimate disease) are being excluded from clinical trial participation in an inadvertent race- or gender-biased manner. Last but certainly not least, this work emphasizes the need to monitor patients serially in clinical practice with full pulmonary function testing and not just spirometry, as this could miss disease progression in up to 15% of patients with isolated diffusion defect, a group of patients that have been shown in several studies to be at increased risk of pulmonary vascular involvement, fibrotic pulmonary sarcoidosis, and increased mortality (3, 17).

Beyond misclassification of disease and outcome by focusing on FVC, Sharp and colleagues also draw attention to other potential biases that maybe associated with failure to fully recognize variability in patterns of pulmonary function impairment. For example, they found that there was an association between phenotypic pulmonary function impairment, smoking status, and

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disease duration since diagnosis (11). Sarcoidosis has long been recognized as a disease predominantly of nonsmokers/never-smokers (18), yet it is possible that smoking influences the phenotypic pulmonary impairment and should be further evaluated in future studies. This also applies to duration of disease: patients with longer disease duration are more likely to have a combined obstructive and restrictive phenotype, whereas more recently diagnosed patients are more likely to have normal lung function (11).

Although elegant in design and execution, the study by Sharp and colleagues has several limitations. First, it is a cross-sectional study, so it is unknown if baseline phenotypic impairment has any bearing on rate of disease progression or mortality. A recently published study that included six international interstitial lung disease expert centers in Europe and the Unites States revealed that although baseline pulmonary function differed by center, the rate of change in each of the pulmonary function parameters was similar across centers (19). This will need to be further explored in a cohort such as this. It will be important to note if disease progression varies by phenotype and, within each phenotype, if there is variability of disease progression by race, gender, and other sociodemographic variables. Similarly, studies in large prospective cohorts will also be necessary to determine if there are any prognostic implications of these phenotypes by race, gender, disease duration, or smoking status. As noted above, Kouranos and colleagues showed that presence of a combined phenotype was associated with increased mortality in a predominantly White population (3), however, this will need to be further explored in a more racially diverse population such as this. Another limitation of this study is that there are no data on individual symptom burden and health-related quality of life (HRQoL), so an association between symptoms, HRQoL, and pulmonary function phenotype cannot be determined. The recently published sarcoidosis treatment guidelines affirm that the two indications for treatment of sarcoidosis are the presence of symptoms negatively affecting HRQoL and/or evidence of disease progression with risk to organ function or increased risk of mortality (12). Determining an association between pulmonary function phenotype, race, gender, symptom burden, and HRQoL may have therapeutic implications and thus have some relevance in clinical practice, and may help appropriately select patients for targeted clinical trials. Finally, this study does not provide information on socioeconomic status and environmental exposures. As the authors rightly note, race is an imperfect construct, and future studies are needed to help tease out the varying contributions of genetics, socioeconomic status, environmental exposures, and other sociodemographic variables to disease severity and phenotypic presentation.

In all, Sharp and colleagues are to be congratulated for laying the foundations for this great work and should be encouraged to build on their findings by further exploring all the nuances of these important associations. It may also be worthwhile to consider leveraging larger cohorts built from collaborations across multiple centers within and outside the United States to further develop these findings. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Preventing Continuous Damage in Primary Ciliary Dyskinesia: Is Airway Inflammation a Potential Target?

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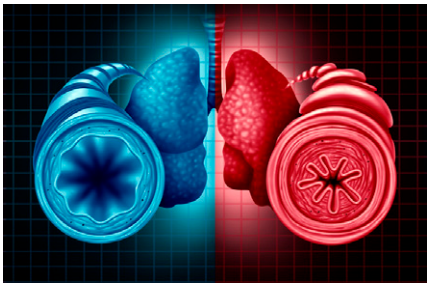

Primary ciliary dyskinesia (PCD) is a multiorgan disease with symptoms related to ineffective or absent beating of motile cilia in different body systems (1). It typically presents early in life with unexplained respiratory distress in the first 24 hours after birth; other cardinal symptoms include chronic productive cough and persistent rhinosinusitis, both usually beginning during infancy (1). Lung disease in people with PCD is characterized by impaired mucociliary clearance, recurrent bacterial infection, and pulmonary exacerbations resulting in progressive obstructive lung disease and bronchiectasis (1, 2).

Neutrophil-dominated inflammation of the airways with elevated levels of neutrophil chemoattractants is well documented in PCD (3–5). Airway epithelial cells respond to inhaled bacteria by producing proinflammatory cytokines to recruit neutrophils and other immune cells to the site of infection (6). The antibacterial response of neutrophils is essential to contain infection and includes phagocytosis, neutrophil extracellular trap formation, and the release of reactive oxygen species and proteases (7). In healthy subjects, the inflammatory response is usually restrained and resolved by antiinflammatory cytokines, but it tends to persist in chronic airway diseases, including PCD and cystic fibrosis (CF) (3). There is also evidence to suggest that abnormal mucus clearance can initiate and potentially maintain airway inflammation independent of infection (8). The link between inflammation and the subsequent course of lung disease has been studied extensively in CF (9, 10), but data are currently lacking for PCD.

In this issue of *AnnalsATS*, Sagel and colleagues (pp. 67–74) present the findings of the first multicenter observational study on airway inflammation in pediatric patients with PCD (11). Sputum inflammatory markers such as neutrophil elastase (NE), interleukin (IL)-1β, IL-8, and tumor necrosis factor-α concentrations correlated positively with abnormal computed tomography findings and negatively with lung function (11). No significant difference was found between the different groups of ciliary defects, but sputum NE, IL-1β, and tumor necrosis factor-α concentrations were higher in those with positive sputum cultures for common bacterial pathogens.

The finding of persistent neutrophilic inflammation in PCD is consistent with previous single-center studies that evaluated differences in airway inflammation between patients with PCD and patients with CF. Bush and colleagues demonstrated that IL-8 sputum concentrations are higher in PCD than CF, although some of the measurements were performed during pulmonary exacerbations (5). We had previously assessed airway inflammation in a small group of patients with PCD at the time of clinical stability, during pulmonary exacerbations, and after treatment in comparison with patients with CF infected with similar bacterial pathogens (4). Sputum neutrophil counts were elevated in patients with stable PCD, and, at the time of exacerbation, absolute neutrophil counts were significantly higher in PCD than in CF, even though bacterial density was higher in the CF group. Markers of airway inflammation improved with treatment in both groups, but a significant decrease in NE activity after the antibiotic course was only seen in patients with PCD. Therefore, although both diseases are characterized by neutrophilic inflammation, differences exist, especially during pulmonary exacerbation and in the response to antibiotic treatment, which need to be explored further to better understand the specifics of airway inflammation in both diseases.

Higher sputum neutrophil counts in patients have previously been linked to clinical severity, as reflected by increased cough frequency (12), but the study by Sagel and colleagues is the first to demonstrate that measurements of airway inflammation are associated with impaired lung function and structural damage. These findings show a linkage to disease progression and could serve as possible markers for disease trajectories and severity. Although the findings reported by Sagel and colleagues do not necessarily prove causation, such measurements may help to further our

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