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Interstitial lung abnormalities: risk and opportunity

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Medical imaging has provided previously unimagined opportunities to study human disease. In the thorax, it has helped researchers to understand how lung structure affects function, appreciate the multiple comorbid disorders accompanying chronic pulmonary disorders, and monitor responses to therapeutic intervention.^{1,2} In view of the increasing use of medical imaging in at risk smokers, the ability to identify disease at its earliest and potentially curable stages can be added to this list.

In the 1980s thoracic radiologists put forth the phrase “dirty lung” to describe the parenchymal inflammation and remodelling evident in the chest radiographs of smokers.³ That there is scarring and fibrosis in the lungs of such patients does not surprise many in the medical community, but more recent research suggests that some of these findings share similarities with, and might in some cases even be the precursor to, devastating disorders like pulmonary fibrosis.⁴ These subtle radiographic changes might therefore represent interstitial disease at its earliest state. Although to leap from these interesting observations to thoughts of intervention and prevention is tempting, such intentions must be tempered by the present understanding of disease progression and the somewhat limited treatments available to progressors.^{5,6}

Repeated studies have shown that 6–8% of all smokers older than 50 years have some degree of interstitial lung abnormalities in their parenchyma.^{7,8} Additional population-based investigations suggest that this disorder might not even be a product of smoking but rather one of age.⁴ These same studies have also convincingly shown that these abnormalities are associated with single nucleotide polymorphisms in the promoter region of the gene encoding for mucin 5B (*MUC5B*), a mutation which is linked to established pulmonary fibrosis.⁷ Finally, interstitial lung abnormalities are associated with decrements in exercise capacity, increased symptoms, and an increased risk of all-cause and respiratory-specific mortality.^{4,9} The aggregate of these data suggest that these interstitial lung abnormalities could be treated with the existing array of drugs approved for idiopathic pulmonary fibrosis (IPF). Although there is clear logic to attenuating disease progression at its earliest stages, several gaps exist in the scientific literature that prevent broad implementation of such a strategy.

The prevalence of IPF is estimated to range from 1 to 63 per 100 000 in the general population.¹⁰ Even if such estimates are off by a factor of ten, it is clear that the vast

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majority of people with interstitial lung abnormalities do not succumb to end-stage fibrotic lung disease. There must therefore be subtypes of interstitial lung abnormalities that include static incidental radiological findings, transient manifestations of a noxious exposure or event, and those that truly represent pulmonary fibrosis at its early stages. It is impractical and medically unsound to treat all patients with interstitial lung abnormalities with pirfenidone or nintedanib. What then are the next steps to translate the growing body of scientific literature on interstitial lung abnormalities into an early intervention and cure?

There are many radiological features labelled as interstitial lung abnormalities. These include centrilobular nodules, patchy areas of ground glass, interstitial thickening, reticular and nodular opacities, and honeycombing.^{4,8} These probably represent a diversity of biological processes, including those that lead to emphysematous dilation of the distal airspaces and those that result in fibrosis of the parenchyma. Researchers need to identify a biomarker or series of biomarkers with which patients can be stratified to such divergent disease trajectories. This requires longitudinal observation of cohorts at risk, but even more importantly, a consensus on what features are being identified. Centre-to-centre and expert-to-expert reproducibility in describing subjective features on CT scan are notoriously poor.¹¹ One fix is to have a single reader responsible for all image interpretation. A second and more tenable solution is to provide materials to educate the research community, a precedent which is well established in multiple thoracic diseases such as emphysema and lung cancer. These educational materials could be provided by the European Respiratory Society, the American Thoracic Society, or multinational groups of experts such as the Fleischner Society, a society which has provided a wealth of information on the radiological characterisation of the lung in health and disease.

The second step is collaboration and the aggregation of larger cohorts for clinical investigation. Although interstitial lung abnormalities are associated with *MUC5B*, in view of the approximately 20% prevalence of this promoter polymorphism in non-Hispanic white people, pulmonary fibrosis is probably not monogenic but rather complex, as is increasingly appreciated in COPD.⁷ Such complexity suggests that biological signals will be weak and their detection will require the assessment of large numbers of people. The final and most obvious strength to collaboration is the invaluable and necessary contributions provided by experts in imaging, clinical investigation, clinical care, biology, and omics to the understanding of fibrotic lung disease.

Engagement of the academic community with the pharmaceutical and other industries at the earliest stages of investigation is also crucial. There is generally an opaque window dividing the two groups, which is not only due to the presence of proprietary intellectual property, but also self-imposed strategies for the mitigation of conflict of interest. There is no easy solution to broadly improve this relationship, but perhaps it can be addressed in part by the creation of a consortium of academics and industry to collectively plan the best ways to leverage present and future resources focused on this disorder.

Finally, one of the most pressing questions is what should a clinician do with the unexpected discovery of interstitial lung abnormalities? Can the abnormalities be ignored? Is the clinician obligated to follow up on these abnormalities with a series of dedicated

investigations? When should they order the next scan and how should they counsel patients? This might be a situation in which genetics and imaging can be used together to improve clinical care. Recent investigation, published within the past year, suggests that patients with interstitial lung abnormalities who have at least one copy of the *MUC5B* promoter polymorphism are more likely to have a progressive loss of lung function than patients without the polymorphism.¹² For such patients the choice of counselling and follow-up are quite clear. They are likely to have the earliest stages of what could be a progressive interstitial lung disease and should undergo repeated evaluation. However, most patients with interstitial lung abnormalities will not fall into this category. For these patients, insufficient comprehensive data exist to definitively state who should be followed up and at what interval. Perhaps this could be the topic of the second half of a consensus guidance document alluded to earlier. Until such data are available and well defined approaches to care are in place, clinicians must continue to use their best clinical judgment.

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