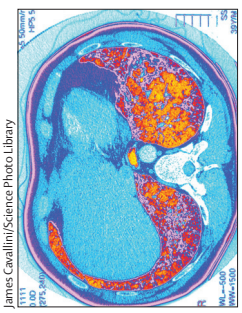
Chronic hypersensitivity pneumonitis in the setting of definite IPF: does the current study undermine IPF guideline recommendations?



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Guidelines are constructed to allow less expert practitioners to base optimum management on an accurate diagnosis. In idiopathic pulmonary fibrosis (IPF), the most prevalent diagnostic problem is the discrimination between IPF and disorders in which inflammation precedes and leads to fibrosis, especially chronic hypersensitivity pneumonitis. The distinction matters greatly. Immunosuppressive therapy was recently found to be harmful in IPF,[1] but is often appropriate in chronic hypersensitivity pneumonitis. Treatment recommendations for IPF in the 2011 American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society, and Latin American Thoracic Association guidelines are contingent on a definite diagnosis of IPF, which cannot be made without a surgical biopsy in patients with atypical high-resolution CT appearances.[2] By contrast, there is a widespread international consensus, captured in the 2011 guideline recommendations, that in the correct clinical context, high-resolution CT appearances typical of a pattern of usual interstitial pneumonia obviate the need for biopsy.

In *The Lancet Respiratory Medicine*, Ferran Morell and colleagues[3] report that among 46 consecutive patients meeting ATS/ERS 2011 criteria for a diagnosis of IPF, including nine with histological confirmation of a usual interstitial pneumonia pattern and all with appearances typical of usual interstitial pneumonia on high-resolution CT, a subsequent diagnosis of chronic hypersensitivity pneumonitis was made in 20 patients (43%; 95% CI 29–58). At first sight, these intriguing findings raise serious questions about current guideline recommendations. If the studied cohort is typical of patients with IPF in general, the logical deduction is that a supposedly definite diagnosis of IPF, based on high-resolution CT appearance alone, might be incorrect in a large minority of cases. The authors state that their findings support the 2011 guideline recommendations (with respect to the need to carefully exclude environmental causes). However, the need to identify environmental triggers compatible with chronic hypersensitivity pneumonitis was also emphasised in the 2000 IPF guidelines;[4] worryingly, with the application of the 2000 recommendations, an environmental cause was not, in fact, identified prospectively in the formulation of a diagnosis of IPF in these patients. Furthermore, in the post-PANTHER era, with immunomodulation currently stigmatised in IPF, the findings seem to cast serious doubt with respect to IPF treatment recommendations, when the diagnosis is based on high-resolution CT features. This, in turn, raises the important question of whether the current indications for a diagnostic surgical biopsy need to be expanded. Thus, the nature of the studied population and the criteria used to diagnose chronic hypersensitivity pneumonitis must be considered carefully.

In common with many referral centre populations, the cohort was younger than IPF populations drawn from secondary practice, in whom the median age is roughly 70 years.[5] The demographic profile of the studied cohort resembles that of pharmaceutical populations, also subject to substantial selection bias. However, whether referral-centre selection bias towards younger patients could truly account for such a strikingly high prevalence of chronic hypersensitivity pneumonitis seems doubtful: the current observations are striking when set against referral centre experience at large. Of greater concern is the possibility that the prevalence of chronic hypersensitivity pneumonitis has been artificially amplified by the mode of diagnosis. It should be stressed that in most of the patients ultimately diagnosed with chronic hypersensitivity pneumonitis, there were histological features consistent with the diagnosis, although, it seems, not sufficiently diagnostic to undermine the initial diagnosis of IPF. It appears that biopsy features thought to be compatible, including the presence of bronchocentric abnormalities in the setting of a usual interstitial pneumonia pattern, were given greater diagnostic credence by the presence of specific IgG signal. In another patient subset, the diagnosis of

chronic hypersensitivity pneumonitis was based on bronchial provocation testing, again with non-definitive histological support in some cases.

Are these diagnostic criteria for chronic hypersensitivity pneumonitis sufficiently robust in the setting of a moderately severe fibrosing interstitial lung disease (as opposed to hypersensitivity pneumonitis patients with a less fibrotic clinical phenotype, in which antigen exposure is often obvious)?[6] In IPF, there is major epithelial disruption leading to a substantial increase in epithelial permeability, as judged by the clearance of inhaled radiolabelled diethylene triamine penta-acetic acid.[7] There is, thus, a loss of the normal anatomical barrier between the immune system and inhaled particles with potential antigenicity. Furthermore, recent data indicate that immune dysregulation, as judged by an excess of autoantibodies (which are linked to disease behaviour), is a frequent occurrence in IPF.[8] In view of the fact that inhaled antigens have immediate access to a dysregulated immune system in the specific setting of IPF, can it be assumed that specific IgG signal (which merely reflects antigen exposure) and positivity to provocation testing are truly indicative of chronic hypersensitivity pneumonitis and not mere secondary phenomena? Even discounting this possibility, the unresolved question is whether the diagnostic criteria used for chronic hypersensitivity pneumonitis in the current study truly justify a change in diagnosis from IPF to chronic hypersensitivity pneumonitis in most of the reported cases. The prevailing pathogenetic model for IPF in recent years is one of recurrent epithelial damage:[9] is it not plausible that in some patients with evolution to so-called typical IPF, a hypersensitivity trigger might be one of a number of damaging triggers responsible for the initiation of disease which is typical of IPF in all other aspects?

Like all provocative reports, Morell and colleagues' study raises more questions than it answers. Is underlying chronic hypersensitivity pneumonitis truly as prevalent in the setting of a usual interstitial pneumonia pattern on high-resolution CT as is suggested in the current study, or does the report represent a unique referral centre cluster of chronic hypersensitivity pneumonitis related to feather bedding? Does this report have major implications for future guideline statements, in view of the fact that IPF was diagnosed prospectively in these patients at an expert centre? Will we have cause to regret the 2011 guideline recommendation that bronchoalveolar lavage is not warranted in the majority of patients with supposedly definite IPF? To what extent can a more rigorous questionnaire-based process capture patients with chronic hypersensitivity pneumonitis in this context? Above all, is there truly an outcome distinction between chronic hypersensitivity pneumonitis and IPF in the specific context of a usual interstitial pneumonia pattern on high-resolution CT (as suggested by preliminary data in the current study)? If so, is an anti-inflammatory treatment approach more efficacious in these patients or does disease tend to progress inexorably despite therapy? Only when these questions are answered will the true significance of the current observations become apparent. Until this happens, current guideline recommendations related to definite IPF should continue to be followed.

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I declare that I have no conflicts of interest.

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