Hypersensitivity pneumonitis: An infrequent cause of chronic lung fibrosis in Africa?

The advent of antifibrotic drugs such as nintedanib and pirfenidone has heralded a new and exciting era in the field of the interstitial lung diseases (ILDs), many of which progress to end-stage fibrosis despite immunomodulatory treatment. Until recently, the management of patients who develop lung fibrosis has essentially been palliative. The initial trials of antifibrotic drugs for idiopathic pulmonary fibrosis (IPF)[1,2] were met with great enthusiasm and optimism, as clinicians now had pharmacological tools to alter the trajectory of this dismal disease. These findings were extended to other progressive fibrosing ILDs in the subsequent SENSCIS[3] and INBUILD[4] trials.

In this issue of *AJTCCM*, Seixas *et al.*[5] report the findings of a cross-sectional retrospective study of outpatients with chronic fibrotic hypersensitivity pneumonitis (f-HP) attending a district ILD clinic in Portugal. All patients were assessed by a multidisciplinary team and were followed up for a minimum of 1 year.

Of their 83 patients with hypersensitivity pneumonitis (HP), 63 (75.9%) had evidence of f-HP. In analysing the subjects with f-HP and a behaviour pattern of progressive fibrosis, the authors used the same criteria as the INBUILD study, viz. at least one of the following within the past 24 months in antifibrotic drug-naive patients: (*i*) a relative decline in forced vital capacity (FVC) ≥10% of predicted value; (*ii*) a relative decline in FVC of 5 - 9% of predicted value + worsening of respiratory symptoms or increased extent of fibrosis on a high-resolution computed tomography scan (HRCT); and (*iii*) worsening of respiratory symptoms + increased extent of fibrosis. Of the 63 f-HP patients, 21 (33.3%) fulfilled criteria for progressive fibrosing hypersensitivity pneumonitis (PF-HP). Compared with the f-HP patients without evidence of progressive fibrosis, the PF-HP group was more likely to demonstrate a pattern of usual interstitial pneumonia (UIP) or a UIP-like pattern on HRCT (61.9% v. 38.1%) and was more likely to experience acute exacerbations (26.2% v. 14.3%). The most common inciting agents for HP were avian proteins (57.1%) and moulds (25.4%).

The American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS) and Asociación Latinoamericana de Tórax (ALAT) have since published an updated clinical practice guideline in 2022[6] in which the lung function criteria for progressive pulmonary fibrosis (PPF), the preferred term for PF-ILD, have been changed to: (*i*) *absolute* decline in FVC ≥5% predicted within 1 year of follow-up; or (*ii*) *absolute* decline in DLCO (diffusing capacity of the lung for carbon monoxide) (corrected for haemoglobin) ≥10% predicted within 1 year of follow-up. Patients with PPF must demonstrate deterioration in at least two of the following three domains: symptoms, lung function, and HRCT changes.

The formalisation of a definition for PPF raises the question whether antifibrotic drugs should be prescribed in this category of patients irrespective of the underlying cause. So far, only the INBUILD study[4] has explored this. In the active arm of this multicentre double-blind, placebo-controlled phase 3 trial, 663 patients with non-IPF PF-ILD were given nintedanib for 52 weeks. Patients with HP comprised 26.1% of the study population. While nintedanib showed a statistically significant lower decline in FVC over the 52-week study period in the overall population and in the subset with a UIP-like fibrotic pattern on HRCT scan (difference in decline 107.0 mL and 128.2 mL, respectively, compared with the placebo group), subgroup analysis of the 84/173 subjects with chronic HP showed a less impressive benefit of 72.9 mL/year.[7] However, the study was not designed or powered to analyse the effect of nintedanib on specific ILD subgroups. It should also be noted that when analysing the data stratified by HRCT features (UIP-like v. other fibrotic patterns), statistically significant benefit was shown only in the UIP-like group.

Although nintedanib is promising as an antifibrotic agent in non-IPF PPF-ILD, clinicians should be cautiously optimistic, as the INBUILD trial is the only published trial in this field so far. Other considerations include whether there are differences in response between different subgroups of non-IPF ILD and whether the concurrent use of immunosuppressive agents, e.g. in connective tissue disease-related ILD, should be advocated. In the INBUILD trial, patients who were receiving azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, rituximab, cyclophosphamide or oral glucocorticoids >20 mg/day were excluded. However, at the discretion of the investigator, the addition of these drugs was permitted 6 months into the trial if there was significant clinical deterioration in the ILD or connective tissue disease.

While both pirfenidone and nintedanib, antifibrotic drugs with different mechanisms of action, showed similar benefit in IPF,[2,8] it is a great pity that the RELIEF study, a double-blind, randomised, placebo-controlled phase 2b trial of pirfenidone in patients with PF-ILD, was prematurely terminated owing to slow recruitment.[9]

There is probably no other disease that demands a sleuth-like diagnostic approach more than HP. Antigens causing HP may be found in the home, in the workplace and in recreational environments. These antigens may be categorised into three groups: microbes (bacteria, fungi, mycobacteria), proteins (animal proteins, plant proteins) and chemical agents. Chronic HP may easily be misdiagnosed as IPF, not only by clinicians but also by radiologists and pathologists.[10-13] In a study by Fernández Pérez *et al.*,[14] of 142 cases of surgical lung biopsy-proven HP, 53% had no identifiable inciting antigen. After adjusting for age, lung fibrosis and smoking, the median survival was 8.0 years where the antigen was identified, but only 2.9 years where the antigen remained elusive. The median survival was 16.9 years in those without lung fibrosis, but only 4.9 years in those with fibrosis.

The global prevalence of HP appears to vary widely,[15] but it is rarely reported from Africa. A literature search for case series of African patients with HP (including the old term 'extrinsic allergic alveolitis'), and also a search for reports on the two most common causes, avian antigens and moulds, yielded only four articles. The largest series (40 cases) was that of bird fancier's disease in Western Cape Province, South Africa.[16] Other reports comprised 5 cases of summer-type HP in Eastern Cape Province[17] (now recognised as hypersensitivity to inhalation of *Trichosporon cutaneum*, a fungus that grows in mouldy, decaying organic matter in hot and humid environments, and the

commonest cause of HP in Japan),[18] a single case of bird fancier's lung in a 12-year-old boy in the Western Cape,[19] and a single case (antigen not stated) in a series of 42 children in KwaZulu-Natal Province with chronic lung disease.[20]

What makes chronic HP a particularly challenging diagnosis is that it is not always preceded by acute disease, which is more easily recognisable; standardised and validated antigen preparations and immunoassays for diagnosis are not available; cut-off values for quantitative immunoglobulin G assays have not been validated; and lymphocytosis on bronchoalveolar lavage is not always present.[21] The clinical practice guideline on the diagnosis of HP endorsed by the ATS, JRS and ALAT[22] has replaced the categories of acute, subacute and chronic HP with two categories, non-fibrotic and fibrotic HP. The rationale for this change is that the evolution of the disease is not always clear. In addition, the presence or absence of fibrosis provides a more practical approach to management.

Are we misdiagnosing patients with chronic HP in Africa, or is it a rare disease on our continent? This is a call to clinicians not only to actively interrogate patients regarding exposure to possible antigens, but also to increase local awareness by publishing confirmed cases.

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