Update in Diffuse Parenchymal Lung Disease 2007

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CLINICAL ADVANCES

Diagnosis and Classification of Fibrosing Lung Disease

It is now widely accepted that the diagnostic reference standard for interstitial lung disease is multidisciplinary evaluation, with the integration of clinical, radiologic, and histologic data (1). However, published data generated by leading clinicians, radiologists, and histopathologists cannot be extrapolated to practice outside tertiary centers. In a study from Michigan, a previously reported multidisciplinary diagnostic algorithm (2) was compared between expert and community practitioners using a common dataset (3). Diagnostic agreement was moderately good between expert participants and improved significantly when a final diagnosis was formulated from clinical, imaging, and biopsy data. By contrast, agreement on the final diagnosis was only fair between community physicians, even though diagnostic agreement improved as data were integrated. These findings underline what is likely to become an increasingly important issue: the need for regional clinics in diffuse lung disease, with ready access to specialist skills in key disciplines. Further studies are now required to quantify the value added by expert evaluation. In Flaherty and colleagues' studies (2, 3), the greatest disparity between the two groups lay in the diagnosis of nonspecific interstitial pneumonia (NSIP), which was more often identified by academic practitioners than by community participants, who tended to prefer a diagnosis of idiopathic pulmonary fibrosis (IPF).

NSIP, initially viewed as a "provisional" entity in the deliberations of the American Thoracic Society/European Respiratory Society International Consensus Committee (4), is often a source of diagnostic confusion. Idiopathic NSIP and NSIP secondary to disorders such as hypersensitivity pneumonitis (HP), drug-induced lung disease, and, especially, connective tissue disease (CTD), are often subcategorized, but recent data suggest that this distinction may be largely artificial. In a cohort of patients with idiopathic NSIP, careful evaluation disclosed a very high prevalence of clinical and serologic abnormalities strongly suggestive of underlying undifferentiated CTD or "CTD in waiting" (5), lending support to the hypothesis that idiopathic NSIP is, in reality, CTD confined to the lungs in many cases (6). Further important insights came from a study in which outcomes in biopsied patients were compared between idiopathic NSIP, IPF, and pulmonary fibrosis in CTD (7). Severity-adjusted survival in idiopathic NSIP was virtually identical with that of NSIP in CTD, in keeping with a systemic autoimmune hypothesis for idiopathic NSIP. By contrast, mortality was higher in patients with IPF than in patients with CTD and usual interstitial pneumonia (UIP). Interestingly, mortality in UIP was higher in rheumatoid arthritis (RA) than in other CTDs and was only marginally lower than in IPF, although the small size of the RA subgroup is an important caveat. UIP was more prevalent than NSIP in this RA cohort, and, based on earlier reports (8–10), appears to be much more prevalent in RA than in other CTDs.

On the basis of these and earlier observations, it appears that the entity of NSIP in the current classification of the idiopathic interstitial pneumonias (IIPs) should now be reappraised. It has also been argued that the current classification of the IIPs creates difficulties in the search for new therapies, by causing undue polarization between competing pathogenetic hypotheses (11).

In HP, fibrotic NSIP and UIP both occur, and gene expression data are suggestive of underlying HP in a subset of patients with apparently idiopathic NSIP (12). The relative prognostic significance of these patterns in HP is not yet known but, based on a recent report, it appears that computed tomography (CT) findings of extensive reticular disease, with or without honeycombing, and traction bronchiectasis are strongly indicative of underlying fibrotic disease (13). Further CT studies in larger cohorts of patients with HP can be anticipated, comparing outcomes in relation to CT patterns of NSIP and UIP.

Prevalence and Outcome of Fibrosing Lung Disease

In IPF, the rare occurrence of a response to therapy (regression of dyspnea and improvements in pulmonary function tests) has now been linked to histologic components of organizing pneumonia and lymphoplasmacytic inflammation (14). However, in the great majority of cases, deterioration occurs sooner or later despite treatment. Typically, this takes the form of insidious and predictable deterioration over time, but acute and often catastrophic declines after periods of stability are increasingly recognized. These episodes, termed "acute exacerbations of IPF" when the etiology is unknown, are poorly understood, but their 2-year prevalence in IPF may exceed 10% (15). In a consensus statement, issued as a perspective, a welcome attempt has been made to standardize diagnostic criteria; possible pathogenetic mechanisms and future research directions are also discussed (16).

Recent reports have suggested that IPF is substantially more prevalent than previously reported, both in the United States (17) and in the United Kingdom (18). Support for these findings comes from the observation that mortality from pulmonary fibrosis increased by approximately 30% in men and 40% in women between 1992 and 2003, with 60% of deaths due to the disease itself (19). The authors highlight the fact that mortality from pulmonary fibrosis now exceeds that of many malignancies, such as bladder cancer, acute myeloid leukemia, and multiple myeloma. In common with the British Thoracic Society study of cryptogenic fibrosing alveolitis (CFA) (20), secondary causes of pulmonary fibrosis were excluded, and the terms "pulmonary fibrosis" and "CFA" were inclusive, covering all cases of apparently idiopathic disease and not IPF alone. Broad definitions are both unavoidable and desirable in epidemiologic studies and, in any case, IPF must necessarily be responsible for the great majority of fatalities in pulmonary fibrosis of unknown origin. However, terms such as "pulmonary fibrosis,"

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and especially "CFA," used elsewhere as a synonym for IPF, can cause confusion when used in a broad idiopathic context. A separate term is increasingly needed for the clinical presentation studied by epidemiologists (21).

Lung Disease in Systemic Sclerosis

Unlike previous years, no major studies of new therapies were published in fibrosing lung disease in 2007. However, for the first time in this field, the lasting effects of treatment after trial cessation were quantified. The Scleroderma Lung Study (SLS) group reported that, after 1 year of placebo-controlled oral cyclophosphamide for pulmonary fibrosis in systemic sclerosis (SSc), the benefits of active treatment had persisted at 6 months but not at 1 year (22). Importantly, the treatment benefit consisted of the prevention of disease progression in more advanced fibrotic disease, rather than regression of reversible inflammatory disease. By demonstrating internal consistency, these follow-up data strongly endorse the credibility of the previously reported treatment effect (23). One obvious implication is that oral cyclophosphamide therapy should be consolidated by a less toxic agent in the longer term. Intravenous cyclophosphamide and oral mycophenolate mofetil have both been proposed as suitable longer term treatments, or even as substitutes for the initial use of oral cyclophosphamide (24). A further important issue was the problem of selection bias in placebo-controlled studies, especially when open therapy is available with the same agent. Patients with severe or rapidly progressive disease tend to receive open treatment, with the result that trial cohorts may be characterized by milder and less progressive disease, with little chance of large treatment benefits. In support of this view, open treatment was prescribed by local physicians in less than 20% of patients during the year after cessation of trial treatment in the SLS study (22), suggesting that patients with the most to gain from cyclophosphamide therapy were underrepresented in the trial (24). This caveat may also apply to other therapeutic studies in fibrosing lung disease.

The SLS group has illuminated lung disease in SSc, demonstrating the benefits offered by a consortium in less prevalent disorders. In recent publications of their cohort with lung disease, they document improvements in health-related quality of life with the use of cyclophosphamide for 1 year (25) and establish that the pulmonary benefits of cyclophosphamide apply equally to the limited and diffuse cutaneous subgroups (26). Publication of their bronchoalveolar lavage (BAL) data, expected in the near future, will be of great interest. Although historically considered to provide useful prognostic information in SSc, the presence of a BAL neutrophilia was recently found in a large SSc cohort to be linked only to early mortality and not to long-term survival or the rapidity of pulmonary function decline (27).

Genotype–Phenotype Interactions and Applied Technology in Fibrosing Lung Disease

The most important advances in this area during 2007 related to familial pulmonary fibrosis. In a study of familial IPF, Tsakiri and colleagues used linkage in two families to locate the disease gene for IPF in chromosome 5, and identified mutations in the telomerase that cosegregated with pulmonary disease (28). Proband sequencing in 44 additional affected families disclosed five other telomerase mutations, not seen in control subjects, with a mutation also found in 1 of 44 patients with sporadic IPF. Thus, it appears that mutations resulting in telomere shortening are associated with a marked increase in susceptibility to adult-onset IPF. However, familial pulmonary fibrosis also includes other forms of fibrosing lung disease. In a study of 164 subjects from 18 kindreds affected with familial IPF, high-resolution CT (HRCT) abnormalities suggestive of interstitial lung disease were present in over 20% of asymptomatic individuals (29). Compared with the patients with known familial IPF, those with asymptomatic disease on HRCT were younger, and in both groups the prevalence of smoking was significantly higher than in family members without lung disease. Surgical lung biopsies in six patients with asymptomatic disease showed patterns of UIP (n = 3), NSIP (n = 1), HP (n = 1), and cellular interstitial and organizing pneumonia (n = 1). These findings argue for a genetic predilection to fibrosing disease in general in some families, with the specific histologic pattern determined by genetic or environmental cofactors. Other recent reports of genotype–phenotype interactions included the observation that, in six patients with alveolar microlithiasis, mutations in the SLC34A2 gene were uniformly present (30) and a case report of pulmonary lymphangeiomyomatosis in a karyotypically normal man without tuberous sclerosis complex showed similar findings (31).

In an interesting report, the concept of "percolation," which relates to transmission of events across complex networks, was invoked in a model of pulmonary fibrosis and coexistent emphysema (32). Mechanical dysfunction from these processes was simulated by a network of springs, with randomly stiffening of individual springs but cutting of springs under greatest tension, to capture the separate mechanical effects of fibrosis and emphysema. Percolation thresholds, related to linkage of stiffened springs across the model and to a sufficient profusion of cut springs, identified sudden and striking increases and decreases in elastance, respectively. By implication, the concept of percolation may account for the often poor relationship between symptomatic change and the evolution of parenchymal pathology when pulmonary fibrosis and emphysema coexist.

PATHOBIOLOGIC CONCEPTS

Inflammation and Fibrosis: Déjà Vu All Over Again?

Progressive pulmonary fibrosis appears to be the coalescence of a complex mix of environmental and genetic factors. Clinically, interstitial lung diseases remain poorly characterized, thus hampering definitive progress in our understanding of their etiopathogenesis. However, the use of global transcription analysis via DNA microarray and proteomic analysis via tissue microarray has provided important clues that will not only aid in the diagnosis of these diseases but also reveal therapeutic targets (33, 34). Major progress was made in the identification of the genetic factors that might contribute to the magnitude and duration of pulmonary fibrotic responses. Many of the published studies were of a confirmatory translational design involving concomitant analysis of human and murine tissue samples. Again, bleomycin sulfate was the predominate trigger used in the experimental investigation of pulmonary fibrosis.

Yang and colleagues (35) provided a detailed gene expression profile of familial and sporadic (or nonfamilial) interstitial pneumonia. Patients with UIP and NSIP were included in their IIP analyses, as were normal control subjects. These data highlighted that, regardless of the type of IIP (UIP vs. NSIP), there was a predominance of genes regulating extracellular matrix and chemokine activity in the lung of patient biopsies relative to control biopsies. The observation that NSIP differed little from UIP is surprising given the clinical distinction observed between these forms of IIP and other studies that did reveal a difference at the transcript level (12). Further investigation of this finding with a larger sample size is certainly warranted. Familial IIP appeared to be a more severe version of IIP, because this group of patients expressed all of the transcripts that distinguished sporadic IIP from control biopsies,

but the levels of expression were higher (35). Experimental analysis of CXCL12, an inflammatory CXC chemokine transcript of interest from the human microarray, revealed a major biologic role for this chemokine and its corresponding receptor CXCR4 in bleomycin-induced experimental fibrosis.

Tzouvelekis and colleagues (36) provided a comparative expression profile in the bleomycin model of fibrosis but extended their analysis to include a meta-analysis of publicly available microarray datasets relevant to human IPF and/or experimental pulmonary fibrosis. Surprisingly, this meta-analysis revealed a number of genes in common among all the datasets, and these investigators were able to further "mine" these genes using numerous statistical tools. Two major deregulated pathways emerged: integrin and hypoxia signaling (36). The role of hypoxia in the pathogenesis of pulmonary fibrosis was explored further via semiquantitative polymerase chain reaction and proteomic tissue microarray; hypoxia inducible factor (HIF)-1α and HIF target genes were found to be overexpressed in IPF hyperplastic type II alveolar epithelial cells. Obviously, HIF-1α is triggered under hypoxic conditions but this factor is also driven during normoxic inflammatory conditions, particularly in the presence of tumor necrosis factor (TNF)-α.

Pottier and colleagues (37) addressed the issue of genetics in the susceptibility to bleomycin-induced fibrosis via a microarray analysis of a susceptible and a resistant mouse strain. Although these types of microarray-driven studies in established bleomycin-induced pulmonary fibrosis have been reported in the past, the present study focused on the early inflammatory events after bleomycin challenge and identified dipeptidyl-peptidase I (DPPI or cathepsin C) and tissue inhibitor of matrix metalloproteinase (TIMP)-3 as novel immune/inflammatory genes, which were upregulated only in the susceptible mouse strain. This study raises the interesting possibility that fibrotic responses in the lung relate to poorly regulated or dysregulated immune or inflammatory responses. Extending this concept further, Baran and coworkers (38) directly examined phagocytic cell byproducts, namely macrophage colony stimulating factor (M-CSF) and CC chemokine ligand 2 (CCL2). Although both factors have been examined in the context of several forms of tissue remodeling, this study highlights the link in function of M-CSF and CCL2 in pulmonary fibrosis. Mice genetically deficient in either immune factor were protected from bleomycin-induced fibrosis, highlighting the therapeutic potential in targeting one or both of these mediators in interstitial lung disease. The authors make the case for targeting M-CSF because this mediator was elevated in BAL samples from patients with IPF, and M-CSF induced CCL2 expression by mouse bone marrow–derived macrophages (38). These findings should be balanced with those of Ren and colleagues (39) who demonstrated that alveolar macrophages, but not blood monocytes, from patients with IPF exhibited a global down-regulation in gene expression, and therefore activation. One explanation for this decreased transcription was found in the levels of transcription factor II-H, which were significantly lower in IPF compared with normal alveolar macrophages.

Immune cells, other than macrophages, and including dendritic cells are elevated and appear to be active in IPF, as shown by Marchal-Somme and coworkers (40). An explanation for the accumulation of dendritic cells in the lungs of patients with IPF is not presently known but altered epithelial cells and fibroblasts in patient biopsies were found to highly express several chemotactic factors, including CCL19, CCL20, CCL22, and CXCL12, that favor dendritic cell recruitment.

Taken together, these studies bring immune and inflammatory mechanisms back into focus within this field, and serve to suggest that a causal link exists between inflammation and pathologic pulmonary fibrosis.

Targeting Experimental Fibrosis: The Advent of Cell-specific and the Enhancement of Drug-based Antifibrotic Therapies

The exact manner in which the immune and/or inflammatory response contributes to pulmonary fibrosis remains to be answered. Mora and colleagues (41) directed their attention to the relevance of an inappropriately controlled viral infection as one root cause for progressive interstitial fibrosis. They showed that murine γ-herpesvirus infection in mice genetically lacking the IFN-γ receptor promotes the development of pulmonary fibrosis but only if the replication of this herpesvirus was not appropriately controlled with an antiviral agent (cidofovir) or via gene modification of the virus (41). These studies raise the exciting possibility that the pathogenesis of human IPF might be directly related to recurring viral (particularly large DNA viruses such as Epstein-Barr virus and herpesviruses) infection, explaining the ongoing alveolar epithelial injury and subsequent myofibroblast activation in this disease. Antiviral therapy might provide therapeutic efficacy in patients with recurring pulmonary, cell-lytic viral infections.

An alternative strategy for reversing the inappropriate remodeling response associated with pulmonary fibrosis was present by Serrano-Millar and colleagues (42). In their study, intratracheal transplant of alveolar type II cells was performed at Days 3, 7, or 15 after intratracheal bleomycin challenge in rats, and lungs were analyzed from these and control groups at Day 21 after bleomycin. Remarkably, this approach led to reduced collagen deposition in all treatment groups (42).

Although the role of T cells in bleomycin-induced pulmonary fibrosis is controversial (43), Fujimoto and colleagues (44) provided compelling evidence that pharmacologic suppression of nuclear factor (NF)-κB in T cells not only prevented pulmonary fibrosis, but also worked therapeutically in a bleomycin-induced pulmonary fibrosis model. SP100030 is a T-cell–specific inhibitor of NF-κB and activator protein (AP-1) in T cells, and the authors showed that this agent inhibited the inflammatory and the fibrotic phases of bleomycin-induced pulmonary fibrosis. One intriguing explanation for the therapeutic efficacy of SP100030 relates to the effect of this compound on the balance between coagulation and fibrinolytic factors. As the authors suggest, a shift toward a predominance of coagulation over fibrinolysis promotes fibrosis, and T cells appear to either directly or indirectly contribute to the promotion of coagulation over fibrinolysis.

Imatinib mesaylate is a tyrosine kinase inhibitor regulating the activation of bcr-abl, c-kit, and platelet-derived growth factor receptor in immune and nonimmune cells. This drug has been shown to prevent the development of fibrosis, but its efficacy is markedly attenuated when it was administered therapeutically during established pulmonary fibrosis. Azuma and colleagues (45) provided an explanation for the drop-off in potency of imatinib: the induction of α_1-acid glycoprotein (AGP), a major drug binding protein, during fibrosis binds imatinib and prevents its antifibrotic effects. The inclusion of erythromycin and clarithromycin, which compete with imatinib for AGP, markedly bolstered the antifibrotic effects of imatinib *in vitro* and *in vivo*. Together, these studies provide multiple treatment options worthy of consideration in the treatment of human IPF.

HP: Inappropriate Immune Activation due to Microchimerism?

HP is a grouping of antigen-driven, inflammatory lung diseases. Various antigens have been identified in HP and *Saccharopolyspora rectivirgula* (SR) is the causative agent in a form of HP also referred to as farmer's lung. SR induces an HP-like disease in mice and this model has been used extensively to study the immune mechanisms that account for disease. Considerable

evidence exists pointing to the importance of Th1-type cells in the pathology associated with clinical and experimental HP. Given the importance of Th1 cytokines, Matsumo and colleagues (46) addressed the hypothesis that the Th1 phenotype during experimental HP could be regulated using a transcriptional factor called GATA binding protein-3 (GATA-3). Although GATA-3 induces Th2 cytokines in T cells, it also has a marked suppressive effect on Th1 cytokine production by T cells. Therefore, using GATA-3–overexpressing transgenic mice, the investigators showed that the overexpression of GATA-3 attenuated the development of experimental HP via the suppression of Th1 cytokine elaboration and polarization of this cytokine response.

Although it is appreciated that environmental antigens drive HP, these diseases only affect a subset of exposed individuals. This anomaly prompted Bustos and coworkers (47) to turn their attention to an endogenous explanation, and they were struck by the preponderance of women of childbearing age with these diseases. They hypothesized that an endogenous stimulus for HP might be the presence of fetal microchimeric cells, and the presence of male fetal microchimerism was examined in peripheral blood, BAL, and lung tissue from female patients with HP and IPF, and healthy women. Male cells were detected in the lung tissues from a subgroup of patients with HP, but no microchimeric cells were detected in IPF lung samples (47). Many of the microchimeric cells were either macrophages or $CD4^+$ or $CD8^+$ T cells. These data raise the interesting possibility that the microchimeric immune cells might be participating in the immune response that characterizes HP.

Receptor for Advanced Glycation End Products in Sarcoid

Sarcoidosis is another T-cell–driven disease characterized by the appearance of specific noncaseating granulomas in various organs. The genetic basis of this disease remains poorly described. Campo and colleagues (48) were interested in a gene that mapped to the same chromosomal region as butyrophilin-like-2, another gene associated with sarcoidosis. This gene is the receptor for advanced glycation end products (RAGE), which recognizes multiple tertiary structures, such as advanced glycation end products, byproducts of glycation, and oxidation of lipids and proteins. The investigators detected RAGE in sarcoid biopsies and found that there was an increase in functional variant of RAGE within similar biopsies. These findings raise the possibility that genetic susceptibility to sarcoid is related to increased RAGE expression and/or altered function. Further studies regarding RAGE in sarcoid are certainly warranted on the basis of these data.

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