Review Article

Recent advances in interstitial lung disease research

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Abstract

The interstitial lung diseases are a diverse collection of disorders characterized by impaired gas exchange, restricted physiology on lung function testing, and diffuse parenchymal lung infiltrates on radiography. Although the interstitial lung diseases are many (Table 1), in routine clinical practice, the most commonly encountered in general internal medicine practice are sarcoidosis, idiopathic pulmonary fibrosis, and connective tissue disease-associated interstitial lung diseases. In immunocompromised patients, infection is the most common cause of diffuse lung infiltrates and must be ruled out before any attempt to treat with immune altering agents like corticosteroids. This review will focus on the more clinically significant recent advances in the broad field of interstitial lung disease research, with emphasis on the more common interstitial lung diseases occurring in immunocompetent hosts.

Advances in the classification of idiopathic interstitial lung diseases

Idiopathic pulmonary fibrosis (cryptogenic fibrosing alveolitis in the British literature), is one of the commonly encountered interstitial lung diseases, with an estimated prevalence of 5-20 per 100,000.[1] Formerly, the term idiopathic pulmonary fibrosis was used to describe a variety of idiopathic interstitial pneumonias (listed in Table 1), characterized clinically by finger clubbing and bibasilar "velcro" crepitations on examination. It is now apparent that these findings are not specific, and may be associated with any of the idiopathic interstitial pneumonias listed in Table 1.

Keywords

Intersitial lung disease, advances

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A recent joint statement by the American Thoracic Society and the European Respiratory Society, recommended that the term idiopathic pulmonary fibrosis be restricted to patients with the histopathologic lesion of usual interstitial pneumonia (Table 1).[1] These guidelines resulted from the demonstration by numerous groups that the prognosis of patients with the lesion of usual interstitial pneumonia is distinctly worse than other types of idiopathic interstitial pneumonia.[2-5] The median survival of patients with usual interstitial pneumonia is 3-5 years, and response to corticosteroid therapy is uniformly poor.[1,2, 5] In contrast, the other idiopathic interstitial pneumonias are frequently steroid-responsive, and most patients survive >10 years after diagnosis.[1,2] As a result of these recent findings, it is recommended that definite diagnosis with lung biopsy be considered in all patients suspected of having an idiopathic interstitial pneumonia.

Advances in Diagnostic Imaging: the High Resolution CT scan

The chest high resolution CT scan (HRCT) emerged over the 1990s as an indispensable non-invasive diagnostic tool.[6] Whereas conventional CT of the chest examines 7- to 10-mm slices obtained at 10-mm intervals, HRCT examines 1.0- to 1.5-mm slices at 10-mm intervals, illustrating lung parenchyma in much better detail than conventional CT. In patients with interstitial lung disease, a systematic analysis of HRCT patterns is very important, permitting a diagnostic accuracy ranging from 50 to 90% (in selected series comparing HRCT with histopathology), depending on disease entity, and the experience of the interpreting radiologist.[7-11] Characteristic HRCT appearances have been described in sarcoidosis, idiopathic pulmonary fibrosis, pulmonary Langerhans' cell Histiocytosis, pulmonary alveolar proteinosis, and lymphangioleiomyomatosis.[10,12,13] In the appropriate clinical setting, a characteristic HRCT may enable a provisional diagnosis without resort to lung biopsy. HRCT is also useful to guide the selection of lung regions to biopsy when either bronchoscopic or surgical lung biopsy is planned. It is important to remember that the utility of HRCT in diagnosing interstitial lung disease is directly proportional to the degree of expertise of attending radiologists reading the scans. It is also essential to emphasize that confirmation of the diagnosis by histopathology remains essential prior to embarking on potentially toxic immunosuppressive trials, with the exception of those cases when the HRCT findings and clinical data are absolutely characteristic of the disease entity.

Table 1: *Classification of the interstitial lung diseases**

Interstitial Lung Diseases	Examples
Granulomatous interstitial lung diseases	Sarcoidosis Berylliosis
Interstitial lung diseases of known cause	Inhalation of foreign antigen (hypersensitivity pneumonitis) Drug-induced (bleomycin,amiodarone,radiation,nitrofurantion,methotrexate) Connective tissue diseases (rheumatoid disease, scleroderma, poly/dermatomyositis, SLE) Asbestos
Idiopathic interstitial pneumonias	Usual interstitial pneumonia† Desquamative interstitial pneumonia Respiratory-bronchiolitis associated interstitial lung disease Bronchiolitis obliterans with organizing pneumonia Non specific interstitial pneumonia Acute interstitial pneumonia
Other forms of interstitial lung disease	Pulmonary Langerhans' cell histiocytosis Lymphangioleiomyomatosis Pulmonary Alveolar Proteinosis Lymphoid interstitial pneumonia

*This is not a comprehensive list of the interstitial lung diseases, but a simplified classification system.
†Usual interstitial pneumonia is the histologic lesion associated with the clinical diagnosis of idiopathic pulmonary fibrosis.

Lung biopsy: when, why, who, and how to biopsy

Changes in the classification of idiopathic interstitial pneumonias and novel therapies for interstitial lung diseases provide important reasons to pursue lung biopsy. The decision to perform lung biopsy in patients with interstitial lung disease depends on available resources, and the potential benefit that knowledge of a specific histopathological diagnosis may have on therapy, or prognosis. A practical example is the clinical situation of suspected idiopathic pulmonary fibrosis in a relatively young individual. The fact that usual interstitial pneumonia has a remarkably worse prognosis than other histopathological subsets provides a compelling reason to recommend lung biopsy. However, in an elderly patient with identical clinical features, lung biopsy may not be in the patient's best interest, since the risk of the procedure may outweigh the potential benefit of establishing a specific diagnosis. Furthermore, long-term immunosuppressive therapy or lung transplantation may not be practical therapeutic options in older individuals.

Lung biopsy may be performed by bronchoscopy or surgically (video-assisted surgical thoracotomy (VATS) or standard open thoracotomy). Bronchoscopic lung biopsy has a limited role in the diagnosis of most interstitial lung diseases (with some exceptions), because tissue samples obtained are often too small to allow a specific histopathological diagnosis. However, in patients suspected of having sarcoidosis, lymphangitic carcinomatosis, or eosinophilic pneumonia, bronchoscopic biopsy may be of substantial yield, and obviate the need for more invasive testing. In medical centers with limited access to surgical lung biopsy, it is reasonable to consider bronchoscopic biopsy in all patients with equivocal HRCT patterns, particularly if one is contemplating a trial of immunosuppression.

In addition to enabling lung biopsy, bronchoscopy also provides an opportunity to perform bronchoalveolar lavage (BAL). BAL is safe, minimally invasive, and provides specific information in specific disorders. Specific diagnoses that may be established by BAL include alveolar proteinosis, lymphangitic carcinomatosis, and alveolar cell carcinoma (which may mimic interstitial lung disease). BAL also provides clinically helpful information in the following situations: (1) increased numbers of eosinophils in acute or chronic eosinophilic pneumonia, (2) asbestos bodies in asbestosis, (3) foamy cells with lamellar inclusions in amiodarone-induced pneumonitis, (4) hyperplastic and atypical type II pneumocytes in cytotoxic drug-induced lung injury, (5) an increase in CD1a positive cells in Langerhans' cells histiocytosis, and (6) a bloody effluent with abundant hemosiderin in alveolar macrophages (>20% of total macrophage numbers) in diffuse alveolar hemorrhage secondary to pulmonary hemorrhage syndromes. Although these findings are non-diagnostic (for example foamy cells may be seen in patients on amiodarone therapy without pneumonitis), they may provide useful additional clues to the potential cause of interstitial lung disease. Quantifying the type of inflammatory cell infiltrate in BAL may also suggest specific diagnoses. For instance, sarcoidosis and hypersensitivity pneumonitis are associated with a lymphocytosis, whereas chronic eosinophilic pneumonia is associated with an increased BAL eosinophil count.

BAL has been used as a research tool to enhance understanding of pathogenesis of various types of interstitial lung disorders. In this regard, BAL findings contributed to the characterization of idiopathic pulmonary fibrosis as a condition with a predominant T-helper-2 cytokine profile (Th-2: T-helper cells are subsets of T cells that express the CD4 receptor and

play an important role in host responses to antigens), whereas BAL findings in sarcoidosis and hypersensitivity pneumonitis are characterized by a Th1-dominant profile. The clinical value of BAL to assess the activity of disease processes and to provide prognostic information is still under debate.

In a significant proportion of patients with interstitial lung disease, definitive diagnosis cannot be established without surgical lung biopsy. In these situations, the risks of the surgical procedure have to be put into the context of presumed benefit of obtaining a specific diagnosis. Surgical lung biopsy is associated with a relatively small but appreciable mortality (approximately 3%) even when performed by experienced surgical teams. Adequate lung tissue samples should be at least 2 cm in diameter and are ideally obtained from separate sites to increase diagnostic yield.

Advances in the diagnostic approach for interstitial lung disease

Histopathologic evaluation was considered by many as the "gold standard" for diagnosis in interstitial lung disease. That perception is now changing. Although surgical lung biopsy often provides a definitive diagnosis in patients with challenging clinical lung disease, it is also fraught with certain difficulties that must be appreciated. Recently, Flaherty and colleagues documented the problem of "sampling error", in which divergent histopathologic diagnoses in two or more biopsy sites may be found.[14] This is an extremely important issue since sampling lung tissue that is not significantly involved with the disease process may lead to an incorrect or improper characterization of the underlying lung disease. The likelihood of sampling error should be minimized by using HRCT to select multiple biopsy sites representative of the full range of morphologic appearances. A second important consideration is interobserver variation between pathologists. In recent studies, substantial observer variation occurred between experienced specialist thoracic histopathologists.[15] This may occur because of lack of familiarity with interstitial lung disease pathology, or due to histopathologic appearances that may be intermediate between two entities. It is because of these issues that clinical and imaging data become key determinants of a final consensus diagnosis.

With the advent of an ever-increasing range of serological, radiographic, and molecular diagnostic techniques, the diagnosis of many interstitial lung diseases has evolved significantly over the past decade. The availability of new agents to treat specific interstitial lung diseases mandates that an accurate diagnosis be established prior to embarking on therapy that may be associated with considerable cost and adverse effects. Numerous novel therapies are being tested in phase 2 and 3 clinical trials for various interstitial lung diseases, a testimony to the substantial recent advances made in molecular, genetic, and immunological understanding of interstitial lung diseases. In the remainder of this review, advances in therapy of interstitial lung diseases will be discussed.

The idiopathic interstitial pneumonias and smoking-related interstitial lung diseases

There are no therapies known to improve survival of patients with idiopathic pulmonary fibrosis. Traditionally, corticosteroids have been the mainstay of pharmacologic therapy, although this has never been proven in prospective or randomized trials to confer any objective improvement in lung function or survival advantage. While some studies showed subjective benefit with corticosteroid use,[16] others reported that corticosteroids and immunosuppressive treatments were ineffective.[17-19] This discrepancy can be explained by the fact that some of the earlier studies were contaminated by the inclusion of corticosteroid-sensitive idiopathic interstitial lung diseases such as non-specific interstitial pneumonia. The lack of effectiveness of prednisone and other anti-inflammatory agents brought about a important change in what is currently believed to be relevant to the pathophysiology of idiopathic pulmonary fibrosis. Previously considered to be an inflammatory disease, expert opinion and general consensus have now shifted to a concept of abnormal tissue healing resulting in fibrosis as a consequence of a predominance of T helper lymphocyte type 2 cytokines (or alternatively a relative lack of opposing T helper type 1 cytokines).[20]

The frustration resulting from lack of effective therapies together with emerging concepts on pathophysiology that challenge the inflammatory hypothesis have fueled an enormous amount of activity, culminating in numerous ongoing clinical trials. Based on molecular studies and laboratory animal studies, numerous agents have been proposed for management of idiopathic pulmonary fibrosis, and a number of these agents are currently undergoing testing in randomized clinical trials.

Interferon-gamma is one of the novel biological agents. A preliminary study conducted on 18 patients with histopathologically-proven idiopathic pulmonary fibrosis treated for 12 months with interferon gamma-1b plus prednisolone was associated with substantial improvement in lung function.[21] Unfortunately, this study was not confirmed by a large phase 3 multi-center placebo-controlled double-blinded randomized trial, that failed to show a beneficial effect of interferon-gamma therapy on overall mortality and progression in lung function decline.[22] Subset analysis from this trial suggested that treatment with interferon-gamma may confer a survival benefit to patients with mild to moderate disease (as defined by the degree of restriction on pulmonary function testing). This conclusion is of doubtful significance considering that it is based on post-hoc sub-group analysis and therefore may not be statistically valid. There are also concerns regarding the use of interferon-gamma in patients with advanced disease, as there is data to suggest that patients with advanced idiopathic pulmonary fibrosis have a worse outcome with interferon-gamma therapy.[23] Before additional data from larger trials on interferon-gamma are forthcoming, it is reasonable to conclude that there is no convincing evidence to support the routine use of interferon gamma, with the exception of patients with early idiopathic pulmonary fibrosis (defined by FVC>55% predicted

and symptom onset of less than 12 months). Considering the considerable cost associated with this therapy (> $50,000.00 annually per patient in the US) and potential adverse effects, significant caution should be exercised prior to prescribing this medication, even to patients with early stage disease.

Other novel agents being evaluated include inhibitors of the pro-inflammatory cytokine tumor necrosis factor-alpha (TNF-alpha), inhibitors of endothelin-1 (bosentan), and imatinib mesylate (a protein-tyrosine kinase inhibitor). Enthusiasm for these therapies in idiopathic pulmonary fibrosis is based on in vitro data, animal studies, and reports of efficacy in isolated patients or small case series.[24-26] Data from ongoing clinical trials should be available in the next 1 to 3 years. The anti-oxidant N-acetylcysteine (NAC) is also under investigation in a phase 3 clinical trial that should be completed in the near future. Other molecular targets under investigation include antagonists of transforming growth factor-beta (TGF-β, a cytokine with a prominent role in the formation of scar tissue) and biological inhibitors of integrin receptors (integrins are a superfamily of cell surface proteins that regulate binding of cells to extracellular matrix components).

Although ineffective in the management of idiopathic pulmonary fibrosis, corticosteroids are very useful in the management of other interstitial lung diseases including BOOP, non-specific interstitial pneumonia, desquamative interstitial pneumonia and others. It is important to remember that many of the aforementioned diseases may be clinically and radiographically very similar to idiopathic pulmonary fibrosis, and that one should strive to make an accurate diagnosis prior to dismissing the use of corticosteroids on the presumption of probable pulmonary fibrosis.

Another recent concept that has modified the way we think about idiopathic interstitial pneumonias is the appreciation that smoking may induce or alter the course of certain interstitial lung diseases. It is apparent that some interstitial lung diseases occur almost exclusively in smokers, and are sometimes collectively referred to as smoking-related interstitial lung diseases.[27, 28] These disorders include desquamative interstitial pneumonia, respiratory bronchiolitis-associated interstitial lung disease, and pulmonary Langerhans' cell histiocytosis.[28] In addition to the causal relationship to smoking, these diseases have been reported to spontaneously improve upon smoking cessation,[29] can recur in a transplanted lung following the resumption of smoking, and histopathological findings of all of these lesions may occur in the same individual.[30] The recognition that these diseases are related to smoking is not just a matter of semantics. The cornerstone of therapy for these patients is smoking cessation, in the absence of which, immunosuppressive therapy may have no effect whatsoever. In addition, smoking is now considered to be a risk factor for the development of idiopathic pulmonary fibrosis and acute eosinophilic pneumonia.[31]

Sarcoidosis

The cornerstone of pharmacotherapy for sarcoidosis remains corticosteroids; however, not all patients with sarcoidosis need therapy. A recently consensus statement published by American Thoracic and European Respiratory Societies provides an excellent review on the challenges associated with treatment of sarcoidosis, and confirms prior opinion that cardiac or neurological involvement, hypercalcemia, and ocular disease which cannot be controlled by topical therapy are best managed by judicious use of oral corticosteroid therapy.[32] Management of pulmonary sarcoidosis (which occurs in about 90% of patients) remains challenging. It is well-established that patients with stage 1 disease (bilateral hilar adenopathy but no lung infiltrates on chest radiograph) do not require therapy and generally have an excellent prognosis. Patients with stage 2 or 3 disease (involvement of lung parenchyma in association with or without hilar adenopathy) are the ones at risk of developing progressive lung fibrosis and irreversible lung injury. Although intuitively patients with stage 2 or 3 disease would seem to be the sub-group to whom aggressive therapy should be targeted, controversy and doubt remain regarding the timing of use of oral corticosteroid therapy, the dose and duration of therapy, and ultimately the long-term effect of corticosteroid therapy on lung function. A systematic review of published studies on corticosteroid therapy in stage 2 and 3 pulmonary sarcoidosis concluded that use of oral steroids was associated with improvement in chest radiography and small improvements in vital capacity and diffusing capacity measurements.[33] A more recent systematic analysis of published data reported that oral steroids improved radiographic findings, symptoms and spirometry of patients with Stage 2 and 3 disease over a period of 3-24 months. However, there was little evidence that objective lung function improved.[34] Although the optimal dose and duration of corticosteroids has not been studied in randomized trials, it is currently recommended that for patients requiring treatment, an initial dosage of 20-40 mg/day of prednisone or its equivalent on alternate days is used with evaluation of response following 3 months. Among steroid responders, the dose should be slowly tapered to 5-10 mg/day or an every other day regimen, and treatment continued for a minimum of 12 months. Azathioprine is useful as a steroid sparing agent in patients requiring long-term oral corticosteroids.

For patients with progressive symptoms in spite of adequate steroid therapy, numerous second-line agents have been proposed as effective for disease control, yet none have undergone rigorous testing by randomized trials. Hydroxychloroquine is effective for control of cutaneous sarcoid,[35, 36] and has also been successfully used to treat sarcoid-associated hypercalcemia, arthritis, neurological disease, and pulmonary disease.[37-39] The TNF-alpha inhibitors infliximab and etanercept have both been used in small case series of patients with sarcoidosis refractory to corticosteroid therapy, with conflicting outcomes.[40-46] Most reports suggest that Infliximab is superior to Etanercept in controlling severe sarcoidosis and should be the agent of choice if TNF-alpha inhibition is to be considered in patients with severe, refractory sarcoid. Other agents that might function as antagonists of TNF-alpha include Pentoxifylline and Thalidomide.

Pentoxifylline has been reported to have efficacy in the management of various complications associated with sarcoidosis, and is a useful alternative to high-dose corticosteroids or monoclonal TNF-alpha inhibitors in selected patients.[47] Thalidomide is predominantly used to manage cutaneous sarcoid and has very little proven activity for other manifestations of sarcoid.[36] Recently, oral Methotrexate (10-25mg/week) was reported to have some efficacy in controlling the interstitial lung disease associated with sarcoid, although it is unclear whether it has any efficacy as a single-agent or as a steroid-sparing agent.[48] Use of methotrexate in any patient with interstitial lung disease is also complicated by the potential for development of methotrexate-associated pneumonitis, which may be impossible to distinguish from natural progression of the underlying lung disease.[49]

Interstitial lung disease associated with connective tissue diseases

Interstitial lung disease frequently complicates the course of many rheumatic diseases and can result from a variety of histological lesions identical to the idiopathic interstitial pneumonias.[50] Although the relative frequency of occurrence of these histopathological lesions is not definitively established, it seems that non-specific interstitial pneumonia accounts for a large proportion of rheumatic-associated interstitial lung disease. Whether the natural history and response to therapy of interstitial lung disease associated with rheumatic disease is identical to that of the same lesions occurring in patients with no underlying disease is uncertain, and needs to be addressed in prospective studies. In parallel to what is observed with idiopathic pulmonary fibrosis, the occurrence of usual interstitial pneumonia in patients with connective tissue disease generally portends a poor response to corticosteroid therapy and an unfavorable prognosis. It is still unclear whether usual interstitial pneumonia occurring in patients with connective tissue disease is the same disease as that occurring in the sporadic idiopathic form, and recent studies suggest that subtle but important differences exist.[51] Other forms of interstitial pneumonia, particularly non-specific interstitial pneumonia, are often steroid responsive and have a more favorable long-term prognosis.

Treatment of rheumatoid disease-associated interstitial lung disease depends on the histopathology, extent of other organ involvement, and the potential presence of secondary pulmonary hypertension. Many patients are treated with corticosteroids at doses of 0.5-1mg/kg/day, either as a single agent or in combination with azathioprine or cyclophosphamide. Although commonly used in practice, these immunosuppressive programs have never been subjected to rigorous prospective trials, and the risk to benefit ratio remains a subject of speculation. Recent studies suggest that cyclophosphamide and prednisone combination therapy seems to stabilize scleroderma-associated interstitial lung disease in the majority of patients.[52] However, most of these patients have the non-specific interstitial pneumonia lesion that is typically very responsive to corticosteroid therapy, and the role of cyclophosphamide as an adjuvant remains contentions. Other treatments currently under investigation for the management of rheumatic disease-associated interstitial lung diseases are infliximab and bosentan.

Pulmonary Alveolar Proteinosis

Pulmonary alveolar proteinosis is a rare interstitial lung disease characterized by the accumulation of proteinecaous exudates in the alveolar spaces. Although rare, this disease is worth mentioning because specific treatment is now available for this condition. Granulocyte colony macrophage stimulating factor (GM-CSF: a cytokine that stimulates the granulocytes, macrophages, dendritic cells, and bone-marrow precursors of platelets) administered by either subcutaneous injection or aerosolized form, has recently been demonstrated to effectively control disease course and provides a very useful alternative to the traditional therapy of whole lung lavage.[53, 54]

Management of Pulmonary Hypertension Complicating Interstitial Lung Diseases

It is increasingly evident that many patients with interstitial lung disease develop clinically significant pulmonary hypertension. Pulmonary hypertension may occur as a result of chronic hypoxemic vasoconstriction, direct pulmonary vascular involvement by the disease process, and obliteration of pulmonary vasculature as a result of destruction of normal lung tissue. Pulmonary hypertension affects right ventricular function by imposing afterload on the right ventricle, leading to reduced right-sided cardiac function, cor pulmonale, and reduced cardiac output. The development of pulmonary hypertension in patients with interstitial lung disease does not occur solely in advanced stages of disease and may even be present at the time of presentation. Until recently, many clinicians hesitated to treat secondary pulmonary hypertension because of limited availability of oral or intravenous drugs that affect the pulmonary circulation without causing excessive systemic vasodilatation. The situation has changed with the availability of novel oral agents like the prostacyclin analogue beraprost sodium, the phosphodiesterase inhibitor sildenafil, and the endothelin-1 antagonist bosentan. These agents already have an established role in the management of primary pulmonary hypertension, but require careful study for a role in the setting of interstitial lung disease. These medications (and others currently in phase 1-2 studies) may have beneficial effects that extend beyond vasodilation, including anti-fibrotic and anti-inflammatory effects.[55-57] Whether or not reducing the pulmonary artery pressure of patients with secondary pulmonary hypertension complicating interstitial lung disease alters mortality is unknown.

Final comments

The interstitial lung diseases are a fascinating collection of lung diseases that occur at any age group and may develop as a consequence of an extraordinarily broad collection of systemic diseases. The importance of a careful history and physical examination cannot be overstated, and may obviate many expensive diagnostic tests. The diagnosis and management of interstitial lung diseases often requires active discussion and collaboration between the clinician, surgeon, pathologist and radiologist. Recent studies challenge the dogma that lung biopsy is the "gold-standard" for diagnosing interstitial lung disease. Rather than the lung biopsy per se, the new gold-standard for the diagnosis is the combined input from the diagnostic studies (radiology, pathology, and functional testing) and the clinical evaluation that allows a confident diagnosis in many situations. It is necessary that the clinician review all pertinent radiological and histopathological data if the clinical picture does not fit with the findings on diagnostic testing.

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