

PILOT™ MISSION STATEMENT

PILOT™ is a national education initiative designed to provide physicians with a comprehensive continuing medical education program that focuses on the early and accurate diagnosis of idiopathic pulmonary fibrosis (IPF), while addressing educational objectives critical to optimizing disease intervention and management.

IDIOPATHIC PULMONARY FIBROSIS: EVOLVING CONCEPTS IN PATHOGENESIS

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The investigation of pulmonary fibrosis has led to new paradigms that are potentially relevant to idiopathic pulmonary fibrosis (IPF). However, many questions remain, and additional research is needed to improve our knowledge of this complex process. An important issue relevant to the "missing link" between basic science and clinical research is that we lack information that pertains to the complete natural history of the pathogenesis of IPF. We are left with only descriptive "snap-shots" of the histopathology of each of the idiopathic interstitial pneumonias (IIPs). A thorough understanding of the natural history of these IIPs would allow appropriate clinical and basic science investigation of different mechanisms and therapeutic intervention(s) that may be operative at different stages of the disease process.

What do we know about the natural history of IPF?

Usual interstitial pneumonia (UIP) has been classified as the histopathological hallmark of IPF. UIP consists of temporal heterogeneity with areas of normal lung tissue, "new active fibrosis" (ie, fibroblastic foci), and "old fibrosis" (ie, honeycomb cysts).^{1,3} This description suggests that areas of the lung have undergone different temporal "hits," resulting in both new organizing fibrosis and old fibrotic areas of the lung within the same low-power microscopic view. While UIP is the histopathology seen in IPF, this histopathology has also been reported in the end-stage of chronic asbestosis, chronic hypersensitivity pneumonitis, and various collagen vascular disorders with associated interstitial lung disease.^{4,5} If UIP is the end-stage histopathology of several known etiologies, then this supports the notion that UIP may represent the end-stage entity of a variety of pathological disorders, rather than the initial manifestation of a specific disease, such as IPF. Therefore, we are missing the characteristics of the early and intermediate phases of the pathogenesis of the process that leads to UIP.

Does the ultrastructural analysis of UIP provide insight into the pathogenesis of IPF?

Previous studies have provided significant knowledge about this process. Ultrastructural

analyses of lung tissue from IPF patients demonstrate the following features:

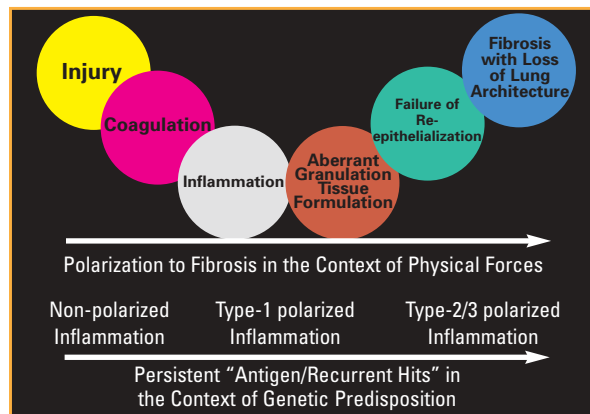
- (1) Endothelial cell and type I pneumocyte injury with damage of the alveolar-capillary basement membrane.
- (2) Intra-alveolar exudative organization with fibrosis and associated fibroblast/myofibroblast migration through defects in the alveolar wall, formation of intraluminal "buds" that progress to obliteration of the alveoli, and fusion of adjacent alveolar structures.
- (3) Development of fibroblastic foci that represent exudative organization.
- (4) Fibrosis within the alveolar airspace/interstitium has parallel-arranged fibroblasts/myofibroblasts enmeshed in extracellular matrix.⁶⁻⁹

leads to a loss of type I epithelial and endothelial cells, proliferation of type II cells, loss of alveolar space integrity, recruitment and proliferation of stromal cells, and deposition of extracellular matrix (ECM) and end-stage fibrosis.¹⁰⁻¹² However, neither the initial injury/inflammatory event nor the mechanisms responsible for the perpetuation of chronic inflammation and ECM deposition are known. Recurrent "hits" related to environmental "antigens," microbes, or systemic vascular events may promote overlapping events of exaggerated inflammation with repeated injury, leading to the loss of alveolar-capillary cellularity and basement membrane integrity and a subsequent failure to re-establish the normal alveolar architecture. This cycle of dysregulated repair (ie, fibroblast proliferation and extracellular matrix deposition within alveoli and interstitium) progresses inexorably to end-stage fibrosis.^{10,11,13}

An alternative hypothesis

The hypothesis that persistent chronic inflammation leads to fibrosis has been challenged recently. In fact, it has been postulated that chronic inflammation plays little or no role in the pathogenesis of UIP.¹⁴⁻¹⁶ This concept has led to a movement to embrace an alternative hypothesis; that is, pulmonary fibrosis results from epithelial injury and abnormal wound repair in the absence of preceding inflammation.¹⁶ While this hypothesis is interesting, it has little basis for substantiation for the following reasons:

- (1) The interpretation that inflammation does not contribute to UIP is based only on a "snap-shot" view of the histopathology of UIP (ie, one point in time without understanding of pathogenesis or natural history).
- (2) Superphysiological and tonic expression of cytokines in certain animal models have led to the interpretation that fibrosis can occur in the absence of inflammation. However, in these same animal models there are actually increased numbers of inflammatory cells (ie, macrophages).
- (3) Injury to any tissue is always followed by an inflammatory response and subsequent



However, it remains to be determined whether the fibroblastic focus in UIP is the pathological progenitor lesion of all subsequent pulmonary fibrosis (ie, "new and old"), or whether the fibroblastic foci simply represent nothing more than the "loss of alveoli" with a subsequent organizing fibrosing response, as supported by ultrastructural studies.⁶⁻⁹

For years, the prevailing hypothesis for the pathogenesis of UIP held that chronic inflammation plays an important role in the pathogenesis of pulmonary fibrosis. This postulate was based on the notion that injury/inflammation of the alveolar-capillary cellular constituents and basement membrane

repair. Why should the lung have developed a unique strategy for responding to injury that bypasses the inflammatory component and proceeds directly to fibrosis?

- (4) A poor response to conventional anti-inflammatory therapy administered at the end-stage of a fibrotic process does not preclude the possibility that inflammation is a key component of the early stage.
- (5) Finally, the hypothesis fails to take into account the events that initiate injury, perpetuate subsequent dysregulated repair, and fit with the histopathology of temporal heterogeneity associated with UIP.

Multiple hits/recurrent injury hypothesis

Although there has been no published study that has evaluated temporal biopsies from the same patient with IIP to determine the natural history of the pathogenesis of these disorders and whether they may evolve over time into UIP, several studies are beginning to highlight important issues relevant to the pathogenesis of UIP associated with IPF. Zuo and colleagues performed microarray analysis of genes that were upregulated in UIP, as compared to "normal control" specimens from patients who had undergone thoracic surgery for reasons other than interstitial lung disease. The investigators obtained eight lung specimens from patients with UIP; six were from patients with idiopathic UIP (ie, IPF), and two lung specimens were from patients with UIP who had rheumatoid arthritis and Sjögren's syndrome.¹⁷ They found groups of selected genes that were substantially upregulated in fibrotic lungs that clustered into the following functional categories: smooth muscle markers; extracellular matrix, growth factors, and proteases; cytokines, chemokines, and antioxidants; and complement, immunoglobulins, and amyloid.¹⁷ While one could argue that this study was flawed on the basis that it did not detect genes that have already been identified by using conventional strategies, this study did provide evidence of significantly upregulated genes in UIP that are normally found in association with chronic inflammation/immune responses (ie, cytokines,

chemokines, antioxidants, complement, immunoglobulins, and amyloid).¹⁷

In further support of the notion that the lungs of IPF patients may be exposed to a persistent or recurrent "antigen" is the multicenter study from Hunninghake and colleagues,¹⁸ who used high-resolution CT to examine radiologic findings associated with a pathologic diagnosis of UIP. They found that 28 of 51 (55%) patients with idiopathic UIP had mediastinal lymphadenopathy, whereas, only 7 of 34 (21%) non-UIP patients had the same findings ($P = 0.002$). This finding suggests that the majority of patients with idiopathic UIP (ie, IPF) have an ongoing lymphoproliferative process in response to some unknown "antigen or antigens." Taken together, the two studies by Zuo and Hunninghake^{17, 18} demonstrate that genes (ie, immunoglobulin genes) are upregulated in response to some "antigen" and that the host is responding with lymphoproliferation. Moreover, these findings do not support the contention that pulmonary fibrosis results from epithelial injury and abnormal wound repair in the absence of preceding inflammation.

Finally, two recent studies have further demonstrated that IIPs do not necessarily occur in isolation or behave as a single disease, but rather may occur as a continuum or overlap with features of chronic inflammation to end-stage fibrosis. Flaherty and colleagues found significant histopathological variability in surgical lung biopsies from patients with IIP.¹² Forty-seven percent of the IIP patients exhibited the histopathology of UIP in all lobes (mean age = 63.3 years). Interestingly, however, UIP was found to coexist with nonspecific interstitial pneumonia (NSIP) in 26% of patients (mean age = 57 years).¹² In the remaining 28%, NSIP was found alone (mean age = 53.1 years).¹² Moreover, evaluation of multiple biopsies obtained from the same lobe (10% of patients) revealed the presence of features consistent with both NSIP and UIP in 73%.¹² These findings demonstrate interlobar and intralobar histopathologic variability of IIP, and the coexistence of IIPs with

components of chronic inflammation (ie, NSIP) with more fibrosis (ie, UIP).

These findings have been further substantiated by Katzenstein and colleagues,¹⁹ who found concomitant UIP with NSIP in a majority of explanted lung specimens from patients undergoing lung transplantation. Does this mean that we have different "disease" processes within the same patient's lung or lobe, or does this support the contention that UIP may represent the end-stage of a continuum of the natural history of nonspecific interstitial pneumonitis (NSIP)? The mean age difference of the patients in Flaherty's study suggests that the natural history of UIP may represent the transformation of NSIP to UIP that takes place over a decade in time.¹² Furthermore, this supports the notion that chronic inflammation and response to persistent or recurrent "antigen" may represent an earlier phase in the pathogenesis of the development of UIP.

The finding that UIP can co-exist with NSIP supports the notion that, indeed, chronic inflammation may be an integral process in the pathogenesis of UIP. Therefore, a modification of the two previous hypotheses for the pathogenesis of UIP should be considered. This hypothesis suggests that inflammation is subsequent to "injury," and recurrent exposure to injury and/or antigen results in a polarization of the response from Type 1 to Type 2 in an effort to "wall off" the area of injury through the formation of scar tissue. This hypothesis can be viewed as sequentially overlapping events that occur subsequent to "antigen exposure/recurrent hits" in the context of a genetic predisposition. Moreover, these events are related to the following mechanisms:

- (1) "Injury" occurs in the context of genetic predisposition. For example, surfactant protein C mutation may provide a foundation for an aberrant response of alveoli to injury with failure to normally "re-expand" during repair
- (2) Inflammation/innate immunity that starts to

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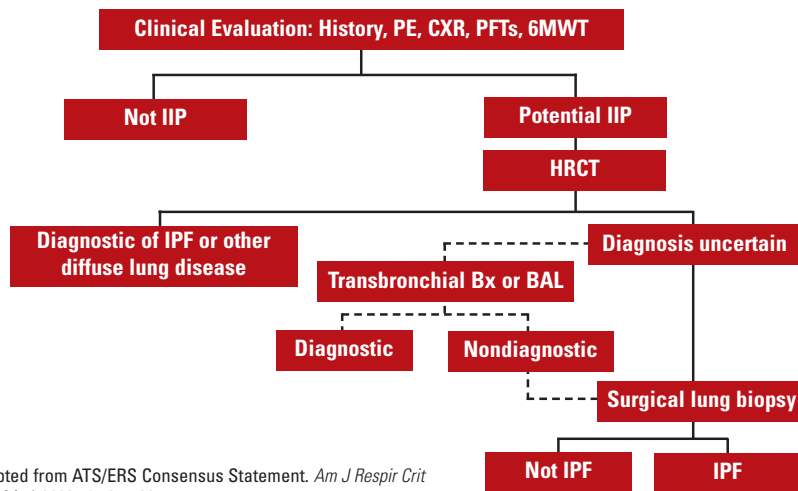
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Approach to Diagnosing IPF



Adapted from ATS/ERS Consensus Statement. *Am J Respir Crit Care Med.* 2002;165:277-304.

- polarize toward a predominate type 1 (Th1) response, ultimately transitions to a predominate type 2 (Th2) profibrotic environment. Transition from type 1 (Th1) to type 2 (Th2) host response as a result of "persistent antigen exposure/multiple hits"
- (3) Altered efferocytosis (clearance of apoptotic cells) with persistence of inflammation that supports polarization toward a profibrotic type 2 cytokine environment
 - (4) Loss of basement membrane integrity, which jeopardizes the re-establishment of the normal alveolar architecture
 - (5) Aberrant epithelial signaling leading to apoptosis and impaired proliferation in response to injury in the context of the loss of basement membrane. This process contributes to failure of re-epithelialization of the alveolar-capillary wall and re-establishment of the gas exchange unit.
 - (6) Aberrant vascular remodeling that supports fibrosis, and may contribute to increased shunt and hypoxemia.
 - (7) Pulmonary fibrosis is the ultimate final pathway of failed attempts to architecturally re-organize alveoli, due to multiple events that include:
 - (a) Enhanced recruitment of mesenchymal stem cells that differentiate into myofibroblasts vs differentiation of resident cells to myofibroblasts.
 - (b) Anti-apoptotic and proliferative nature of fibroblasts/myofibroblasts in the microenvironment.
 - (c) Enhanced production of ECM by fibroblasts/myofibroblasts.

In summary, what are the directions that we should take in order to improve our knowledge about the pathogenesis of pulmonary fibrosis? At a minimum, they should include a better understanding of the natural history of the interstitial lung disorder that leads to the end-stage lesion of UIP and the development of therapeutic strategies that can target specific aberrant pathways during the pathogenesis of pulmonary fibrosis.

Acknowledgments

Funding by the National Institutes of Health grant P50HL67665 and The France Foundation.

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CASE STUDY

COURTESY OF STEVEN A. SAHN, MD

HISTORY OF PRESENT ILLNESS

A 50-year-old Caucasian male presented with three months of progressive dyspnea that followed an episode of purulent bronchitis. He would become short of breath after climbing one flight of stairs. He noted the presence of a mild yet persistent dry cough but was more concerned with his dyspnea. The patient denied the presence of joint pain, skin lesions, myalgias, or systemic symptoms like fever, fatigue, or generalized malaise.

PAST MEDICAL HISTORY

The patient's past medical history was unremarkable except for a recent episode of Raynaud's phenomenon. He denied any history of coagulopathy or deep vein thrombosis (DVT). He was taking no medications associated with interstitial lung disease and had no drug allergies.

SOCIAL HISTORY

The patient had a remote history of smoking (3 packyears). He denied any occupational exposures or bird exposures.

FAMILY HISTORY

The patient denied the presence of any interstitial lung diseases or connective tissue diseases in his immediate family members.

PHYSICAL EXAMINATION

On examination, the patient was a pleasant male, appearing his stated age and in no acute distress. His vital signs are listed below:

• Pulse	87 bpm
• Blood Pressure	145/80 mm Hg
• Respirations	29 bpm
• Height	5' 11"
• Weight	190 lbs
• SaO ₂	98% RA

Examination of his head and neck was unremarkable. Auscultation of his chest revealed diminished expansion of his chest bilaterally with bibasilar and axillary crackles. His heart had a regular rate and rhythm without murmurs, rubs, or gallops, and his abdomen was benign. Examination of his extremities revealed mild bilateral swelling of his fingers with a few maculopapular lesions over the dorsum of his right fingers. He did have periungual erythema but no telangiectasias, calcinosis, sclerodactyly, or skin thickening. There was no clubbing of the extremities.

The patient underwent a six-minute walk test in which he walked a total of 1,600 feet and had an oxygen saturation drop to a nadir of 84%. His electromyogram (EMG) showed scattered small-amplitude, brief, polyphasic changes, fibrillations, and a diminished number of motor units.

PULMONARY FUNCTION TESTS

TLC% PREDICTED	FVC% PREDICTED	FEV ₁ % PREDICTED
54%	54%	63%
FEV ₁ /FVC% PREDICTED	DL _{CO} % PREDICTED	DL _{CO} %* PREDICTED
86%	47%	102%

*Adjusted for alveolar volume

ROOM AIR ARTERIAL BLOOD GAS

pH	pCO ₂	pO ₂
7.42	31 mm Hg	84 mm Hg
HCO ₃ [*]		SaO ₂
31 mmol/L		98%

*Calculated

LABORATORY AND SEROLOGIC TESTING

- CBC WBC 8.5 x 10⁹/mm³; Hct 45%, Hb 15 g/dL; Plts 310 x 10⁹/μL
- ESR 6 mm/h
- Aldolase 17.8 U/L
- CK 891 IU/L
- RF 3 IU/mL
- ANCA Negative
- ANA Negative
- Jo-1 Positive

ADDITIONAL TESTS



CHEST RADIOGRAPH

A chest x-ray was then performed and revealed reticular opacities predominately in the bases bilaterally. There was no evidence of lymphadenopathy or pleural disease.



HIGH-RESOLUTION COMPUTED TOMOGRAPHY

A high-resolution computed tomography (HRCT) scan with 2 mm cuts of the lung fields showed bibasilar reticular infiltrates with peripheral honeycomb changes. There were no alveolar opacities.



MUSCLE BIOPSY

Histopathologic examination of the patient's muscle tissue revealed endomysial and perivascular mononuclear infiltration with focal inflammatory cell invasion of non-necrotic muscle fibers. These findings were consistent with an inflammatory myopathy.

CLINICAL COURSE

A diagnosis was made and the patient was initially treated with 60 mg of prednisone daily with a good response.

SUMMARY

- 50-year-old male with a history of dyspnea and Raynaud's phenomenon
- Diagnosis: polymyositis (PM) and interstitial lung diseases (usual interstitial pneumonia type)
- Swollen fingers and rash, elevated aldolase and CK, and EMG abnormalities also suggest an underlying autoimmune process and specifically PM.
- The definitive diagnosis was made with a muscle biopsy displaying an inflammatory myositis.

Interstitial lung disease (ILD) is a common finding in patients with PM, and the clinical presentation can be variable. Some patients, such as the one in this case, present with slowly progressive dyspnea, while others have an acute onset or even no symptoms at all. Moreover, with respect to the onset of evident symptoms of myositis or ILD, these patients are divided into three categories:

- (1) Myositis preceding ILD
- (2) ILD preceding myositis
- (3) Simultaneous presentation of ILD and myositis.

Antibody tests, such as anti-Jo-1 antibody are useful in screening for the presence of autoimmune and connective tissue diseases associated with ILD. Other tests, such as CXR, HRCT, PFTs, and a lung biopsy can help identify which of the various different ILDs might be afflicting a particular patient. In this case, the presence of bibasilar honeycombing and reticular opacities on HRCT, and restrictive pulmonary physiology in combination with decreased diffusion capacity point to idiopathic pulmonary fibrosis (IPF).

It is critical to note that the ILDs have a heterogeneous presentation when associated with autoimmune diseases. The physician must maintain a high index of suspicion for autoimmune diseases in the presence of an ILD and realize that pulmonary complications are a leading source of morbidity and mortality in such patients.