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Pulmonary Fibrosis Identification:
Lessons for Optimizing Treatment

"IPF Updates" Monograph Series

CASE DISCUSSIONS

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CME INFORMATION

Needs Statement/Intended Audience

This activity has been planned in accordance with the need to provide pulmonologists and other health care providers with a continuing medical education activity that addresses the best practices for management of patients with IPF.

Educational Activity Learning Objective

Upon completion of this activity, the participants should be able to:

- Describe the most appropriate lung function tests to assess and manage patients with IPF

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INTRODUCTION

Various interstitial lung diseases (ILDs) can present with similar clinical, radiologic, and histologic features. This case-based monograph explores issues of diagnosis that may face pulmonologists. Idiopathic pulmonary fibrosis (IPF) is the most common and devastating of the idiopathic interstitial pneumonias (IIPs). It is a disease characterized by slowly progressive respiratory insufficiency with typical clinical and high-resolution CT scan (HRCT) features. Long term survival is poor. Proper diagnosis is critical for prognosis, trial participation, and potential life-saving interventions such as lung transplantation. IPF has been defined by the pathologic finding of usual interstitial pneumonia (UIP) in the absence of known causes of this pattern.

A definitive diagnosis of UIP/IPF is established when lung pathology shows UIP in the right clinical setting. UIP can be found with many diffuse parenchymal diseases such as occupational exposure (asbestos), collagen vascular disease, chronic hypersensitivity pneumonia, genetic disorders such as Hermansky-Pudlak syndrome, and drug toxicities. Several studies have demonstrated the value of the HRCT as a surrogate for histology. HRCT can establish the diagnosis of IPF with a high degree of confidence when clear-cut evidence of fibrosis is present (traction bronchiectasis and honeycombing) in the absence of certain features (profuse ground glass densities, pleural effusions, nodules) and in the appropriate clinical setting. This method avoids the risks of surgical lung biopsy, which may be considerable in certain patients.

A diagnostic challenge arises when the histological picture is UIP and the HRCT is not classical for UIP. A careful and extensive history and a systematic multidisciplinary approach become essential to accurate diagnosis. The cases illustrated here highlight the importance of this approach.

USUAL INTERSTITIAL PNEUMONIA (UIP) IN SCLERODERMA

Written by Jeffrey A. Golden, MD

Chief Complaint

A 62-year-old man presented with progressive shortness of breath (SOB), which has been developing over the past 2 years.

History of Present Illness

Two years before his pulmonary evaluation, the patient began having SOB while hiking at an elevation of 8,000 feet. The SOB became progressively worse over the past 12 months. A month prior to presentation, while hiking at a similar elevation, he developed severe SOB requiring admission to a local hospital. The admitting physician gave a diagnosis of high altitude pulmonary edema.

On discharge, he was dependent on supplemental oxygen and was referred to a pulmonologist. His pulmonologist noted the patient's history of classic Raynaud's phenomenon associated with development of gastroesophageal reflux disease (GERD) over the prior two years.

The patient reported no exposures such as birds, mold, or down comforters that would suggest hypersensitivity pneumonitis, though he had been exposed to hot tubs. His only chemical exposure was to malathion he sprayed in his backyard garden.

Medical & Surgical History

The patient had an orchiectomy 11 years ago for seminoma and radiation. He is allergic to penicillin, and is currently taking nifedipine, furosemide, and a statin. There is no known family history of lung disease or rheumatologic disorders. The patient quit smoking 15 years ago, but has a history of 30 pack-years cigarette consumption.

Physical Examination

The patient lost 15 pounds over the last year, which he attributes to decreased appetite. A HEENT exam revealed chronic sinusitis and multiple sinus surgeries in the past, but no skin tightness around his mouth or jugular vein distention. He has high blood pressure, hyperlipidemia, and hypothyroidism.

The patient appears generally well, with the following vital signs:

- BP: 110/70
- Pulse: 85 RR
- Respiration: 26 breaths/minute

There were no findings of pulmonary hypertension. Auscultation revealed inspiratory crackles over the lower half of the chest.

The fingers had few telangiectasias but showed mild skin tightening (sclerodactyly). Upon referral, the rheumatologist noted multiple capillary dilatations and some drop-out on capillaroscopy. No arthritis or synovitis was detected.

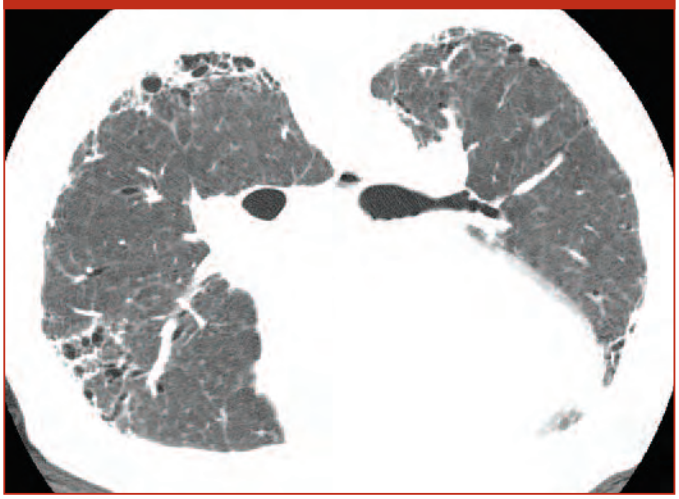
A blood workup revealed that the patient was positive for ANA antibodies with a titer of 1:320, a speckled pattern with a negative Sm antibody result, and a negative Scl-70 antibody result. An echocardiogram revealed an estimated pulmonary artery systolic pressure of 55 mm Hg.

Initial PFT Data

- FVC: 2.9, 63% of predicted
- DL_{CO}: 9.9 mL/min/mm Hg, 30% of predicted
- DL_{CO}/TLC: 2.6, 54% of predicted

Given the progressive dyspnea associated with severe decrement in the DL_{CO} and physical examination suggesting scleroderma, an HRCT scan was done to investigate likely ILD. A normal CT scan would suggest scleroderma-related pulmonary vascular disease.

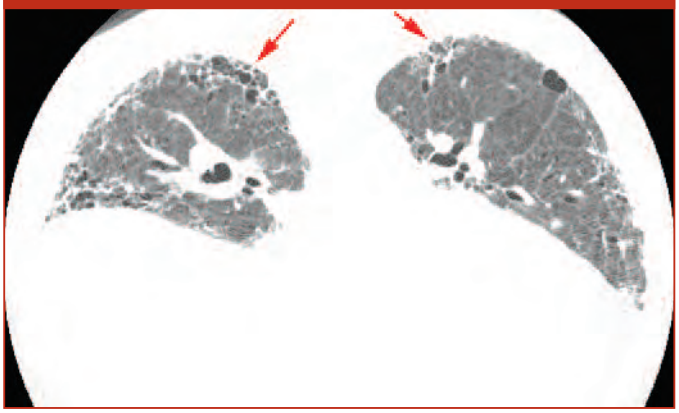
Figure 1. Prone HRCT at the mid-lung level, obtained on 6/3/02.



Chest CT Scan

A prone HRCT through the mid lungs (Figure 1) and lower lobes (Figure 2) was obtained on 6/3/02. The HRCT shows honeycombing (arrows) with a subpleural and basal predominance. Bilateral subpleural reticulation and honeycombing associated with traction bronchiectasis predominantly in the lower lobe is consistent with UIP.

Figure 2. Prone HRCT at the lower lobe level, obtained on 6/3/02. Arrows indicate honeycombing.



Other conditions that might be considered at this point include NSIP, organizing pneumonia (BOOP), and desquamative interstitial pneumonia (DIP). NSIP much more commonly results in reticulation and traction bronchiectasis; honeycombing is uncommon and minimal in extent. BOOP much more commonly results in patchy consolidation; honeycombing is unusual. DIP much more commonly results in ground-glass opacity; in this condition, honeycombing is also rare.

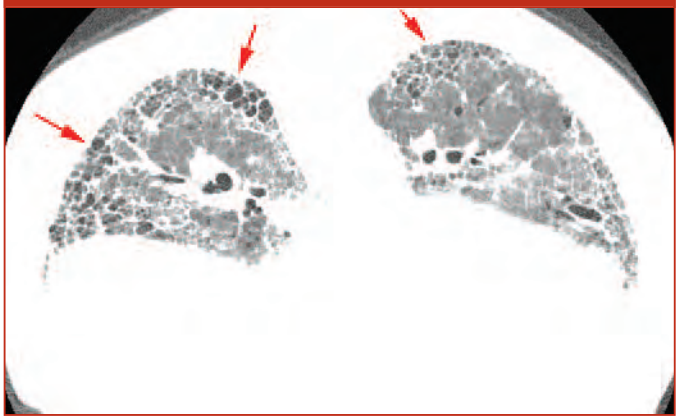
Conditions that are suggested by the clinical and radiographic findings and therefore should be included in the differential diagnosis include IPF, collagen vascular disease, asbestosis, drug-induced reaction or end-stage hypersensitivity pneumonia. However, the most likely diagnosis for this patient is scleroderma. The rheumatologist concurred.

This patient presents with a radiographic picture consistent with UIP. Radiographic patterns consistent with either limited (CREST syndrome [calcinosis/Raynaud's/esophageal dysmotility/ sclerodactyly/telangiectasia]) or diffuse scleroderma include NSIP, UIP, and normal lung parenchyma with findings of elevated pulmonary artery pressure (more commonly associated with CREST).

Clinical Course

The patient was started on mycophenolate mofetil and bosentan. He stabilized and was followed with clinical and pulmonary exams for 6 months. He experienced acute worsening without specific etiology and was hospitalized. He was intubated for 9 days during this hospitalization. After discharge, his clinical status severely worsened. The CT scan at this time revealed worsening of peripheral fibrosis and honeycombing with an enlarged main pulmonary artery (Figure 3).

Figure 3. Follow-up HRCT on 1/23/03. Arrows indicate areas of honeycombing.



The patient experienced a decrease in pulmonary function:

- FVC 2.3 L, 66% predicted
- DL_{CO} 6.3 mL/min/mm Hg, 19% predicted

An echocardiogram revealed that his estimated pulmonary artery pressure increased from 55 mm Hg to 90 mm Hg. This change was associated with severe enlargement of the right ventricle and reduced systolic function associated with a new pericardial effusion.

He was admitted for further evaluation, which included a cardiac catheterization. This procedure revealed a pulmonary artery pressure of 68/19 with a mean PA pressure of 39 mm Hg and pulmonary artery resistance of 9.13 Woods units. He was started on epoprostenol without acute benefit. He was considered for lung transplant and placed on extra corporeal membrane oxygenation, but developed gangrene of his left hand that was attributed to progressive systemic sclerosis. The patient died of respiratory failure 1 week later. Lung tissue was removed at autopsy and examined by histology, as shown in the following figures (Figures 4, 5, 6).

Figure 4. Sections from the peripheral lung show extensive subpleural fibrosis with irregularly shaped airspaces. This subpleural microscopic honeycombing (arrows) is a typical finding in UIP.

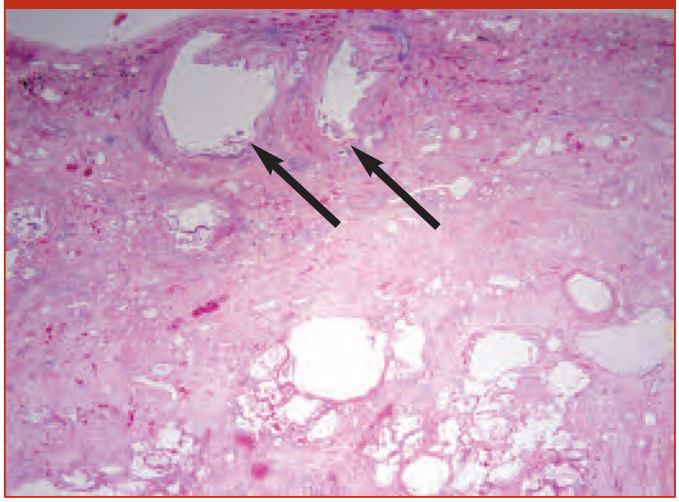


Image courtesy of Kirk D. Jones, MD

Figure 5. The interstitium shows dense fibrosis with thickened alveolar septal walls (arrows) in several areas.

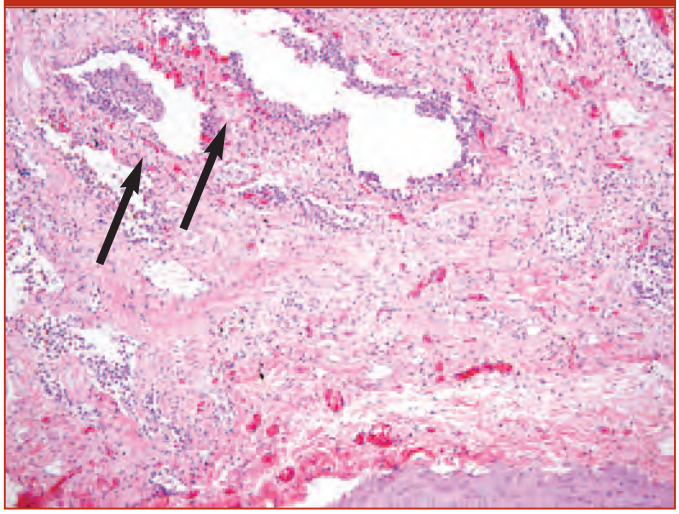


Image courtesy of Kirk D. Jones, MD

Figure 6. Other regions show nearly normal delicate alveolar septal walls (arrows) adjacent to regions of fibrosis (thick arrow). This heterogeneity is often observed in UIP.

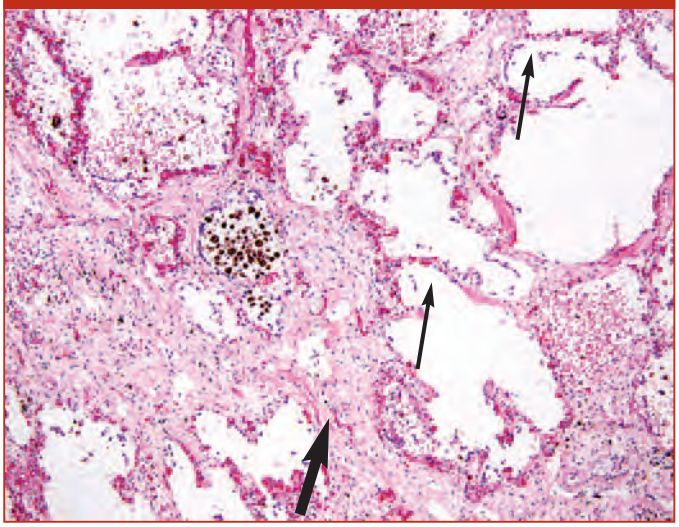


Image courtesy of Kirk D. Jones, MD

Discussion

This patient had substantial progressive lung disease coincident with his initial manifestation of scleroderma. The rheumatologist's opinion was that the patient suffered from either limited or early diffuse scleroderma. He developed an acute worsening that could imply that, like IPF, other fibrotic diseases may be associated with acute exacerbations. Typical of fibrotic lung disease, severe worsening is associated with pulmonary hypertension with right heart failure. The pulmonary hypertension in this case is probably multifactorial, with potential contributions from fibrotic lung disease, hypoxia, and possibly primary pulmonary vascular involvement resulting from connective tissue disease. Although this patient shows UIP, it is important to think of scleroderma as a process that has a potential for a vascular component given pulmonary arteriopathic histologic changes and associated pulmonary hypertension in the presence or absence of significant parenchymal fibrosis. In the US, the annual incidence of scleroderma is up to 10,000 cases; 80% develop some degree of pulmonary impairment, and half of these develop moderate or severe lung involvement. Respiratory failure is the most common cause of morbidity and mortality among patients with scleroderma. As in this case, the onset of pulmonary involvement is most common within the first 3 years after the onset of scleroderma.[1,2]

Depending on the completeness of the evaluation, evidence of pulmonary disease is found in over 70 percent of patients with scleroderma. Pulmonary involvement is second in frequency only to esophageal involvement as a complication of scleroderma and has surpassed renal involvement as the most common cause of death. Interstitial pneumonia (or ILD) and pulmonary vascular disease associated with pulmonary arterial hypertension (PAH), are the most frequent types of lung involvement. Affected patients have a worse prognosis than patients with scleroderma who are free from pulmonary involvement. In contrast to lung involvement in other connective tissue disorders, the pulmonary manifestations of scleroderma only rarely precede systemic clinical manifestations.[1,3]

The case reviewed represents an example of UIP in a patient with scleroderma. Most series reports describing histologic findings in scleroderma (also referred to as "fibrosing alveolitis") were published prior to refinements of pathological classification of the ILDs.[4] The histopathologic features of UIP include temporal heterogeneity with established interstitial fibrosis and honeycombing, chronic inflammatory cell infiltrate with fibroblastic foci adjacent to areas of established fibrosis as well as the presence of normal alveoli. There are no histological features distinguishing idiopathic UIP (idiopathic pulmonary fibrosis, IPF) and UIP associated with connective tissue diseases. Although this case exemplifies UIP in scleroderma, non-specific interstitial pneumonia (NSIP) is now being recognized as the major pattern of interstitial pneumonia in this systemic disorder.

Interstitial Lung Disease in Scleroderma-Pattern and Prevalence

Although the pattern of UIP can occur in scleroderma patients with clinical and radiologic interstitial pneumonia, the much more frequent pattern is NSIP. This term was first used in HIV patients and subsequently employed to describe idiopathic or connective tissue-related interstitial pneumonia by Katzenstein in 1994.[4] In contrast to the UIP histology of the present case, NSIP shows uniform involvement of the alveolar walls. NSIP cases where the chronic inflammation of the alveolar wall is associated with minimal or no fibrosis are defined as "cellular" NSIP and those with uniform fibrosis are referred to as "fibrotic" NSIP.[3]

Recognition of the NSIP histologic pattern has caused a resurgence of interest in the prevalence and prognosis of interstitial pneumonia. However, the frequency of this pattern in patients with connective tissue disease is still uncertain, as most published data precede the recognition of NSIP as distinct from UIP.[3] In scleroderma there are only limited systematic investigations characterizing the histologic patterns of interstitial pneumonia.

The best histologic series employing the new classification criteria for interstitial pneumonias was done by Bouros and colleagues.[5] In that study, about 80% of scleroderma patients had NSIP and the UIP pattern was at most 15%. In a smaller study by Kim, NSIP occurred in 68% of 19 patients and UIP in 26% (5/19).[6] The unique aspect of the investigation from the Royal Brompton Scleroderma Unit is the large sample size and systematic analysis that sometimes included surgical lung biopsy.[5] Over a 12-year period, 476 scleroderma patients were evaluated.

As the authors point out there is always selection bias in histopathologic series of patients with ILD. To minimize this bias, it was the policy of this scleroderma unit to undertake surgical lung biopsies, when possible, if ILD was thought to be clinically significant based on symptoms and pulmonary function. The largest groups of patients excluded were those with no evidence of lung involvement and a subgroup who were considered to have trivial or minor pulmonary fibrosis. A small group was excluded because they were either too compromised and/or declined to undergo biopsy. Virtually all patients had CT scan abnormalities. The biopsy decision was not based on radiologic appearances. There was no difference in the prevalence of NSIP before or after 1991 when this unit began to use CT scan to distinguish typical and atypical UIP. This series is the best systematic clinical and histologic investigation of scleroderma-related interstitial pneumonia.

In this study, 80 patients with interstitial pneumonia ("fibrosing alveolitis") associated with scleroderma underwent surgical biopsy and constitute the study population. NSIP occurred in 78% (62/80) and histologic UIP occurred in 8% (6/80) patients. An additional 6 patients had end-stage lung disease (ESL) so the total of UIP/ESL was 15% (12/80). The histologic definition of ESL in this paper included uniform honeycombing and complete loss of lung architecture, which may have reflected UIP and biopsy sampling. NSIP was subclassified and most of these patients had fibrotic NSIP: cellular NSIP in 24% (15/62) and fibrotic NSIP in 76% (47/62). It was not possible to distinguish between patients with NSIP and UIP by clinical parameters including lung function. Six other patients were excluded from this analysis due to other patterns including respiratory bronchiolitis-interstitial lung disease in 4 patients who were current smokers. Of note, 4 of the 80 patients (5%) died of lung cancer.

Interstitial Lung Disease in Scleroderma-Pattern and Prognosis

In connective tissue diseases, the prognostic significance of different interstitial pneumonia patterns (UIP, cellular and fibrotic NSIP) needs further investigation. The study by Kim

suggests a better prognosis for patients with the NSIP pattern than those with UIP histology, but this was a small study with short follow-up.[6] In the Bouros study, the five-year survival was not different between the two fibrotic patterns, NSIP (91%) and UIP/ESL (82%, $P = 0.33$). This finding persisted after controlling for age, gender, initial FVC, and initial diffusing capacity (DL_{CO}) and when NSIP patients were compared separately to UIP patients. In this paper that documented the increased frequency of NSIP relative to UIP, mortality was more strongly associated with disease severity at presentation (FVC, $P = 0.004$ and DL_{CO}, $P = 0.007$) and serial trends in DL_{CO} than to specific histology. Also, survival and serial FVC and DL_{CO} did not differ between cellular and fibrotic NSIP. Similarly, the pattern of cutaneous involvement (limited versus diffuse scleroderma) was not correlated to outcome.[5]

Although they do not specify the pattern of ILD, other authors also conclude that end-stage lung disease in scleroderma can be predicted from baseline lung function.[7] Only a subset of scleroderma patients with pulmonary involvement progress to severe restrictive disease. Of almost 900 patients in the University of Pittsburgh scleroderma data base, 60% never had FVC less than 75%; 25% had moderate restrictive lung disease (FVC 50% to 75%); and 13% had severe disease (FVC < 50%).[2] Progressive disease was most common in those initially presenting with moderate or severe restriction.[8] Patients presenting with normal pulmonary function are at very low risk for developing end-stage lung disease.[7]

Summary

The UIP pattern is found in less than 15% of patients with scleroderma and interstitial pneumonia; NSIP is substantially more prevalent. A similar finding has been reported with other connective tissue diseases.[9] This contrasts with idiopathic disease where UIP is prevalent. Another distinction from idiopathic disease is that patients with connective tissue disease and UIP or NSIP have about the same prognosis; both groups have a relatively good outcome (80% five-year survival).[5]

The differences in pattern and prognosis in scleroderma relative to idiopathic disease may reflect different biology.[9] Perhaps therapy is more effective than in idiopathic disease in preventing progression to the generally more fibrotic patterns of UIP or fibrotic NSIP.[3] In contrast, in Tansey's study of connective tissue diseases other than scleroderma, mortality of patients with fibrotic NSIP was similar to that of patients with idiopathic NSIP.[9]

Studies on pattern and prognosis of ILD in patients with connective tissue diseases have included only small numbers of patients. Also, the systemic processes of CTD can result in symptoms, early detection, and possible "lead time bias" in comparison to UIP associated with lung-specific IPF. The suggestion from the Bouros scleroderma investigation that mortality in NSIP does not differ from UIP or from UIP/ESL must be validated with large systematic studies that would ideally involve lung histology. Only few studies have looked at the prognosis of ILD associated with connective tissue disease since NSIP was recognized as a distinct pathologic entity.[9] CT scanning may diminish recourse to lung biopsy in the future even though CT scans have their own limitation in distinguishing NSIP from UIP. Neither histology nor CT scans give perfect discrimination between fibrotic NSIP and UIP.[10] Microscopic honeycombing suggesting histologic UIP may provide a pathological diagnosis not afforded by CT scan. Nevertheless, lung biopsy may be reserved for only very atypical CT patterns.[3]

The presence of UIP in a small proportion of the patients with scleroderma-associated interstitial pneumonia does raise questions for future analysis. Does this pattern in a patient with scleroderma suggest a worse prognosis and/or response to therapy than NSIP? How do these outcomes

compare with idiopathic processes? Can ongoing studies such as the NIH Scleroderma Lung Study II comparing mycophenolate mofetil to cyclophosphamide help predict patient outcomes for specific patterns of ILD (UIP; cellular or fibrotic NSIP)? Does baseline or serial DL_{CO} predict outcome better than pattern of interstitial pneumonia or changes in FVC? If so, mortality in scleroderma may also relate to progression of pulmonary vascular disease and right heart failure. Finally, can an interstitial pattern predict which patients experience acute exacerbation?

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DERMATOMYOSITIS/ANTISYNTHETASE SYNDROME

Written by Maria L. Padilla, MD

Presentation

A 48-year-old male patient presented in the summer of 2006 with rapidly increasing shortness of breath and flu-like illness. He had experienced exertional dyspnea for 2 years. The patient experienced dyspnea upon climbing less than one flight of stairs or walking less than one city block and also had a nonproductive cough. The primary care physician successfully treated complaints of myalgia and arthralgia with low-dose steroid therapy. Though his pain responded to steroids, his dyspnea did not improve.

History

His medical history included diabetes and mild renal insufficiency. He had occasional symptoms of GERD, which were relieved by OTC antacids. He had no history of Raynaud's syndrome, arthritis, skin rashes, and no family history of collagen vascular diseases. Other family history was non contributory. He never used tobacco, but had passive exposure from his smoking spouse. He is a moderate consumer of alcohol (5 drinks/wk) and is a business owner. His home is a possible source of mold exposure, but the patient recalled no history of exposure to hot tubs, saunas, birds, asbestos, pulmonary toxins. No relevant information was revealed upon review of systems.

Examination

Physical examination revealed blood pressure of 150/95, pulse of 101, respiration rate of 16, and oxygen saturation of 98% on room air. He was well developed and well nourished, in no acute distress. A lung exam revealed bilateral rales with pronounced P2. The patient had folliculitis of the skin, trace edema of his extremities, but no clubbing or cyanosis. Laboratory analysis of blood revealed:

- Creatinine 1.6-1.9
- Hgb 10-11 g
- ESR 104
- CPK, aldolase and LFTs within normal limits on repeated testing
- Serology
  - ANA, Sclero 70, ANCA, anti-SS-A/Ro, La, anti-smith, anticentromere, ACA, B2 glycoprotein, anti P-serine, BNP, IEP all negative
  - Anti-Jo1 and anti PL-12 tests positive
  - Elevated sedimentation rate (104)

Baseline echocardiogram showed mild concentric LV hypertrophy, normal ejection fraction and absence of pulmonary hypertension.

Pulmonary Function Tests

Date	FVC (% predicted)	FEV_1 (% predicted)	TLC (% predicted)	DL_{CO}(%)
4/6/06	3.96 L (74)	3.42 L (84)		
5/10/06	3.35 L	2.66 L (59)	55	48
6/23/06	2.50 L (45)	2.15 L (49)		43

6-Minute Walk Test (6MWT)- the initial 6MWT shows desaturation

Date	Distance (ft)	Max Sat	Min Sat	O_2 Requirement (L)
6/4/06	1920	95	87	2

A radiology report furnished by the PCP indicated increased bibasilar markings on the chest X-ray, and an HRCT performed in April 2006 showed honeycombing, interlobular septal thickening, and areas of ground glass density (Figure 1). Traction bronchiectasis began to appear in the follow-up HRCT done 5 months later (Figures 2 and 3).

Figure 1. HRCT scan on 4/6/06 at the carina level. Features include honeycombing (gold arrow), septal thickening, and ground-glass densities. No convincing traction bronchiectasis is present.

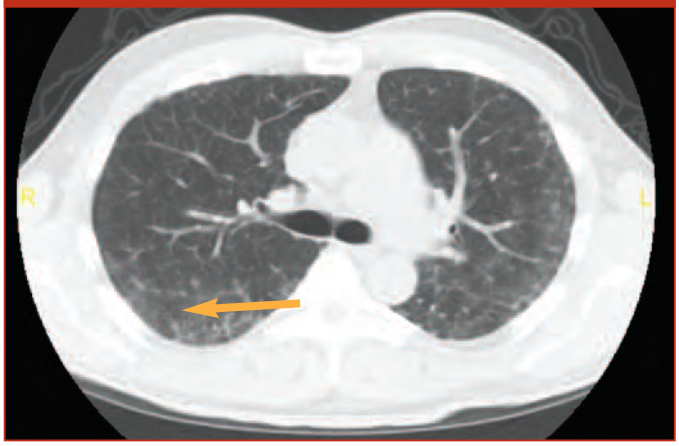
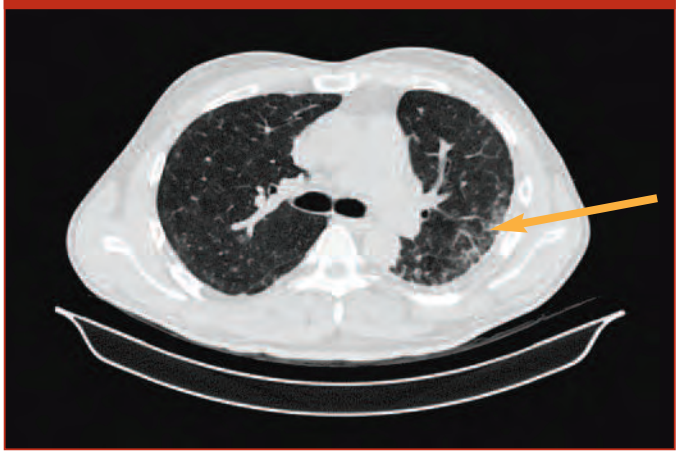


Figure 2. HRCT scan on 9/8/06 at the mid-lung level. Features include honeycombing (gold arrow).



Histology showed fibrosis with remodeling and honeycombing, septal thickening and inflammatory infiltrate resembling areas of NSIP, poorly formed fibroblastic foci, and peribronchiolar lymphocytic infiltrate (Figures 4a-4d).

Figure 3. HRCT scan on 9/8/06 at the basal level. Traction bronchiectasis (gold arrow) and honeycombing (red arrow) are evident. Some pleural effusion in the left lung developed after the surgical biopsy.

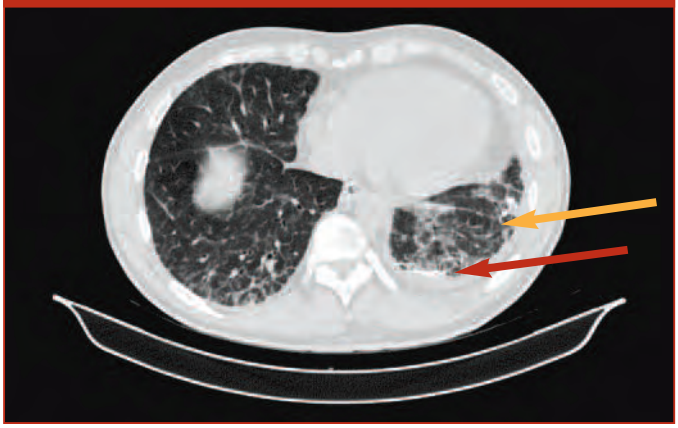


Figure 4a. Fibrosis with remodeling and honeycombing (arrow).

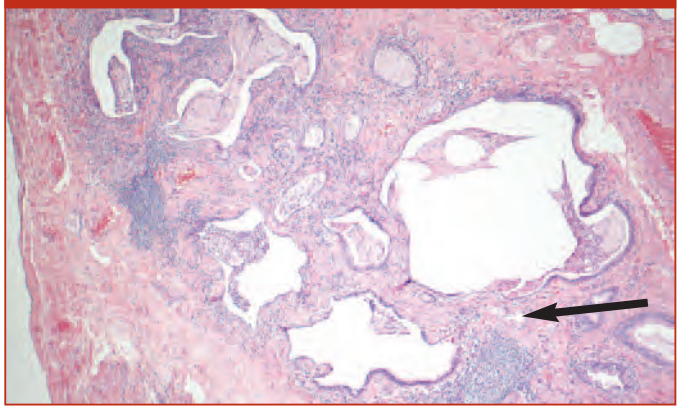


Image courtesy of Mary Beth Beasley, MD

Figure 4b. Septal thickening and inflammatory infiltrate (arrow) resembles areas of NSIP.

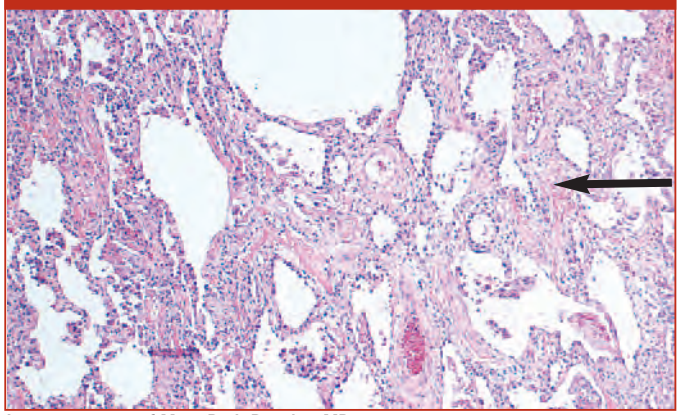


Image courtesy of Mary Beth Beasley, MD

Figure 4c. Poorly formed fibroblastic focus (arrow).

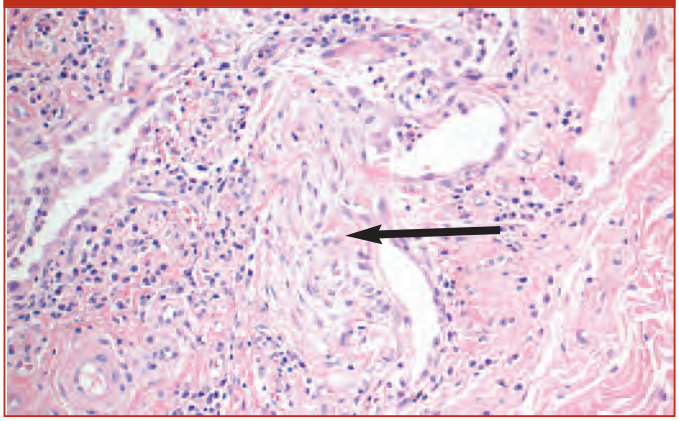


Image courtesy of Mary Beth Beasley, MD

Figure 4d. Peribronchiolar lymphocytic infiltrate (arrow).

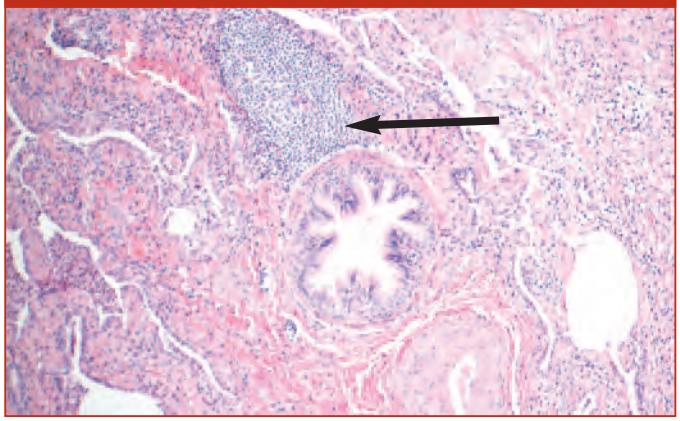


Image courtesy of Mary Beth Beasley, MD

The diagnosis of UIP/IPF was made on the basis of fibrosis, honeycombing, fibroblastic foci, and chronic inflammation. This diagnosis prompted referral for clinical trial participation. The patient was evaluated for participation in a therapeutic trial for IPF. Review of his clinical history, laboratory data, and histology led to diagnosis of UIP associated with antisynthetase syndrome/dermatomyositis and not IPF. The degree of ground-glass densities observed by HRCT, a history of febrile illness, abnormal serologic findings, and presence of inflammatory infiltrate and mixed histologic pattern are not typical features of IPF. The constellation of findings supported the diagnosis of UIP associated with the antisynthetase syndrome/ dermatomyositis. Since the diagnosis was not consistent with the inclusion criteria of the clinical trial, the patient was not enrolled.

Clinical Update

The patient was treated with low-dose prednisone, the immunosuppressant agent mycophenolate, N-acetylcysteine, and a proton pump inhibitor for GI prophylaxis. He had an initial improvement in clinical and functional status with stabilization of PFTs after an early increase in FVC and FEV_1. His requirement for oxygen supplementation disappeared. His stability is maintained despite gradual tapering of immunosuppressive regimen. Repeated echocardiograms have failed to detect pulmonary hypertension.

Pulmonary Function Tests

Date	FVC (% predicted)	FEV_1 (% predicted)	TLC (% predicted)	DL_{CO}(%)
6/23/06	2.50 L (45)	2.15 L (49)		43
9/8/06	3.21 L (58)	2.61 L (60)		
4/12/07	3.66 L (66)	2.96 L (68)		
7/7/08	3.63 L (66)	2.75 L (64)		45
10/19/09	3.53 L (65)	2.89 L (68)		34
1/7/10	3.51 L (64)	2.84 L (67)		38

6MWT				
Date	Distance (ft)	Max Sat	Min Sat	O_2 Requirement (L)
6/4/06	1920	95	87	2
8/20/07	1020	98	92	0
3/5/08	1520	97	92	0
10/19/09	1180	96	91	0

Pulmonary function studies are consistent with restrictive lung disease. Despite functional improvement the CT scan remains abnormal with evidence of fibrosing lung disease.

Figure 5. HRCT on 3/5/08 at the level of the carina. Images demonstrate focal honeycombing, peripheral subpleural densities (red arrow), and septal thickening (gold arrow).

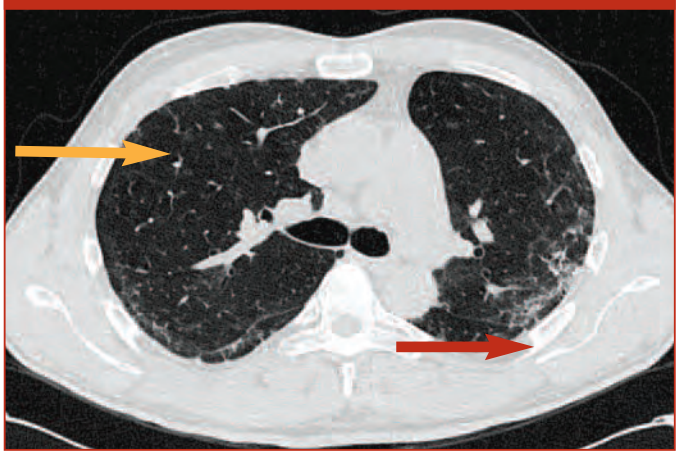


Figure 6a. HRCT on 1/7/10 at the bases of the lung.

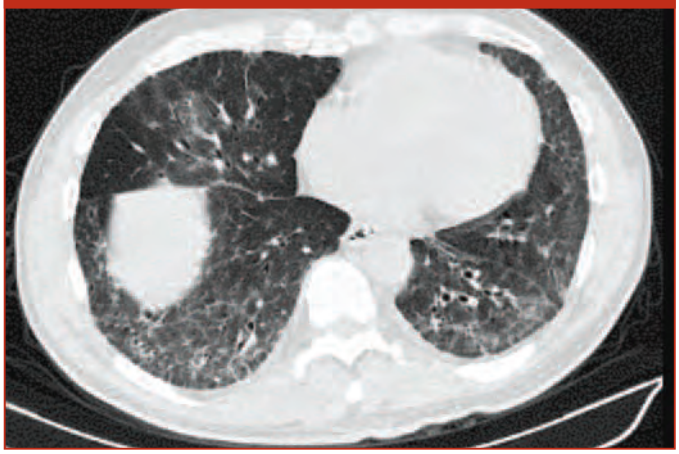
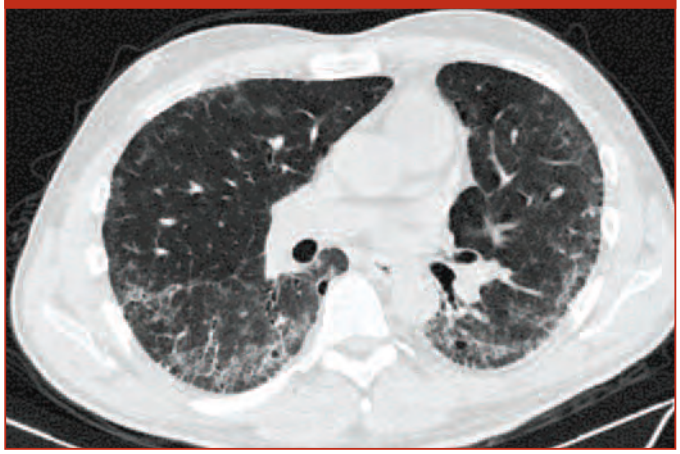


Figure 6b. HRCT on 1/7/10 slightly below the mid-lung level. Progressive honeycombing and traction bronchiectasis are evident.



The patient has remained clinically stable despite radiographic progression of honeycombing and traction bronchiectasis. The patient subsequently developed a rash consistent with dermatomyositis. He continues to do well.

Discussion

Respiratory involvement is common in the inflammatory myopathies. Its presence impacts adversely the course of illness. In one study, respiratory involvement was observed in 61% of patients with diagnosed DM/PM.[1] In 39% an ILD was present and in the rest myopathic restrictive lung disease was evident. The true incidence of ILD in dermatomyositis is not known but has been reported to be about 30%.

The antisynthetase/dermatomyositis syndrome is a chronic autoimmune disorder characterized by autoantibodies and clinical manifestations that may include myositis, interstitial lung disease, arthralgia, cutaneous signs, and fever.

The most common of these disorders is dermatomyositis/polymyositis (DM/PM) associated with the anti-Jo1 antibody to the histidine tRNA synthetase. Other antisynthetase antibodies have also been implicated in the development of the syndrome and are associated with ILD.

Exposure to toxic substance such as cleaning fluids, epoxies, and silica has been associated with DM and muscle weakness.

The presentation of ILD in the antisynthetase syndrome may be acute or gradual. In about one-third to one-half of the patients with DM/PM and ILD, an antisynthetase antibody is detected. The presence of antisynthetase antibodies has been considered a risk factor for lung involvement, but most studies document that their presence does not alter the outcome.[1] ILD may be associated with anti-Jo1 antibodies as the sole clinical manifestation without evidence of overt myositis, and is frequently characterized by an acute onset presentation with respiratory insufficiency, fever, and specific HRCT patterns. The presentation with acute respiratory complaints and pneumomediastinum carries a poor prognosis.

Multiple histologic patterns have been reported, including non-specific pneumonia (most common), usual interstitial pneumonia, acute interstitial pneumonia, diffuse alveolar damage, and organizing pneumonia. Bronchoalveolar lavage may show CD4/CD8 ratio < 1, though this test is not routinely done. Other autoantibodies typical of conditions such as rheumatoid arthritis or Sjögren's syndrome may also be present.

Patients with DM/PM typically show a good immediate response to corticosteroid (CS) therapy, especially in cases presenting acutely; but recurrences are frequent. The combination of CS and immunosuppressive agents (IS) appears to be more effective than corticosteroids alone. In a multicenter study evaluating patients with antisynthetase antibodies who presented initially with ILD with or without extrapulmonary symptoms, about two-thirds of the patients had stable ILD, while the final third displayed progression with respiratory insufficiency.[2] A combination of CS and IS was required to control ILD in most cases.

Severe adverse effects of treatment may be observed and infections or sepsis may complicate the course. There is a 10% incidence of associated neoplasm. Development of pulmonary hypertension is not uncommon. The five-year survival has been reported to be about 60–82%.[2,3] The presence of antibodies does not alter the prognosis of the disease. Early testing for anti-synthetase antibodies, particularly anti-Jo1, and CK determination is useful in patients presenting with ILD, particularly those with acute onset of respiratory insufficiency, fever, basal consolidations, basal irregular lines, and diffuse patchy ground glass opacities on HRCT.

Our patient presented with possible IPF. Though histologic UIP was evident, several findings did not support a diagnosis of IPF:

- Fever and acute rapidly progressive dyspnea is not typical of IPF unless the patient is presenting in acute exacerbation of the disease
- The radiographic finding of significant ground-glass densities is not typical of IPF
- The histopathology was consistent with UIP but had too much inflammation for classical UIP/IPF
- The serology results suggested a diagnosis of UIP secondary to the antisynthetase syndrome

Our patient has not developed overt myositis, but subclinical myositis has not been excluded by a muscle biopsy. However, he has developed a rash that is consistent with this diagnosis. He responded well to a combination of CS

and immunosuppressant. Despite gradually decreasing doses, his pulmonary function is relatively stable and he has not developed other complications such as pulmonary hypertension or neoplasia. His CT scan has remained abnormal despite clinical response. Lung transplantation has been discussed with the patient as a potential therapeutic intervention in the event of decline in function.

Teaching points:

1. Not all UIP is IPF.
2. Serologic evaluation of all patients with IIP/UIP is important, especially those with atypical clinical presentation and clinical trial candidates.
3. Patients may respond to conventional treatment, which can affect the diagnosis and long term prognosis.
4. Collagen vascular-associated lung disease is more frequent than appreciated and pulmonary abnormalities may precede rheumatologic manifestations.
5. Though IPF/UIP is a common ILD, features that support an alternative diagnosis must be considered.

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HYPERSENSITIVITY PNEUMONITIS

Written by Maria L. Padilla, MD

History of Present Illness

A 52-year-old Caucasian male presented with a history of shortness of breath (SOB). The onset was insidious, but had become especially noticeable over the last year. He is somewhat sedentary and on reflection believes that he has had SOB on and off over the last 9 years. The patient describes a chronic cough with occasional sputum production. He recently started an exercise program and is able to walk for about 10 minutes on a treadmill, but only on a level plane.

The patient has hypertension and has been taking lisinopril for 5 years. For 15 years he smoked 1 pack per day, but stopped 17 years ago. He is a jeweler by occupation. He lives with his wife and son in a townhouse. The family has one dog and two parakeets. The patient lost some weight recently, but he is uncertain how much. His hand joints have been painful intermittently for the last year.

Physical examination revealed significant clubbing and some bibasilar inspiratory crackles. Pulmonary function was assessed on July 25, 2009.

- **TLC:** 2.1 L (32%)
- **FVC:** 1.3 L (29%)
- **FEV_1:** 1.00 L (32%)
- **FEV_1/FVC ratio:** 77%
- **Diffusing capacity DL_{CO}:** 6.1 mL/min/mm Hg (18%)

Six-Minute Walk Test

The patient's resting SpO_2 was 92% and the 6MWT was administered on room air. He desaturated to 82% after walking 2:50 minutes and the test was suspended. He then was ambulated on supplemental oxygen. He required 4L/minute via nasal cannula to maintain his SpO_2 > 90% for 6 minutes, during which he walked 250 meters. The patient was started on supplemental oxygen.

The patient's dyspnea showed no significant bronchodilator response. A chest X-ray showed diffuse bilateral interstitial infiltrates and an HRCT was ordered.

Figure 1. Upper Lobes. Fine honeycombing (red arrows) and a mosaic pattern (areas of trapped air or uninvolved lung, blue arrows) are present.

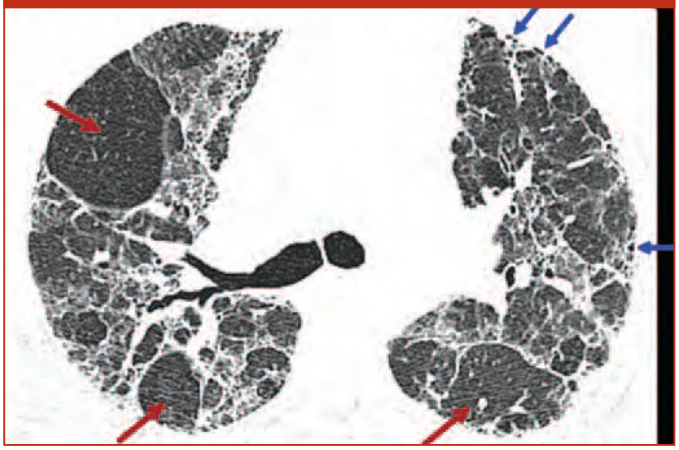

Image courtesy of W. Richard Webb, MD

Figure 2. Mid Lung.

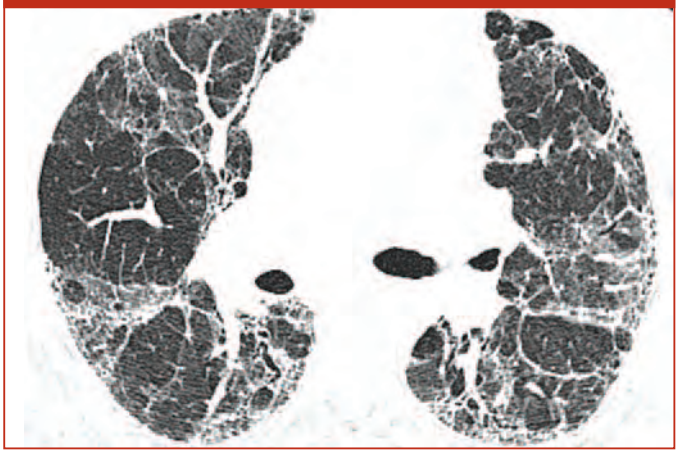

Image courtesy of W. Richard Webb, MD

Three HRCT slices from the upper lobes **(Figure 1)**, mid lung **(Figure 2)**, and lower lobes **(Figure 3)** are presented. The disease involves the entire cross section of lung, and does not predominate in the subpleural regions. These sections also show that the disease involves the upper lobes to a similar degree as the lower lobes.

Figure 3. Lower Lobes.

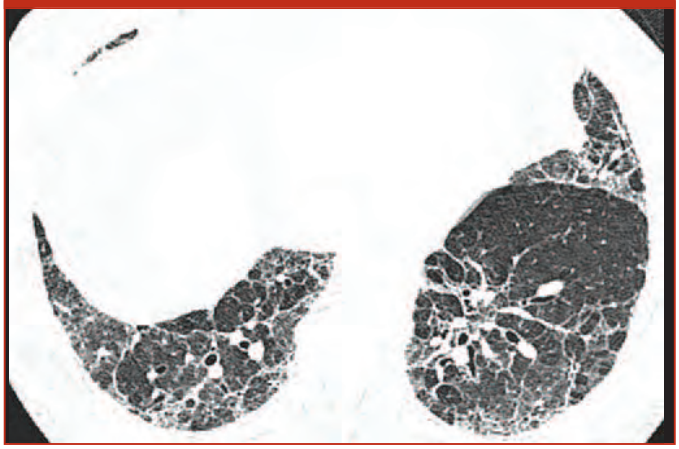

Image courtesy of W. Richard Webb, MD

Several possible diagnoses should be considered. The HRCT pattern of honeycombing is typical of IPF. However, in IPF mainly the lower lobes are affected. The subpleural predominance in IPF is not observed in this patient.

NSIP also tends to predominate in the lower lobes, while chronic hypersensitivity pneumonitis (HP) tends to involve the lungs more diffusely. Fibrosis is typical in chronic HP and honeycombing may be seen. Chronic HP may also show areas of lucency, a clear feature in this case (blue arrows, **Figure 1**), due to focal air trapping. This finding is not seen in IPF or NSIP.

This patient's HRCT is typical of chronic HP.

The history of bird exposure is consistent with this conclusion. The next diagnostic step to confirm chronic HP would be a serologic study that includes a hypersensitivity panel. A positive serum precipitins test to avian antigen would support this diagnosis, though the finding is not definitive by itself. Because of the patient's history of weight loss and joint pains, it would be prudent to rule out an underlying connective tissue disorder.

Fiberoptic bronchoscopy and bronchoalveolar lavage are useful diagnostic modalities in some forms of interstitial lung diseases. A transbronchial biopsy (TBBx) procedure usually provides insufficient material to diagnose IPF. However, the diagnosis of HP can be made by examination of TBBx material if poorly formed granulomas and bronchocentric inflammation are seen. If this patient has HP, it is likely an advanced form of the disease. In such cases, only nonspecific fibrotic changes may be seen and they would not be sufficient to make the HP diagnosis. With this expectation and the risks of TBBx for a patient with marginal lung function the TBBx was not recommended for this patient.

Serologic Studies

- ANA, RF, anti-SCL 70 and other serologic markers were all negative. ESR was elevated at 40 mm/hour.
- Serum precipitating IgG test for avian antigen was positive.
- Bronchoscopy with BAL was deemed safe and was performed. All cultures were negative and the cell count revealed a lymphocytosis (55%) with predominant CD8+ cells, supporting the diagnosis of HP.

The clinical diagnosis of HP was made.

A VATS biopsy was performed to confirm the HP diagnosis and assess degree of inflammation and reversibility. This procedure carries higher risks in patients with marginal pulmonary function. Eliminating exposure to the birds and perhaps a trial course of steroids may also have been an acceptable alternative at this point.

Figure 4. The biopsies show a destructive fibrosis ("fibrosis pattern") inconsistently involving lobules (L). This resembles to some extent the "temporally heterogeneous" appearance of UIP. Moreover, microscopic honeycombing (MHC) is present.

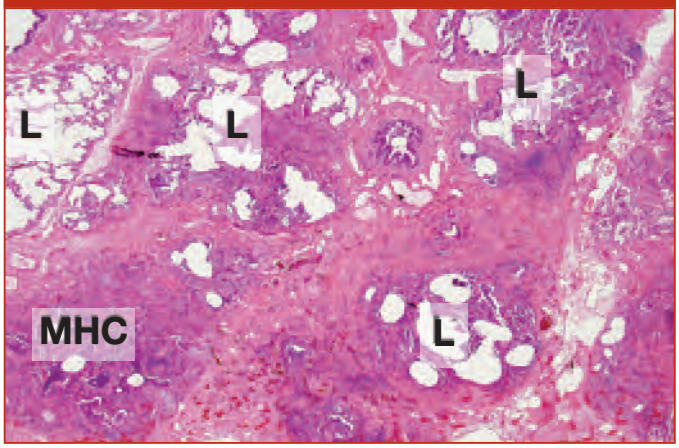

Image courtesy of Kevin O. Leslie, MD

Figure 5. In other areas, the fibrosis is more peripheral within lobules and can be seen beneath the pleura (P). A branching bronchiole can be seen centrally (Br).

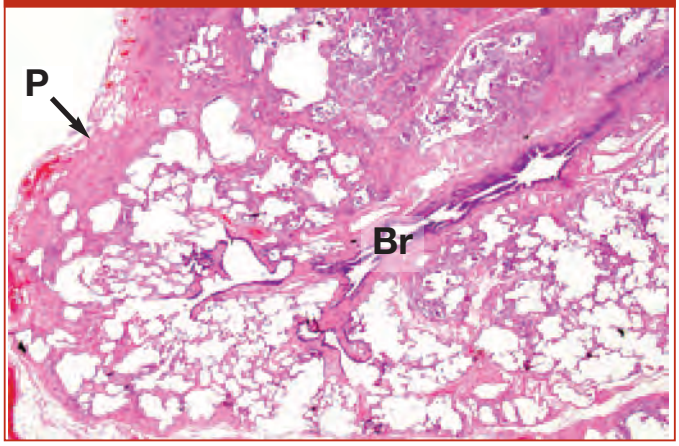

Image courtesy of Kevin O. Leslie, MD

The patterns seen in these histology images are consistent with UIP/IPF. The UIP pattern of lung fibrosis can develop in HP as well as in systemic connective tissue disease manifesting in the lung (especially RA and scleroderma). Rarely, chronic drug reactions and asbestosis can also produce this pattern. A clinical diagnosis of IPF can be made only after these other potential causes have been rigorously excluded.

Figure 6. At higher magnification, diffuse chronic inflammation is present and involves lung away from areas of destructive fibrosis. The interstitium is focally widened by pale pink histiocytes (arrow). These are the interstitial granulomas of hypersensitivity pneumonitis (see Figure 7). Without these small non-necrotizing granulomas, this picture would be consistent with "nonspecific interstitial pneumonia" (NSIP) of cellular type (little or no fibrosis apparent here).

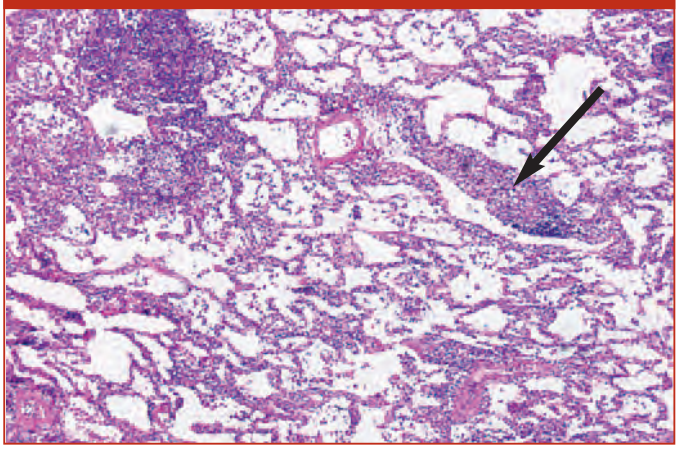

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Figure 7. At high magnification, characteristic small interstitial granulomas of HP can be seen (black arrow), adjacent to a bronchiole (Br). This bronchiole is inflamed and tortuous with redundant infoldings.

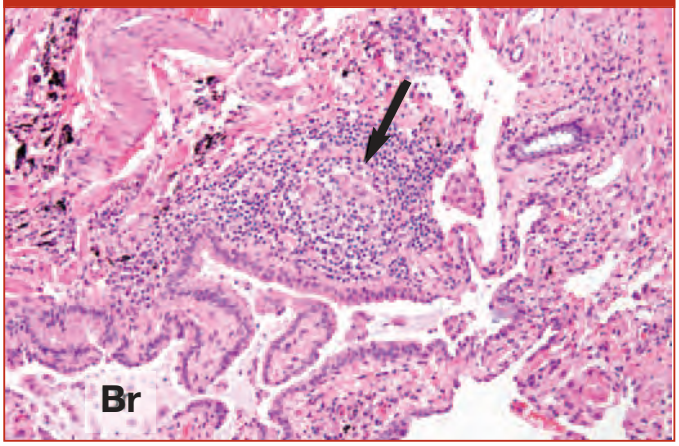

Image courtesy of Kevin O. Leslie, MD

Hypersensitivity pneumonitis is characterized by the presence of small non-necrotizing interstitial granulomas **(Figure 7)**. Sarcoidosis is characterized by the presence of well-formed non-necrotizing granulomas in a lymphatic distribution (pleura, interlobular septa, and

bronchovascular bundles). So-called "hot tub lung" is characterized by the presence of necrotizing and non-necrotizing intra-alveolar and interstitial granulomas. Granulomas are not an expected finding in UIP/IPF or cellular NSIP. A rare granuloma may be seen in UIP/IPF, but never as an integral component of this fibrosing interstitial pneumonia.

What are the next steps for managing this patient? Getting rid of the birds is a wise idea. The ongoing antigen stimulation and inflammation might be contributing to irreversible fibrosis. While a course of steroids is a prudent idea, it is unlikely that this will reverse the advanced fibrosis. Nonetheless, this is reasonable, as the degree of inflammation detected on the biopsy suggests a component of reversible disease. The patient should be evaluated for lung transplantation.

The patient is started on a course of prednisone at 40 mg a day. He returns in 6 weeks and repeat PFTs and a 6MWT are obtained.

Repeat Pulmonary Function Tests (PFTs)

- **TLC:** 2.3 L (37%)
- **FVC:** 1.45 L (34%)
- **FEV_1:** 1.1 L (34%)
- **FEV_1/FVC ratio:** 76%
- **Diffusing capacity DL_{CO}:** 6.4 mL/min/mm Hg (18%)

A six-minute walk test on 4 L nasal oxygen cannula is performed. The patient walks 275 meters and desaturates to 87%

Conclusion

- There hasn't been any significant change in the patient's PFTs
- There is insufficient evidence of a meaningful response to the steroid therapy/bird removal
- It appears that the patient's only recourse is a lung transplant and he is listed in the UNOS registry. He continues on the steroids with a slow taper in anticipation of his transplant.

Discussion

Hypersensitivity pneumonitis (HP) represents a heterogeneous group of disorders resulting from inhalational exposure. The clinical scenario depends on the intensity and type of exposure and the patient's response.[1,2] Chronic HP usually presents with insidious cough, dyspnea, fatigue, and weight loss. There may be a history of acute episodes. The antigens documented to lead to these syndromes are numerous.[1-4] There is no definitive diagnostic test, so a comprehensive approach including history, physical examination, laboratory studies, radiological studies, and invasive studies is required.[3]

HRCT in patients with subacute hypersensitivity pneumonitis often show ground-glass opacity, which may be diffuse, patchy and geographic in distribution, or centrilobular in location, appearing as multiple small ill-defined nodules. Consolidation is less common. In addition, it is common to see patchy or lobular areas of lucency. These represent focal areas of air trapping associated with bronchiolitis, and are accentuated on expiratory scans. The combination of ground-glass opacity and patchy areas of lucency is highly suggestive of HP.[5]

Radiology and histology can be helpful in diagnosis.[6,7] A bronchoalveolar lavage (BAL) is a sensitive tool to detect an alveolitis in patients with suspected HP; a marked lymphocytic lavage may be particularly useful.[8] A report of 1971 patients who underwent BAL (66 with HP) noted that the likelihood of HP increased with BAL lymphocytosis and a decreased CD4:CD8 ratio.[9]

The typical finding of a surgical lung biopsy is bronchiolocentric interstitial pneumonitis accompanied by poorly-formed interstitial granulomas. Bronchiolitis and

focal areas of organizing pneumonia are also commonly present. The interstitial pneumonitis is typically composed of lymphocytes, plasma cells, and macrophages.[1] Greater fibrosis in HP may be associated with a worse prognosis.[10] The histopathologic findings alone are not specific and require a differential diagnosis that includes atypical mycobacterial infection, connective tissue diseases, and low grade malignant lymphoma of extra-nodal marginal zone B-cell type.

The management of these disorders generally begins with antigen avoidance. Corticosteroids appear to favorably affect initial recovery from farmer's and bird fancier's lung, although long-term outcomes do not appear to be changed.[11,12]

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CONCLUSION

The cases presented underscore several important points:

1. Not all UIP is IPF. Certain histological features such as increased inflammation, peribronchiolar distribution, or presence of poorly formed granulomas should cause consideration of a specific etiology. The prognoses of alternative diagnoses may be different. Some studies have reported a better prognosis for UIP associated with collagen vascular disease than for IPF. Diagnosis will guide therapeutic strategies.

2. HRCT can establish a diagnosis of UIP with high degree of confidence when classical features of fibrosis are present. Certain characteristics may suggest an etiology other than idiopathic UIP. Studies have demonstrated the value of HRCT in prognosis of the idiopathic interstitial pneumonias.

3. Serologic markers improve the accuracy of interstitial pneumonia diagnosis and are especially useful in patients with atypical features. Excluding diseases that may have a better prognosis or different response to conventional therapy is important. Interstitial lung disease in collagen vascular disorder is more frequent than generally appreciated. It may precede or follow rheumatologic symptoms by months or years. The prognosis of the various presentations spans the spectrum from acute rapidly fatal to more chronic and indolent disease.

4. A multidisciplinary approach to diagnosis improves accuracy, focuses treatment options, and optimizes management.

ATTESTATION/EVALUATION

To obtain *AMA PRA Category 1 Credit™*, participants are required to:

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BIAS, FAIR BALANCE

Was this activity fair, balanced, objective, and free from commercial bias? ❑ Yes ❑ No

If no, please state reason(s) _____

PRACTICAL APPLICATION

4 = strongly agree 3 = agree 2 = disagree 1 = strongly disagree

(a) _____ What I learned at this activity has increased my confidence in assessing patients with ILD

(b) _____ What I learned at this activity will improve my ability to care for my patients with ILD

(c) _____ What I learned at this activity will result in an improvement in my patients' ILD management

(d) Do you intend to make changes or apply new information to your practice as a result of this activity?
_____ Yes, I plan to make changes*
_____ I'm not sure, but I'm considering changes*
_____ No, I already practice these recommendations

*If yes or considering changes, please check off what you intend to do differently or incorporate into your clinical management of patients with IPF as a result of this educational activity.
_____ Utilize serologic detection of autoantibodies in the diagnosis of ILDs
_____ Evaluate patients for inhaled antigen exposure
_____ Consider IPF as well as other conditions when a finding of UIP is obtained
_____ Use a multidisciplinary approach in diagnosing and managing patients with atypical presentations or with extrapulmonary findings
_____ Other, please specify

_____

BARRIERS

What are the top 3 barriers that might inhibit your ability to incorporate any of the above changes into your clinical practice?

1. _____ 2. _____ 3. _____

DEMOGRAPHIC QUESTIONS

How did you hear about this CME activity?

❑ Web Search ❑ Colleague ❑ Direct Mail

Number of years in practice: ❑ ≤ 5 ❑ 6–10 ❑ 11–15 ❑ 16–20 ❑ 21–25 ❑ > 25

How many of your patients are being managed for IPF?

❑ ≤ 5% ❑ 6-20% ❑ 21-40% ❑ 41-60% ❑ > 60%

May we contact you in the future with a brief survey to assess how you have used the information presented at this activity or to assess other educational needs? ❑ Yes ❑ No

ACTIVITY EVALUATION

4 = strongly agree *3 = agree* *2 = disagree* *1 = strongly disagree*

Upon completion of this activity, I will be able to:

_____ Describe the most appropriate lung function tests to assess and manage patients with IPF

Please rate the overall content presented in this activity: ❑ Too basic ❑ Appropriate ❑ Too complex

ONGOING UNMET EDUCATIONAL NEEDS

Recommendations for future CME topics in this disease area: _____

_____

_____

_____

POSTTEST ANSWERS

Record your Posttest answers by filling in the blank with the correct letter from the corresponding question:

1. ❑ a ❑ b ❑ c ❑ d

_____

2. ❑ a ❑ b ❑ c ❑ d

_____

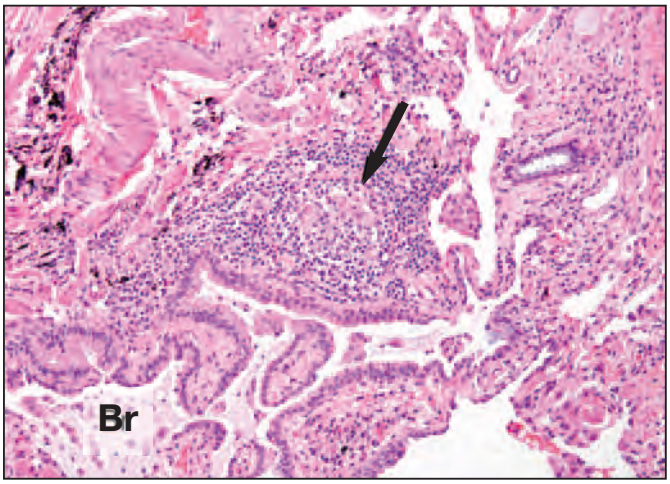
3. ❑ a ❑ b ❑ c ❑ d ❑ e

POSTTEST

1. A 63 yo woman is referred to you because PFT values have been deteriorating over the past 12 months. Her PFTs and physical exam suggest restrictive pulmonary disease, and you suspect IPF. A prone HRCT confirms honeycombing with a subpleural and basal predominance and some ground glass opacity. What should be your next step?

a. Begin a course of prednisone to give her symptomatic relief and narrow the diagnosis
b. Order a serology panel to eliminate autoimmune connective tissue disease
c. Even though she can perform daily functions well, it is best to evaluate her for lung transplantation early
d. Only a lung biopsy can confirm the diagnosis, which should be done at this point

2. What is the structure indicated by the arrow and of which disease is it typical?



a. Small interstitial granuloma, characteristic of HP
b. Fibroblastic focus, characteristic of IPF
c. Peribronchiolar lymphocytic infiltrate, characteristic of NSIP
d. Microscopic honeycombing, characteristic of UIP secondary to several possible diseases

3. Which of the following statements is true about diagnosis of pulmonary involvement in connective tissue disease?

a. Analysis of lung biopsy samples is rarely indicated because of advanced imaging methods and the negative risk/benefit of surgical biopsy
b. Serologic markers frequently precede pulmonary symptoms and thus antibody analysis is an important component of diagnosis
c. Acute exacerbations are a hallmark of IPF and an occurrence can exclude a diagnosis of CTD
d. Scleroderma manifests in the lung as histologic NSIP. In the absence of this pattern, scleroderma can be excluded
e. Answers a, b, and d are true

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