INTERSTITIAL LUNG DISEASE (A HAJARI CASE, SECTION EDITOR)

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The Diagnostic Approach to Interstitial Lung Disease

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Abstract

Purpose of Review Interstitial lung diseases are a heterogeneous group of disorders characterized by varying degrees of inflammation and scarring of the lung parenchyma. Diagnosis can be challenging and requires careful multidisciplinary appraisal of carefully obtained history, physical examination, serological profile, imaging, and, at times, lung tissue. We aim to provide a roadmap for the diagnosis of ILD.
Recent Findings The diagnostic criteria for IPF, which is the deadliest form of idiopathic interstitial pneumonia, and HRCT pattern classification have been updated. Transbronchial cryobiopsies are becoming more prevalent but overall diagnostic yield compared to surgical lung biopsy is not known.
Summary A technically adequate high-resolution CAT scan of the chest (HRCT) is a central element but a multidisciplinary evaluation of all available evidence is fundamental for the diagnosis of ILD.

Keywords Interstitial lung disease · Idiopathic pulmonary fibrosis · Pulmonary fibrosis

Introduction

Interstitial lung disease (ILD) (or diffuse parenchymal lung disease) is a heterogeneous group of non-neoplastic disorders characterized by damage to the lung parenchyma with inflammation and fibrosis leading to progressive loss of function and death. They share a common clinical presentation that includes persistent cough and dyspnea on exertion or at rest associated with physiological impairment measured by pulmonary function tests, hypoxemia and characteristic radiographic and histological patterns [1]. An epidemiological study from Bernalillo County in New Mexico estimated that the overall incidence of ILD is approximately 26.1 and 31.5 cases/100,000 in females and males, respectively [2, 3]. Idiopathic Pulmonary Fibrosis (IPF) alone is estimated to have a prevalence of approximately 495 cases/100,000-person years in 2011 [3].

Despite the many similarities, each of the more than 150 disorders grouped under this umbrella has very distinct etiologies and natural history (Fig. 1). Treatment and various management decisions are often diagnosis-specific and may vary considerably [4]. Distinguishing the specific ILD diagnosis requires a very systematic process that integrates clinical data, imaging, and sometimes, histology [5].

In this manuscript, we suggest a general roadmap for the diagnostic approach of a patient presenting with ILD. We will highlight the important clues provided by a detailed history, physical examination as well as the initial physiological and serological assessments. We will also emphasize the importance of appropriate imaging techniques and discuss integration of high-resolution CT scan (HRCT) patterns in the ILD diagnostic algorithm and, lastly, we will discuss the role of lung biopsy and the importance of a multidisciplinary approach.

## History and Physical Examination

Demographics and Family History

IPF is the most common of the idiopathic interstitial pneumonias and is thought to be a disease related to aging [6, 7]. Sporadic cases of IPF occur predominantly among Caucasians older than age 50 and it is slightly more prevalent among males [7]. Approximately 5 to 20% of IPF cases are "familial" [8], with two or more members of the same family being affected. The clinical characteristics of sporadic and

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Fig. 1 Interstitial lung disease classification
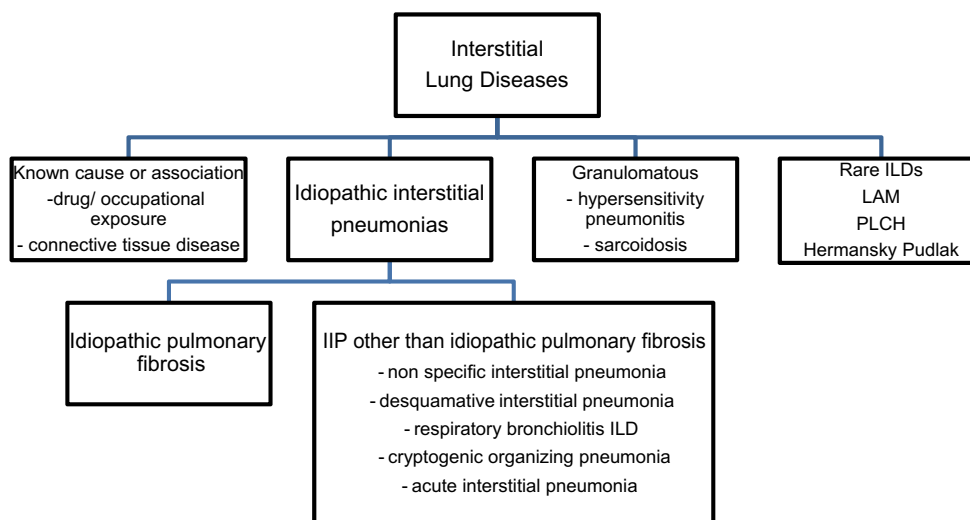
familial cases of IPF are largely the same [9]. In contrast, ILD related to connective tissue disorders (CTD-ILD) are typically more prevalent among younger adults and racial minorities, and a major risk factor for developing a CTD is having a first degree relative with the diagnosis [10]. Sarcoidosis has higher prevalence among African American women and its incidence also clusters in families [11]. Lymphangioleyomyomatosis (LAM) occurs exclusively in premenopausal women [12]. Hermasnky-Pudlak Syndrome is a rare genetic condition that has a higher incidence among Puerto Ricans [13] and, although it has a clinical presentation that is very similar to IPF, it typically affects much younger individuals [14].

Exposures

A detailed history with type, duration, and intensity of exposure is a crucial step in the evaluation of a patient with ILD. Certain conditions such as acute hypersensitivity pneumonitis (AHP) and acute silicosis are associated with short-term high-intensity exposure while others, such as asbestosis, smoking-related-ILDs, and chronic hypersensitivity pneumonitis (CHP) are usually the result of many years of exposure. CHP is often related to exposure to an obvious antigen such as avian proteins but in some cases, the cause can be elusive (Table 1) [15]. The importance of identifying the inciting antigen needs to be underscored as failure to do so may be an independent predictor of worse prognosis among patients with CHP [16].

Respiratory bronchiolitis-ILD (RB-ILD) and desquamative interstitial pneumonia (DIP) are virtually always related to cigarette smoking. Similarly, pulmonary Langerhans cell granulomatosis (PLCH) is typically a disease of younger smokers that present with dyspnea on exertion and nodular and cystic lung disease in HRCT.

Pneumoconiosis is a group of chronic lung diseases caused by occupational exposure to different dusts/fibers such as silica, coal, or asbestos. Silicosis can present in a spectrum ranging

from acute silicosis, accelerated silicosis and more chronic forms depending upon the type and duration of exposure [17].

Table 1 Common antigens related to hypersensitivity pneumonitis and usual sources

Antigen	Usual source
Microbial antigens	
Aspergillus species	Moldy grains, tobacco, malt
Alternaria species	Wood, wood pulp
Bacilus subtilis	Detergent enzymes
Botrytis cinerea	Detergent enzymes
Cryptostroma corticale	Moldy maple bark
Mycobacterium avium	Contaminated water
Mucor stolonifer	Moldy paprika
Penicillium casei	Cheese mold
Saccharopolyspora rectivirgula	Moldy hay
Thermophilic actinomycetes	Moldy hay, grain, mushrooms, potatoes
Animal antigens	
Animal fur protein	Animal fur
Avian proteins	Bird feather
Gerbil proteins	Gerbil
Fish protein	Fish meal
Mollusk shell protein	Oyster shell dust
Rat proteins	Rats
Silk worm larvae proteins	Silk worm larvae
Wheat weevil	Infested wheat
Plant antigens	
Tea	Tea dust
Coffee	Coffee dust
Soyabean	Soyabean hulls
Chemical antigens	
Anhydrides	Plastics
Isocyanates	Paints, plastics
Pyrethrum	Insecticides

In the case of interstitial lung disease related to asbestos exposure (asbestosis), the latency period for disease development is inversely proportional to the degree of exposure and usually ranges from 10 to 20 years [18]. Similarly, the progression of coal worker's pneumoconiosis (CWP) into massive fibrosis is influenced by duration and total cumulative exposure as well as concomitant infections [19].

Hundreds of drugs have been listed as potential causes of interstitial lung disease and toxicity can be idiosyncratic or dose-dependent mediated as either a direct effect or of particular metabolite (s). Unfortunately, there are no specific clinical, radiological or even histological features for the diagnosis. Patients may present with respiratory failure as in sulfasalazine-induced acute pneumonitis or a more chronic fibrosing lung disease as in amiodarone or nitrofurantoin toxicity. Hence, when faced with a case of ILD, one must take a careful and detailed history of drug intake that includes dosing, timing, and latency. Given the ever-evolving number of agents, particularly biologicals used for the treatment of malignancies and auto-immune disorders, it is challenging for clinicians to stay updated on emerging reports of lung toxicity. Resources such as *pneumotox.com* curate a comprehensive and frequently updated review of the literature on drug-related lung toxicity.

Physical Examination

A careful physical examination may offer clues to the specific diagnosis of a patient presenting with interstitial lung disease. Lung auscultation often demonstrates bibasilar crackles that sound like two pieces of velcro™ being slowly pulled apart in conditions such as IPF, fibrotic idiopathic NSIP, scleroderma, rheumatoid arthritis, and asbestosis. The presence of wheezing suggests some overlap with diseases that affect the airways such as combined pulmonary fibrosis and emphysema (CPFE), eosinophilic granulomatosis with polyangiitis, or concomitant asthma. Wheezing may also be present in cases of bronchiolitis and CHP in addition to "squeaks" and "pops" on inspiration [20, 21]. Digital clubbing is a non-specific finding that may be present in up to 50% of IPF patients at the time of diagnosis [5]. Most connective tissue disorders and other systemic conditions may be associated with subtle physical findings that are clues to the diagnosis (Table 2). As an example, systemic sclerosis is often associated with facial telangiectasias, reduced mouth aperture, skin thickening, and digital ulcerations. Inflammatory myopathies may be associated with mechanic's hands and dermatomyositis may present with an erythematous rash over the knuckles (Gottron's papules).

Pulmonary Function Tests

Evaluation of the lung physiology is of limited diagnostic value if not integrated in the overall clinical context. Pulmonary

Table 2 Common clinical features associated with connective tissue disorders

Connective tissue disorders	Signs and symptoms
Systemic sclerosis	Gastroesophageal reflux, telangiectasias, Raynaud's, skin rash, skin thickening
Rheumatoid arthritis	Stiffness and swelling of smaller joints
Dermatomyositis/ polymyositis	Mechanic's hands, Grotton's papules, Raynaud's, heliotrope rash, proximal muscle weakness
Sjogren's syndrome	Dry eyes, dry mouth, recurrent swelling of salivary glands

function testing is more often used to assess disease severity, progression, and response to therapy. Most cases of ILD present with a reduction in static lung volumes. The spirogram usually demonstrates a proportional reduction of forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1) that characterizes restriction. Obstructive abnormalities with/without elevation of lung volumes are less frequent but may help narrow the diagnosis to one of the conditions that may affect the airways (Table 3) [22–24]. Most patients with IPF have a substantial smoking history, so the presence of concomitant emphysema is not infrequent. Patients with combined pulmonary fibrosis and emphysema (CPFE) may present with relatively preserved lung volumes, which may delay the recognition of the underlying pathology [25, 26]. Often, the only clue is a disproportionally low diffusion capacity for carbon monoxide (DL_{CO}), which can also be seen in ILD patients with secondary pulmonary arterial hypertension (PAH).

Oxygen levels should be measured at rest and during exertion during the clinical investigation of patients with ILD [5]. The finding of hypoxemia during exertion is a common finding and may portent worse prognosis for patients with ILD [27].

Serological Evaluation

Data from a series of registries suggest that connective tissue diseases are the third most common cause of interstitial lung disease (CTD-ILD) [28]. In the USA, it is estimated that the prevalence of CTD-ILD is approximately 7.1 and 11.6/100,000 persons for men and women, respectively [2] and a significant number of patients with rheumatoid arthritis and scleroderma

Table 3 ILDs that may be associated with obstructive pattern in PFTs

Combined COPD and ILD
Hypersensitivity pneumonitis
Sarcoidosis
Constrictive bronchiolitis
Lymphangioleiomyomatosis
Pulmonary Langerhans cell histiocytosis

will have evidence of interstitial abnormalities in chest imaging during the course of their disease [29, 30]. Furthermore, ILD is a leading cause of death among patients with systemic sclerosis and rheumatoid arthritis [31, 32]. The determination of whether a patient presenting with ILD has a CTD can be very challenging. An ILD may be the sole initial manifestation of a CTD [33, 34] and the absence of extrapulmonary signs and symptoms may delay clinical suspicion and subsequent investigation. Hence, serological evaluation is strongly recommended for all patients presenting with an ILD despite the lack of high-quality evidence to inform how comprehensive that evaluation ought to be for a patient without extrapulmonary manifestations. The ATS/ERS/JRS/ALAT guidelines on the diagnosis of IPF issues a broad recommendation for serological testing, with the majority of the panelists listing C-reactive protein, erythrocyte sedimentation rate, ANA (by immunofluorescence), RF, myositis panel, and anti-CCP as part of the initial panel [35••]. Bahmer and colleagues propose a stepwise approach whereby all ILD patients should have an ANA (tested by indirect immunofluorescence) along with Ro/SSA, La/SSB, and Jo-1 as these autoantibodies may be missed by the ANA screening. Finally, they argue that the elevated prevalence of rheumatoid arthritis and the fact that an interstitial lung disease may be the initial presentation of ANCA-mediated vasculitis, justifies that one also obtains CCP, RF, and ANCAs as part of the initial evaluation [36]. Further testing including the t-RNA synthetase-related autoantibodies should be checked if the suspicion is corroborated by physical examination findings and/or elevation of muscle enzymes. Positive serologies without overt clinical manifestations of connective tissue disease in the setting of ILD may necessitate a rheumatological evaluation. We have a low threshold for Rheumatology referral for younger patients, particularly those belonging to a racial minority or those with HRCT findings that are atypical for UIP. A Rheumatologist may unveil unrecognized, and sometimes subtle, physical findings such as nail fold capillary abnormalities, diminished mouth aperture, or mechanic's hands.

Imaging

Although a plain chest radiograph may demonstrate the presence of ILD, its value is usually limited to suggesting whether the disease affects predominantly the upper or lower zones. High-resolution computer assisted tomography (HRCT) has become the most important element in the diagnostic algorithm of interstitial lung diseases and a technically adequate study can be diagnostic, abrogating the need for a lung biopsy [37].

HRCT images should be obtained with the patient in the prone position, with thin sections (< 2 mm) using a high spatial resolution reconstruction algorithm in both full inspiration and expiration [38, 39]. Volumetric CT acquisition is preferred to non-contiguous imaging since it improves characterization and

delineates extent and distribution of the disease [40]. Images obtained in full inspiration decrease lung attenuation and help with better visualization interstitial abnormalities, particularly reticular and ground glass opacities [39]. On the other hand, expiratory views may identify mosaic attenuation and air trapping that can be associated with chronic hypersensitivity pneumonitis or certain connective tissue diseases [41]. This is a very important element, as CHP is a common mimicker of IPF [42].

Prone positioning helps in reducing dependent atelectasis, better visualization of the posterior lung bases, and recognition of findings such as fine reticulations which can be missed with supine imaging. Prone images may also facilitate confirming the diagnosis of honeycombing by reducing inter-observer variability [43, 44].

The main HRCT patterns seen in ILD include honeycombing, reticular opacities, traction bronchiectasis, and ground glass opacities. A given pattern may be related to a specific diagnosis (Table 4), and hence requires familiarity with terminology and features. Honeycombing is defined as clustered, thick-walled cystic spaces of similar diameters, generally measuring between 3 and 5 mm, but occasionally up to 25 mm in size [45]. A single subpleural layer of two or three contiguous cysts is sufficient for diagnosing honeycombing [46]. Honeycombing noted on CT corresponds histologically to honeycomb cysts from revised alveolar spaces and bronchiolectasis but microscopic honeycombing can be present in the absence of visible honeycombing in a HRCT.

Traction bronchiectasis represents dilation of the bronchioles secondary to surrounding retractile fibrosis [45] and may be associated with worse outcomes [47]. It can be challenging

Table 4 HRCT patterns and associated diseases

HRCT pattern	Disease
Typical UIP	Idiopathic pulmonary fibrosis
	Rheumatoid arthritis
	Asbestosis
	Hypersensitivity pneumonitis
Probable UIP	Idiopathic pulmonary fibrosis
	Hypersensitivity pneumonitis
	Rheumatoid arthritis
	Sjogren's disease
	Systemic sclerosis
	Dermatomyositis
Indeterminate for UIP	Hypersensitivity pneumonitis
	Sarcoidosis
	Silicosis
	Pneumoconiosis
Features consistent with non-IPF diagnosis	Hypersensitivity pneumonitis
	Lymphangioleiomyomatosis
	Respiratory bronchiolitis-ILD
	Lymphangitic carcinomatosis

to differentiate peripherally-located traction bronchiectasis from honeycombing, so it is recommended that sequential multiplanar images enhanced by post processing algorithms are used when this question arises [48••].

Reticular opacities can be either fine or coarse interlaced curvilinear lines that are associated with thickening of the pulmonary interstitium and, at times, microscopic honeycombing.

Ground glass opacities are areas of obfuscation of the lung parenchyma by faint white opacities through which underlying bronchial and vascular structures are still identifiable. It may represent alveolar filling processes such as what is observed with desquamative interstitial pneumonia (DIP) or interstitial inflammation as seen in NSIP (idiopathic or secondary to CTD).

A white paper from the Fleischner society on diagnostic criteria for IPF [48••] recommends that HRCT patterns be classified based on whether it is consistent with UIP or otherwise (Table 5). Features such as peribronchovascular opacities and cystic changes are suggestive of "diagnosis other than IPF" such as sarcoidosis and LAM or PLCH, respectively.

Appraisal of the HRCT pattern and the predominant location of the ILD (Table 6) is a critical step, but it is ultimately up to the clinician and often to the multidisciplinary team to arrive at the most likely diagnosis by integrating all the clinical and imaging data available.

Bronchoalveolar Lavage, Transbronchial Biopsy, Bronchoscopic Cryobiopsy, and Surgical Lung Biopsy

Occasionally, a diagnosis cannot be defined even after careful review of the clinical history, physical examination, imaging, and serological data. As one ponders on the need for an invasive procedure, the main considerations are diagnostic yield, safety, and whether the results are likely to affect the management.

Bronchoalveolar lavage (BAL) is considered to be safe in patients with ILD [49] but there is data suggesting an increased

Table 6 Predominant location of interstitial abnormalities and disease association

Predominant location	Disease association
Upper zone	Sarcoidosis, pulmonary Langerhans cell histiocytosis, hypersensitivity pneumonitis, pneumoconiosis
Lower zone	Idiopathic pulmonary fibrosis, rheumatoid arthritis, scleroderma, asbestosis

risk of acute exacerbations following the procedure in patients with IPF [50]. When performed, no less than 100 mL and no more than 300 mL of normal saline should be instilled in a subsegment [51•]. In general, BAL findings are considered to be neither sensitive nor specific in ILD but in certain conditions, it may provide enough evidence to support (or refute) a diagnosis. A milky appearing fluid with PAS-positive debris is consistent with pulmonary alveolar proteinosis and fluid aliquots that are increasingly bloody-appearing are seen in patients with diffuse alveolar hemorrhage. Sarcoidosis has a higher proportion of lymphocytes and stable IPF patients tend to have a higher neutrophil count [52]. A differential eosinophil count ≥ 25% suggests eosinophilic pneumonia, whereas 5% or more of CD1a positive cells corroborates the diagnosis of Pulmonary Langerhans' cell histiocytosis [53]. The recent updated guidelines on the diagnosis of IPF suggest that a BAL be considered for patients with ILD of unknown cause presenting with a HRCT pattern different than UIP [35••].

The utility of a transbronchial biopsy (TBBx) in the diagnosis of ILD is hampered by the small size of specimens and frequent presence of crushing artifacts, which can be minimized by use of an alligator forceps, although a cup forceps may be more likely to obtain alveolated tissue [54]. In a recent series, more than half of the specimens obtained via TBBx were deemed inadequate [55]. Overall, TBBx is felt to be safe, and recent report estimates the risk of pneumothorax to be approximately 7% in patients with pulmonary fibrosis and it

Table 5 Proposed HRCT pattern classification for IPF diagnosis

	Typical UIP	Probable UIP	Indeterminate for UIP	Features consistent with non-IPF diagnosis
Distribution	Basal predominant (occasionally diffuse), and subpleural predominant; distribution is often heterogenous	Basal and subpleural predominant; distribution is often heterogenous	Variable or diffuse	Upper-lung or mid-lung predominant fibrosis, peribronchovascular predominance with subpleural sparing
Features	Honeycombing; reticular pattern with peripheral traction bronchiectasis or bronchiolectasis; absence of features to explain an alternate diagnosis	Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis; honey combing is absent; absence of features to explain an alternate diagnosis	Evidence of fibrosis with some inconspicuous features suggestive of a non-UIP pattern	Any of the following: predominant consolidation, extensive pure ground glass opacity (without acute exacerbation), extensive mosaic attenuation with extensive sharply defined lobular air trapping on expiration, diffuse nodules or cysts

Table 7 Common histological findings in patients with CTD-ILD

	RA	SLE	Scleroderma	PM/DM	Sjogren's
UIP	+++		++	+	+/−
NSIP	++		++	++	+
BOOP	+			+	
LIP					++
DAD		+			

RA, rheumatoid arthritis; *SLE* systemic lupus erythematosus; *PM/DM*, polymyositis/dermatomyositis; *UIP*, usual interstitial pneumonia; *NSIP*, non-specific interstitial pneumonia; *BOOP*, bronchiolitis obliterans and organizing pneumonia; *LIP*, lymphocytic interstitial pneumonia; *DAD*, diffuse alveolar damage

was directly associated with disease severity [56]. TBBx has relatively low diagnostic yield in ILD but when combined with clinical and HRCT data and in the context of a multidisciplinary discussion among experts, it may provide enough evidence for a confident diagnosis in 20–30% of cases [55]. Genomic analysis and machine learning technology may improve the utility of TBBx for the diagnosis of UIP but this promising methodology has not been broadly validated [57].

Bronchoscopic cryobiopsies require deep sedation and endotracheal rigid intubation in the operating room. Biopsies are obtained via a flexible cryoprobe that freezes the tissue for samples that are 0.5 to 1 cm in size [58]. The advantages of the CryoBx over TBBx are related to the larger sizes of the specimens which allow for a better evaluation of the overall pattern of lesion and lack of crushing artifact [59]. The overall diagnostic yield of CryoBx is unknown as there has been no study comparing it to the more invasive surgical lung biopsy (SLBx). However, the diagnostic yield of CryoBx in isolation

Fig. 2 Diagnostic algorithm. PFTs, pulmonary function testing; BAL, bronchoalveolar lavage; TBBx, transbronchial biopsy; TBCryoBx, transbronchial cryobiopsy
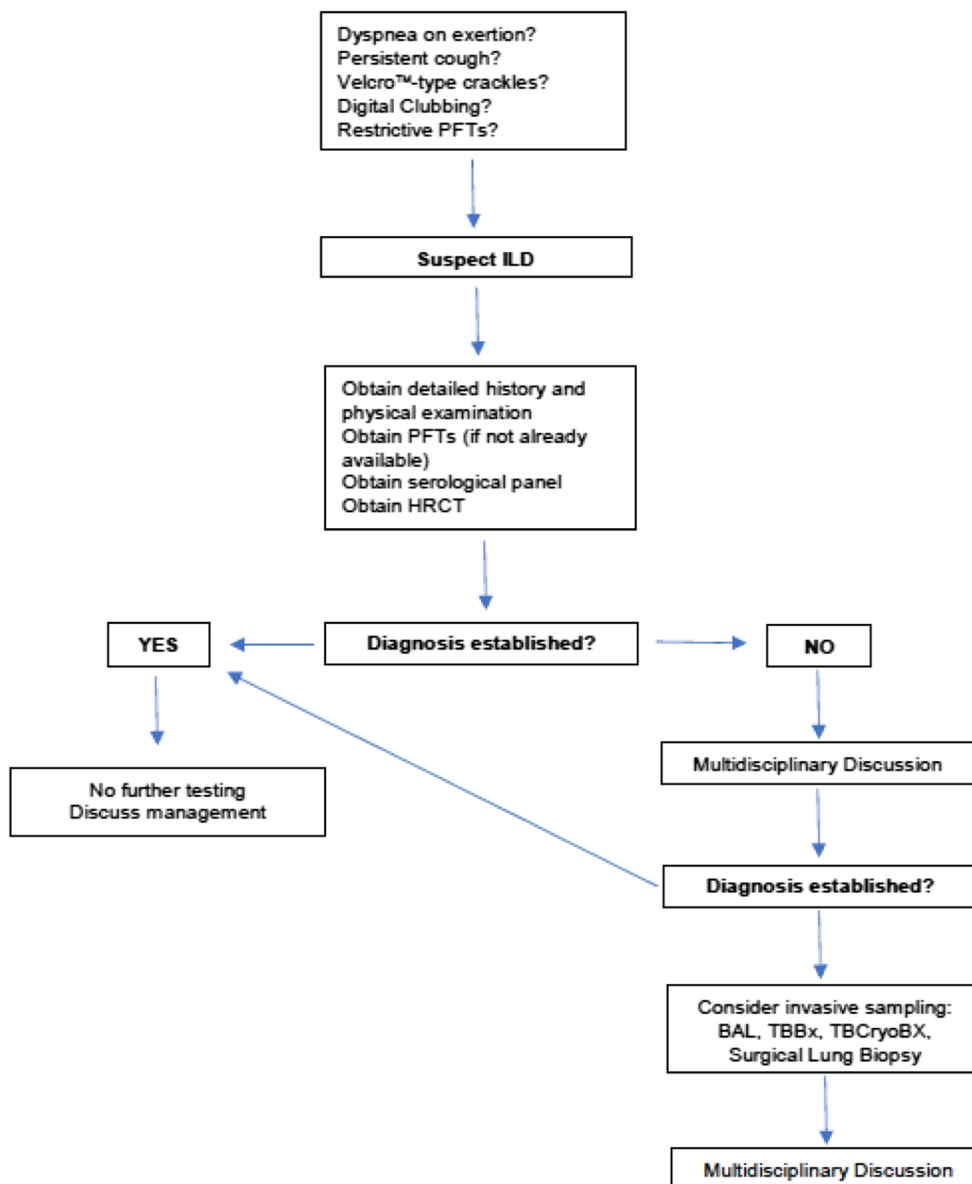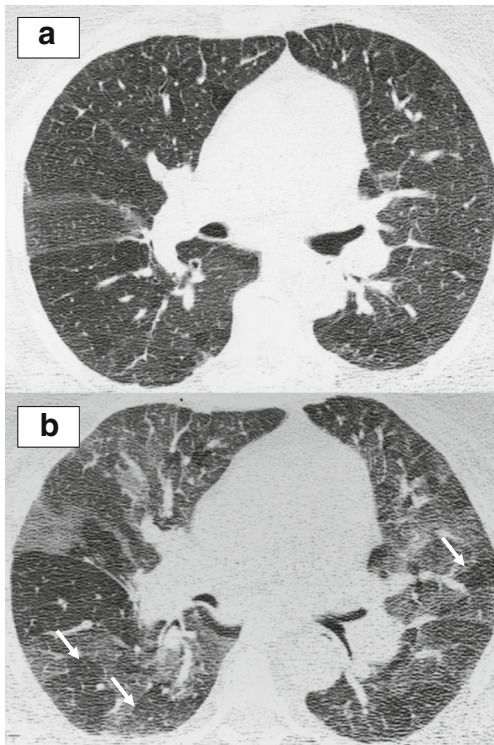
Fig. 3 HRCT images in inspiration (3.A) and expiration (3.B). Note diffuse patchy ground glass opacities in inspiration and mosaic attenuation in expiration, consistent with air trapping (white arrows)

and in the context of a multidisciplinary discussion is quite good and estimated to be approximately 83% and 79% respectively. Safety concerns remain an issue, with incidence of pneumothorax and moderate to severe bleeding reported to be 12% and 39% respectively [60•, 61].

A surgical lung biopsy may be indicated in cases where the diagnosis cannot be confidently established with data from a careful clinical evaluation, radiology, and/or less invasive histological sampling. The 2011 ATS/ERS/JRS/ALAT Guidelines on the diagnosis and management of IPF suggests that a surgical lung biopsy be performed in cases where the HRCT demonstrates a pattern different than "definite UIP" and in the absence of other data suggesting an alternative diagnosis [5, 62]. The
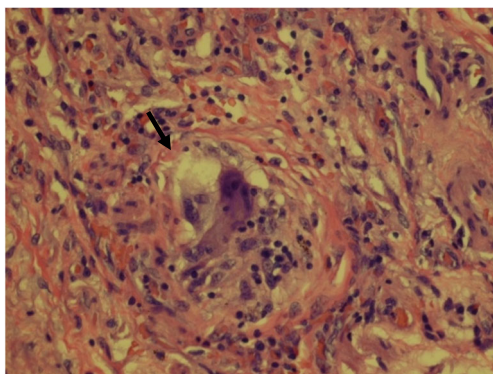

Fig. 4 High power view of a poorly formed non-caseating granuloma (black arrow)
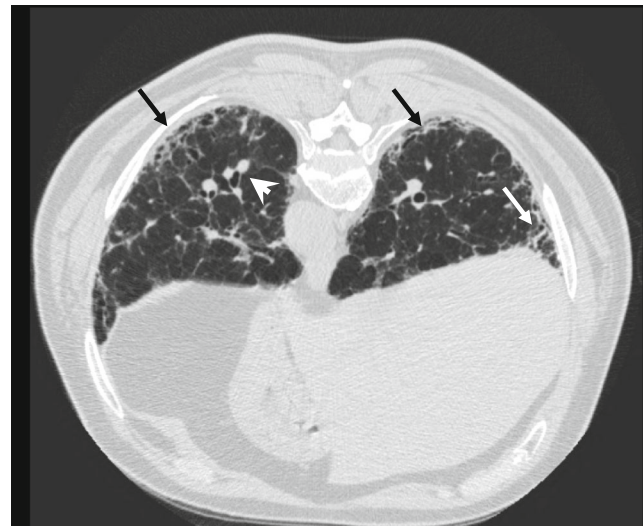
Fig. 5 Predominantly lower lobe and subpleural reticulation (white arrows), traction bronchiectasis (arrow heads) and areas of honeycombing (black arrows). Findings are consistent with "typical UIP pattern"

updated 2018 guidelines maintained that recommendation [35••]. One can also consider a SLBx in a patient with established diagnosis of ILD presenting with new and atypical features [62]. The mortality associated with a SLBx can be substantial. Acutely ill patients undergoing the procedure may have in-hospital mortality rates in excess of 15%. The risk of death related to an elective SLBx in clinically stable patients is estimated to be less than 5% but this number varies greatly in the literature and is likely related to patient selection and experience of the surgical team [63, 64]. The risk of poor outcomes following a SLBx is higher among males and increases with age and the number of comorbidities [63]. Most SLBx are now been performed thoracoscopically and at least two lobes should be sampled given the frequent histologic variability noted in cases of ILD [65]. The
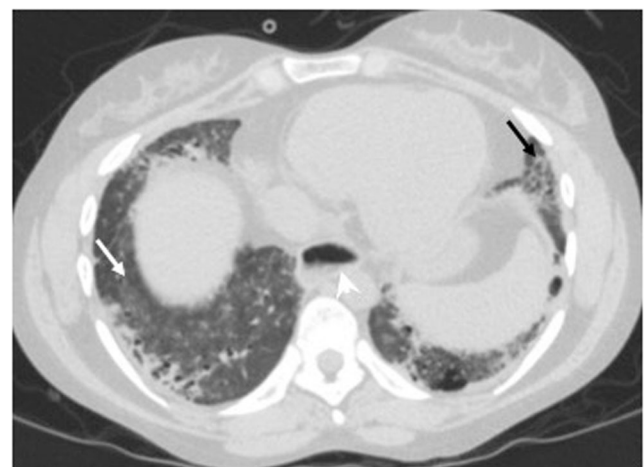
Fig. 6 Extensive faint ground glass opacities (white arrow) predominating in the lower lung zones, along with few areas of coarse reticulation (black arrows) and no overt honeycombing. The esophagus is patulous (arrow head)

findings of a surgical biopsy should not be considered the final diagnosis in a patient with ILD as many diseases may share histological patterns (Table 7). The biopsy samples should always be reviewed in the context of a multidisciplinary appraisal of all the available clinical and imaging data [5, 66]. Unfortunately, in many instances, only a provisional diagnosis can be issued and prospective clinical surveillance for further clues will remain an important aspect of patient management.

Conclusions and Summary of the Diagnostic Algorithm

Invariably, it is the primary care provider that suspects the presence of lung disease. We recommend that any patient presenting with a constellation of manifestations that includes dyspnea on exertion/exercise limitation, persistent cough, digital clubbing, and/or crackles on lung auscultation be investigated for ILD. Once ILD is suspected, the first step is a comprehensive history and physical examination, followed by pulmonary function tests, serologies, and a HRCT. In most cases, a diagnosis can be made with a good level of confidence; otherwise, if considering an invasive procedure, one ought to conduct a multidisciplinary discussion, which should be repeated if tissue is actually obtained (Fig. 2). It is important to underscore the fact that not all MDDs end in a consensus diagnosis. Obtaining a biopsy may always not be feasible based on age, comorbidities, severity of the disease, or patient preferences. In such cases, one may have to establish a "provisional" diagnosis based on the available evidence and continue to seek for clues that may come forth over time. Important clues include response to empirical therapies and the development of systemic manifestations of underlying connective tissue diseases.

Integrating the Data—Case Examples

Case 1

History and Physical Examination A 70-year-old Caucasian female presented for a second opinion on a diagnosis of IPF that had been established via surgical lung biopsy in another institution. She had a 9-month history of dyspnea on exertion in addition to mild persistent asthma, fibromyalgia, and irritable bowel syndrome. There was no family history of ILD or CTD. She worked as a waitress and had daily exposure to second-hand smoking. She owned a plum-headed parakeet for 10 years. On physical examination, there were bibasilar inspiratory crackles and a few inspiratory and expiratory squeaks in the upper zones.

Pulmonary Function Testing FVC 73%, FEV_1 78%, ratio 0.81, TLC 70%, D_LCO 55%. No hypoxemia in a 6-min walk test.

Serological Evaluation ANA, CCP, RF, Scl-70, SSA, SSB, RNP, c-ANCA, p-ANCA, Jo1, MI 2, PL7, PL12, EJ, OJ, SRP, KU, U2 SN RNP: negative

HRCT Interstitial changes more pronounced in the lower lung zones, there was no overt honeycombing and the predominant finding is ground glass opacities. Expiratory views demonstrated areas of lobular air trapping (Fig. 3).

Lung Biopsy Findings included areas of normal lung interspersed with areas affected by dense fibrosis and remodeling. A few fibroblast foci and airway-centered poorly formed non-caseating granulomas were present (Fig. 4).

Multidisciplinary Discussion The patient's age is certainly consistent with original diagnosis of IPF. She had significant exposures and smoking-related ILD such as RB-ILD and DIP may occur with second-hand exposure to cigarette smoking. Her exposure to a pet bird and the presence of upper zone bronchiolar sounds (squeaks) are concerning for CHP. She had no manifestations of a CTD and a negative serological panel makes this diagnosis unlikely. Her PFTs demonstrate a restrictive pattern that is consistent with the presence of ILD. The lack of airflow obstruction does not rule out the possibility of CHP or concomitant emphysema or asthma. Her HRCT findings are very important. She has extensive areas of ground glass opacities but also some fibrotic changes manifested as reticulation and mild traction bronchiectasis. The absence of honeycombing is also relevant as is the presence of mosaic attenuation and areas of clear lobular air trapping. In the most recent classification proposed by the Fleischner Society [48••], her HRCT would be classified as "most consistent with a non-IPF diagnosis". Her long history of exposure to a pet bird, the physical examination findings, and the presence of air trapping in the HRCT does support a diagnosis of CHP and the findings in surgical lung biopsy, although consistent with CHP, did not really add any significant information to what was already known without it. This case is an example of how careful appraisal of all the evidence arising from a comprehensive exposure history and a technically adequate HRCT may abrogate the need for an invasive procedure.

Final Diagnosis Chronic hypersensitivity pneumonitis

Case 2

History and Physical Examination Sixty-one-year-old Caucasian male presented with 18-month history of dyspnea and non-productive cough. No occupational or household exposures. No family history of ILD or CTD. Never smoker. Lung auscultation revealed bibasilar inspiratory crackles.

Pulmonary Function Testing FVC 65%, FEV$_1$ 71%, ratio .77, TLC 68%, D$_L$CO 59%. Six-minute walk test: nadir SpO2 was 87%. Maximum HR 110 bpm

Serological Evaluation ANA, CCP, RF, Scl-70, SSA, SSB, RNP, c-ANCA, p-ANCA, Jo1, MI 2, PL7, PL12, EJ, OJ, SRP, KU, U2 SN RNP: negative

HRCT Extensive subpleural reticulation that predominates in the lower lung zones and areas of honeycombing. No air trapping on expiratory views. Findings consistent with "typical UIP pattern" (Fig. 5).

Multidisciplinary Discussion This is an older Caucasian male without any significant exposures and no evidence of an autoimmune disease presenting with dyspnea on exertion, cough, restrictive PFTs, hypoxemia on exertion, and UIP pattern in a good quality HRCT. In this case, there is no need for further testing and a lung biopsy is not indicated.

Final Diagnosis Idiopathic pulmonary fibrosis

Case 3

History and Physical Examination Thirty-six-year-old African American female presented with 2 years of progressive dyspnea. She endorsed frequent episodes of heartburn and the sensation that her food "is not going down". Her fingers turn blue and hurt during the colder months. An aunt died of "lupus". She denied any household or occupational exposures. The physical examination revealed thickening of the skin on her face with limited mouth aperture. She had active Raynaud's and skin changes consistent with sclerodactyly. Lung auscultation demonstrated bibasilar inspiratory crackles. Heart auscultation demonstrated a loud S2.

Pulmonary Function Testing FVC 48%, FEV$_1$ 53%, TLC 60%, D$_L$CO 30%. Six-minute walk test: nadir SpO2 was 82%.

Serological Evaluation Positive ANA (1:1280, nucleolar pattern) and Scl-70. All others: negative

HRCT Extensive faint ground glass opacities predominating in the lower lung zones, along with few areas of coarse reticulation and no overt honeycombing. Esophagus appears patulous (see Fig. 6).

Multidisciplinary Discussion This is a young African American female with a family history of CTD presenting with manifestations suspicious for Systemic Sclerosis, which is corroborated by serological results. The findings of a loud S2 on physical examination and disproportionally low DLCO are concerning for secondary pulmonary arterial hypertension, which has a high incidence in Systemic Sclerosis. Her HRCT

demonstrates a pattern consistent with fibrotic NSIP, which can be seen in cases of ILD secondary to CTD. A patulous esophagus also raises the suspicion for systemic sclerosis. Taken together, the data is consistent with ILD secondary to systemic sclerosis, complicated by esophageal dysmotility and probable secondary pulmonary arterial hypertension. In this case, a biopsy is not indicated as it would neither change the diagnosis nor affect management.

Final Diagnosis ILD secondary to underlying CTD (systemic sclerosis)

Compliance with Ethical Standards

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