An Integrated Approach to Diagnosing Interstitial Lung Disease

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Clinical Vignette

A previously healthy 67-year-old male former smoker of 25 pack-years reports worsening exertional dyspnea and an occasionally productive cough. An initial evaluation for potential cardiac etiologies does not reveal any obvious cause and the patient subsequently undergoes a pulmonary function test (PFT) and chest computed tomography (CT). The PFT reveals slightly reduced flow rates and lung volumes in a restricted pattern, with a diffusion capacity of the lung for carbon monoxide of 62% predicted. The CT shows peripheral and lower lung predominant reticulation and traction bronchiectasis without honeycombing, nodularity, ground glass, or mosaicism. The community radiologist reports this as a possible usual interstitial pneumonia pattern based on previous clinical practice guidelines, and the patient is considered to have unclassifiable ILD by his initial respirologist given the absence of a clear cause and an inconclusive imaging pattern.

The patient is referred to an ILD center and has an extensive assessment that more confidently excludes the possibilities of fibrotic hypersensitivity pneumonitis, connective tissue disease-associated interstitial lung disease (ILD), or drug-induced ILD. A multidisciplinary discussion is performed in collaboration with an experienced chest radiologist who concludes that the CT pattern is that of probable UIP using the updated contemporary clinical practice guidelines. On that basis, the patient is provided a working diagnosis of idiopathic pulmonary fibrosis (IPF) and a surgical lung biopsy is felt to be unwarranted in that context. The patient is offered and agrees to start taking an antifibrotic medication.

Introduction

Interstitial lung disease (ILD) is a collection of approximately 200 diverse conditions that result in inflammation and/or fibrosis of the lung parenchyma. Common fibrotic ILD subtypes include idiopathic pulmonary fibrosis (IPF), connective tissue disease-associated ILD (CTD-ILD), and fibrotic hypersensitivity pneumonitis (HP), with a substantial percentage, also considered to have an unclassifiable ILD. Fibrotic ILDs are chronic and progressive diseases that are frequently characterized by disabling dyspnea and cough, reduced quality of life, and early mortality. The prognosis of IPF, which is the most common idiopathic interstitial pneumonia (IIP), appears to be improving with slightly longer median survival in recent cohorts (3–5 years from the time of diagnosis) compared to the historical median survival of 2–3 years [1]. The incidence and prevalence of common fibrotic ILDs are also increasing [2], although it is not clear whether this reported increase is simply a consequence of greater recognition.

Distinguishing ILD subtypes is challenging, often requiring a multidisciplinary effort by an experienced team of ILD clinicians, chest radiologists, and lung pathologists [3, 4]. This multidisciplinary discussion (MDD) of relevant clinical, radiological, laboratory and histopathological features is best accomplished with a face-to-face dynamic interaction of these subspecialists. Previous studies have suggested higher diagnostic accuracy, represented by greater diagnostic agreement, in academic centers compared to healthcare providers working in community settings [5]. Diagnoses assigned by experienced physicians working in academic centers similarly carry greater prognostic significance compared to diag-

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noses by less experienced clinicians, also suggesting higher diagnostic accuracy among experts [6]. The clinical impact of the MDD approach is illustrated by the change in diagnosis and change in treatment for approximately 50% of patients subjected to this process [7, 8].

In this chapter, key components of the clinical, radiological, laboratory, and bronchoscopic and histopathological assessment are discussed, followed by a review of the typical approach to the integration of these features. This chapter focuses on fibrotic ILD subtypes given the more frequent diagnostic challenges that are encountered with these diseases. The specific features of each major ILD subtype are provided in the chapters that address each of these diagnoses.

Overview of ILD Diagnosis

Patients with fibrotic ILD typically present with chronic onset of dyspnea that becomes noticeable over several months or even years. Unless ILD is detected incidentally, dyspnea is almost universally present at the time of diagnosis. Approximately 85% of patients also report chronic cough at the time of diagnosis, which can be even more disabling than dyspnea in some patients [9]. These symptoms and associated functional limitations are nonspecific, with more frequent etiologies such as chronic obstructive pulmonary disease (COPD) and heart disease typically being considered by general practitioners prior to identification of ILD on chest imaging. As a consequence, patients with ILD are frequently provided one of these incorrect diagnoses based on an incomplete evaluation, and frequently spend months and sometimes years being ineffectively treated for these conditions before the correct diagnosis is made. Aside from the emotional toll that accompanies a missed diagnosis [10], these delays can have a significant prognostic impact with worse survival in patients who have a delayed referral to an experienced ILD center [11]. It is therefore important that general practitioners consider ILD in their differential diagnosis of new unexplained dyspnea, cough, or functional limitation, potentially using some of the clinical features described below to help identify these patients at an earlier stage of their disease.

Once ILD is considered, patients will typically undergo a pulmonary function test and chest imaging. Based on their relative availability and lack of radiation exposure, pulmonary function tests are often used as a screening tool for patients at risk for ILD or as the first test in patients with a new suspected ILD; however, many patients with early ILD have normal pulmonary function tests or only a mild isolated reduction in gas transfer (i.e., a reduced diffusion capacity of the lung for carbon monoxide [DLCO]). Pulmonary function tests are therefore not sensitive nor specific enough to rule in or rule out ILD in many of the more common clinical scenarios.

The definitive tool used to identify the presence of an ILD is computed tomography (CT), with most conventional CT scanners now providing the appropriate high-resolution images that are needed to adequately characterize ILD morphology. ILD can be subclassified radiologically into fibrotic and non-fibrotic forms, with non-fibrotic subtypes of ILD including a variety of inflammatory, cystic, and nodular processes. Within each of these main ILD patterns, there are additional sub-patterns that further narrow the differential diagnosis, with many of these sub-patterns being diagnostic when considered in the corresponding clinical context. For example, patients with usual interstitial pneumonia (UIP) pattern without an underlying identified etiology after a thorough clinical and laboratory evaluation can be provided a confident diagnosis of IPF without the need for tissue confirmation [12].

The specific diagnostic criteria for each ILD subtype are provided in the corresponding chapters, with the remainder of this chapter focusing on the general approach that applies across the full spectrum of clinical settings and how various features should be integrated in order to arrive at a final diagnosis.

Clinical Assessment

There are no clinical features that are pathognomonic for ILD. Dyspnea, cough, and functional limitation are frequent manifestations of ILD, but are also observed in other more common diseases such as COPD and heart disease. The presence of a family history of ILD, hypoxemia, auscultatory crackles, or clubbing are nonspecific features, but should prompt consideration of fibrotic ILD in patients with chronic dyspnea, cough, or functional limitation. Importantly, auscultatory crackles are not typical findings of asthma, COPD, or CHF other than during acute exacerbations or episodes of volume overload. Hypoxemia and clubbing are not common findings in these conditions and also indicate the need to consider alternative or additional diagnoses. The initial evaluation in patients with any of these high-risk features should typically include complete pulmonary function tests (pre- and post-bronchodilator spirometry, lung volumes, and DLCO) and CT imaging of the chest. Patients with features suggesting a predisposing condition (e.g., connective tissue

disease, recent exposure history) should be approached in a similar manner in the context of new or worsening dyspnea, cough, or functional limitation.

A more comprehensive clinical assessment is required in patients with ILD that has been documented by chest CT with the primary goal of identifying an underlying etiology, in addition to assessing disease severity. This assessment should include a thorough history that identifies both risk factors and associated symptoms of different ILD subtypes. This can broadly be categorized as features suggesting an underlying chronic systemic disease (i.e., CTD-ILD), a history of exposure to agents known to cause ILD (e.g., antigens associated with HP, drugs associated with drug-induced ILD, inorganic exposures associated with pneumoconioses), and other ILD risk factors (e.g., age, smoking, dysphagia, comorbidities). Some of these risk factors can be very subtle; however, this is a critical component of the evaluation of ILD since identifying one of these risk factors for ILD can eliminate the need for more invasive testing in the appropriate clinical and radiological context.

The physical exam for a patient with newly identified ILD follows a similar approach. Auscultatory crackles suggest the presence of fibrosis and have prognostic significance in some ILD subtypes [13], but do not help distinguish among fibrotic ILD subtypes. The presence of inspiratory squeaks or expiratory wheeze suggests an airway-centered process such as hypersensitivity pneumonitis [14], but is not sensitive or specific enough to alter the decision of whether to pursue additional more invasive testing. Clubbing was historically thought to suggest IPF, but is now recognized as a nonspecific manifestation of a variety of fibrotic ILDs. The extrapulmonary examination has greater utility in distinguishing the cause of ILD, including a musculoskeletal and dermatologic evaluation that is used to identify what can be subtle manifestations of a CTD or systemic vasculitis. Signs of right heart dysfunction in the context of mild ILD can suggest systemic sclerosis or another CTD as a cause of the ILD, but this is less specific in more advanced ILD that can be associated with pulmonary hypertension regardless of the underlying etiology of the ILD.

Although there are many clinical features that help distinguish ILD subtypes, there is no standardized method for integrating these individual features in the diagnosis of ILD. This is therefore a subjective process that depends on the thoroughness of the evaluation, the experience of the clinician, and the information conveyed by the remainder of the multidisciplinary team. As a result, the clinical assessment is typically conceptualized as a gestalt impression of the relative likelihood of different ILD diagnoses, which is then refined after a review of imaging findings with a chest radiologist or in the context of a full MDD.

Radiological Assessment

The initial imaging study that suggests an ILD is often a plain chest radiograph; however, this is an insensitive test that is often normal in patients with mild ILD. A chest CT with high-resolution images (spatial resolution of <1.5 mm) is required for adequate morphological assessment that can frequently be combined with clinical and laboratory data to arrive at a confident diagnosis. CT protocols typically used in evaluating patients with ILD include continuous image acquisition and performance of both inspiratory and expiratory scans. Images acquired in the prone position are sometimes helpful in patients with mild abnormalities in order to help distinguish early ILD from dependent atelectasis. Chest CT can also be used to document disease severity and progression, with this most often being a qualitative assessment. This can include the demonstration of overt worsening of fibrosis, or often subtle changes in morphology in a given lung region from a more inflammatory (e.g., ground glass) to a more fibrotic appearance. Assessing the severity of disease on chest imaging can be difficult as the lung will typically contract with worsening fibrosis, with the progressively fibrotic lung taking up less intrathoracic space compared to the remaining normal or potentially hyperexpanded lung. It is frequently helpful to also inspect earlier abdominal and cardiac imaging studies that can provide a general sense of previous ILD severity, which is particularly useful for the assessment of long-term disease progression.

For patients with ILD, it is important for chest radiologists to comment on individual features, disease distribution, and overall pattern. Individual features relevant to the characterization of ILD include reticulation, traction bronchiectasis, honeycombing, ground glass, consolidation, and gas trapping (Fig. 31.1). The location of abnormality should be considered according to its craniocaudal distribution, including upper, lower, and diffuse locations (Fig. 31.2). Some ILDs are also characterized by subpleural, peripheral (sometimes with subpleural sparing), or peribronchovascular involvement (Fig. 31.3). These features and their distribution are integrated to identify specific imaging patterns. For example, a UIP pattern is characterized by peripheral and lower-lung predominant reticulation, traction bronchiectasis, and honeycombing, with minimal ground glass, consolidation, or gas trapping (Fig. 31.4) [12, 15]. An NSIP pattern often has similar features with peripheral and lower-lung predominant reticulation and traction bronchiectasis, but with subpleural sparing in 25% of patients, and variable amounts of ground glass that can represent either microfibrous or concurrent inflammation (Fig. 31.5) [16, 17]. A CT suggesting fibrotic HP will frequently have gas trapping in addition to other findings of inflammation and fibrosis [18],

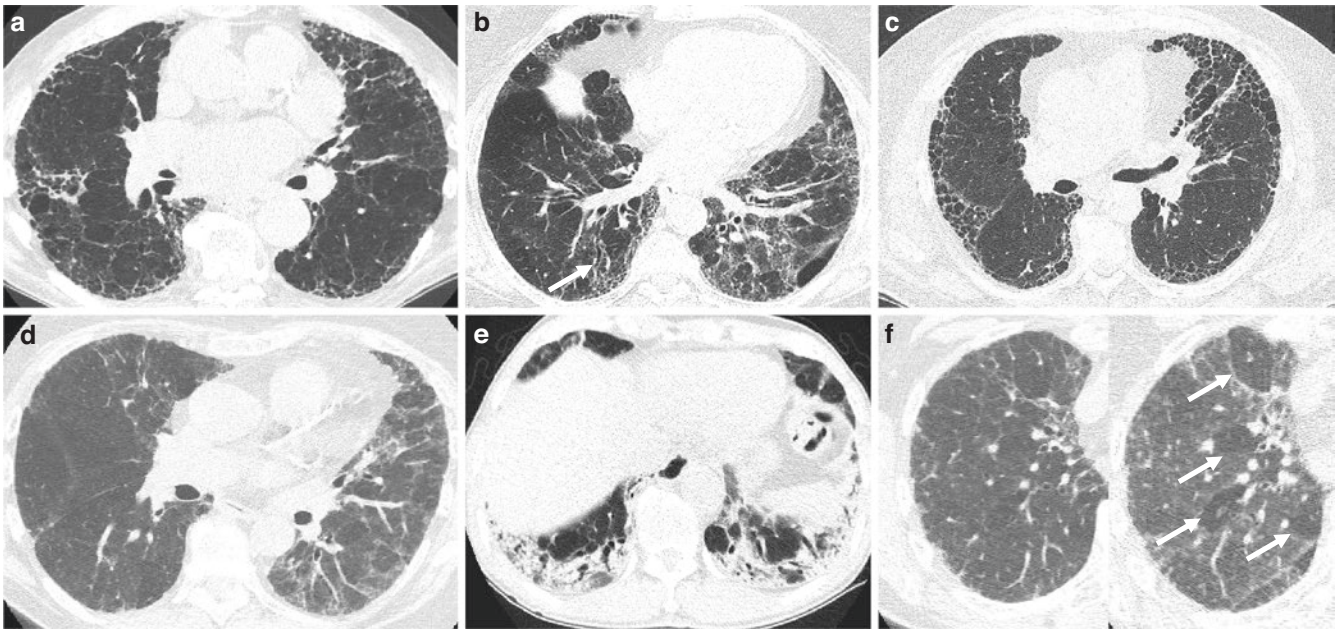

Fig. 31.1 Radiological features of interstitial lung disease, including (**a**) reticulation (lines of scar tissue), (**b**) traction bronchiectasis (arrow), (**c**) honeycombing, (**d**) ground glass, (**e**) consolidation, and (**f**) lobular areas of gas trapping (arrows) comparing inspiratory (left) to expiratory (right) images

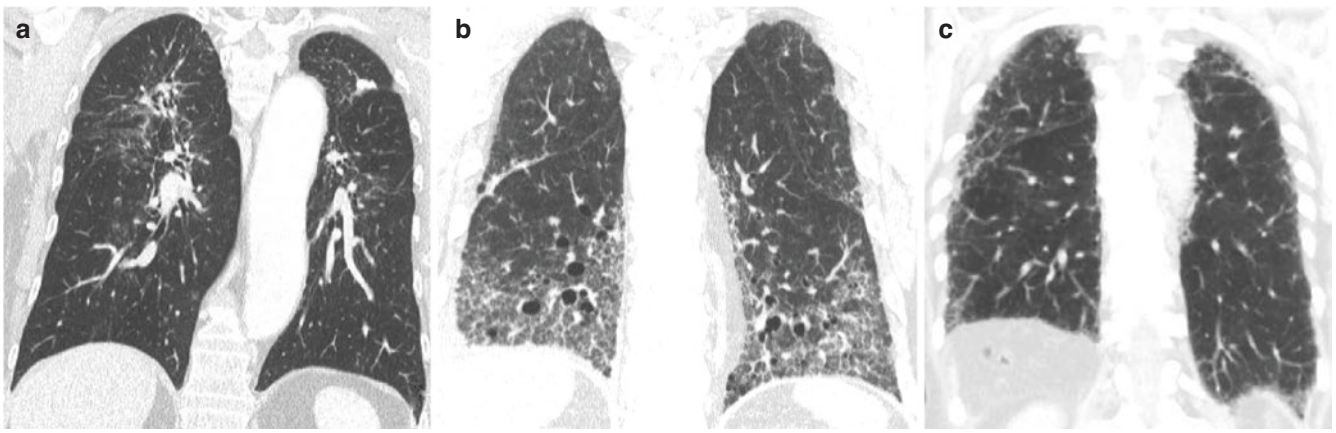

Fig. 31.2 Common craniocaudal distributions of ILD, including upper lung predominance in a patient with sarcoidosis (**a**), lower lung predominance in a patient with idiopathic pulmonary fibrosis (**b**), and diffuse involvement in a patient with hypersensitivity pneumonitis (**c**)

and will more often have an upper lung or diffuse distribution that can also have some peribronchovascular extension (Fig. 31.6) [19].

The overall pattern suggested by a chest radiologist requires contextualization with the clinical scenario. Some diagnoses (e.g., CTD-ILD, drug-induced ILD) can be associated with multiple imaging patterns, while some imaging patterns (e.g., UIP, NSIP) can be seen in a variety of ILD subtypes. The decision of whether to move on to more invasive bronchoscopic or histopathological sampling is therefore dependent upon the combined clinical-radiological impression. This clinical-radiological integration is provided in relatively clear terms for making a diagnosis of IPF with recent guidelines providing a similar approach for the diagnosis of HP [12, 20]; however, this is currently less standardized for idiopathic

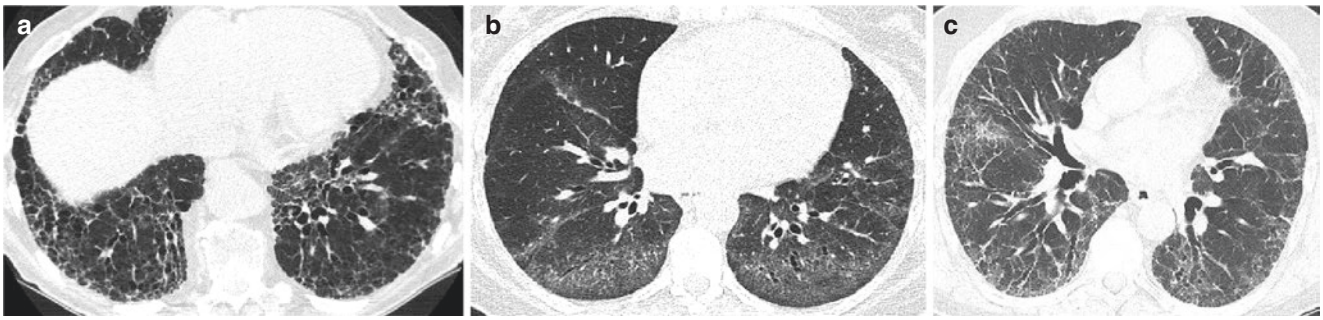

Fig. 31.3 Fibrotic ILD demonstrating a peripheral pattern with subpleural involvement in a patient with biopsy-proven usual interstitial pneumonia (**a**), peripheral pattern with subpleural sparing consistent with nonspecific interstitial pneumonia in a patient with systemic sclerosis (**b**), peripheral pattern with peribronchovascular extension in a patient with biopsy-proven hypersensitivity pneumonitis (**c**)

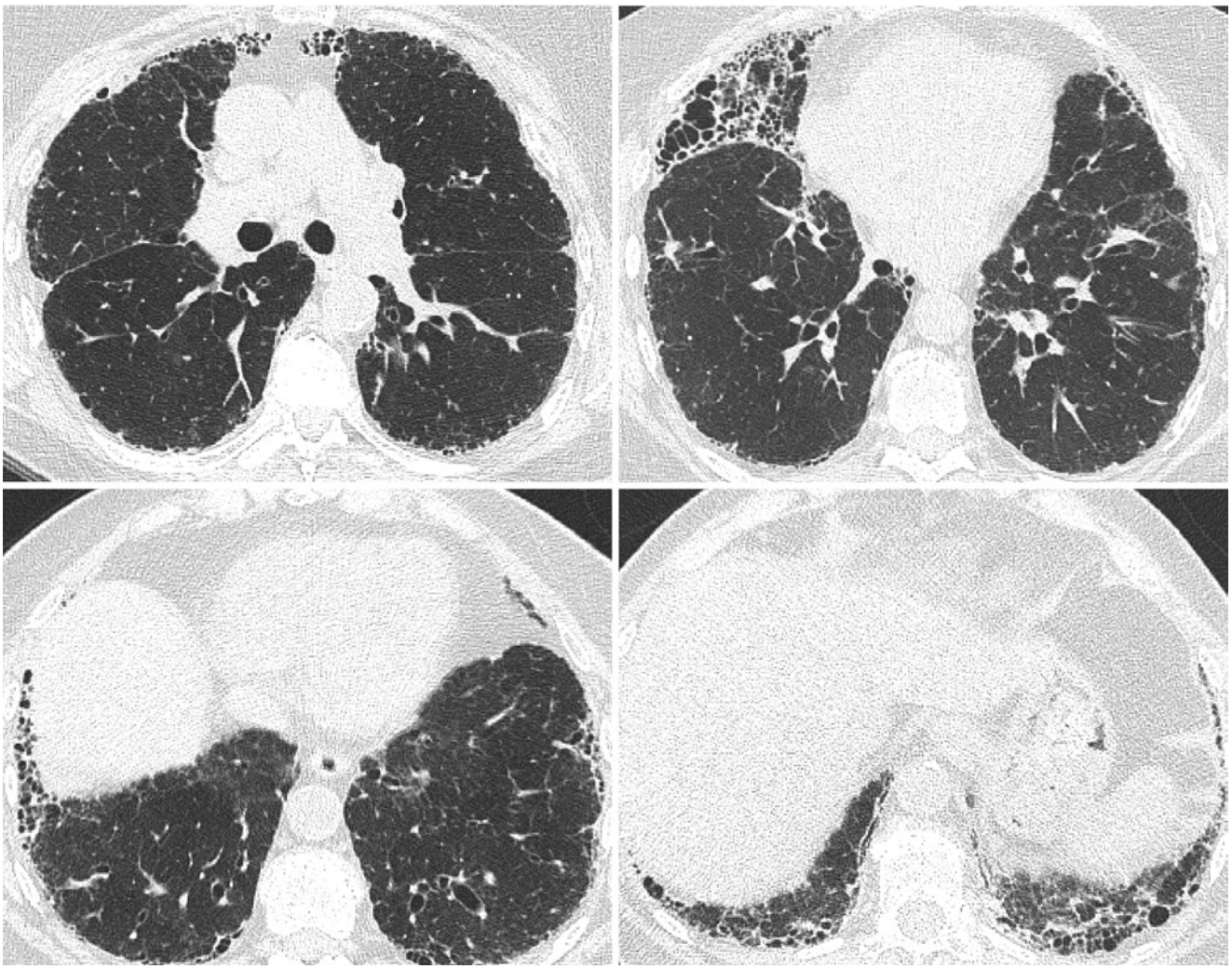

Fig. 31.4 Transaxial chest CT in a patient with idiopathic pulmonary fibrosis showing a pattern of usual interstitial pneumonia, characterized by lower lung predominance of peripheral reticulation, traction bronchiectasis, and honeycombing

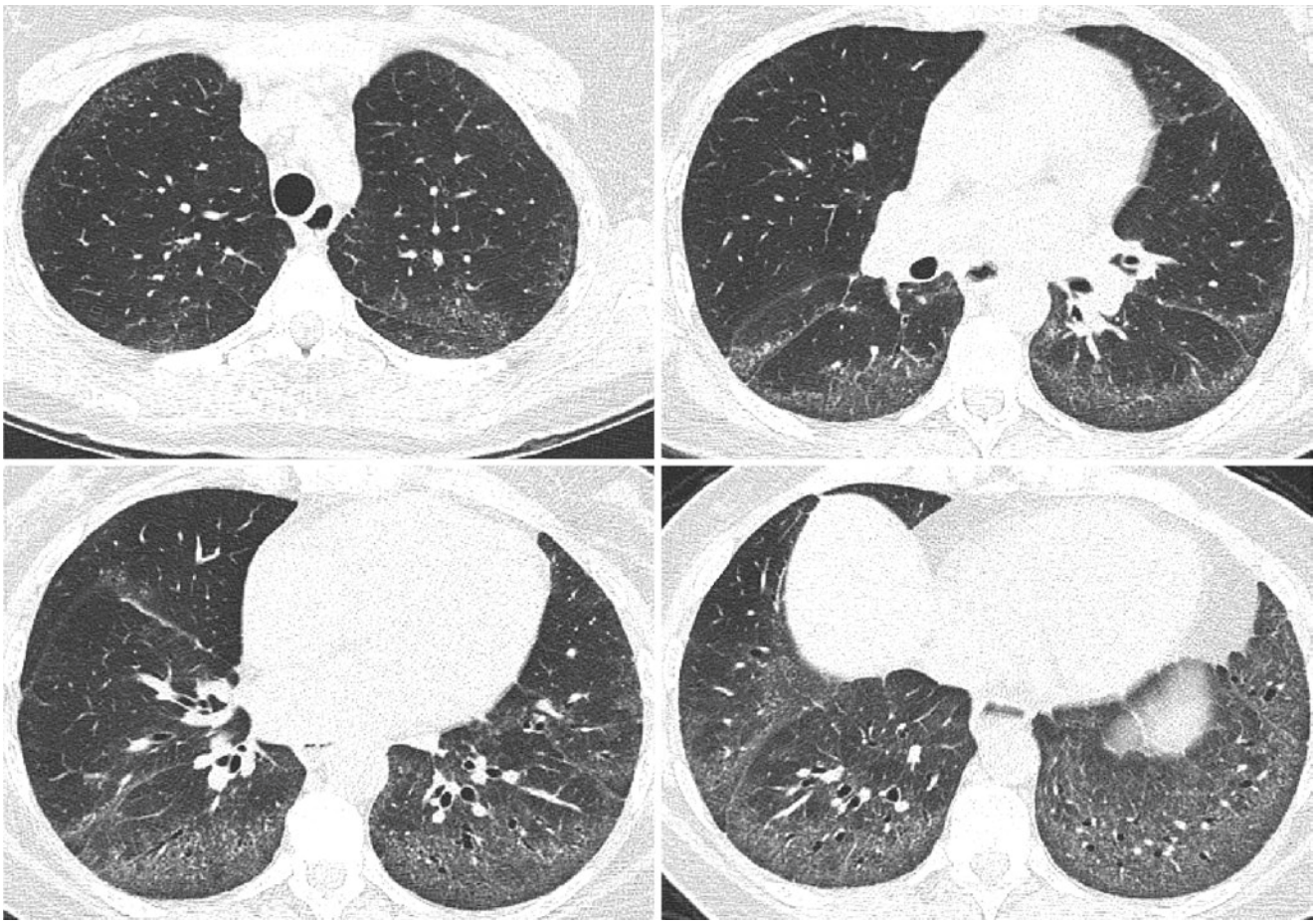

Fig. 31.5 Transaxial chest CT in a patient with systemic sclerosis showing a pattern of nonspecific interstitial pneumonia, characterized by lower lung predominance of ground glass, reticulation, and traction bronchiectasis in a peripheral distribution, but with immediate subpleural sparing

NSIP, which lacks established diagnostic criteria. Previously suggested criteria for idiopathic NSIP required a surgical lung biopsy to confidently make this diagnosis given the frequent alternative diagnoses that are identified on biopsy in patients with an imaging pattern suggestive of NSIP (e.g., IPF, fibrotic HP, CTD-ILD) [17]. For this reason, identifying an imaging pattern of NSIP was not considered sufficient to make a diagnosis of idiopathic NSIP. Conversely, identifying an imaging pattern of UIP is specific enough for a histopathological pattern of UIP that further confirmation of this with biopsy is not necessary for most patients [12]. Common to all of these imaging patterns is the need to integrate a thorough clinical assessment with a careful radiological evaluation.

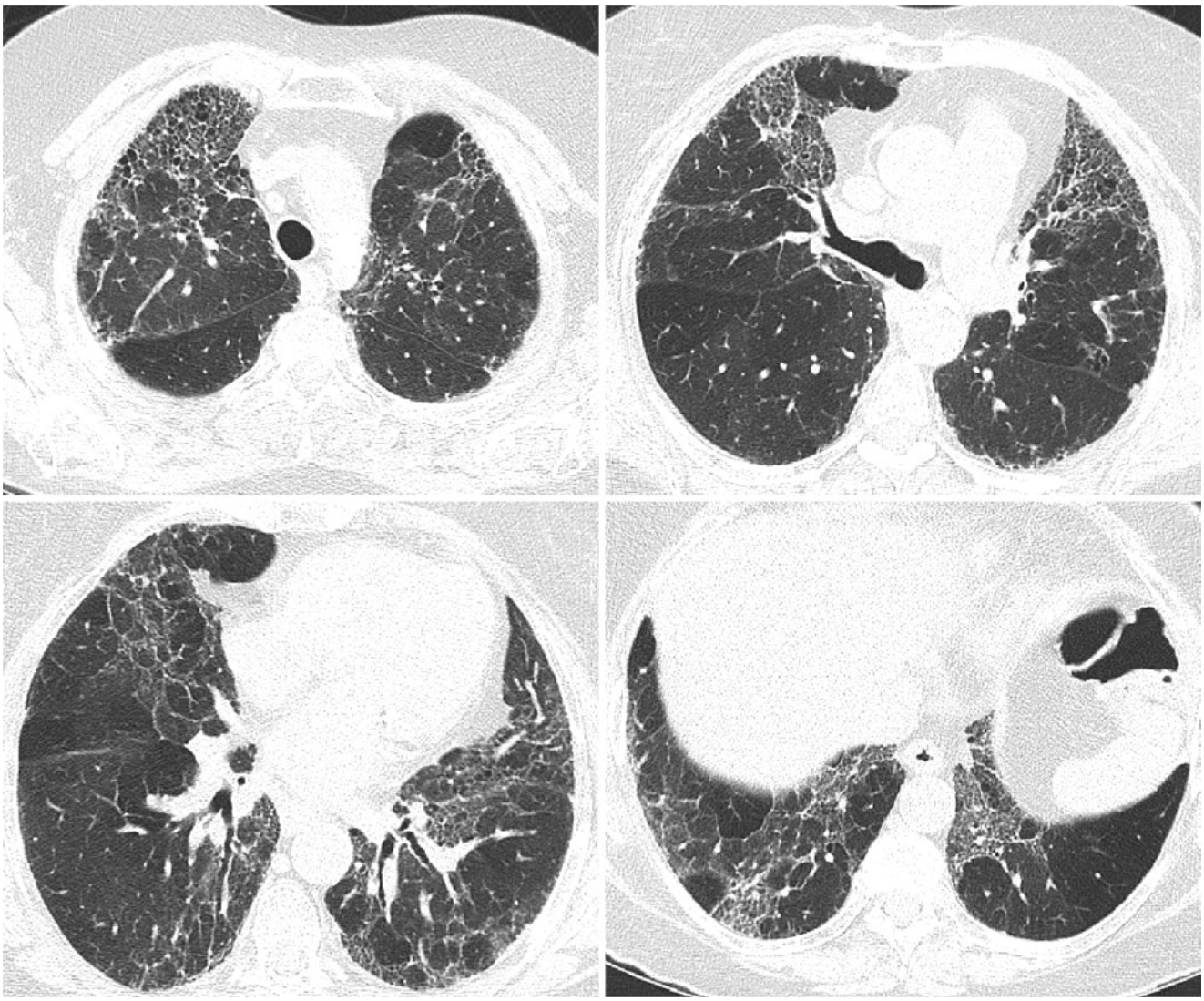

Fig. 31.6 Transaxial chest CT in a patient with exposure to bird antigen showing features of hypersensitivity pneumonitis, including diffuse craniocaudal involvement of ground glass, reticulation, mosaicism, and areas of lobular sparing

Laboratory Assessment

The laboratory assessment for ILD typically follows confirmation of ILD on CT imaging. This assessment is primarily composed of autoimmune serologies used to suggest the presence of a CTD or systemic vasculitis, with additional specific tests pursued in some patients. Clinical practice guidelines on the diagnosis of IPF recommend screening for autoimmune disease in patients with suspected IPF [12], with the majority of panelists routinely testing for C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), antinuclear antibodies (ANA), rheumatoid factor, anti-cyclic citrullinated peptide, and a myositis panel. Additional autoimmune serologies are generally reserved for patients with negative initial studies who still have a high suspicion of an underlying CTD, including anti-cytoplasmic antibodies (ANCAs) in patients with a possible vasculitis. Patients with ILD will frequently have abnormal autoimmune studies even in the absence of overt extrapulmonary manifestations. These results then have to be contextualized with the clinical and radiological findings in order to determine whether these autoimmune markers are false positives or whether a patient might have a subtle autoimmune disease that is predominantly affecting the lung. Although criteria for interstitial pneumonia with autoimmune features (IPAF) were proposed exclusively as a research tool to support further study of this population [21], this designation may be helpful to guide further evaluation and management decisions in these patients who have relatively specific autoimmune features despite not meeting criteria for a defined CTD. The appropriateness of this approach still requires validation in future studies and endorsement in updated clinical practice guidelines.

Additional laboratory studies are considered on a case-by-case basis. These include serum immunoglobulin levels and IgG subclasses that are helpful in suggesting IgG4 disease or immunodeficiency (e.g., as a cause of lymphocytic interstitial pneumonia [LIP]; Fig. 31.7). Testing for human immunodeficiency virus (HIV) is particularly relevant in patients with LIP, but HIV is also a risk factor for other ILD subtypes and is an important comorbidity to identify prior to initiation of immunosuppressive therapy. Vascular endothelial growth factor-D (VEGF-D) is frequently increased in lymphangioleiomyomatosis and is specific enough that a biopsy is not required in the appropriate clinical setting when high VEGF-D levels are present (Fig. 31.8) [22]. Genetic evaluation for patients with ILD (e.g., MUC5B) may be helpful for family counseling [23] but does not currently have sufficient prognostic or therapeutic impact to justify widespread use.

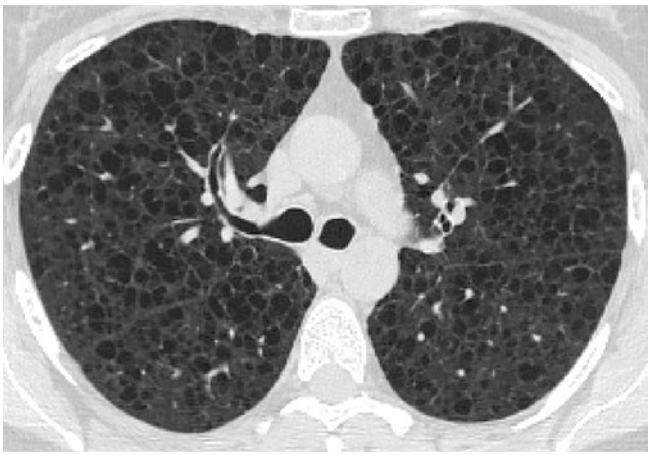

Fig. 31.8 Transaxial chest CT in a patient with lymphangioleiomyomatosis showing diffuse thin-walled cysts

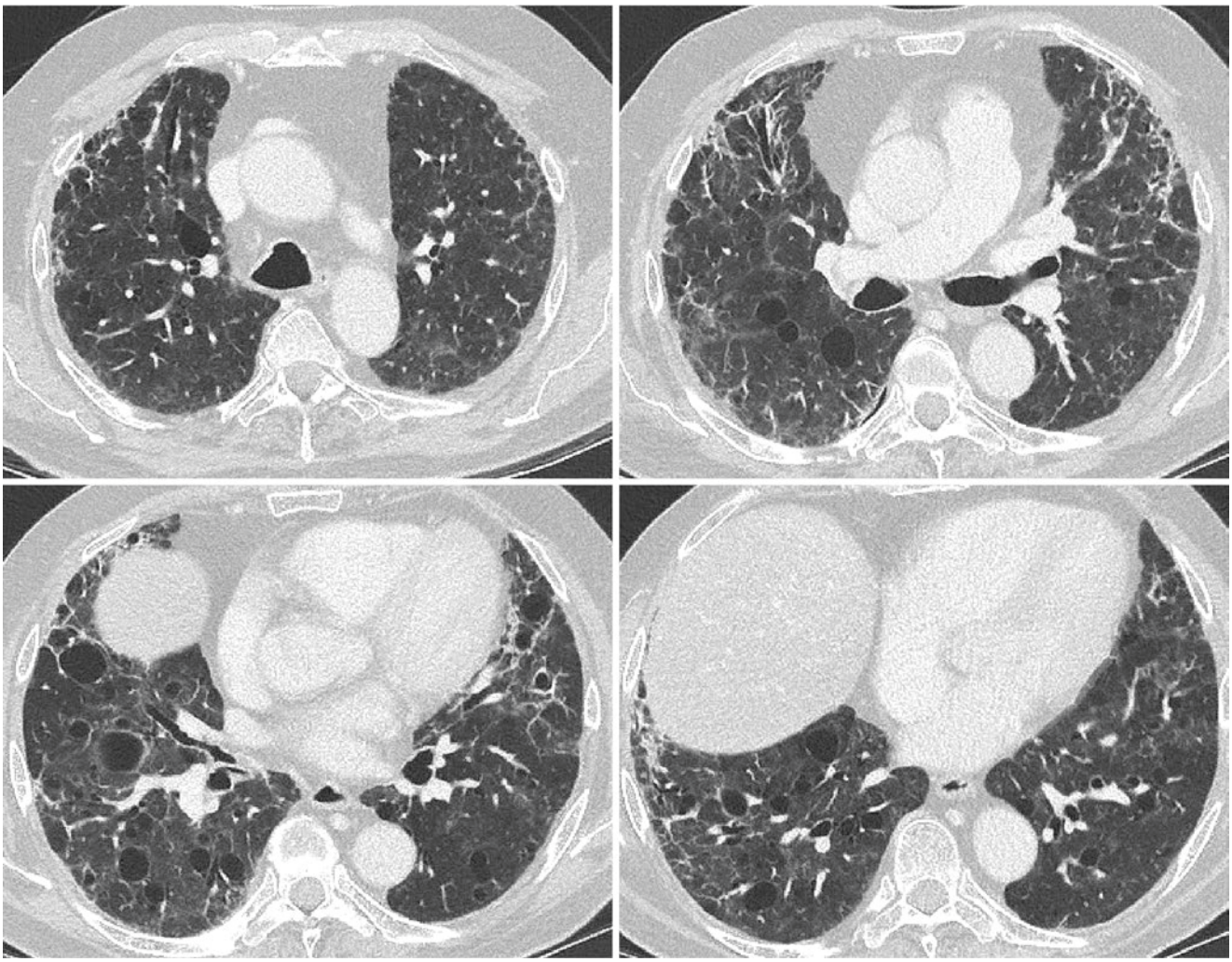

Fig. 31.7 Transaxial chest CT in a patient with human immunodeficiency virus infection showing features of lymphocytic interstitial pneumonia, including multiple thin-walled cysts as well as predominantly peripheral reticulation and traction bronchiectasis with some peribronchovascular extension

Many of these laboratory studies are highly specific in the appropriate context and can eliminate the need for more invasive studies. These tests should thus be considered in all patients prior to the pursuit of histopathological sampling. Conversely, false positives are also common with many of these tests, indicating the need to contextualize abnormal laboratory studies with clinical and radiological features, ideally supported by an MDD of experienced individuals.

Bronchoscopic and Histopathological Assessment

The decision of whether to perform a bronchoscopy or a surgical lung biopsy should be made on a case-by-case basis after considering all information available after less invasive tests. Bronchoalveolar lavage cellular analysis showing lymphocytes >30% can be useful to suggest HP in the appropriate setting [24]; however, the absence of a lymphocytosis is less helpful in excluding fibrotic HP. Transbronchial biopsies are typically unhelpful in fibrotic ILD although can be diagnostic in some patients [25], particularly in sarcoidosis, while more complex genetic or molecular analyses of bronchial biopsies may also provide diagnostic information in some situations [26, 27]. The utility of transbronchial lung cryobiopsy varies across studies; [28] however, this can be a helpful test when performed in an appropriate setting and with results interpreted within a multidisciplinary discussion [29]. Lymph node biopsies can also be diagnostic in sarcoidosis, but are not informative in other fibrotic ILD subtypes.

Whether to pursue a surgical lung biopsy is a major decision in the evaluation of fibrotic ILD given the potential for complications, including mortality [30, 31]. It is therefore critical that all patient data be considered prior to the performance of this more invasive test, including both the potential utility of a biopsy and the potential for procedure-related complications. Specifically, a surgical lung biopsy should only be pursued if there is a reasonable expectation of establishing a diagnosis and affecting management decisions. For example, it may be appropriate to delay surgical lung biopsy in patients with mild and non-progressive ILD that would not likely be treated regardless of the diagnosis, recognizing that having IPF on the differential diagnosis may still suggest a role for biopsy in mild ILD given the apparent benefit of antifibrotic therapy in patients with early IPF [32, 33]. There are several risk factors for complications from surgical lung biopsy, suggesting that biopsy should be avoided in patients older than 75 years of age, with a high or low body mass index, on supplemental oxygen, with pulmonary hypertension, or with severe ILD (e.g., DLCO <35–45%). In these situations, patients may need to be provided with a working diagnosis, with diagnostic confidence that might still be sufficient to support the initiation of therapy [34].

If a biopsy is pursued, it is important to ensure adequate sampling in terms of both the number and size of biopsies. For transbronchial biopsies and transbronchial lung cryobiopsies, typically 5–7 different biopsies are obtained from different regions of a single lung, while surgical lung biopsies should be obtained from upper, mid, and lower lungs. Recommendations have been provided for how to perform both transbronchial lung cryobiopsy and surgical lung biopsy, including the desired size of each sample [35, 36]. Isolated pathologist interpretation of lung tissue is suboptimal [3, 5, 37], and it is, therefore, critical that all biopsies are evaluated by an experienced lung pathologist as part of an MDD.

Integration of Individual Features

The integration of individual features to support a diagnosis of fibrotic ILD is fluid, with the approach varying for each case. A central concept of this process is to consider new data as they become available in order to reassess diagnostic confidence. Most importantly, there is a need to carefully consider the potential impact of invasive procedures such as a surgical lung biopsy before these are performed. This is best accomplished through an MDD, which should ideally be performed both before considering and after completing a lung biopsy. A common approach to the diagnostic process is shown in Fig. 31.9.

Multidisciplinary Discussion

MDD is a dynamic process in which clinical, radiological, laboratory and histopathological data are integrated to arrive at a final diagnosis. MDD is the current standard for diagnosing fibrotic ILD [16], emphasizing that no single domain is sufficient to make an ILD diagnosis in isolation. This approach increases diagnostic confidence [3], particularly among experienced subspecialists [5], and can also be used to improve prognostication and facilitate management decisions, through either establishment of a confident diagnosis or with a less confident working diagnosis [6, 34]. In particular, the distinction between IPF and non-IPF fibrotic ILD has important implications given the worse prognosis of IPF compared to other fibrotic ILDs [38], and the use of antifibrotic therapies in IPF and the use of predominantly immunosuppressive medications in non-IPF fibrotic ILDs. Several recent studies suggest MDD results in a change in diagnosis and in pharmacotherapy recommendation in approximately half of all patients [7, 8].

The participants of an MDD vary across centers [4], typically including at a minimum an ILD clinician, a chest radiologist, and a lung pathologist, as well as trainees from all

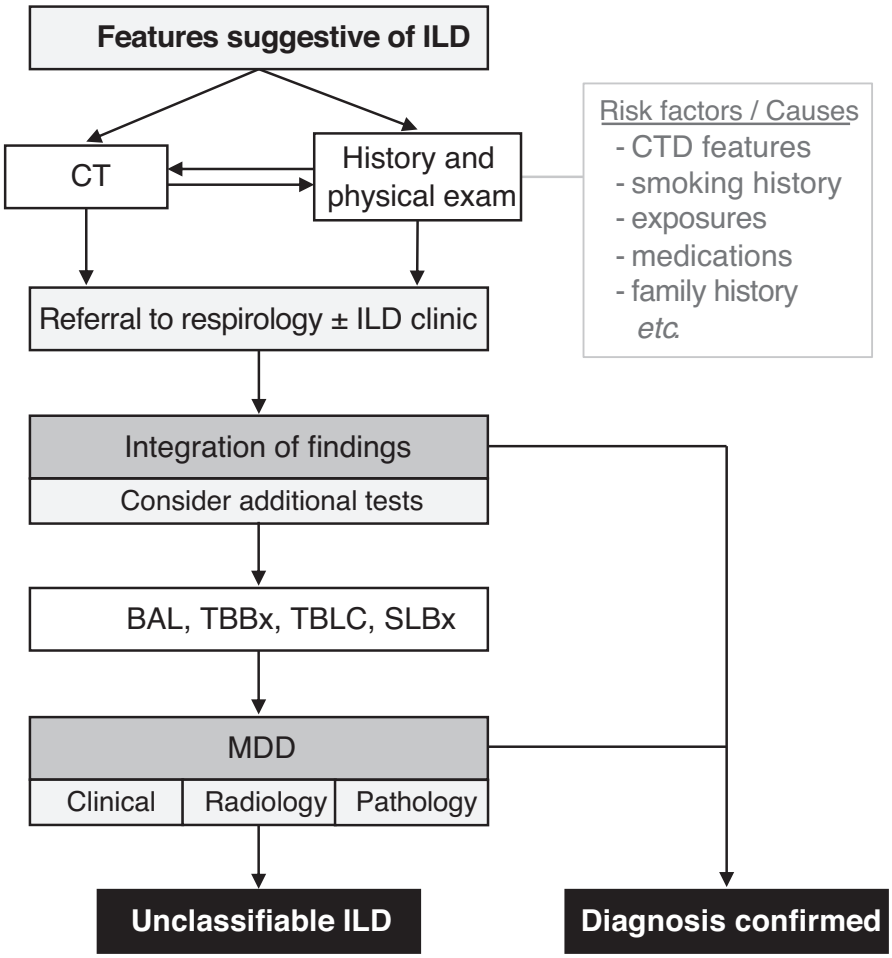

Fig. 31.9 Proposed algorithm for the diagnostic process for patients with fibrotic ILD. BAL, bronchoalveolar lavage, CTD, connective tissue disease; MDD, multidisciplinary discussion; SLBx, surgical lung biopsy; TBBx, transbronchial biopsy; TBLC, transbronchial lung cryobiopsy

disciplines. Some ILD MDDs also include a rheumatologist, thoracic surgeon, or nurse specialist. Most ILD MDDs are face-to-face with a structured approach to the presentation of relevant data that is followed by discussion. Typically, the clinician first presents the relevant clinical and laboratory features, followed by the radiologist presenting imaging findings, and the pathologist presenting pathological findings if performed. There is frequent discussion and requests for clarification of individual findings and overall clinical impression at each stage of this process, with a secondary goal to also educate the participants. Presentation of full CT scans and biopsy slides (or electronically captured images of the complete slides) is preferred to the presentation of only selected images. Ideally, patient volume is sufficient to support at least monthly meetings, with at least several patients reviewed at each MDD. Following a review and discussion of all relevant data, each patient should be provided a consensus diagnosis (or a list of differential diagnoses if a single diagnosis cannot be confirmed) as well as specific recommendations for additional testing and/or treatment.

Some centers are unable to support an MDD with all desired features and are forced to consider alternative approaches. For example, some geographic regions have limited access to a chest radiologist or lung pathologist and instead use a virtual MDD that allows review of relevant patient information without the physical presence of all individuals. An additional strategy is to have patient information sent to a central MDD that reviews all relevant data in a face-to-face meeting, potentially including actual imaging studies and biopsy slides. Recommendations are then provided by the MDD to a remote physician without the patient being seen by an ILD clinician [7]. Although both of these approaches are likely inferior to a comprehensive in-person assessment of a patient at an ILD clinic followed by a review at a face-to-face MDD, these are likely viable alternatives that improve access to necessary expertise for selected patients. These approaches also provide an excellent opportunity for ongoing education of referring physicians.

Diagnostic Ontology

The primary goal in evaluating a patient with ILD is to arrive at a confident diagnosis; however, this is inherently a subjective process and there is often substantial uncertainty even

after open and collaborative discussions among an experienced multidisciplinary team. Even in patients who are provided a specific diagnosis, there is frequently some diagnostic uncertainty that can have important management implications [39]. A key purpose of the MDD is to also document this uncertainty and provide recommendations for how this uncertainty might impact management decisions or prompt future investigations that could solidify a specific diagnosis. Importantly, all ILD diagnoses should be reconsidered at subsequent visits, and this is particularly true for patients without a confident diagnosis.

One way to document this uncertainty is to categorize ILD diagnoses as confident (≥90% confidence), provisional high confidence (70–89%), and provisional low confidence (51–69%) [39]. Using this framework, patients with a confident diagnosis typically do not require additional testing. Additional testing may be appropriate in those with a provisional high confidence diagnosis (e.g., 70–89%), but this level of confidence may be sufficient to support management decisions in some situations, with this unresolved uncertainty needing to be balanced against the potential benefits and risks of additional more invasive tests [34]. Accepting lower diagnostic confidence is particularly relevant to situations in which IPF has already been confidently excluded from the differential diagnosis, given the relatively similar prognosis and approach to pharmacotherapy for the remaining diagnostic possibilities; however, this needs to be carefully assessed on a case-by-case basis. Overall, this approach appears to have therapeutic and prognostic utility despite the lack of specific standardization [6, 34], although additional studies are needed to document its reproducibility and validate its clinical utility.

Unclassifiable ILD

Unclassifiable ILD is defined as the absence of a leading diagnosis that is considered more likely than not (i.e., there is no diagnosis that is considered at least 51% likely after MDD) [39]. This situation applies to approximately 12% of patients with an ILD even after a surgical lung biopsy and MDD [40]. Common reasons for ILD being considered unclassifiable include an incomplete evaluation, the presence of multiple findings that are suggestive of distinct ILD subtypes, and identification of only nonspecific findings that are not diagnostic of any single ILD [40]. The high prevalence of unclassifiable ILD in experienced centers should not be interpreted as justification for the avoidance of potentially diagnostic tests. It remains important for many reasons that physicians establish a confident diagnosis whenever feasible, striking a balance between the benefits of narrowing the differential diagnosis and the risks of invasive tests.

Whether to pursue invasive tests or to accept diagnostic uncertainty is often a challenging discussion to have with patients who must be the focal point of this shared decision. In some situations, patients may be comfortable with their ILD remaining unclassifiable and will refuse tests that the physician believes would be appropriate. In the other less common extreme, patients may wish to pursue all available testing to the point that physicians may need to refuse the performance of a specific test that is unlikely to be diagnostically helpful or that may be unsafe. Although patients are left with an unclassifiable ILD in both of these situations, MDD can often help limit the differential diagnosis and/or determine what management approach is most appropriate, including what pharmacotherapy could be attempted for low confidence working diagnosis. Beyond these initial discussions, it is important to regularly revisit the diagnosis in the event that new information allows for narrowing of the differential diagnosis. This could include disease behavior or response to treatment, results of new or repeated tests (e.g., repeat autoimmune serologies), or identification of a cause of ILD that was not initially apparent (e.g., a new CTD diagnosis or newly recognized exposure). It is not uncommon for unclassifiable ILD to be characterized as a specific ILD subtype upon reassessment after such new information becomes available.

Conclusions

In summary, the diagnosis of ILD is frequently challenging given the need to integrate information from multiple complex domains, but without a standard method of doing so. The ideal approach to diagnosing ILD includes a face-to-face MDD of at least an experienced ILD clinician, chest radiologist, and lung pathologist, which results in the establishment of a more confident and likely more accurate diagnosis. MDD leads to a change in management for approximately half of the patients, resulting in more appropriate use of medications that are likely to alter disease course, and avoidance of medications that have limited potential for benefit as well as a significant risk of harm. In regions without full access to a comprehensive MDD, alternative strategies may still provide benefits; however, there are many potential approaches and limited data on which of these provides the optimal outcomes for patients.

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