3 Multidisciplinary Discussion in Diffuse Parenchymal Lung Disease

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3.1 Introduction

Interstitial lung disease (ILD) is a heterogeneous group of disorders with varying clinical-radiological presentation and evolution. The most common idiopathic ILD is IPF which has an unpredictable clinical course, including cases with slowly progressive decline and cases with rapid deterioration. Prognosis is poor, with a median survival of 3–5 years. In the last decade, many advances have been made in the understanding of IPF pathogenesis, and two antifibrotic drugs, pirfenidone [1] and nintedanib [2], have become available for IPF treatment. In this context, an accurate IPF diagnosis is of particular importance to optimize the care of patients with ILDs, discriminating those who may benefit from steroid and immunosuppressive treatments from IPF patients for whom the immunosuppressive therapy may be detrimental. The ATS/ERS/JRS/ALAT guidelines emphasize the importance of the multidisciplinary team (MDT) diagnosis to correctly identify IPF patients [3]. The MDT should be composed of specialists of relevant disciplines, to integrate all available clinical, radiological, and pathological data.

3.2 The Past: The Role of Histology and Radiology

Before the recognition of the multidisciplinary diagnosis as the gold standard for ILD diagnosis, pathology was considered the reference standard for many years. The preeminent role of pathology was based on two historical developments. Firstly, Averill Liebow, the founding father of modern lung pathology, was the first to classify the interstitial lung diseases in 1965, and the current classification of ILDs still takes its root from this classification scheme [4]. Secondly, several studies proved that pathology carries important prognostic information, particularly distinguishing usual interstitial pneumonia (UIP) form other patterns [5].

However pathology in the diagnosis of ILDs has several limitations and alone is patently insufficient. It has been shown that the interobserver agreement between pathologists in ILD diagnosis is poor, with an overall kappa value of only 0.38 for the first-choice diagnosis, and a high confidence diagnosis could be achieved by expert pathologists in only 39% of cases [6].

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Other limitation of histopathology is related to the observation that two or more biopsies taken from the same patient can manifest divergent histopathological patterns as described by Flaherty et al. [7]. With regard to the histological distinction between UIP and nonspecific interstitial pneumonia (NSIP), 26% of patients presented different histopathological patterns in different lobes, proving that the UIP diagnosis based on a single lung specimen from one lobe can be misleading.

As for radiology, the level of interobserver agreement among practising thoracic radiologists in the diagnosis of idiopathic interstitial pneumonias (IIPs) has been estimated by Aziz et al. as moderate or very good on the basis of HRCT features, especially for IPF [8]. Several other studies have reported on the interobserver agreement for a CT diagnosis of IPF/UIP with conflicting results. All of these studies involved thoracic radiologists with high expertise in the interpretation of diffuse parenchymal lung diseases on CT [9].

Walsh et al. showed that interobserver agreement for the ATS/ERS/JRS/ALAT CT criteria for UIP among an international group of thoracic radiologists of varying levels of experience is at best moderate and is not significantly increased among thoracic radiologists with greater levels of experience. The most frequent diagnostic difficulty in the interpretation of CT scan was the separation of patients with IPF/UIP, fibrotic NSIP, and CHP which can only be achieved based on CT appearances alone in approximately 50% of cases [10].

Several studies have shown that radiology alone is patently insufficient to discriminate IPF form other fibrotic ILDs, when IPF doesn't have the typical UIP pattern appearance. Sverzellati et al. showed that three expert radiologists, blinded to any clinical information, when asked to make an IPF diagnosis on the basis of CT scan, missed it in 62% of cases. Among 123 patients with various chronic ILDs, including a core group of 55 biopsy-proved cases of IPF, 34 (62%) of 55 biopsy-proved IPF cases were regarded as alternative diagnoses, and the first-choice diagnoses, expressed with high probability, were NSIP (53%), chronic hypersensitivity pneumonitis (HP, 12%), sarcoidosis (9%), and organizing pneumonia (3%). This study clearly demonstrates that CT scan findings when non-diagnostic for UIP may overlap with other ILDs [11]. Similarly Flaherty et al. showed that 26 (35%) of 73 patients with UIP at biopsy had a thin-section CT appearance more akin to that of NSIP [12].

The recognition of the limitations in using pathology, clinical evaluation, and radiology data in isolation led to the creation and implementation of multidisciplinary discussion of ILD cases. Several other studies have reported on the interobserver agreement for a CT diagnosis of IPF/UIP with conflicting results. All of these studies involved thoracic radiologists with high expertise in the interpretation of diffuse lung diseases on CT [9].

3.3 The MDT

The multidisciplinary diagnosis is a dynamic process that requires the integration of clinical, radiologic, and pathologic data. The benefits of integrating radiological, histopathological, and clinical data in IIPs diagnosis have been reported in several studies. Flaherty et al. demonstrated that a consensus diagnosis, reached after exchange of clinical, radiological, and histopathologic information, often differs from the initial diagnosis reached by the individual clinician, radiologist, or pathologist working in isolation, leading to the idea of a multidisciplinary approach to the IIP diagnosis might be more accurate. Radiologists, pathologists, and chest physicians took part in this study and were allowed to change their initial diagnosis as more information were added. Physicians changed more often their initial diagnosis when patients had a clinical and radiographic scenario suggestive of non-IPF IIP, while in patients with a presentation considered typical for IPF, the diagnosis was accurate in more than 95% of cases emphasizing the central role for HRCT in the cases presenting with the UIP radiologic pattern.

When clinical and radiological information were added, pathologists changed their diagno-

sis in 19% of cases. This result empathizes the importance of combining histological, radiological, and clinical data and that neither radiology nor histology alone can provide a secure diagnosis of ILD. The level of agreement was particularly high between radiologists, even if they changed more frequently their diagnosis compared to clinicians after revision of histological data. The level of agreement between all participants improved with discussion and with the addition of subsequent clinical, radiological and particularly pathological information, thus confirming the importance of integrating those information in the dynamic scenario of multidisciplinary team discussion [13].

Similarly Thomeer et al. showed that although the level of agreement between radiologists for IPF diagnosis was only moderate (κw = 0.40) and the level of agreement between pathologists was fair (κw = 0.30), the overall accuracy of the multidisciplinary team diagnosis of IPF was good (87.2%). The IPF diagnosis proposed by chest physician was rejected in 12.8% of cases after the revision of CT scan and pathological data by groups of radiologist expert committee, underlining the importance of MDT in the correct diagnosis [14].

The 2002 ATS/ERS classification of IIIPs [15], the 2013 update, and the 2011 guidelines [3] for the diagnosis of IPF strongly recommend the interaction and information exchange between radiologists, pathologists, and clinicians to reach the final diagnosis. Thus, the MDT is proposed as the gold standard for ILD diagnosis. Despite ERS/ATS recommendations, no guideline statement regulating MDT has been published, and there are some unresolved issues regarding the composition of the MDT, its governance, its validation, the selection of cases to be discussed, its purpose, and the optimal frequency of the MDT meetings (MDTM).

The first study evaluating the level of agreement between international multidisciplinary teams (MDTs) of experts in IIPs since the 2013 ATS/ERS update was conducted by Walsh et al. [16]. In this study each MDT, consisting of at least 1 clinician, radiologist, and pathologist, from 7 countries (Denmark, France, Italy, Japan, the Netherlands, Portugal, and the UK), evaluated 70 cases of interstitial lung disease in a two-stage process: (1) the radiologist, pathologist, and clinician independently evaluated each case and selected up to five differential diagnoses from a group of ILDs. Clinicians had only access to clinical information and high-resolution CT scan without report or pathology results. Radiologists and pathologists just knew age, sex, and smoking status for the patient with high-resolution CT (for radiologist) and digitalized surgical lung biopsy slides (pathologist). (2) These specialists participated in MDT reviewing all data and selecting up to five differential diagnoses. The inter-MDT agreement on diagnostic likelihoods was good for IPF (weighted kappa coefficient (κw) of 0.71, interquartile range (IQR) 0.64–0.77) and connective tissue disease (CTD)-related ILD (κw = 0.73, IQR 0.68–0.78), moderate for NSIP (κw = 0.42, IQR 0.37–0.49), and fair for HP (κw = 0.29, IQR 0.24–0.40). High-confidence diagnoses of IPF were given in 77% of cases by MDT, in 65% of cases by clinicians, and in 66% of cases by radiologists showing that inter-MDT agreement for the diagnosis of IPF is good, with clinicians having only marginally lower levels of agreement than MDTs for this diagnosis. Compared to clinicians or radiologists, MDT made diagnosis of IPF with high confidence more frequently. In patients without surgical lung biopsy, inter-MDT agreement and interobserver agreement between clinicians for the diagnosis of IPF were similar (κw = 0.71 [IQR 0.64–0.77]), thus implying that in cases in which the clinical-radiological scenario of IPF is sound and clear, the MD discussion of cases has a marginal role and probably can be neglected.

By contrast, MDT agreement for the diagnosis of HP and NSIP was low (κ value, respectively, κw = 0.29 [0.24–0.40], NSIP κw = 0.42 [0.37–0.49]) (in both cases with or without lung biopsy), reflecting the urgent need for clarity and standardized diagnostic international criteria.

Diagnostic agreement between MDTs was higher compared to agreement between clinicians, radiologists, and pathologists in the setting of ILDs, especially assessing IPF diagnosis. Moreover, the good diagnostic accuracy of MDT diagnosis was validated by the nonsignificant

greater prognostic separation of an IPF diagnosis made by MDTs than by individual specialists; in particular a significant prognostic separation was observed in seven of seven MDTs (HR 2.61–5.30 $p < 0.05$), in five of seven clinician teams, and in four of seven radiologist teams. The same analysis for pathologist team was not significant probably due to the small number of cases.

3.4 Composition of MDT

Despite the clear utility and importance of ILD-MDTs, the constitution and governance of these meetings have not been explicitly addressed. Based on the original studies by Flaherty et al. [13], it might be suggested that MDT should at a minimum be composed by a clinician, a radiologist, and a pathologist. In recent times, more expansive models including rheumatologists, thoracic surgeons, and ILD nurses have been suggested. The role of the rheumatologists in the MDTs has been investigated in a recent study showing that among seven international expert multidisciplinary groups evaluating ILD cases, new diagnoses of CTD-ILD were constructed in approximately 10% of patients [16]. The authors of this study suggest that rheumatologists should take part in MDT because some patients present with subtle clinical features or serological abnormalities that imply an autoimmune process without meeting established criteria for a specific CTD. Recently, an ERS/ATS task force was formed in order to establish consensus on how to classify these patients, and specific diagnostic criteria were established to define cases of interstitial pneumonia with autoimmune features (IPAF) lacking the criteria for a specific rheumatologic disease [17].

Determining whether a patient has a diagnosis of CTD-ILD rather than IIP may impact treatment decisions and influence prognosis, especially in cases presenting with UIP pattern on CT scan that may be difficult to differentiate from IPF. Despite the fact that IPF antifibrotic drugs have been recently tested in clinical trials for CTD-ILD treatment, the treatment of IPF and CTD-ILD remains strikingly divergent, and the use of antifibrotic is still not approved in CTD-ILDs. Currently CTD-ILDs are treated with immunosuppression [18] in contrast to IPF, in which immunosuppression is ineffective or potentially harmful [19]. CTD-ILDs occur most commonly in the context of an established CTD, but can be the first and/or only manifestation of an occult CTD or occur in patients who have features suggestive of an autoimmune process, but not meeting diagnostic criteria for a defined CTD (IPAF) [17]. The identification of IPAF or of some complex CTD-ILDs cases requires the combination of specific clinical, serologic, and morphologic features. The identification of IPAF patients and the difficulties related to clinical diagnosis of some CTD cases may require the rheumatologist evaluation; this implies that rheumatologist should participate in MDT discussions only after a careful clinical evaluation of the patient.

3.5 MDT Diagnosis Is Influenced by Components

Although MDTM diagnoses are more confident and they reach higher levels of agreement compared to individual participants, the performance of the MDT is dependent on the experience of its components, as demonstrated by Flaherty et al. who evaluated the diagnostic agreement between academic and community-based physicians in ILD diagnosis in an interactive approach involving radiologists, clinicians, and pathologists and found a significant disagreement between academic-based clinicians and community-based physicians. The most evident discordance was for the evaluation of cases of HP, NSIP, and IPF. Final diagnostic agreement was higher between academic physicians (κ 0.55–0.71) and community physicians (κ 0.11–0.56). Interestingly, community pathologists were more influenced in their final diagnosis by interaction with clinicians and radiologists compared to academic pathologists. This study also showed that academic physicians in a multidisciplinary setting display better diagnostic agreement and consider a greater range of diagnoses, compared to community physicians [20].

Walsh et al. have recently conducted an international study aimed to evaluate the importance of

expertise in the MDT diagnosis of IPF made by nonacademic clinicians, university-affiliated clinicians, and an international panel of IPF experts using three surrogates of diagnostic accuracy: diagnostic confidence, diagnostic agreement, and prognostic accuracy. No randomized trials have ever been conducted to demonstrate MDT diagnosis results in improved patient survival. In the absence of a reference standard, separations in mortality between patients diagnosed with IPF and those diagnosed with other ILDs have been used to evaluate the diagnostic skills of clinicians. A total of 1141 respiratory physicians and 34 IPF experts participated to the study, evaluating 60 cases of ILDs without interdisciplinary consultation.

Accuracy of IPF diagnosis made by university hospital-based practitioners with greater than 20 years of experience was equivalent to that of international IPF experts, proving that academic status and experience level of physicians are independently associated with greater prognostic discrimination between diagnoses of IPF and other ILDs. Participating in weekly MDT meetings by nonacademic physicians increased prognostic accuracy of IPF diagnosis to that achieved by IPF experts [21].

MDT diagnosis is defined as a "consensus" among participants and may be influenced by individual personalities in the dynamics of MDT so that the final diagnosis may ultimately be more reflective of the strongest voice in the room. Jo et al. conducted a study among 12 expert centres based on an internet questionnaire regarding the constitution and governance of their MDT. Interestingly, chest physicians adopted a dominant role in MDT diagnosis in 90% of meetings, and for 70% of cases, the referring physician was also responsible for documenting the diagnosis. Just in 30% of cases, the final diagnosis was left to the clinician following multidisciplinary discussion [22].

3.6 Final Scope of MTD

A great debate is ongoing regarding the role of MDT meetings in the evaluation of patients with ILDs. In oncology, multidisciplinary boards are widely applied and have demonstrated a significant impact on treatment decisions through collaboration between specialists, including palliative care. In contrast, the role of MDT in ILDs is limited to the diagnostic evaluation even though there is an increasing range of therapeutic choices for ILDs, including antifibrotic therapy for IPF, antigen avoidance for chronic hypersensitivity pneumonitis, immune suppression for inflammatory and connective tissue disease-related ILD, and lung transplantation and palliative care in case of end-stage lung disease [23].

Therapeutic choices available, including the availability of active clinical trials, patient's own wishes, and clinical context including frailty, have a great impact on the MDTM decision. In addition to evaluating new cases, revising diagnoses based upon disease behaviour and response to therapy is an important role of MDTM discussion especially for patients whose disease behaviour is unexpected and could not have been predicted on initial assessment. Revisiting existing diagnoses on the basis of clinical behaviour and evolution may lead to change the initial diagnosis and to change therapeutic approach.

3.6.1 Comparison Between Cryobiopsy and Surgical Biopsy in MDT Discussion

Surgical lung biopsy (SLB) is still considered an important diagnostic step in the diagnosis of ILDs when the clinical-radiological features are not specific even though SLB has never been validated as a gold standard test. However surgical lung biopsy is associated with significant mortality (2–4%) and adverse effects such as chronic chest pain observed in more than 50% of the cases lasting for months, prolonged air leakage, infections, and prolonged hospitalization [24]. In addition, many patients with suspected ILD may be unable to undergo SLB because of their comorbidities, even if histopathological confirmation may be helpful to reach the correct diagnosis. For all those reasons, SLB is obtained in <15% of ILD cases, and the indication to biopsy has to be carefully considered by the MDT. Regarding the interobserver agreement in SLBs, some studies

have shown that it is higher (κ = 0.42) when UIP pattern is identified; but is low when NSIP pattern (κ = 0.29) or chronic HP patterns (κ = 0.36) are evaluated [6].

Transbronchial cryobiopsy is a new diagnostic approach recently introduced into clinical practice as a promising and less invasive alternative to SLB to diagnose ILDs. Cryobiopsy allows attainment of larger, higher quality lung tissue samples without the crush artefacts seen with conventional transbronchial lung biopsy using flexible forceps [25]. It has been shown that the specimen size is directly related to the diagnostic yield and the sampling of different segments of the same lobe appears to increase the diagnostic confidence or at least to reduce the number of samples needed to identify the UIP pattern [26].

A recent study by Casoni et al. has also demonstrated that pathologists can detect UIP pattern with high confidence in about half of the cases with a very good overall interobserver agreement [27]. Our group reported a sensitivity for UIP detected by transbronchial forceps biopsy of only 30% for expert pathologists, and these data have recently been confirmed in a study that found transbronchial forceps biopsy useful to reach a confident and accurate multidisciplinary diagnosis in only 20–30% of patients with ILDs, with the majority of cases requiring SLB to reach a definite diagnosis. In suspected cases of non-IPF, particularly HP and NSIP, the diagnosis is much more difficult, and in this setting, transbronchial forceps biopsy has little role, with a negative predictive value for a UIP diagnosis ranging between 46 and 55% [28].

In a recent study, we evaluated the impact of the addition of transbronchial cryobiopsy/SLB information to the multidisciplinary diagnosis of ILDs. Transbronchial cryobiopsy increased diagnostic confidence in the multidisciplinary diagnosis of IPF and also increased self-reported confidence levels, to a similar extent compared to SLB. Specifically, the proportion of IPF cases diagnosed with a high degree of confidence increased from 16 to 63% after adding cryobiopsy [29]. Moreover, cryobiopsy changed the initial clinical-radiological impression in 26% of cases, reclassifying 73% of those as IPF. In line with previously published studies, these data show that in cases in which the initial clinical-radiological scenario is inconclusive, pathology adds the most important piece of information, regardless if it is obtained by surgery or transbronchial cryobiopsy.

3.7 Conclusion

According to the current ATS/ERS/JRS/ALAT guidelines, the MDT consensus has replaced histopathology alone as the gold standard for the diagnosis of ILDs. MDT discussion of cases improves diagnostic confidence and agreement compared to individual observers. However, no guidelines exist in literature to describe in detail how the MDTs should be conducted and many of the specifics remain unclear. There are no published guidelines concerning the composition, frequency of MDTs, or the kind of ILD cases that really need to be discussed. There is a need for evidence-based clinical guidelines regarding the constitution and governance to reach the best clinical outcomes [30, 31].

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