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Commentary:

Multi-Disciplinary Team (MDT) approach in the management of CTD-ILD: the way forward

Authors:

Ben Rowlands MRCP(UK) MBiochem

Speciality Trainee, Respiratory Medicine, Southwest Deanery, UK

Harsha Gunawardena MRCP(UK) PhD

Consultant | Rheumatology, Autoimmune CTD and Vasculitis, North Bristol NHS Trust, UK

Introduction

Interstitial lung disease (ILD) encompasses a spectrum of fibro-inflammation diseases of the lung parenchyma that can be idiopathic or secondary to either specific exposures or another underlying pathological process; including as a manifestation of autoimmune connective tissue disease (CTD) (1)(2). In a proportion of patients, the presenting or predominant feature of CTD will be ILD. In others, ILD may be insidious and can present long after the initial CTD diagnosis (2). Identification of certain phenotypic risk factors can be helpful, but there remain significant gaps in understanding with regards to the exact relationship between the two and how this translates into optimal management strategies.

There remains as yet no clear consensus of diagnostic methodology for determining if patients have an autoimmune CTD in the early stages of ILD diagnosis. A number of requirements must be fulfilled including clinical assessment for extra-pulmonary manifestations, robust autoimmune serological testing, with review of radiology and / or histopathological patterns (2). This requires specific clinical expertise to ensure appropriate clinical interpretation and consensus diagnosis. Without this, the clinical significance of results and outcome of positive test interpretation may result in misclassification; in particular patients with idiopathic pulmonary fibrosis (IPF) patients being reclassified as having a CTD-ILD. With distinct induction treatment options available for each, correct classification of IPF and CTD-ILD patients is now critical to ensure appropriate and optimal management (2)(3).

Some patients will not meet classification criteria for a specific CTD, but will have a phenotype that falls into the recently conceived criteria for diagnosing interstitial pneumonia with autoimmune features (IPAF) (4). However, IPAF criteria have not been validated by any form of gold standard (5). Dogmatic application the IPAF diagnostic criteria may lead misclassification between IPAF and CTD-ILD, again with significant consequences in terms of treatment and prognosis. Conversely, application of IPAF criteria can identify patients with ILD predominant CTD, such as some subtypes of anti-synthetase syndrome (ASSD), rheumatoid lung ILD sine rheumatoid or other *formes-frustes* of CTD overlap. In some respects, this simply highlights that current rheumatological classification criteria need revision. For example, the lack of well-established clinical and serological classification criteria for ASSD presents a particular challenge in this regard.

Heterogeneity of CTD-ILD

CTD-ILD phenotypes encompass greater heterogeneity than other forms of ILD such as IPF. This includes disease presentation and progression with time. Anti-synthetase syndrome, idiopathic inflammatory myopathies, rheumatoid arthritis, Sjogren's, systemic lupus erythematosus and systemic sclerosis are all associated with a range of ILD phenotypes (1)(2)(6). The highest estimated prevalence rates of diffuse parenchymal lung disease are noted in systemic sclerosis, inflammatory myositis syndromes and rheumatoid arthritis when subclinical ILD is included (1)(7).

Histology from CTD-ILD patients demonstrates a spectrum of inflammatory and fibrotic processes. Parenchymal disease is often accompanied by overlapping airways, pleural, pulmonary vascular disease. This presents increased challenge to correctly diagnose the underlying aetiology and may

impair response to treatment. CTD-ILD also represents a high level of uncertainty in terms of disease progression, with some diseases mild and non-progressive whilst others proceed with a continuous sharp decline (8–10).

Increasingly recognised are subsets of patients with an initial diagnosis of idiopathic interstitial pneumonia that have evolved into CTD-ILD diagnosis. This insidious development may lead to patients receiving no or sub-optimal treatment after their initial diagnosis. Recognising this group often requires re-evaluation by the MDT; developing clinical signs and response to treatment can have a major impact on this assessment.

IPAF Criteria

IPAF was the ‘catch all’ nomenclature coined to categorise and create consensus regarding patients with idiopathic interstitial pneumonia (IIP) and elements of autoimmune disease identified from at least two of three domains: 1) clinical signs or stigmata of CTD 2) serological markers 3) morphological evidence from either radiological ILD pattern, histopathology or specific areas of respiratory involvement in addition to ILD (4). This enables division of a cohort of patients that would otherwise be classified as IPF who may respond to anti-inflammatory and immunomodulatory treatments rather than supportive observational management or in some cases anti-fibrotics medication. However, the diagnosis of a defined CTD excludes patients from the IPAF classification. This may result in scenarios where classification rather than diagnostic criteria are used to inappropriately exclude CTD. For example, would we argue that a patient with a) mechanic’s fingers (one clinical domain) b) anti-PL12 autoantibodies (one serological domain) c) usual interstitial pneumonia (one morphologic domain) has lung dominant ASSD and not IPAF. Therefore, some cohorts of patients categorized with IPAF, simply have this *formes-frustes* or ‘undeclared occult’ CTD reflecting the limitations of traditional rheumatology criteria as previously highlighted.

Heterogeneity of the MDT – key members

Respiratory

The BTS guidelines recommend that there should be specific clinics for ILD patients, with an MDT led by a respiratory consultant with a sub-speciality interest in ILD (3). This expedites comprehensive history taking and the identification of any risk factors. Their departments will facilitate resting spirometry and full pulmonary function testing, including carbon monoxide transfer factor and a 6-minute walk test. These will aid with diagnosis, prognostication and monitoring for changes over time. Respiratory physicians will also provide the skills for bronchoalveolar lavage and transbronchial lung biopsy when indicated.

Historically, respiratory clinicians are also well placed to liaise with other services. This includes thoracic surgeons when surgical biopsy is required, regional pulmonary arterial hypertension MDTs and referral to transplant centres. They are also well placed to interact with their local counterparts who can retain ownership of ongoing routine care; which should also include acute care and supportive services such as pulmonary rehabilitation.

Radiology

Thoracic radiologists with a subspecialist interest in ILD are an essential component of the MDT. High resolution computed tomography (HRCT) imaging of the chest has become central to identifying and characterizing ILD. HRCT phenotyping leads to a change of initial diagnosis in 51% of patients (11). However, the complexity of this differentiation is exemplified by large discrepancies in inter-observer observation (12). This is why consistent ILD reporting is paramount, with key expert individuals that share radiology MDT responsibility. As specific patterns of ILD on HRCT are more predominant with certain disease phenotypes this can have a large effect on the correct diagnosis of CTD-ILD (13). There is ongoing work to improve HRCT phenotyping as well as disease quantification.

Histopathology

Historically, surgical biopsy was considered the gold standard for determination of ILD phenotype (3)(14). However, there are significant limitations of patient fitness for sampling, reasonable chance of sampling error and without established criteria there is poor inter-observer agreement amongst expert histopathologists as to disease phenotype (15)(16). Diagnostic agreement is higher when histopathologists are included in MDT discussions (17,18). In general, there is good agreement IPF and CTD-ILD, but poor agreement HP and idiopathic NSIP.

Rheumatology (with specialist autoimmune immunology expertise)

Rheumatology physicians in autoimmune CTD are invaluable for being sensitive to the demographic, clinical history and phenotypic information indicative of a CTD-ILD. There is a trend towards increasing reliance on serological hallmarks of systemic autoimmune disease, which when used in conjunction with clinical features can confirm early diagnosis (19,20). CTD-ILD rheumatology specialists can ensure extended autoantibody testing that may not be available to other centres. Moreover, interpretation of results and correlation with clinical features is paramount to ensuring accurate diagnosis. This requires a two-step process: a) robust ANA immunofluorescence (IIF) screening, followed by b) extended CTD autoantibody immunoblot testing utilising new assays that include a wide array of autoantigen targets now recognised in overlap CTD, particularly systemic sclerosis and myositis syndromes. It is important to highlight that serology must correlate, for example a strong cytoplasmic stain on IIF with ASSD autoantibody on blot with the correct pattern of interstitial pneumonia and additional extra-pulmonary features. Whereas a 'typical older patient' with UIP, with a nuclear ANA on IIF and multiple positives on immunoblot where the target autoantigen does not match the IIF staining pattern and additional clinical features has: a) false positive serology b) has IPF and should not be incorrectly diagnosed as CTD-ILD. CTD ILD rheumatologists can provide robust autoantibody interpretation in the wider clinical context. In addition, decisions about management of CTD-ILD are often based on a rheumatologist's experience in clinical practice, as well as trial evidence with at present limited multi-centre trials.

Other key members of the wider MDT:

Respiratory and CTD Specialist Nurses

Nurse specialists can facilitate a more holistic approach to patients' journey. This includes education, forming part of the patients' support network and management of symptoms or medication side-effects. They can also provide a first point of contact for patients should new problems arise, acting

to gate-keep and signpost within the service (3,21). This is exemplified by 90% of patients using ILD specialist nurses as their main healthcare contact concerning their IPF (22). There is also an increasing role of respiratory and rheumatology specialist pharmacists who can facilitate and help manage high-cost drug pathways, prescribing and monitoring.

Palliative Care

Certain ILD phenotypes are associated with significant decline in quality of life and survival. Palliative care specialists can offer effective pharmacological and psychosocial management strategies. They can not only improve quality of life throughout the disease course, but also facilitate sensitive and appropriate advanced care planning leading to timely patient-centred end-of-life care (23)(3,21).

The role of the MDT and treatment pathways

Complex CTD-ILD treatment decisions require a combination of consensus MDT experience and judgment alongside clinical evidence and guidelines to formulate an appropriate holistic approach for patients. There remains a paucity of well-controlled trials of existing and novel therapeutic agents in CTD-ILD relative to other autoimmune diseases; this is largely a consequence of the heterogeneity that CTD-ILD presents. There remains a significant challenge to recruit enough patients of a particular phenotype to be certain of outcomes. However, centralised MDT assessment of CTD-ILD patients can considerably increase recruitment into these trials. There is a real opportunity to develop CTD-ILD network MDTs who can bring clinical subgroups together to facilitate larger scale registries. This will enable harnessing of observational cross-sectional and longitudinal data to assess natural history, response to treatment and survival as well as inclusion in novel therapeutic trials.

Most patients with CTD-ILD will stabilise on recognised immunosuppression, which include Cyclophosphamide, Mycophenolate, calcineurin inhibitors and Rituximab regimes (24)(25)(26)(27). Recent randomised controlled trials have demonstrated that nintedanib and tocilizumab reduce deterioration of FVC in ILD associated with systemic sclerosis (28)(29). Nintedanib has also been shown to reduce progression in patients with other forms of fibrosing ILD, not just in IPF (30)(31)(32). Some patients may have undiagnosed CTD-ILD, and this would represent an adjunctive combination treatment option, as a number will progress despite immunosuppression. Therefore, access to continuing evaluation by the MDT can adapt treatments to a patient's clinical response. The MDT capture of larger numbers of patients with these rare conditions can lead to optimal standardised treatment regimens; that can be continued and monitored by peripheral centres. This will encompass novel and high-cost therapies that these peripheral centres might not have access to, widening the care that can be offered to individuals.

Individualised MDT treatment decisions involving balancing the potential benefits and risks should occur following informed discussion with the patient (Figure 2). It can prove challenging for patients to access centralised MDT assessment, but remote virtual consultations will improve patient care.

Summary

This heterogenic nature of this cohort of patients presents correspondingly varied challenges for classification, diagnosis, treatment, prognostication and research. Early recognition of often rare and complex disease is essential as this influences management and prognosis; poor outcomes have been demonstrated with delays in specialist assessment.

A mechanism for managing this complexity sits with an equally diverse multi-disciplinary team (MDT) of experts available at specialist centres, whose primary aim is optimal care of patients with ILD. Bringing together this level of expertise can help to mitigate some of the pitfalls of formulaic criteria, but may come at a cost of accessibility to patients within a region. Single centre trials have shown that the CTD-ILD MDT is sensitive and specific for CTD-ILD or IPAF diagnosis (5). Further work has also highlighted the frequency of reclassification following MDT review after initial diagnosis and period of treatment. Ultimately, this is leading to a paradigm shift from the traditional gold standard of histopathological diagnosis of ILD from lung biopsy to integrated and dynamic MDT interaction.

Multidisciplinary team care of CTD-ILD patients will improve disease awareness, leading to earlier disease detection, diagnosis and access to treatment with established and novel therapeutic agents. Improved exposure to rare subsets of patients will also improve understanding of individual disease phenotypes and how this influences their prognosis. Overall, this will lead to improvements in patient care pathways, clinical and psychosocial outcomes.

Figures:

Figure 1: A CTD-ILD MDT model

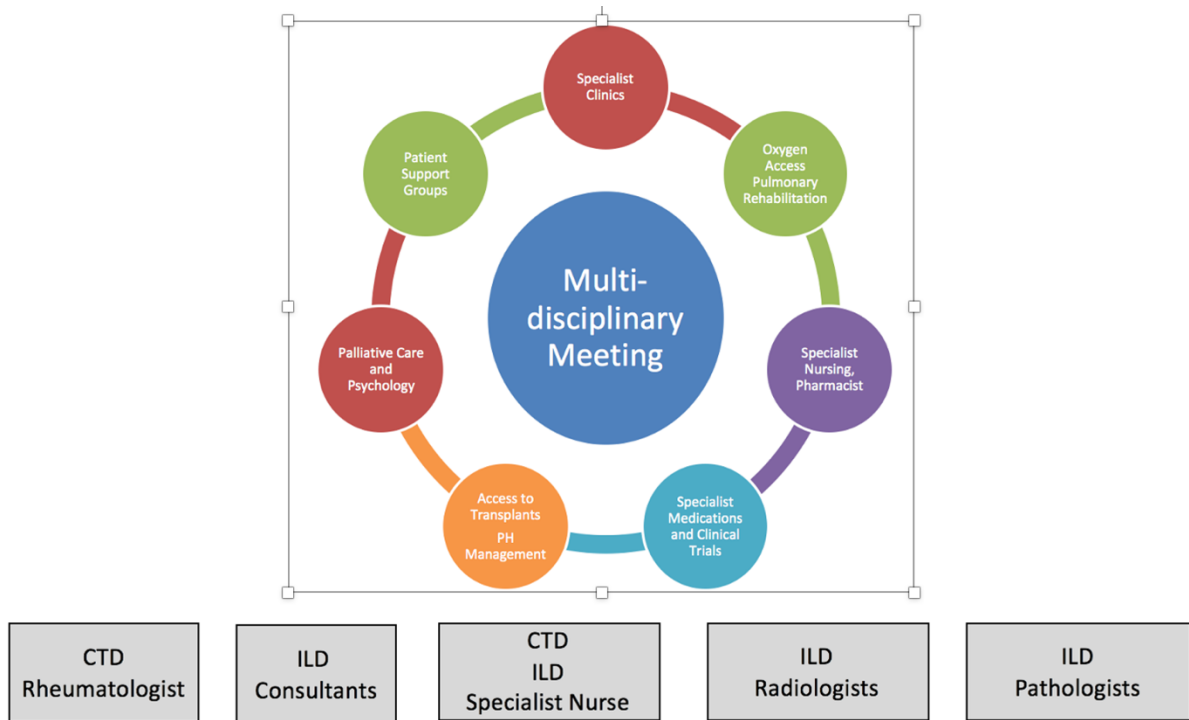
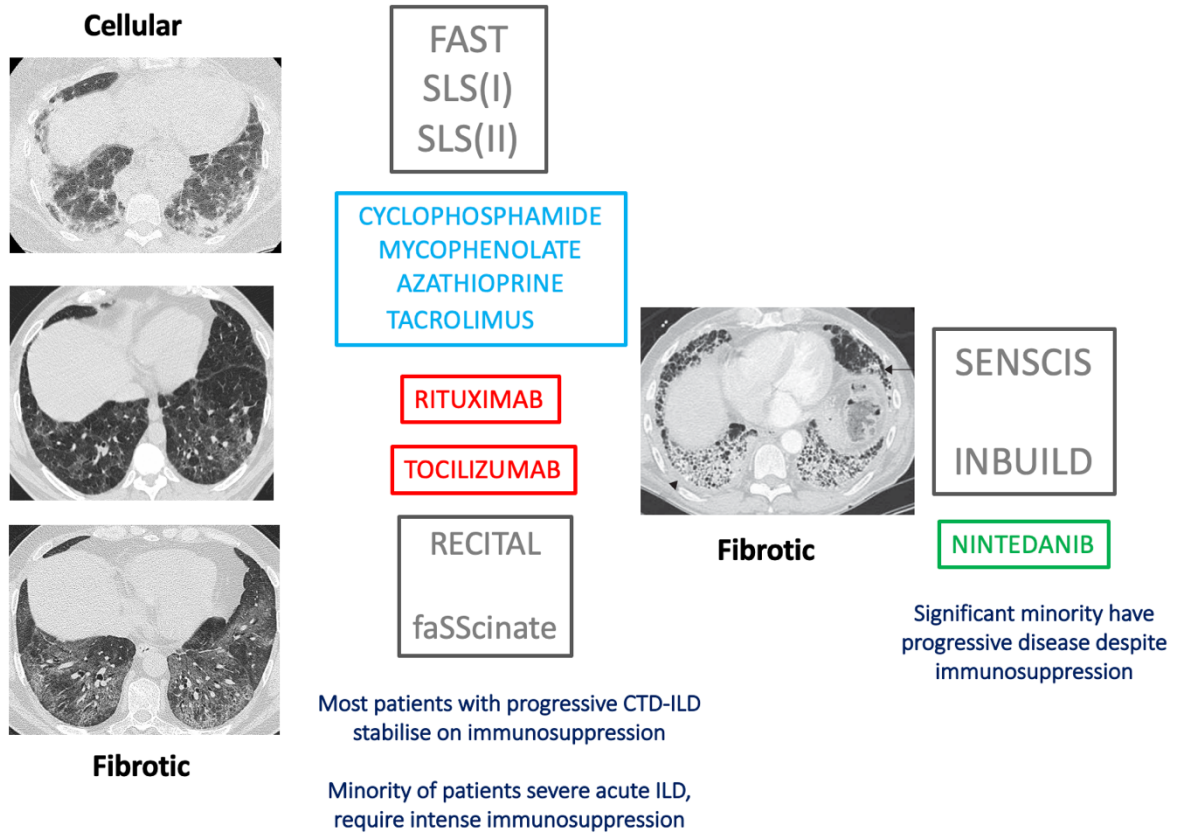


Figure 2:

Current treatment options for CTD-ILD available to the MDT



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