Best Practice & Research Clinical Rheumatology 30 (2016) 39–52

Contents lists available at ScienceDirect

Best Practice & Research Clinical Rheumatology

journal homepage: www.elsevierhealth.com/berh

3

Connective tissue disease-related interstitial lung disease

M. Kristen Demoruelle [a], Shikha Mittoo [b], Joshua J. Solomon [c, *]

[a] University of Colorado Denver, Division of Rheumatology, Aurora, CO, USA
[b] University of Toronto, Division of Rheumatology, Mount Sinai Hospital, Toronto, Ontario, Canada
[c] National Jewish Health, Division of Pulmonary and Critical Care Medicine, Denver, CO, USA

Keywords:
Connective tissue disease
Interstitial lung disease
Clinical management
Treatment

A B S T R A C T

Interstitial lung disease (ILD) is commonly present in patients with an underlying connective tissue disease (CTD), particularly those with systemic sclerosis, rheumatoid arthritis, and inflammatory myositis. The clinical spectrum can range from asymptomatic findings on imaging to respiratory failure and death. Distinguishing features in the clinical, radiographic, and histopathologic characteristics of CTD–ILD subsets can predict prognosis and treatment response. Treatment often consists of combinations of immunosuppressive medications, but there is a paucity of guidance in the literature to help clinicians determine appropriate screening and management of CTD–ILD. As such, there is a critical need for studies that can elucidate the natural history of the CTD–ILD, as well as clarify optimal therapies for CTD patients with ILD.

Introduction

Pulmonary disease is commonly reported in association with connective tissue disease (CTD). One of the more severe forms of pulmonary involvement in CTD is interstitial lung disease (ILD), which refers to varying degrees of inflammation and fibrosis involving the interstitial compartment of the lung. CTD–ILD can range from an incidental finding on radiographic imaging to a rapidly progressive illness leading to respiratory failure and death. It has been described in up to 90% of patients with a

* Corresponding author. National Jewish Health, 1400 Jackson St., Southside Building, Office #G08c, Denver, CO 80206, USA.
E-mail address: SolomonJ@NJHealth.org (J.J. Solomon).

http://dx.doi.org/10.1016/j.berh.2016.04.006
1521-6942/

definable CTD depending on the modality of diagnosis. The highest prevalence is observed in patients with systemic sclerosis (SSc), rheumatoid arthritis (RA), and polymyositis/dermatomyositis (PM/DM) [1–3]. CTD–ILD can have a significant adverse effect on quality of life and is a leading cause of mortality, highlighting the importance of accurate diagnosis and appropriate clinical management [4]. Given the complexities of diagnosis and paucity of treatment trials, management of patients with CTD–ILD is challenging. In this study, we will discuss the distinguishing features of CTD–ILD in SSc, RA, and PM/DM; recent advances in clinical management; and the steps needed to improve our ability to care for patients with CTD–ILD, including the role of longitudinal observational cohorts, well-designed clinical trials, and a structured approach to provide patient care.

Characteristic features of CTD–ILD

CTD–ILD is a broad term including any diffuse parenchymal lung disease in patients with a definable CTD or a constellation of signs, symptoms, and lab abnormalities suggestive of a CTD. Many CTD patients are diagnosed with ILD after overt respiratory symptoms, such as exertional breathlessness or cough, prompt an evaluation with pulmonary function testing (PFT) and/or radiographic imaging. However, a subset of CTD patients have no pulmonary symptoms and are diagnosed with ILD incidentally after chest imaging is obtained for other reasons (e.g., lung cancer screening, coronary calcium screening, evaluation for pulmonary embolism), an entity referred to as “subclinical” CTD–ILD. ILD can also occur in the presence of autoimmune features that do not meet classification criteria for a specific CTD, a condition often referred to as lung-dominant CTD [5] or interstitial pneumonia with autoimmune features (IPAF) [6].

At present, the exact etiology of CTD–ILD is not known. It has been hypothesized that the lung may be an innocent organ that is targeted by disease-specific autoantibodies generated elsewhere. Another hypothesis is that certain subtypes of CTD begin with a lung-based process. In the latter, it is proposed that a lung injury that triggers local inflammation induces autoantigen expression that can in turn lead to autoantibody generation in the lung. This process could be perpetuated by subsequent binding of the disease-associated autoantibodies and antigen in the lung, leading to further lung inflammation and fibrosis [7]. In line with this hypothesis, in RA patients, generation of disease-specific antibodies has been shown in the lung [8,9], and the presence of RA-related antibodies in the lung is associated with more severe lung damage in RA–ILD [10]. Also supporting this hypothesis, ILD can precede joint disease in a subset of patients with RA–ILD [11–14].

While there are many similarities among the different subsets of CTD–ILD, some distinguishing features are also important to consider (Table 1). For example, the majority of CTD–ILD patients display a pattern on high-resolution computed tomography (HRCT) or histopathology of nonspecific interstitial pneumonia (NSIP) with or without organizing pneumonia (OP) (Fig. 1). NSIP is a more inflammatory subtype of ILD and the most common pattern observed in SSc (68–77%) [15,16], PM/DM (65–82%) [17,18], Sjogren's syndrome (28–61%) [19,20], and undifferentiated connective tissue diseases (UCTD) (83%) [21]. By contrast, RA patients with ILD have a higher incidence of a pattern of usual interstitial pneumonia (UIP) on HRCT or histopathology, a more fibrotic subtype of ILD (Fig. 2) [13,22,23]. In general, the specific ILD pattern can predict response to treatment, with the more inflammatory ILDs (cellular NSIP and OP) showing a greater response to immunosuppression than the more fibrotic ILDs (fibrotic NSIP and UIP).

Prognosis also differs between subsets of CTD–ILD, although this is mostly reflective of the underlying histopathologic differences. For example, RA–UIP has the worst prognosis of the CTD–ILDs [13,23–25], with a 5-year survival rate of 36%. However, RA–NSIP has a 5-year survival of 94% [26]. Similarly, the 5-year survival of SSc-, PM/DM-, and Sjogren's syndrome-associated ILD patients, with a predominance of NSIP, ranges from 60% to 85% [17,19,27].

Challenges of CTD–ILD diagnosis

Diagnosis of ILD among CTD patients is challenging and requires interdisciplinary discussions and knowledge of unique nuances related to specific CTD subtypes. Particular challenges exist around symptom and physiologic evaluation. Dyspnea may be underreported because of functional