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Interstitial lung disease in the course of systemic connective tissue diseases: A common problem for rheumatologists and pulmonologists

ABSTRACT

Interstitial lung disease is a common and dangerous complication of many rheumatic diseases. Progress over the last several years has increased diagnostic capabilities, led to emergence of new therapeutic options and, above all, resulted in deeper awareness of the severity of the problem. Interstitial diseases are a heterogeneous group differentiated through histo-

pathological and imaging examinations. Prognosis and recommended therapy depend not only on the form of the interstitial disease, but also largely on its underlying rheumatic disease. The aim of this article is to present the pathology that is the interstitial lung disease and the current knowledge on its treatment.

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KEY WORDS: interstitial lung disease; connective tissue disease; diagnosis; therapy

INTRODUCTION

The term „interstitial lung disease” (ILD) covers a broad spectrum of pathologies whose common feature is inflammation and/or fibrosis of pulmonary interstitium. Prognosis and therapeutic options differ significantly depending on the form of the ILD. Based on their aetiology, ILDs can be divided into idiopathic ILDs (iILDs) and ILDs with known causes, which can include connective tissue diseases, taken drugs or infections [1]. Involvement of lungs in the course of systemic connective tissue diseases (CTD-ILD, connective tissue disease-associated interstitial lung disease) is a common complication (Fig. 1, 2) which significantly decreases the quality of life and increases the mortality rate of patients with that disorder. The aim of this article is to present CTD-ILDs, demonstrate difficulties in terms of diagnosis, discuss the current and

new therapeutic options and emphasise the importance of multidisciplinary cooperation between rheumatologists, pulmonologists and radiologists in taking care of patients with pulmonary complications.

HISTOLOGICAL PICTURE

The appearance of pathological lesions in a healthy lung is important for diagnosis of ILDs. The respiratory zone of lungs comprises respiratory bronchioles, alveolar ducts and pulmonary alveoli. The structures which separate individual pulmonary alveoli are called alveolar septa. They are composed of alveolar walls, capillaries which surround the alveoli and a small amount of connective tissue proper. The term „interstitial” refers to elements located between the membranes which line the lumina of the alveoli and the capillary endothelium (Fig. 2). It concerns both a small number

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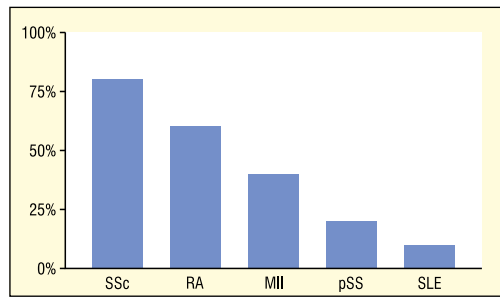


Figure 1. Frequency of occurrence of ILDs in individual rheumatic diseases

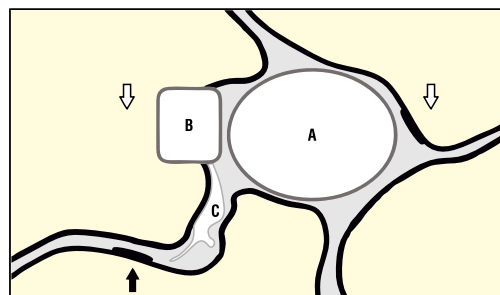


Figure 2. Diagram of microscopic structure of alveolar septum. White arrow — alveolar lumen; black arrow — type I pneumocyte responsible for gas exchange; grey colour — pulmonary interstitium; a — capillary; b — single fibroblast surrounded by extracellular matrix; c — type II pneumocytes responsible for production of surfactant

of cells and the extracellular matrix composed of collagen (types I and III are dominant), elastin, glycosaminoglycans, proteoglycans and adhesive protein (fibronectin, fibrillin) [3]. The course of ILDs entails both inflammatory lesions, visible primarily as oedema of alveolar septa and infiltration of inflammatory cells (lymphocytes, macrophages), and fibrotic lesions, dominated by proliferation of fibroblasts and myofibroblasts and accumulation of collagen, which leads to widening of alveolar septa and complete distortion of lung architecture

(microscopic honeycombing). Both processes reduce the diffusion area for respiratory gases, hindering their permeation through the respiratory barrier, which clinically manifests itself as dyspnoea, typically accompanied by dry coughing.

DIAGNOSIS

Results of histopathological examination of a biopsy specimen and radiological images of lungs involved in the course of CTD-ILDs are similar to corresponding iILDs [4]. The most commonly described forms include nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), lymphocytic interstitial pneumonia (LIP), diffuse alveolar damage (DAD) and organising pneumonia (OP). Table 1 presents the frequency of occurrence of individual types of ILDs in relation to the most common CTDs.

There are various techniques for collecting tissue specimens; however, due to fairly frequent complications, they are not widely used in routine diagnosis. It is, in turn, based on pulmonary function tests and imaging tests, especially computed tomography and ultrasound scans; ultrasound scans are characterised by lower specificity, but they are repeatable and do not entail exposure to radiation. Currently, the most useful diagnostic tool is high-resolution computed tomography (HRCT). For this reason, this article will present interpretation of HRCT images, together with histopathological examination. It should be noted, however, that in each case the choice of tests should be considered on an individual basis.

NONSPECIFIC INTERSTITIAL PNEUMONIA

Nonspecific interstitial pneumonia is the most common form of CTD-ILD. The fibrosis and inflammatory lesions revealed in histolog-

Table 1. Comparison of frequency of occurrence of histological and radiological subtypes in discussed rheumatic diseases

	UIP	NSIP	OP	LIP
RA	+++	++	+	+
SSc	+	+++	+	
IIM	+	+++	+++	
SLE	+	++	+	
pSS	+	++	+	+

UIP — usual interstitial pneumonia; NSIP — nonspecific interstitial pneumonia; OP — organising pneumonia; LIP — lymphocytic interstitial pneumonia; RA — rheumatoid arthritis; SSc — systemic sclerosis; IIM — idiopathic inflammatory myopathies; SLE — systemic lupus erythematosus; pSS — primary Sjögren's syndrome

Frequency of occurrence is marked as follows:

+++ the most common histological and radiological subtype

++ moderately common subtype, non-dominant

+ rarely encountered ILD subtype

ical examination are characterised by the same stage of advancement. Thickening of alveolar walls is even, fibrotic foci typical of UIP cannot be distinguished, and the lung architecture is preserved [6]. HRCT reveals: symmetrical foci of ground-glass opacities, reticular opacities and, in advanced stages, traction bronchiectasis and reduced lobe volumes, especially in the parabasal regions of the lungs [6, 7]. Depending on the dominant type of lesions, NSIP can be divided into cellular (inflammatory) NSIP, characterised by both better prognosis and better response to treatment, and fibrotic NSIP, in which fibrosis is dominant and which can be similar to UIP in terms of clinical picture and prognosis.

USUAL INTERSTITIAL PNEUMONIA

Usual interstitial pneumonia presents a heterogeneous distribution of inflammatory lesions and fibrosis at various stages of advancement alternating with healthy tissue. Pathological lesions are located mainly subpleurally, perilobularly and periacinally. Manifestations include fibrotic foci and irregular thickening of alveolar septa; bronchial metaplasia of alveoli and formation of microcysts with mucin deposits in the lumina of terminal airways may also occur. The entire process leads to distortion of lung architecture, visible, among others, as microscopic honeycombing [8]. HRCT image is dominated by reticular opacities and honeycombing located symmetrically in the lower regions of the lungs. Traction bronchiectasis is frequently visible [9]. Currently, search is underway for radiological markers specific to UIP in the course of a CTD-ILP, which would differentiate it from idiopathic pulmonary fibrosis (IPF). It has been suggested that such markers may include: the anterior upper lobe sign (AULS), which means the presence of lesions typical of UIP located in the anterior and upper as well as lower regions of the lungs, with omission of the remaining regions, the exuberant honeycombing sign (EHS), when the lesion covers more than 70% of lung tissue, and the straight edge sign (SES), when the border between the fibrotic process in the lower regions of the lungs and healthy tissue takes the shape of a straight line in the frontal plane [10].

ORGANISING PNEUMONIA

Histological examination of OP identifies only an inflammatory infiltration in the

pulmonary interstitium. Fibroblasts and myofibroblasts which accumulate in the alveoli and alveolar ducts and are surrounded by large amounts of collagen extracellular matrix are the dominant pathology, which does not lead to distortion of lung architecture. In HRCT, OP presents an image of ground-glass opacities and consolidations within the lower regions of the lungs; less frequent manifestations include bronchiectasis, reticular opacities and the reverse halo sign (denser parenchyma surrounding a ground-glass opacity) [12]. Differentiation between CTD-OP and cryptogenic OP (COP) on the basis of imaging and histological examinations is often impossible. Nevertheless, it has been suggested that CTD-OP is characterised by greater interstitial lung involvement (> 25% of lung volume or more than 4 lobes) and more massive consolidations (> 10% of lung volume), with lesions less frequently located around bronchovascular bundles [12].

LYMPHOCYTIC INTERSTITIAL PNEUMONIA

In histological examination, LIP presents dense interstitial infiltration composed primarily of reactive B and T lymphocytes, with addition of plasma cells, macrophages and histiocytes, which leads to widening of alveolar septa. These lesions can be disseminated, but are located mainly along the bronchovascular bundles, interlobular septa and pleurae. HRCT reveals numerous cysts bilaterally within the pulmonary parenchyma; other possible manifestations include nodules and, less frequently, ground-glass opacities and bronchiectasis [13].

DIFFUSE ALVEOLAR DAMAGE

Diffuse alveolar damage is an acute pulmonary pathology whose histological picture changes dynamically. The acute phase is characterised by interstitial oedema, intra-alveolar haemorrhage and presence of hyaline membranes, while the proliferative phase is characterised by proliferation of fibroblasts in the interstitium and in lumina of the alveoli, leading to fibrosis. Early-stage imaging tests may not capture a developing DAD. Extensive ground-glass opacification is the first dominant feature in HRCT images; consolidations are revealed next, and advanced stages exhibit bronchiectasis, reduced lung volume, reticular opacities, small cysts and crazy paving [14].

Table 2. Known risk factors for development and progression of interstitial lung disease (ILD)

CTD	Risk factors for development and progression of ILD
RA	Dominant subtype: UIP Male sex Advanced age Smoking Autoantibodies: RF, anti-CCP? Variant of MUC5B gene promoter High activity of the disease
SSc	Generalised form of the disease Male sex Advanced age African American ethnicity Low DLCO, FVC Involvement of more than 20% of pulmonary parenchyma (HRCT) Lymphadenopathy of anti-Scl70 autoantibodies High CRP, ESR
IIM	Presence of anti-MDA5, anti-Jo1, anti-Pl7, anti-Pl12, anti-OJ, anti-Ro52 and anti-SAE antibodies No or weakly expressed myositis component in clinical picture
pSS	Extensive lung involvement (HRCT) UIP subtype Male sex Advanced age Presence of extraglandular symptoms Presence of anti-Ro52 and ANA-HEp2 antibodies High CRP

CTD — connective tissue disease; ILD — interstitial lung disease; UIP — usual interstitial pneumonia; RF — rheumatoid factor; RA — rheumatoid arthritis; SSc — systemic sclerosis; HRCT — high-resolution computed tomography; CRP — C-reactive protein; ESR — erythrocyte sedimentation rate; IIM — idiopathic inflammatory myopathies; SLE — systemic lupus erythematosus; pSS — primary Sjögren's syndrome
The most common risk factors for ILD development in rheumatic patients are advanced age, male sex, presence of specific antibodies and high activity of inflammatory condition in laboratory tests. Patients exhibiting factors listed in the table should be subjected to increased diagnostic vigilance in terms of ILD development.

RHEUMATOID ARTHRITIS

Respiratory tract involvement is a frequent complication of rheumatoid arthritis (RA). The incidence rate of RA-ILDs is estimated at 109 cases per 100,000 patients per year [15]. Approx. 10% of patients have a symptomatic form of ILD, while most (up to 58%) have asymptomatic ILD [16]. Unlike other CTD-ILDs, the dominant form of RA-ILDs is UIP, leading to more severe course and worse prognosis. ILDs are the second most common cause of death of RA patients. Known factors for development and progression are shown in Table 2. The effect of methotrexate (MXT) and leflunomide therapy on development and progression of ILDs remains a point of contention [17]. Subclinical forms of ILD require no additional treatment. The symptomatic and progressive form, however, presents a challenge; for this form, administration of glucocorticoids (GCs), mycophenolate mofetil (MMF), azathioprine (AZA) or cyclophosphamide (CYC) should be considered as first-line treatment. Most literature data

suggests that with respect to progressive and aggressive form of RA-ILD, caution should be exercised when employing TNF inhibitor therapy, while administration of MTX and leflunomide should be avoided [18–20]. In small-scale observational studies which made use of tacrolimus (TAC), tocilizumab, abatacept, rituximab (RTX) or tyrosine kinase inhibitors, some patients exhibited improvement in pulmonary function parameters and reduced dyspnoea; however, there are no large-scale randomised trials which would make it possible to assess the actual effect of these drugs on ILDs. At the moment, high expectations for inhibiting the progression of ILDs are associated with new antifibrotic drugs: nintedanib and pirfenidone, of which the former was registered for progressive therapy of CTD-ILDs [18–20].

SYSTEMIC SCLEROSIS

Systemic sclerosis (SSc) is a disease characterised by highly varied clinical picture and prognosis. Lung involvement (manifested both as pulmonary hypertension and as an ILD) is

currently the leading cause of death of SSc patients. The incidence rate of SSc-ILDs is estimated at 1364 cases per 100,000 patients per year [15]. ILD-type lesions in imaging tests are present in most patients, but only some develop a clinically symptomatic form, typically NSIP (Table 2) [21]. Treatment of clinically silent forms is based on standard guidelines for management of SSc published by EULAR. So far, no clear algorithm for treatment of progressive forms of ILD has been established [22]. Observational and retrospective studies, as well as a small number of randomised trials, have demonstrated effectiveness of immunosuppressive drugs (CYC, MMF, RTX) in inhibition of progression of SSc-ILDs. Currently, only nintedanib (registered in the EU and the US) and tocilizumab (registered in the US) have received recommendation for treatment of the progressive form of SSc-ILD. In aggressive, refractory cases, lung transplantation or stem cell transplantation should also be considered.

IDIOPATHIC INFLAMMATORY MYOPATHIES

Idiopathic inflammatory myopathies (IIMs) cover a broad spectrum of systemic diseases which cause primarily muscular and dermal symptoms. The risk of development of an ILD and prognosis depend mainly on the form of myositis and correlate with specific serological profile of patients. For two most common forms: dermatomyositis (DM) and polymyositis (PM), ILDs occur in 10–40% of patients. It has been observed that the more the myositis component dominates the clinical picture of the patient, the lower the risk of development of lung disease. Taking into account the immune profile, it has been found that for Caucasian population, patients with antibodies specific to antisynthetase syndrome (anti-Ro52 and anti-SAE) are at a significant risk of development of ILD [23]. The anti-MDA5 antibodies, found much more frequently in Asian patients, occur in 72–100% of patients with rapid, refractory course of ILD and are associated with high mortality. Idiopathic inflammatory myopathy-associated interstitial lung diseases (IIM-ILDs) usually occur as NSIP or OP. Recommended treatment depends on the estimated risk of progression. In mild and moderate cases, recommendations include large doses of GCs and inclusion of immunosuppressive drugs (MMF, AZA, cyclosporine [CSA]). In severe or rapidly pro-

gressing cases, large doses of GCs are used in combination with RTX, CYC or immunoglobulins, and if that proves ineffective, it is recommended to employ triple therapy (large doses of GCs, CYC and TAC or RTX). Lung transplantation is the last-line treatment. So far, no clear indications for management have been established [24].

PRIMARY SJÖGREN'S SYNDROME

Diagnosing ILDs in the course of primary Sjögren's syndrome (pSS) is frequently difficult, as this syndrome is often comorbid with bronchiolitis, dry tracheal mucosa and dry bronchial mucosa, hindering identification of ILDs which appear only when the syndrome has continued for many years. Nevertheless, in approx. 10% of patients, ILD precedes symptoms of the dryness syndrome [25]. Interstitial lung disease is diagnosed in 13–30% of pSS patients, and the incidence rate of pSS-ILDs is estimated at 196 per 100,000 cases [15]. The course of lung disease may be asymptomatic or slowly progressive, rarely progressive. Compared to other CTD-ILDs, most pSS-ILDs are characterised by a relatively mild course (Table 2). The most commonly described type of pSS-ILD is NSIP (45%) (Table 1). If a pSS-ILD in the form of LIP is diagnosed, it is essential to preclude monoclonal growth, as lymphoma can develop in as many as 4% of patients [26, 27] the second most common autoimmune rheumatic disease. Approximately 16% of patients with Sjögren's demonstrate pulmonary involvement with higher mortality and lower quality of life. Research Question: Clinical practice guidelines for pulmonary manifestations of Sjögren's were developed by the Sjögren's Foundation after identifying a critical need for early diagnosis and improved quality and consistency of care. Study Design and Methods: A rigorous and transparent methodology was followed according to American College of Rheumatology guidelines. The Pulmonary Topic Review Group (TRG).

The latest guidelines for management suggest treatment of only symptomatic forms of pSS-ILD. First-line drugs are GCs, possibly combined with MMF or AZA. For severe, rapidly progressing forms, RTX or CYC should be considered. If that proves ineffective, antifibrotic drug therapy is recommended; further progression may require qualification for lung transplantation [26].

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus-associated interstitial lung disease (SLE-ILD) is relatively less frequent (occurring in 8–10% of patients) and typically takes the form of NSIP. It is usually characterised by slow, chronic course and fairly good prognosis. It should be noted, however, that in these patients, lung involvement may manifest itself as acute lupus pneumonitis (ALP). Frequency of occurrence of ALP is estimated at 1–4% of patients. This complication is characterised by high mortality (50%). Symptoms of ALP include sudden fever, dyspnoea, dry cough and hypoxaemia [15]. Lung HRCT reveals symmetrical ground-glass opacification and consolidations. Treatment of SLE-ILD proposed by experts is combination therapy employing GCs and „steroid-sparing drugs” (usually CYC or, in more mild cases, MMF or AZA) [27].

INTERSTITIAL PNEUMONIA WITH AUTOIMMUNE FEATURES

In 2015, a new disease entity — interstitial pneumonia with autoimmune fea-

tures (IPAF) — was identified. It encompasses cases of ILDs with accompanying clinical or laboratory markers typical of CTDs, but insufficient for a definite diagnosis of a CTD. Incidence and prevalence of IPAF remain unknown. Available literature suggests that prognosis in case of IPAF is better compared to IPF and worse compared to CTD-ILD, and the dominant types are NSIP and UIP [15].including systemic sclerosis (SSc

CONCLUSIONS

CTD-ILD is a pathology characterised by varied clinical picture and prognosis. Therapeutic strategies differ not only depending on the stage of the disease or its histological and radiological subtype, but also on the underlying rheumatic disease. Table 2 presents a list of factors predisposing to progression and aggressive course of ILDs. Multidisciplinary cooperation is a prerequisite for making a correct diagnosis, ensuring the best-quality therapy for the patient and vigilant monitoring of the course of the disease.

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