

Pneumologia

Systemic sclerosis-related interstitial lung diseases: diagnosis and treatment approach

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Abstract

English:

Interstitial lung disease (ILD) frequently occurs in systemic sclerosis (SSc), significantly increasing the mortality risk. Diagnosing ILD associated with SSc (SSc-ILD) necessitates a vigilant approach due to the absence of respiratory symptoms in some patients. Early high-resolution computed tomography (HRCT) screening for SSc diagnosis is imperative, as ILD can manifest across all SSc patients. Regular monitoring, encompassing pulmonary function tests, symptom assessment and periodic HRCT scans, is crucial for monitoring disease progression and guiding treatment strategies. Immunotherapy, typically the primary treatment for SSc-ILD, along with nintedanib, an approved antifibrotic agent, has demonstrated effectiveness in preserving lung function. Effective diagnosis and management of SSc-ILD require a comprehensive patient-centred approach aimed at optimising outcomes and enhancing quality of life.

Keywords

diagnosis • lung disease • SSc-ILD • systemic sclerosis • therapeutic

Bolile interstițiale pulmonare asociate cu sclerodermia sistemică: abordare diagnostică și terapeutică

Rezumat

Romanian:

Boala interstițială pulmonară (ILD) apare frecvent în cadrul sclerodermiei sistemice (SSc), crescând semnificativ riscul de mortalitate. Diagnosticarea ILD asociate cu SSc (SSc-ILD) necesită o abordare vigilentă, având în vedere absența simptomelor respiratorii la unii pacienți. Realizarea timpurie a unei tomografii computerizate de înaltă rezoluție (HRCT) este esențială la pacienții diagnosticați cu SSc, deoarece ILD poate apărea la toți acești pacienți. Monitorizarea regulată, care include teste funcționale respiratorii, evaluarea simptomelor și examinări HRCT periodice, este crucială pentru urmărirea progresiei bolii și pentru ghidarea strategiilor terapeutice. Imunoterapia, tratamentul de primă linie în SSc-ILD, împreună cu nintedanib — un agent antifibrotic aprobat — s-a dovedit eficientă în conservarea funcției pulmonare. Diagnosticarea și managementul eficient al SSc-ILD necesită o abordare cuprinzătoare, centrată pe pacient, cu scopul optimizării rezultatelor clinice și al îmbunătățirii calității vieții.

Cuvinte-cheie

diagnostic • boală pulmonară • SSc-ILD • sclerodermie sistemică • terapeutic

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Introduction

Interstitial lung diseases (ILDs) encompass a large group of over 200 parenchymal disorders characterised by inflammation and fibrosis within the interstitial tissues (1–3). These diseases are classified based on clinical assessment, radiological imaging or histopathological findings. ILDs are further categorised by their underlying causes into groups such as autoimmune ILDs, idiopathic interstitial pneumonias, sarcoidosis, hypersensitivity pneumonitis and others (4, 5). Systemic sclerosis (SSc) is an autoimmune disease that can lead to the development of ILD. Similar to other ILDs, ILD associated with systemic sclerosis (SSc-ILD) is marked by inflammation and fibrosis of the lungs as observed on high-resolution computed tomography (HRCT). ILD is a prevalent manifestation of SSc and is linked to a significantly increased risk of early mortality (6, 7).

Review

Definition

SSc is a rare connective tissue disease that believed to occur in genetically susceptible individuals due to environmental triggers. Patients with SSc typically experience vasculopathy, immune dysfunction, cellular inflammation and fibrosis, which can affect not only the skin but also several internal organs, including the lungs (8). The disease is initiated by microvascular trauma, which induces inflammation and an autoimmune response (5, 6). Transforming growth factor (TGF)- β is a key factor in the development of lung fibrosis in SSc-ILD, contributing to extracellular matrix accumulation and immune response regulation. Type 2 helper T cells, which secrete interleukin (IL)-4 and IL-13, also play a role in fibrosis. Additionally, thrombin levels are elevated in the lungs of SSc-ILD patients, likely due to cellular injury. Beyond its role in coagulation, thrombin promotes fibrosis by increasing fibroblast proliferation in response to fibrinogen and facilitating their differentiation into myofibroblasts (9).

Based on the extent of skin involvement, SSc is classified into two categories: limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) (8). LcSSc affects only the skin of the face, hands, forearms and feet, whereas dcSSc involves skin extending to the proximal elbows and sometimes the trunk. In 2013, a joint working group of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) published new criteria for the classification of SSc. These criteria include pulmonary arterial hypertension (PAH) and/or ILD as clinical features that must be identified in individuals suspected of having SSc, particularly when skin thickening of the fingers extending to the proximal metacarpophalangeal joints is absent (6, 7).

Several risk factors have been identified for the development of SSc-ILD, including older age at disease onset, male sex, shorter disease duration (<5 years), African–American race, presence of dcSSc, presence of anti-topoisomerase I antibody (anti-Scl-70) and/or absence of anticentromere antibody, and presence of ground-glass opacification or fibrosis on HRCT (6, 10). However, these risk factors are not absolute. Physicians need to be aware that ILD may develop in both patients with lcSSc and dcSSc (6).

Epidemiology

SSc has a global prevalence that estimated to be 3–24 per 100,000 individuals. Approximately 50% of patients with SSc develop ILD (7, 8). The epidemiology of SSc-ILD varies based on geographical regions. According to a systematic review and meta-analysis by Qiu et al. (8), around 56% of patients with SSc in East Asia develop ILD. In Europe, the prevalence of SSc-ILD is estimated to be 1.7–4.2 per 100,000 individuals, while in the United States, it is estimated to be 7.3 per 100,000 individuals (11, 12). Current studies show that ILD is the leading cause of death in patients with SSc, contributing to 17%–35% of all deaths in this population. A study from a single US centre examining the causes of death in 1508 patients with SSc found that the percentage of deaths attributed to pulmonary fibrosis increased from 6% in 1972–1976 to 33% in 1997–2001. Additionally, an analysis of 5850 patients in the EULAR Scleroderma Trials and Research Group (EUSTAR) database showed that from 2004 to 2008, 35% of SSc-related deaths were due to pulmonary fibrosis. These findings support the assertion that ILD or pulmonary fibrosis has become the most frequent cause of death in patients with SSc (6, 7).

Diagnosis

Not all patients with SSc-ILD exhibit respiratory symptoms, necessitating a high level of suspicion from physicians to identify the condition. The risk of developing ILD is highest early in the course of SSc. Comprehensive evaluations, including clinical assessment, pulmonary function tests (PFTs) and chest HRCT, should be performed for all patients suspected of having SSc-ILD. During the first 3 years after diagnosis, it is crucial to conduct PFTs every 4–6 months. Routine assessments are essential for the early detection and evaluation of disease progression (6).

SSc-ILD can be diagnosed by identifying fibrosis, commonly at the lung bases, on chest HRCT and/or by hearing crackles during chest auscultation, which sound like ‘Velcro’ being torn apart. Chest HRCT in patients with SSc-ILD typically shows a pattern of non-specific interstitial pneumonia (NSIP). The presence of pleuroparenchymal fibroelastosis

(PPFE)-like lesions on HRCT may also indicate a poor prognosis (6, 13). PFTs in patients with SSc-ILD typically reveal a restrictive pattern, characterised by reduced forced vital capacity (FVC) and diffusion capacity of the lung for carbon monoxide (DLCO). However, in some patients with evident fibrosis on chest HRCT, FVC may appear normal. Both a low FVC on PFTs and more extensive fibrosis observed on chest HRCT independently predict mortality in patients with SSc-ILD (14).

The clinical course of SSc-ILD varies among patients, with some experiencing a gradual decline in lung function while others exhibit rapid progression. Progression is marked by worsening respiratory symptoms, decline in FVC or DLCO, exercise-induced oxygen desaturation and increased fibrosis extent on chest HRCT. Surgical lung biopsy is not commonly performed in SSc patients unless the HRCT imaging pattern is atypical or there are suspicions of other differential diagnoses or complications (6, 15, 16).

Treatments

Treatment for patients with SSc-ILD is individualised, with decisions based on specific patient circumstances. Routine monitoring is recommended due to the potential for disease progression at any stage. If significant changes or evidence of disease progression emerge, such as worsening respiratory symptoms related to ILD, decline in lung function or increased fibrosis observed on chest HRCT, physicians should consider initiating pharmacological therapy. Options include nintedanib as monotherapy or in combination with mycophenolate mofetil (MMF) and/or cyclophosphamide (CYC). Following pharmacological intervention, ongoing assessment of disease progression is essential. If inadequate response or continued progression occurs, treatment may need to be escalated by adjusting drug choice or dosage, evaluating suitability for lung transplant, or in selected cases, considering haematopoietic stem cell transplantation (6, 15, 16).

Antifibrotic agents

Given the clinical and mechanistic similarities between idiopathic pulmonary fibrosis (IPF) and SSc-ILD, nintedanib and pirfenidone, an approved therapy for IPF, are also considered for treating SSc-ILD (6).

Nintedanib acts as an antifibrotic agent by inhibiting fibroblast proliferation, migration, differentiation and extracellular matrix secretion. In animal models of SSc-ILD, nintedanib exhibits anti-inflammatory effects and supports vascular remodelling. It can be administered as monotherapy or in combination with CYC/MMF (6, 16).

The SENSICIS trial, a randomised, placebo-controlled study, investigated the efficacy of nintedanib in patients with SSc-ILD. Participants were aged ≥ 18 years, and they had non-Raynaud's symptoms ≤ 7 years before screening, $\geq 10\%$

pulmonary fibrosis on HRCT, and PFT results showing 30%–89% predicted DLCO and 40% predicted FVC. Eligible patients were those on low-dose prednisone or receiving MMF or methotrexate. Of the 580 patients randomized in a 1:1 ratio, 287 received 150 mg of nintedanib twice daily and 288 received placebo. The primary endpoint demonstrated that the annual decline in FVC (mL/year) in the nintedanib group over 52 weeks was significantly lower than in the placebo group, with a difference of 41.0 mL/year (95% confidence interval [CI]: 2.9, 79.0; $P = 0.035$), representing a 44% relative reduction (6, 17). The most common side effect of nintedanib was mild or moderate diarrhoea. Other adverse events included mild elevations in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels, less than three times the upper limit of normal. These elevations typically normalise with dose reduction or a short treatment interruption (18–20).

Pirfenidone is currently approved for IPF but has not yet received approval for other progressive fibrotic ILDs. Although research indicates that pirfenidone inhibits fibroblast proliferation and differentiation and reduces collagen synthesis, as demonstrated in *in vitro* and animal models, its exact mechanism of action is still unclear. Currently, a trial Scleroderma Lung Study-III (SLS-III) is underway to evaluate pirfenidone in combination with MMF for treating active and symptomatic SSc-ILD patients (6, 21).

CYC

According to EULAR recommendations, CYC is the preferred initial treatment for patients with SSc-ILD. CYC, a cytotoxic immunosuppressant, modulates lymphocyte function to suppress inflammation and reduce fibrosis. This potent agent effectively induces and maintains remission in autoimmune and inflammatory diseases. The Scleroderma Lung Study-I (SLS-I; oral CYC vs. placebo for 1 year) and Fibrosing Alveolitis in Scleroderma Trial (FAST; monthly IV CYC for 6 months plus alternating oral prednisone and daily azathioprine vs. placebo for 12 months) showed modest improvements in FVC. Patient-reported outcomes in the SLS-I study indicated significant benefits in cough, functional disability, dyspnoea and mental well-being. However, FVC improvement did not persist 12 months after treatment cessation, highlighting the need for ongoing immunosuppressive therapy. Physicians should be aware of potential CYC toxicities, including bone marrow suppression (leukopenia, neutropenia and thrombocytopenia), bladder cancer and haematuria (6, 22).

MMF

In addition to CYC, MMF is a common treatment for patients with SSc-ILD. MMF inhibits inosine monophosphate dehydrogenase, thereby impairing lymphocyte

proliferation and migration. Observational studies suggest that MMF treatment may stabilise or improve FVC. The Scleroderma Lung Study-II (SLS-II) compared oral MMF (3 g/day for 2 years) with oral CYC (titrated to 2 mg/kg/day for 1 year followed by placebo). MMF was found to be non-inferior to CYC, with fewer treatment discontinuations and fewer adverse events (weight loss, leukopenia and thrombocytopenia) observed in the MMF group. This trial provides clinicians with a similarly effective yet safer option for managing SSc-ILD, potentially avoiding the long-term fertility and malignancy risks associated with CYC use (6, 22).

Supportive care

Supportive care aimed at alleviating symptoms and improving health-related quality of life (HRQL), such as pulmonary rehabilitation and patient/caregiver education, should be prioritised in the management of patients with SSc-ILD. Pulmonary rehabilitation has demonstrated efficacy in enhancing symptoms such as dyspnoea, exercise capacity (measured by the 6-min walk distance) and overall HRQL in SSc-ILD patients. However, further studies are necessary to fully evaluate the effectiveness of non-pharmacological treatments. Palliative care should be accessible at all stages of the disease and tailored to individual patient needs. Comprehensive management should also address the treatment of concurrent complications or comorbidities that may arise in SSc-ILD patients (6).

Follow-up and monitoring

In the initial 3–5 years of the disease, regular PFTs should be conducted every 3–6 months for all patients with SSc-ILD. Routine repeat HRCT scans are not recommended. However, repeat HRCT may be considered in cases of worsening symptoms where it could impact treatment decisions, or when there is suspicion of radiographic progression in clinically stable patients with declining PFT results. This approach aims to optimise monitoring while minimising unnecessary imaging (23).

Conclusion

Diagnosing SSc-ILD is challenging due to its diverse and non-specific symptoms, often leading to delays in detection. Essential diagnostic tools include HRCT scans and PFTs. Regular monitoring is crucial, particularly early after diagnosis, to monitor disease progression and guide treatment decisions. Treatment mainly focuses on antifibrotic and immunosuppressive therapies customised to each patient's needs, acknowledging that not all patients require treatment.

A multidisciplinary approach ensures comprehensive assessment, continuous monitoring, and effective management of SSc-ILD, enhancing patient outcomes and quality of life.

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Institutional review board statement

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Informed consent statement

No informed consent was necessary.

Data availability statement

Data used to support the findings of this study are available from the corresponding author upon request.

Conflict of interest

The authors declare no conflict of interest.

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