Histol Histopathol (2025) 40: 49-56

Histology and Histopathology
From Cell Biology to Tissue Engineering

ORIGINAL ARTICLE Open Access

Histopathological aspects of usual interstitial pneumonia in patients with systemic connective tissue diseases

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Summary. Five cases of patients with systemic connective tissue diseases (CTD) who developed connective tissue disease-associated interstitial lung disease (CTD-ILD) with progressive pulmonary fibrosis (PPF) are reported here. Unspecified ILD was diagnosed using high-resolution computed tomography (HRCT). Histologically, all cases were usual interstitial pneumonia (UIP) with findings of advanced (3/5) to diffuse (2/5) fibrosis, with a partially (4/5) to completely (1/5) formed image of a honeycomb lung. The fibrosis itself spread subpleurally and periseptally to more central parts (2/5) of the lung, around the alveolar ducts (2/5), or even without predisposition (1/5). Simultaneously, there was architectural reconstruction based on the mutual fusion of fibrosis without compression of the surrounding lung parenchyma (1/5), or with its compression (4/5). The whole process was accompanied by multifocal (1/5), dispersed (2/5), or organized inflammation in aggregates and lymphoid follicles (2/5). As a result of continuous fibroproduction and maturation of the connective tissue, the alveolar septa thickened, delimiting groups of alveoli that merged into air bullae. Few indistinctly visible (2/5), few clearly visible (1/5), multiple indistinctly visible (1/5), and multiple clearly visible (1/5) fibroblastic foci were present. Among the concomitant changes, areas of emphysema, bronchioloectasia, and bronchiectasis, as well as bronchial and vessel wall hypertrophy, and mucostasis in the alveoli and edema were observed. The differences in the histological appearance of usual interstitial pneumonia associated with systemic connective tissue diseases (CTD-UIP) versus the pattern associated with idiopathic pulmonary fibrosis (IPF-UIP) are discussed here. The main differences lie in spreading lung fibrosis, architectural lung remodeling, fibroblastic foci, and inflammatory infiltrates.

Key words: Fibroblastic foci, Honeycombing, Idiopathic pulmonary fibrosis, Interstitial lung disease, Progressive pulmonary fibrosis

Introduction

Systemic connective tissue diseases (CTD) encompass a diverse group of chronic inflammatory

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www.hh.um.es. DOI: 10.14670/HH-18-777

Abbreviations. ANA, antinuclear antibodies; CTD, systemic connective tissue diseases; CTD-ILD, connective tissue disease-associated interstitial lung disease; CTD-PPF, connective tissue disease-associated progressive pulmonary fibrosis; CTD-UIP, usual interstitial pneumonia associated with systemic connective tissue diseases; DAD, diffuse alveolar damage; HRCT, high resolution computed tomography; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; IPF-UIP, usual interstitial pneumonia associated with idiopathic pulmonary fibrosis; LIP, lymphoid interstitial pneumonia; NITBLDTS, National Institute of Tuberculosis, Lung Diseases and Thoracic Surgery in Vyšné Hágy, Slovak Republic; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; PPF, progressive pulmonary fibrosis; TBCB, transbronchial lung cryobiopsy; UIP, usual interstitial pneumonia.

conditions originating from non-infectious causes. Clinically, they manifest a wide spectrum of symptoms with varying prognoses, often extending beyond musculoskeletal involvement (Kishaba, 2022). Antinuclear antibodies (ANA) commonly characterize systemic CTD, with distinct fluorescence patterns aiding disease classification (Bahmer et al., 2016). CTD itself may be accompanied by interstitial lung involvement with fibrotic lung remodeling. However, this does not represent a separate entity, rather, it is part of a spectrum of changes within systemic connective tissue disease-associated interstitial lung disease (CTD-ILD). The histopathological pattern often observed in CTD-ILD is that of usual interstitial pneumonia (UIP); thus, we can refer to it as CTD-UIP. Interstitial lung diseases (ILD) generally encompass a broader group of diseases, several of which may be associated with the histological pattern of UIP. The microscopic picture of UIP is dominated by areas of more or less mature fibrosis with a sharp transition to adjacent, minimally affected lung parenchyma, with a limited inflammatory infiltrate, resulting in the characteristic honeycombing of the lung. The histological findings should be correlated with the clinical presentation and with high-resolution computed tomography (HRCT) findings, as the UIP pattern itself, although well-developed in processed material, may be diagnostically relevant to several distinct clinical entities. The most common and most severe clinical variant with a microscopic picture of UIP is idiopathic pulmonary fibrosis (IPF), which corresponds to a specific form of a chronic fibrotic interstitial pulmonary process of unknown etiology in adults. IPF is a distinct entity with a poorer prognosis compared with CTD-ILD (Strange and Highland, 2004; Strand et al., 2014). Despite this distinction, CTD-ILD should not be downplayed, as a proportion of cases may also present with aggressive behavior in the form of progressive pulmonary fibrosis (CTD-PPF). Research indicates that 25% of patients with CTD-ILD progress to CTD-PPF, which corresponds to a poorer prognosis and premature death (Lee et al., 2023). Consequently, CTD-ILD emerges as a risk factor within CTD. Therefore, cases involving interstitial lung manifestations linked to systemic CTD should be subject to multidisciplinary consultation (Castillo et al., 2018; Teoh et al., 2022). Given the non-specific clinical symptomatology often accompanying CTD, the diagnosis poses unique challenges, potentially prolonging the diagnostic process compared with other diseases.

The complexity of the differential diagnosis of interstitial lung diseases is evident from the above-mentioned studies. The prominent pulmonary symptomatology may be misinterpreted as IPF during the differential diagnosis under certain conditions. Moreover, some CTD-ILD cases may take on the character of CTD-PPF; therefore, this possibility must be considered in all patients with systemic inflammatory and autoimmune diseases. However, it remains unclear from the literature, whether the development of CTD-UIP changes is of a slow, gradual nature or spontaneous, and whether CTD-UIP can be histologically differentiated from IPF-UIP through clear staining techniques. This article aims to describe histopathological findings that could be helpful in the differential diagnosis and suggest a tendency toward an aggressive course of the disease, based on the cases of five patients with CTD-ILD exhibiting a progressive pulmonary fibrosis characteristic of CTD-PPF.

Materials and methods

Ethical aspects

The lung samples were obtained from the archives of the Department of Pathology of the National Institute of Tuberculosis, Lung Diseases and Thoracic Surgery (NITBLDTS) in Vyšné Hágy, Slovak Republic. The possibility of using the samples for research purposes was approved by the ethics committee of the NITBLDTS in Vyšné Hágy (1/2022 Ek NITBLDTS).

Description of the cases

The material was obtained by a videothoracoscopic lung biopsy from five patients with systemic CTD who were diagnosed and hospitalized at NITBLDTS in Vyšné Hágy. Basic data regarding the patients are presented in Table 1.

Case 1

A woman under the care of a rheumatologist for systemic sclerosis, with Raynaud's syndrome, and functional esophageal involvement. Recently, she complained repeatedly of breathing difficulties. The examinations revealed positivity for antibodies against cell nuclei - nucleolar type (ANA +++), detected by indirect immunofluorescence. The HRCT examination resulted in a diagnosis of unspecified interstitial lung disease. Subsequently, a videothoracoscopic lung biopsy from the lower lobe of the right lung was performed at a specialized clinic.

Table 1. Basic data.

Label	Sex	Age	Primary disease	Work activity
1	F	29	Systemic sclerosis	Administrative worker
2	F	36	Rheumatoid arthritis	School psychologist
3	F	52	Rheumatoid arthritis	Professional chef
4	F	62	Rheumatoid arthritis	Sales assistant in a shopping center
5	F	67	Sjögren's syndrome	Head of the school canteen

F: Female.

Case 2

A woman under the care of a rheumatologist for rheumatoid arthritis. She recently reported coughing, sweating, mild dyspnea, and weight loss without dieting. Occasional chest pain after exertion. Indirect immunofluorescence revealed the positivity of antibodies against cell nuclei - homogeneous type (ANA+). The HRCT examination described diffuse interstitial lung disease with findings of fibrotic changes, as well as both emphysema and honeycombing. A biopsy was performed of the upper lobe of the left lung using videothoracoscopy.

Case 3

A woman with rheumatoid arthritis undergoing immunosuppressive therapy, under the care of a rheumatologist. She initially experienced mild fatigue for several months, followed by a gradual worsening of symptoms including shortness of breath, exhaustion, and increased coughing frequency. Indirect immunofluorescence revealed positivity for antibodies against cell nuclei – nucleolar type (ANA+++). The HRCT examination revealed findings consistent with unspecified interstitial lung disease. Subsequently, the patient underwent a biopsy of the lower lobe of the right lung by videothoracoscopy.

Case 4

A woman with rheumatoid arthritis under the care of a rheumatologist complained that she recently experienced difficulty breathing after exertion and joint pain in both upper and lower extremities. She had a persistent dry cough. The patient was positive for antinuclear antibodies (ANA+). The HRCT revealed a pattern of diffuse pneumopathy with an interstitial pulmonary process. The patient underwent a videothoracoscopic biopsy of the lower lobe of the right lung.

Case 5

A woman with Sjögren's syndrome, under the care of a rheumatologist, complained of chronic fatigue and shortness of breath on exertion. She had recently been seen repeatedly for recurrent laryngitis. Associated diseases included hyperlipidemia, hepatopathy, macular degeneration, and osteoporosis. The patient tested

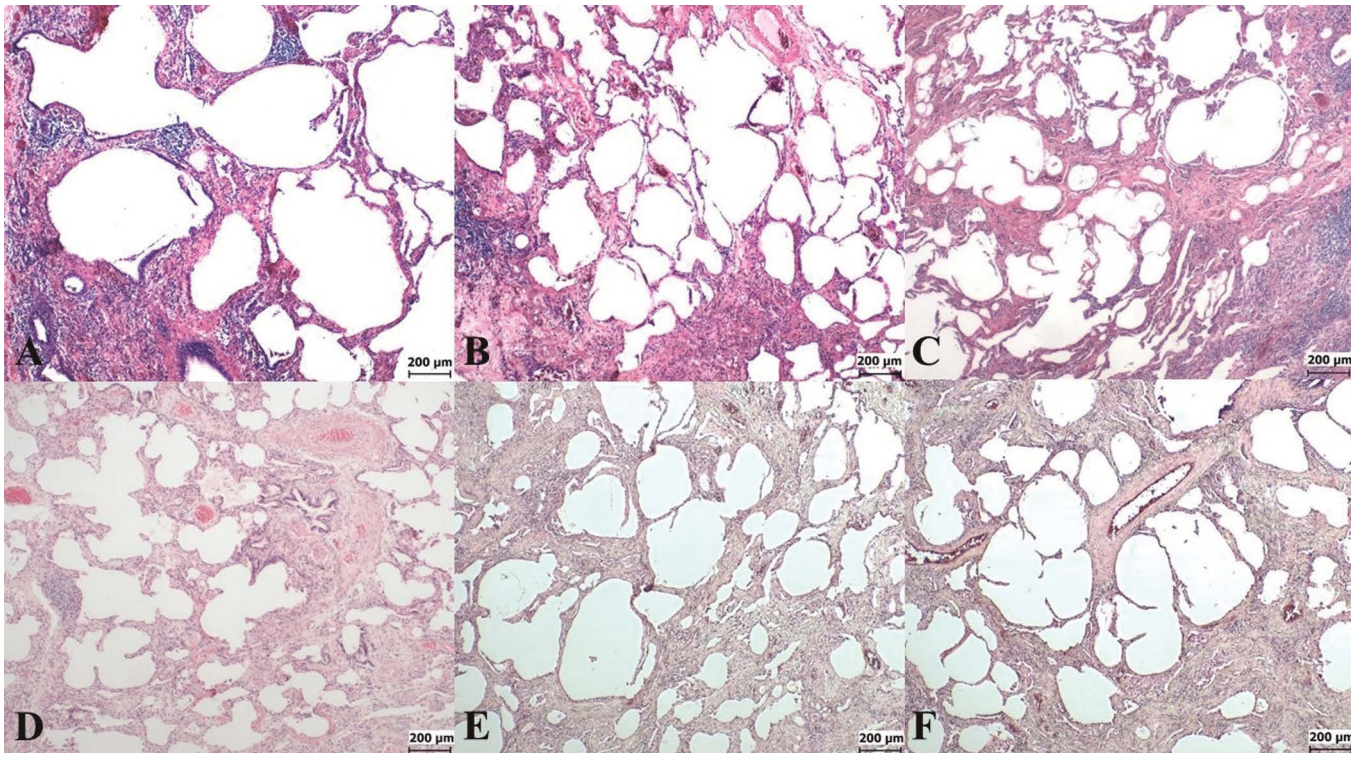

Fig. 1. Fibrosis spreading subpleurally from the periphery with sharper borders with adjacent preserved airspaces **(A)**, extending into more central parts of the lung via the alveolar ducts **(B)**, with thickening of the alveolar ducts with the accretion of connective tissue **(C)**. In the more central parts, there is gradually spreading fibrosis through alveolar ducts with thickened septa and with maturation of the connective tissue **(D)**, and gradual sheathing of the alveolar clusters **(E)**, which fuse together and merge into shapeless optically empty air spaces with a pattern of honeycombing of the lungs **(F)**. A persistent dispersive or clustering round-cell inflammatory infiltrate is visible in the image. HE. Scale bar: 200 μm.

positive for antinuclear antibodies (ANA++). The HRCT examination revealed unspecified interstitial lung disease. The patient underwent a biopsy of the lower lobe of the right lung by videothoracoscopy.

Histological processing of the material

The collected specimens were fixed in a 10% formalin solution and delivered to the pathology department, where they were processed by standard histological techniques in paraffin blocks. Subsequently, they were cut on a rotary microtome to produce slices with a thickness of 3-5 μm. The first series of sections was stained with clear Hematoxylin-eosin (Bamed, s.r.o., Czech Republic), and the second series was stained with Masson's trichrome (Bamed, s.r.o., Czech Republic) to detect fibrosis. The slides were evaluated using a BX53 Olympus light microscope (Olympus, Japan).

Results

Histological findings

The examined material showed pronounced fibroblastic proliferation and connective tissue remodeling of the lung parenchyma, with findings of UIP characterized by massive fibrosis (predominantly with subpleural spreading in some areas), displaying sharper borders against the adjacent preserved lung parenchyma (Fig. 1A-F). Temporal heterogeneity with alternating sections of indistinctly demarcated areas maturing into fully mature fibrosis was observed in the central regions of the parenchyma. Areas of fibrosis were in contact with or encapsulating preserved air spaces (Fig. 2A-F). A portion of the alveoli was compressed with preserved lining, whereas another portion exhibited a spectrum of changes like alveolar lining proliferation, including bronchiolization of alveoli. Adjacent compressed bronchi showed smooth muscle hypertrophy, along with a mass of vital erythrocytes in the lumen of the vessels. This was accompanied by concomitant smooth muscle hypertrophy of the vessel walls and focal intimal endothelial proliferation. Elsewhere, isolated sheathed torn alveoli with residual alveolar septa merging into air bullae were visible. Sections of fully mature fibrosis were present in places. Edema was observed around the alveolar ducts. Occasional indistinct miniature proliferations of a sparse connective tissue network of myxoid appearance, characteristic of fibroblastic foci, were visible. (Fig. 3 A-F). The picture was complemented by a more or less intense, predominantly clustering distributive round-cell inflammatory infiltrate and perivascular round-cell inflammatory infiltrate. In

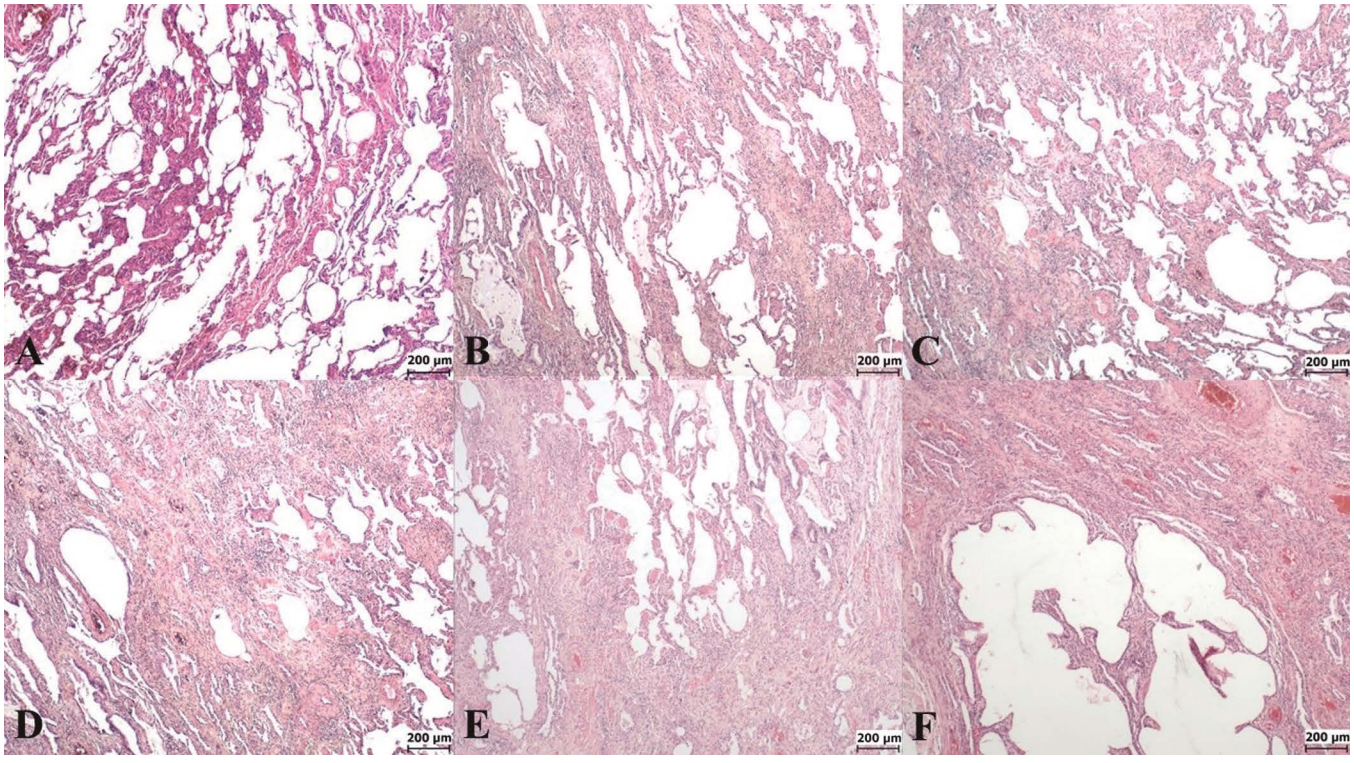

Fig. 2. In the affected parts, fibrosis spreads by penetration of the alveolar ducts from multiple sites simultaneously, with the preserved airspace being compressed **(A)**. The fibrosis itself appears to be progressive with intense diffuse spreading via alveolar ducts **(B)**, and continuously expanding spaces affected by connective tissue remodelling at the expense of air spaces **(C, D)** with a few separating alveolar clusters **(E)** and, in places, air bullae isolated by the surrounding fibrous tissue **(F)**. HE. Scale bar: 200 *μ*m.

places, foci of round-cell inflammatory cellularization were arranged in aggregates or individual lymphoid follicles. The quantitative assessment of the results is shown in Table 2.

Discussion

Diagnosis of interstitial lung diseases is considered a complex problem that requires multidisciplinary cooperation, with adequate instrumentation and laboratory facilities. Diagnosis based on microscopic images alone without accompanying clinical data or HRCT findings may be deemed insufficient or even hazardous nowadays. Since the microscopic picture of UIP may manifest across different clinical entities, differentiating them solely based on histological examination poses a challenge for pathologists. A correct differential diagnosis holds significant prognostic and therapeutic implications. For instance, two studies described differences between IPF-UIP and fibrotic hypersensitivity pneumonitis, focusing on patterns of fibrosis, the presence of fibroblastic foci, lung honeycombing appearance, and the presence of air bullae and granulomas (Hamblin et al., 2022; Matěj, 2023). In our cases, lung fibrosis is the most common, and its extent may be biased by the number and selection of samples from the material provided. Nevertheless, it was possible to categorize the histological findings into major and minor, and describe the characteristics of the UIP pattern within them. These could be utilized in the differential diagnosis to distinguish between various types of UIP. Our findings agree with those of IPF-UIP (Makovická et al., 2024). In cases of CTD-UIP, fibrotization progresses subpleurally and centripetally to central parts of the lungs, or larger fibrotic foci may develop in central areas, subsequently compressing the surrounding parenchyma and eventually overgrowing alveolar septae and fusing with one another. This contrasts with IPF-UIP, where we have documented a more progressively accelerated fibrosis with unequivocal predisposition. In CTD-UIP cases, few blandly developed fibroblastic foci were present, whereas in IPF-UIP cases, they were more numerous and easily identifiable. Similarly, one paper documented that CTD-UIP patients had smaller fibroblastic foci compared with IPF-UIP, while rheumatoid arthritis patients exhibited larger lymphoid aggregates. An increased incidence of multilobar nonspecific patterns of interstitial pneumonia has also been documented in CTD-UIP as opposed to IPF-UIP (Cipriani et al., 2012). As the presence of fibroblastic foci is associated with progressive fibrosis behavior, it can be concluded that CTD-UIP will be characterized by a better prognosis. The spread of fibrosis in CTD-UIP cases is regularly accompanied by a round-cell inflammatory infiltrate that persists even in areas of mature fibrosis, clustering into variably sized

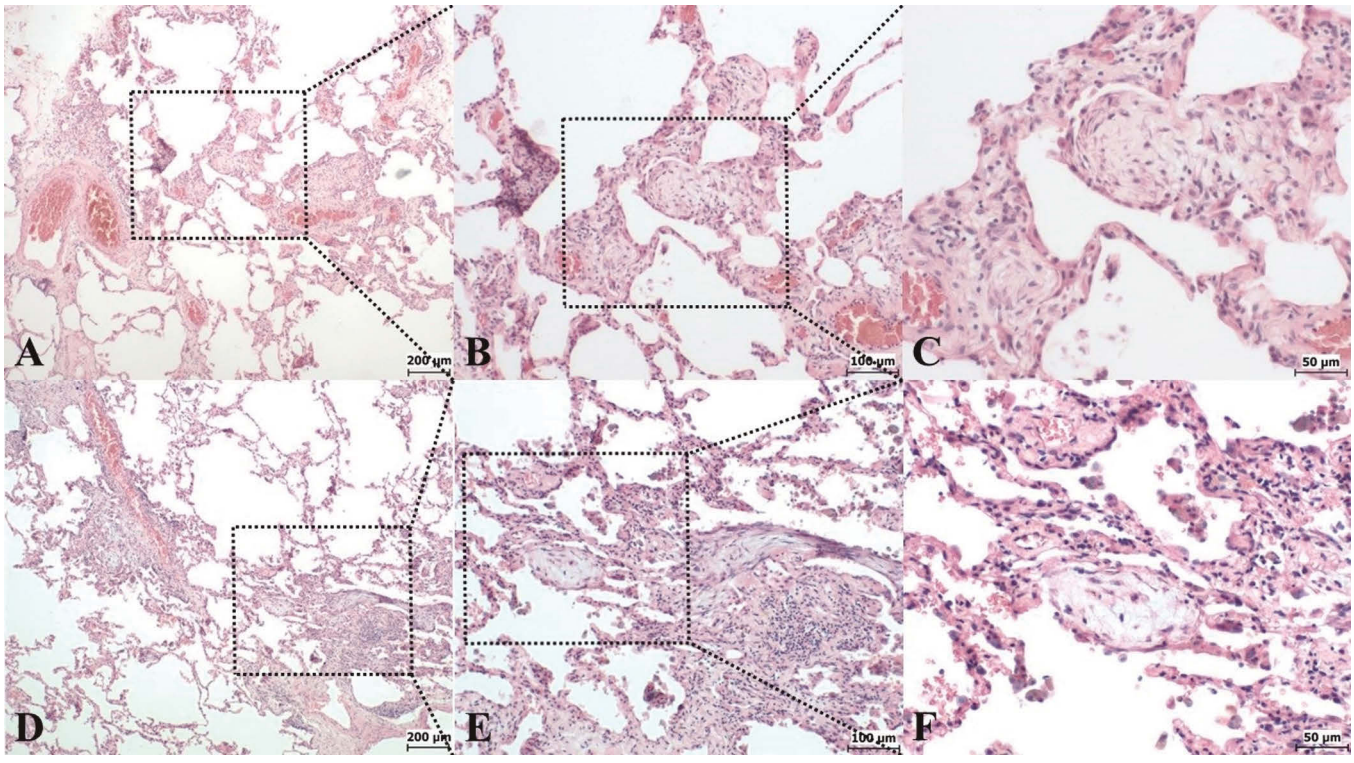

Fig. 3. The terrain of interstitial fibrosis of the lung shows multiple clearly visible miniature islands of the character of fibroblastic foci **(A)** and multiple indistinctly visible formations of the character of fibroblastic foci **(B)**. HE. Scales Bars: A, D, 200 μm; B, E, 100 μm; C, F, 50 μm.

Table 2. Histological characteristics of CTD-UIP.

Changes	Findings	Presence	Characteristics
Major	Fibrosis	0/5	Initial
		3-5	Advanced
		2-5	Diffuse
	Honeycombing	0/5	Not formed
		4-5	Partially formed
		1-5	Fully formed
	Fibrosis spread	2-5	Subpleurally to the more central parts of the lungs
		0/5	From the more central parts of the lungs to subpleaurally
		2-5	By fusion of fibrotic foci via alveolar ducts
		1-5	Without clear anatomical predisposition
	Architectural reconstruction	0/5	Transfer from one location without compression of adjacent airspace
		0/5	Transfer from one location with compression of adjacent airspace
		1-5	Fusing foci without compression of the adjacent airspace
		4-5	Fusing foci with compression of the adjacent airspace.
	Inflammation	0/5	Absent
		0/5	Focal
		1-5	Multifocal
		2-5	Dispersive
		0/5	Diffuse
		2-5	Organizing into aggregates and lymphoid follicles
Concomitant	Fibroblastic foci	0/5	Absent
		2-5	Few, vaguely visible
		1-5	Few, clearly visible
		1-5	Multiple, vaguely visible
		1-5	Multiple, clearly visible
	Emphysema	0/5	Absent
		0/5	Individual
		5-5	Clearly visible
	Bronchioloectasia	0/5	Absent
		2-5	Individual
		3-5	In several places
		0/5	Diffuse
	Bronchiectasis	4-5	Absent
		1-5	Individual
		0/5	In several places
		0/5	Diffuse
	Bronchial wall hypertrophy	1-5	Absent
		2-5	Individual
		0/5	In several places
		2-5	Diffuse
	Vessel wall hypertrophy	1-5	Absent
		1-5	Individual
		0/5	In several places
		3-5	Diffuse
	Mucostasis of alveoli	3-5	Absent
		1-5	Individual
		1-5	In several places
		0/5	Diffuse
	Squamous metaplasia of pneumocytes	5-5	Absent
		0/5	Individual
		0/5	In several places
		0/5	Diffuse
	Edema	0/5	Absent
		4-5	Focal
		1-5	Multifocal
		0/5	Dispersive
		0/5	Diffuse
	Bleeding	5-5	Absent
		0/5	Focal
		0/5	Multifocal
		0/5	Massive

foci or even lymphoid aggregates. Such a pattern was not unequivocal in IPF-UIP cases; however, in cases involving various rheumatic diseases, the presence of lymphoplasmatic infiltrates is useful for distinguishing CTD-UIP from that related to IPF-UIP (Lupi et al., 2023). This finding, especially the presence of plasma cells, could indicate an autoimmune disease but it is still speculative to consider it unequivocally conclusive. Based on the presence of plasma cells, CTD-UIP cannot be definitively distinguished, as they have also been observed in areas of fibrotic remodeling in IPF-UIP (Ali et al., 2021; Prele et al., 2022). On the other hand, other research has documented differences in the presence and activity of B-cells in the context of UIP in autoimmune diseases compared with IPF-UIP. This finding is presented as a candidate in terms of potentially distinguishing the mentioned pathology (Zhao et al., 2018). In our opinion, the potential immunohistochemical evidence of B cells and T cells in the context of UIP would be less significant in terms of positivity alone. However, the potential organization of CD45 cells could be helpful in cases of CTD-UIP. On the other hand, we acknowledge that the presence of plasma cells and neutrophils alone may be interpreted to be a result of regulatory activities of the immune system, which undoubtedly plays a role in controlling pathogenic immune responses, including the regulation of inflammation in the context of fibrosis. These facts have been highlighted in our work on the importance and roles of macrophages in the prognosis of solid lung tumors (Muri et al., 2022). The differences in our reported findings could also be due to exogenous factors, and, indeed, CTD-UIP patients were mostly young, non-smokers, and females (Alhamed, 2015). In our study, five female subjects were included and all were smokers. Recently, surgical lung biopsy has been gradually abandoned. It provides sufficient material, nevertheless, it is associated with a risk of disease exacerbation, especially in patients with advanced pathology, and is also burdened with postoperative complications. Less invasive transbronchial lung cryobiopsy (TBCB) is an option, yet it provides a limited amount of biopsy material and is also associated with a risk of exacerbation, as well as potential post-procedural complications. Currently, HRCT is clearly preferred for diagnosis, as it eliminates the risks associated with virtually all lung biopsy techniques and allows the assessment of fibrotic remodeling of the lung parenchyma at the level of the organ as a whole, with the possibility of describing even the finest characteristics of patterns of organization, distribution, and spread of fibrosis. The search for differences in the histological pattern of UIP of different etiologies is justified. It may be beneficial in cases of individuals with uncertain findings on HRCT and an indeterminate clinical course of the disease who can undergo lung biopsy with an acceptable level of risk. In some cases, interstitial lung involvement may come to the forefront of the clinical symptomatology of systemic connective tissue disease, or symptoms due to this involvement may long precede other CTD symptomatology. Further research into the differential diagnosis of UIP could take the path of special immunohistochemical and molecular investigations that would not only elucidate the probable etiology but also help uncover the pathomechanisms involved in the development of fibrosis in a given case. It is important to keep in mind that there is a risk of diagnostic confusion between interstitial lung involvement associated with systemic CTD and IPF (Antin-Ozerkis et al., 2012; Cottin, 2013; Pugashetti et al., 2023), as well as the potentially variable course of interstitial lung involvement associated with systemic CTD. Therefore, it would be particularly beneficial to uncover histological attributes of UIP indicating a potentially fulminant course of pulmonary involvement. As noted above, efforts to differentiate individual clinical entities based on clear staining have encountered the problem of the absence of unequivocal histologic patterns. Our study was based on five cases that were collected over several years; however, the results highlight the need for further exploration in this field. It would therefore be appropriate to compare the microscopic findings of the initial and advanced stages of CTD-UIP with those of IPF-UIP. Beyond their diagnostic value, the results could provide further insights into the pathophysiology of CTD-PPF. It seems that the problem may be more extensive than originally thought. Meanwhile, nonspecific interstitial pneumonia (NSIP), CTD-UIP, organizing pneumonia (OP), diffuse alveolar damage (DAD), and lymphoid interstitial pneumonia (LIP) have been described in CTD-ILD cases in the past (de Lauretis et al., 2011). In the cases presented herein, CTD-ILD progressed aggressively and reached the stage of progressive pulmonary fibrosis. Genetic factors, such as abnormalities in the regulation of the immune system and inflammation, may play a role in the development of CTD-PPF, which could become a regulator of fibrotization of the lung (Makovický, 2015; Chiang and Parimon, 2023). Further investigations should, therefore, illuminate the mechanisms underlying the initiation of lung fibrosis in CTD-UIP. These findings should then be used in personalized medicine, addressing not only diagnosis but also predisposition to lung fibrosis and its prognostic significance.

Conclusion

Despite the constantly improving conditions, including the acquisition of more modern technical equipment by individual departments and the enhancement of laboratory facilities in specialized centers focusing on selected diseases, many of these diseases are still only diagnosed at the florid stage. This is associated with a poorer prognosis for affected individuals. As a related finding, interstitial lung involvement may occur in patients with systemic CTD, exhibiting a wide range of dynamics in the progression of pulmonary dysfunction. A proportion of patients

develop PPF with histological findings consistent with CTD-UIP, characterized by spreading fibrosis, architectural remodeling of the lung, and the presence of few or multiple indistinctly visible fibroblastic foci. The microscopic pattern is further defined by the presence of an inflammatory infiltrate. These findings could aid in the differential diagnosis of CTD-UIP within ILD.

Acknowledgements. We thank Ing. Lenka Literáková for her excellent histology technical assistance.

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Accepted June 10, 2024