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# Pathology of Interstitial Pneumonia Associated with Hypothyroidism — Report of Three Cases

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## Abstract

Recently, idiopathic pulmonary fibrosis (IPF) associated with hypothyroidism was proposed as a possible link showing worse prognosis than IPF. We have reviewed our archives of interstitial pneumonias (IPs) and examined pathologic and clinical features of IPs associated with hypothyroidism to understand its variations. Pathologically, two cases showed usual interstitial pneumonia pattern, and one case showed non-specific interstitial pneumonia pattern. Small airway disease was a common histological feature in all cases. Two cases showed association with flavor of connective tissue disease (CTD). Diagnoses by multidisciplinary discussion for the three cases were IPF, unclassifiable IP, and systemic sclerosis associated interstitial lung disease. Our cases indicated that IPs associated with hypothyroidism may show not only IPF but also other histological types and probable connection to CTD. Furthermore, these three cases did not fit with predicted prognosis by histological patterns.

**Keywords:** Pulmonary fibrosis; Radiology; Connective tissue disease; Prognosis

## Introduction

Interstitial pneumonias (IPs) are a group of inflammatory diseases affecting the pulmonary interstitium, and background pathogenesis has not fully been understood. Currently, a majority of IPs is considered as idiopathic, however, increasing numbers of reports suggested their direct or indirect relationship with systemic diseases such as connective tissue disease (CTD) or allergic reaction to inhaled antigen such as bird related antigen as seen in hypersensitivity pneumonia [1-3]. In regards to the connection between CTD and idiopathic IPs, ERS/ATS Task Force on Undifferentiated Forms of CTD-ILD has suggested the new term for the patients who have some features of CTD, but not meet rheumatologic criteria for CTDs, interstitial pneumonia with autoimmune features (IPAF) and the criteria for them [4]. Other than that, idiopathic pulmonary fibrosis (IPF) associated with hypothyroidism was proposed by Oldham et al. [5] as a possible link showing worse prognosis than IPF. Whether IPF associated with hypothyroidism being distinctive disease or not is uncertain at this point, and whether hypothyroidism can associate with other types of IP by histology or not is unknown either.

We have reviewed consecutive cases in our archives of IPs, and three cases were identified to have both IPs and hypothyroidism out of 210 ILD cases from single respiratory institute. We observed pathological variations and clinical features associated with hypothyroidism to see if there is any specific trend.

## Clinical Summary

None of the three cases had a previous history of thyroidectomy or radioiodine ablation or a statement of congenital hypothyroidism, and detailed clinical characteristics of the three cases were summarized in Table 1.

### Patient 1

A 75-year-old male ex-smoker with a Brinkman index (BI), which is defined as numbers of cigarette smoked per day times smoking years, of 150 developed a non-productive cough and dyspnea for one year. He had a clinical history of hypothyroidism and received the hormone replacement therapy. He was diagnosed as IP and was on prednisolone due to the progression of respiratory symptoms. The patient started to receive long term oxygen therapy two years after the biopsy due to slow progression of the disease. A chest radiograph showed fine reticular opacities in bilateral lower lung zones. Chest computed tomography (CT) demonstrated reticular and ground-glass opacities with traction bronchiectasis predominantly in lower lung zones (Figure 1A and 1B). Honeycombing was not seen. Radiological diagnosis was possible usual interstitial pneumonia (UIP) pattern.

### Patient 2

A 72-year-old male ex-smoker with a BI of 700 who had hypothyroidism and received the hormone replacement therapy developed a cough and was pointed out to have crackles on auscultation. He had cheek erythema that has waxed and waned for four years and appeared pedal edema for two years. His blood test was positive for anti SS-A antibody, however, there was no symptom suggestive for Sjögren's syndrome. His serum test was also positive for IgG antibodies against bird serum antigens. A chest radiograph depicted faint ground-glass shadow in bilateral lung fields. Chest CT showed diffuse ground-glass opacities with traction bronchiectasis predominantly in lower lung zones (Figure 1C and 1D). Honeycombing was not found.

### Patient 3

A 39-year-old female non-smoker who had a clinical history of

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| Characteristics | Patient 1 | Patient 2 | Patient 3 |
|---|---|---|---|
| Age | 75 | 72 | 39 |
| Gender | Male | Male | Female |
| Smoking status | Ex-smoker (Brinkman index of 150) | Ex-smoker (Brinkman index of 700) | Never-smoker |
| Exposure | None | Construction, porcelain industry | None |
| Respiratory symptoms | A non-productive cough<br>Shortness of breath | A cough | Dyspnea on exertion |
| Other symptoms | None | Leg edema, cheek erythema | None |
| Physical findings | Clubbing, crackle | Crackle | Cyanosis, crackle, rash, Raynaud, dysphagia, xerostoma, dry eye |
| Auto-antibody | ANA, 1:40 | ANA, 1:640; RAPA, 1:320; SS-A 8 u/ml | ANA, 1:2560; RAPA, 1:320;<br>SS-A, 8 u/ml; Scl-70, 32 u/ml |
| Diagnosis of CTD | None | None | SSc, SjS |
| HP | No data | Parrots, 24.7 ug/ml; Budgerigar, 14.4 ug/ml | No data |
| KL-6, u/mL | 2046 | 4800 | 595 |
| SP-D, ng/mL | 158 | 374 | 148 |
| FVC, % predicted | 78.2 | 71.3 | 83.8 |
| $FEV_1$, % predicted | 98.9 | 75.6 | 74.2 |
| DLCO, % predicted | 71.0 | 59.4 | 53.4 |
| $PaO_2$, Torr | 84.9 | 67.0 | 80.2 |
| Diagnosis by MDD | IPF/UIP | Unclassifiable IP | SSc associated ILD |
| Survival data | Slow progression but alive 5 years after the diagnosis | Stable for 4 years after the diagnosis | Dead 1 year after the diagnosis |

ANA: Anti-Nuclear Antibody; RAPA: Rheumatoid Arthritis Particle Aggregation; SS-A: anti SS-A antibody; Scl-70: anti Scl-70 antibody; CTD: Connective Tissue Disease; SjS: Sjögren's Syndrome; SSc: Systemic Sclerosis; HP: Hypersensitivity Pneumonitis; Parrots: Measurement of IgG Specific to Parrots Antigens; Budgerigar: Measurement of IgG Specific To Budgerigar Antigens; MDD: Multidisciplinary Discussion; IPF: Idiopathic Pulmonary Fibrosis; UIP: Usual Interstitial Pneumonia; ILD: Interstitial Lung Disease.

**Table 1:** Clinical characteristics of the three cases.

systemic sclerosis (SSc), Sjögren's syndrome and hypothyroidism developed dyspnea on exertion. She was on prednisolone and beraprost sodium due to a progression of arthralgia and muscular pain and received the hormone replacement therapy for hypothyroidism. She further underwent plasmapheresis for the worsening of dermal sclerosis. A chest radiograph demonstrated faint ground-glass shadow in bilateral lung fields. Chest CT showed ground-glass and reticular opacities with traction bronchiectasis predominantly in lower lung zones. Subplerural sparing was also seen (Figure 1E and 1F). Honeycombing was not seen.

## Pathological Findings

Detailed pathologic findings were summarized in Table 2, and diagnoses by the multidisciplinary discussion (MDD) were given based on 2013 ATS/ERS update of the international multidisciplinary classification of idiopathic interstitial pneumonias [6].

### Patient 1

The biopsies were taken from three sites (S5, S8, S9). The all lobes had similar histological features. The distribution of fibrosis was basically patchy and peripheral dominant inside the lobules (Figure 2A). Areas of diffuse fibrosis similar to NSIP were also mixed. The dense fibrosis was more severe in lower lobe where microscopic honeycomb changes were also found (Figure 2C). Fibroblastic foci were conspicuous at the transitional area between dense fibrosis and normal lungs. Mild cellular bronchiolitis was found in the majority of bronchioles, which especially showed mild to moderate constrictive changes, cellular infiltrations, and peribronchiolar fibrosis (Figure 2E). Interstitial lymphoid aggregates with germinal centers and diffuse lymphoplasmacytic infiltration, suggestive findings of IPAF were not found [4]. The pathological diagnosis of probable UIP was given. After the MDD, the case was finally diagnosed as IPF.

### Patient 2

The lung biopsies were obtained from three lobes (S5, S8, S9). All demonstrated dense fibrosis with severe architectural destruction. The number of fibroblastic foci was small. Definite honeycomb change was not seen. Occasional interstitial giant cells and one focus of poorly formed granuloma were seen (Figure 2D). The distribution of fibrosis was patchy and peripheral (Figure 2B). Marked airway centered fibrosis and small airway disease such as cellular bronchiolitis and peribronchiolar fibrosis were also noted (Figure 2F). Moderate degree of both interstitial lymphoid aggregates with germinal centers and diffuse lymphoplasmacytic infiltration indicative of IPAF were seen [4]. The basic pathological pattern was considered as UIP, however, due to the presence of airway centered change and one focus of granuloma, chronic hypersensitivity pneumonia was considered. On the other hand, due to the presence of IPAF morphological domains along with the patient's serum autoantibodies' positivity, SS-A, 8 u/ml; ANA, 1:640, also raised the possibility of CTD associated interstitial lung disease (ILD). The diagnosis of unclassifiable IP was given by MDD due to the complex clinical and histological characteristics.

### Patient 3

The biopsies were performed on three lobes (S5, S8, S9). The all lobes demonstrated uniform and temporally homogeneous dense and chronic fibrosis (Figure 3A-3C). The alveolar architectures were fairly preserved (Figure 3B), cellular infiltration was relatively mild, and fibroblastic focus was absent in all lobes. Mild cellular bronchiolitis associated with interstitial lymphoid aggregates were frequent findings (Figure 3D), and vascular wall thickening was also identified. Findings suggestive for acute lung injury were not identified. Based on the above findings, the pathologic diagnosis of fibrotic NSIP was given. The association with the background CTD was strongly suspected by histology, and after a MDD, a final diagnosis of SSc associated ILD was made.

## Discussion

In this case report, we reported the clinical and pathological

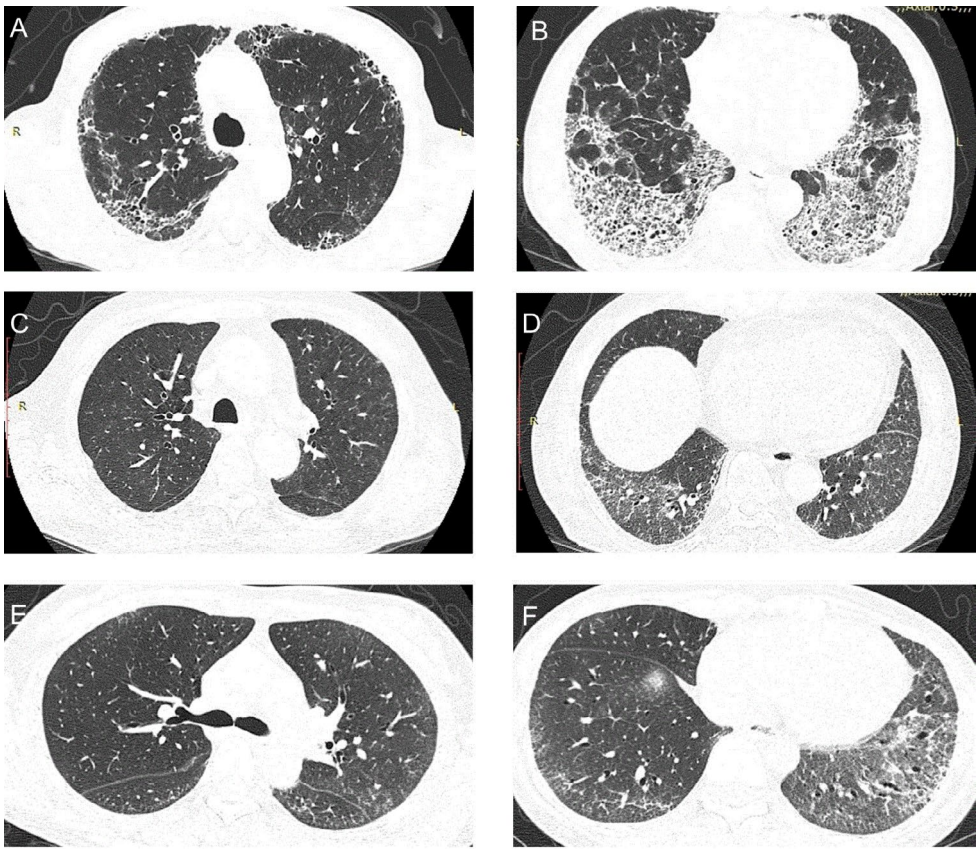


**Figure 1:** CT images of three cases. Patient 1: A, B; Patient 2: C, D; Patient 3: E, F. (A, B) Chest CT demonstrated reticular and ground-glass opacities with traction bronchiectasis predominantly in lower lung zones. (C, D) Chest CT showed diffuse ground-glass opacities with traction bronchiectasis predominantly in lower lung zones. (E, F) Chest CT showed ground-glass and reticular opacities with traction bronchiectasis predominantly in lower lung zones. Subpleural sparing was also seen.

| Variable | Patient 1 | Patient 2 | Patient 3 |
|---|---|---|---|
| Dense fibrosis | ++ | ++ | + |
| Peripheral distribution | + | ++ | - |
| Fibroblastic foci | ++ | + | - |
| Architecture destruction | ++ | ++ | - |
| Honeycombing | + | - | - |
| Smooth-muscle hyperplasia | + | + | - |
| Adjacent normal lung | - | + | - |
| Elastosis | ++ | + | - |
| Loose fibrosis | ++ | + | ++ |
| Cellular IP | ++ | - | + |
| Diffuse involvement | + | - | ++ |
| Architecture preserve | - | - | ++ |
| Focal OP | ++ | + | - |
| Interstitial Giant cell + Cholesterin cleft | - | + | - |
| Airway-centered IP | + | ++ | - |
| Small airway disease | + | ++ | + |
| Pleuritis | + | - | + |
| Dense perivascular collagen | + | + | + |
| Extensive pleuritis | - | - | - |
| Lymphocyte aggregation with GC | - | ++ | + |
| Diffuse lymphoplasmacytic infiltration | - | ++ | - |
| Pathological diagnosis | UIP | UIP | fibrotic NSIP |

IP: Interstitial Pneumonia; OP: Organizing Pneumonia; GC: Germinal Centers; UIP: Usual Interstitial Pneumonia; NSIP: Non-Specific Interstitial Pneumonia.

**Table 2:** Histological findings of the three cases.

features of three cases which have IPs associated with hypothyroidism. Those cases were originally diagnosed as IPF, SSc associated ILD, and unclassifiable IP. Oldham et al. [5] reported 33 IPF cases associated with hypothyroidism and suggested a link between IPF and hypothyroidism, nevertheless, our cases indicate that basic histological patterns and background conditions of IPs associated with hypothyroidism may vary. In contrast, small airway disease was found as a common histological finding in all cases. The association between airway disease and hypothyroidism was reported by Birring et al. [7] which is consistent with our findings. Several studies reported that small airway disease, such as follicular bronchiolitis, was a characteristic feature in the CTD related IP [8-10]. Due to the known association between hypothyroidism which is mediated by autoimmune mechanisms and CTD [11], association to CTD was expected in the series. The fact that two of three patients showed either definite CTD or autoimmune clinical and pathological features was reasonably consistent with the scenario. Putting all together, as is for other CTD, the idea that hypothyroidism occasionally induces ILD may be reasonable.

Another discussion point is a discrepancy between histological patterns and expected prognosis. Based on several literatures, it is fair to say that the prognosis of cases with histologic UIP pattern is worse than that with NSIP pattern regardless background etiologies [12-14]. However, two cases with histological UIP showed either slow progression or stable physical status whereas the case with histological NSIP progressed to death in one year. The clinical course is also somewhat inconsistent with the report of Oldham et al. [5].

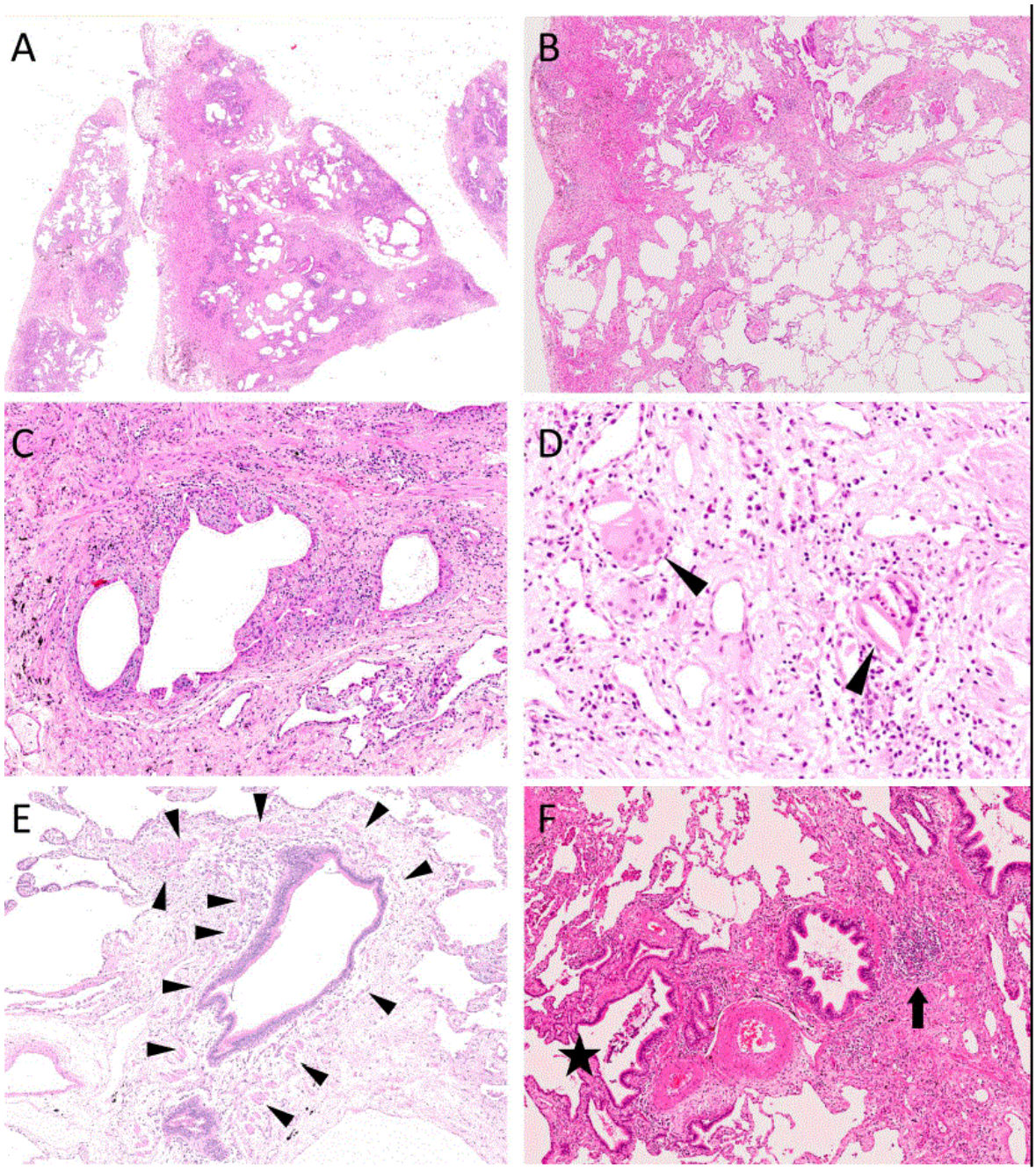


**Figure 2:** Histopathological images of patient 1 and 2 showing usual interstitial pneumonia pattern. Patient 1: A, C, E; Patient 2: B, D, F. (A, B) Low-power view of patchy and peripheral dominant distribution of interstitial fibrosis shows usual interstitial pneumonia patterns. (C) Microscopic honeycomb change is identified in the patient 1. (D) In the tissue from the Segment 8 in the patient 2, giant cells associated with cholesterol clefts (arrow heads) are noted inside the fibrotic stroma. (E, F) Small airway diseases are seen in both patients. In the patient 1, the majority of membranous bronchioles are associated with granulation tissues between surrounding smooth muscle layer (arrow heads) and epithelial cells. Mild cellular infiltration along with fibrosis expanding to lung parenchyma is also noted (E). In the patient 2, Cellular infiltration with interstitial lymphocyte aggregates (arrow) is frequent findings around membranous bronchioles. Fibrosis and peribronchiolar metaplasia (asterisk) are found in several places (F).

Considering the complex clinical backgrounds and the small number of our cases, the effect to the clinical course of IPs by the association of hypothyroidism may be uncertain. They may be affected not only by hypothyroidism but also by the other factors such as associated CTDs or exposure to causative antigens. Needless to say, case reports do not prove anything, and further investigation to determine direct clinical importance of hypothyroidism to IP especially to the cases other than IPF may be needed.

## Disclosure Statement

This report received no financial or material support. Junya Fukuoka is holding stocks of Pathology Institute Corp; Hiroyuki Taniguchi

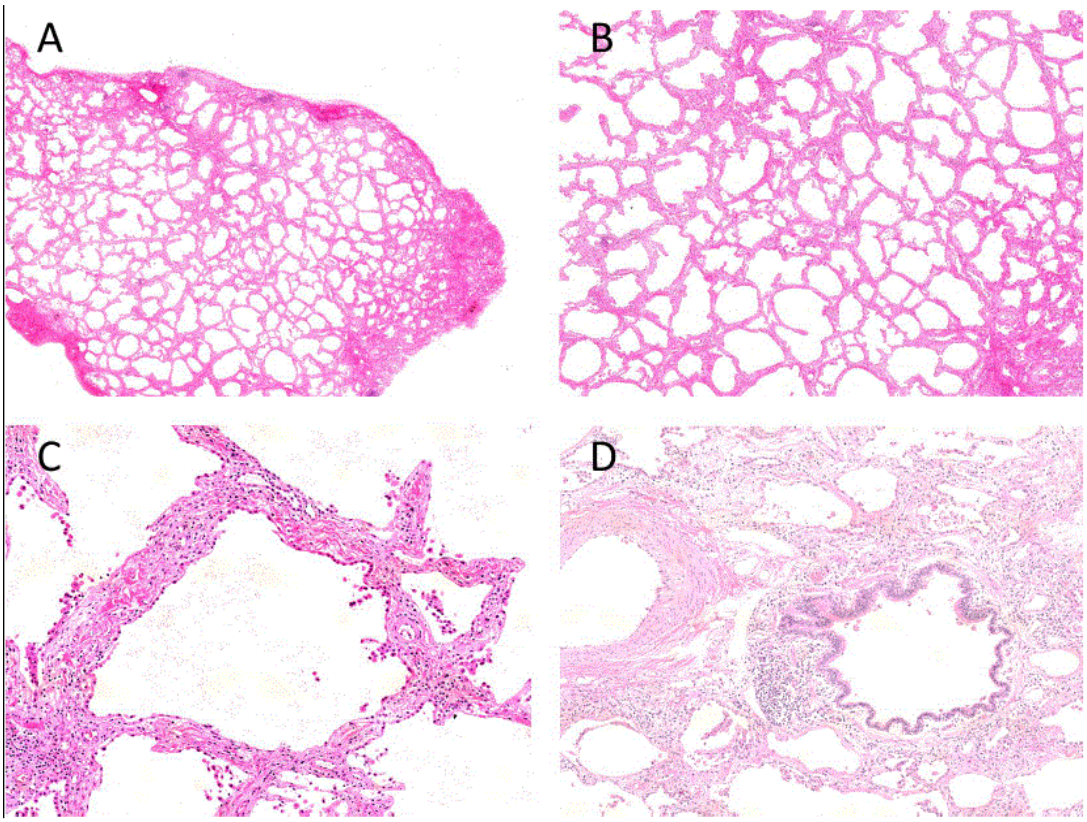


**Figure 3:** Histopathological images of patient 3. (A) Low-power view shows diffuse distribution of the fibrotic disease. (B) Medium-power view shows fairly preserved architecture of the basic lung. (C) High-power view confirms the temporally homogenous dense collagenous fibrosis. Fibroblastic focus is absent. (D) Mild cellular bronchiolitis associated with interstitial lymphoid aggregates is seen frequently.

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