Original article

Chronic Interstitial Pneumonia in Young Patients Undergoing Lung Transplantation or Autopsy: Clinico-radiologic-pathologic Observations from a Single Institution

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Abstract

Purpose

To retrospectively evaluate high-resolution computed tomography (HRCT) findings and clinical diagnoses of chronic interstitial pneumonia (IP) with a poor prognosis in young patients (≤50 years).

Materials and methods

HRCT images of 8 men and 7 women (mean age, 34.8 years) obtained before lung transplantation or autopsy were reviewed. After reviewing whole lung specimens and pathologic diagnoses, all patients were clinically diagnosed according to the 2010 idiopathic pulmonary fibrosis/usual interstitial pneumonia (IPF/UIP) consensus statement.

Results

HRCT images revealed intralobular reticular opacity, air cysts, ground glass opacity, traction bronchiectasis, and interlobular septal thickening. Intralobular reticular opacity was the most extensive finding. Abnormal findings existed predominantly in both the peripheral and lower lung zones in only 1 patient. Classifications of HRCT patterns were "UIP" (n = 2), "inconsistent with UIP" (n = 11), and "indeterminate UIP" (n = 2). Multidisciplinary diagnoses were "IPF/UIP" (n = 1), "possible IPF/UIP" (n = 1), "IP with connective tissue disease" (n = 7), "fibrotic nonspecific IP" (n = 1), and "unclassified IP" (n = 5).

Conclusion

The most extensive HRCT finding was intralobular reticular opacity. Most HRCT

images differed from typical IPF/UIP, and IPF/UIP was uncommon in young patients with chronic IP with a poor prognosis.

Keywords

Chronic interstitial pneumonia, Young, High-resolution computed tomography

Introduction

Chronic interstitial pneumonia (IP) with a poor prognosis is uncontrollable and intractable. Usually, this disease occurs in the elderly (> 50 years), and the majority are clinically diagnosed with idiopathic pulmonary fibrosis (IPF)/usual interstitial pneumonia (UIP). There is no proven pharmacological therapy for IPF/UIP [1] and its prognosis was reported as having a median survival of < 3 years [2, 3]. Conversely, in the young (≤ 50 years), chronic IP with a poor prognosis is not well known.

Nadrous et al. [4] reported that there was no significant difference in clinical, radiological, or pathological features between IPF/UIP in the young versus the elderly; high-resolution computed tomography (HRCT) imaging revealed typical findings of IPF/UIP in 16 of 21 patients < 50 years with IPF/UIP. However, in a clinical situation, HRCT imaging sometimes reveals atypical findings such as IPF/UIP in the young with chronic IP with a poor prognosis. This may be because IPF/UIP is uncommon in the young, unlike in the elderly. An age > 50 years had been 1 minor criterion for a presumptive diagnosis of IPF/UIP based on the 2000 American Thoracic Society (ATS)-European Respiratory Society (ERS) consensus statement [5], although this minor criterion is now removed. However, there have been few large studies of HRCT findings, HRCT diagnosis, and clinical diagnosis of chronic IP with a poor prognosis in the young. In this study, we retrospectively evaluated HRCT findings and clinical diagnoses of chronic IP with a poor prognosis in the young ≤ 50 years.

Materials and methods

Informed consent was obtained from all patients before performing computed tomography (CT). The ethics committee at our institution approved the present retrospective

study and waived the requirement for informed consent for the use of medical patient data.

Patients

Between October 1998 and December 2010, 115 patients with severe lung disease were enrolled in the Japan Organ Transplant Network at our institution. Of these, 17 patients with IP fulfilled all of the following criteria of this study: ≤ 50 years, a treatment period ≥ 1 year, underwent HRCT, and underwent pathologic diagnosis of the whole lung. Two patients were excluded because of unavailable HRCT imaging or iatrogenic IP caused by bone marrow transplantation. Thus, 15 patients (8 men and 7 women; mean age, 34.8 years ± 10.8 [standard deviation]; range, 13–50 years) were included in this study (**Table 1**). Thirteen patients underwent bilateral lung transplantation and 1 underwent single lung transplantation; 1 died of progression of lung disease and underwent autopsy. Four patients had a history of connective tissue disease (CTD), 2 had a familial history of IPF/UIP, and 3 had both. Eight patients did not meet the criteria of lung-dominant CTD [6], and these 8 patients had neither the clinical nor serologic features indicative of IP with autoimmune features, based on the classification criteria [7]. No significant occupational exposure was reported in any patient. Four patients had a smoking history (mean, 30.6 pack-years; range, 13–62.5 pack-years) and the others had never smoked. All patients were resistant to medical therapy and exhibited respiratory depression. They fulfilled 1 of the following conditions: vital capacity or total lung capacity under 60% of the predictive value, hypoxemia at rest under 60 Torr, or grade III to V dyspnea according to the Hugh-Jones classification [8].

Evaluation of HRCT findings

All patients underwent CT (Aquilion 16 or Aquilion 64; Toshiba Medical Systems Corporation, Otawara, Japan; or Light Speed Scanner; GE Healthcare, Milwaukee WI, USA)

within 5 months of undergoing lung transplantation or at autopsy. CT images were obtained at the end of inspiration with patients in the supine position. The HRCT scanning protocol consisted of the reconstruction of 1–3-mm collimation sections with a high spatial frequency algorithm at 1- or 2-cm intervals. CT images were photographed at window settings appropriate for viewing the lung parenchyma (window level, -600 to -700 Hounsfield Units; window width, 1200–1500 Hounsfield Units).

HRCT images were reviewed retrospectively by consensus by 3 thoracic radiologists with 8, 22, and 33 years of experience, respectively. Observers were blinded to the clinical and histological information. Consensus interpretation was simultaneously arrived at by the 3 radiologists by discussion. The presence of the following 10 abnormal HRCT findings were evaluated: intralobular reticular opacity, air cysts (including emphysematous bulla), honeycombing, ground glass opacity (GGO), air space consolidation, traction bronchiectasis, interlobular septal thickening, thickening of the bronchovascular bundle, distortion, and ill-defined centrilobular nodules. These abnormal HRCT findings were defined based on previous definitions [9, 10]. If intralobular reticular opacity overlapped with GGO, intralobular reticular opacity was given priority. If GGO appeared without reticular opacity, the abnormal finding was evaluated as GGO.

The lungs were divided into 6 zones (the upper, middle, and lower zones in both lungs). The upper zone was defined as the lung above the level of the tracheal carina; the lower zone as the lung below the level of the inferior pulmonary vein; and the middle zone as the lung portion between the upper and lower zones. The extent of involvement of abnormal HRCT findings was evaluated visually and independently in each lung zone. For 5 findings (intralobular reticular opacity, air cysts, honeycombing, GGO, and air space consolidation), a score was assigned on

the basis of the percentage of lung parenchyma that showed evidence of abnormal findings and was estimated to the nearest 5% of parenchymal involvement based on the scoring system reported by Sumikawa et al. [11]. The overall percentage of involvement (i.e., median and mean scores of the 6 lung zones) was calculated.

After assessing the presence and extent of abnormal findings, observers evaluated the predominant distribution of the findings. Predominance was assessed as being in the "upper lung zone," "lower lung zone," or as "diffuse lung involvement." Upper lung zone predominance was considered present when most abnormal findings were above the level of the tracheal carina; lower zone predominance was considered present when most abnormal findings were below this level; and diffuse lung involvement was considered present when neither was predominant. The anatomic distribution was also evaluated and noted to be a "peripheral pattern" if there was a predominance of abnormal findings in the outer third of the lung, a "peribronchovascular pattern" if there was predilection for the peribronchovascular areas, or a "diffuse pattern" if there was no predominance. Observers finally classified the cases as a "UIP pattern", "possible UIP pattern", or "inconsistent with UIP pattern," according to the 2010 ATS-ERS consensus statement [1]. In addition, HRCT findings were diagnosed as "indeterminate UIP pattern", according to the categories reported by Chung et al [12], when the findings were not suitable for any of these 3 patterns.

Pathologic and clinical diagnosis

All whole lung specimens were reviewed by a lung pathologist with 34 years of experience. All pathologic specimens were fixed with 10% formalin, embedded in paraffin wax, and stained with hematoxylin-eosin or elastica-Masson stain for conventional microscopy. Pathologic images were obtained through a digital microscope camera (DS-Fi1; Nikon; Tokyo,

Japan). All patients were classified into subgroups according to the 2010 ATS-ERS consensus statement [1]. Thereafter, all patients were clinically diagnosed according to the consensus statement [1]. Patients were diagnosed with "unclassified IP" when both the multidisciplinary diagnosis did not satisfy the criteria for a UIP pattern and the histologic patterns were not classified as any other type of IP.

Statistical analysis

Friedman's test and Wilcoxon's signed-rank test with Bonferroni correction were used to compare the extent of 5 abnormal findings (intralobular reticular opacity, air cysts, honeycombing, GGO, and air space consolidation). Thereafter, we compared the most extensive finding with the other 4 findings. *P*-values < 0.05 for Friedman's test and < 0.0125 for Wilcoxon's signed-rank test with Bonferroni correction were considered statistically significant. All statistical analyses were performed using SPSS software (version 22.0; IBM, Armonk, NY, USA).

Results

A summary of each patient is shown in **Table 1**.

HRCT findings and diagnosis

The mean total extent of parenchymal abnormalities on HRCT was 85% ± 17. Intralobular reticular opacity, air cysts, GGO, traction bronchiectasis, and interlobular septal thickening were present in all patients. HRCT findings are shown in **Table 2**. The most extensive finding was intralobular reticular opacity (median, 37.5%; mean, 39%; interquartile range, 15–65%). The median extent of air cysts, honeycombing, GGO, and air space consolidation was 10% (mean, 19%; interquartile range, 5–20%), 5% (mean, 10%; interquartile

range, 0–10%), 5% (mean, 9%; interquartile range, 5–10%), and 5% (mean, 7%; interquartile range, 5–10%), respectively (**Table 2**). The median maximum size of honeycombing on the HRCT images of the patients was 2.9 mm (mean, 3.5 mm; interquartile range, 1.7–6.0 mm). Only 1 patient (patient 13) had honeycombing >10 mm.

In multiple comparisons, there were significant differences (P = 0.01) by Friedman's test. Intralobular reticular opacity was significantly higher than 3 other findings (vs. GGO [P = 0.003], consolidation [P = 0.001], and honeycombing [P = 0.009]; Wilcoxon's signed-rank test with Bonferroni correction).

Regarding distributions on HRCT images, lower lung predominance, upper lung predominance, and diffuse lung involvement were present in 6, 3, and 6 patients, respectively (**Table 3**). The anatomic distributions were noted to be a peripheral pattern, peribronchovascular pattern, and diffuse pattern in 3, 5, and 7 patients, respectively (**Table 3**). The diagnoses from HRCT findings were UIP pattern (n = 2; **Fig. 1**), inconsistent with UIP pattern (n = 11; **Fig. 2**), and indeterminate UIP pattern (n = 2) (**Table 1**). In 2 patients, HRCT findings were diagnosed as "indeterminate UIP pattern" because the images showed uniformly diffuse abnormal findings in the whole lung (**Fig. 3**).

Pathologic and clinical diagnosis

The pathologic diagnoses were "UIP" (n = 5), "probable UIP" (n = 4), "possible UIP" (n = 1) and "not UIP" (n = 5). Microscopic honeycombing was seen in 13 cases (87%). However, most honeycombing was very small (<2 mm) and included mucus retention. None of patients, except for those diagnosed as having IP with CTD, had pathological features indicative of IP with autoimmune disease. Intralobular reticular opacities on the HRCT images corresponded to marked fibrosis such as bridging fibrosis in the pathologic findings.

Multidisciplinary diagnoses were IPF/UIP (n = 1), possible IPF/UIP (n = 1), IP with CTD (UIP [n = 2], fibrotic nonspecific interstitial pneumonia [NSIP; n = 2], unclassified [n = 3]), fibrotic NSIP (n = 1), and unclassified IP (n = 5).

One patient, whose HRCT diagnosis was "indeterminate UIP pattern" and pathological diagnosis was "probable UIP", was diagnosed as having unclassified IP. In 4 of 8 patients who did not meet the criteria of CTD, pathological findings revealed marked centrilobular fibrosis and bridging fibrosis, which are common in chronic hypersensitivity pneumonitis (CHP). However, because they had neither the other pathologic features nor clinical features of CHP, their pathologic diagnosis was "not UIP" and the multidisciplinary diagnosis was "unclassified IP."

Discussion

Several diseases, such as IPF/UIP, familial IPF, and CTD-related IP were reported as chronic IP in the young < 50 years [4]. IPF/UIP was uncommon in our 15 younger patients; only 2 patients (13%) were clinically diagnosed with IPF/UIP.

Many investigators have already reported detailed HRCT findings of IPF/UIP [11–16]. Honeycombing is a core finding of IPF/UIP and is helpful when distinguishing this disease from other IPs [11]. Abnormal findings exist predominantly in the peripheral and lower lung zones [11, 13, 17]. Additionally, GGO and reticular opacity were reported as other predominant findings [17]. The majority of our HRCT findings were different from typical findings of IPF/UIP. Our results showed an extremely large disease extent (mean, 85%) in the whole lung compared with previous reports (34.1% [11] and 20.17–28.60% [18]). In addition, intralobular reticular opacity was the most extensive finding (median and mean scores, 37.5% and 39%,

respectively). Conversely, the honeycombing score (median and mean, 5% and 10%, respectively) was not so different in extent in the whole lung, in contrast with previous reports (mean score, 4.4% [11] and 7.04% [18]). Furthermore, distributions were different from those of typical IPF/UIP: abnormal findings existed predominantly in both the peripheral and lower lung zones in only 1 patient (7%).

The wider extent of abnormal findings on HRCT images in the present study seemed to be consistent with the findings of end-stage IP. Honeycombing was said to enlarge slowly over time [14, 19]. However, honeycombing on the HRCT images was smaller in our study than in previous reports [19]. Honeycombing was observed pathologically in all patients, except 2 patients, although most honeycombing was smaller than 2 mm and included mucus retention. Therefore, honeycombing could not been detected on HRCT. Although 10 patients were pathologically diagnosed with UIP, probable UIP, or possible UIP, only 2 were diagnosed with UIP pattern based on HRCT images. We presumed that another reason for the discrepancy between the HRCT and pathologic findings was as follows: the craniocaudal distributions were different from those of typical IPF/UIP. Upper or mid-lung predominance is 1 HRCT criterion for "inconsistent with UIP pattern" [1]; upper lung predominance was seen in 3 patients (20%).

Our results showed that reticular opacity was the most common finding on HRCT imaging, although it was unclear whether this finding existed from an early stage because the patients' progress was not followed from an early stage. If reticular opacity exists in the majority of patients with early-stage IP with a poor prognosis but does not exist in patients with IP with a better prognosis, this finding may be a predictor of poor convalescence in younger patients with IP with a poor prognosis.

Familial IPF is a rare condition defined as the presence of IPF in at least 2 family

members [5] and is a distinct entity that should be considered separately from non-familial IPF [20]. In our study, 2 patients (13%) had familial IPF without CTD. Familial IPF accounts for less than 5% of all patients with IPF [21–23]. Nadrous et al. [4] reported that 3 (14%) of 22 IPF/UIP patients < 50 years had familial histories. Nishiyama et al. [24] reported that the HRCT findings of familial IPF resemble those of sporadic IPF; however, familial IPF had a lower prevalence of honeycombing and a lower prevalence of a lower lung predominant distribution than non-familial IPF. Among our 2 patients, there was no case with a typical UIP pattern on HRCT; their abnormalities showed diffuse patterns and diffuse lung involvement.

Patients with CTD-related UIP were younger than patients with IPF/UIP [18, 25]. Patients may subsequently manifest overt features of an underlying CTD that was subclinical at the time IP was diagnosed [25]. Patients with CTD-related IP have a better prognosis than patients with idiopathic IP [26, 27]. However, IP is referred to as 1 factor related to a poor CTD prognosis [28]. The present study included 7 patients (47%) with a history of CTD. No patient except 1 was diagnosed with UIP pattern based on HRCT findings, while 5 of 7 were diagnosed as having UIP/probable UIP based on pathologic findings. This discrepancy may be because honeycombing was hidden in reticular shadows on HRCT images. Kono et al. [25] reported that HRCT imaging showed no statistically significant difference between the CTD-related UIP and IPF/UIP groups with regard to the presence or distribution of each finding. Conversely, Song et al. [18] reported that patients with CTD-related IP often had atypical IPF/UIP patterns and had marginally significantly lower scores for honeycombing compared with IPF/UIP patients; their results were similar to ours.

This retrospective study enrolled a small number of patients, and there was the potential for a patient selection bias, as all patients were from a single institution. Only a small

proportion of younger patients with chronic IP with a poor prognosis were evaluated. Three radiologists simultaneously performed a consensus interpretation of evaluation of HRCT findings. The results may have been affected by the senior radiologist's interpretation. It is very difficult to diagnose CHP histologically [29]. Four patients had the pathological findings of centrilobular fibrosis and bridging fibrosis; however, the multidisciplinary diagnosis was unclassified IP. Therefore, patients with CHP may have actually been included. Our study was not designed to compare the clinical, radiological, and pathological features of the young with IP with a poor prognosis with those with a better prognosis. Additionally, only patients whose whole lung was obtained by transplantation or autopsy were enrolled. Thus, our study enrollment decreased. However, this study is interesting and important because there was no previous report evaluating radiological, pathological, and clinical diagnoses using the whole lung in the young with chronic IP with a poor prognosis. The specimen obtained by surgical biopsy was an evaluation of only a part of the organ, and the condition of the lung at autopsy is worse because of post mortem changes.

In conclusion, the most extensive HRCT finding was intralobular reticular opacity. Most HRCT images differed from typical IPF/UIP. IPF/UIP was uncommon in the young with chronic IP with a poor prognosis.

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Figure legends

Figure 1. Idiopathic pulmonary fibrosis (IPF)/usual interstitial pneumonia (UIP) in a 50-year-old man (patient 13).

The high-resolution computed tomography image shows honeycombing (arrow) and intralobular reticular opacity (arrowhead) in a predominantly peripheral distribution in the lower lobe of the right lung.

Figure 2. Unclassified interstitial pneumonia in a 30-year-old man (patient 6).

A) The high-resolution computed tomography image shows diffuse reticulation and small air cysts (arrows) in the peripheral zone in the middle and lower lobe of the right lung. The diagnosis is "inconsistent with usual interstitial pneumonia (UIP) pattern."

B) The pathologic specimen is stained with hematoxylin-eosin. The peripheral area of dense fibrosis contains bronchiectatic spaces (arrows). The internal lung tissue is divided by fibrosis connecting bronchioles or interlobular septa, which appears as "bridging fibrosis" (arrowheads). Normal lung tissue remains in fibrous connection. The patient's pathological diagnosis is "not UIP"

Figure 3. Unclassified interstitial pneumonia in a 44-year-old woman (patient 8).

A) The high-resolution computed tomography image shows diffuse reticulation and traction bronchiectasis (arrow) without macroscopic honeycombing in a random distribution in the middle lobe of the right lung, and is diagnosed as "indeterminate usual interstitial pneumonia (UIP) pattern."

B) The pathologic image of the hematoxylin-eosin stained sample shows honeycombing

(arrows) in the peripheral zone (left side of the image) and inflammatory and fibrous changes (arrowheads) without honeycombing in the internal zone (right side of the image), and is diagnosed as "probable UIP (atypical)." The borders of the 2 zones are unclear. The size of honeycombing is very small, as seen in idiopathic pulmonary fibrosis.

Table 1

Table 1. Summary of Information on Patients, HRCT Diagnosis, Pathologic Diagnosis, and Multidisciplinary Diagnosis

Case No.	Age (y)/ Sex	CTD	Familial history of interstitial pneumonia	HRCT diagnosis (pattern)	Pathologic diagnosis	Multidisciplinary diagnosis
1	38/F	–	Yes	indeterminate UIP	UIP	possible IPF/UIP
2	46/M	rheumatoid arthritis	–	UIP	UIP	IP with CTD (UIP pattern)
3	29/F	unclassified CTD	–	inconsistent with UIP	probable UIP	IP with CTD (fibrotic NSIP pattern)
4	42/F	–	Yes	inconsistent with UIP	not UIP	unclassified IP
5	13/M	–	–	inconsistent with UIP	probable UIP	fibrotic NSIP
6	30/M	–	–	inconsistent with UIP	not UIP	unclassified IP
7	50/F	–	–	inconsistent with UIP	not UIP	unclassified IP
8	44/F	–	–	indeterminate UIP	probable UIP	unclassified IP
9	22/M	juvenile rheumatoid arthritis	–	inconsistent with UIP	UIP	IP with CTD (unclassified)
10	21/M	juvenile rheumatoid arthritis	Yes	inconsistent with UIP	probable UIP	IP with CTD (unclassified)
11	38/M	systemic sclerosis	Yes	inconsistent with UIP	UIP	IP with CTD (UIP pattern)
12	32/F	–	–	inconsistent with UIP	not UIP	unclassified IP
13	50/M	–	–	UIP	UIP	IPF/UIP
14	32/F	microscopic polyangiitis	Yes	inconsistent with UIP	not UIP	IP with CTD (unclassified)
15	35/M	Dermatomyositis	–	inconsistent with UIP	possible UIP	IP with CTD (fibrotic NSIP pattern)

HRCT = high-resolution computed tomography, CTD = connective tissue disease.

UIP = usual interstitial pneumonia, IPF = idiopathic pulmonary fibrosis, IP = interstitial pneumonia, NSIP = nonspecific interstitial pneumonia.

Table 2

Table 2. HRCT Findngs in All Patients

Findings	Number of patients (%)	Median extent (%)	Interquartile range of extent (%)
Intralobular reticular opacity	15 (100)	37.5	15–65
Air cysts	15 (100)	10	5–20
Ground glass opacity	15 (100)	5	5–10
Air space consolidation	13 (87)	5	5–10
Honeycombing	12 (80)	5	0–10
Traction bronchiectasis	15 (100)	–	–
Interlobular septal thickening	15 (100)	–	–
Distortion	12 (80)	–	–
Thickening of bronchovascular bundle	6 (40)	–	–
Centrilobular nodules	5 (33)	–	–

HRCT = high-resolution computed tomography

Table 3

Table 3. Distribution of HRCT Abnormal Findings in Whole Lung

	Peripheral pattern	Peribronchovascular pattern	Diffuse pattern	Total (%)
Upper lung zone predominance	1	0	2	3 (20)
Lower lung zone predominance	1	5	0	6 (40)
Diffuse lung involvement	1	0	5	6 (40)
Total (%)	3 (20)	5 (33)	7 (47)	15 (100)

Figure 1

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Figure 2A

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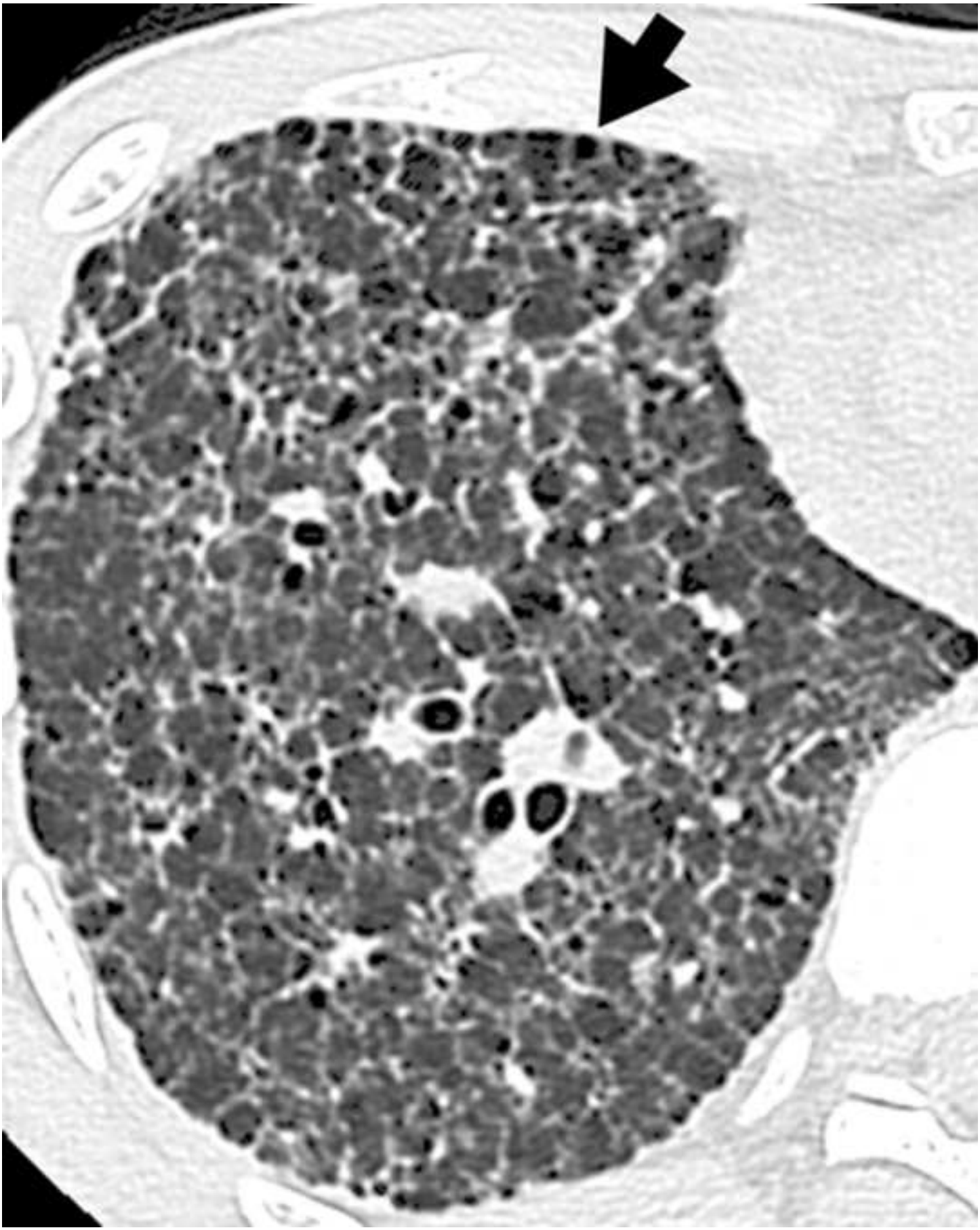

Figure 2B

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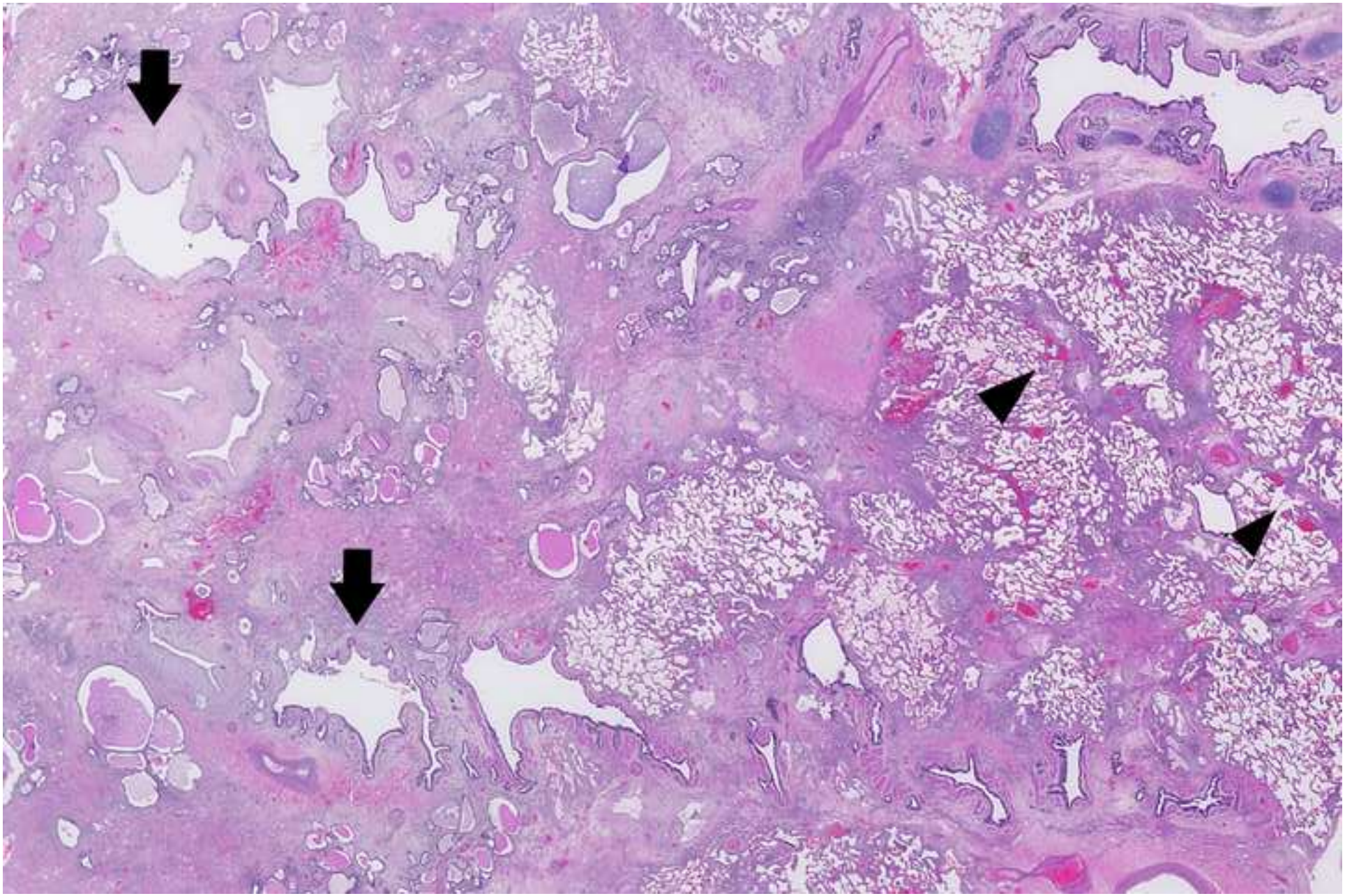

Figure 3A

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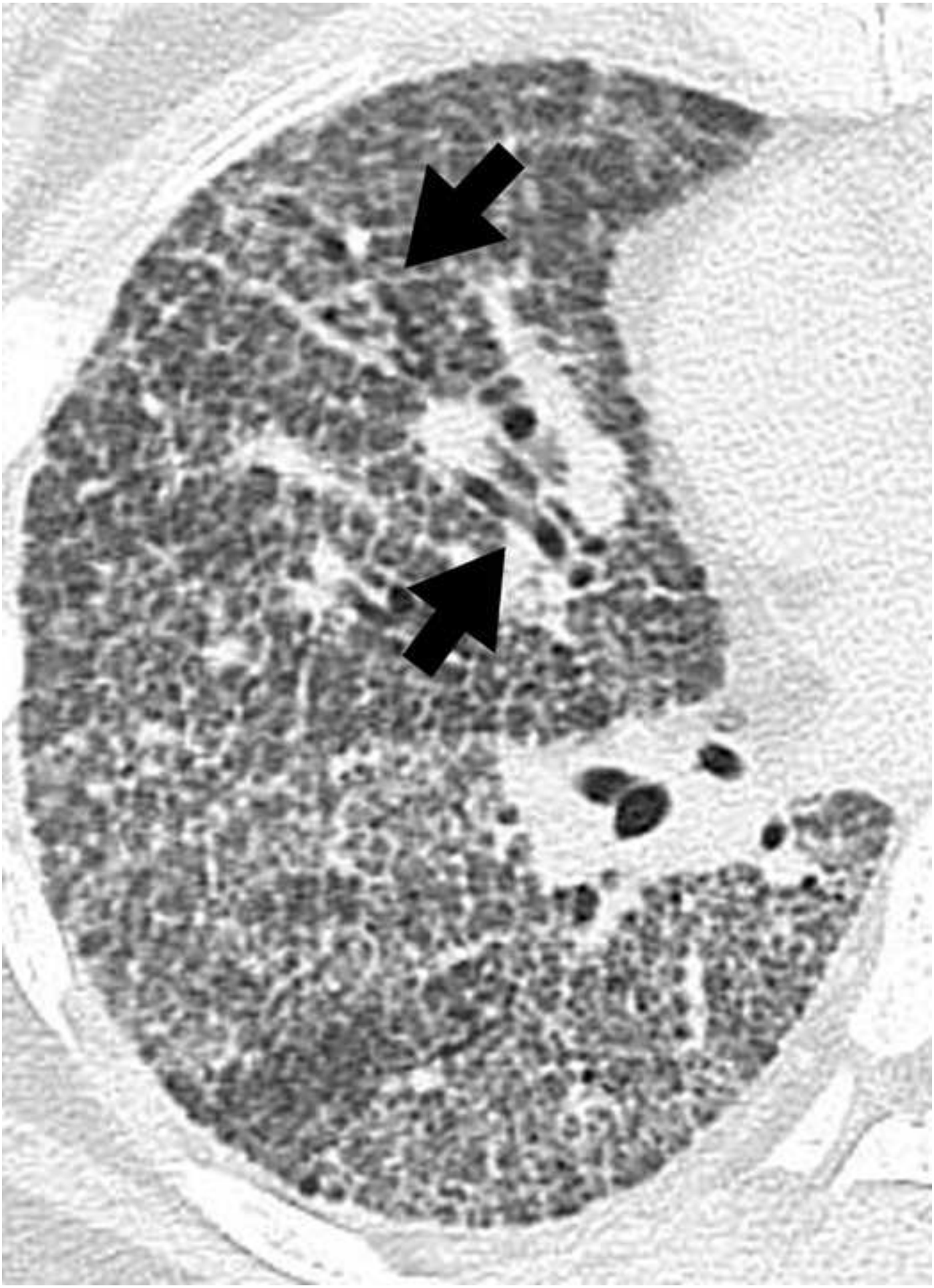

Figure 3B

Click here to download Figure Figure 3B.tif