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Radiologic-Pathologic Correlation

# Usual interstitial pneumonia end-stage features from explants with radiologic and pathological correlations☆

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is the most frequent and severe idiopathic interstitial pneumonia, with typical high-resolution computed tomography (HRCT) features and histologic pattern of usual interstitial pneumonia (UIP); its main differential diagnosis is fibrotic nonspecific interstitial pneumonia (F-NSIP). Usual interstitial pneumonia was mainly described from lung biopsies, and little is known on explants. Twenty-two UIP/IPF explants were analyzed histologically and compared with previous open lung biopsies (OLBs; n = 11) and HRCT (n = 19), when available. Temporospatial heterogeneity and subpleural and paraseptal fibrosis were similarly found in UIP/IPF explants and OLB (91%-95%). Fibroblastic foci were found in 82% of OLBs and 100% of explants, with a higher mean score in explants ($P = .023$). Honeycombing was present in 64% of OLBs and 95% of explants, with a higher mean score in explants ($P = .005$). Almost 60% of UIP/IPF explants showed NSIP areas and 41% peribronchiolar fibrosis; inflammation, bronchiolar metaplasia, and vascular changes were more frequent in UIP/IPF explants; and Desquamative Interstitial Pneumonia (DIP)-like areas were not common (18%-27%). Numerous large airspace enlargements with fibrosis were frequent in UIP/IPF explants (59%). On HRCT, honeycombing was observed in 95% of the cases and ground-glass opacities in 53%, correlating with NSIP areas or acute exacerbation at histology. Six patients had combined IPF and emphysema. Lesions were more severe in UIP/IPF explants, reflecting the worsening of the disease. Usual interstitial pneumonia/IPF explants more frequently presented with confounding lesions such as NSIP areas, peribronchiolar fibrosis, and airspace enlargements with fibrosis sometimes associated with emphysema.



## 1. Introduction

Idiopathic pulmonary fibrosis (IPF) is the most frequent and the most severe idiopathic interstitial pneumonia. It is a chronic and progressive fibrotic disease limited to the lung, which predominates in males and smokers. Idiopathic pulmonary fibrosis is a clinicopathologic entity with a dismal prognosis and no response to anti-inflammatory therapy. According to the 2011 ATS/ERS/JRS/ALAT guidelines, the diagnosis of IPF is based on high-resolution computed tomography (HRCT) findings, including reticulations and honeycombing predominating in subpleural regions, with or without traction bronchiectases, a histologic pattern of usual interstitial pneumonia (UIP), and the exclusion of known causes of interstitial pneumonias, especially environmental exposure, medication, or systemic disease [1]. The histologic pattern of UIP is defined by dense fibrosis responsible for architectural distortion, subpleural and paraseptal honeycombing, patchy involvement of the lung with areas of normal lung, fibroblastic foci, and none of the following criteria, that is, hyaline membranes, organizing pneumonia (except in the setting of an acute exacerbation [AE] of the disease), marked inflammation, predominant airways changes, and other features suggesting an alternative diagnosis. However, because of interobserver discrepancies between pathologists reported in several studies and the possibility of sampling issues, histopathology is no longer the criterion standard for the diagnosis of IPF [2–6]. Pathologists are asked to describe the pattern of interstitial lung disease rather than to make definite diagnosis, patterns being further discussed along with clinicoradiologic findings and included in a final consensus diagnosis [1].

*Abbreviations:* IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia; F-NSIP, fibrotic nonspecific interstitial pneumonia; OLB, open lung biopsy.

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The main clinical and histologic differential diagnosis of UIP/IPF is represented by nonspecific interstitial pneumonia (NSIP) [7], which is associated with a better prognosis and response to corticosteroids [8,9]. In contrast to UIP, the NSIP pattern is characterized histologically by uniform distribution of interstitial inflammation and fibrosis lacking the patchwork involvement of UIP. However, the NSIP fibrotic pattern may be difficult to distinguish from the UIP pattern.

As most histologic criteria for interstitial lung diseases have been described from open lung biopsies (OLBs), the present study was conducted to describe the end-stage histologic features of UIP on explants, to compare them with previous OLB when available, and to make a correlation between radiology, OLB, and explants.

## 2. Materials and methods

Twenty-two patients transplanted for pulmonary fibrosis were identified from the University Hospital of Grenoble files between 1991 and 2009 and from the University Hospital Lyon-Est files between 2000 and 2009.

Lung explants' specimens were available for analysis in all cases. In addition, OLBs performed prior to the lung transplantation were available for review in 11 cases (50%). All biopsies and explants were retrospectively analyzed by 4 pathologists (M.R., S.L., F.T., L.C.) blinded to the clinicoradiologic data. The slides were analyzed with a multiviewing microscope, and a consensual diagnosis was made. An average of 3 hematoxylin-eosin-saffron slides (ranging from 1 to 7) per OLB and 11 hematoxylin-eosin-saffron slides (ranging from 2 to 18) per explant were available. The histologic criteria for UIP were temporospatial heterogeneity, subpleural and paraseptal fibrosis, honeycombing, fibroblastic foci, and areas of normal lung; other findings included smooth muscle metaplasia, bronchiolar metaplasia, vascular changes (posthypoxic pulmonary arterial hypertension [PAH]), inflammation and germinal centers, bronchiolar fibrosis, organizing pneumonia, diffuse alveolar damage, alveolar macrophage accumulation (DIP-like areas) and NSIP areas (observed in more than 1 lobule), dust deposition (except carbons), and granulomas. In addition, the presence of enlarged and restructured airspaces measuring up to 5 mm we called *airspace enlargement with fibrosis* (AEF) was also recorded. For most criteria, a semiquantitative scoring was made (Table 1). The histologic patterns retained were UIP, probable AE of UIP, fibrotic nonspecific interstitial pneumonia (F-NSIP), UIP/F-NSIP (when it was not possible histologically to decide between UIP and F-NSIP), or unclassifiable fibrosis.

High-resolution computed tomography (HRCT) was available in 19 cases. Two thoracic radiologists (G.F., A.J.), unaware of the clinical data and histology, reviewed retrospectively the CT scans. Only 1 HRCT per patient was analyzed, corresponding to the last HRCT performed before lung transplantation. According to the 2011 ATS/ERS/JRS/ALAT consensus [1], HRCT findings characteristic of IPF were combination of reticular opacities, honeycombing in subpleural, basal predominant distribution with or without subpleural traction bronchiectasis, and absence of peribronchovascular nodules or micronodules, cysts or consolidation, extensive ground-glass opacities, diffuse mosaic attenuation/air-trapping as well as upper or mid-lung predominance, or peribronchovascular predominance of the lesions. Special attention was given to honeycombing, focal ground-glass opacities, emphysema, and airspace enlargement with fibrosis. Radiologic diagnoses included IPF, probable AE of IPF, F-NSIP, IPF/F-NSIP, or unclassifiable fibrosis.

Clinical features included associated diseases, tobacco exposure, and pulmonary function tests: forced vital capacity, forced expiratory volume in 1 second, total lung capacity (TLC), diffusing capacity of the lung for carbon monoxide ($Dl_{CO}$), diffusion coefficient, blood oxygen partial pressure, and carbon dioxide partial pressure. All patients with domestic and occupational environmental exposures, drug toxicity, or connective tissue disease were excluded.

**Table 1**
Pathological criteria analyzed in OLBs and explants

| Pathological criteria | Yes/No or score |
|---|---|
| Temporospatial heterogeneity | Yes/No |
| Subpleural and paraseptal fibrosis | Yes/No |
| Honeycombing | 0;1;2 |
| Fibroblastic foci | 0;1;2;3 |
| Areas of normal lung | Yes/No |
| Smooth muscle metaplasia | 0;1;2 |
| Bronchiolar metaplasia | 0;1;2 |
| Vascular changes | 0;1;2 |
| Presence of adipocytes | 0;1;2 |
| Inflammation | 0;1;2;3 |
| Germinal centers | Yes/No |
| Organizing pneumonia | 0;1;2 |
| Diffuse alveolar damage | 0;1;2 |
| Alveolar macrophage accumulation/DIP-like areas | 0;1;2 |
| NSIP-like areas | Yes/No |
| Peribronchiolar fibrosis | Yes/No |
| Dust deposits | Yes/No |
| Granulomas | Yes/No |
| AEF | Yes/No |

Following the recommendations of the evidence-based guidelines for diagnosis and management of IPF by the ATS/ERS/JRS/ALAT statement [1], the final diagnosis was proposed on the basis of multidisciplinary discussion between pulmonologists, radiologists, and pathologists. These final diagnoses were UIP/IPF or AE of UIP/IPF (Table 2). Statistical analysis was done using the Student *t* test with the software Origin.6 (OriginLab, Wheeling, IL, USA).

## 3. Results

### 3.1. Clinical data

Fourteen patients (64%) were smokers, and 20 were men and 2 were women; the mean age at the time of lung transplantation was 55 years. One patient had been formerly treated for tuberculosis, and for 3 patients, lung cancer (1 squamous cell carcinoma and 2 adenocarcinomas) was incidentally found on explants (Table 2).

The mean data of pulmonary function before transplantation were as follows: forced vital capacity 43.1% ± 12.0% of predicted; forced expiratory volume in 1 second, 44.9% ± 12.2% predicted; TLC, 43.6% ± 8.4% predicted; $DL_{CO}$, 32% ±15.9% predicted; diffusion coefficient, 74.7% ± 32.3% predicted; blood oxygen partial pressure, 8.2 ±2.0 kPa; and carbon dioxide partial pressure, 5.5 ± 1.22 kPa in room air. Delay between pulmonary function tests and transplantations ranged from 0.5 to 17 months, with an average of 6 months and a median of 5.5 months. $Dl_{CO}$ values were not available when patients were too dyspneic to perform apnea testing. In those cases, the last $Dl_{CO}$ performed before transplantation was retrieved.

#### 3.1.1. Final multidisciplinary diagnosis

After a combination of clinical data, HRCT, and histologic patterns on OLB when available and/or on explants, the final diagnoses were UIP/IPF for 19 cases and AE of UIP for 3 (Table 2).

### 3.2. Pathological findings in the UIP/IPF group and comparison between biopsies and explants

The mean delay between OLB and transplantation was 13 months (2-120 months). A heterogeneous temporospatial involvement of the lung was observed in 91% (10/11) of the OLB and in 91% (20/22) of the explants. Subpleural and paraseptal distribution of fibrosis was also observed in 91% (10/11) of OLB and 95% of explants. Fibroblastic