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Microscopic organizing pneumonia and cellular non-specific interstitial pneumonia are widespread in macroscopically normal-appearing lung tissue in idiopathic pulmonary fibrosis

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Idiopathic pulmonary fibrosis (IPF), characterized histologically by usual interstitial pneumonia (UIP), is the most severe form of idiopathic interstitial pneumonia. The various forms of idiopathic interstitial pneumonia, including IPF/UIP, non-specific interstitial pneumonia (NSIP), and organizing pneumonia (OP) are generally classified into precisely defined, non-overlapping distinct disorders.¹ Although peripheral and basilar UIP is essential to the diagnosis of IPF, it remains unknown whether UIP represents a unique, pathogenic histologic pattern or represents the end-result of several histologic processes. This lack of a complete understanding of lung injury patterns in IPF is likely due to few if any lung biopsy samples obtained in patients with early sub-clinical disease, and to difficulties with sampling more normal-appearing areas with surgical lung biopsy. Understanding lung histology patterns throughout the IPF lung may potentially identify early patterns of injury and assist with insight into disease pathogenesis.

Methods

We sought to histologically characterize uninvolved or less involved regions in 23 IPF patients by sampling macroscopically normal-appearing tissue in lung explants. Prior to transplant, 21 of 23 patients had end-stage disease without abrupt deterioration, and 2 patients had sub-acute deterioration. No patients were on extracorporeal membrane oxygenation pre-transplant, and no patients had explant histology consistent with an acute exacerbation of IPF. By gross examination of the 23 explants (Figure S1, available on the jhltonline.org Web site), 89 macroscopically normal-appearing areas were identified and

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Supplementary material

Supplementary data are available in the online version of this article at www.jhltonline.org.

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sampled. Microscopic analysis with hematoxylin and eosin and quantitative assessments of foci of OP ($>100\ \mu\text{m}$) and cellular NSIP were performed on one tissue section from each area. Immunohistochemistry was performed using α -smooth muscle actin (α -SMA) and desmin. Tissue sections from healthy donor lungs were used as controls. Data represented as continuous variables are reported as median (first quartile, third quartile). Statistical analyses were performed using the Mann-Whitney *U* test. The study was reviewed and approved by the University of Maryland Institutional Review Board (HP-44077).

Results

All 23 patients (Caucasian: 18 men, 2 women; African American: 2 men, 1 woman) had idiopathic disease and definite UIP on lung explant analysis. Median age was 66 (64, 71) years, and time from diagnosis to transplant was 26 (18, 43) months. Five patients were lifelong non-smokers, and 18 patients had a 20 (15, 38) pack-year history of smoking. Medication use included prednisone ($n = 18$), N-acetylcysteine ($n = 9$), and azathioprine ($n = 6$). No patient received pirfenidone or nintedanib.

At the time of transplant, forced vital capacity was 50% (38%, 59%) predicted, diffusion capacity of the lung for carbon monoxide was 35% (26%, 43%) predicted, and mean pulmonary artery pressure was 23 (20, 28) mm Hg. Chest computed tomography imaging patterns demonstrated definite UIP ($n = 9$), possible UIP ($n = 8$), or inconsistent UIP ($n = 6$), and thus, 17 patients had definite IPF and 6 patients had possible IPF.¹

Histologic findings from the 89 macroscopically normal-appearing areas are reported in Table 1. When compiled per patient, all 23 patients demonstrated microscopic foci of OP, and the numerical count was 31 (29, 43) foci of OP per patient. Cellular NSIP was identified in 22 of 23 patients, and the percentage tissue involvement was 35% (19%, 66%) per patient. Microscopic foci of OP and cellular NSIP from representative patients are shown in Figure 1.

When compiled per tissue section, 52 and 37 sections were obtained from central and peripheral (sub-pleural) areas, respectively. There were 822 total microscopic foci of OP observed in the 89 sections, which were interstitial (72%), paraseptal (16%), or peri-bronchiolar (12%) in location. There were 8 (5, 14) foci of OP per tissue section and 4.4 (2.2, 7.0) per tissue section/ cm^2 . For cellular NSIP, 55 of 89 sections had $>25\%$ involvement, and there was 40% (10%, 80%) cellular NSIP involvement per tissue section. Areas of UIP were seen in some sections, but were absent or minimal in the majority. Twelve tissue sections (median dimension, 1.3 [1.0, 1.4] cm^2) from three healthy donor lungs were used as controls, and no microscopic foci of OP or cellular NSIP were observed in any of the control sections analyzed.

α -SMA staining (myofibroblasts) was assessed in five microscopic foci of OP from one representative section in each patient from a macroscopically normal-appearing area. All 115 foci of OP assessed expressed α -SMA: 66 intensely, 42 moderately, and 7 mildly. Desmin staining was performed in one representative section from 14 patients, and aberrant

smooth muscle cells within the lung distinct from normal structures were identified in 8 of 14 sections analyzed.

Histologic findings in macroscopically normal-appearing tissue were correlated with clinical variables (Table S1, available at www.jhltonline.org). Higher amounts of cellular NSIP were associated with fewer pack-years of smoking ($p = 0.003$), absence of prednisone use ($p = 0.004$), lower forced vital capacity ($p = 0.002$), and pulmonary hypertension ($p = 0.011$). There was no difference in α -SMA staining intensity between patients with definite IPF and possible IPF ($p = 0.74$).

Discussion

Although IPF is characterized by UIP histology in macroscopically scarred areas, we found widespread α -SMA-expressing foci of OP and cellular NSIP in macroscopically normal-appearing areas. These findings are likely to be perceived as unexpected findings since the various forms of interstitial pneumonia (IPF/UIP, NSIP, and OP) are generally classified into rather precisely defined, distinct non-overlapping disorders.¹ These findings raise several possibilities that have not been significantly considered previously. First, although IPF manifests predominantly in peripheral and basal regions, our data show that lung injury is actually widespread throughout the lung (centrally and peripherally), suggesting that peripheral and basal regions may be merely those most susceptible to permanent scarring, possibly resulting from differences in static and dynamic transpulmonary pressure gradients throughout the lung.^{2,3}

Second, the histologic findings of OP, cellular NSIP, and UIP may represent a continuum of lung injury response, with OP and cellular NSIP representing earlier phases of injury and UIP representing a later stage.^{4,5}

Third, although OP and cellular NSIP are generally regarded as having relatively good prognoses, our patients had very poor prognoses (required lung transplantation a median of 26 months after diagnosis), suggesting that prognosis is likely more a result of the etiology and/or temporal nature (finite vs ongoing) of lung injury rather than a specific histologic pattern.

The presence of UIP in any tissue section has been associated with poor outcomes and is thus helpful clinically;⁵ however, the classification of patients as IPF/UIP, NSIP, or OP is likely an oversimplification when attempting to understand disease mechanisms and design therapies for patients with idiopathic interstitial pneumonia.

Our study has several potential limitations. Our patient group consisted almost entirely of Caucasian men, although IPF does occur most commonly in this demographic. Second, we did include six patients with possible IPF, but our statistical analyses showed no differences in histologic findings between definite IPF and possible IPF patients. Third, the use of explant tissue has been criticized at times as representing “burned out” or end-stage disease, but our findings actually demonstrated active inflammation (cellular NSIP) and active lung injury response (foci of OP) in the IPF explant.

In conclusion, although IPF is manifested by peripheral and basilar UIP, we observed widespread microscopic foci of OP and cellular NSIP in the majority of the lung sections from macroscopically normal-appearing and often centrally located areas of IPF explants. Our observations raise numerous molecular possibilities regarding mechanisms of disease, and further exploration of these findings may lead to better understanding of IPF and, ultimately, to more efficacious therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Travis WD, Costabel U, Hansell DM, et al. ATS/ERS Committee on Idiopathic Interstitial Pneumonias. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med*. 2013; 188:733–48. [PubMed: 24032382]
2. Leslie KO. Idiopathic pulmonary fibrosis may be a disease of recurrent, tractional injury to the periphery of the aging lung: a unifying hypothesis regarding etiology and pathogenesis. *Arch Pathol Lab Med*. 2012; 136:591–600. [PubMed: 22136526]
3. Todd NW, Atamas SP, Luzina IG, Galvin JR. Permanent alveolar collapse is the predominant mechanism in idiopathic pulmonary fibrosis. *Expert Rev Respir Med*. 2015; 9:411–8. [PubMed: 26165208]
4. Strieter RM. Pathogenesis and natural history of usual interstitial pneumonia: the whole story or the last chapter of a long novel. *Chest*. 2005; 128(5 Suppl):526–32S.
5. Flaherty KR, Travis WD, Colby TV, et al. Histopathologic variability in usual and nonspecific interstitial pneumonias. *Am J Respir Crit Care Med*. 2001; 164:1722–7. [PubMed: 11719316]

Figure 1.

Histologic findings from macroscopically normal-appearing tissue from representative patients, with each hematoxylin and eosin horizontal pair representing low and high magnification images from a single patient. Two representative patients are shown in panels A and B and in C and D, with low magnification demonstrating preserved background lung architecture, numerous foci of organizing pneumonia (OP; arrows) but without cellular non-specific interstitial pneumonia (NSIP), and high magnification showing well-formed foci of OP approximately 400 to 1,000 μ m in size. A third patient is shown in panels E and F, which demonstrate widespread cellular NSIP, with numerous inflammatory cells within alveolar

septae 50 to 100 μm in thickness, and numerous foci of OP (arrows, inset). A fourth patient is shown in panels G and H, which demonstrate widespread cellular NSIP but without identifiable foci of OP. Panels I and J demonstrate intense α -smooth muscle actin staining of two representative foci of OP: panel I from the patient in panels A and B, and panel J from the patient in panels C and D.

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Table 1

Microscopic Findings (Hematoxylin and Eosin) in Tissue Sections From Macroscopically Normal-Appearing Areas

Variable	No. (%) or median (1st, 3rd)
Compiled per patient	
Patients	23
Tissue sections per patient	4 (4, 4)
Foci of OP, total numerical count per patient	31 (29, 43)
No. of patients with numerical foci of OP counts	
>40 foci of OP	7
21–40 foci of OP	14
1–20 foci of OP	2
No foci of OP	0
Cellular NSIP, percentage involvement per patient	35 (19, 66)
No. of patients with cellular NSIP percentage	
>90% involvement	2
76%–90% involvement	3
26%–75% involvement	11
1%–25% involvement	6
No involvement	1
Compiled per tissue section	
Total tissue sections	89
Central	52
Peripheral (sub-pleural)	37
Section dimension, cm ²	2.0 (1.5, 2.4)
Total numerical count of foci of OP, all sections	822
Interstitial location	588 (72)
Paraseptal location	134 (16)
Peri-bronchiolar location	100 (12)
Foci of OP, numerical count per section	8 (5, 14)
No. of sections with numerical foci of OP counts	
>15 foci of OP	14 (16)
6–15 foci of OP	51 (57)
1–5 foci of OP	18 (20)
No foci of OP	6 (7)
Foci of OP, numerical count per section per cm ² tissue	4.4 (2.2, 7.0)
Cellular NSIP, percentage involvement per section	40 (10, 80)
No. of sections with cellular NSIP percentage	
>90% involvement	9 (10)
76%–90% involvement	15 (17)
26%–75% involvement	31 (35)
1%–25% involvement	22 (25)

Variable	No. (%) or median (1st, 3rd)
No involvement	12 (13)
No. of sections with UIP percentage	
No involvement	29 (32)
1%–10% involvement	32 (36)
11%–33% involvement	13 (15)
34%–75% involvement	14 (16)
>75% involvement	1 (1)

NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; UIP, usual interstitial pneumonia.