A better understanding of the HRCT features of Idiopathic Pulmonary Fibrosis using micro-computed tomography.

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Learning objectives

HRCT changes in patients with early and even advanced idiopathic pulmonary fibrosis (IPF) often present as a repeating almost geometrical (reticular) pattern, suggesting disease/damage that expands following the contours of a matching anatomic structure. The purpose of this study is to better understand the underlying lung changes responsible for the HRCT features of IPF. We have used micro-CT to study these HRCT changes and tried to determine the relationship between these abnormalities and the components of the secondary pulmonary lobule which is generally considered the basic HRCT anatomical unit of the lung parenchyma.
Background

In 2002 and 2013 the American Thoracic Society and European Respiratory Society set up an international multidisciplinary consensus classification of the different idiopathic interstitial pneumonias, obtained from an integrated clinical, radiologic and pathologic approach (1, 2). In this document imaging is stated to play a crucial role in the diagnosis of IPF. When typical HRCT features are present, diagnosis is often possible avoiding an invasive biopsy. Unfortunately in many cases diagnosis is hampered by the absence of typical or presence of atypical HRCT signs. A closer look at the CT features of IPF by studying HRCT - micro-CT correlates, helps to better understand the structural abnormalities of the lung and their typical and atypical presentation on HRCT. Using the preparation method described by McDonough et al. (3) small cores of lung tissue were taken from an inflated explanted lung of a patient with end stage IPF and scanned using a SkyScan 1172 micro-CT. The micro-CT images of these small cores were then correlated with the pre-transplant in vivo HRCT. Areas with a different severity of disease were studied and specially developed software (AIR) was used to exactly match the areas of both CT’s. Special attention was given to the relationship between the pathology and the anatomy of the secondary pulmonary lobule.
Imaging findings OR Procedure details

No visible abnormalities on HRCT

Some cores were taken in regions without visible changes on HRCT. The encircled region on the HRCT image in figure 1A delineates the area where a core of lung tissue was taken. A large bronchus with accompanying artery is seen (blue and red arrow) surrounded by an area free of abnormalities. On micro-CT (Fig. 1B) the large bronchus with bifurcation and the accompanying artery can be recognized. Although HRCT seemed normal, some abnormalities can be seen on micro-CT: areas of increased density surrounding the bronchus (yellow arrows) and deformed alveoli/alveolar airspaces (green arrows).

Minor abnormalities on HRCT

On figure 2A a HRCT image with a centrally located vessel (red arrow) and some small densities at the periphery of the core (yellow arrows) is seen. On micro-CT (Fig. 2B) we were able to identify the terminal bronchiole (blue arrowhead) with its accompanying arteriole (red arrowhead), with the first much broader than the latter. Parts of secondary pulmonary lobules surrounding this bronchovascular bundle were also visible (purple interrupted lines). At the septa of these secondary pulmonary lobules multiple small islands of increased density (yellow arrows) can be seen. The alveoli surrounding these dense islands have a deformed appearance, as if traction is exerted on them (green arrows).

Linear/ reticular pattern

Figure 3 and 4 are images from the same core, with figure 3 picturing a more cranial level and figure 4 a more caudal level, each with the matching levels of HRCT and micro-CT. At the cranial level HRCT shows some irregular densities (yellow arrows) on a background of otherwise normal lung parenchyma. At the caudal level these irregular areas of increased densities start to look like an interrupted framework. On micro-CT, areas of irregular densities (yellow arrows) in or against the interlobular septa with spikes or linear spurs to the adjacent alveoli can again be depicted. These adjacent alveoli are also deformed. On a detail image of the lower part of figure 4B (Fig. 5) a respiratory bronchiole terminating abruptly in one of such irregular shaped densities is seen (blue arrow).

Reticular pattern with few small cysts
On figure 6A the same areas of increased densities (yellow arrows) as in figure 3A and 4A are seen, with in addition what looks like a small cyst (orange arrow) in one of these areas. Micro-CT (Fig. 6B) confirms the presence of a small cavity (orange arrow) arising in an area of increased density (yellow arrows).

Cysts/ honeycombing

Cores were also taken in those areas of the lung that show multiple clearly visible cysts on HRCT. Figure 7A shows a HRCT image of an area with a cluster of cysts (orange arrow) at the bifurcation of an artery (red arrow). These cysts are also seen on micro-CT (Fig. 7B, orange arrows), where they seem to arise in the previously described irregular areas of increased density (yellow arrows). These cysts seem to be connected to each other and to the bronchial system.

Figure 8A shows another very abnormal area on HRCT with visible traction bronchiectasis (blue arrows), a reticular pattern and multiple small cysts (orange arrows) on a background of increased attenuation. On micro-CT (Fig. 8B) these bronchiectasis can be seen together with an almost complete destruction of normal lung architecture and the presence of multiple cysts (orange arrows) of which only the largest cysts are visible on HRCT.

Distribution

- **Peripheral distribution:** we know from pathology that the initial fibrotic scarring starts at the periphery of the second pulmonary lobule (4). We have shown that the reticular pattern seen on HRCT correspond to a peripheral distribution of irregular densities (Fig. 3 and 4) on micro-CT. Although it is not clear, at this moment, whether these densities represent areas of fibrotic scarring or collapsed lung tissue, some of them probably correspond with the initial islands of fibrotic scarring seen on pathology.

- **Geographic heterogeneity:** in figure 9A an almost clear cut interface between a normal area and a predominantly cystic area is seen on HRCT (green arrowheads). On micro-CT this border seems to be formed by traction and/or compression of alveoli in the on HRCT 'unaffected' area adjacent to these large cysts (green arrows).

- The **apicobasal gradient** and **subpleural distribution** are of course 'macroscopic' HRCT features, but we can clearly see that they correspond to the degree of severity of the disease on micro-CT, with only some irregular shaped densities on the top and central lung parts, larger densities with more pronounced deformity of surrounding alveoli and beginning cyst formation within the densities somewhat lower and overt cystic changes in the bases.
Fig. 1: A. HRCT: The yellow circle indicates the region where the core is taken. Blue arrow = large airway. Red arrow = accompanying artery. B. Micro-CT of the core: Blue arrow = large airway. Red arrow = artery. Yellow arrows = areas of increased density around this airway. Green arrows = deformed alveoli/alveolar airspaces.

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Fig. 2: A. HRCT: Red arrow = vessel. Yellow arrows = small densities at the periphery of the core. B. Micro-CT: Red arrow = vessel. Blue and red arrow heads = terminal bronchiole with its accompanying arteriole respectively. Purple interrupted line = border areas of the acini and secondary pulmonary lobule. Yellow arrows = multiple small islands of increased density at the septa. Green arrows = alveoli surrounding these dens islands, having a deformed appearance, as if traction is exerted on them.

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**Fig. 3:** A. HRCT: Yellow arrows = some irregular densities. B. Micro-CT: Purple interrupted line = outlining of a secondary pulmonary lobule. Yellow arrows = areas of increased density in/against the interlobular septa.

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**Fig. 4:** A. HRCT: Yellow arrows = irregular densities that look like an interrupted framework, resembling a secondary pulmonary lobule. B. Micro-CT: Purple interrupted
line = border of a secondary pulmonary lobule. Yellow arrows = areas of increased density in/against the interlobular septa, more pronounced then in figure 3.

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**Fig. 5:** Detail of lower part of figure 4B: a respiratory bronchiole (blue arrow) terminating abruptly in an irregular shaped density.

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Fig. 6: A. HRCT: Yellow arrows = Streaky irregular densities. Orange arrow = small cyst. B. Micro-CT: Yellow arrows = areas of increased density. Orange arrow = a small cavity arising in an area of increased density.

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**Fig. 7:** A. HRCT: Red arrow = artery. Orange arrow = cluster of cysts in an area of increased density. B. Micro-CT: Red arrow = artery. Orange arrows = cysts in an area of increased density (yellow arrows).

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**Fig. 8:** A. HRCT: Very abnormal lung area with traction bronchiectasis (blue arrows), reticular pattern and small cysts (orange arrows) on a background of increased lung attenuation. B. Micro-CT: Blue arrows = bronchiectasis. Orange arrows = diffuse cystic changes.

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Fig. 9: A. HRCT: Clear cut interface between a normal area and a predominantly cystic area (green arrow heads). B. Micro-CT: At this border there seems to be traction and/or compression of alveoli in the 'unaffected' area adjacent to these large cysts (green arrows).

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Conclusion

In this study, we tried to get a better understanding of the underlying lung changes responsible for the HRCT features of IPF by examining micro-CT images of lung areas with a different severity of disease.

We have shown that IPF related lung changes are already present in those areas of the lung that seem to be normal or almost normal on HRCT. This is in line with previous studies showing that pathology-proven IPF can present without the typical HRCT features (5, 6).

The reticular pattern seen in IPF is related to an increase in tissue density at the periphery of the secondary pulmonary lobule. In more diseased areas clusters of cysts arising in these areas of increased tissue density are seen. The microcysts initially seen on HRCT correspond with these small cystic changes and also with bronchiolectasis. Finally, honeycombing seems to be caused by progressive enlargement of these cystic tissue densities, that gradually extend towards the centrilobular region and finally replace the entire lobule. These progressive micro-CT findings, correlating with a progressive degree of disease on HRCT, kind of match what Akira et al (7) described in 1993. He studied the CT's of proven IPF-patient through the disease course. He saw that areas of ground-glass attenuation preceded and were predictive of the development of irregular linear densities and finally honeycombing. The explant lung of our study is from a patient with severe IPF, which was the reason for the transplantation. So the early stage of IPF with ground-glass attenuation on HRCT was not present in our specimen, but the rest of the sequences seems to match this and other previous studies (7, 8).

With help of micro-CT we have actually delivered more evidence that the different HRCT features correspond to the way IPF progresses throughout the disease course. We also have shown that micro-CT can be very useful for studying the morphologic changes of lung diseases at every stage of the disease, even when no abnormalities can be depicted on HRCT. The next step will be to correlate these micro-CT findings with histology.
References


