## PATHOLOGY AND RADIOLOGY: WHAT DO THEY LEARN FROM EACH OTHER?

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**Case 1**

*Clinical data:* 61-year old male, smoking history, GERD
*Radiology dx:* **probable UIP**

There is loss of lung volume with signs of fibrosis. There are cysts in the upper lung zone, unclear whether they represent honeycombing or emphysema without surrounding fibrosis. In the lung bases there are rounded cysts visible, aided by the presence of extrapleural fat deposition (see also pathology), indicating volume loss and there is evidence of honeycombing.

*Pathology dx:* **definite UIP**

In the upper lobe section, emphysema is present (no honeycombing because it is not composed of small airways) accompanied by various amounts of fibrosis. In the lower lobe section, the peripheral secondary lobules are collapsed, accompanied by edema of interlobular septa and honeycombing spaces. Volume loss of the lung parenchyma is compensated by increased extrapleural fat.

**Case 2**

*Clinical data:* 54-year old male, progressive dyspnoea on exertion, heavy smoker
*Radiology dx:* **smoking-related diffuse parenchymal lung disease**

In the upper lobe many cysts are visible suggestive of emphysematous spaces with fibrosis around them and there is traction bronchiectasis. At the lung bases, there appears to be less cysts. The expiratory examination shows lobular attenuation differences (air trapping), indicative of significant small airway disease. The 'holes' are limited to the upper lung zones and disappear towards the basis. Mosaic attenuation is accentuated on MinIP.

*Pathology dx:* **smoking-related diffuse parenchymal lung disease**

In the upper lobe there is air space enlargement, which is associated with fibrosis, and there are focal areas of organizing pneumonia. There is also significant small airway injury and subepithelial fibrosis. Macrophages are present, which is characteristic of smoking-related lung injury.

In the lower lobe there is no secondary lobular collapse. Small airway injuries persist in the lower lobe, which is a common lesion in smokers.



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**Case 3**

*Clinical data:* 75-year old male, smoking history, vapes marijuana
*Radiology dx:* **indeterminate UIP, probable aspiration**

There is asymmetry and evidence of fibrosis in the upper lobe (which turned out to be honeycombing on basis of pathology), and mosaic attenuation on the expiratory scan.

*Pathology dx:* **indeterminate UIP, aspiration**

In the upper lobe, there is collapse of secondary lobules and small airway-centred fibrosis. In the lower lobe there is airway-centred lung injury. A diagnosis of UIP/IPF can not be confirmed based on the lower lobe findings. There are aspirated food particles in all three lobes.

**key messages**

- Although it is not part of the current assessment, collapse, small airway injury and loss of volume are features of UIP; loss of lung volume is one of the most helpful signs of a UIP pattern.
- Lung volume loss is associated with increased epipleural fat deposition and pulling down of the major fissure; looking for abnormalities in the area between the rib and lung can help in the diagnosis.
- The amount of abnormalities increase from the top to the base of the lung (best visible on coronal scan); collapse at the top of the lung is prevented by increased stretch.
- Smoking-related diffuse parenchymal lung disease is characterised by airspace enlargement and fibrosis, smokers' macrophages, and small airway injury.
- Asymmetric disease (right-sided) is suggestive of aspiration.

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## INTERSTITIAL LUNG ABNORMALITIES: WHAT ARE THEY AND WHAT DO THEY MEAN?

CHRIS RYERSON, MD, FRCPC

Interstitial lung abnormalities (ILAs) are common, and are defined by incidental identification of non-dependent abnormalities in which there is >5% involvement in individuals without suspected ILD. They can be grouped into three main categories: centrilobular, subpleural, and mixed abnormalities. Compared to those without ILAs, patients with ILAs are generally older, have a higher BMI, more pack years, and lower GOLD stage. ILA is associated with lower total lung capacity, a two-fold increase in mortality and is often a precursor to ILD. Around 5-10% of at-risk populations (e.g. smokers) develop ILA, of which 20-40% show radiological progression within two years. From an imaging perspective there is a three-step approach towards the diagnosis of ILAs:

1. look for features that would exclude ILA (e.g. dependent lung atelectasis, friction fibrosis, respiratory bronchiolitis, focal or unilateral abnormality, edema and aspiration);
2. assess whether there is any of the lung patterns present seen with ILA (ground glass opacities, reticulation, traction bronchiectasis, honeycombing, and non-emphysematous cysts); and

3. define the extent and location. The location of ILA can be non-subpleural, subpleural non-fibrotic or subpleural fibrotic, which are in that particular order associated with increasing risk of progression and mortality. When it is difficult to define injury as greater or less than 5% of lung volume, it is better to call it an ILA, as follow-up often sorts out the issue.

HRCT is required to identify ILAs; in a small subset of radiologically challenging cases pathology may provide clear evidence. It is important to identify ILA and to predict by radiological and clinical features which patients are more likely to progress. These patients should be actively monitored and managed with prevention strategies such as smoking cessation and exposure avoidance. Standards have been proposed for reporting, evaluating and managing ILAs.

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## PROGRESSIVE PHENOTYPE OF INTERSTITIAL FIBROSIS: DEFINITION, DIAGNOSIS AND TREATMENT

KEVIN BROWN, MD AND DAVID LYNCH, MB, BCH

Based on whether there is an identifiable cause, fibrosing ILDs can be separated into idiopathic interstitial pneumonia (IIP) and non-IIP, which can be further defined by the HRCT pattern. Clinical, physiological and imaging results are taken together in the multidisciplinary discussion to come to either a confident diagnosis or working diagnosis. If the diagnosis still has a high degree of uncertainty, a biopsy can aid to the diagnosis. Patients with IPF (UIP pattern) have worse prognosis than those with an NSIP pattern. Based on similar progression patterns seen in the INPULSIS (IPF) and INBUILD (PF-ILD) studies, future disease behaviour may however be quite similar. While the pathological pattern at baseline is a predictor of outcome, at 6 months the prognosis is determined by disease behaviour. In the INBUILD trial, progressive fibrosis (PF-ILD) was defined as the presence of ≥1 of the following criteria within the previous 24 months: relative decline in FVC ≥10% predicted, relative decline in FVC 5-<10% predicted and worsened respiratory symptoms, relative decline in FVC 5-<10% and increased extent of fibrosis on HRCT, or worsened respiratory symptoms and increased extent of fibrosis on HRCT. The new ATS/ERS/JRS/ALAT Clinical Practice Guideline of 2022 suggests that progression of pulmonary fibrosis is defined as at least two of the following three criteria occurring within the past year with no alternative explanation: worsening respiratory symptoms, physiological evidence of disease progression, and radiological evidence of disease progression.

The radiological patterns of progressive fibrosis can vary, and especially for non-IPF ILDs it is challenging to predict in which way the patterns are going to progress. Patterns of progressive fibrosis include increased extent or coarseness of reticular abnormalities, new or increased honeycombing, increased traction bronchiectasis, new ground glass opacity with traction bronchiectasis, new fine reticulation or increased lobular volume loss. To define progression of fibrosis it is important to not only look at the most recent CT scan, but all CT scans from past years as well. Quantitative CT is increasingly used to assess progressive fibrosis in practice due to its higher objectivity and reliability. Antifibrotic therapy has shown to slow the rate of decline in FVC across different subgroups of PF-ILD, suggesting an overlapping pathobiological mechanism in patients with progressive pulmonary fibrosis.



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## DRUG-INDUCED LUNG DISEASE IN ONCOLOGY: DIAGNOSIS AND TREATMENT

CHARLES POWELL, MD AND CORNELIA SCHAEFER-PROKOP, MD, PHD

Many drugs to treat cancer may induce ILD. The diagnosis of drug-induced ILD requires an interdisciplinary approach in which clinical information is required for the differential diagnosis. It is thought to be clinically underdiagnosed. The diagnosis is made by the presence of new parenchymal opacities on chest CT that are associated with the initiation of the drug, and exclusion of other causes, such as infection, radiation pneumonitis or malignancy. Drug exposure can trigger different types of ILD, although NSIP, organizing pneumonia and diffuse alveolar damage are most common. For radiological evaluation, it is important to know specifics about former therapeutic approaches (radiation, chemo/immunotherapy) and whether the patient has pre-existing lung disease or underlying systemic disease, as radiological findings in itself are aspecific. A lung biopsy is non-specific for drug-induced ILD and often not necessary, but may be useful to exclude alternative diagnoses, such as sarcoidosis. In a meta-analysis of 879 cancer patients treated with trastuzumab deruxtecan, drug-induced ILD occurred in approximately 16% of the patients. Risk factors for drug-induced ILD in cancer include Japanese ethnicity, longer history of disease, moderate/severe baseline renal function and pre-existing lung disease. In 95% of the cases, ILD occurs during the first year of treatment. Once the diagnosis is made, the severity of the disease is graded according to the CTCAE pneumonitis severity assessment. Drug-related pneumonitis is well manageable if it is detected early and if it is treated appropriately. Management depends on the grade of severity. According to a position paper of the Fleischner society, in most cases, the suspected drug should be discontinued as soon as drug-related pneumonitis is expected, except when a patient is treated with specific agents such as Osimertinib, for which monitoring may be appropriate, as findings may be transient. Steroids are effective in patients with pneumonitis of grade 2 or higher.

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## SARCOIDOSIS: DIFFERENT PHENOTYPES AND TREATMENT

ATHOL WELLS, MD AND SUJAL DESAI, MD, FRCP, FRCR

Sarcoidosis can be caused by many different triggers, including mycobacterial and fungal antigens. Patients may have very diverse patterns of disease behaviour as well as lung function impairment. It is therefore likely that sarcoidosis is a cluster of different diseases. A Delphi study with 146 experts from 28 countries demonstrated consensus on seven distinct phenotypes in sarcoidosis, including nodular and fibrotic phenotypes. The experts strongly agreed that HRCT should be performed at baseline in patients with sarcoidosis and evidence of pulmonary interstitial involvement. Observer agreement among radiologists and chest physicians in identifying these phenotypes on HRCT scans of patients with sarcoidosis was, however, very low. This suggests that there is a disconnect between written explanations of patterns and what experts see on HRCT scans.

Treatment guidelines are largely based on clinician experience. Historically, there was a tendency to treat all patients with evidence of active sarcoidosis. As a result, many patients now have treatment-related comorbidities that are largely related to excess use of steroids. Patients with sarcoidosis should be treated when there is danger, i.e., risk of death or permanent disability from major organ involvement, or when the disease causes unacceptable loss of quality of life. The current guideline reinforces first-line therapy with steroids, second-line therapy with methotrexate, azathioprine or other immunosuppressants, and third-line therapy with anti-TNF

agents. In the context of danger, it is recommended that patients are treated with an initial high dose therapy to switch off activity, which may lead to a lower total steroid dose over the next years. Risk stratification is needed to inform management strategies. Thresholds for $DL_{CO}$, CPI, disease extent on CT and the presence of pulmonary hypertension are all danger signals. Therefore, CT and pulmonary function tests should be integrated in the evaluation of severity. Quantitative CT is expected to play a much greater future role in defining irreversible disease.

## CLINICAL CASE DISCUSSIONS

Specialists from three different ILD expertise centers in the Netherlands presented several interesting cases, including familial IPF, environment-induced ILD, CTD-ILD, ILD with pulmonary hypertension, and sarcoidosis. The cases were presented by Jan Grutters, MD, PhD (St. Antonius Ziekenhuis Nieuwegein), Pim de Jong, MD, PhD (UMC Utrecht), Marlies Wijsenbeek, MD, PhD (Erasmus MC), Ieneke Hartmann MD, PhD (Maasstad Ziekenhuis Rotterdam), Esther Nossent, MD (UMC Amsterdam) and Onno Mets, MD, PhD (UMC Amsterdam).

**The most important learnings from these cases were:**

- A multidisciplinary discussion with specialists from different disciplines, such as a radiologist, pathologist and pulmonologist, is important for the diagnosis and management of patients with ILD.
- Genetic testing can be done in patients with a family history of ILD, as long as there is the opportunity for providing appropriate counselling.
- In many patients with stable ILD or ILA, COVID infections can trigger a progressive phenotype.
- COVID vaccination seemed to have triggered acute exacerbations in some patients with slowly progressing pulmonary fibrosis.
- Exposure to triggers at even an early age could cause damage and subsequent strain in the lung, inducing self-perpetuating progression of damage. Unlike UIP, injury by acute inhalation is seen right around the airways (bronchocentric distribution).
- Pulmonary hypertension is common in patients with pulmonary fibrosis and is associated with worse prognosis.
- Active monitoring is important to detect progression of fibrosis and start antifibrotic treatment early.

Report by: Carmen Paus, MSc and Gabry Mies, PhD | Medical writers BKC Media