Differential diagnostic challenge: an approach to diffuse lung disease

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The description “diffuse lung disease” (DLD) is used to describe diseases that are diffusely spread over an important part of the lung (not necessarily symmetric) and that show CT changes that are composed in a repeating arrangement. Since many of these diseases predominantly or partly involve the pulmonary interstitium the term “interstitial” is also often used or added: diffuse interstitial lung disease (DILD) or diffuse parenchymal and interstitial lung disease (DPILD).

Many DPILD’s have a known cause but often the cause is unknown and especially in the group of idiopathic DPILD’s the diagnosis may be difficult. This may be related to the often aspecific clinical presentation but also to the overlapping pathological findings and the atypical radiological presentation. Moreover, different classifications have been proposed and clinicians, pathologists and radiologists may not use the same terminology to describe a disease entity. Until recently pathology was considered as the “gold standard” in the diagnosis of these DPILD’s. However, the introduction of high resolution CT (HRCT) has changed this.

Indeed HRCT is in part responsible for the radical change in the diagnostic work-up of diffuse lung diseases that has occurred in the past few years. Instead of histopathologic evaluation being the gold standard for diagnosis, it is nowadays accepted that an integrative approach of clinical, radiologic and, when necessary, pathologic data is the best approach: the more data are available, the higher the level of agreement and the diagnostic confidence become.

The radiologist plays an important role in this multidisciplinary group. HRCT, staying the imaging modality that offers the highest image detail of the lung, is indeed very often able to make the correct diagnosis, especially when typical patterns of this disease are present, reason why lung biopsy may be avoided. However, when CT signs are atypical, a diagnosis may not be possible until after thorough clinico-radiologic correlation. But even then, diagnosis can be difficult and when there is discordance between clinical and radiological findings, a lung biopsy may be indicated necessitating again a formal multidisciplinary discussion. Therefore it is important that radiologists know the HRCT features of the different DIPLD and understand as well how these features come about, i.e. understand the pathological correlate of the CT changes.

Since, as mentioned earlier, the CT abnormalities in DPILD are composed in a repeating arrangement, CT diagnosis of these diseases is predominantly based on the recognition of this arrangement by describing 2 components: 1) what do we see: the appearance pattern, and 2) where do we see it: the distribution pattern. Classically 4 appearance patterns are described: the nodular pattern and the linear pattern where disease presents respectively as nodules or as lines, the pattern where disease shows a predominant increase in lung attenuation and finally the pattern where disease has affected the lung in such a way that its attenuation has decreased. The distribution pattern describes how the disease is distributed throughout the lung both macroscopically (upper, middle, lower part of the lung, axial, central, peripheral lung region) and submacroscopically (in relation to the pulmonary
lobule). By determining the distribution pattern it is often possible to decide whether the disease has entered the lung or whether it is distributed through the lung by airway/airspace, vascular, lymphatic or interstitial pathways. Although the recognition of a pattern may be easy and straightforward, some lung changes are difficult to categorise because patterns are very often mixed and may change during the course of the disease. Finally, it is important to emphasize that, in order to describe these appearance and distribution patterns, a good knowledge of lung anatomy is mandatory. Especially the components of the pulmonary lobule should be known in detail.

Pulmonary lobule

The pulmonary lobule is defined as the smallest unit of lung structure margined by connective tissue septa. It is supplied by a group (3-12) of terminal bronchioles, is irregularly polyhedral in shape and is approximately 1 to 2.5 cm on each side. Although the overall configuration of the pulmonary lobule and its relationship to other lobules appear to be almost entirely random, the organisation of the individual anatomic components of the lobule is quite precise and is similar from lobule to lobule.

The pulmonary lobules are demarcated from each other by interlobular connective tissue septa that contain the pulmonary veins and lymphatics surrounded by connective tissue. The central part of the lobule contains the terminal bronchiolar branches that supply the lobule, their accompanying pulmonary arterioles and adjacent to them some supporting connective tissue and some lymph vessels. The lobular lung parenchyma is the part of the lobule surrounding the lobular core and contained within the interlobular septa. It consists of functioning lung grouped in 3–12 acini, each supplied by a terminal bronchiole that contain alveoli (organised in alveolar ducts and sacs) and their associated pulmonary capillary bed together with their supplying small respiratory bronchioles and arterioles and with draining veins. This parenchyma is supported by connective tissue stroma surrounding the acini and the individual alveolar ducts and sacs.

Nodular pattern

The nodular pattern is characterised by the presence of multiple nodular opacities with a maximum diameter of 3 cm. A nodule with a diameter less than 1 cm can be defined as a “small nodule”, whereas a nodule larger than 1 cm is often called a “large nodule”. The term “micronodule” usually refers to a nodule smaller than 7 mm in diameter. The CT assessment of the nodular pattern is based on: 1) their size (small or large); 2) their appearance (well-defined or ill-defined); 3) their attenuation (soft tissue or ground-glass density) and 4) their distribution. Especially the study of the distribution of the nodules in relation to the different anatomic parts of the pulmonary lobule (centrilobular, septal (perilymphatic) or at random) may be important for differential diagnosis.
Linear pattern

The linear pattern is characterised by the presence of multiple lines. Since these lines very often cross one another the term reticular pattern is used as well. However, this ‘netlike’ appearance needs not be present, and the number of lines can also be limited. In this situation the term linear opacity is preferred. The differential diagnosis of linear opacities in the lung is predominantly based on the identification of their localisation and on the study of their appearance (smooth, irregular).

When evaluating linear opacities on a CT scan it is important to examine whether these lines are caused by thickening or broadening of one or more components of the pulmonary lobule. Basically such a thickening or broadening can cause 3 patterns: 1) a coarse reticular pattern with the size of the pulmonary lobules (lobular reticular pattern); 2) a fine reticular network with smaller reticulations than the previous one (intralobular reticular pattern), and 3) centrilobular branching lines that extend as spider legs from the centre to the periphery of the pulmonary lobule. A coarse reticular pattern (lobular reticular pattern) may be formed when the interlobular lines are thickened (septal lines). A fine reticular pattern (intralobular reticular pattern) results from thickening of the intralobular interstitium surrounding the acini and from linear deposition of material within — or collapse of the airspaces at the borders of the acini. Involvement of the centrilobular peribronchovascular tissue, lymphatics, bronchioles and vascular structures may cause centrilobular branching lines. Larger linear opacities not related to a component of the pulmonary lobuli may be seen when the subpleural tissue is thickened, or in the lung parenchyma when atelectasis and fibrosis occur (parenchymal bands, irregular linear opacities, and when parallel with the pleural surface, subpleural lines).

Increased lung attenuation

The increased lung attenuation pattern is caused by an increase in density of the lung parenchyma. Depending on the degree of involvement two types of increased lung attenuation can be described: 1) ground-glass opacity or ground-glass attenuation when involvement is mild; 2) consolidation when involvement is more advanced. The term ground-glass attenuation is used to describe a hazy increase in lung opacity with preservation of the bronchial and vascular markings. Ground-glass attenuation can be nodular, focal, regional, multi-focal or diffuse. It can be homogeneous and heterogeneous and it can have sharp or blurred margins. It is important to emphasize that the presence of ground-glass opacity does not necessarily indicate pathology. Physiologic ground-glass attenuation can be seen in the dependent lung areas and is then caused by a gravity related increase in perfusion and a decrease in the amount of intra-alveolar air. Ground-glass attenuation is also a normal finding on the expiratory CT scans when the amount of air in relation to tissue and blood is decreasing. Lung consolidation, on the other hand, is always a pathologic finding and this term is used to describe an increase in pulmonary parenchymal attenuation that obscures the margins of the vessels and airways. Although the margins of the airways are obscured the lumen may be visible when it contains air typically causing an air-bronchogram. Also consolidation can be nodular, focal, regional, multi-focal or diffuse. It
can be homogeneous and heterogeneous and it can have sharp or blurred margins. A sharp border is often resulting from an adjacent normal anatomic structure such as a lung fissure. When the CT scan shows an increased lung attenuation pattern differential diagnosis is not only guided by the study of the distribution pattern of the disease but also by the clinical evolution (chronic versus acute course of the disease).

Decayed lung attenuation

Decrease in lung attenuation can be caused by an abnormal increase in the amount of air in the lung without obvious lung destruction (air-trapping) or by abnormal decrease in the intravascular blood volume and, as a result, an abnormal calibre of the vessels that are beyond the resolution of CT (hypoperfusion). It can also be caused by tissue destruction and tissue loss, which can be cystic or cystlike or can be the result of pulmonary emphysema. A decrease in attenuation of the lung parenchyma is always pathologic but does not necessarily indicate that irreversible lung destruction is present. This differentiation between decreased lung attenuation with and without lung parenchyma destruction is a very important first step in the differential diagnosis.

Combination of patterns

In many cases a combination of two or even more patterns is seen. A mixture of patterns can be caused by a new disease that is superimposed on an already existing lung disease (for example: emphysema) but often one disease may show two or more patterns either at the same time or during its course. The presence of 2 or more patterns often complicates the interpretation of the abnormalities. The challenge is to separate the two patterns and to determine their characteristics. One should try to determine the predominant pattern and, when possible, define which pattern has most recently developed. Fortunately, the simultaneous presence of two or more patterns can create “mixed patterns” that have their own differential diagnosis list. Examples are: 1) the mosaic pattern, which is a patchwork of areas with increased (ground-glass attenuation) and normal areas or areas with decreased lung attenuation (hypoperfusion); 2) the crazy paving pattern, which combines linear opacities and ground-glass opacity and 3) the tree-in-bud pattern, which combines centrilobular branching lines and nodular opacities.

Lung fibrosis

Several DPILD’s can lead to the development of pulmonary fibrosis. Connective tissue diseases, but also occupational, environmental and medication exposure are known to cause pulmonary fibrosis. Diffuse pulmonary fibrosis may, however, also develop without an obvious cause. It is very important to recognize the signs of pulmonary fibrosis which are:
Take home points

The diagnosis of idiopathic diffuse parenchymal and interstitial lung disease requires a multidisciplinary approach.

The radiological diagnosis is based on the study of the appearance and the distribution pattern of the disease.

A good knowledge of the anatomy of the lung and especially of the pulmonary lobule is mandatory not only for diagnosis but also for adequate discussion with the clinician and the pathologist.
Suggested reading


