High-resolution CT Findings of Diffuse Lung Disease: Review Article

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Introduction

Computed tomography (CT), particularly high-resolution CT (HRCT), defines detailed lung morphology, and is useful in evaluating diffuse lung disease. It allows assessment of the anatomic changes as well as physiologic responses in patients with diffuse lung disease. We herein review the HRCT findings of diffuse lung disease according to classification based on their predominant appearances.

Key words: lung, HRCT, diffuse lung disease.

Anatomy and Physiology

To appreciate the lung parenchyma on HRCT, it is most important to understand the anatomy of the secondary pulmonary lobule.

The secondary pulmonary lobule is the basic respiratory unit; it is supplied by several terminal bronchioles and is surrounded by connective tissue septa (interlobular septa). The pulmonary veins and lymphatic channels are within the interlobular septa. The central portion of the secondary lobule (the lobular core) contains bronchioles, pulmonary arteries and supporting connective tissue.

The limit of HRCT resolution is bronchi of 1-2 mm in diameter and vessels of 0.1-0.2 mm in diameter. Both the lobular bronchioles and arteries are about 1 mm in diameter. On HRCT, the lobular arteries and their branches that are within 3-5 mm of the pleural surface can be seen as branching, Y-shaped or dotlike structures near the center of the secondary lobule. On the other hand, the intralobular bronchioles cannot normally be visualized.

Bronchioles that do not have cartilage are classified into membranous bronchioles and respiratory bronchioles. The respiratory bronchioles, which contain alveoli in their walls, participate in gas exchange in addition to gas conduction. Physiologically, airways smaller than 2 mm in diameter including small cartilaginous bronchi and membranous and respiratory bronchioles account for only 25% of airway resistance. Therefore, small airways must become severely narrowed before there are detectable abnormalities on pulmonary function tests. HRCT can be helpful in the evaluation of small airway abnormalities.

Technique

HRCT makes detailed visualization of the lung parenchyma possible. The technique of HRCT consists of using thin collimation (1-2 mm) and reconstruction with a high-spatial frequency algorithm and targeting image. It produces greater spatial resolution than with possible with conventional 10-mm-collimation CT.

On noncontiguous HRCT scans with thin collimation, true nodules may be sometimes difficult to distinguish from “nodular” vessels because only a short segment of vessels is visible. For this reason, we routinely obtain HRCT scans in several sections in addition to contiguous conventional scans.

It is important to obtain scans in both the supine and prone positions at each level in evaluating interstitial lung disease that tends to involve the dependent portions of the lung. Dependent areas of increased attenuation are seen in approximately 30% of healthy subjects (Fig. 1). Performing scans in both positions allows us to differentiate this artefact from true pathology.

Expiratory CT has recently been used to reveal physiologic changes seen in small airway diseases. Severe air trapping is easy to diagnose using inspiratory CT, but subtle air trapping can only be detected by expiratory CT. During full expiration, the normal lung parenchyma shows a homogeneous increase in attenuation whereas the lung parenchyma with air trapping remains lucent.

Classification of diffuse lung diseases

HRCT findings of diffuse lung disease can be classified into four types based on their appearances: linear and reticular opacities, nodules and nodular opacities, increased lung attenuation, and decreased lung attenuation including mosaic perfusion.
Dependent areas of increased attenuation (arrows), which is so-called dependent opacity, are seen when the patient is supine (A) and resolve when the patient is prone (B).

Linear and Reticular Opacities

Thickening of the interstitium of the lung is the main cause of linear and reticular opacities seen on HRCT. Linear and reticular opacities can be detected as peribronchovascular interstitial thickening, interlobular septal thickening, parenchymal bands, subpleural and intralobular interstitial thickening, honeycombing, subpleural lines and centrilobular abnormalities. Of these peribronchovascular interstitial thickening and interlobular septal thickening are discussed below.

Peribronchovascular interstitial thickening is discerned as increases in the diameter of the pulmonary artery and in the bronchial wall thickness. Thickening of peribronchovascular interstitium can be smooth, nodular or irregular in contour. Smooth thickening is commonly seen in patients with lymphangitic spread of carcinoma (Fig. 2) and interstitial pulmonary edema. Nodular thickening occurs in sarcoidosis (Fig. 3) and lymphangitic spread of carcinoma. Irregular thickening, which is caused by peribronchovascular and adjacent lung fibrosis, is seen in patients with idiopathic pulmonary fibrosis, sarcoidosis, silicosis (Fig. 4) and chronic hypersensitivity pneumonitis.

Since the interlobular septa are rarely discernible on HRCT in normal subjects, the presence of numerous clearly visible interlobular septa usually indicates interstitial abnormalities. Interlobular septal thickening can also...
Fig. 3 Nodular peribronchovascular interstitial thickening (arrow) in a patient with sarcoidosis. Interlobular septal thickening and centrilobular nodules are also visible.

Fig. 4 Irregular peribronchovascular interstitial thickening caused by peribronchovascular and adjacent fibrosis in a patient with silicosis. Centrilobular and subpleural nodules (arrows) are also seen. Subpleural interstitial thickening results in nodular thickening of the left major fissure (arrowheads).
appear smooth, nodular or irregular on HRCT. Smooth thickening is seen in patients with lymphangitic spread of carcinoma (Fig. 5)\textsuperscript{12,13}, interstitial pulmonary edema, alveolar proteinosis (Fig. 6)\textsuperscript{16,17} and amyloidosis\textsuperscript{18}. Nodular or "beaded" thickening occurs in patients with lymphangitic spread of carcinoma (Fig. 7)\textsuperscript{12,13}, sarcoidosis\textsuperscript{14,19}

Fig. 5 Smooth interlobular septal thickening in a patient with lymphangitic spread of carcinoma. Lobules in the more central lung appear hexagonal or polygonal.

Fig. 6 Smooth interlobular septal thickening in association with geographic ground-glass opacity, termed "crazy-paving" appearance, is characteristic of alveolar proteinosis.

Fig. 6A

Fig. 6B

Fig. 7 Nodular or "beaded" septal thickening (arrows) in a patient with lymphangitic spread of carcinoma.
Table 1  Diffuse lung diseases with centrilobular opacities

<table>
<thead>
<tr>
<th>Bronchiolar and Peribronchiolar Diseases</th>
<th>Perilymphatic Diseases</th>
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<tbody>
<tr>
<td>Diffuse panbronchiolitis (DPB)</td>
<td>Histiocytosis X</td>
</tr>
<tr>
<td>Endobronchial spread of infection</td>
<td>Asbestosis</td>
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<tr>
<td>Bronchopneumonia</td>
<td>Bronchial carcinoma</td>
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<tr>
<td>Cystic fibrosis</td>
<td>Constrictive bronchiolitis</td>
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<td>Hypersensitivity pneumonitis</td>
<td>(Bronchiolitis obliterans)</td>
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<td>Respiratory bronchiolitis</td>
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<td>Histiocytosis X</td>
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<td>Asbestosis</td>
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<td>Bronchioloalveolar carcinoma</td>
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<td>Constrictive bronchiolitis</td>
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Perilymphatic Diseases

Nodules and Nodular Opacities

The presence of nodules and nodular opacities can be of great value in the differential diagnosis of diffuse lung disease. The appearances of nodules can classified as well-defined and ill-defined. Interstitial nodules seen in patients with granulomatous disease are usually well-defined despite their small size. On the other hand, air-space nodules, also called "acinar nodules", tend to be ill-defined. The distribution of the nodules is more important for making a differential diagnosis than their appearances, and it is classified into random, perilymphatic and centrilobular.

Miliary tuberculosis and hematogenous metastases tend to be randomly distributed in relation to the structures of the secondary lobule. In the patients with histiocytosis X and silicosis, numerous nodules may appear to be randomly distributed.

The nodules distributed in the peribronchovascular and centrilobular interstitium, interlobular septa and subpleural regions in relation to lymphatics are termed perilymphatic. This finding is characteristically seen in patients with sarcoidosis, silicosis and lymphangitic spread of carcinoma. In patients with sarcoidosis, nodules are predominantly peribronchovascular (Fig. 3) and subpleural in location. In patients with silicosis, nodules are most frequently seen in centrilobular and subpleural regions (Fig. 4). When nodules are present in patients with lymphangitic spread of carcinoma, they are predominantly located within the thickened interlobular septa (Fig. 7) and peribronchovascular interstitium. Especially nodular septal thickening may result in a "beaded" appearance.

Centrilobular nodules can be seen in patients with a variety of diseases that affect the bronchioles, pulmonary arteries and lymphatics. Bronchiolar diseases that secondarily involve the peribronchiolar interstitium and alveoli are the most frequent cause of centrilobular opacities (Table 1). Centrilobular nodules and prominent branching structures correspond to bronchial and peribronchiolar inflammation, and bronchiolar dilatation with intraluminal secretion resulting in a tree-in-bud appearance, respectively. These findings are commonly seen in patients with diffuse panbronchiolitis (DPB) (Fig. 8), endobronchial spread of infection and cystic fibrosis. In addition to these findings, patients with DPB usually show evidence of air trapping and mosaic perfusion which are predominant features in patients with constrictive bronchiolitis (see under heading Decreased Lung Attenuation). In patients with hypersensitivity pneumonitis (Fig. 9) and respiratory bronchiolitis, ill-defined centrilobular nodules are seen associated with patchy ground-glass opacities. Centrilobular nodules can be present in patients with bronchiolitis obliterans organizing pneumonia (BOOP). The combination of consolidation and ground-glass opacity, however, is more common.
**Increased Lung Attenuation**

Areas of increased lung attenuation are generally divided into ground-glass opacity or consolidation. Ground-glass opacity is defined as a hazy increase in lung attenuation that does not obscure the underlying vessels. On the other hand, increased lung attenuation with obscuration of the underlying vessels is referred to as a consolidation. Ground-glass opacity and consolidation are often patchy in appearance and the lesions are sharply demarcated by spared region, making the so-called geographic appearance (Figs. 6 and 10). Ground-glass opacity often indicates disease activity.

A large number of diseases are associated with ground-glass opacity and/or consolidation (Table 2). Ground-glass opacity is seen most commonly in patients with hypersensitivity pneumonitis (Fig. 10) and respiratory bronchiolitis, alveolar proteinosis (Fig. 6), pneumocystis carinii pneumonia (Fig. 11), and desquamative interstitial pneumonia. Respiratory bronchiolitis, which is also referred to as smokers’ bronchiolitis, involves mainly the respiratory bronchioles and is characterized by the presence of pigmented macrophages in the alveoli. The majority of patients have no symptoms and normal findings on HRCT. As mentioned above, common findings in patients with alveolar proteinosis are a geographic distribution of ground-glass opacity and smooth thickening of the interlobular septa. The combination of these findings are referred to as the “crazy-paving” appearance with strongly suggestive of this disease (Fig. 6).

Consolidation is the main abnormality seen in patients with BOOP (Fig. 12) and eosinophilic pneumonia (Fig. 13). BOOP is characterized pathologically by an organizing pneumonia in the peripheral alveoli and by

<table>
<thead>
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<th>Table 2 Diffuse lung diseases with ground-glass opacity and/or consolidation</th>
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<td><strong>Ground-glass opacity dominant</strong></td>
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<td>Hypersensitivity pneumonitis</td>
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<td>Respiratory bronchiolitis</td>
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<td>Alveolar proteinosis</td>
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<tr>
<td>Pneumocystis carinii pneumonia</td>
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<td>Desquamative interstitial pneumonia</td>
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<tr>
<td>Sarcoidosis</td>
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<td>Usual interstitial pneumonia (UIP)</td>
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<td><strong>Consolidation dominant</strong></td>
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<td>Eosinophilic pneumonia</td>
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<td>Acute interstitial pneumonia</td>
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<td><strong>Ground-glass opacity and consolidation</strong></td>
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<tr>
<td>Bronchioalveolar carcinoma</td>
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<td>Pulmonary edema</td>
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<td>Pulmonary hemorrhage</td>
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Fig. 9 Defined centrilobular nodules of ground-glass opacity (arrows) associated with consolidation and ground-glass opacity in a patient with hypersensitivity pneumonitis.

Fig. 10 Geographic ground-glass opacity in a patient with hypersensitivity pneumonitis. Some lung regions are spared (arrows).
intraluminal granulation tissue within the bronchioles and alveolar ducts. Most cases are idiopathic, but in some cases there is an apparent cause for a pathologically identical reaction (BOOP reaction). Because the functional and radiographic findings of BOOP are essentially the same as those of organizing pneumonia, BOOP is also termed cryptogenic organizing pneumonia (COP).

Recently, bronchiolitis is pathologically classified as proliferative or constrictive. In proliferative bronchiolitis, intraluminal granulation tissue is present within the bronchioles and alveolar ducts. BOOP/COP is the most common cause of proliferative bronchiolitis. While in constrictive bronchiolitis, the pathologic hallmark is extensive fibrosis of the bronchiolar wall which leads to irreversible airflow obstruction. The suggested "obliterative bronchiolitis" as a synonym for constrictive bronchiolitis.

Fig. 11 Diffuse ground-glass opacity associated with spared regions in a patient with Pneumocystis carinii pneumonia.

Fig. 12 BOOP/COP with patchy areas of air-space consolidation in peripheral distribution.

Fig. 13 Chronic eosinophilic pneumonia. It is difficult to differentiate from BOOP/COP.

Fig. 14 Multiple thin-walled lung cysts of various sizes surrounded by normal lung parenchyma in a patient with lymphangioleiomatosis.
Decreased Lung Attenuation

Areas of decreased lung attenuation are seen in a variety of abnormalities including lung cysts, emphysema, bronchiectasis, honeycombing and "mosaic perfusion". In this review, lung cysts and mosaic perfusion are discussed.

The term lung cyst is usually used to refer to a thin-walled, air-containing lesion. Lung cysts are commonly seen in patients with histiocytosis X and lymphangioleiomyomatosis (LAM) (Figs. 14 and 15). In the early stage of histiocytosis X, centrilobular nodules representing granulomas located in the peribronchiolar and adjacent alveolar intersititium are commonly seen. Cavitated nodules and lung cysts occur later in the course of the disease. In most patients with histiocytosis X and LAM, the cysts are usually interspersed within the normal lung parenchyma. In patients with histiocytosis X, some cysts are confluent and can have bizarre shapes. In patients with LAM, on the other hand, the cysts appear round and more uniform in size, and the confluent cysts seen in histiocytosis X are less common.

Lobular and segmental areas of decreased lung attenuation interspersed with areas of normal or increased attenuation are referred to as a mosaic perfusion (Figs. 16 and 17). It is due to decreased perfusion of areas with bronchiolar obstruction and flow redistribution to normal areas. Pulmonary vessels in the areas of decreased attenuation often appear narrow, which can be helpful in distinguishing mosaic perfusion from ground-glass opacity. Although mosaic perfusion can also be caused by pulmonary artery abnormalities, it is most frequent in patients with small airway obstruction, especially with constrictive bronchiolitis.

As described above, constrictive bronchiolitis is characterized by peribronchiolar inflammation and fibrosis associated with airflow obstruction. It is also referred to as obliterative bronchiolitis or pure bronchiolitis obliterans. Constrictive bronchiolitis represents a nonspecific reaction and can be seen in a number of clinical contexts (Table 3). The CT features of constrictive bronchiolitis may be divided into direct and indirect signs. The direct sign is centrilobular nodules and branching structures but it is uncommon. Mosaic perfu-
Table 3 Causes of constrictive bronchiolitis

Infection
- Viral infection, Mycoplasma

Inhaled toxins
- Nitrogen dioxide, Sulfur dioxide, Ammonia

Drugs
- Penicillamine

Collagen vascular disease
- Rheumatoid arthritis, Progressive systemic sclerosis, Systemic lupus erythematosus

Chronic rejection
- Lung transplant, Heart/lung transplant

Chronic graft versus host disease
- Bone marrow transplant

Idiopathic

Constrictive bronchiolitis is one of the indirect signs of constrictive bronchiolitis. Others are bronchiolitis and air trapping (Fig. 18). The expiratory CT is useful in the diagnosis of air-trapping and in distinguishing mosaic perfusion from ground-glass opacity.

Constrictive bronchiolitis is usually associated with a patchy distribution on both lungs. Swyer-James syndrome is a variant of postinfectious constrictive bronchiolitis in childhood that mainly involves one lung or a portion of one lung.

Conclusions

HRCT findings of diffuse lung disease are reviewed according to classification based on their predominant appearances. In select cases, as described above, HRCT findings can be diagnostic or limit the differential diagnosis to a few possibilities, although often nonspecific. HRCT is also helpful in detecting lung disease in patients with normal radiographs, in assessing disease activity, and in planning biopsy procedures.

References