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# Radiographic Signs and Patterns in Interstitial Lung Disease

Ayesha Nasrullah, MBBS,* Shaimaa Fadl, MBchB,* Jitesh Ahuja, MBBS,* Haodong Xu, MD, PhD,† and Gregory Kicska, MD, PhD*

## Introduction

Thoracic computed tomography (CT), specifically high-resolution CTs (HRCTs), plays an essential role in diagnosing diffuse pulmonary lung disease. Although diffuse lung diseases often present with nonspecific radiographic findings, there are a small number of radiographic signs and patterns that are more specific and can be used to narrow the differential diagnosis.

## Honeycombing

Honeycombing is a term used to describe multiple air-filled cystic spaces usually 3-10 mm in diameter that are stacked in rows or clusters (Fig. 1a). Honeycombing occurs in a subpleural distribution and the cysts have well-defined walls.[1] Honeycombing can be microcystic (<4 mm cysts), macrocystic honeycombing (>4 mm cysts), or mixed microcystic and macrocystic. Multiplanar reformats can be helpful in differentiating honeycombing from traction bronchiectasis and paraseptal emphysema.

Honeycombing is the most specific sign associated with usual interstitial pneumonia (UIP) pattern of interstitial lung disease (ILD).[2] In a study done by Lynch et al., honeycombing was present in up to 90% of the patients with a diagnosis of idiopathic pulmonary fibrosis (IPF).[3] Similarly, Hunninghake et al. showed that a diagnosis of UIP could be established with a sensitivity of 74%, a specificity of 81% (Table 1), and a positive predictive value of 85% if lower lobe honeycombing (odd ratio 5.36) and upper lung irregular lines (odds ratio 6.28) were present on HRCT.[4] Another study conducted by Sumikawa et al. demonstrated that the HRCT feature that distinguished IPF from cellular nonspecific interstitial pneumonia (NSIP) and fibrotic NSIP were the extent of honeycombing (odds ratio, 5.16 and 2.10, respectively).[5]

Honeycombing can sometimes constitute more than 70% of the fibrotic portions of the lungs in ILDs and this can be referred to as "exuberant honeycomb sign" (Fig. 1b and c). It is associated more commonly with connective tissue diseases (CTD) UIP rather than IPF UIP.[6] Honeycombing can be present in other conditions such as NSIP and chronic hypersensitivity pneumonitis (HP). However, ground glass opacities dominate in NSIP and honeycombing, if present, is usually minimal. Similarly, HP can also demonstrate honeycombing, but other features such as centrilobular nodules, mosaic attenuation, and upper lobe predominant fibrosis are often present, differentiating it from UIP.[7]

## Subpleural Sparing

Subpleural sparing describes a lung parenchymal abnormality such as ground glass opacities, reticulation or honeycombing that spares the extreme periphery of the lung that abuts the pleura (Fig. 2). Subpleural sparing is most commonly associated with NSIP,[8] and if present, it suggests NSIP is more likely than UIP or HP.

A study conducted by Silva et al., which had 66 patients, showed that subpleural sparing if present on a HRCT was one of the best predictors for NSIP and was very useful in differentiating NSIP from UIP and HS ($P$ value $< 0.01$). This study described relative subpleural sparing as a characteristic feature of NSIP and found that it was one of the best predictors of NSIP, being present in 64% of patients with NSIP, in 11% with chronic HP, and in 4% with IPF.[9]

## Four Corners Sign

Four corner sign is a term used to describe a pattern of fibrosis that disproportionately involves the anterolateral aspects of the upper lobes and the posterosuperior aspects of the lower lobes (Fig. 3a and b). This sign, when present on

*Department of Radiology, University of Washington Medical Center, Seattle, WA.
†Department of Pathology, University of Washington Medical Center, Seattle, WA.

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Address reprint requests to Ayesha Nasrullah, MBBS, Department of Radiology, University of Washington Medical Center, 1959 NE Pacific St, Seattle, WA 98195. E-mail: ayshanas@uw.edu


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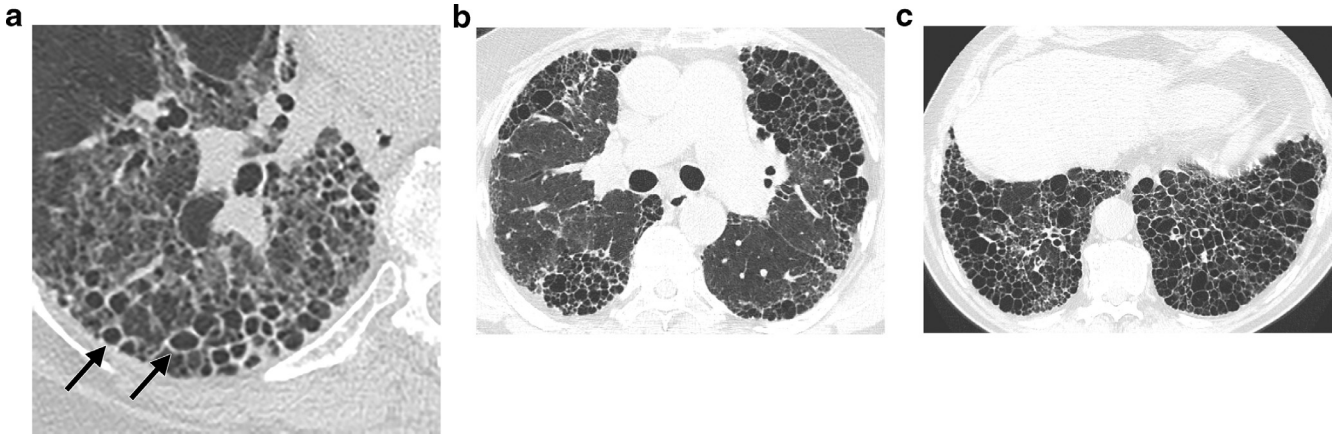


**Figure 1** (a) Honeycombing sign in a 75-year-old woman with the diagnosis of usual interstitial pneumonia. Axial HRCT of the chest shows peripheral and lower predominant multilayers of cysts (arrows). (b and c) Exuberant honeycombing in a 65-year-old man with history of rheumatoid arthritis and underlying diagnosis of usual interstitial pneumonia. Axial HRCT of the chest shows peripheral- and lower lobe predominant florid honeycombing compatible with "exuberant honeycomb sign." HRCT, high-resolution computed tomography.

**Table 1** Sensitivity and Specificity of the Associated Signs in Diffuse Lung Disease

| Signs in Diffuse Lung Disease | Associated Diseases | Sensitivity, Specificity |
|---|---|---|
| Honeycombing[4] | UIP | 74%, 81% (*controls included HS, sarcoidosis and NSIP patients) |
| Four corners sign[9] | (SSc-ILD). | 28.6%, 97.6% (*controls – IPF) |
| Straight edge sign[10] | CTD associated ILD. | 25%, 94% (*controls – IPF) |
| Subpleural sparing | NSIP | No data |
| Apicobasal gradient | UIP | No data |
| Spatial homogeneity | NSIP | No data |
| Spatial heterogeneity | UIP | No data |
| Temporal homogeneity | NSIP | No data |
| Temporal heterogeneity | NSIP | No data |
| Head cheese sign | HP, Sarcoidosis, atypical bacterial infections. | No data |
| Galaxy sign | Sarcoidosis | No data |
| Atoll sign | COP. | No data |
| Crazy paving | Pneumocystis pneumonia, PAP, sarcoidosis, ARDS, pulmonary hemorrhage | No data |

**Note: Prevalence data is provided in the text of the manuscript.**

HRCT, is usually very specific for systemic sclerosis-related ILD (SSc-ILD).

A recent study conducted by Walkoff et al. demonstrated a strong association between the four corner sign and SSC-ILD (Table 1). On HRCT examination, this sign had a sensitivity of 28.6% (95% confidence intervals, 17.2%, 43.6%) and a specificity of 97.6% (95% confidence intervals, 87.7%, 99.6%) for SSc-ILD.[10]

## Straight Edge Sign

The straight edge sign (SES) is used to define reticulation which is confined to the lung bases and has a sharply demarcated border; most easily identifiable in the craniocaudal plane (Fig. 4). This sign, if present, is thought to be strongly associated with CTD-associated ILD and can be useful in differentiating UIP pattern CTD-ILD from UIP pattern IPF.

A recent study conducted by Chung et al. showed that the SES when present had a sensitivity of 25% and specificity of 94% for UIP pattern CTD-ILD (Table 1) when compared with UIP pattern idiopathic interstitial fibrosis ($P < 0.001$).[6]

A follow-up study conducted by Zhan et al. demonstrated that the SES was much more commonly seen in NSIP than UIP (46.6% compared with 3.3%, respectively; $P < 0.001$), postulating that SES likely signals NSIP or cases of UIP that arose from NSIP.[11]

## Apical-Basal Gradient

Apical-basal gradient is a descriptive term used when an abnormality such as reticulation or honeycombing progressively increases in intensity from the apex toward the lung base, confirming an obvious increasing gradient from the apex toward the base (Fig. 5a and b). This is best depicted in the coronal reformats of the HRCT.

This finding is most commonly associated with UIP where the common HRCT features such as honeycombing and reticulation progressively increase in gradient from the apex toward

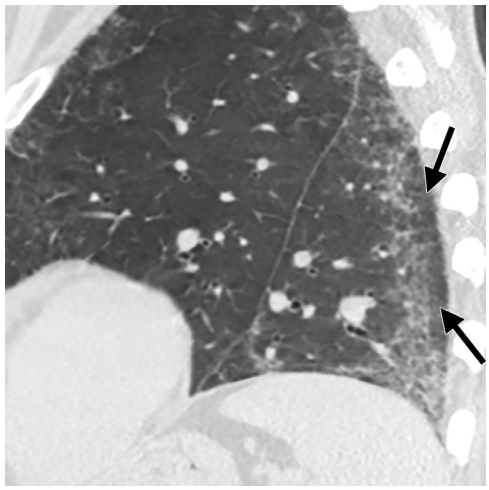

**Figure 2** Subpleural sparing in 61-year-old man with history of scleroderma. (a) Axial and (b) sagittal HRCT of the chest shows peripheral predominant ground glass opacities and reticulation with relative sparing of the immediate subpleural periphery. The patient was diagnosed with NSIP. HRCT, high-resolution computed tomography; NSIP, nonspecific interstitial pneumonia.

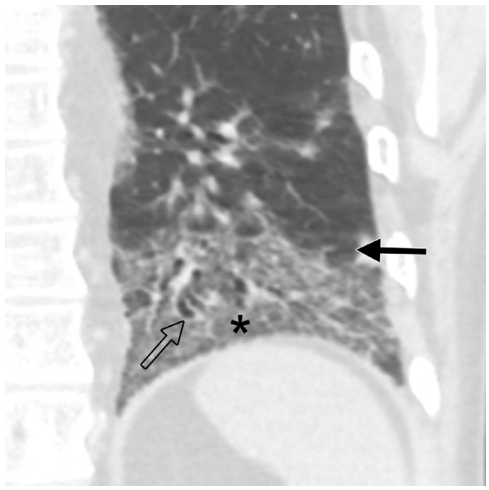

**Figure 4** Straight edge sign in a 46-year-old man with connective tissue disease. Axial and coronal HRCT of the chest shows lower lobe predominant pulmonary fibrosis characterized by ground glass opacity, reticulation (black asterisk), and traction bronchiolectasis (open arrow). There is a straight interface between the lung fibrosis and the normal lung parenchyma perpendicular to the lateral chest wall (black arrow). HRCT, high-resolution computed tomography.

the lung base.[4,12] In NSIP, the predominant ground glass opacities commonly associated with the disease process also involve lower lung lobes to a greater extent, however, an obvious apicobasal gradient, as seen in UIP, is usually missing.[13]

## Spatial Homogeneity/ Heterogeneity

Spatial homogeneity on a pathology sample denotes uniform and homogenous involvement of the lung parenchyma with a particular disease process. Conversely, spatial heterogeneity denotes patchy and heterogenous lung involvement with normal lung in between.

On HRCT, spatial homogeneity is seen as homogenous and confluent disease process involving the lung parenchyma whereas spatial heterogeneity is seen as patchy and heterogenous involvement of lung parenchyma sometimes with normal interspersed lung parenchyma (Fig. 6a and b). Spatial homogeneity is commonly associated with NSIP and spatial heterogeneity is usually seen with UIP.

A study conducted by Elliot et al. showed that UIP was more likely than NSIP to be patchy in distribution and to demonstrate a subpleural predominance reflecting the spatial inhomogeneity seen pathologically ($P < 0.001$ for both).[14]

## Temporal Homogeneity/ Heterogeneity

Temporal homogeneity on a biopsy specimen denotes that there is a single stage of disease seen in the entire specimen (Fig. 7c). Conversely, temporal heterogeneity denotes that there are different stages of the disease process seen in the same biopsy specimen (Fig. 6c). Temporal homogeneity is a feature of NSIP whereas temporal heterogeneity is usually seen with UIP.[15]

NSIP affects the lung parenchyma in a spatially homogenous pattern with uniform involvement of the alveolar septae by interstitial infiltrates in the same stage of inflammation or fibrosis.[16] On HRCT, this feature of temporal homogeneity is

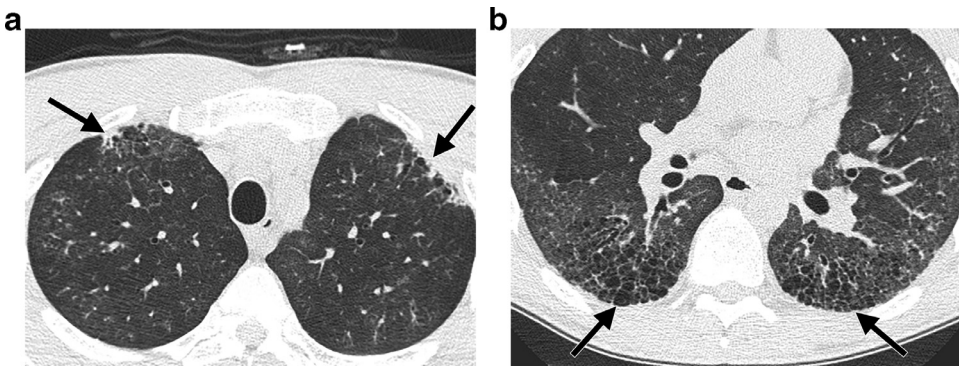


**Figure 3** Four corner sign in a 36-year-old man with a history of scleroderma. Axial HRCT of the chest shows subpleural reticulations, ground glass opacities, and traction bronchiectasis within the anterior upper lobes (arrows) and the posterior medial aspects of the lower lobes (arrows). HRCT, high-resolution computed tomography.

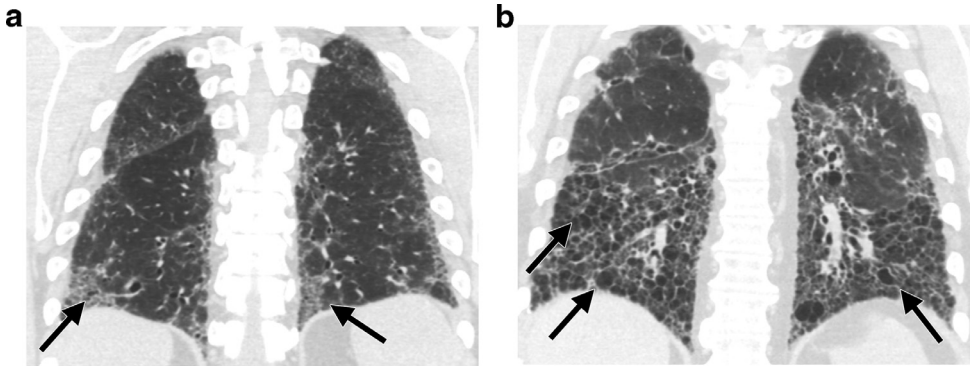


**Figure 5** Apico-basilar gradient. (a) Coronal HRCT of the chest shows peripheral and lower lobe predominant reticulation and ground glass opacities (arrows) in a patient diagnosed with NSIP. (b) Coronal HRCT of the chest shows peripheral and lower predominant, honeycombing, and traction bronchiectasis (arrows) in a patient diagnosed with UIP. HRCT, high-resolution computed tomography; NSIP, nonspecific interstitial pneumonia.

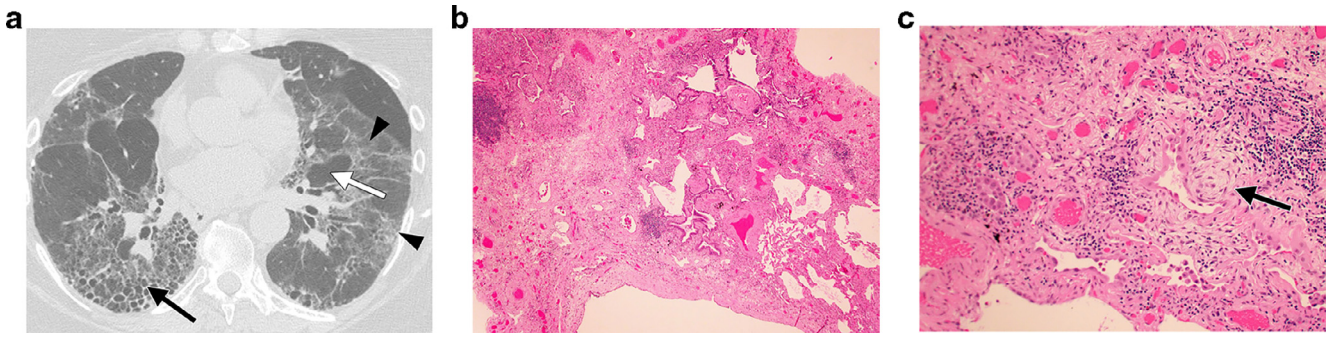


**Figure 6** Characteristics of UIP. (a) Axial HRCT shows spatial heterogeneity in the form of areas of fibrosis alternating with normal lung parenchyma. Note also the presence of honeycombing which represent end stage fibrosis and areas of ground glass representing earlier stage of fibrosis. The presence of different stages of fibrosis at the same time is referred to as temporal heterogeneity. (b) Histopathology images with hematoxylin and eosin stain (H&E) with 10× magnification shows spatial heterogeneity in the form of subpleural fibrosis and honeycombing along with interstitial chronic inflammation with lymphoid aggregates. Areas of normal lung architectures in between are present. (c) Histopathology images with 20× magnification show temporal heterogeneity in the form of fibroblast focus (black arrow) denoting active fibrosis juxtaposed with dense end stage fibrosis. HRCT, high-resolution computed tomography.

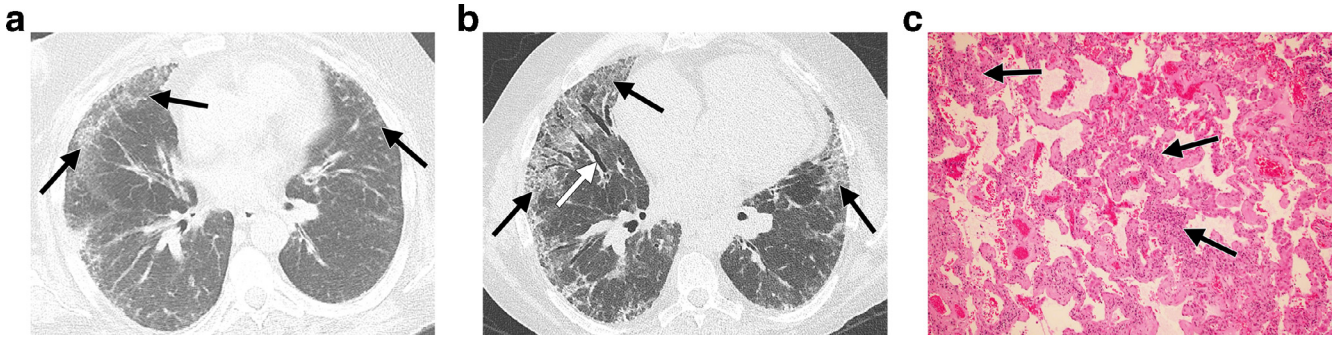


**Figure 7** Temporal homogeneity of NSIP. (a and b) Axial HRCTs show fibrosis in the form of peripheral predominant reticulation and to lesser extent ground glass opacities representing homogenous stage of fibrosis (black arrows) which progressed evenly and uniformly to more fibrosis over the years evident by the traction bronchiectasis (white arrow). (c) Histopathology images with H&E stain (10× magnification) show uniform chronic interstitial inflammation and fibrosis causing uniform diffuse thickening of the alveolar walls (black arrows). HRCT, high-resolution computed tomography.

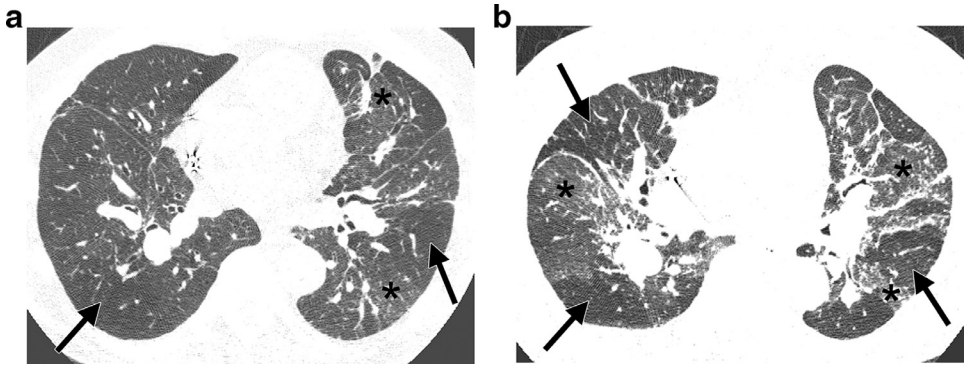


**Figure 8** Air trapping sign in a 75-year-old woman with history of chronic hypersensitivity pneumonitis. (a) Axial HRCT of the chest on inhalation shows mosaic attenuation of the lung parenchyma with mixed regions of low (black arrows) and high attenuation (black asterisk). (b) Axial HRCT on exhalation shows no change on the density of the low attenuation areas demonstrating air trapping (black arrows). The high attenuation regions increase further in density (black asterisk) confirming that these regions represent normal intervening lungs parenchyma. HRCT, high-resolution computed tomography.

seen as uniform and homogenous involvement of the lung parenchyma by ground glass or reticulation with no areas of normal interspersed lung parenchyma (Fig. 7a and b).[14]

In UIP, there is patchy fibrosis with coexistent lesions at different stages of fibrosis.[16] On HRCT, this manifests as patchy areas of lung parenchymal involvement with different stages of fibrosis.[14]

## Mosaic Attenuation

Mosaic attenuation is used as a descriptive term when there are adjacent secondary pulmonary lobules of different attenuation present on the inspiratory scan of a HRCT. This abnormality can be caused by air trapping in small airways disease or by differential perfusion in a pulmonary vascular disease.[17] Occasionally, an interstitial or alveolar filling process such as infection can create the appearance of mosaic attenuation, but in such cases the different attenuating regions of lung will not be confined to the secondary pulmonary lobules.

The cause of mosaic attenuation cannot be determined in studies that only contain images acquired during inhalation, which is the reason HRCT also acquires images during exhalation. Hence, further differentiation between various etiologies causing mosaic attenuation can be made by evaluating for the presence of air trapping on expiratory scans. If air trapping is present, then the low attenuation areas (abnormal segments) will not change in density during the expiratory scans, whereas the high attenuation regions (normal segments) will increase in density. Hence the expiratory scans will accentuate the difference in regional attenuation confirming the presence of air trapping (Fig. 8a and b). However, if air trapping is not present then all the lung regions of different attenuation will increase in density on exhalation.[18,19]

## Head Cheese Sign

On HRCT, the head cheese sign describes lobular areas of 3 different attenuations; low, normal, and high, which is reminiscent of the head cheese cold cut.[20]

The head cheese sign is caused by a disease process that has both obstructive and infiltrative components.[21] The low attenuation areas on the inspiratory HRCT represent air trapping—which can be confirmed on expiratory scans. The high attenuation regions correspond to areas of patchy ground glass opacity caused by inflammation (Fig. 9).

The head cheese sign is classically described in HP. Ancillary features such as ground glass attenuation centrilobular nodules point toward a diagnosis of HP.[22]

## Galaxy Sign

Galaxy sign is used to describe coalescing fine nodules that are composed of a large central nodule or opacity with surrounding smaller nodules, an appearance reminiscent of the distribution of stars in a galaxy. This sign is most commonly seen in sarcoidosis (Fig. 10) and described in pulmonary tuberculosis.

A study conducted by Nakatsu et al. demonstrated that the galaxy sign was seen in up to 27% of patients with sarcoido-

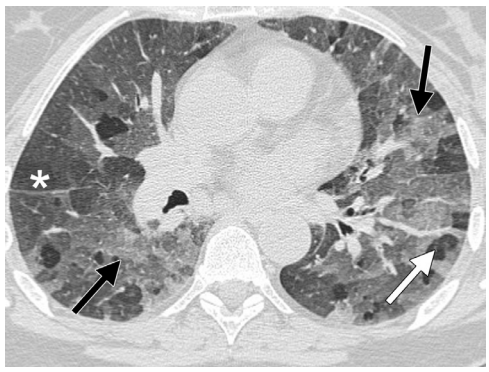

**Figure 9** Head cheese sign in a 62-year-old woman with history of chronic hypersensitivity pneumonitis from mold exposure. Axial HRCT of the chest shows combination of areas of ground glass opacities (black arrows), areas of low attenuation representing air trapping (white arrow), and areas of normal attenuation of the lung parenchyma (white asterisk). HRCT, high-resolution computed tomography.

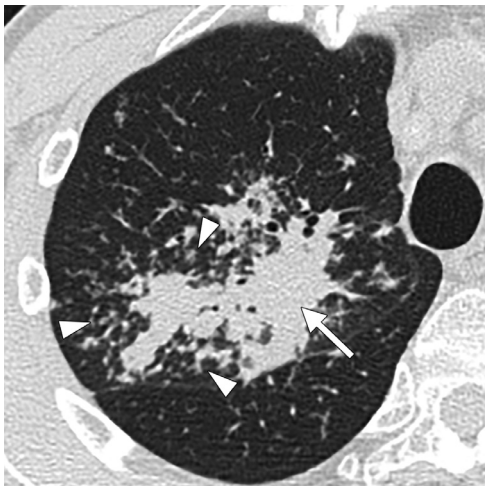

**Figure 10** Galaxy sign in a 59-year-old man with history of sarcoidosis. Axial HRCT of the chest shows right upper lobe mass-like consolidation (white arrow) surrounded by small nodules (arrow heads). HRCT, high-resolution computed tomography.

sis.[23] Another study carried out by Heo et al. showed that galaxy sign could be seen in active tuberculosis. However, in tuberculosis this was associated with tree-in-bud pattern too.[24]

## Atoll Sign

Atoll sign is also known as the reverse halo sign. This sign is used on HRCT when there is a central ground glass opacity surrounded by denser crescent or ring of consolidation (2 mm or more in thickness; Fig. 11). This sign can be seen in cryptogenic organizing pneumonia (COP), invasive fungal infections in an immunocompromised host, sarcoidosis, and tuberculosis.

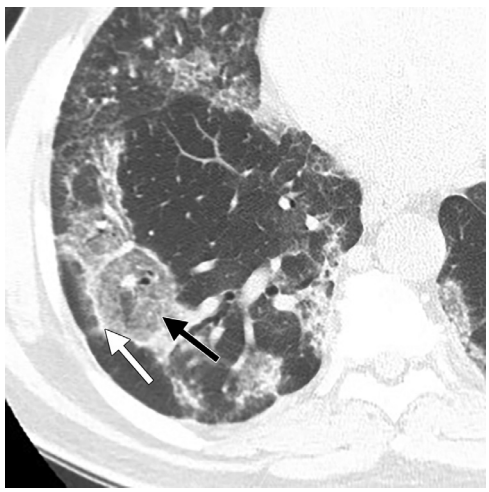

**Figure 11** Atoll sign (reverse halo sign) in a 61-year-old man with history of waxing and waning lesions responsive to steroids. Axial HRCT of the chest shows right lower lobe ground glass opacity (black arrow) with thin relatively smooth peripheral rind of consolidation (white arrow) consistent with reversed halo sign. The patient was diagnosed with organizing pneumonia. HRCT, high-resolution computed tomography.

Initially the atoll sign was thought to be associated exclusively with COP. A study conducted by Kim et al. in 2003 demonstrated that atoll sign was seen in up to one-fifth of the patients with COP and was relatively specific to this disease.[25]

However, additional studies showed that this sign could be seen in other infectious and noninfectious pulmonary diseases. Marchiori et al. showed that the atoll sign was seen in active tuberculosis and COP, and that the presence of nodular walls or nodules inside the reversed halo could be used to differentiate the 2 diseases. When nodules were present, active pulmonary tuberculosis was more likely than COP.[26]

In an immunocompromised host, the reverse halo sign strongly suggests an invasive fungal infection such as Mucor or Rhizopus.[27,28] Other diseases in which this sign can be seen are granulomatosis with polyangiitis (formerly Wegener granulomatosis) and sarcoidosis.[29]

## Crazy Paving

Crazy paving is a descriptive term used when there is diffuse ground glass opacity superimposed on inter and intralobular septal thickening (Fig. 12).

The differential considerations for crazy paving include etiologies such as pneumocystis pneumonia, alveolar proteinosis, sarcoidosis, adult respiratory distress syndrome, and pulmonary hemorrhage.[30,31] Crazy paving can also be seen in pulmonary edema, lipoid pneumonia, and adenocarcinoma spectrum lesions (formerly known as bronchoalveolar carcinoma). The diagnostic possibilities can be reduced by considering clinical presentation, history, and additional radiological signs.

## Conclusion

The diagnosis of diffuse lung disease is aided by the recognition of patterns on HRCT and radiographic signs when present help indicate specific ILD diagnosis. The evidence associated with each of these signs differs. In some cases,

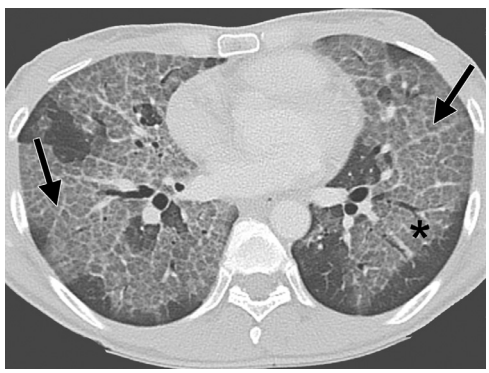

**Figure 12** Crazy-paving sign in 40-year-old man with pulmonary alveolar proteinosis. Axial HRCT of the chest shows bilateral areas of ground glass opacity (black asterisk) combined with superimposed inter- and intralobular septal thickening (arrows). This pattern resembles paving with broken pieces of stones or concrete. HRCT, high-resolution computed tomography.

such as honeycombing, air trapping or subpleural sparing, they can be used to establish a most likely diagnosis or exclude diagnostic possibilities. In other cases, such as the atoll sign, they generate a set of diagnostic possibilities that can be used in conjunction with patient symptoms and history to suggest a likely diagnosis.

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