Beyond Metastatic Disease: A Pictorial Review of Multinodular Lung Disease With Computed Tomographic Pathologic Correlation

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Multinodular lung disease is routinely encountered on chest computed tomography (CT). Pulmonary nodules may be categorized as perilymphatic, random, or centrilobular, based on their CT distribution. Recognition of the pattern of distribution allows the differential diagnosis to be narrowed to a few common diseases. This review illustrates the CT appearance and provides a practical differential diagnosis of each pattern of nodules.

Secondary Pulmonary Lobule

Patterns of distribution of multinodular lung disease are described with relation to the secondary pulmonary lobule. The secondary pulmonary lobule is the smallest unit of lung function margined by connective tissue septa (interlobular septa) (Figure 1). Pulmonary veins and lymphatics course within the interlobular septa at the edges of secondary lobules. The artery and bronchus supplying each secondary pulmonary lobule are named the centrilobular artery and bronchus (Figure 1). The centrilobular artery and bronchus lie adjacent to one another, and are accompanied by pulmonary lymphatics. Pulmonary lymphatics, in addition to their locations within the interlobular septa and along bronchoarterial bundles, are present within the pleura.

Perilymphatic Nodules

A perilymphatic pattern describes nodules in the expected distribution of pulmonary lymphatics: along pleural surfaces, interlobular septa, and the peribronchovascular interstitium (Figure 2). Keys to the recognition of a perilymphatic nodular pattern are identification of subpleural and peribronchovascular nodules. The “pipe-cleaner sign” describes the beaded appearance of bronchovascular bundles that results from nodules within peribronchovascular lymphatics. The beaded appearance resembles that of a pipe cleaner, a brush originally used to clean smoking pipes (Figure 3). Diseases in which perilymphatic nodules predominate include sarcoidosis, lymphangitic carcinomatosis, silicosis, and coal worker’s pneumoconiosis (CWP).

Sarcoidosis

Sarcoidosis is a multisystem granulomatous disease of unknown etiology characterized by the presence of noncaseating granulomata. The lung is the most commonly affected organ [1]. Although sarcoidosis can have a myriad of appearances on CT imaging of the chest, it is most commonly characterized by paratracheal and symmetric bilateral hilar lymphadenopathy and perilymphatic nodules. Nodules in sarcoidosis predominate along bronchovascular bundles and along pleural surfaces [2]. Pulmonary parenchymal abnormalities in sarcoidosis are almost always bilateral and predominate in the upper lobes. Confluent alveolar opacities, conglomerate masses, traction bronchiectasis, air trapping, and architectural distortion also may be present.
Pulmonary Lymphangitic Carcinomatosis

Pulmonary lymphangitic carcinomatosis (PLC) is the dissemination of tumour in the lymphatic system of the lungs. The pathologic hallmark of PLC is the presence of malignant cells in the lymphatic vessels of bronchovascular bundles, interlobular septa, and pleura. PLC occurs most commonly with adenocarcinomas of the lung, breast, gastrointestinal system, prostate, and kidney. In most cases, the tumour spreads hematogenously to the lungs and then invades the pulmonary lymphatics and surrounding interstitium [3]. PLC is characterized on CT by smooth and/or nodular thickening of the peribronchovascular interstitium, interlobular septa, and pleura [4,5] (Figures 4 and 5). PLC may be diffuse, unilateral, or focal. The perilymphatic pattern of PLC may occur in conjunction with imaging features of hematogenous spread of tumour, which produces a mixed pattern of both perilymphatic and randomly distributed nodules.

Pneumoconioses

Pneumoconioses are lung diseases caused by the inhalation of dusts. Silicosis, CWP, and asbestosis are the most commonly occurring pneumoconioses. A perilymphatic pattern of nodules may be seen in either silicosis or CWP (Figure 6). Silicosis is caused by the inhalation of fine particles of crystalline silicon dioxide (silica). Occupations such as mining, quarrying, tunneling, stonecutting, and sandblasting are associated with silicosis. CWP is caused by exposure to coal dust, which contains silica. A clinical history of exposure is essential for the diagnosis of silicosis and CWP. The characteristic abnormality in simple silicosis-CWP is small well-circumscribed nodules, centrilobular, and subpleural predominant, and that usually are 2-5 mm in diameter [6]. Nodules predominate in upper and posterior lungs as a result of diminished lymphatic clearance in these regions [6]. The disease is considered “complicated” when nodules coalesce to form larger nodules (at least 1 cm in diameter) and masses.

Random Nodules

Randomly distributed nodules are usually the result of hematogenous dissemination. In distinction to perilymphatic...
nodules, random nodules show no consistent relationship to any secondary pulmonary lobular structures. They are found, roughly equally, in relation to the visceral pleura, interlobular septa, and the center of the secondary pulmonary lobule (Figure 7A). The distribution is bilateral and symmetric. A basilar predominance of nodules is frequently present due to preferential blood flow to the lung bases [7]. As a result of their hematogenous origin, nodules may have “feeding vessels” [7]. The differential diagnosis for the random pattern includes hematogenous metastases (Figures 7B and 8), miliary disease (Figure 7C), septic emboli (Figure 7D), and angioinvasive fungal infection (Figure 9).

Hematogenous Metastases

Hematogenous metastases to the lungs frequently originate from the breast, gastrointestinal tract, kidney, and

Figure 3. (A) Pipe cleaner, a brush originally used to clean smoking pipes. (B) Pipe-cleaner sign in sarcoidosis. Note the beaded appearance of several bronchovascular bundles (arrows); 10-mm-thick axial maximum intensity projection images can be helpful in demonstrating the pipe-cleaner appearance of nodules studding the bronchovascular bundles. This figure is available in colour online at http://carjonline.org/.

Figure 4. Lymphangitic carcinomatosis from nonsmall-cell bronchogenic carcinoma. Note the nodular thickening of the interlobular septa and interlobar fissures (arrows).

Figure 5. Lymphangitic carcinomatosis from renal cell carcinoma (RCC). (A) A sagittal reformatted computed tomography image, showing extensive pleural involvement with tumour extension along interlobar fissures (asterisks). (B) Lung specimen in a different patient with metastatic RCC, showing lymphangitic spread of tumour along the interlobar fissures (arrows). This figure is available in colour online at http://carjonline.org/.

Figure 6. (A) Pipe cleaner, a brush originally used to clean smoking pipes. (B) Pipe-cleaner sign in sarcoidosis. Note the beaded appearance of several bronchovascular bundles (arrows); 10-mm-thick axial maximum intensity projection images can be helpful in demonstrating the pipe-cleaner appearance of nodules studding the bronchovascular bundles. This figure is available in colour online at http://carjonline.org/.
Figure 6. Pneumoconioses. Hard metal pneumoconiosis with perilymphatic distribution. (A) Multiple subpleural nodules (black arrows) in addition to some septal (arrowheads) and centrilobular (white arrows) nodules. (B) Open lung biopsy specimen from same patient, showing a septal nodule (solid arrow) along an interlobular septum (dashed arrows) and a large subpleural nodule (asterisk) (hematoxylin and eosin, 4x). Also note the peribronchovascular nodule (arrowhead). Br = bronchus; PA = pulmonary artery branch. (C) Silicosis. Perilymphatic nodules in silicosis and coal worker’s pneumoconiosis predominate in the upper and posterior lungs as a result of diminished lymphatic clearance in these regions. This figure is available in colour online at http://carjonline.org/.

Figure 7. Random nodules: Schematic (A), metastatic adenocarcinoma of lung (B), miliary histoplasmosis in a patient who was positive for human immunodeficiency virus (C), and septic emboli (D). In distinction to perilymphatic nodules, random nodules show no consistent relationship to any secondary pulmonary lobular structures. They are found in relation to the visceral pleura, interlobular septa, and center of the secondary pulmonary lobule to be roughly equally. Randomly distributed nodules usually are the result of hematogenous dissemination and often are bilateral and relatively symmetric. This figure is available in colour online at http://carjonline.org/.
prostate. They typically manifest on CT as smoothly marginated nodules. When few in number, they tend to have a basilar and/or peripheral predominance. When numerous, they tend to be uniformly distributed throughout the lungs. Nodules tend to be evenly distributed with respect to lobular anatomy and may range from a few millimeters to more than 1 cm in size.

Miliary Disease

Miliary nodules are usually the result of hematogenous dissemination of infection or malignancy. Miliary infections may occur in cases of tuberculosis as well as fungal infection, including histoplasmosis, coccidioidomycosis, and candidiasis. Miliary metastases are frequently due to thyroid cancer, renal cancer, and melanoma [7]. Miliary nodules tend to be well defined and are ≤3 mm in diameter [8].

Septic Emboli

Septic embolism may occur as a result of infected indwelling catheters and/or devices or intravenous drug use. Septic emboli also may originate within peripheral veins at sites of thrombophlebitis. Septic emboli manifest on CT as randomly distributed nodules, frequently in varying stages of cavitation as
a result of intermittent seeding of the lungs by infected material. Peripheral wedge-shaped areas of infarction may coexist.

**Centrilobular Nodules**

Centrilobular nodules occur within the center of secondary pulmonary lobules and are separated from pleural surfaces, fissures, and interlobular septa by several millimeters (Figure 10). Diseases that involve the small airways are the most common etiology of centrilobular nodules. The differential diagnosis of centrilobular nodules includes infectious bronchiolitis, respiratory bronchiolitis (RB), and hypersensitivity pneumonitis (HP).

Figure 10. Centrilobular nodules. (A) Centrilobular nodules occur within the center of secondary pulmonary lobules. Nodules are separated from pleural surfaces, fissures, and interlobular septa by several millimeters. (B) Centrilobular nodules due to pneumonia in a patient with human immunodeficiency virus. Nodules are seen within the center of several secondary pulmonary lobules in the right middle lobe. Note that nodules are separated from the right major fissure by several millimeters. This figure is available in colour online at [http://carjonline.org/](http://carjonline.org/).

Figure 11. (A) Right lower lobe “tree-in-bud” opacities secondary to Moraxella catarrhalis infection in a 59-year-old male heart transplantation recipient. (B) Lung specimen in a case of bacterial bronchopneumonia, showing a “tree-in-bud” opacity (arrow) as well as numerous additional centrilobular nodules. This figure is available in colour online at [http://carjonline.org/](http://carjonline.org/).
Infectious Bronchiolitis

Infectious bronchiolitis represents inflammation of the bronchiolar wall or bronchiolar lumen as a result of infection. Infectious bronchiolitis may be caused by a variety of organisms, including bacteria, mycobacteria, fungi, viruses, and mycoplasma. Findings on CT include poorly defined centrilobular nodules and clusters or rosettes of nodules. Tree-in-bud opacities also occur within the center of the secondary pulmonary lobule in patients with infectious bronchiolitis. Tree-in-bud opacities are the result of dilated, impacted bronchi and are visualized as Y- or V-shaped branching micronodular structures on CT (Figure 11). These opacities are so named because they resemble a budding tree in spring. The most common etiologies of tree-in-bud opacities are pulmonary infection and aspiration.

Respiratory Bronchiolitis

RB is a common finding in persons who smoke cigarette. If pulmonary symptoms are present, then the condition is known as RB-interstitial lung disease. RB is characterized histologically by the presence of macrophages filling respiratory bronchioles and adjacent alveolar ducts and/or alveoli [9]. Findings on CT include poorly defined centrilobular nodules and ground-glass opacities with an upper lung predominance [10,11] (Figure 12).

Hypersensitivity Pneumonitis

HP, or extrinsic allergic alveolitis, is a granulomatous inflammatory lung disease caused by the inhalation of antigenic organic particles or fumes. Antigens include plant products, animal products, aerosolized microorganisms, and organic chemicals. Typical findings in the subacute phase include ground-glass opacities and small ill-defined centrilobular nodules [12,13] (Figure 13). Mosaic attenuation and air trapping, frequently present in the subacute phase of HP, are findings that may help differentiate HP from RB [12].

Conclusion

Recognition of subpleural nodules, septal thickening, and the “pipe-cleaner sign” of nodules along central bronchovascular bundles are keys to the diagnosis of a perilymphatic distribution of pulmonary nodules. Randomly distributed nodules show no consistent relationship to any secondary pulmonary lobular structures and are bilateral and symmetric. Centrilobular nodules occur in the center of secondary pulmonary lobules. Recognition of the pattern of distribution allows the differential diagnosis to be narrowed to a few common diseases.

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References


