A diffuse pattern of pulmonary nodules, ranging from a few millimeters to 1 cm in diameter, may indicate interstitial or airspace disease (Algorithm 1). The predominant location of the nodules may provide a clue to the underlying condition. For example, fissural or pleural surfaces are frequently involved in sarcoidosis. Upper lobe predominance suggests silicosis or coal workers’ pneumoconiosis; whereas lower lobe preponderance is more likely in asbestosis or hematogenous metastases, and bronchocentric predominance suggests sarcoidosis or Kaposi sarcoma. The nodules may have a miliary distribution (tuberculosis, silicosis, sarcoidosis, metastases), cavitate (septic emboli, metastases, infection) (Fig. 1), or calcify (tuberculosis, silicosis, metastases).

Multiple lung nodules may have a random or centrilobular pattern. Random nodules can have variable density and are most often uniformly distributed (Fig. 2). The nodules are typically of hematogenous origin and thus are situated close to small vessels. They may also occur near the pleural surfaces. In silicosis, the random nodules predominate in the middle and upper lung zones, whereas metastases are most prevalent in the lung bases.

Centrilobular nodules are not adjacent to the pleural surfaces and the interlobular septa, often separated from them by a lucent rim. Centrilobular nodules are usually caused by diseases in which the original lesion develops near bronchioles. Nodules may presents with a ground-glass appearance when there is involvement of the adjacent peribronchiolar airspaces (Fig. 3).

The tree-in-bud pattern is a manifestation of inflammatory, usually infectious, disease affecting the smallest bronchi and their adjacent alveoli. The “trees” represent dilated bronchioles filled with mucus, pus, or fluid; the “buds” are due to clusters of filled alveoli that have poorly defined margins and are seen in a centrilobular location.

Algorithm 1—Flow chart shows algorithm for treatment of multinodular disease.
Sarcoidosis

Sarcoidosis is a systemic inflammatory disease that predominantly involves the lungs but also may affect the joints, eyes, kidneys, and skin. The disease most commonly develops between the ages of 25 and 40 years. Although the exact cause of sarcoidosis is unknown, it may reflect a disproportional immunologic reaction against a bacterial or environmental antigen. The diagnosis of sarcoidosis is often made when characteristic findings are detected incidentally on a chest radiograph obtained for unrelated symptoms. Patients may have persistent cough or such systemic manifestations as erythema nodosum, uveitis, arthralgia, arthritis, and hypercalcemia. The most common complication of sarcoidosis is respiratory failure due to pulmonary fibrosis. Cardiac involvement can result in myocardial infarction, arrhythmias, or even sudden death.

Fig. 1—Cavitation in septic emboli. A and B, CT images at level of carina (A) and lung bases (B) show emboli as primarily peripheral nodules (white arrows), one of which is cavitated (black arrow).

Fig. 2—Random nodules in metastatic melanoma. CT image at level of lung bases shows metastases of varying sizes and shapes throughout lung parenchyma (arrows).

Fig. 3—Centrilobular nodules in aspiration pneumonia. CT at level of right lower lobe in patient with history of chronic aspiration. A and B, CT image obtained at level of right lower lobe vein (A) shows scattered ground-glass nodules (arrows). At slightly more caudal level (B), these nodules coalesce into larger areas of ground-glass opacities (arrows).
The classic radiographic appearance of bilaterally symmetric enlargement of hilar and para-tracheal nodes develops in up to 90% of patients with sarcoidosis. The outer borders of the enlarged hila are usually lobulated. About 20% of patients have diffuse parenchymal disease, most commonly a reticulonodular pattern that predominantly involves the upper lung zones and may lead to extensive interstitial pulmonary fibrosis. The nodal enlargement typically resolves as the parenchymal disease develops, unlike lymphoma or tuberculosis. The bilateral symmetry differs from tuberculosis, and there is no retrosternal involvement as in lymphoma.

On thin-section CT, sarcoidosis typically presents as irregular micronodules (1–5 mm) with interstitial thickening that extends along the bronchovascular bundles from the hilum to the periphery, predominantly in the upper lung zones (Figs. 4 and 5). In late stages, fibrous distortion of lung parenchyma may be seen at CT before it is apparent on chest radiographs. Other manifestations of sarcoidosis at CT include ground-glass opacities, alveolar sarcoidosis (airspace nodules and consolidation with air bronchograms), cysts and cavitation (in necrotizing sarcoidal angiitis), and bronchial wall thickening and airway stenoses.
Diffuse Pulmonary Nodules

**Silicosis**

Silicosis is an irreversible occupational lung disease caused by chronic inhalation of dust containing crystalline silica, which causes diffuse inflammation that leads to lung fibrosis and emphysema. Silica exposure most often occurs in people who work in construction, mining, sandblasting, stonecutting, and the manufacture of abrasives as well as those who work with glass, pottery, and on railroads. Most who develop the disease are men under 50 years old. The symptoms of silicosis develop about 20 years after initial exposure. Some affected individuals are asymptomatic, whereas those with more severe disease present with cough, dyspnea, and increased sputum (black sputum in coal workers).

On chest radiographs, the earliest and most characteristic findings are small, well-circumscribed round nodules that predominantly involve the posterior portions of the upper lungs and are likely to calcify. Hilar and mediastinal lymphadenopathy are common; characteristic peripheral eggshell calcification of the enlarged nodes (5% of cases) is virtually pathognomonic of silicosis. The parenchymal pulmonary nodules increase in size and number as the disease advances, eventually forming conglomerate masses (> 1 cm) that are usually irregular and ill defined with peripheral stranding. This process is usually symmetric and located in the upper lobes or superior segments of the lower lobes and tends to progressively migrate toward the hilum as the fibrotic process progresses. The volume of the lungs progressively decreases and cavitation can occur.

On thin-section CT, silicosis typically appears as fine nodular opacifications (1–10 mm) that are diffusely scattered throughout both lungs in a centrilobular and subpleural location (Fig. 6). In mild disease, they may be seen only in the upper lobes and have a posterior predominance. The nodules calcify in about 3% of cases, and chains of subpleural nodules may produce pseudoplaques. Unlike lymphangitic spread of carcinoma and sarcoidosis, the nodules in silicosis infrequently occur in relation to thickened interlobular septa. The development of progressive massive fibrosis, indicating the presence of complicated disease, is always associated with a background of small nodules visible on thin-section CT.

**Malignancy**

*Hematogenous Metastases*

Pulmonary metastases occur in 20–30% of malignancies, usually the result of hematogenous spread of tumor cells. Less commonly, they are secondary to lymphatic spread. Endobronchial spread is unusual but can occur with head and neck malignancies as well as renal and breast carcinomas.

On chest radiographs, pulmonary metastases most commonly produce smooth nodules with well-defined margins that predominantly involve the lower lobes. Depending on their mode of growth, they can vary from diffuse micronodular shadows resembling military disease (especially the snowstorm of thyroid carcinoma) to multiple large, well-defined “cannonballs” (primarily with choriocarcinoma and seminoma). Cavitation occurs in about 4% of metastases, most commonly from squamous cell neoplasms (also adenocarcinomas of the large bowel and sarcomas).
On CT, hematogenous metastases typically appear as small discrete nodules that have a peripheral and basal predominance when limited in number but a uniform distribution when there are innumerable lesions (Figs. 7 and 8). Some nodules may appear to be related to small branches of pulmonary vessels. Lymphangitic metastases, which are thought to be most often of hematogenous origin with secondary growth into the lymphatic system, produce smooth or nodular thickening of the peribronchovascular interstitium and interlobular septa with preservation of normal lung architecture at the lobular level (Fig. 9). Hilar lymphadenopathy occurs in approximately 50% of cases.

**Lymphoma**

Lymphoma most commonly presents as painless cervical or supraclavicular lymphadenopathy. Cough or chest pain may reflect mediastinal involvement, and splenomegaly is often evident. Today, about 90% of patients with lymphoma are cured of the disease.

One manifestation of secondary lymphoma is multiple nodules, which often have fuzzy outlines and are most numerous in the lower lobes. This appearance is usually associated with mediastinal and hilar lymph node enlargement. Cystlike lesions may simulate central cavitation.

**Bronchioloalveolar Carcinoma**

Bronchioloalveolar carcinoma (BAC) is a subtype of adenocarcinoma of the lung that is distinguished by its peripheral location, well-differentiated cytology, growth along intact alveolar septa (lepidic growth pattern), and tendency for both bronchial and lymphatic spread. BAC is divided histologically into mucinous, nonmucinous, and mixed subtypes. Distinguishing mucinous from nonmucinous subtypes has significant therapeutic and prognostic implications.

BAC is three to four times more likely to develop in smokers, especially heavy smokers with long-term exposure. Nevertheless, about one third of cases occur in individuals who have never smoked and a similar number are former or intermittent smokers. Other postulated risk factors for BAC include fibrotic scarring in the lung, occupational exposure, and viral infection.

Multiple discrete small nodules, either randomly distributed or primarily centrilobular, in BAC may mimic hematogenous metastases (Fig. 10). A more common appearance of this condition is diffuse, patchy, or multifocal areas of consolidation that are peribronchovascular and contain air bronchograms or air-filled cystic spaces. Because fluid and mucus produced by the tumor are of low attenuation, a characteristic appearance in BAC is the “CT angiogram sign,” in which contrast-enhanced pulmonary vessels appear denser than surrounding opacified lung.

**Fig. 7—**Metastases from prostate cancer. Two relatively uniform metastases are seen in right and left lung (arrows).

**Fig. 8—**Metastases from renal cell cancer.

A, CT image obtained at level of carina shows nodules in both central and peripheral lung parenchyma (arrows).

B, CT image obtained at lower lobe base shows tiny metastases in very peripheral location (arrows).
Diffuse Pulmonary Nodules

In addition to these manifestations of BAC, it should not be forgotten that early adenocarcinoma may also present as small pulmonary nodules (Fig. 11).

Kaposi Sarcoma

Kaposi sarcoma, the most common AIDS-related multicentric neoplasm, has a propensity to involve the skin, lymph nodes, gastrointestinal tract, and lungs. Kaposi sarcoma develops in about 15–20% of patients with AIDS, almost all homosexual or bisexual men, and pulmonary involvement occurs in about 20% of them. The most common signs and symptoms are dyspnea and cough; hemoptysis may develop in advanced stages.

Irregular (flamed-shaped) and ill-defined peribronchovascular nodules combined with peribronchovascular and interlobular septal thickening, pleural effusions, and lymphadenopathy may develop in patients with Kaposi sarcoma. In most cases, the presence of typical nodules on CT and a parahilar distribution of abnormalities allow Kaposi sarcoma to be distinguished from other thoracic complications of AIDS.

Respiratory Bronchiolitis

Respiratory bronchiolitis (RB) is characterized by distortion of the respiratory bronchioles, with irregular projections of epithelium and smooth muscle into the lumen. A distinct interstitial lung disease, known as respiratory bronchiolitis–associated interstitial lung disease (RB–ILD), has been described in smokers or former smokers and is a histologic reaction to dusty envi-
ronments. Histologically, there is an accumulation of pigmented macrophages within the respiratory bronchioles and the surrounding airspaces, with minimal associated mural inflammation. Patients may appear subacutely with cough and dyspnea in their 30s or 40s; less often, they present with pneumothorax, hemoptysis, or acute respiratory failure.

Chest radiographs are normal in individuals with uncomplicated RB and about half of those with RB–ILD. The remainder of patients with RB–ILD have normal lung volumes but some thickening of the bronchial walls and a fine reticulonodular pattern.

On thin-section CT, RB–ILD typically produces faint micronodular nodules (3–5 mm) and patchy ground-glass opacities that may be widespread but predominantly tend to involve the upper lobes (Fig. 12).

Infection

Numerous infectious diseases can present the pattern of multiple pulmonary nodules. In septic emboli, which is most commonly

Fig. 11—Adenocarcinoma. CT image obtained at level of right lower lobe shows two parenchyma nodules, both histologically proven to be adenocarcinoma. One nodule is of soft-tissue density and well defined (white arrow). Second nodule is ill-defined and has heterogeneous texture and less density (black arrow).

Fig. 12—Respiratory bronchiolitis. A–C, CT images obtained at various levels of right upper lobe show centrilobular emphysema (white arrows). Emphysematous lesions are surrounded by subtle, ill-defined airspace nodules, typical of disease (black arrows).
Diffuse Pulmonary Nodules

causpby endocarditis or an infected central catheter, the nodules are diffusely distributed and frequently cavitate. A characteristic appearance is feeding vessels in association with the peripheral nodules.

In reactivation tuberculosis, innumerable tiny, discrete, relatively well-defined nodules may be diffusely distributed throughout both lungs, producing a miliary pattern that reflects endobronchial spread of infection (Fig. 13). Thin-section CT may detect the presence of diffuse lung involvement when corresponding chest radiographs are normal or show only minimal or limited disease. Multiple small and larger nodules also may be a feature of atypical (nontuberculous) mycobacterial infection (Figs. 14 and 15). The presence of small nodules in areas of lung distal to a dominant consolidative focus of infection probably results from endobronchial spread.

A pattern of miliary or larger pulmonary nodules may be a manifestation of fungal infection. The most common cause is histoplasmosis, in which the generally round or oval nodules are well circumscribed and often calcify. Other fungal disorders that can produce multiple pulmonary nodules include coccidioidomycosis, blastomycosis, and candidiasis. More irregular and poorly defined masses may be seen in *Pseudomonas* infection, and
well-circumscribed cystic masses with the predilection of the periphery of the lower lobes are a characteristic appearance of Paragonimus westermani. In varicella pneumonia (adults more than children), there is often a miliary pattern of pulmonary nodules that heal with diffuse calcifications (as in histoplasmosis). Parasitic diseases that may produce military nodules include schistosomiasis and filariasis.

A common finding on thin-section CT in infectious lung disease is the tree-in-bud pattern, in which centrilobular bronchial dilatation and filling by mucus, pus, or fluid resembles a budding tree. The pattern of patchy clusters of small nodules and branching soft-tissue opacities is generally most pronounced in the lung periphery (within 3–5 mm of the pleural surface) and associated with abnormalities of the larger airways.

Aspergillosis is a fungal infection that often occurs in preexisting cavities caused by tuberculosis, fungal disease, or sarcoidosis. The disease develops in immune-compromised patients and typically presents with cough, fever, chills, dyspnea, and chest pain. A halo or ground-glass opacity surrounding focal dense parenchymal nodules is a characteristic CT appearance of invasive pulmonary aspergillosis (Fig. 16). The halo and central nodule are reported to reflect, respectively, a rim of coagulation necrosis or hemorrhage surrounding a central fungal nodule or infarct.

**Small Airway Disease**

Small airway disease (SAD) refers to a spectrum of disorders in which inflammation of the smallest bronchi and bronchioles with minimal emphysema leads to distortion and obliteration of small airways. Diseases affecting the small airways are difficult to detect by traditional diagnostic tests. There must be widespread involvement before the appearance of symptoms and abnormalities on pulmonary function testing or chest radiography. However, on thin-section CT, changes associated with SAD are accurately detected.

One manifestation of SAD is multiple small nodules, which are often found abundantly along the bronchovascular bundles and histologically prove to be centered about abnormal bronchioles (Fig. 17). Individual abnormal regions generally can be separated from other involved areas by normal or near-normal lung parenchyma. However, if the nodules coalesce, larger consolidations or airspace opacities may occur.

**Hypersensitivity Pneumonitis**

Also known as extrinsic allergic alveolitis, hypersensitivity pneumonitis refers to a group of allergic lung diseases that are caused by chronic inhalation of a variety of organic and chemical antigens that leads to an immunologic response of the lung tissues. The most common forms are farmer’s lung and bird fancier’s lung.
Diffuse Pulmonary Nodules

The radiographic findings vary with the stage of the disease. In the acute phase, chest radiographs are normal in 90% of cases. There may be a fine nodular or reticulonodular pattern or airspace consolidation (primarily in the lower lobes) that is often misdiagnosed as pneumonia. In the subacute stage, 90% of chest radiographs are abnormal, showing poorly defined small nodules or lung opacifications with obscuration of vascular margins. In chronic disease, the major findings are fibrosis with architectural distortion and volume loss.

On thin-section CT, hypersensitivity pneumonitis appears acutely as small, ill-defined centrilobular nodules and bilateral airspace consolidation (Fig. 18). In the subacute stage, there are patchy ground-glass opacities with ill-defined centrilobular nodules. Characteristic mosaic perfusion generally affects the middle and lower lung. In the chronic stage of hypersensitivity pneumonitis, lung fibrosis produces honeycombing, traction bronchiectasis, and architectural distortion. There also may be reticular opacities randomly distributed in the peri-
bronchial and subpleural regions. A combination of these findings can also be seen in early stages of nonspecific interstitial pneumonia, in which parenchymal nodules and early architectural distortion are key features (Fig. 19).

**Miscellaneous Conditions**

Many disorders are extremely rare but have been included for the sake of completeness.

**Alveolar Microlithiasis**

Alveolar microlithiasis is a rare disorder of unknown cause characterized by diffuse bilateral deposition of intraalveolar microliths. Most prevalent in Turkey, which accounts for 33% of the world’s cases, in half of patients there is a genetic anomaly that is familial autosomal recessive. Despite radiographic abnormalities, about 70% of patients with alveolar microlithiasis are asymptomatic when the diagnosis is made. These patients later may develop cough and dyspnea, and slow progression of the disease may eventually result in respiratory or cardiac failure.
**Diffuse Pulmonary Nodules**

Alveolar microlithiasis produces diffuse, very fine micronodules of calcific density. A characteristic appearance on chest radiographs is the black pleura sign due to contrast between the extreme density of the lung parenchyma on one side of the pleura and the ribs on the other side.

**Amyloidosis**

Amyloidosis represents a heterogeneous group of disorders characterized by abnormal extracellular accumulation of insoluble fibrillar proteins. Vascular deposition of these substances leads to fragility and bleeding. Patients may be asymptomatic or present with cough, respiratory insufficiency, hemoptysis, recurrent pneumonia, and involvement of other organs or tissue (heart, kidney, tongue, gastrointestinal tract, skin, and muscle).

Discrete masses of amyloid may develop in the rare parenchymal form of the disease. Multiple nodules may cavitate and show calcification or ossification. The nodular parenchymal form of the disease has a better prognosis than the tracheobronchial (obstructive) or diffuse interstitial type.

**Papillomatosis of the Lung**

Papillomatosis is a human papillomavirus infection that involves the larynx in 95% of cases. Airway dissemination seeding the lung occurs in < 1% of cases, most frequently in children or young adults, and surgical manipulation of a laryngeal papilloma increases the likelihood of this complication.

Papillomas of the lung typically obstruct the airways, resulting in peripheral atelectasis and obstructive pneumonia. A rare manifestation is round, sharply circumscribed nodules that frequently cavitate (often resembling advanced cystic bronchiectasis).

**Polyarteritis**

Poorly defined nodules, often associated with patchy consolidations, are a rare manifestation of polyarteritis. The pulmonary appearance in this condition typically shows progression and regression of lesions on serial studies, reflecting the appearance of new lesions and the healing of old ones. The CT angiography visualization of multiple arterial aneurysms in one or more abdominal organs is considered virtually diagnostic of this disease.

**Pulmonary Arteriovenous Fistulas**

Pulmonary arteriovenous fistula is an abnormal direct communication between pulmonary arteries and pulmonary veins, which may be acquired or congenital and produce high blood flow through the right-to-left shunt. About one third are multiple, and about 50% have hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease). A definitive diagnosis requires identification of the feeding artery and the draining vein.

Pulmonary arteriovenous fistulas appear as sharply defined, round or oval, often slightly lobulated nodules that predominantly involve the lower lobes. The lesions may change in size between the Valsalva and the Müller maneuver.

**Pulmonary Hemosiderosis**

Pulmonary hemosiderosis most commonly affects young individuals and is characterized by recurrent episodes of diffuse pulmonary hemorrhage without an identifiable cause. A fine miliary pattern of densely calcified or ossified nodules diffusely scattered throughout the lungs may develop in patients with long-standing mitral stenosis (or other causes of elevated left atrial pressure) who have had multiple episodes of hemoptysis.

**Pulmonary Varices**

Pulmonary varices are characterized by rare congenital or acquired tortuosity and dilatation of the pulmonary veins just before their entrance into the left atrium. The varicosities change shape and size with the Valsalva and Müller maneuvers (similar to arteriovenous fistulas).

On imaging, pulmonary varices appear as multiple round, well-defined opacities. On chest radiographs, they most commonly are seen on lateral images projecting posterior and inferior to the hilar structures. Anatomically, varices are most often solitary and preferentially involve the right lower lobe pulmonary vein.
Rheumatoid Necrobiotic Nodules

This rare manifestation of rheumatoid lung disease tends to wax and wane in relation to the activity of rheumatoid arthritis and the presence of subcutaneous nodules. Rheumatoid lung nodules may be associated with pneumoconiosis (Caplan syndrome). They generally appear as smooth, well-circumscribed nodules that predominantly occur in peripheral subpleural locations. Cavitation is common, producing thick-walled lesions with smooth inner margins. A miliary pattern of pulmonary nodules may occur in the early subacute stage of the disease before the development of the more characteristic diffuse interstitial pulmonary fibrosis.

Wegener Granulomatosis

Wegener disease, now often called “antineutrophil cytoplasmic autoantibody (ANCA)-associated granulomatous vasculitis,” is a necrotizing granulomatous vasculitis of small to medium vessels without associated infection. Of unknown cause, the classic triad consists of abnormalities involving the sinuses, lungs, and kidneys.

In the chest, Wegener granulomatosis typically produces round, fairly well-circumscribed nodules that may simulate metastases. Cavitation (thick-walled with irregular, shaggy inner margins) develops in approximately half the patients. Rarely, small fine nodules may develop in combination with larger, more ill-defined densities, representing a diffuse granulomatous reaction occurring around vessels.

Suggested Reading