IV FOCAL AND MULTIFOCAL LUNG DISEASE

Roland H. Ingram, Jr., M.D.

Chest physicians, when consulted, most often begin their consultation by examining standard posteroanterior and lateral chest radiographs. In doing so, they assess the differential diagnostic probabilities and possibilities on the basis of the radiographic pattern. This serves to focus their efforts on history taking and the physical examination, and it facilitates their defining of proper diagnostic measures, which in turn guide therapeutic and management advice. This subsection utilizes this approach in discussing and categorizing a wide range of lung diseases, most of which are approached in more depth in other sections and subsections.

Assessment of Chest Radiographs

Focal and multifocal lung diseases are classified into seven categories on the basis of chest radiography: (1) focal pulmonary infiltrates, (2) multifocal pulmonary infiltrates, (3) true segmental infiltrates, (4) cavitary infiltrates, (5) single small nodules, (6) large masses, and (7) multiple nodules. These radiographic patterns may be caused by infectious diseases, neoplastic diseases, or noninfectious, nonneoplastic disorders. The differential diagnoses for the seven categories are dissimilar but by no means mutually exclusive. Many diseases that usually cause focal infiltrates can produce multifocal infiltrates [see Focal Pulmonary Infiltrates, below]. Other disorders nearly always present as multiple infiltrates, and the pathology only rarely localizes to one area [see Multifocal Pulmonary Infiltrates, below]. Infiltrates that conform perfectly to the segmental anatomy of the lung usually result from an abnormality of the bronchus or pulmonary artery leading to the infiltrate [see True Segmental Infiltrates, below]. Cavitary infiltrates, single small nodules, large masses, and multiple nodules have distinct differential diagnoses.

Diagnosis of a focal or multifocal lung disorder starts with the abnormal chest radiograph or with abnormal findings from newer imaging techniques. In each category of radiographic pattern, the clinical features of the illness, the presence or absence of associated pleural or mediastinal abnormalities, and ancillary laboratory tests all serve to narrow the differential diagnosis. In some disorders, the combined radiographic, clinical, and laboratory presentation is virtually specific. In other disorders, cytologic, histopathologic, or microbiologic information is necessary to make a specific diagnosis.

In each of the seven categories, infectious diseases and neoplastic diseases are more common than noninfectious, nonneoplastic disorders. Many of the infectious and neoplastic entities, however, are discussed in great detail in other subsections; this subsection focuses on those noninfectious, nonneoplastic disorders that are relatively common and are not discussed elsewhere in depth.

Focal Pulmonary Infiltrates

When a focal infiltrate is dense, it is likely that pus, blood, water, or tissue is filling alveolar spaces. A focal infiltrate that is patchy and less dense suggests a less advanced stage of disease process. Many conditions can cause a focal infiltrate that is visible on the chest radiograph [see Table 1].

Infectious diseases

Bacterial Pneumonia

The most common cause of a focal infiltrate is bacterial pneumonia. Five clinical features in combination strongly suggest the diagnosis: (1) acute onset, (2) a new or increasing infiltrate on the chest radiograph [see Figure 1a], (3) fever, (4) purulent sputum, and (5) a white blood cell count that is either high, low, or shifted to the left. Absence of one or more of these features does not eliminate the possibility of bacterial pneumonia but does increase the probability of an alternative diagnosis.

Because many different types of bacteria can cause pneumonia, a precise etiologic diagnosis cannot be made either on clinical grounds or by a chest radiograph. Positive blood cultures have near-perfect specificity but low sensitivity, whereas positive sputum cultures can only suggest a specific etiology. *Streptococcus pneumoniae* is the most common cause of bacterial pneumonia, accounting for perhaps 85% of all cases in otherwise healthy young adults. However, many other bacteria also cause pneumonia, with a higher incidence in patients with chronic medical conditions and advanced age. These include *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Legionella pneumophila* [see 7:XX Pulmonary Infections].

An even wider range of pathogens cause pneumonia in patients in intensive care units. These include virulent gram-negative bacilli with high potential for antibiotic resistance, such as *Pseudomonas aeruginosa* and *Enterobacter*, *Serratia*, and *Proteus* species. Other infectious causes of focal infiltrates include *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, mycobacteria, viruses, rickettsiae, fungi, and parasites.

Neoplastic diseases

Alveolar cell carcinoma and lymphoma commonly present as focal pulmonary infiltrates, though they also cause multifocal infiltrates. Bronchogenic lung cancer usually produces a nodule or a mass but can cause a focal dense infiltrate. The ab-

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noninfectious, nonneoplastic disorders

Fever and chills are absent. Metastases are less common than with other primary lung neoplasms, and the course of the illness is longer. Alveolar cell carcinoma is not related to smoking. Diagnostic tests should begin with sputum cytology, followed by fiberoptic bronchoscopy with bronchoalveolar lavage and transbronchial biopsy or, if needed, open lung biopsy with a traditional or a video-assisted thoracoscopic approach. Localized disease can sometimes be resected; radiation therapy and chemotherapy have no important role [see 12:IV Principles of Cancer Treatment].

Lymphoma

Lymphoma can also produce a focal, dense consolidation. With Hodgkin disease, there may be multiple contiguous areas of tumor involvement that grow and merge, resulting in a dense infiltrate with irregular borders. Hilar and mediastinal adenopathy are nearly always present. Pleural effusions occur in as many as 30% of patients. Diagnostic strategies include fiberoptic bronchoscopy, aspiration biopsy of the infiltrate or of the mediastinal nodes (using needles that obtain a tissue core), mediastinoscopy, and pleural biopsy. Biopsy of associated cervical nodes or of the bone marrow is helpful in some cases. Treatment is systemic.

In non-Hodgkin lymphoma, the chest radiograph may show a dense infiltrate with regular margins, similar to the infiltrate seen in bacterial pneumonia or alveolar cell carcinoma. Mediastinal and hilar node involvement may be absent. Pleural effusion occurs in one third of patients [see 12:XI Malignant Lymphomas].

Radiation Pneumonitis

Radiation pneumonitis follows pulmonary irradiation after a lag time that is somewhat dose dependent. Symptoms include nonproductive cough, dyspnea, and fever. These symptoms develop approximately 8 weeks after completion of a course of radiation therapy consisting of 4,000 cGy; they develop 1 week earlier for each additional 1,000 cGy administered. Onset is usually subacute. There may be rales and signs of consolidation. Hyperpigmentation of the skin overlying the irradiated lung is common but does not correlate with the severity of lung injury. Laboratory findings include leukocytosis and hypoxemia. Bronchoalveolar lavage may rule out tumor and infection—a determination that is most important in making a differential diagnosis— and may demonstrate dysplastic type II cells, the presence of which suggests radiation injury. Lavage also reveals excess lymphocytes in both involved and uninvolved areas. Drug-induced lung injury causes similar cytopathic changes in type II cells, but usually, neutrophilic inflammation is also present.

The chest radiograph shows an infiltrate of variable density. A highly characteristic infiltrate has sharp edges and conforms exactly to the radiation port. Occasionally, high-resolution computed tomography shows regions of air-space consolidation that are not visible on routine chest radiography [see 1 Cardiovascular Medicine]. Many patients gradually improve over a few weeks. When the disease is severe, glucocorticoid therapy is often used, with uncertain benefit. Because of fever and fear of superinfection, antibacterial therapy is often given, also with uncertain benefit. Typically, the involved area of the lung scars and contracts with time, and the chest radiograph shows progressive volume loss [see 14:V Chronic Diffuse Infiltrative Lung Disease].

Lipoid Pneumonia

Lipoid pneumonia is a noninfectious, inflammatory lung disorder caused by the aspiration of mineral oil or other oily substances. It is most common in elderly patients and others with impaired swallowing. With or without impaired swal-

Figure 1  (a) This chest radiograph demonstrates a focal left lower lobe infiltrate caused by bacteremic pneumococcal pneumonia in a 22-year-old man. (b) A focal right upper lobe infiltrate caused by alveolar cell carcinoma is revealed in this chest radiograph of a 71-year-old woman. (c) The focal right lower lobe infiltrate in this chest radiograph is the result of lipoid pneumonia in a woman who is 68 years of age.
lowing, lipoid pneumonia can result from the use of petroleum jelly or other oily substances applied to the lips or nose to relieve chronic dryness. The most common symptom is a chronic cough, which may be caused by coexisting lung disease rather than lipoid pneumonia; fever is uncommon. Often, the disease is discovered on a routine chest radiograph that shows a focal, dense infiltrate, usually in a lower lobe or in the right middle lobe [see Figure 1c]. The radiographic appearance of such an infiltrate in a relatively asymptomatic patient suggests chronic pneumonia or lung cancer. CT scanning may show an extremely low density infiltrate produced by accumulated lipid; the density typically ranges from −60 to −150 Hounsfield units (water is 0). In contrast, the density of lung cancers usually ranges from +60 to +150 Hounsfield units. Lipid-laden macrophages can be demonstrated with the oil red O stain, which colors lipid droplets bright red. The stain can be applied to bronchoalveolar lavage specimens or transthoracic aspirates. A positive test supports the diagnosis, but some caution is necessary. Endogenous lipid pneumonia may occur distal to an obstructed bronchus, and in such cases, the lipid is derived from the breakdown of cell membranes. Thus, bronchoscopy is still needed to rule out an obstructed bronchus even after demonstration of lipid-laden macrophages by needle aspiration. A variety of other lung disorders, such as pulmonary hemorrhage or primary and metastatic cancers, can also be associated with lipid-laden macrophages. To establish the diagnosis of exogenous lipid pneumonia, it is necessary to analyze carefully all the clinical, cytopathologic, and radiographic findings, including the results of CT scanning. Many cases are diagnosed only after thoracotomy for resection of a presumed malignancy. The only specific therapy is avoidance of exposure to mineral oil and other lipid-containing agents. Lipoid pneumonia usually improves slowly after exposure to the agent is eliminated, though complete clearing of the infiltrate does not always occur.

Lung Contusion

Lung contusion is an important cause of focal, usually dense infiltrate. It results from blunt chest trauma, most often from falls or motor vehicle accidents. Usually within hours after trauma, an infiltrate develops deep beneath the impact point, representing blood and edema in the lung. Associated injuries, such as rib fractures and traumatic pneumothorax, may be present.

Focal shunting through the area can cause refractory hypoxemia. If the injury is severe enough, the entire area may become necrotic and form a large cavity with irregular inner margins.

Lobe Torsion

Torsion of a lobe of the lung is rare and usually occurs postoperatively, particularly after resection of the left upper lobe. The vascular pedicle of the remaining left lower lobe twists and is compromised, and the lobe increases in density as it fills with blood and edema fluid. The diagnosis is often made by radiography but can be difficult. The differential diagnosis includes unilateral lung infection, edema, and hemorrhage. Treatment involves surgical relief of the torsion in early cases or resection of the lobe if it is no longer viable.

Multifocal Pulmonary Infiltrates

Most disorders that cause single infiltrates can also cause multiple infiltrates [see Table 2]. Pneumococcal pneumonia and other bacterial pneumonias are occasionally multifocal [see Figure 2a]; viral and mycoplasmal pneumonias are commonly multifocal or diffuse. Clinical features of pneumonia with multiple infiltrates are similar to clinical features of pneumonia

Table 2—Major Causes of Multifocal Pulmonary Infiltrates

<table>
<thead>
<tr>
<th>Cause</th>
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<td>Infectious</td>
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<td>Mycoplasma pneumonia</td>
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<td>Influenza</td>
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<td>Tuberculosis</td>
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<td>Endemic fungal pneumonias</td>
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<td>Invasive aspergillosis</td>
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<td>Neoplastic</td>
<td>Alveolar cell carcinoma</td>
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<td>Lymphoma</td>
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<td>Noninfectious, nonneoplastic</td>
<td>Simple eosinophilic pneumonia</td>
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<td>Chronic eosinophilic pneumonia</td>
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<td></td>
<td>Bronchiolitis obliterans organizing pneumonia</td>
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<tr>
<td></td>
<td>Allergic granulomatosis and angiitis</td>
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<tr>
<td></td>
<td>Sarcoidosis</td>
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with one infiltrate, except that severity increases with extent of disease. Pulmonary thromboemboli can also produce multifocal infiltrates; a normal chest radiograph, unilateral or bilateral pleural effusions, and focal infiltrate or atelectasis are other possible radiographic patterns for pulmonary thromboemboli. Septic pulmonary emboli often cause multiple infiltrates [see Multiple Nodules, below]. Finally, sarcoidosis is perhaps the most protean of all the noninfectious and nonmalignant lung disorders [see 14:V Chronic Diffuse Infiltrative Lung Disease]. A diffuse infiltrate with or without hilar adenopathy is the usual presentation [see Figure 2b].

**Infectious Diseases**

**Tuberculosis**

Primary tuberculosis is often focal and often associated with ipsilateral hilar adenopathy, especially in children. Most diagnosed adult cases of tuberculosis, however, result from reactivation of latent infection. Reactivation tuberculosis is often multifocal. Bilateral infiltrates in the upper lung zones are most characteristic. The upper lung zones are favored sites, because a higher ratio of ventilation to perfusion results in higher local oxygen tension, which enhances growth of *Mycobacterium tuberculosis*. The apical and posterior segments of the upper lobes are most commonly involved, followed by the apical-posterior segments of the lower lobes. The lingula, the middle lobe, and the basal segments of the lower lobes can all be involved by bronchogenic spread. Concomitant pleural disease occurs in a minority of patients.

Cavitation is frequent, but even in the absence of cavitation, the diagnosis of tuberculosis should be considered when multifocal infiltrates are present. Atypical radiographic patterns, including isolated lower lobe infiltrates, are particularly common in elderly, debilitated patients. These patterns can complicate and delay diagnosis. Atypical radiographic features, including midlung or lower lung field infiltrates, hilar adenopathy, and absence of cavitation, can be seen in immunocompromised patients, especially in patients with AIDS [see 7:XXXIII HIV and AIDS].

**Endemic Fungal Pneumonias**

Endemic fungal pneumonias are acquired by inhalation of aerosolized particles (usually small respirable spores) rather than by microaspiration of pharyngeal organisms—the mechanism of infection for most pyogenic bacterial pneumonias. Severe cases of endemic fungal pneumonia usually involve multiple areas; blastomycosis and coccidioidomycosis often cause multiple dense alveolar infiltrates [see 7:XXXVII Mycotic Infections].

**Melioidosis**

Melioidosis is an indolent bacterial pneumonia caused by the gram-negative bacillus *Burkholderia pseudomallei*. It is most common in Southeast Asia and may appear in patients months or even years after they have migrated to nonendemic areas. Multifocal infiltrates are characteristic. The clinical illness resembles tuberculosis except that upper lobe predominance is not as striking in melioidosis.

**Invasive Aspergillosis**

An opportunistic fungal infection that is also acquired by inhalation, invasive aspergillosis occurs in patients who experience a decrease in the number of function of phagocytes. Prolonged neutropenia from cytotoxic chemotherapy for acute leukemia is the most common predisposing factor. High-dose glucocorticoid therapy also predisposes to this infection, as do several immunosuppressive regimens used for solid-organ transplantation and, especially, for bone marrow transplantation. Clinical features include fever, dyspnea, pleuritic chest pain, hemoptysis, and hypoxemia. The chest radiograph shows characteristic multiple dense infiltrates, which may be nonsegmental, wedge shaped and peripheral, or even nodular. Individual lesions may cavitate, particularly as the number of neutrophils begins to rebound after chemotherapy. During this recovery time, the patient is at the highest risk for major hemoptysis [see Section 7:XXXVIII Mycotic Infections in the Compromised Host].

Diagnosis is difficult because actual tissue invasion must be determined. However, any positive culture for *Aspergillus* from sputum or bronchoscopic specimens has high predictive value in the patient with profound neutropenia. Such cultures are valuable but less specific in transplant recipients or other moderately immunosuppressed patients and are often unhelpful in patients with chronic bronchiitis, who are frequently colonized with this organism. Negative cultures never rule out the diagnosis of invasive aspergillosis.

**Neoplastic Diseases**

Two neoplasms that present as focal infiltrates [see Focal Pulmonary Infiltrates, above] also commonly present as multifocal infiltrates: alveolar cell carcinoma [see Figure 2c] and Hodgkin disease. Hodgkin disease, however, almost always has associated hilar and mediastinal adenopathy, whereas alveolar cell carcinoma almost never does. Lymphomatoid granulomatosis, an angiocentric T cell lymphoma of variable grade, usually presents as multiple pulmonary nodules [see Multiple Nodules, below] but can also present as multifocal pulmonary infiltrates.

**Noninfectious, Neoplastic Disorders**

Several unusual noninfectious, nonneoplastic pulmonary diseases may produce multiple areas of lung infiltration.

**Simple Eosinophilic Pneumonia**

Patients with simple eosinophilic pneumonia, often called Löffler syndrome, have nonproductive cough and fever. The chest radiograph shows patchy infiltrates, typically in the lower lung fields; the infiltrates resolve within 1 to 2 weeks. The main clue to the diagnosis is an increase in the number of peripheral eosinophils, often to 60% or more of the total white blood cell count. Bronchoalveolar lavage is seldom indicated, because patients are only mildly ill; when lavage is done, it reveals pulmonary eosinophilia. The main causes of this pneumonia are drugs and worms—usually nematodes such as *Ascaris* and *Strongyloides*, which migrate through the lung during one phase of infection. Treatment includes either discontinuation of an offending drug or elimination of a worm identified in a stool sample. Drugs that cause the syndrome include but are not limited to carbamazepine, chlorpromazine, cocaine, imipramine, isoniazid, naproxen, nitrofurantoin, penicillins, sulfonamides, and tetracycline.

**Tropical Pulmonary Eosinophilia**

Tropical pulmonary eosinophilia, which is caused by immunologic hyperreactivity to microfilariae, is characterized by...
dyspnea, wheezing, and coughing, all of which are worse at night, as well as fever, weight loss, and fatigue. The chest radiograph reveals interstitial micronodular lesions that may be diffuse or multifocal. Peripheral blood eosinophilia is in excess of 3,000/mm³; the serum IgE levels are extremely high, and antibodies to microfilariae are present. Two filarial parasites, *Wuchereria bancrofti* and *Brugia malayi*, are causative agents. Response to the antifilarial drug diethylcarbamazine can be dramatic. It may be necessary to treat the patient longer than a month to eradicate the organisms and to avoid the progressive interstitial fibrosis that can result from incomplete therapy. Blood eosinophilia is less prominent in patients with chronic forms of the disease. Patients who have lived in areas where tropical pulmonary eosinophilia is endemic can present with restrictive or obstructive lung disorders that are the residua of episodes of tropical eosinophilia that occurred earlier in life.

**Chronic Eosinophilic Pneumonia**

Chronic eosinophilic pneumonia is more serious than simple eosinophilic pneumonia. It primarily affects women between 20 and 40 years of age; however, it has been reported in patients of both sexes and of all ages. Most patients have moderate to severe illness lasting from one to several months, with fever, night sweats, nonproductive cough, shortness of breath, and weight loss. About one third of patients have a history of asthma, and up to one half have some atopic history, including allergic rhinitis and nasal polyps. About one half of patients have wheezing as part of their clinical presentation, some for the first time. The chest radiograph may show dense peripheral infiltrates that are often referred to as reverse pulmonary edema or the photographic negative of pulmonary edema. When the clinical presentation and chest radiograph are highly typical, the diagnosis can be made clinically. About two thirds of patients have peripheral eosinophilia; a minority have an elevated serum IgE level. Bronchoalveolar lavage shows increased eosinophils and increased lymphocytes. Open lung biopsy, which is seldom required, shows lymphocytes and eosinophils in alveolar walls and spaces, as well as bronchiolitis obliterans in up to one third of specimens.

The etiology of chronic eosinophilic pneumonia is unknown. The disease may represent a hypersensitivity response to unknown antigens or may be an idiopathic immunologic activation. Treatment with glucocorticoids is highly effective. Prednisone is usually given in a starting dosage of 40 to 60 mg daily. Symptoms improve within days, and the radiograph clears within weeks. After remission, glucocorticoids are slowly tapered, usually over several months. When relapses occur, they respond to increases in the dose of glucocorticoids back up to 40 to 60 mg daily.

**Acute Eosinophilic Pneumonia**

Idiopathic acute eosinophilic pneumonia (AEP) is another syndrome that presents as multifocal infiltrates. Blood eosinophilia is usually absent, and the onset is acute, generally within several days. Patients may have fever and severe hypoxemia and may progress to respiratory failure. There is usually no history of atopy. There are rales on physical examination but rarely any wheezing. The prime diagnostic consideration is severe community-acquired pneumonia. The chest radiograph shows bilateral infiltrates that may progress to diffuse infiltrates. Unlike the case with chronic eosinophilic pneumonia, there is no tendency to peripheral subpleural localization. Increased septal markings (Kerley B lines) are seen in about one third of cases. Diagnosis of AEP is usually made by bronchoalveolar lavage, which shows over 25% eosinophils (mean, 37 ± 2.5). Culture for respiratory pathogens is negative. There is a rapid response to glucocorticoid therapy. One regimen is 1 mg/kg of I.V. methylprednisolone four times daily until clinical response occurs, followed by a short course of lower-dose oral prednisone gradually tapered over 2 to 4 weeks. There is little tendency for patients to experience relapse after a course of therapy. The etiology of this immune disorder is unknown. In addition to the increase in pulmonary eosinophils, pathobiologic features include an increase in the number of helper T cells and neutrophils in the lung and elevated concentrations of interleukin-5 (IL-5) in lavage fluid.

**Bronchiolitis Obliterans Organizing Pneumonia**

Bronchiolitis obliterans alone is a distinct pathologic process in which distal airways are filled with plugs of loose connective tissue containing fibroblasts and inflammatory cells [see 14:III Chronic Obstructive Diseases of the Lung]. Clinical manifestations in patients with this pathology include severe airflow obstruction and poor response to bronchodilator therapy; chest radiographs show no infiltrates. Some cases are idiopathic, but others are associated with specific immunologic abnormalities, such as rheumatoid arthritis, graft versus host disease (GVHD) in bone marrow transplant recipients, and chronic rejection in lung transplant recipients.

Bronchiolitis obliterans organizing pneumonia (BOOP) is a pathologic entity that is also (and perhaps more descriptively) called cryptogenic organizing pneumonia. The lung parenchyma is involved, and alveolar spaces are filled with loose connective tissue that contains fibroblasts and mixed inflammatory cells. The process also involves contiguous distal airways, so the characteristic plugs of bronchiolitis obliterans are also seen. Clinical features of BOOP are different from those of isolated bronchiolitis obliterans and include unifocal or multifocal infiltrates on a chest radiograph, generally restrictive rather than obstructive physiology, and good response to therapy in some cases.

As in isolated bronchiolitis obliterans, the pathologic findings in BOOP are nonspecific and may occur with viral infections, toxic exposures (including inhalation of nitrogen dioxide), and hypersensitivity pneumonitis [see 14:V Chronic Diffuse Infiltrative Lung Disease]. However, buried in this pathologic entity, there seems to be a specific, probably immunologic, primary lung disorder with its own clinical and radiographic features. It is sometimes called idiopathic BOOP to distinguish it from cases in which the pathologic findings are similar but the cause is known. Many drugs have been implicated in the pathogenesis, including bleomycin, gold, methotrexate and multiple antibacterial agents. Perhaps one half of all cases with the characteristic pathologic findings are idiopathic, although the exact percentage depends greatly on patient selection.

Idiopathic BOOP is a chronic parenchymal lung disease that is clinically distinct from idiopathic pulmonary fibrosis; it responds better to glucocorticoid therapy and has a better prognosis. Most patients have a flulike, febrile illness at onset; the fever resolves, but a nonproductive cough persists. Malaise and weight loss are common. Half of the patients have dyspnea. The chest radiograph often shows multiple dense peripheral infiltrates. A less common pattern of idiopathic BOOP is a dense lobar infiltrate, which resembles bacterial pneumonia in radiographic appearance. Because of the long course of the ill-
ness, clinical suspicion often focuses on chronic pulmonary infections, such as blastomycosis or even alveolar cell carcinoma. The most common features on CT scanning, which shows the extent of disease better than a chest radiograph, include patchy bilateral air-space consolidation, small nodular opacities, and bronchial wall thickening and dilatation. In half of cases, these abnormalities are mainly subpleural; in the other half of cases, they are distributed throughout the affected lobes.

The diagnosis of BOOP can often be made on transbronchial lung biopsy. In cases in which an open lung biopsy is needed, the video-assisted thoracoscopic technique has become the established procedure. Fully two thirds of patients with BOOP respond dramatically to glucocorticoid therapy. The usual initial dosage of prednisone is 40 to 60 mg daily. After remission, the dosage is tapered to 20 mg daily and is maintained at that level for 4 to 6 months, after which the dosage is tapered to zero. Some patients experience relapses and require subsequent courses of therapy, and a few patients require prolonged therapy, for many months or even years.

**Allergic Granulomatosis and Angitis**

Also known as Churg-Strauss syndrome, allergic granulomatosis and anititis is rare. Almost all patients with allergic granulomatosis and angitis have a strong history of atopic allergy with preexisting bronchial asthma for an average of 5 to 10 years before diagnosis of the vasculitis. Patients present with fever, shortness of breath, and a variety of complaints related to skin and nerve involvement (e.g., purpura, painful skin nodules, skin infarction, footdrop, wristdrop, or painful neuropathy). Myocardial involvement occurs in a minority of patients but on occasion can dominate the clinical presentation. Wheezing is common. Clinically significant renal involvement is uncommon. In 25% of cases, the chest radiograph shows peripheral infiltrates or nodules that seldom cavitate. Pleural effusion, pericardial effusion, or both may occur with or without infiltrates. Laboratory findings include anemia and leukocytosis. The hallmark of the diagnosis, however, is a striking peripheral eosinophilia that exceeds the level seen in asthma (often rising to an absolute eosinophil count of 10,000/mm³ or higher) and that correlates with disease activity. Diagnosis is made clinically and is sometimes supported by histopathologic evidence of disease obtained by skin biopsy and, less commonly, by lung biopsy. The treatment regimen is similar to that described for BOOP. Prednisone is given in an initial oral dosage of 40 to 60 mg/day and then tapered after 4 to 6 weeks to about 20 mg/day and maintained at this dosage for 6 to 12 months, before a slow taper is attempted under careful clinical observation. Clinical findings, particularly the high eosinophil count, are followed closely during therapy and monitored during remission.

Churg-Strauss syndrome, though rare, most often occurs in patients with bronchial asthma. There is an association between Churg-Strauss syndrome and treatment of asthma with leukotriene inhibitors. Onset of the vasculitis usually occurs as glucocorticoids are tapered during therapy with these agents. It is possible that some cases represent occult Churg-Strauss disease that is initially suppressed with glucocorticoids and then flares with glucocorticoid withdrawal. However, at least one case has been reported in a patient with no recent glucocorticoid use.

**Other Noninfectious, Nonneoplastic Multifocal Disorders**

Other immunologic lung diseases can produce multifocal infiltrates. Wegener granulomatosis is the most common lung vasculitis. The radiographic spectrum of illness includes infiltrates and nodules that are usually multiple and often cavitate [see Cavitary Infiltrates, below].

Collagen vascular disease can be associated with multifocal lung involvement. Pneumonitis associated with systemic lupus erythematosus (SLE) may be diffuse but may also appear as dense lower lobe infiltrates. Other clinical and serodiagnostic features of SLE are present. Systemic sclerosis and mixed connective tissue disease usually present as diffuse interstitial infiltrates, often with basilar predominance [see 15:IV Systemic Lupus Erythematosus].

Lung disease associated with rheumatoid arthritis takes many forms, including pulmonary fibrosis, pleural effusions, and necrotic pulmonary nodules, the pathologic appearance of which is similar to that of subcutaneous rheumatoid nodules [see 15:II Rheumatoid Arthritis]. Peripheral dense masslike infiltrates may also occur. Some lesions may cavitate; such lesions are most common in men with high-titer rheumatoid factor and subcutaneous rheumatoid nodules.

Other noninfectious, nonmalignant disorders that can cause multifocal infiltrates include silicosis and other diseases caused by inorganic dust inhalation. With extensive disease, progressive massive fibrosis may develop, producing large opacities. These opacities begin in peripheral areas of the lung and migrate centrally as lung volume is lost. The chest radiograph almost always shows a background of small nodules that are most prominent in the upper lobe. Patients have productive cough and dyspnea on exertion. The physiologic findings are typical of restrictive disease, but many patients also have airflow obstruction resulting from cigarette smoking or from airway damage caused by massive dust overload.

Caplan syndrome occurs in patients with rheumatoid arthritis who have been occupationally exposed to coal dust or other particulates, such as silica, asbestos, aluminum dust, and iron dust. The tendency to form large, masslike infiltrates is more pronounced in these patients than it is in other patients with rheumatoid arthritis. The infiltrates are multiple and may be more than 5 cm across. They are often somewhat nodular and may cavitate and even calcify. Histologically, they resemble other rheumatoid necrotic nodules except that the foreign particulate matter can be easily demonstrated. The occupational history and the nodules and fibrosis evident on the chest radiograph are diagnostic clues.

In ankylosing spondylitis, a spondyloarthropathy that leads to a stiff spine, calcification of spinal ligaments results in a characteristic radiographic appearance, the so-called bamboo spine [see 15:III Seronegative Spondyloarthropathies]. Chest wall expansion is impaired, and lung volumes are somewhat reduced. Patients may develop characteristic dense fibrous or fibroblastic infiltrates that are always limited to the upper lung zones. The chest radiograph mimics that of tuberculosis, and cavitation may occur. Once cavities have developed, abnormal air spaces may become colonized with Aspergillus species, causing fungus balls and even a locally invasive disease termed chronic necrotizing aspergillosis. The lung disease associated with ankylosing spondylitis does not progress to lower lung zones and by itself does not progress to respiratory insufficiency. Dyspnea on exertion and nonproductive cough are the usual symptoms. Once Aspergillus colonization or infection has occurred, symptoms from the local fungal infection may predominate; such symptoms include hemoptysis, productive cough, and mild to moderate constitutional symptoms. Locally invasive As-
pergillus infection may extend directly to the pleura but almost never spreads hematogenously to distant sites.

Many drugs can cause simple eosinophilic pneumonia, with patchy bilateral infiltrates as a result of hypersensitivity reactions. Multifocal infiltrates can also occur as a manifestation of drug toxicity, especially acute nitrofurantoin-related pulmonary toxicity and amiodarone-related pulmonary toxicity. With amiodarone-related lung disease, the infiltrates may be bilateral and more prominent in upper lung zones. The drug profile must be reviewed carefully in any patient with unexplained multifocal pulmonary infiltrates.

Exogenous lipid pneumonia may also cause bilateral dense infiltrates, usually in both lower lobes.

**True Segmental Infiltrates**

A chest radiograph that shows nearly complete involvement of a single lung segment, especially if associated with volume loss, should raise suspicion that there is disease in the bronchus or in the pulmonary artery supplying that segment [see Table 3].

**Infectious diseases**

Common bacterial pneumonias caused by *S. pneumoniae* and *H. influenzae* are usually not truly segmental unless an entire lobe is involved. In contrast, involvement of one or more discrete segments, often at the lung bases, is common in *Mycoplasma pneumonia* [see Figure 3a].

Three types of pneumonia exhibit a strong tendency for angioinvasion and cause dense, wedge-shaped peripheral infiltrates resulting from combined infection and infarction of a lung segment. Patients may have fever and purulent sputum from the infection, and they may have hemoptysis and pleural pain from lung infarction. *Aspergillus* and *Mucor* species are important causes of this syndrome in immunosuppressed patients, particularly those with neutropenia or those receiving high-dose glucocorticoid therapy [see 7:XXXVIII Mycotic Infections in the Compromised Host]. *Pseudomonas* pneumonia is an important cause of this syndrome in debilitated patients [see 7:X Infections Due to Haemophilus, Moraxella, Legionella, Bordetella, and Pseudomonas].

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<th>Example Causes</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplastic</td>
<td></td>
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<tr>
<td>Noninfectious, nonneoplastic</td>
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</table>

**Table 3** Major Causes of True Segmental Infiltrates

Bronchiectasis is a disease of the airways that can present as a peripheral segmental infiltrate, from dilated bronchi filled with mucus and infiltrate, and as an associated volume loss. Air-liquid levels may be seen in dilated saccular airways. Because CT scanning is more sensitive and specific than chest radiography in documenting bronchiectasis, it has replaced bronchography in the diagnosis of this process. The usual clinical presentation is a chronic cough that produces purulent sputum. Therapy includes suppressive antibiotics, postural drainage, and, in rare and highly selected cases, surgical resection of focal disease [see 14:III Chronic Obstructive Diseases of the Lung].

Tuberculosis is a parenchymal lung disease but may also involve the airways heavily. Bronchiectasis is a common late sequela. Because it occurs most often in upper lobar bronchi, it is well drained; hence, little or no sputum is produced (so-called dry bronchiectasis). Hemoptysis, often massive, can occur in patients who have no history of chronic cough and sputum. True segmental infiltrates may be seen early or late in the course of this chronic infection.

Pulmonary aspergillosis is an uncommon and, usually, very late complication of AIDS. Endobronchial aspergillosis is one...
form of the illness that often presents as true segmental infiltrates of the involved segment or segments. Pulmonary aspergillosis in AIDS may also present as multiple nodules and single or multiple infiltrates.

**neoplastic diseases**

Malignant lung tumors that arise in the lung parenchyma present as nodules or masses. Malignant tumors that arise in central airways block a segment of the lung, leading to distal infection, atelectasis, or both; the infection or atelectasis conforms perfectly to the obstructed segment, lobe, or lung. Symptoms include cough and hemoptysis or purulent sputum, as well as fever from the postobstructive pneumonia.

**Carcinoid Lung Tumors**

Carcinoid tumors of the lung are low-grade adenocarcinomas [see 12:VI Lung Cancer]. Most carcinoid tumors arise in central airways, so they present as segmental infiltrate or atelectasis more often than primary lung cancers [see Figure 3b]. Carcinoid tumors grow more slowly and metastasize less often than primary lung cancers, and they are not related to cigarette smoking. Although the mean age of incidence is 55 years, carcinoid tumors are almost evenly distributed across adulthood; in contrast, the incidence of primary lung cancer increases markedly with age. Despite their relative infrequency, carcinoid tumors account for a high percentage of lung tumors in patients in their third and fourth decades but only a tiny percentage of tumors in patients of advanced age.

**Other Lung Tumors**

Several other lung tumors typically grow in central airways and also present as segmental infiltrate, atelectasis, or both. Adenoid cystic carcinomas, known as cylindromas, and mucoepidermoid carcinomas are low-grade cancers of the mucous glands that usually occur in the trachea or central bronchi. The clinical presentation is similar to that of carcinoid tumors, but mucous gland tumors occur less than one tenth as often as carcinoid tumors. The histopathologies of cylindromas, mucoepidermoid carcinomas, and carcinoid tumors differ.

Benign lung tumors are uncommon. Most are hamartomas, which present peripherally as nodules [see Single Small Nodules, below]. Benign tumors presenting in the central airways are extremely rare; most are fibromas or lipomas.

**noninfectious, nonneoplastic disorders**

**Foreign Bodies**

Aspiration of a foreign body is an important cause of a segmental infiltrate. However, only 10% of foreign bodies are radiodense. When they are, they can often be identified immediately on the radiograph. When the foreign body is invisible on the radiograph, the diagnosis requires a bronchoscopic examination. Bronchoscopy should be performed if the clinician can combine the clinical history (e.g., altered consciousness, choking spell, irritative cough, repeated infections, or hemoptysis) with the finding of a true segmental infiltrate on the chest radiograph.

**Amyloidosis and Sarcoidosis**

Pulmonary amyloidosis exhibits many different radiographic patterns, including diffuse infiltrates and single or multiple nodules or masses. Amyloid deposition in a central airway may cause obstruction, leading to segmental infiltrates. Sarco-

coidosis also displays many patterns [see 14:V Chronic Diffuse Infiltrative Lung Disease]. It commonly presents as diffuse interstitial disease with or without enlarged hilar and mediastinal lymph nodes, but it also has many uncommon presentations, including multiple nodules and endobronchial sarcoidosis with a segmental infiltrate.

**Asthma**

Simple mucous plugging during an acute exacerbation of asthma can lead to a segmental or lobar infiltrate and atelectasis. This pattern frequently occurs as the patient is improving, perhaps because hyperinflation is resolving and the airways are no longer so widely dilated. The problem resolves with continued glucocorticoid treatment. Bronchoscopy is not indicated and may be dangerous during an acute exacerbation [see 14:II Asthma].

**Allergic Bronchopulmonary Aspergillosis**

Allergic bronchopulmonary aspergillosis, which is also associated with asthma, is a hypersensitivity disease that primarily affects the central bronchi [see 7:XXXVIII Mycotic Infections in the Compromised Host]. Immediate and delayed hypersensitivity are involved in pathogenesis. Onset of disease occurs most often in the fourth and fifth decades, and virtually all patients have long-standing atopic asthma. Even those few patients who do not have a history of documented asthma exhibit airflow obstruction when they present with this disorder. The typical patient has a long history of intermittent wheezing, after which the illness evolves into a more chronic and more highly symptomatic disorder with fever, chills, pulmonary infiltrates, and productive cough.

The chest radiograph may show a segmental infiltrate or segmental atelectasis, most commonly in the upper lobes [see Figure 3c]. One infiltrate may clear, only to be followed by another infiltrate in a different location. When the patient presents with typical symptoms, the branching, fingerlike shadows from mucoid impaction of dilated central bronchi are pathognomonic of allergic bronchopulmonary aspergillosis. The laboratory features of the illness are important clues to the diagnosis. High titer of specific IgE antibodies against Aspergillus antigens are a specific marker and show high sensitivity in patients with exacerbations of disease. In fact, the titers correlate with disease activity and are used to follow the effects of therapy. Other clinical and laboratory features include the following:

1. Eosinophil count higher than that seen in extrinsic asthma (usually greater than 1,000/mm³) but less than the levels seen in Churg-Strauss syndrome (often more than 10,000/mm³)
2. Total IgE levels higher than those usually seen in extrinsic asthma (usually greater than 1,000 ng/ml)
3. Expectorated cylindrical plugs (i.e., casts of small airways), usually brown, that show hyphae on direct microscopic examination after wet mounting on a slide and digestion with potassium hydroxide
4. Positive sputum cultures for Aspergillus
5. Positive skin tests to Aspergillus antigens, demonstrating both immediate and delayed hypersensitivity

CT scans showing typical central bronchiectasis are highly supportive of the diagnosis of allergic bronchopulmonary aspergillosis. Pulmonary function tests almost always show
some degree of obstruction from the underlying asthma. During an exacerbation, the airflow obstruction may be worse or remain unchanged, and the main acute finding may be an additional restrictive component with an acute decrease in vital capacity and total lung capacity.

The clinical course of allergic bronchopulmonary aspergillosis varies. Patients must receive enough glucocorticoid therapy to prevent destruction of bronchi (and eventual lung fibrosis) but not so much as to cause needless steroid toxicity. When the disease is active, daily doses of prednisone (0.5 mg/kg) are given until there is clinical improvement, which often takes 2 weeks. The patient then takes a similar dose every other day for several months. The dose taken every other day is gradually tapered to zero or to the lowest level that will suppress both the symptoms and the level of specific IgE against Aspergillus antigens. Careful clinical and immunologic monitoring permits early treatment of exacerbations with short bursts of higher-dose prednisone to minimize chronic pulmonary damage. In light of improved pathologic studies showing that allergic bronchopulmonary aspergillosis is a semi-invasive process, azole antifungal agents have become a recommended adjunctive therapy that appears to reduce corticosteroid dosage and the attendant side effects.9

Pulmonary Infarction

Obstruction of a segmental artery by thromboembolism can cause pulmonary infarction [see 1:LVIII Venous Thromboembolism]. The infarct is often peripheral and wedge shaped and occasionally has a clearly defined central limit that forms a pleurally based truncated cone, the so-called Hampton hump. Dyspnea, pleuritic chest pain, and, occasionally, hemoptyis are the clinical features of pulmonary infarction. An associated pleural effusion is commonly seen.

Cavitary Infiltrates

Cavitation of the lung results from a suppurative infection, a rapidly growing neoplasm, or a destructive immune process such as vasculitis [see Table 4]. As with other focal and multifocal infiltrates, infections and neoplasms are most common and must be considered first.

Infectious Diseases

Pyogenic bacteria can cause necrosis and thus cavitation of the lung. S. pneumoniae rarely cavitates; when cavitation occurs, it usually indicates a mixed infection with anaerobic bacteria. Gram-negative aerobic pneumonias, including those caused by K. pneumoniae or P. aeruginosa, cavitate more frequently. A gram-negative pneumonia may produce a large, dense infiltrate, with multiple cavities appearing as the illness progresses. Staphylococcal pneumonia acquired from microaspiration may cause influenza or may occur de novo [see 7:1 Infections Due to Gram-Positive Cocci]. Multiple small cavities are frequent. Pyemic staphylococcal infection, often caused by right-sided endocarditis, typically causes scattered, round infiltrates, which often enlarge and then cavitate. Parapneumonic effusions and empyema are fairly common with either form of staphylococcal pulmonary infection.

A mixed anaerobic infection often produces a single, rounded, putrid lung abscess, which can be as large as 10 cm in diameter and which frequently has an air-liquid level. Mixed infections may also cause a focal infiltrate with multiple small cavities. In lung gangrene (a rare entity), vascular compromise, focal vasculitis, and thrombosis of the involved lobe occur. The entire lobe cavitates, leaving chunks of necrotic lung floating in liquid pus. Anaerobic bacteria are probably involved in the etiology of most cases of lung gangrene, either alone or as part of a mixed infection with aerobic organisms. Diagnosis of this entity is based on the radiographic findings.

Blebs and bullae are thin-walled structures that may be congenital but usually result from emphysema. When bacterial superinfection is present, these cystic spaces may develop air-liquid levels and surrounding infiltrates. In the absence of old chest radiographs, it may be difficult to differentiate true cavitation from superinfection of bullae, or so-called bullitis.

Suppurative Infections

Chronic suppurative infections typically cause necrosis. Tuberculosis usually involves the upper lobes [see 7:II Infections Due to Mycobacteria]. Cavities are generally small to medium in size, have thick walls, and do not exhibit air-liquid levels [see Figure 4a]. There are often associated nodular infiltrates and fibrosis. Atypical mycobacterial infections, especially those caused by M. avium complex, often present as larger and more dramatic cavities, partly because such infections tend to occur in patients with underlying bullous lung disease. Infected, preexisting, abnormal air spaces caused by the underlying disease are difficult to distinguish from new necrosis of the lung caused by M. avium complex.

Histoplasmosis is a granulomatous infection that rarely cavitates in normal hosts. Blastomycosis and coccidioidomycosis have a mixed granulomatous and pyogenic histopathology, and lung necrosis is more common [see 7:XXXVII Mycotic Infections]. Aspergillus and Mucor infections lead to lung necrosis and infarction and frequently cavitate [see 7:XXXVIII Mycotic Infections in the Compromised Host]. Nocardia infections are subacute but also suppurative and may present as single or multiple cavitory lesions. Individual lesions tend to be round and well circumscribed; air-liquid levels are common [see 7:IV Infections Due to Gram-Positive Bacilli].

Parasitic Infections

Parasitic infections with cavities include echinococcal cysts, which are located in the lower lobes; the cysts are thin walled and have an irregular liquid level caused by collapse of the cyst wall [see 7:XXXV Helminthic Infections]. Although uncommon in the United States, echinococcosis is very common in parts of Africa and Asia. Paragonimiasis is most often acquired in East and Southeast Asia; infiltrates, pleural effusions, and impres-
Cavitation in noninfectious, nonneoplastic disease is usually caused by a destructive immunologic process, such as vasculitis or rheumatoid necrobiotic.

**Wegener Granulomatosis**

The most common lung vasculitis, Wegener granulomatosis is characterized by necrotizing granulomas of the upper and lower respiratory tracts, necrotizing glomerulonephritis, and other features of systemic vasculitis [see 10:VII Vascular Diseases of the Kidney]. The mean age at onset is 40 years, but Wegener granulomatosis may occur at any age; it is slightly more prevalent in men. Clinical features vary greatly and relate to the sites of involvement. Systemic symptoms include fever, malaise, and weight loss. Upper airway findings include rhinorrhea, sinus pain and drainage, nasal and nasopharyngeal ulcers, and otitis media. Respiratory symptoms include cough, dyspnea, and hemoptysis. Skin, eye, or joint involvement is common, and renal involvement is extremely common. The chest radiograph shows nodules or infiltrates, which are multiple about 90% of the time. About 70% of the time, at least one lesion is cavitary [see Figure 4c]. Nonspecific laboratory findings include anemia, leukocytosis, thrombocytosis, and an elevated erythrocyte sedimentation rate. About 50% of patients have an elevated level of rheumatoid factor, but the fluorescent antinuclear antibody assay is usually negative.

The best noninvasive diagnostic criterion for Wegener granulomatosis is the presence of anticytoplasmic autoantibodies, also called antineutrophil cytoplasmic antibodies (ANCA). ANCA tests have two main patterns. Cytoplasmic ANCA (cANCA) tests are characterized by staining of the cytoplasm of the neutrophils (the autoantibody detected is directed against serine proteinase-3). Perinuclear ANCA (pANCA) tests are characterized by staining that is largely confined to the perinuclear area of the target cells (a broader range of autoantibodies is detected). The most disease-specific pANCA test is that against myeloperoxidase (MPO), the identification of which entails additional testing. Rarely does a patient have both pANCA-MPO and cANCA, but having either of the two has a sensitivity of 85.5% and a specificity of 98.6% for Wegener granulomatosis or systemic vasculitis with the overlap syndrome (i.e., microscopic polyarteritis with pulmonary and renal involvement).

pANCA tests can be positive for antibodies other than MPO in some healthy persons and in patients with various autoimmune disorders, including rheumatoid arthritis, Sjögren syndrome, sprue, and chronic hepatitis. The specificity and sensitivity of the cANCA test plus pANCA-MPO test are similar to those of other well-accepted diagnostic antibody tests, including anti–double-stranded DNA antibodies for active SLE and anti–acetylcholine receptor antibodies for myasthenia gravis. Although the tests for ANCA represent a diagnostic advance, histopathologic diagnosis is still desirable. If pulmonary lesions are the only site for biopsy, open lung or thoracoscopic lung biopsy is preferred over transbronchial biopsy. Diagnostic histopathology shows granulomas and necrotizing vasculitis.

If not treated, most patients with Wegener granulomatosis die within 1 year. Broad immunosuppressive therapy with a combination of cyclophosphamide and glucocorticoids dramatically improves the prognosis. Ninety percent of patients...
improve with this therapy, and more than 75% achieve remission. The therapy is toxic and prolonged, usually taking many months to induce remission, after which the cyclophosphamide is often continued for 1 year. More than half of patients relapse within 5 years, necessitating an additional long course of toxic therapy. Recently, novel therapies have been tried in refractory cases; these therapies include anti-CD20 chimeric monoclonal antibodies. Severe and potentially lethal adverse drug effects with standard therapy include immunosuppression (leading to opportunistic infections), cyclophosphamide-induced cystitis, and, in rare instances, bladder cancer and myelodysplasia.

Patients with so-called limited Wegener granulomatosis, a milder disease of the upper airway and lungs, who have no major renal disease or life-threatening systemic illness sometimes respond well to long-term trimethoprim-sulfamethoxazole therapy, either as initial therapy or for prevention of relapse after initial response to more standard therapy. The reason for the success of trimethoprim-sulfamethoxazole therapy is unknown; no infectious agent has been identified as a primary cause of Wegener granulomatosis or as a trigger for its initial appearance or later relapse.

**Single Small Nodules**

Single small nodules, often called coin lesions, are usually primary lung cancers or granulomas [see Table 5]. It is important to detect and thoroughly evaluate such lesions because over 90% of cancers discovered at this stage can be cured. In general, given the high frequency of lung cancer, a nodule must be assumed to be malignant until it is proved benign. This is true even for small nodules detected only by CT. Nodules must be removed unless they can be proved benign; unless they can be assumed to be benign on the basis of their remaining unchanged or on the basis of the young age of the patient; or unless the patient cannot tolerate a surgical procedure. A benign etiology can be assumed if a chest radiograph taken 2 or more years earlier shows the lesion to have been the same size as or larger than it is currently. Such a situation could arise if the lesion went unrecognized on the initial film. (Unless the patient is younger than 35 years, it is inappropriate simply to follow a coin lesion.) There are also classic benign patterns of calcification that obviate further assessment of single small nodules. For granulomas, such patterns include dense, perfectly central targets of calcium, ring calcification, and solid, dense calcification of the whole nodule. For pulmonary hamartomas, patterns include the so-called popcorn calcification pattern. (It should be noted that small specks of calcium and eccentric clumps of dystrophic calcium are often seen in malignant tumors). Thin-section CT with contrast enhancement is another way to prove that a nodule is benign. Lesions of −20 Hounsfield units that do not enhance with contrast are always benign; lesions that do enhance are either tumors or active granulomas. A fine-needle biopsy may provide a specific benign diagnosis by histopathologic examination, cytologic examination, or culture of a microorganism.

If a patient with a pulmonary nodule is younger than 35 years, the chance of malignancy is low enough to justify serial follow-up every 6 months for 2 years. For patients of any age with a proven malignancy or a growing nodule and for all patients older than 35 years in whom the nodule cannot be proved benign, the lesion should be resected unless the patient cannot tolerate the required surgery. The patient’s tolerance is largely determined by cardiopulmonary reserve and associated illnesses. Video-assisted thoracoscopic surgery decreases the morbidity of nodule resection.

**Infectious Diseases**

Most infectious lung nodules are granulomas. Histoplasmosomas are by far the most common, especially in the vast areas of the central United States drained by the Ohio and Mississippi rivers. Histoplasmosomas rarely cause harm; the problem they pose, however, is in proving that they are not cancerous [see above and Figure 5a]. In the deserts of the southwestern United States, coccidioidomycosis is a common cause of a peripheral...

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**Figure 5**  (a) A histoplasmaoma presents as a solitary nodule in the upper right lower lobe (arrow) in this chest radiograph of a 50-year-old man. (b) This solitary nodule in the apex of the left lung (arrow) proved to be an adenocarcinoma. The patient is a 63-year-old woman who has a history of heavy smoking. (c) In this chest radiograph of a woman who is 24 years of age, the solitary nodule of a bronchogenic cyst can be seen in the left lower lobe, behind the cardiac shadow (arrow).
neoplastic disorders

Lung cancers of each cell type can produce solitary nodules. This presentation is most characteristic of adenocarcinoma [see Figure 5b], but squamous cell, large cell, small cell, and even alveolar cell cancers can present as nodules. A single nodule is seldom a metastatic lesion. About 25% of carcinoid tumors present as nodules. A single nodule that is almost always discovered after resection for presumed lung cancer is infection with *Dirofilaria immitis*, the dog heartworm [see 7:XXXVII Helminthic Infections]. A lesion cannot, however, be presumed to be a granuloma just because there is immunologic evidence of infection by a particular pathogen remote to the lung, such as a positive skin test or positive serodiagnostic titers. To exclude the diagnosis of cancer, the organism must be identified directly or by culture from the sputum or from material obtained by needle aspiration.

noninfectious, nonneoplastic disorders

Nodules are rarely noninfectious and nonneoplastic. Bronchogenic cysts and arteriovenous malformations can present as a single nodule [see Figure 5c]. Pulmonary sequestrations are usually larger [see Large Masses, below]. Rheumatoid nodules, Wegener granulomatosis, and pulmonary amyloidosis are rare disorders that seldom present as a single nodule.

Intrapulmonary lymph nodes can also present as small, solitary lung nodules. In one series, 17 of 96 patients who underwent excision of well-circumscribed peripheral pulmonary nodules had this pathology. All the intrapulmonary lymph nodes were located within 20 mm of a visceral pleural surface.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td><em>Bacterial pneumonia</em> (round pneumonia)</td>
</tr>
<tr>
<td></td>
<td><em>Blastomycosis</em></td>
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<tr>
<td></td>
<td><em>Cryptococcosis</em></td>
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<tr>
<td></td>
<td><em>Invasive aspergillosis, mucormycosis</em></td>
</tr>
<tr>
<td>Neoplastic</td>
<td><em>Primary lung cancer</em></td>
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<td></td>
<td><em>Alveolar cell carcinoma</em></td>
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<tr>
<td></td>
<td><em>Lymphoma</em></td>
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<tr>
<td>Noninfectious, nonneoplastic</td>
<td><em>Sequestration</em></td>
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<tr>
<td></td>
<td><em>Bronchogenic cyst</em></td>
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</table>

All were in the lower lobes or middle lobe. They could not be distinguished radiographically from neoplasm or granuloma. Improved radiologic image quality and use of CT will likely increase the number of intrapulmonary lymph nodes detected as small nodules.

A relatively uncommon cause of a solitary lesion is rounded atelectasis, which can produce a lesion up to 5 cm in diameter. Rounded atelectasis is always adjacent to the pleura and may have a comet-tail appearance, with the “tail” pointing toward the hilum. The nodular density represents the curling up of atelectatic lung tissue adjacent to a chronic pleural process. A more common pseudotumor is found with pleural effusions caused by congestive heart failure. Collections of liquid appear as rounded lesions on the posteroanterior radiograph, most often in the major fissure. Lateral films often show fissural loculation of liquid.

Large Masses

Neoplasms are the most common cause of lesions larger than 6 cm in diameter. Other conditions only rarely cause such large masses [see Table 6].

infectious diseases

Bacterial pneumonia occasionally presents as a round infiltrate. An anaerobic lung abscess can also produce a homogeneous round infiltrate before cavitation. This can occur when the bronchi associated with an anaerobic lung abscess are oc-

Figure 6  (a) Mucor infection caused the large dense mass revealed in the right lung on this chest radiograph. The patient is a 74-year-old man who has had prolonged neutropenia, caused by myelofibrosis. (b) A large mass, the most common presentation of large cell carcinoma, can be seen in the right upper lobe in the chest radiograph of a male smoker who is 66 years of age. (c) This chest radiograph of a 31-year-old woman shows a large mass in the right lower lobe adjacent to the diaphragm. The mass is an intralobar sequestration.
cluded, thereby preventing pus from escaping and air from entering.

Cryptococcal infection can produce a solitary mass up to 10 cm in diameter, often with few inflammatory symptoms. Blastomycosis, however, is the fungal infection that most frequently causes a rounded mass. It is often found in the apical posterior segment of the lower lobe, projecting over the hilum on a standard posteroanterior chest radiograph. Blastomycosis is one of the more common benign conditions that are discovered at thoracotomy for presumed lung cancer [see 7:XXXVII Mycotic Infections].

Invasive pulmonary aspergillosis and pulmonary mucormycosis occur in patients with neutropenia or in patients with depressed neutrophil function, usually caused by high-dose glucocorticoid therapy. Although each of these diseases most often presents as multifocal infiltrates [see Multifocal Pulmonary Infiltrates, above], these entities can also produce a focal infiltrate or a large, rounded mass [see Figure 6a].

**Neoplastic diseases**

Large masses are most often large cell carcinoma [see Figure 6b] but are not uncommonly adenocarcinoma or squamous cell carcinoma. Alveolar cell carcinoma commonly presents as a slowly growing mass, often occupying most of a lobe or lung. Hodgkin and non-Hodgkin lymphoma may present as masses [see 12:XI Malignant Lymphomas]. The former, but not the latter, almost always displays hilar adenopathy, mediastinal adenopathy, or both.

**Noninfectious, nonneoplastic disorders**

Bronchopulmonary sequestration may be intralobar or extralobar and typically presents as a large mass with well-defined edges [see Figure 6c]. Intralobar sequestrations are located in the posterior basal segment adjacent to the diaphragm, and two of three sequestrations are located on the left. Extralobar sequestrations are contiguous with the diaphragm, and 90% are located on the left; they are not as limited as intralobar sequestrations to the posterior segment.

Lipoid pneumonia and pulmonary contusion usually present as infiltrates [see Focal Pulmonary Infiltrates, above] but can sometimes mimic round masses. Bronchogenic cysts can also present as large masses.

**Multiple Nodules**

Hematogenous metastases are the most likely cause of multiple nodules, especially if the patient is not febrile and the nodules vary widely in size. Because hematogenous spread to the lung usually occurs over time, different nodules have shorter or longer growth intervals before discovery. Other causes of multiple nodules are uncommon [see Table 7]. The differential diagnosis for multiple nodules is different from that for single small nodules or large masses.

**Infectious diseases**

*Endocarditis and Endovascular Infections*

Pyemic abscesses are most commonly caused by right-sided endocarditis [see 7:XVIII Infective Endocarditis] or by other endovascular infections; *S. aureus* is the most common pathogen. Most patients have high fever and shaking chills. The white blood cell count is usually elevated and shifted toward neutrophils and neutrophil precursors, and blood cultures are usually positive. If the cause is endocarditis, a tricuspid murmur may be heard, and brisk venous pulsations in the neck (large V waves with rapid Y descent) may provide evidence of a leaky

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**Table 7** Major Causes of Multiple Pulmonary Nodules

<table>
<thead>
<tr>
<th>Cause</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td>Septic emboli, multiple granulomas</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Metastatic carcinoma</td>
</tr>
<tr>
<td>Noninfectious, nonneoplastic</td>
<td>Arteriovenous malformations, Wegener granulomatosis, sarcoidosis and amyloidosis, rheumatoid nodules</td>
</tr>
</tbody>
</table>

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Figure 7  (a) Multiple nodules, some with cavitation and some with air-liquid interfaces, are visible in this chest radiograph of a male I.V. drug abuser who is 34 years of age. The nodules are the result of tricuspid valve endocarditis caused by *Staphylococcus aureus*. (b) This chest radiograph of a 37-year-old woman with primary laryngeal cancer reveals metastatic squamous cell carcinoma. As is characteristic, the nodules vary widely in size, and some demonstrate cavitation. (c) This radiograph shows a 49-year-old man with Wegener granulomatosis, characterized by multiple nodules that vary widely in size and that have cavitated in some cases.
valve. Transthoracic echocardiography reveals vegetations in about half of cases; transesophageal echocardiography reveals vegetations in more than 80% of cases. The chest radiograph demonstrates multiple small nodules, which are usually 1 to 3 cm in diameter [see Figure 7a]. With time, the lesions may grow and cavitate. Subpleural nodules are frequently associated with pleural effusions, which may be sterile but often are highly inflammatory parapneumonic effusions or even frank empyema.

Other Infections

Multiple pulmonary nodules may also be caused by subacute or chronic infections. Melioidosis, for example, can present as multiple nodules [see Multifocal Pulmonary Infiltrates, above]. Patients often have chronic symptoms that are similar to those of tuberculosis. Nodules may be grouped in one area of the lung and may grow, coalesce, and cavitate as the disease progresses. *Nocardia* infections can also produce multiple nodules, which frequently cavitate [see :IV Infections Due to Gram-Positive Bacilli]. Over half of the patients who have *Nocardia* infections are immunosuppressed; sometimes, low-grade fever is the only symptom. Other patients have productive or nonproductive cough. Patients may also have associated subcutaneous nodules or brain abscesses, both of which are the result of hematogenous spread from the lung.

Coccidioidomycosis and paragonimiasis can produce scattered nodules. Often, the disease is relatively inactive and the only clinical finding is an abnormal chest radiograph. Individual lesions may soften and then be evacuated by expectoration of central necrotic areas, leaving thin-walled cavities. Histoplasmosis is a very frequent cause of multiple asymptomatic lung nodules. There are usually fewer than five nodules, and the lesions rarely if ever cavitate. Calcification is common but takes many years—at least 10 years in adults and somewhat less time in children. Dense, nearly total calcification is generally a strong indicator of a benign lesion. Small amounts of eccentric calcification, however, are frequently seen in rapidly growing primary and metastatic tumors, perhaps as a result of necrosis and subsequent calcification.

Extensive echinococcal infection can produce multiple large masses in the lung. One or more of the lesions may be cavitary. The patient may be afebrile, and the initial diagnosis is often metastatic cancer. However, a CT scan will show that the density of echinococcal lesions in Hounsfield units is close to zero. In this way, metastatic cancer can be eliminated as a diagnosis. Other echinococcal lesions may be found in the liver, kidneys, or other viscera. Surgery is impossible because of the extent of the disease (e.g., bilateral and extrapulmonary), but prolonged courses of antiparasitic therapy can be surprisingly effective.

**Neoplastic Diseases**

Metastatic carcinoma is the single most important cause of multiple pulmonary nodules [see Figure 7b]. Diagnosis is made by presumption if there are extensive metastases and an obvious primary cancer or by transthoracic needle aspiration biopsy if there is clinical uncertainty.

Lymphomatoid granulomatosis is a rare pulmonary disorder that usually presents as multiple pulmonary nodules or as multiple or diffuse infiltrates. The radiographic presentation mimics metastatic carcinoma or pulmonary vasculitis—particularly Wegener granulomatosis. Immunohistochemical methods have established that lymphomatoid granulomatosis is an angiocentric T cell lymphoma of variable grade. The disease is extranodal, involving the lung and, in a substantial minority of cases, the skin and the central nervous system. It is most common in men in their sixth and seventh decades. In untreated cases, survival is less than 1 year, but survival may be prolonged by the use of combination therapy with prednisone and cyclophosphamide or, if that fails, by more aggressive combination chemotherapy as employed against T cell lymphoma.

Posttransplant lymphoproliferative disorders (PTLDs) often present as multiple well-circumscribed pulmonary nodules. These disorders are related to infection with Epstein-Barr virus and may have polymorphic or monomorphic populations of lymphocytes, the latter being more aggressive and frankly malignant. AIDS-related lymphoma is a non-Hodgkin B cell lymphoma, also related to Epstein-Barr virus infection; it is similar to the monoclonal type of PTLD and often presents as multiple pulmonary nodules. Patients with other types of intensive immunosuppression also may occasionally develop multinodular pulmonary lymphoma. A feature shared by all these disorders is the absence of associated mediastinal adenopathy. Pulmonary Kaposi sarcoma in patients with AIDS and other immunosuppressive conditions can also present as multiple pulmonary nodules.

Two other related neoplastic entities, found exclusively in women, produce multinodular lung lesions that are most often asymptomatic: multiple pulmonary fibroleiomyomatous hamartomas, which are thought to arise within the lung, and so-called benign metastasizing uterine leiomyomas, which are thought to arise in the uterus. The two neoplasms are identical histopathologically and have often been shown to have estrogen receptors. These hamartomas and leiomyomas are most often benign and may regress spontaneously. Hysterectomy, oophorectomy, and antihormonal therapy have been tried in rare cases of progression, without much effect.

**Noninfectious, Nonneoplastic Disorders**

Only a few noninfectious, nonneoplastic conditions present as multiple pulmonary nodules. Pulmonary arteriovenous malformations are multiple in as many as one third of cases; half of those are associated with hereditary hemorrhagic telangectasia (Osler-Weber-Rendu disease) [see :IV Cutaneous Tumors and :V Hemoglobinopathies and Hemolytic Anemias]. Sometimes, the chest radiograph is so suggestive of this disorder that it is virtually diagnostic, especially when a feeding artery and a draining vein are visualized. To prove the diagnosis and to identify all the lesions, however, pulmonary angiography is always necessary. Patients may present with a number of clinical syndromes, including hemoptysis, hypoxemia, congestive heart failure, and systemic embolization. Invasive radiologic procedures have been developed to embolize the fistulas. These procedures are usually preferable to resection. Even if a large symptomatic lesion is resected, smaller lesions may grow and become symptomatic, leading to a series of resections and extensive loss of lung.

Wegener granulomatosis often causes multiple lung nodules [see Cavitary Infiltrates, above, and Figure 7c]. Rheumatoid nodules [see Multifocal Pulmonary Infiltrates and Cavitary Infiltrates, above] should also be included in the category of multiple pulmonary nodules. The infiltrates are multiple, are frequently discrete and well circumscribed (i.e., nodular), and sometimes cavitate. Temporal arteritis can produce multiple nodular lesions with fever, cough, and weight loss and should be consid-

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ered in elderly patients. Pulmonary hyalinizing granuloma is an obscure cause of multiple bilateral pulmonary nodules.22

Sarcoidosis and amyloidosis may produce multiple well-defined nodules, mimicking metastatic carcinoma. The nodules may be the only manifestations of these diseases. Histopathologic diagnosis is required, either by transthoracic needle aspiration biopsy or by open lung biopsy. There is no specific treatment for nodular amyloidosis, which has a better prognosis than other forms of pulmonary amyloidosis (e.g., diffuse interstitial infiltrates or endobronchial amyloidosis).

Additional Information

Additional information on focal and multifocal lung disease may be obtained from the National Heart, Lung, and Blood Institute (http://www.nhlbi.nih.gov/nhlbi/nhlbi.htm) and the American Thoracic Society (http://www.thoracic.org).

The author has no commercial relationships with manufacturers of products or providers of services discussed in this subsection.

References


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