Other Intrathoracic Tumors

Udaya B. S. Prakash, MD, FCCP

Objectives:

1. Discuss the tumors (other than primary lung cancer).
2. Describe carcinoid, cylindroma, hamartoma, etc.
3. Discuss metastatic malignancy in the thorax.
4. Discuss tracheobronchial amyloidosis.

Key words: carcinoid; cylindroma; hamartoma; lymphoma; metastatic tumors; mucoepidermoid carcinoma; papilloma

Carcinoid

Pulmonary carcinoid, previously known as bronchial adenoma, is a bronchogenic malignant tumor. The tumor is thought to arise from the pulmonary neuroendocrine cells of the surface or glandular epithelium of conducting or transitional airways. Pulmonary carcinoid is separate and different from the gastrointestinal carcinoid. There is no association with smoking and the etiology of carcinoid is unknown. Pulmonary carcinoids constitute less than 3% of all pulmonary neoplasms. The tumor is slightly more common in females (F: M = 1.6:1) and the mean age at diagnosis is about 45 years. Carcinoids may present as central (bronchial) or peripheral lesions. Central carcinoids make up 80% of pulmonary carcinoids and originate in lobar or segmental bronchi. Central tumors present earlier with cough, hemoptysis, and localized or posture-dependent wheezing (particularly if the tumor is pedunculated). Peripheral carcinoids present later as solitary nodules. The average tumor is 3 cm in diameter, and most tumors extend extraluminally (iceberg tumors). Central carcinoid almost always produces symptoms such as cough, expectoration, wheezing, and chest pain. Hemoptysis is a feature in at least 50% of patients. Pedunculated tumor may produce posture-dependent cough and wheezing. Postobstructive atelectasis may cause fever and purulent sputum. Peripheral tumors may go undetected unless they produce symptoms secondary to paraneoplastic syndromes. Most are about 4 cm in diameter and are well circumscribed.

- Arises from pulmonary neuroendocrine cells; unrelated to smoking.
- Constitutes less than 3% of all lung neoplasms.
- Central carcinoids make up 80% of all pulmonary carcinoids.
- Young patient (<50 years) with cough, wheezing, and hemoptysis.

Atypical carcinoid tumors exhibit clinical and histologic features suggestive of an aggressive behavior. Atypical carcinoids constitute less than 10% of all pulmonary carcinoids. Imaging studies may show spread of the tumor to adjacent areas such as lymph nodes, pleura, pericardium, etc. Morphologic analysis shows increased mitotic activity, nuclear pleomorphism and hyperchromasia associated with prominent nucleoli and increased nuclear/cytoplasmic ratio, and areas of increased cellularity with loss of typical architecture. Although the typical carcinoid has "typical" histologic features, it is not uncommon for an initial misdiagnosis of small-cell carcinoma even in typical carcinoid. A diagnosis of small-cell carcinoma in a younger (<45 years) nonsmoker should therefore be questioned.

- Pathology: typical and atypical
- Atypical: 10% of all primary pulmonary carcinoids.
- Spread to adjacent areas is common.
- Histology occasionally confused with that of small-cell carcinoma.

As the majority of carcinoids are centrally located and produce cough and hemoptysis, chest radiographs may not show specific features. Obstruction by tumor may exhibit segmental or lobar atelectasis on chest radiographs; this is the most common chest radiographic manifestation. Secondary oligemia due to reflex vasoconstriction is a well-documented chest radiographic feature of bronchial carcinoid. Bronchiectasis and mucus plug formation is uncommon, even in chronic cases. Peripheral carcinoid tumors present as solitary pulmonary nodules and demonstrate homogeneous density, good margination, and lobulation. They are more commonly seen in right upper and middle lobes and lingula. Calcification is not a feature. Tomography or CT may be necessary for staging if local or distant spread is suspected. Bronchoscopy is indicated in almost all cases of

central carcinoids. There is no contraindication to bronchoscopic biopsy The textbook description of "shiny, glistening, vascular" tumor is not always present, and many diagnoses are made only after biopsy. Furthermore, many noncarcinoid lesions can have the above description. Sputum cytology is generally unrewarding and TTNA, if a good core of tissue is obtained, may provide the diagnosis. Laboratory tests do not help in the diagnosis unless the patient presents with features of one of the paraneoplastic syndromes (see below).

- Lobar/segmental atelectasis is the most common chest radiographic finding.
- Oligemic lung fields secondary to reflex vasoconstriction.
- Vascular tumor, but bronchoscopic biopsy is not contraindicated.

Pulmonary carcinoid is well known to produce paraneoplastic syndromes due to the release of neuroendocrine products: corticotropin (ACTH), antidiuretic hormone, growth hormone-releasing factor (possibly growth hormone), pancreatic polypeptide, gastrin-releasing peptide (bombesin), vasoactive intestinal peptide, calcitonin, and serotonin. Other chemicals, including carcinoembryonic antigen, have been reported. ACTH production may lead to Cushing's syndrome. Many patients with ACTH-producing carcinoid have peripheral tumor, which remains undetected until the patient develops features of Cushing's syndrome. Refractory hypertension and hypokalemia are two prominent features of carcinoid-associated ACTH production. Release of growth hormone-releasing factor or growth hormone by carcinoid has resulted in acromegaly. Zollinger-Ellison syndrome has been described as part of multiple endocrine neoplasia syndrome in patients with carcinoid. Carcinoid syndrome is rare (<1%) with pulmonary carcinoids. Estimation of 5-hydroxyindoleacetic acid should be obtained only if clinical features suggest carcinoid syndrome.

- Paraneoplastic syndrome due to hormonal production relatively common.
- ACTH production may lead to Cushing's syndrome.
- Refractory hypertension, hypokalemia, and Cushing's: think of carcinoid.
- Typical carcinoid syndrome is very rare in bronchial carcinoid.

All carcinoid tumors should be surgically resected if there is no evidence of unresectability. There are many reports of bronchoscopic resection using laser or other therapies to remove endoluminal tumor (Chest 1995; 107:556-8). This constitutes suboptimal treatment because the removal of bronchoscopically visible lesion alone may not cure the extrabronchial portion of the tumor (J Bronchol 1996; 3:85-7). The 5-year survival: typical 89% and atypical 75% (ns); the 10-year survival: typical 82% and atypical 56% ($p < 0.05$). Nodal involvement and distant metastases occur in 10% and 3%, respectively, in the typical carcinoid and in >50% and >65%, respectively, in the atypical tumor. If regional lymph nodes are involved, the 5-year survival is <70%. Radiotherapy and chemotherapy elicit variable to poor response.

- All carcinoid tumors should be surgically resected, if they are resectable.
- Overall 5-year survival in stage I disease (typical carcinoid) is above 90%.
- Atypical carcinoid: metastases develop in 50%-70%.

Cylindroma

Cylindroma (adenoid cystic carcinoma) is a tumor of the tracheobronchial mucous glands. Histologic features are similar to those of salivary gland tumors. The etiology is unknown and smoking does not predispose patients to the development of this tumor. Nearly 80% of the tumors occur in the trachea and mainstem bronchi and the rest arise from lobar bronchi. Up to 10% may be located in the periphery. Cylindroma represents up to 80% of reported tumors of tracheobronchial glands. Patients are in their mid-40s and there is no sex predilection. Cylindroma is locally invasive and exhibits a prolonged course. In the trachea, most tumors arise in the upper or lower third and along the junction of cartilaginous and membranous portions of the airway. The neoplasm grows into the tracheobronchial lumen as a polypoid or smooth-surfaced tumor, with submucosal extension being common. Overlying epithelium may remain intact or ulcerate. Symptoms include cough, hemoptysis, dyspnea, wheezing, and recurrent pneumonitis. Chest radiographs may remain normal in patients with tracheal lesions. CT is helpful in assessing extraluminal and hilar/mediastinal extension. Treatment is by resection and end-to-end anastomosis.

For unresectable tumors, recurrent palliative laser therapy is indicated. Cylindroma shows poor response to radiotherapy and chemotherapy. Because of the slow growth, prolonged survival (10 to 15 years) is common. Frequent follow-up is necessary to identify recurrence or local spread.

- Tumors of tracheobronchial mucous glands; locally invasive.
- Not associated with smoking; no known etiology.
- More than 80% of tumors occur in the trachea and mainstem bronchi.
- Think of cylindroma in a middle-aged patient with refractory "asthma."
- Malignancy in "slow motion"; therefore, prolonged course.

Mucoepidermoid Carcinoma

A rare neoplasm of the tracheobronchial tree, mucoepidermoid carcinoma constitutes less than 0.5% of all pulmonary carcinomas. Morphologic features are similar to those in salivary mucoepidermoid carcinomas and show uniform cells arranged in sheets or trabeculae; individual cells are polygonal or columnar with vacuolar or mucus-containing cytoplasm that is eosinophilic. These cells are organized in epidermoid fashion. There is no clear association between smoking and the tumor. Both a low-grade and an aggressive type have been described. The tumors are located in the mainstem or lobar bronchi. Tracheal involvement is unusual and occurs in the region of the main carina. Bronchoscopic appearance is similar to that in cylindroma (see above). The tumor usually involves the bronchial wall but the high-grade form may extend to extrabronchial sites. The average age of patients is 35 years for the low-grade type and 45 years for the high-grade type, with slightly increased male predominance. Many cases have occurred in patients younger than 20 years of age. Symptoms include cough, hemoptysis, wheezing, and postobstructive pneumonia. One series of 13 patients reported a 4-year survival in eight patients following surgery.

- Can be slow-growing or aggressive.
- Located in the mainstem and lobar bronchi and near main carina.
- Bronchoscopically similar to cylindroma.
- Age group of patients: 35 to 45 years; same as carcinoid patients.

Hamartoma

Well-circumscribed benign tumor of developmental origin and made up of cartilage and fat. Hamartomas constitute 5% to 8% of all solitary pulmonary nodules. The majority are located in the lung parenchyma and measure less than 4 cm in diameter. Fewer than 5% are endobronchial. Most hamartomas develop in those older than 60 years of age (male to female ratio, 2-3:1) and are detected during routine chest radiography. Chest radiography and tomography show a well-defined solitary nodule (<4 cm) with "popcorn" calcification in 25%. There is no predilection for any lobe or lung zone. Serial chest radiography may show slow growth and suggest a slow-growing malignancy. CT typically shows adipose tissue and calcification, if the latter is present. Multiple hamartomas are rare. Most hamartomas are asymptomatic, although hemoptysis and spontaneous pneumothorax can occur. Endobronchial lesions may produce cough, hemoptysis, atelectasis, and chest pain.

- Fewer than 10% of all solitary lung nodules are hamartomas.
- Slow growth may suggest carcinoma; malignant transformation very rare.
- Fewer than 5% are endobronchial.
- "Popcorn calcification" on tomography in 25%; adipose tissue on CT.
- Age of patients: above 60 years.

Other Primary Pulmonary Tumors

Pulmonary Tumorlets

These represent a tiny (<3 mm in diameter, multiple to innumerable), organized proliferation of neuroendocrine cells adjacent to small bronchioles detected at autopsy or in resected surgical specimens of patients with bronchiectasis or various fibrotic lung disorders. Most patients are older women. The tumorlets very likely represent hyperplastic cells, even though some have argued that these represent tiny peripheral carcinoid tumors. Cellular features resemble those of carcinoid. Most are benign and asymptomatic. Only one patient has been described with Cushing's syndrome caused by tumorlets.

- Multiple parenchymal lesions measuring more than 3 mm in diameter.
- Due to benign proliferation of neuroendocrine cells.

- More common in older women.
- Majority are asymptomatic; paraneoplastic features are very uncommon.

Papillomatosis

Caused by human papillomavirus, papillomatosis morphologically reveals a branching or coarsely lobulated tumor composed of epithelium-lined fibrovascular stalks arising from and projecting above an epithelial surface. There is a predilection for papilloma to grow at the junctions between ciliated respiratory mucosa and squamous epithelium (Ann Otol Rhinol Laryngol 1993;102: 580-3). An association has been documented between maternal genital warts and development of laryngeal papillomatosis in children. Nearly 60% of children with respiratory papillomatosis are born to mothers with genital papillomas during pregnancy or parturition. These tumors are usually multiple and recurrent. Children between the ages of 18 and 36 months develop laryngeal papillomatosis. In fewer than 2%, these occur in distal airways. They also tend to occur at sites of resected papillomatosis and tracheostomy. Viral DNA has been shown in normal laryngeal mucosa during clinical remission. Spontaneous resolution is seen in most children. Long periods (10 to 15 years) may elapse from the time of laryngeal lesions to the appearance of tracheobronchial lesions. The adult form of the disease is rare and may occur in the absence of childhood disease; adult disease constitutes fewer than 12% of all cases of papillomatosis of the airways. Laryngobronchoscopy will show typical miniature "grape-bunch" appearance of translucent whitish warty growths projecting into the airway lumen. Histologic features consist of broadly stalked growths lined by a flattened squamous epithelium that matures normally. Obstruction of distal airways may produce segmental or lobar atelectasis, particularly in children. The overall prognosis is excellent in more than 90% of patients. Recurrent resection by laryngoscopy and/or bronchoscopy using CO_2 laser is the standard therapy. Antiviral agents are being tried.

- Caused by human papillomavirus, types 6 and 11.
- Primarily a pediatric disease; fewer than 12% of patients are adults.
- Tend to occur at sites of resected papillomatosis and tracheostomy.

In a small percentage of patients, papillomas progress to involve the distal trachea and bronchial tree as well as the lung parenchyma. Segmental or lobar atelectasis may occur with endobronchial obstructing lesions, whereas pulmonary parenchymal involvement may mimic nodular cancer. The lung lesions measure 1.5 to 5.0 cm in diameter and may undergo cavitation. Frequently, the cavities get filled up, presumably from regrowth of papillomas, only to recavitate. Since the risk of developing squamous cell carcinoma is high in these patients (16% of 102 patients; Acta Otolaryngol 1994; 114: 209), close surveillance is necessary (Chest 1994; 105:1887-8). The mean time between onset of papilloma and diagnosis of cancer is 24 years (range, 4 to 55 years). Biopsy may show coexistence of carcinoma with papillomas. Radiation therapy to papillomas enhances the risk of malignancy. The clinical course and prognosis in those with carcinoma are similar to others with common type of squamous cell carcinoma.

- Predisposes to development of squamous cell carcinoma in chronic cases.
- Pulmonary parenchymal involvement; nodules and cavitated lesions.
- Distal tracheal and bronchial involvement can occur.

Solitary papillomatoses are sometimes considered separate from the multiple variety discussed above. These are less common than the multiple variety and almost always occur in middle-aged and older patients (males much more than females). The adult form of the disease is considered to be less aggressive. It is most likely that it is unrelated to the juvenile papillomatosis discussed above. Solitary papillomas are generally located in lobar or segmental bronchi as spherical tumors measuring 0.5 to 1.5 cm in diameter. Pathologic features are identical to those in juvenile papillomatosis (see above). Carcinoma in situ or invasive squamous cell carcinoma may develop at the site of the papilloma. Bronchoscopic resection and periodic follow-up may be necessary.

- Occur in middle-aged and older patients (males much more than females).
- Located in lobar or segmental bronchi; 0.5 to 1.5 cm diameter.
- Predisposes to in situ or invasive squamous cell carcinoma.

Metastatic Neoplasms

The incidence of intrathoracic metastasis from tumors originating from extrathoracic sites ranges from 30% to 55%. Pleuropulmonary spread occurs as a result of direct extension, hematogenous spread via pulmonary or bronchial arteries, or lymphogenous spread via pleuropulmonary lymphatics. Intrathoracic metastases produce six types of chest radiographic features: parenchymal nodule(s), interstitial (lymphangitic) and intrathoracic lymphadenopathy with attendant complications (extrinsic compression of airways and diaphragmatic paralysis), endobronchial lesions, tumor emboli, and pleural effusion.

- Incidence of intrathoracic metastasis is 30% to 55%.

Lung Nodule(s)

Pulmonary nodules are the most common manifestation of metastatic disease. They are usually the result of tumor emboli. They are multiple in 75% of cases and occur in lower lung zones. The size can vary. The "cannonball" metastases arise from highly vascular primary tumor such as thyroid cancer, renal cell carcinoma, choriocarcinoma, or osteogenic sarcoma. Cavitation occurs in 5% to 10% of nodules and is more common in tumors originating in the head and neck area, urogenital areas, and intestines. Calcification occurs in metastatic osteogenic sarcoma, chondrosarcoma, or synovial sarcoma. Solitary metastatic nodules constitute about 5% of all solitary lung nodules. Solitary nodules are more common in rectosigmoid malignancies, sarcomas of bone, and cancers of breast, kidney, testis, and melanoma.

- Most common manifestation of metastatic disease.
- Solitary metastatic nodules constitute 5% of all solitary pulmonary nodules.
- Multiple in 75%; more common in lower lung zones.
- Cavitation in fewer than 10%, especially head and neck tumors.
- Multiple nodules more common in vascular primary tumors (thyroid, kidney, osteogenic sarcoma, and choriocarcinoma).

Interstitial/Lymphangitic Neoplasms

Tumor involves lymphatic channels as well as interstitium. Interstitial process, Kerley's B lines, and coarse reticulonodular markings in lung bases can be seen on chest radiography. Usually bilateral, it can begin as a unilateral process. The common primary tumors that cause this type of metastasis arise in breast, pancreas, prostate, and stomach. Pleural involvement is present in most cases. Progressive dyspnea is the most common symptom.

- Lymphatic channels and interstitium involved.
- Kerley's B lines on chest radiography; CT shows septal lines and nodules.
- Carcinoma of breast, pancreas, prostate, and stomach (adenocarcinomas).

Endobronchial Metastasis

Autopsy studies show high rate (20% to 50%) of endobronchial metastasis even though the clinical incidence is lower. Luminal extension occurs as a result of direct extension of parenchymal or lymph node tumor or by submucosal tumor spread. Endobronchial metastases are more likely from primary tumors of breast, colorectum, kidney, prostate, Hodgkin's disease, and melanoma.

- Due to direct luminal extension or submucosal lymphatic spread.
- Cancers of breast, colon, Hodgkin's disease, kidney, melanoma, prostate, and rectum.

Tumor Emboli

Tumor emboli are seen most frequently with adenocarcinomas of breast, lung, or stomach, and hepatoma. Choriocarcinoma, right atrial myxoma, and renal tumors also produce tumor emboli. Tumor embolism can lead to infarction and death in patients with hepatoma and renal cell carcinoma. Lymphangitic spread occurs commonly with tumor emboli. Secondary pulmonary hypertension occurs from subacute or chronic recurrent tumor emboli. Symptoms may include dyspnea, pleuritic pain, hemoptysis, and features of pulmonary hypertension.

- Adenocarcinomas of breast, kidney, lung, or stomach, and hepatoma.
- May lead to lung infarction and death in hepatoma and hypernephroma.
- Secondary pulmonary hypertension from subacute or chronic tumor emboli.

Pleural Effusion

Almost any tumor can produce pleural effusion. The most common mechanism is blockage of lymphatics at the hilar lymph node level. Other mechanisms include direct spread, tumor emboli, and lymphangitic spread, and post-obstruction (parapneumonic). Pleural effusion is a late manifestation of breast cancer. Spontaneous pneumothorax is more common with metastatic osteogenic sarcoma. About 5% of peripheral lung tumors (usually adenocarcinoma) present with spontaneous pneumothorax.

- Pneumothorax is more common with metastatic osteogenic sarcoma.

Lymphoproliferative Disorders

Hodgkin's Disease

Intrathoracic involvement in Hodgkin's disease is common, especially in those with advanced stage IIIB or IV disease. The incidence of significant respiratory complications is directly related to the size of mediastinal mass and the extent of the disease. Pleuropulmonary involvement has been observed in more than 70% of patient's with the disease, particularly in the nodular sclerosis subtype. Pleuropulmonary involvement is noted at the time of diagnosis in up to 30%. Most patients with intrathoracic manifestation will exhibit the disease in other organs. Isolated intrathoracic involvement is encountered in fewer than 3% of patients. In patients in their third or fifth decade of life presenting with mediastinal or hilar lymphadenopathy, Hodgkin's disease should be among the most likely diagnostic possibilities. In addition to mediastinal and/or hilar lymphadenopathy, clinical and chest radiographic features include chylous pleural effusion, endobronchial obstruction (due to endobronchial disease), pneumonic consolidation, miliary infiltrations, Kerley's lines, and nodular lesions in pulmonary parenchyma and pleura. Pulmonary nodules can undergo cavitation with thick or thin walls. Involvement of anterior mediastinal and retrosternal nodes is common. Large anterior mediastinal lymph nodes can cause tracheal compression and respiratory distress in supine posture. Pleural effusion is seen in 30% of patients. Endobronchial involvement by Hodgkin's lymphoma occurs in about 5% of patients. Lobar or segmental atelectasis, cough, and hemoptysis may result. The incidence of pneumothorax is 10 times higher than expected. The chest cage (ribs, vertebrae, or sternum) is not uncommonly affected by direct extension; lytic lesions result. Hypertrophic pulmonary osteoarthropathy (HPO) is described in some patients with Hodgkin's disease. Most frequent sites of relapse after radiotherapy are upper mediastinum and lung (in 10%). Primary pulmonary Hodgkin's disease is a distinct entity and denotes involvement of the lung without hilar adenopathy or disseminated disease. As of 1990, 61 cases were reported. This form of Hodgkin's lymphoma is more common in females, typically involves upper lung fields, and may appear as a solitary mass or a multinodular process with or without cavitation.

- Mediastinal adenopathy (seen in >50%) is the most common chest radiographic manifestation.
- Anterior mediastinal adenopathy is common (this is unusual in sarcoidosis).
- Chylous pleural effusion in a young patient.
- Endobronchial disease (seen in 5%) can cause atelectasis.
- Calcification of mediastinal/retrosternal nodes following radiotherapy.
- High incidence of pneumothorax.

Non-Hodgkin's Lymphoma

Intrathoracic involvement (both mediastinal lymphadenopathy and pulmonary parenchymal) is less common than in Hodgkin's disease. Lymphoma limited to lung and/or mediastinal lymph nodes at the time of diagnosis (and for 3 months after diagnosis) has been termed primary pulmonary lymphoma, and involvement of lung and extrapulmonary sites at the time of diagnosis is termed secondary lymphoma. They are usually well-differentiated B-cell tumors of IgM type, although a few cases of IgG and IgA type have been described. The primary pulmonary lymphoma is thought to originate in the bronchus-associated lymphoid tissue, present normally throughout the airways. They usually produce a diffuse interstitial pulmonary process and should be included in the differential diagnosis of lymphocytic interstitial pneumonitis (LIP). Immunohistologic studies including cell clonality studies are important to properly understand and classify these tumors. Overall intratho-

racic involvement in non-Hodgkin's lymphoma is as follows: mediastinal lymphadenopathy in 50%, hilar lymphadenopathy in 35%, pulmonary involvement in 40%, and pleural involvement in 35%. Lung involvement is always accompanied by mediastinal or hilar lymphadenopathy, and parenchymal involvement is observed in four chest radiographic forms: diffuse reticulonodular (most common) is seen in 26% to 50% and may resemble lymphangitic metastasis, nodular (multiple much more than solitary; 2.5 to 4.0 cm in diameter), parenchymal consolidation (mimics pneumonic consolidation with air-bronchogram and rapid evolution), and miliary (least common). Pleural involvement is seen in 35%, usually as a late manifestation. Pleural fluid is an exudate and may be chylous.

- Mediastinal lymphadenopathy less common (45%) than in Hodgkin's disease (65%).
- Parenchymal involvement in 4% compared with 12% in Hodgkin's disease.
- Lymphoma is the most common cause of cardiophrenic lymphadenopathy.
- Primary pulmonary lymphoma is lymphoma limited to the lung and/or mediastinal nodes.
- Increased incidence of lymphoma in hypogammaglobulinemia, Sjögren's disease, eosinophilic granuloma, sarcoidosis, renal transplant, asbestos exposure, AIDS, and chronic immunotherapy.

Pseudolymphoma

Previously, lymphoid tumors that did not fulfill the criteria for malignant lesions were called pseudolymphomas. It used to be difficult to separate pulmonary pseudolymphoma, lymphoma, and other lymphoid neoplasms and infiltrates by simple histologic examination. Although pseudolymphoma was previously considered to be benign, many pseudolymphomas have been reclassified as indolent well-differentiated lymphocytic and lymphoplasmacytic lymphomas on the basis of immunologic proof of clonality. Pseudolymphoma of the lung is characterized morphologically by the presence of a mixed cellular infiltrate, germinal centers, and regional lymph nodes free of lymphoma. Pulmonary manifestations consist of well-delineated nodules, segmental parenchymal consolidation, or diffuse interstitial infiltration. Pulmonary pseudolymphoma is distinguished microscopically from lymphoid interstitial pneumonia by the diffuse infiltrative nature of the latter. Localized lesions are best treated by resection, whereas diffuse lesions may need immunosuppressive therapy.

- Pseudolymphoma represents low-grade B-cell lymphoma.
- Chest radiography reveals a well-defined solitary nodule (<6 cm).
- Localized lesions are best treated by resection.

Angiocentric Malignant Lymphoma

Formerly known as lymphomatoid granulomatosis, AML is a lymphoproliferative disorder and not a primary vasculitis. Clinically and radiographically, AML mimics Wegener's granulomatosis, and hence the original descriptions and some current confusion. Previous terms for AML have included polymorphic reticulosis, midline malignant reticulosis, midline granuloma, and Stewart's granuloma. A newer term, angiocentric malignant lymphoma, has been suggested. The etiology is unknown. AML is a destructive angiocentric process characterized by prominent vascular infiltrates and necrosis of medium-sized and small blood vessels with formation of granulomas. Morphologic analysis of tissues may show a spectrum of benign-appearing LIP to overtly malignant lymphoma in the same patient. A prospective study reported the occurrence of lymphoma in 50% of patients. Lymphomas occurring in patients with AML are T-cell malignant lymphomas.

- AML is a lymphoproliferative disorder and not a vasculitis.
- Destructive angiocentric process with vascular infiltrates, necrosis of medium-sized and small vessels, and formation of granulomas.
- Majority of patients with AML develop T-cell lymphomas.

AML is an uncommon disease. It usually presents during middle age, when it is slightly more common in men. The presenting symptoms of AML are nonspecific; fever, malaise, and weight loss are common. AML affects many organs but it is found with higher frequency in the CNS, skin, kidney, and lymphatic system. Nearly 25% of patients have CNS involvement. Ataxia, hemiparesis, blindness, and dizziness may be the presenting symptoms. About 50% of patients develop skin lesions in the form of erythematous, macular, or plaque-like lesions over the extremities. Leukocytosis (in 30% of patients), leukopenia (in 20% of patients), mild to

moderate elevation of the erythrocyte sedimentation rate, and mild elevations of IgG or IgM may be detected. Urinalysis is usually normal because the glomerulus is characteristically spared.

- Middle-aged patients (men more common than women).
- Lungs, CNS (in 25%), skin (in 50%), kidney, and lymphatic system.
- Ataxia, hemiparesis, blindness, and dizziness may be the presenting symptoms.
- In contrast to Wegener's granulomatosis, glomerulus is characteristically spared.
- Diagnosis of AML requires biopsy of affected organ.

Lung involvement is present in virtually all patients with AML. Cough and dyspnea are prominent respiratory symptoms. Hemoptysis is likely in those with cavitated lung lesions. Chest radiography may show nodular infiltrates that may cavitate and are more frequent in the lower lung zones. One review of 173 patients collected from two separate series noted the following chest radiographic abnormalities: multiple bilateral nodules (80%), cavitation of nodules (30%), air-bronchogram (35%), pleural effusion (33%), atelectasis (30%), pneumonitis / mass-like lesion (30%), and pneumothorax (5%). Presence of hilar or mediastinal lymphadenopathy usually indicates lymphomatous transformation. If head and neck areas are involved, patients may present with symptoms similar to those of Wegener's granulomatosis. Airway involvement is unusual but can be extensive. Pathologic findings described include bronchiolitis obliterans, bronchial ulceration, and destruction and occlusion of bronchioles by masses of inflammatory cells and fibrous tissue. Multiple chemotherapeutic agents with corticosteroid may be needed in patients who demonstrate highly malignant features. Localized lesions in the head and neck area may respond to irradiation. Progressive pulmonary respiratory involvement, usually due to lymphoma and related complications, is the most frequent cause of death. Fever, leukopenia, cutaneous anergy, and hepatomegaly have been reported to indicate poor prognosis.

- Lung is involved in virtually all patients with AML.
- Hemoptysis is likely in those with cavitated lung lesions.
- Chest radiography: bilateral nodular infiltrates or nodules in lower lung zones.
- Cavitation of nodules in 30% and pleural effusion in 33%.
- Hilar / mediastinal lymphadenopathy indicates lymphomatous transformation.

LIP

Lymphocytic interstitial pneumonitis is characterized by infiltration of lung parenchyma by small lymphocytes and variable numbers of plasma cells and transformed lymphocytes. Many patients with LIP eventually develop lymphomas. The original description of LIP included several cases of lymphoma. Most authorities now believe that all cases of LIP represent low-grade lymphomas. It is unclear whether the diseases that cause LIP are premalignant, initially neoplastic, or due to a hypersensitivity reaction with lymphoma developing eventually. The diseases associated with LIP are listed in Table 1.

Many of the entities listed in Table 1 show similar pathologic features, but variably some involve the CNS (AML), skin (Sézary syndrome), kidneys, and lymph nodes outside the thorax with a rapidly fatal outcome. Therefore, disease entities that demonstrate LIP (AML, Sjögren's, and others) should be considered as lymphoproliferative disorders. The occurrence of LIP in patients with AIDS is well recognized, and it occurs with high frequency in children of mothers who are at high risk of developing AIDS.

Table 1—*Causes and Associations of Lymphocytic Interstitial Pneumonitis*

Hodgkin's lymphoma
Non-Hodgkin's lymphoma
Lymphomatoid granulomatosis
Chronic lymphocytic leukemia
Waldenström's macroglobulinemia
Angioimmunoblastic lymphadenopathy
Sézary syndrome
Pseudolymphoma
Sjögren's syndrome
Acquired immunodeficiency syndrome
Children of mothers at high risk for AIDS
Graft-versus-host disease
Congenital agammaglobulinemia
Chronic active hepatitis
Primary biliary cirrhosis
Crohn's disease
Nontropical sprue
Myasthenia gravis
Autoimmune hemolytic anemia
Idiopathic

- Majority of cases of LIP represent low-grade B-cell lymphomas.
- The diagnosis of "idiopathic" LIP is one of exclusion.

Sjögren's Syndrome

Sjögren's syndrome (SS) is a chronic inflammatory and autoimmune disorder, characterized by decreased lacrimal and salivary gland secretion (sicca complex) resulting in keratoconjunctivitis sicca and xerostomia. Original description of SS consisted of a triad of dry eyes, dry mouth, and rheumatoid arthritis. It is now known that patients with other connective tissue diseases, eg, systemic lupus erythematosus, scleroderma, and polymyositis, frequently develop the sicca complex. Sjögren's syndrome can also exist as a primary pathologic entity with no associated disorder. It should be considered a lymphoproliferative disorder because the incidence of lymphoma is increased 44-fold. Additionally, patients with SS have high risk of developing non-Hodgkin's lymphoma, which may affect the lungs. Pulmonary complications are seen in both primary and secondary forms of SS and are reported to occur in about 10% of patients. Pulmonary manifestations described in the literature include diffuse interstitial pneumonitis, desiccation of the upper respiratory tract (xerotrachea), obstructive process involving both large and small airways, localized infiltrates, diffuse pulmonary fibrosis, pneumonic patches, discoid atelectasis, localized pulmonary nodules, bronchitis, asthma, recurrent tracheobronchitis, bronchiectasis, pleurisy, pleural effusion, pulmonary hypertension, amyloidosis, vasculitis, and diaphragmatic myopathy. Many of these complications are uncommon. Among 17 patients with SS, pulmonary hyperinflation with diminished peripheral spirometric flow values was frequent; the levels of serum b2-microglobulin correlated inversely with FVC (Chest 1995; 108:316-9).

- Both primary and secondary SS are lymphoproliferative disorders.
- Incidence of lymphoma is increased greater than 40-fold.
- Non-Hodgkin's B-cell lymphoma in chronic cases.
- Overall incidence of pulmonary complications is about 10%.

Lymphocytic bronchitis may be partly responsible for the obstructive lung disease observed in patients with SS. Infiltration of bronchial mucosa by lymphocytes has been considered a benign process, but without special immunohistologic studies it is difficult to distinguish low-grade lymphomatous involvement of the bronchial mucosa. Nearly 15% of patients with SS develop diffuse interstitial pulmonary process. The clinical problem is one of differentiating LIP from non-LIP without lung biopsy because of the clinical implications (ie, lymphoma). Chest radiography in LIP usually shows diffuse interstitial process, predominantly basal in distribution. Some patients with LIP eventually develop disseminated lymphoma. Pseudolymphomas (see above) are thought to develop in patients with secondary SS alone. Chest radiography may demonstrate rounded mass lesions or nodular lesions. These lesions are usually detected on chest radiography of patients with chronic SS, usually without symptoms. The lesions may be well defined, rounded, usually solitary, and measure from 1.5 to 6 cm. The overwhelming majority of malignant lymphomas reported in patients with SS have been monoclonal B-cell neoplasms. Pulmonary involvement by lymphoma is more likely to occur in those with systemic lymphoma associated with SS. A Mayo Clinic study of 50 patients with SS and associated lymphoma revealed pulmonary involvement in 10 patients. The mean age of the 10 patients was 59.7 years and eight were women; the mean duration of SS was 7.2 years and the mean interval between the onset of SS and lymphoma was 5.4 years. Of the 10 patients, four died from 8 to 48 months after lymphoma was diagnosed. Lung biopsies revealed a spectrum of low- to high-grade lymphomas. While it is difficult to distinguish LIP from malignant lymphoma when the chest radiograph reveals an interstitial process, presence of multiple nodular lesions suggests lymphoma. Hilar lymphadenopathy or masses also suggest a high likelihood of lymphoma. Patients with low-grade lymphomas fare significantly better than those with high-grade lymphoma. Patients with pulmonary lymphomas secondary to SS are believed to have a better prognosis.

- Chest radiography in LIP usually shows a diffuse basal interstitial process.
- Some patients with LIP eventually develop disseminated lymphoma.
- Pseudolymphomas occur in patients with SS.

- Lung involvement (in 20%) by lymphoma occurs in those with systemic lymphoma associated with SS.
- Multiple nodular lesions, masses, or mediastinal / hilar lymphadenopathy in patients with SS suggest lymphoma.

Angioimmunoblastic Lymphadenopathy

This is a disorder in which diffuse obliteration of the lymph node architecture results from the proliferation of small vessels and immunoblasts. Both an autoimmune mechanism and a T-cell defect leading to polyclonal B-cell activation may play roles in the causation of dysproteinemia. The disease is systemic, and even though histopathologic features appear benign, lymphomatous changes are frequent. Angioimmunoblastic lymphadenopathy mimics lymphomas. The disease usually presents as generalized lymphadenopathy with hepatosplenomegaly and constitutional symptoms, and the presence of differentiating features of polyclonal gammopathy, autoimmune hemolytic anemia, and a predilection for men over the age of 50. Chest radiographic features are similar to those of Hodgkin's disease: hilar lymphadenopathy, interstitial infiltrates, and pleural effusion.

- Generalized lymphadenopathy in middle-age (men more common than women).
- Some patients eventually develop disseminated T-cell lymphoma.
- Polyclonal gammopathy and autoimmune hemolytic anemia.
- Chest radiography: mimics findings in Hodgkin's disease.

Castleman's Disease

This is also known as angiofollicular lymph node hyperplasia, giant lymph node hyperplasia, lymph node hamartoma, benign giant lymphoma, multifollicular lymph node hyperplasia, and others. There are three histologic variants (hyaline-vascular, plasma-cell, and mixed), and two clinical types (localized and multicentric). The hyalin-vascular type accounts for 90% of cases and is usually asymptomatic, and the plasma-cell type is associated with systemic manifestations. There is no predilection for age, sex, or race. Intrathoracic manifestations are seen in up to 70% of cases, the most common being the well-defined and lobulated enlargement of anterior mediastinal lymph nodes adjacent to thymus and tracheobronchial tree. Symptoms caused by compression of tracheobronchial tree by enlarged lymph nodes include cough, dyspnea, and hemoptysis. Intrapulmonary lesions, nodules, and pleural effusion are uncommon. CT has shown vascular lesions that are well rounded and lobulated. Once thought to be localized and self-limited, Castleman's disease is now known to manifest as a multisystem disease with progressive clinical course. Localized type can be cured with surgery. Multicentric disease often requires aggressive systemic therapy and carries with it a poor prognosis (Mayo Clin Proc 1995; 70:969-77). Surgical resection is curative if the disease is limited to resectable lymph nodes. Confusion exists in the understanding of Castleman's syndrome and its relation to other syndromes. Crow-Fukase syndrome, also known as POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) has been described in association with Castleman's disease.

- Localized and multicentric types.
- Intrathoracic manifestations in >65% of cases.
- Lobulated enlargement of anterior mediastinal lymph nodes.
- Symptoms caused by compression of tracheobronchial tree.

Other Lymphoproliferative Diseases

Burkitt's Lymphoma: This has been shown to involve the thoracic cage in 35% of patients. Pleural effusion is the most common abnormality and is frequently associated with ascites. Mediastinal lymphadenopathy, pleural nodularity, and lung involvement may be seen.

Mycosis Fungoides: This is a T-cell lymphoma primarily involving the skin. Sézary syndrome is the leukemic phase of mycosis fungoides. Autopsies have shown pulmonary involvement in 50% of patients. Chest radiographic features have included diffuse nodular changes, mediastinal lymphadenopathy, patchy areas of consolidation, and pleural effusion.

- Lung involvement in 50% of patients with mycosis fungoides.

Myeloproliferative Disorders

Leukemia

Pulmonary involvement in leukemia occurs often. The mortality rate associated with respiratory complications in leukemia is about 65%. The type of leukemia, the nature and course of treatment, the presence or absence of significant neutropenia, and degree of overall immunosuppression determine the extent of lung involvement. Most complications are secondary to immunocompromised status of leukemic patients, caused by either the leukemic state itself or treatment. Lung infection is a frequent and often fatal complication that is responsible for nearly 75% of reported deaths in acute leukemia. In one series of 68 leukemic patients with lung infiltrates, 82% of focal and 35% of diffuse infiltrates had infectious causes. Gram-negative organisms are the most commonly involved. Fungal pneumonia occurs in 15% to 25% of patients. *Pneumocystis carinii* pneumonia occurs less often in adults than in children with acute leukemia. In one study of 49 adults with *P carinii* pneumonia (before AIDS became an epidemic), leukemia was the underlying hematologic disorder in 28%.

- High mortality (65%) with lung involvement.
- Most pulmonary complications are due to infections (gram negative).
- Fungal pneumonia in 20%; *P carinii* pneumonia less common.

Autopsy studies have shown that intrathoracic involvement by noninfectious causes is a common late development in leukemia. Mediastinal/hilar adenopathy occurs in 50% of cases, and pulmonary parenchyma is affected in about 25%. Acute myelogenous leukemias produce leukemic infiltrates of lungs more commonly than the chronic varieties. Among the chronic leukemias, lymphocytic leukemias are more likely than the granulocytic type to invade the lung parenchyma. The usual chest radiographic abnormality within lung parenchyma is a diffuse bilateral reticulonodular infiltration resembling that of lymphangitic metastasis, a finding that is not uncommon in the terminal stages. Discrete nodules and infarcts are very rare. The leukemic infiltrates may be parenchymal (focal or diffuse), pleural, peribronchial, or endobronchial. In the so-called Richter's transformation, chronic lymphocytic leukemia (CLL) may convert from a low-grade histologic picture to high-grade non-Hodgkin's lymphoma and produce hilar or mediastinal lymphadenopathy. Pleural effusion, usually unilateral, is second only to mediastinal lymphadenopathy in frequency and is seen in nearly 25% of cases.

- Mediastinal/hilar lymphadenopathy (mild to moderate) in 50% of cases.
- Lung parenchyma affected in 25%; may resemble lymphangitic pattern.
- Pleural effusions (small) in fewer than 25%.

Sustained (>3 weeks) granulocytopenia in leukemic patients poses a significant risk of life-threatening invasive aspergillosis and ARDS. The risk of invasive aspergillosis is proportional to the duration of granulocytopenia. In patients with acute leukemia or following bone marrow transplant, granulocytopenia persisting for longer than 3 weeks is the major risk factor for developing invasive aspergillosis. One study observed that granulocyte recovery with counts above 500/mm^3 was complicated by cavitary pulmonary aspergillosis in 73%. Massive hemoptysis may occur in some patients. Prognosis is uniformly poor, with mortality rates exceeding 65% to 70%. Tracheobronchial invasive aspergillosis is another complication observed in leukemic patients receiving chemotherapy. Prophylactic (empiric) antifungal therapy (intravenous/aerosolized) is being tried to reduce the risk of these complications.

- Prolonged granulocytopenia and lung infiltrates increase risk of diffuse aspergillosis.
- Cavitary aspergillosis is also common in granulocytopenia.
- Tracheobronchial invasive aspergillosis in granulocytopenic patients.

Chronic lymphocytic leukemia is associated with hypogammaglobulinemia caused by inherent abnormalities of B- and T-lymphocyte function in about 50% of patients. Infections, particularly with encapsulated micro-organisms, are a frequent cause of morbidity and mortality.

Hairy cell leukemia is a hematologic malignancy manifested by pancytopenia, splenomegaly, and circulating mononuclear cells with prominent cytoplasmic projections. Infections are secondary to granulocytopenia and defects in cell-mediated immunity. Bacterial, fungal, and mycobacterial infections occur with higher frequency. Dissemi-

nated infections caused by *Mycobacterium kansasii* and *Mycobacterium avium* complex are more likely in patients with hairy cell leukemia.

- Hypogammaglobulinemia in CLL predisposes to lung infections.
- Hairy cell leukemia more prone to develop *M avium* complex.

Pulmonary alveolar hemorrhage is commonly (>50%) detected at autopsy in leukemic patients. Pulmonary hemorrhage is generally associated with thrombocytopenia and may be extensive. Another predisposing cause is invasive pulmonary aspergillosis. The majority of patients with pulmonary alveolar hemorrhage do not exhibit hemoptysis. Respiratory failure occurs as a result of any of the complications discussed above. Furthermore, "leukostasis" of pulmonary vasculature caused by severe leukocytosis (leukocyte count exceeding 200,000/mm^3) and "leukemic cell lysis pneumopathy" within 48 hours of initiation of chemotherapy may cause respiratory failure. ARDS in patients with hematologic disorders, irrespective of the cause, has a mortality rate of 80%.

- Alveolar hemorrhage clinically undiagnosed in most cases.
- Leukemic cell lysis may result in ARDS; high mortality rate.

Pseudohypoxemia or spurious hypoxemia indicates low PaO_2 and normal SaO_2 in the absence of clinical evidence (cyanosis or dyspnea) of tissue hypoxemia. This phenomenon occurs in patients with extreme degrees of leukocytosis. During the in vitro transportation of an arterial blood sample from the patient to the laboratory, the leukocytes in the syringe consume significant amounts of oxygen and hence the measurement reveals low PaO_2 ("leukocyte larceny"). Pseudohypoxemia is also seen in patients with thrombocytosis. Some patients with leukemia may exhibit "secondary" pulmonary alveolar (phospholipo)proteinosis in lung biopsies. This is secondary to the monocytopenia in leukemia. Alveolar macrophages are derived from monocytes, and the deficiency of monocytes in leukemia results in the inability of the limited number of alveolar macrophages to ingest intra-alveolar phospholipids. Also, opportunistic infections (*P carinii* pneumonia, *M avium* complex) and cytotoxic drugs may affect the alveolar clearance of phospholipids. This finding is clinically insignificant, and chest radiography may or may not show patchy areas of alveolar infiltrates caused by this phenomenon.

- Pseudohypoxemia caused by hyperleukocytosis.
- Secondary alveolar proteinosis caused by leukemia and infections.

Plasma Cell Disorders

Amyloidosis

Amyloidosis is a plasma cell disorder of unknown origin characterized pathologically by the extracellular deposition of acellular fibrils derived from the light chain of a monoclonal immunoglobulin. In primary amyloidosis, 35% to 70% of cases show chest radiographic evidence of amyloid deposition in the lung, whereas in secondary amyloidosis, lung involvement is rare. The lower respiratory tract is frequently involved in systemic primary amyloidosis. A review of 126 cases of primary localized amyloidosis of the lower respiratory tract reported the following: hilar or mediastinal lymphadenopathy (5%), tracheobronchial multifocal submucosal plaques (45%), tracheobronchial amyloid with tumor-like masses (8%), discrete nodules in the lung parenchyma (44%), and diffuse alveolar septal amyloidosis (3%). The diffuse alveolar septal form of pulmonary parenchymal amyloidosis is usually associated with systemic amyloidosis and carries the worst prognosis (median survival, 16 months). Impaired gas transfer and a progressively restrictive type of pulmonary function abnormality are common. Diffuse deposition of amyloid in the lung interstitium and alveolar walls can be demonstrated in lung biopsy. Bronchoscopic lung biopsy is a safe and effective diagnostic method to document pulmonary involvement (Ann Intern Med 1996; 124: 407-13). Involvement of pulmonary vasculature in amyloidosis may result in hemoptysis as a result of medial dissection of pulmonary arteries. Pulmonary hypertension has been described in association with diffuse pulmonary amyloidosis (Semin Respir Med 1994;15:238-42). The involvement of the lower respiratory tract may manifest as nodular changes or diffuse infiltrations. Occasionally, amyloidosis can be restricted to the lower respiratory tract. Amyloid nodules in the pulmonary parenchyma tend to be peripheral, grow slowly, may be solitary (amyloidoma) or multiple, and cavitate in one third. In some cases, the nodules undergo cavitation or

calcification and may mimic lung cancer. Primary amyloidosis has presented as an isolated mediastinal mass diagnosed by fine-needle biopsy (Thorax 1995;50:908-9). Pleural effusion is uncommon.

- Hilar/mediastinal lymphadenopathy in fewer than 5%.
- Tracheobronchial multifocal submucosal plaques in 45%.
- Diffuse alveolar septal amyloidosis in fewer than 5%; carries the worst prognosis.
- Amyloidosis restricted to the lower respiratory tract (amyloidoma); grows slowly, may cavitate, and mimics lung cancer.

Macroglossia associated with amyloidosis has been reported to cause airway obstruction and sleep apnea, with laryngeal and subglottic deposition of amyloid contributing to airway obstruction. Diffuse tracheobronchial submucosal plaques result in generalized narrowing of the tracheobronchial tree with progressive stridor, dyspnea, cough, atelectasis, and hemoptysis. Bronchoscopy shows submucosal elevation of the tracheobronchial mucosa and pale, shiny ridges and areas of stenoses with various degrees of luminal narrowing. A deep submucosal bronchoscopic biopsy of the submucosal area is necessary for diagnosis. Although tracheobronchial amyloidosis is an indolent form of disease, hemoptysis and stridor can be life-threatening. Bronchoscopy in localized tracheobronchial amyloidosis will reveal endobronchial tumor-like amyloid masses that are usually polypoid, solitary, and only in major bronchi. Secondary changes include atelectasis or obstructive pneumonitis or bronchiectasis. Localized tracheobronchial amyloidosis may respond to repeated bronchoscopic Nd:YAG or CO_2 laser photoresection. Secondary localized amyloidosis of the lower respiratory tract has been noted in tuberculosis, syphilis, hypogammaglobulinemia, malignancies (usually pulmonary), and carcinoid.

- Amyloidosis can produce sleep apnea due to macroglossia.
- Bronchoscopy is essential for the diagnosis of tracheobronchial amyloidosis.
- Secondary amyloidosis is not a clinically significant problem.
- Tracheobronchopathia osteoplastica is not related to amyloidosis.

Multiple Myeloma

A malignant neoplasm of plasma cells, multiple myeloma manifests primarily by widespread skeletal destruction. Multiple myeloma is frequently associated with anemia, hypercalcemia, and impairment of renal function. Respiratory manifestation is a rare initial feature of multiple myeloma. However, about 25% of patients with multiple myeloma exhibit pleuropulmonary involvement during the course of the disease. Chest radiographic abnormalities may be detected in 25% of cases. Chest radiographs commonly (in 25%) reveal osteolytic thoracic skeletal involvement, particularly in the ribs and sternum. Extension of thoracic skeletal lesions into the chest cage or outside the rib cage produces a typical chest radiographic appearance (see next section, "Plasmacytoma"). Pleural effusion is uncommon. Infiltration of lung parenchyma or airways by the malignant plasma cells is unusual (<2%). Secondary infections in patients treated with chemotherapy are the most common cause of lung infiltrates.

- Pleuropulmonary involvement in fewer than 25%.
- Rib and sternal involvement.
- Lung infiltrates commonly due to secondary infections.

Plasmacytoma

Solitary plasmacytoma of the upper respiratory tract or the pulmonary parenchyma occurs as a result of well-defined (localized) neoplastic proliferation of plasma cells in the absence of generalized plasma cell malignancy. The majority of these tumors arise in the pharynx, with fewer than 5% located in the trachea or lungs. Primary tracheal plasmacytoma, when present, appears as solitary or multiple masses of homogeneous density. Endoluminal lesions can result in airway compromise, atelectasis, wheezing, and hemoptysis. Unusual manifestations include nonosseous pleural lesions, pleural effusions, chylothorax, and pulmonary parenchymal calcification. Chest radiographic features of a plasmacytoma of a rib or chest cage are typically those of a homogeneous mass associated with an osteolytic rib lesion, with the mass normally protruding into the thoracic cage (similar to myeloma). Lung lesions present as solitary nodules and mimic lung carcinoma.

- Localized plasma cell tumor of respiratory tract.
- Majority of tumors occur in pharynx/larynx.
- Tracheal and lung lesions in fewer than 5%.
- Expansile lesions of rib or bony thorax.

Waldenström's Macroglobulinemia

This is a rare plasma cell/lymphocyte disorder of the elderly characterized by anemia, infiltration of bone marrow by abnormal lymphocytes/plasmacytes, monoclonal IgM gammopathy, and hepatosplenomegaly. Pleuropulmonary involvement is relatively common in Waldenström's macroglobulinemia (WM). In a literature review (1980) of pulmonary complications of WM documented by biopsy of pleura and/or lung in 44 patients (26 males; median age, 64 years), mass lesions were noted in 50%, infiltrates in 70%, and pleural effusions in 43%. Mediastinal lymphadenopathy was associated with pulmonary disease in 25%. Two or more of these features were present in 55%. Symptoms were dyspnea (54%), nonproductive cough (33%), and chest pain (7%); 15% were asymptomatic. One third of patients had pulmonary features at the time of initial disease and the rest developed lung involvement 2 to 67 months after the diagnosis of WM. Biopsies showed infiltration of lungs by lymphocytes and plasmacytes. WM is one of the causes of LIP (see above under "LIP"). Chest radiographs exhibit diffuse reticulonodular patterns and occasionally local homogeneous consolidation. Other studies have shown that pleural effusion is present in 50% of patients with WM. Chylothorax is rare.

- Pleuropulmonary involvement in more than 50%.
- Lung infiltrates in more than 60%; pleural effusion in 50%.
- Mediastinal adenopathy in 25%.

Annotated Bibliography

Allen MS. Malignant tracheal tumors. Mayo Clin Proc 1993; 68:680-684

Part of a symposium on intrathoracic neoplasms. Discusses tracheal tumors (adenoid cystic carcinoma, squamous cell carcinoma, and mucoepidermoid carcinoma) and surgical therapy of these tumors.

Bragg DG, Chor PJ, Murray KA, et al. Lymphoproliferative disorders of the lung: histopathology, clinical manifestations, and imaging features. AJR Am J Roentgenol 1994; 163:273-281

Review of histopathology, clinical manifestations, and imaging features of lymphoproliferative disorders including plasma cell granuloma, pseudolymphoma, posttransplantation lymphoproliferative disorders, LIP, and LYG. Castleman's disease, infectious mononucleosis, and angio-immunoblastic lymphadenopathy with dysproteinemia are also discussed.

Capizzi SA, Betancourt EM, Prakash UBS. Tracheobronchial amyloidosis. Mayo Clin Proc 2000; 75:1148-1152

Review of 17 patients with biopsy-proven tracheobronchial amyloidosis (TBA). Nine women and 8 men; mean age 56.6 yrs. The most common symptoms: dyspnea, cough, hemoptysis and hoarseness. Treatment in 4 patients: bronchoscopic forceps debridement, laser excision, and airway debridement, and RoRx.

Chen KT. Amyloidosis presenting in the respiratory tract. Pathol Annu 1989; 24:253-273

This 20-page article with 191 references reviews the pulmonary manifestations of amyloidosis.

Fink G, Krelbaum T, Yellin A, et al. Pulmonary carcinoid: presentation, diagnosis, and outcome in 142 cases in Israel and review of 640 cases from the literature. Chest 2001; 119:1647-1651

Study of 142 cases. Nodal involvement and distant metastases occurred in 57% and 21%, respectively, in the atypical group, and 10% and 3%, respectively, in the typical group. The 5-year survival: typical 89% and atypical 75% (ns). The 10-year survival: typical 82% and atypical 56% ($p < 0.05$). A review of 640 cases from the literature is also included.

Frank JL, Schwartz BR, Price LM, et al. Benign cartilaginous tumors of the upper airway. J Surg Oncol 1991; 48:69-74

A brief review of the benign cartilaginous tumors of the upper airway, including larynx, trachea, and main bronchi.

Gelder CM, Hetzel MR. Primary tracheal tumours: a national survey. Thorax 1993; 8:688-692

Discussion of a mail survey of British physicians over a 10-year period that disclosed 321 tracheal tumors (squamous cell cancer, 174; adenoid cystic, 34; large cell, 19; small cell, 16; adenocarcinoma, 13; and others, 65). The article also reviews seven other publications covering 522 patients with primary tracheal tumors.

Gjevre JA, Myers JL, Prakash UBS. Pulmonary hamartomas. Mayo Clin Proc 1996; 71:14-20

Largest series (215 patients) of histologically confirmed pulmonary hamartomas (1976-1992);141 men and 74 women; 208 patients were asymptomatic. The peak incidence of occurrence was in the seventh decade. The mean size of the hamartomas was 1.5 cm (range, 0.2-6.0 cm). There was no evidence of either a malignant transformation or an unexplained association

with other lung neoplasms.

Grillo HC, Mathisen DJ. Primary tracheal tumors: treatment and results. Ann Thorac Surg 1990; 49:69-77

Discussion based on experience with 198 primary tracheal tumors (squamous, 36%; adenoid cystic, 40%; and carcinoid, 5%), including treatment and survival.

Herrada J, Cabnillas F, Rice L, et al. The clinical behavior of localized and multicentric Castleman disease. Ann Intern Med 1998; 128:657-662

Data from 15 patients with Castleman disease showed that localized disease can be cured with surgery, but complete remissions in patients with multicentric disease can be achieved only with chemotherapy or steroids given at the time of diagnosis.

Kulke MH, Mayer RJ. Carcinoid tumors. New Eng J Med 1999; 340:858-868

A review of all types of carcinoid tumors (135 references).

Limper AH, Carpenter PC, Scheithauer B, et al. The Cushing syndrome induced by bronchial carcinoid tumors. Ann Intern Med 1992; 117:209-214

Cushing's syndrome was the initial clinical presentation in 15 patients with carcinoid tumor. Carcinoid tumors were found later (after the initial work-up for Cushing's) in all 15 patients.

Miller DL, Allen MS. Rare pulmonary neoplasms. Mayo Clin Proc 1993; 68:492-498

Part of a symposium on intrathoracic neoplasms. Discusses clinical characteristics of 80 patients with unusual pulmonary neoplasms. The tumors discovered included lymphoma, carcinosarcoma, mucoepidermoid carcinoma, malignant fibrous histiocytoma, melanoma, fibrosarcoma, leiomyosarcoma, angiosarcoma, hemangiopericytoma, osteosarcoma, and blastoma.

O'Regan A, Fenlon HM, Beamis JF Jr, et al. Tracheobronchial amyloidosis: the Boston University experience from 1984 to 1999. Medicine (Baltimore) 2000; 79:69-79

Description of biopsy-proven tracheobronchial amyloidosis (TBA) in 10 patients.

Rosado de Christenson ML, Abbott GF, Kirejczyk WM, et al. Thoracic carcinoids: radiologic-pathologic correlation. Radiographics 1999; 19:707-736

Excellent review of all types of thoracic carcinoid tumors from the AFIP.

Shah H, Garbe L, Nussbaum E, et al. Benign tumors of the tracheobronchial tree: endoscopic characteristics and role of laser resection. Chest 1995; 107:1744-1751

Perhaps the largest series on the role of bronchoscopy and laser surgery in the treatment of benign tracheobronchial tumors, the article reviews 185 benign tracheobronchial tumors among 3937 patients who underwent laser resection of various tumors of the large airways.

Thomas, CF Jr, Tazelaar HD, Jett JR. Typical and atypical pulmonary carcinoids· outcome in patients presenting with regional lymph node involvement. Chest. 2001; 119:1143-1150

Of the 517 patients with pulmonary carcinoids, 36 patients had regional thoracic lymph node metastasis (23 carcinoid, 11 atypical). Median survival in atypical disease was 26 months. The results suggest that patients with atypical pulmonary carcinoid tumors with regional lymph node metastases have a high likelihood of developing recurrent disease if treated with surgical resection alone and have significantly worse outcome compared to those patients with typical carcinoid tumors with thoracic lymph node involvement.

Utz JP, Swensen SJ, Gertz MA. Pulmonary amyloidosis: the Mayo Clinic experience from 1980 to 1993. Ann Intern Med 1996; 124:407-413

Thirty-five of 55 patients with pulmonary amyloidosis had primary systemic amyloidosis; of the 35 patients, 20 exhibited interstitial pattern, four had tracheobronchial amyloidosis, and seven had localized amyloidomas. The latter group had the best prognosis. The long-term survival was poor in the diffuse variety (median survival, 16 months). Bronchoscopic mucosal/lung biopsy was positive in 14 of 55 patients.

Warren WH, Faber LP, Gould VE. Neuroendocrine neoplasms of the lung: a clinicopathologic update. J Thorac Cardiovasc Surg 1989; 98:321-332

A good update on neuroendocrine tumors of the lung based on experience with 146 cases. The paper addresses the entity "small cell neuroendocrine carcinoma," an aggressive and rapidly disseminating neoplasm, and concludes that even in clinical stage I tumors, patients must be considered to have disseminated metastases.

Notes