

7:30–8:00 AM Coffee and Pastries—Grand Assembly

Cases of the Day

Moderator: Melissa L. Rosado de Christenson, MD

7:30–7:45 AM Case of the Day
Melissa L. Rosado de Christenson, MD

7:45–8:00 AM Case of the Day
Tomás C. Franquet, MD

Scanlon Symposium: Assessment of Diffuse Lung Disease—Part I

Moderator: Jannette Collins, MD, MEd

8:00–8:25 AM Clinical Approach to Diffuse Lung Disease
Richard Helmers, MD

8:25–8:45 AM Imaging of the Idiopathic Interstitial Pneumonias
Jeffrey R. Galvin, MD

8:45–9:05 AM Thoracic Manifestations of Collagen Vascular Disease:
Imaging Findings
Steven L. Primack, MD

9:05–9:25 AM Occupational and Environmental Lung Disease
David A. Lynch, MD

9:25–9:45 AM High-Resolution CT: Technique and Pitfalls
Georgeann McGuinness, MD

9:45–10:00 AM Panel Discussion and Questions

10:00–10:15 AM Break

Scanlon Symposium: Assessment of Diffuse Lung Disease—Part II

Moderator: Melissa L. Rosado de Christenson, MD

10:15–10:40 AM The Clinical Spectrum of Sarcoidosis
Richard Helmers, MD

10:40–11:00 AM Thoracic Sarcoidosis: Patterns and Differential Diagnosis on CT
Caroline Chiles, MD

11:00–11:20 AM Radiation Injury of the Lung
Reginald F. Munden, MD

11:20–11:40 AM The Use of Gallium 67 in Interstitial Lung Disease
David K. Shelton, MD

11:40 AM–Noon Panel Discussion and Questions

Noon–1:00 PM Lunch (on your own)

The Diagnosis of Lung Cancer

Moderator: Paul L. Molina, MD

1:00–1:25 PM Early Lung Cancer Action Project: Findings on Baseline and Annual Repeat Screening CT
Claudia I. Henschke, MD, PhD

1:25–1:50 PM Lung Cancer Screening: Low-Dose CT
Stephen J. Swensen, MD

1:50–2:10 PM Integration of Biomarkers and Imaging Studies for Tumor Detection
Edward F. Patz, Jr, MD

2:10–2:30 PM Staging Lung Cancer and the New Mountain Classification: Multimodality Approach
Theresa C. McLoud, MD

2:30–2:50 PM The Solitary Pulmonary Nodule
Jeffrey S. Klein, MD

2:50–3:20 PM Panel Discussion and Questions

3:20–3:35 PM Break

Other Neoplastic Processes in the Chest

Moderator: Leslie E. Quint, MD

3:35–3:55 PM Pulmonary Metastases: Biology and Radiology
Michelle S. Ginsberg, MD

3:55–4:15 PM Postlobectomy Anatomy
Marvin H. Chasen, MD

4:15–4:35 PM Benign Tumors of the Chest
Dewey J. Conces, Jr, MD

4:35–4:55 PM Neuroendocrine Tumors of the Thorax
Gerald F. Abbott, MD

4:55–5:15 PM The Spectrum of Appearance of Lymphoma
Kitt Shaffer, MD, PhD

5:15–5:30 PM Panel Discussion and Questions

6:30–7:30 PM STR Members' Reception—Cloister Garden

7:30 PM STR Members' Dinner—Valencia

Clinical Approach to Diffuse Lung Disease

Richard Helmers, MD

At the time of publication, no abstract was available.

Imaging of the Idiopathic Interstitial Pneumonias

A Radiologic-Pathologic Correlation

Jeffrey R. Galvin, MD

Learning Objectives

1. Understand the classification and prognosis of the Idiopathic Interstitial Pneumonias
2. Demonstrate the relationship between the histopathology and the imaging findings

Introduction

The process of describing a chest film with “chronic diffuse lung disease” is often frustrating. Different diseases have a similar appearance on the chest radiograph, and the differential diagnosis list often becomes quite lengthy. In addition, the radiographic concept of “alveolar vs. interstitial” infiltrates is often unhelpful. Felson recognized that it was difficult to predict the histologic distribution of lung disease based on the radiographic findings. In fact, there are few lung diseases that involve the interstitium alone and many of the “Idiopathic Interstitial Pneumonias” (IIPs) have accompanying airspace involvement. In some it is the predominant abnormality.

In 1969 Leibow described a classification of the IIPs that included: Usual Interstitial Pneumonia (UIP), Desquamative Interstitial Pneumonia (DIP), Bronchiolitis Obliterans Interstitial Pneumo-

nia (BIP), Lymphoid Interstitial Pneumonia (LIP) and Giant Cell Interstitial Pneumonia (GIP). Over the last 30 years this classification has been refined. It has been established that LIP usually represents a lymphoproliferative disorder and will not be included in this discussion. GIP is a manifestation of hard metal pneumoconiosis and is no longer considered with the IIPs. Two categories have been added. The first is Respiratory Bronchiolitis-Interstitial Lung Disease (RB-ILD) which is currently considered to be a less severe form of DIP. Both diseases are part of a spectrum of smoking related interstitial lung diseases that includes: Respiratory Bronchiolitis (RB), RB-ILD and DIP. The second category that was added to the new classification is Nonspecific Interstitial Pneumonia (NSIP).

The American Thoracic Society and the European Respiratory Society have jointly sponsored a multidisciplinary panel of clinicians, pathologists and radiologists to standardize the classification of the IIPs. Table 1 provides a summary of the imaging findings and differential diagnoses as they relate to histopathologic pattern. This presentation will attempt to clarify the role of the Radiologist in this complex process.

Table 1. The Idiopathic Interstitial Pneumonias

(Based on the American Thoracic Society and European Respiratory Society Consensus Classification. Participating Radiologists: David A. Lynch, MB, David Hansell, MB, Phillippe Grenier, MD, Nestor Muller, MD and Jeffrey Galvin, MD)

Histology	Radiography	CT Distribution	Typical CT Findings	Differential Dx
UIP	Basal-predominant reticular abnormality with volume loss Normal in 10 to 15%	Peripheral, subpleural, basal	Reticular Honeycombing Traction bronchiectasis / bronchiolectasis Architectural distortion Focal ground glass	Asbestosis Collagen vascular disease Hypersensitivity pneumonitis Sarcoidosis
NSIP	Non-specific abnormalities. Normal in 7%	Peripheral, subpleural, basal, symmetric	Ground glass attenuation Irregular lines Consolidation Honeycombing	UIP, DIP, OP Hypersensitivity pneumonitis
RB-ILD	Bronchial wall thickening Ground glass opacity Normal in 14%	Diffuse	Bronchial wall thickening Centrilobular nodules Patchy ground glass opacity Emphysema	DIP NSIP Hypersensitivity pneumonitis
DIP	Ground glass opacity. Normal in 3-22%	Lower zone, peripheral predominance in most. Diffuse in 18%	Ground glass attenuation Reticular lines Honeycombing	RB-ILD Hypersensitivity pneumonitis Sarcoidosis, PCP
DAD	Progressive diffuse ground glass density/consolidation	Diffuse	Consolidation and ground glass opacity, often with lobular sparing. Traction bronchiectasis later	Hydrostatic edema Pneumonia Acute BOOP or acute eosinophilic pneumonia
OP	Patchy bilateral consolidation	Subpleural	Consolidation. Small or large nodules	Infection, Vasculitis Sarcoidosis, Alveolar carcinoma, Lymphoma Eosinophilic pneumonia NSIP

Usual Interstitial Pneumonitis (UIP) and Idiopathic Pulmonary Fibrosis (IPF)

According to an ATS statement published in 2000: IPF is a distinctive type of chronic fibrosing interstitial pneumonia of unknown cause limited to the lung and associated with a surgical lung biopsy showing a histologic pattern of UIP. The diagnosis requires the clinician to exclude other causes of interstitial lung disease and that the patient demonstrate a

restrictive defect on pulmonary functions. The patients are usually older (slight male predominance) who present with gradual onset of dyspnea. The median length of survival from the time of diagnosis is short (2.5-3.5 years). The histology presents a heterogeneous appearance with dense areas of fibrosis abutting normal alveoli. The fibrotic zones show temporal heterogeneity with dense acellular collagen and scattered fibroblastic foci. Areas of honeycombing are common.

Radiographic Findings

The chest x-ray is rarely normal at the time of presentation. Volume loss is common and progresses with time. The typical chest radiographic abnormality is peripheral reticular opacity which is most marked at the bases. In cigarette smokers with IPF the lung volumes may be normal or increased because of associated emphysema.

Computed Tomography

The abnormalities associated with IPF are characteristically basal and peripheral. The most common opacities are reticular and correlate with the presence of fibrosis. Traction bronchiectasis is also associated with the presence of fibrosis. Isolated ground glass attenuation may correlate with evidence of interstitial inflammation, airspace filling by macrophages, patchy fibrosis or a combination of these. Ground glass associated with reticulation or traction bronchiectasis usually indicates fibrosis.

Nonspecific Interstitial Pneumonia (NSIP)

Katzenstein described NSIP in 1994 as a group of interstitial lung disorders that did not meet the histologic criteria for UIP. It is now believed to be a histologic pattern that represents a variety of etiologies. The median age of onset is 45 year without gender predominance. The onset of symptoms is gradual with a wide range (6 months to 3 years). As a group, the prognosis was better than UIP. However, when the NSIP patients are stratified according to the amount of fibrosis on the lung biopsy then there is a clear relationship to mortality. The patients with NSIP who are predominantly fibrotic have a mortality rate that is similar to patients with UIP.

Radiographic Findings

The most common abnormality on the chest radiograph is patchy parenchymal opacity. However, there are few published reports that focus on the chest radiograph.

Computed Tomography

NSIP is associated with a variety of opacities including ground glass, reticular, honeycombing and consolidation. The presence of traction bronchiectasis correlated with the presence of fibrosis. In a study of 50 patients from December 2000, experienced observers considered the CT pattern indistinguishable from UIP in 32%, hypersensitivity pneumonitis in 20%, organizing pneumonia in 14% and other diagnoses in 12%.

Smoking Related Interstitial Lung Disease

Respiratory Bronchiolitis (RB), Respiratory Bronchiolitis-Interstitial Lung Disease (RB-ILD) and Desquamative Interstitial Pneumonia (DIP)

It is now clear that smoking can cause a range of clinically significant interstitial lung diseases. The three diseases represent a spectrum of severity involving small airways inflammation and fibrosis and distal alveolar involvement.

RB is a common incidental finding in the lungs of asymptomatic smokers. Respiratory bronchioles, alveolar ducts and peribronchiolar alveoli contain clusters of dusty brown macrophages. There may be associated peribronchiolar fibrosis. The patients are rarely symptomatic. RB-ILD is distinguished from RB by the prominence of the inflammation and fibrosis. The fibrosis may extend farther from the peribronchiolar area. The separation of the 2 diseases requires clinical assessment. Patients with RB-ILD are symptomatic with functional evidence of lung disease that includes a reduction in diffusing capacity and a restrictive defect on their pulmonary functions. Progression of disease is uncommon if the patient stops smoking or is treated with steroids. DIP was first described in the 1960's and was felt to be an earlier stage of UIP. The patients were younger and were more likely to respond to steroids. The vast majority are cigarette smokers and DIP is now considered the severe end of the smoking related interstitial lung disease spectrum. DIP is a uniform and diffuse process without the bronchocentricity of RB-ILD. There is diffuse alveolar septal thickening and there are numerous intra-alveolar macrophages. The majority of these patients will stabilize or improve with steroid treatment and smoking cessation. The overall survival is 70% after 10 years.

Radiographic Findings

The radiograph is usually normal in patients with RB. Patients with RB-ILD may demonstrate airway thickening (75%) or patchy areas of ground glass (60%). The chest radiograph is normal in 14%. DIP is characterized by the presence of ground glass, with a lower zone predilection and occasionally a peripheral predominance. The radiograph may be normal in DIP.

Computed Tomography

RB is an upper lobe process which is characterized by patchy ground glass and parenchymal micronodules. The ground glass correlates with alveolar filling of the macrophages, alveolar wall thickening and intra-alveolar organization. The

micronodules correlate with peribronchiolar fibrosis and inflammation. The opacities in RB-ILD are more extensive and may involve the lower lobe. The ground glass may be quite widespread and is difficult to differentiate from DIP which is characterized by lower lobe, peripheral ground glass. There may also be reticulation in the periphery that suggests the presence of fibrosis.

Diffuse Alveolar Damage (DAD)

Acute Interstitial Pneumonia (AIP) and the Adult Respiratory Distress Syndrome (ARDS) are clinical entities in which the DAD is the underlying pathology. AIP is a subacute process that develops over days to weeks. The patients often have a prior illness that suggests a viral infection. The patients usually present with hypoxemia and progress rapidly to respiratory failure. The mortality rate is high (50% or more). The histologic features consist of an early exudative phase and a later organizing stage that can progress to fibrosis. The exudative phase demonstrates edema, hyaline membranes and interstitial acute inflammation. Collapse of alveoli contributes to the light microscopic appearance of fibrosis. The organizing phase shows loose fibrosis and type II pneumocyte hyperplasia. If the patient survives, the lung may return to normal.

Radiographic Findings

The chest radiograph reveals bilateral airspace opacification with air bronchograms in essentially all patients. The distribution is often patchy with sparing of the costophrenic angles. The cardiac silhouette and vascular pedicle are normal and interstitial abnormalities such as septal lines and peribronchial cuffing are usually absent. Pleural effusions are also uncommon. The lung volumes are usually low but may be near normal. As the disease progresses the lungs tend to become diffusely consolidated. As DAD moves from the exudative to the organizing stage the radiograph shows less consolidation and presents a ground glass appearance with evidence of parenchymal distortion.

Computed Tomography

In the early exudative phase the lung shows bilateral ground glass opacities that are most often symmetric and patchy with focal sparing of lung tissue. In the minority of cases there will be diffuse involvement of all 5 lobes. The ground glass opacities are neither distinctly subpleural or central. Consolidation is seen in the majority of cases but is not as common as ground glass. The distribution is most often basilar in patients with AIP but can occasionally be diffuse

or rarely have an upper lobe predominance. In patients with classic ARDS the areas of consolidation are most often in the dependent part of the lung suggesting alveolar closure from the weight and hydrostatic pressure of the more superior lung tissue. Intralobular septal thickening and subpleural honeycombing are seen in the minority of cases.

The organizing stage of DAD is associated with distortion of bronchovascular bundles and traction bronchiectasis. The areas of consolidation tend to be replaced by ground glass opacities. Cysts and other lucent areas of lung become more common in the late stages of ARDS.

The few patients who survive show progressive clearing of the ground glass and consolidation. Subpleural, irregular opacities are the residual HRCT findings.

The differential diagnosis of DAD depends on the stage but will include the following: hydrostatic edema, hemorrhage, alveolar proteinosis, bronchioloalveolar cell carcinoma, Desquamative Interstitial Pneumonia and widespread infection.

Cryptogenic Organizing Pneumonia (COP)

Organizing pneumonia is a non-specific response to lung injury. Cryptogenic organizing pneumonia (COP) is a clinicopathologic entity described in 1983. In the United States the term bronchiolitis obliterans organizing pneumonia (BOOP) is more common. COP is preferred as it avoids confusion with bronchiolitis obliterans which is an airways disease. It is a common pattern of repair, which is characterized by distal airspace buds of granulation tissue, and in some patients it is self-perpetuating. The process was first recognized as a failure of resolution in patients with acute bacterial pneumonia. The typical pneumococcal pneumonia goes through a sequence starting with alveolar congestion in which there is edema fluid containing pneumococci, inflammatory cells and fibrin. Typically there is complete resolution with liquifaction of the fibrin by neutrophils and macrophages. In a minority of cases there is organization of the fibrinous exudate resulting in intra-alveolar collections of granulation tissue.

Radiographic Findings

Common findings include unilateral or bilateral areas of consolidation without a predilection for any particular lung zone. The distribution is usually patchy but may be subpleural in a minority of cases. Small nodular opacities are seen in 10-50% of cases. Large nodular opacities (>1cm) are the presenting

radiographic appearance in less than 20% of cases. Lung volumes are normal in up to 75% of cases. The remainder demonstrates reduced lung volumes.

Computed Tomography

Areas of air-space consolidation are present in 90% of patients who are immunocompetent. Ground glass opacities, however, are more common in immunocompromised patients (73%). CT in up to 50% of cases demonstrates a subpleural or peribronchial distribution. Air bronchograms are a consistent finding when consolidation is present. Bronchial wall thickening and dilatation are present in 50% of the patients with consolidation. Small nodules (<10mm) are usually seen along bronchovascular bundles and are evident in up to 50% of cases. Pleural effusions are rare.

Approximately, 15% of patients with organizing pneumonia present with multiple large nodules. These nodules usually have an irregular margin (88%) with air bronchograms (45%). Ancillary findings include pleural tags (38%), spicules (35%), pleural thickening (33%) and parenchymal bands (25%).

Change in Appearance over Time

The majority of patients demonstrate radiographic improvement with treatment. However, the parenchymal shadows change even without treatment. Most patients who respond to steroids are left with small residual opacities.

The differential diagnosis in patients with areas of consolidation includes *Mycobacterium tuberculosis*, atypical TB, alveolar cell carcinoma, lymphoma, vasculitis and sarcoidosis. When the consolidation is subpleural then the diagnosis of chronic eosinophilic pneumonia should be considered. The patients who present with multiple large masses have a differential diagnosis that includes metastatic lung tumor, lymphoma and septic emboli. If the mass is solitary then lung cancer should be considered.

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Organizing Pneumonia

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Thoracic Manifestations of Collagen Vascular Disease: Imaging Findings

Steven L. Primack, MD

Learning Objectives

1. Know the chest radiographic and chest CT findings in patients with collagen vascular disease.
2. Understand the differences in thoracic manifestations of the various collagen vascular diseases.

Introduction

The collagen vascular diseases are characterized by immune-mediated damage to connective tissue at a variety of sites in the body. They frequently cause pulmonary and pleural abnormalities. Although many of the complications can be detected on the chest radiograph, high-resolution CT has been shown to be superior to the radiograph in the assessment of the presence and extent of parenchymal, airway, and pleural abnormalities. The aim of this presentation is to illustrate the characteristic chest radiographic and CT findings associated with collagen vascular disease.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown etiology characterized histologically by deposition of autoantibodies and immune complexes damaging tissues and cells. The presentation is usually systemic with fatigue, malaise, anorexia, fever and weight loss.

During the course of the disease, 50% of patients will develop pleural disease (1). The most common radiographic manifestation of SLE is pleural effusion, which can be unilateral or bilateral and is frequently associated with pericardial effusion.

Pulmonary parenchymal abnormalities are also common. Parenchymal opacification may be due to pneumonia, hemorrhage, acute lupus pneumonitis, or pulmonary edema. Pneumonia is the most common cause of parenchymal opacification (1). Although most cases are of bacterial etiology, opportunistic infections also occur with increased frequency. Pulmonary hemorrhage is another, though less common, cause of air space consolidation. The chest radiograph usually demonstrates extensive bilateral areas of air space consolidation. The findings on CT consist of bilateral areas of consolidation and ground glass opacity. Acute lupus pneumonitis is a diagnosis of exclusion. The chest radiographic findings, simi-

lar to pneumonia and pulmonary hemorrhage, usually consist of bilateral areas of consolidation. Occasionally the consolidation is unilateral.

Pulmonary fibrosis is less common in SLE than in rheumatoid arthritis or scleroderma. HRCT scans demonstrate pulmonary fibrosis much more frequently than chest radiographs. In two recent studies evaluating HRCT scans, fibrosis was present in approximately 30% of cases (2,3). The fibrosis involved predominantly the lung periphery and lower lobes.

Other chest radiographic findings include loss of lung volume related to diaphragmatic dysfunction, pulmonary edema, musculoskeletal changes related to renal failure, and bone changes related to corticosteroid therapy.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune disease of unknown etiology affecting 1% of the population. The classic clinical manifestation is chronic symmetric polyarthritis due to a persistent inflammatory synovitis.

Patients often develop thoracic involvement as their disease progresses. Pleural disease is the most common thoracic manifestation and is seen much more frequently in men. Pleural thickening is seen more commonly than pleural effusion. Pleural effusions are usually unilateral and may be loculated. The pleural effusions usually occur late in the disease and are commonly associated with pericarditis and subcutaneous nodules.

Pulmonary fibrosis occurs in 2% to 9% of patients with RA. Chest radiographs typically demonstrate a reticular or reticulonodular pattern involving the lower lung zones. HRCT demonstrates reticular opacities and irregular interlobular septal thickening predominantly in the lung periphery and lower lung zones. Honeycombing and progressive volume loss develop as the disease progresses. Rarely the fibrosis may be limited to the upper lobes and contain areas of cavitation, mimicking tuberculosis. Similar to any patient with pulmonary fibrosis, there is an increased incidence of lung cancer. The majority of patients with pulmonary fibrosis and RA have a histologic pattern of usual interstitial pneumonia (UIP). However,

many cases have a pattern of nonspecific interstitial pneumonitis (NSIP). In a series of 64 patients with NSIP, 10 (16%) had collagen vascular disease (4). The HRCT findings of NSIP are variable and nonspecific, and consist of areas of ground-glass attenuation, consolidation or a reticular pattern (5). Patients with NSIP have a much better prognosis than patients with UIP.

Pulmonary nodules are uncommon and are usually associated with advanced RA and subcutaneous nodules. The nodules are pathologically identical to subcutaneous nodules. They are usually multiple, well circumscribed, and often result in thick walled cavities.

Patients with RA have an increased prevalence of airway diseases such as obliterative bronchiolitis and bronchiolitis obliterans organizing pneumonia (BOOP). Obliterative bronchiolitis occurs with increased frequency in RA patients regardless of penicillamine or gold therapy. The chest radiograph is usually normal. HRCT may demonstrate a characteristic mosaic pattern of attenuation and perfusion. Abnormal areas of lung have decreased attenuation and vascularity due to redistribution of blood flow away from areas of abnormal ventilation. HRCT scans performed at end-expiration are more sensitive than end-inspiratory scans and show areas of air trapping. The predominant radiographic and HRCT finding in patients with BOOP is air space consolidation which is usually bilateral and tend to have a patchy peripheral or peribronchial distribution.

Follicular bronchiolitis occurs with increased frequency in patients with RA. In a recent series evaluating the HRCT findings of 12 patients with follicular bronchiolitis, 8 patients (66%) had RA (6). The main CT findings were small centrilobular nodules associated with patchy areas of ground-glass attenuation.

Thoracic bony changes of RA include resorption of the distal clavicles and erosive arthritis of the shoulders.

Progressive Systemic Sclerosis

Progressive systemic sclerosis (PSS, scleroderma) is a connective tissue disease of unknown etiology, characterized by the overproduction of collagen leading to fibrosis of the lungs, skin, vasculature and visceral organs. Clinically, patients have skin thickening and tightening, musculoskeletal manifestations, Raynaud's phenomenon, and fibrosis of the lungs, kidneys, and gastrointestinal tract. Two thirds of patients with PSS have clinical pulmonary symptoms, most commonly exertional dyspnea and dry, nonproductive cough.

Pulmonary fibrosis is the most common radiographic finding, being present in 20% to 65% of pa-

tients (7). The fibrosis usually has a basilar predominance, initially as a fine reticular pattern that progresses to coarse reticulation and honeycombing (7). HRCT scanning may demonstrate evidence of fibrosis in patients with normal radiographs (8). In a prospective study of 23 patients with PSS, fibrosis was identified on chest radiography in 39% of patients and on HRCT scans in 91% of patients (8). The predominant abnormalities on high-resolution CT scans consist of areas of ground-glass attenuation, poorly defined subpleural nodules, reticular opacities, honeycombing, and traction bronchiectasis (8,9). As with rheumatoid disease and idiopathic pulmonary fibrosis, the abnormalities have a lower lobe and peripheral predominance. There is an increased incidence of lung cancer in patients with PSS, particularly in the setting of pulmonary fibrosis. Pleural disease is not a common manifestation, and when present, is usually accompanied by parenchymal disease.

Pulmonary hypertension is common and is usually seen in association with diffuse pulmonary fibrosis. However, vascular changes may be present in the absence of pulmonary fibrosis. Pulmonary hypertension usually causes enlargement of the central pulmonary arteries, although this does not occur in all cases.

The esophagus is usually involved clinically and a dilated esophagus may be identified on a chest radiograph or CT scan. Aspiration occurs with increased frequency due to esophageal dysfunction.

Polymyositis/Dermatomyositis

Patients with polymyositis typically present with progressive weakness of proximal striated muscles. Dermatomyositis has additional skin changes. The most common radiographic finding is aspiration pneumonia secondary to pharyngeal muscle weakness. Diaphragm involvement leads to diaphragmatic elevation, reduced lung volumes, and basilar atelectasis.

Interstitial fibrosis occurs in 5%-30% of patients and consists of a fine reticular pattern that progresses to a coarse reticulonodular pattern and honeycombing. The lung bases are most severely involved. Other parenchymal abnormalities include BOOP and diffuse alveolar damage. The HRCT findings of polymyositis/dermatomyositis have been recently described and consist predominantly of linear abnormalities and areas of ground-glass attenuation (10,11). Air space consolidation is often also present, mainly in the mid and lower lung zones with a peribronchial and subpleural distribution. The consolidation is usually due to BOOP.

Sjögren's Syndrome

Patients with Sjögren's syndrome typically present with dry mouth and dry eyes. Pathologically, there is

THORACIC MANIFESTATIONS OF COLLAGEN VASCULAR DISEASE

	SLE	RA	PSS	PM/DM	SJÖGREN'S	AS
Pleural disease	+++	+++				
Pulmonary fibrosis	+	+++	+++	++	+	+
Diaphragm weakness	+++			+++		
Aspiration			+++	+++		
BOOP		++		++		
BO		++				
Bronchiectasis		+			++	
Apical fibrosis						+++

infiltration of exocrine glands by immunoglobulin producing lymphocytes. While the salivary and lacrimal glands are most commonly involved, there is extraglandular involvement in 5% to 10% of cases.

The most common radiographic finding in Sjögren's syndrome is pulmonary fibrosis, seen in 10% to 14% of cases. In a study evaluating the HRCT findings of 50 patients with Sjögren's syndrome, the main abnormalities were bronchiectasis, findings of bronchiolar inflammation, and increased parenchymal lines. There is an increased incidence of lymphocytic interstitial pneumonitis that presents radiographically as a reticulonodular pattern involving predominantly the lower lobes. A recent study described the HRCT findings of lymphocytic interstitial pneumonia (13). The most common findings on HRCT are areas of ground-glass opacity, thickening of bronchovascular bundles and interlobular septa, and cysts.

Patients with Sjögren's syndrome also have an increased risk of developing lymphoma. Lymphoma should be suspected if a chest radiograph demonstrates mediastinal lymphadenopathy or a pulmonary mass.

Ankylosing Spondylitis

Ankylosing spondylitis is an autoimmune disease of unknown etiology primarily affecting the axial skeleton. It has a male to female predominance of 3:1.

Apical fibrosis is the most common pulmonary abnormality evident on the chest radiograph. In a study of chest radiographic findings in 2080 patients

with ankylosing spondylitis, 26 (1.2%) had fibrosis in the upper lobes (14). The radiographic findings of ankylosing spondylitis consist of reticulonodular opacities in the lung apices, which become confluent as the disease progresses (14). Common associated abnormalities include apical bullae and cavitation, potentially mimicking tuberculosis. The HRCT findings were recently described in 26 patients with ankylosing spondylitis (15). The most common abnormalities seen were peripheral interstitial lung disease, bronchiectasis, paraseptal emphysema, and apical fibrosis. Radiographic changes of the spine, consisting of symmetric marginal syndesmophytes ("bamboo spine") are also usually evident when there is apical fibrosis. Chest wall restriction may result from fusion of the costovertebral joints.

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Occupational and Environmental Lung Disease

David A. Lynch, MD

Clinical Approach to Occupational and Environmental Lung Disease

The clinical approach to occupational or environmental lung disease differs substantially from that in other diffuse lung diseases. The radiologist plays an important partnership role in detecting presymptomatic disease in those at risk, contributing to the specificity of the diagnosis, and recognizing “sentinel cases” of disease. In diseases such as hypersensitivity pneumonitis, the radiologist may be the first to suggest the diagnosis. Medicolegal roles for imaging include confirming the presence of a morphologic abnormality compatible with occupational lung disease, identifying other potential causes for disability (e.g. emphysema), and determining the morphologic extent of disease (though this can never serve as the entire basis for compensation).

Hypersensitivity Pneumonitis

The term ‘hypersensitivity pneumonitis’ (HP) and its synonym ‘extrinsic allergic alveolitis’ refer to a spectrum of granulomatous, interstitial, bronchiolar and alveolar-filling pulmonary conditions which result from repeated inhalation of and sensitization to a wide variety of organic aerosols and some chemical antigens. The diagnosis relies on a constellation of findings, not all of which may be present in an affected individual: exposure to a recognizable antigen, characteristic signs and symptoms, abnormal chest findings on physical examination, and abnormalities on pulmonary function tests and radiologic evaluation. The disease is characterized histologically by a lymphoplasmacytic infiltrate, often associated with poorly formed granulomas.

Acute hypersensitivity pneumonitis is typically manifested on the chest radiograph either by diffuse ground glass opacity or by a fine micronodular pattern. In the more chronic form of HP, fibrosis may be manifested by volume loss, reticular opacity and honeycombing. CT is increasingly employed to search for HP, particularly in those with normal chest radiographs. However, a normal high resolution CT cannot be used to exclude HP. However, CT may still be useful in screening studies because an abnormal CT can provide strong support for the diagnosis of HP.

The most typical CT finding in patients with HP is profuse poorly defined micronodules (2,5-9). These micronodules may be found in those with acute, subacute or chronic disease, and in the correct clinical context, are strongly suggestive of HP. Ground glass attenuation may be the predominant or only finding. In subacute and chronic HP, one commonly sees poorly defined nodules and ground glass opacity in association with reticular opacity and occasionally honeycombing. Some patients with chronic HP have been reported to show emphysema (9,10), perhaps related to bronchiolar inflammation and obstruction.

Differential diagnosis of HP includes respiratory bronchiolitis in subjects who are heavy smokers (14). However, most patients with hypersensitivity pneumonitis are non-smokers. In granulomatous lung conditions such as sarcoidosis and chronic beryllium disease, the nodules seen on the chest radiograph and CT tend to be larger, denser and better defined than those of hypersensitivity pneumonitis. Desquamative interstitial pneumonitis may cause diffuse ground glass opacity which is indistinguishable on CT from that seen in HP. Usual interstitial pneumonia may look the

Table 1
Examples of antigens and exposures associated with risk for hypersensitivity pneumonitis

Antigen	Exposure	Syndrome
Microbial agents	Moldy hay	Farmer’s lung
	Hot tub mists	Hot tub HP
	Heated water reservoirs	Humidifier lung
Animal proteins	Bird droppings/feathers	Bird fancier’s lung
Chemicals	Paints and resins	Isocyanate HP

same as chronic HP on CT. Radiologic features which can be helpful in differentiating between UIP and chronic HP include predominance of fibrosis in mid or upper lung zones (9,12), presence of micronodules, and absence of honeycombing in HP (13).

Berylliosis

Exposure to beryllium occurs in a variety of industries (including aerospace, ceramics, dentistry, nuclear weapons and reactors, and several others) where workers may be at risk for disease from either direct or indirect exposure to the metal. Between 1 and 5 percent of those exposed develop chronic beryllium disease (CBD). The histologic appearance of CBD is indistinguishable from sarcoidosis, with noncaseating granulomas accompanied by mononuclear cell infiltrates and variable interstitial fibrosis. The beryllium lymphocyte proliferation test (BeLPT) identifies over 90% of individuals who have CBD. Diagnostic criteria for CBD include: (1) a history of beryllium exposure; (2) demonstration of a beryllium-specific cell-mediated immune response; and (3) granulomas and/or mononuclear cell infiltrates on biopsy in the absence of infection. The radiographic and CT appearances of berylliosis are similar to those of sarcoidosis, though mediastinal and hilar lymphadenopathy is less common.

Silicosis/Coal Workers' Pneumoconiosis

Coal mine dust inhaled by miners and other coal workers predisposes them to chronic bronchitis, simple pneumoconiosis, focal emphysema, complicated pneumoconiosis (progressive massive fibrosis), and mycobacterial pulmonary infection. Inhalation of silica dust occurs in a wide range of occupations, including most types of mining, tunneling, quarrying, sandblasting, foundry work, and ceramics manufacture. Silica causes four distinct clinical patterns of lung disease: acute silicoproteinosis, accelerated silicosis, simple chronic nodular silicosis, and complicated chronic nodular silicosis. Acute silicoproteinosis (e.g. in sandblasting) resembles pulmonary alveolar proteinosis both radiologically and pathologically. In accelerated silicosis, inhalation of high concentrations of silica over a period of as little as five years results in progressive upper lobe fibrosis. Simple or chronic nodular silicosis is the most common manifestation, usually developing after 10 to 50 years of exposure. Silica inhalation predisposes to mycobacterial infection, including *M tuberculosis*, *M kansasii*, and *M avium* complex. More recently, silica has been recognized as a cause of industrial bronchitis, emphysema and lung cancer in excess of that expected from cigarette smoking alone.

The radiographic and CT features of coal workers' pneumoconiosis (21) and silicosis (25,26) are similar. On the chest radiograph, both conditions present with predominantly upper lobe nodules, which may later coalesce to form mass-like opacities (progressive massive fibrosis). Radiologically the nodules of coal workers' pneumoconiosis are often smaller than in silicosis. On CT scanning, pneumoconiosis is characterized by centrilobular or subpleural nodules mainly in the posterior upper lobes. About 20% of coal workers develop irregular opacities suggestive of lung fibrosis, associated with functional impairment (28,29). In some such patients, CT scanning and biopsy have shown changes identical to those of idiopathic pulmonary fibrosis (30,31).

Several recent papers have shown that emphysema develops in a substantial proportion of life-long non-smokers exposed to silica. The presence of pneumoconiosis on CT is a predictor of emphysema extent, and exposure to silica was a significant predictive factor for emphysema even in patients without CT evidence for pneumoconiosis. In silicosis, pulmonary function correlates poorly with the profusion of nodules on CT, but the CT-determined extent of emphysema correlates well with FEV1 and diffusing capacity (25). In a study by Begin et al of workers with silicosis (26), CT demonstrated unsuspected early conglomeration in one third of patients who were classified as having simple silicosis on the basis of the chest radiograph. These subjects had corresponding abnormalities of lung function. A further study by Begin et al shows that combined use of conventional CT and HRCT is the most sensitive technique for detection of pulmonary opacities in subjects with silicosis (23). The inter-observer agreement for CT scan readings was markedly higher than for radiographic interpretations.

Progressive massive fibrosis (PMF), sometimes referred to as complicated pneumoconiosis or conglomerate pneumoconiosis, is much more common in silicosis than in coal workers' pneumoconiosis. On the chest radiograph, PMF presents with oval or round masses, typically seen in the posterior upper lobes, with associated hilar retraction. Sequential evaluation of these masses often shows apparent migration toward the hila, leaving a peripheral rim of cicatricial emphysema. On CT, PMF typically appears as an upper lobe mass (often bilateral) with irregular borders, frequent calcification, and surrounding cicatricial emphysema.

Asbestos-related Diseases

Noncalcified pleural plaques are best seen in profile, along the lateral chest wall on the frontal view, as focal areas of soft tissue thickening. They are most

Table 2
Pleuropulmonary complications of asbestos exposure

Abnormality	Latency	Approximate frequency in asbestos-exposed workers
<i>Benign pleural effusion</i>	5 to 20 years	3 %
<i>Pleural plaques</i>	15 to 30 years	16-80%
<i>Calcified pleural plaques</i>	30 to 40 years	10-50%
<i>Diffuse pleural thickening</i>	10 to 40 years	7-13%
<i>Asbestosis</i>	20 to 40 years	15 to 30%
<i>Lung cancer</i>	≥ 15 years	20-40% (lifetime risk)
<i>Mesothelioma</i>	15 to 40 years	10% (lifetime risk)

common between the fourth and eighth ribs, and are more prevalent on the left than on the right (33). Extrapleural fat may be distinguished from noncalcified pleural plaque by its slightly greater radiolucency, its smooth or wavy contour, and its extension to the apices. Neither fat nor plaque usually involves the costophrenic sulci, a feature which distinguishes them from diffuse pleural thickening which typically causes blunting of the costophrenic sulci. CT scanning is more sensitive than the chest radiograph for detection of pleural plaques (34,35), particularly noncalcified pleural plaques.

Malignant pleural mesothelioma is associated with a history of asbestos exposure in at least 50% of patients, and some studies suggest an even higher association. An unknown percentage of patients may have had previous low level or indirect asbestos exposure. Almost 90% of patients with mesothelioma in one study (37) had a pleural effusion at presentation, while 50% had irregular thickening of the parietal pleura. Pleural plaques were identified on the chest radiograph in one third of cases. On CT scanning, malignant pleural thickening due to mesothelioma, lung cancer or pleural metastasis is recognized by the presence of a circumferential rind of pleural thickening, often associated with nodularity (38).

Asbestosis is interstitial lung fibrosis caused by inhalation of asbestos fibers. The chest radiograph is abnormal in most, but not all, cases of pathologically demonstrated asbestosis (22). The typical radiographic findings in asbestosis are small irregular or reticular opacities, predominating at the lung bases. Honeycombing is evident in more advanced disease. Pleural plaques are absent in about 10% of cases (39). A limitation of chest radiographic assessment of asbestosis is the questionable physiologic and

pathologic significance of the small irregular opacities which are the chest radiographic hallmark of early asbestosis (18,19,20,40). In at least some cases these small irregular opacities appear to be related to a combination of cigarette smoke and asbestos exposure.

HRCT is more sensitive than the chest radiograph for diagnosis of the early changes of asbestosis (34,41,42). HRCT is also useful in diagnosing other diseases such as emphysema which may significantly impair lung function in asbestos-exposed subjects (42). Early asbestosis is manifested on HRCT by peripheral reticular opacities, intralobular lines, prominent centrilobular core structures and interlobular septal thickening. Because of the posterior and basal predominance of the lesions of early asbestosis, examination of the lung bases in the prone position is critical for confirming the fixed nature of septal thickening and curvilinear subpleural lines. More advanced asbestosis is characterized by parenchymal bands of fibrosis, honeycombing and traction bronchiectasis. Clearly, none of these features is specific for asbestosis, and similar changes may be seen in other lung diseases such as IPF (43). When the CT scans of patients with asbestosis are compared with those of patients with IPF, patients with asbestosis have a higher prevalence of parenchymal bands, and a lower prevalence of ground glass opacity (44). Staples et al., Neri et al., and Oksa et al. all have shown that changes of early asbestosis are associated with physiological impairment, even when the chest radiograph was normal. Akira et al demonstrated that the changes of early asbestosis progressed over 1 to 3 years in most cases. A study by Gamsu and colleagues showed that the CT findings of early asbestosis are not perfectly sensitive or specific. However, asbestosis can be diagnosed with confidence when

parenchymal changes are bilateral or present at multiple levels. Also, scoring of the profusion of abnormality on CT correlated significantly ($r=0.78$) with the severity of lung fibrosis on histologic evaluation.

The relative risk of lung cancer in asbestos workers who smoke is 53 times that of non-smoking workers not exposed to asbestos. The corresponding relative risks for non-smoking asbestos workers and for non-exposed smokers were 5 and 11, respectively, suggesting that the effect of asbestos and smoking is multiplicative (49). The latency of asbestos-related lung cancer is usually at least 15 to 20 years. The cell type and location of asbestos-related lung cancer are indistinguishable from cancers associated with cigarette smoking alone, and the clinical presentation is likewise similar. Diagnosis requires histopathologic confirmation, usually via lung biopsy.

Ten percent of workers screened by CT for asbestosis will demonstrate some form of lung mass (50). The large majority of these masses are benign. These benign masses include rounded atelectasis (51-53), intrapulmonary fibrotic bands and fissural pleural plaques (54). The typical CT features of rounded atelectasis include relationship to an area of pleural thickening, lobar volume loss, and a swirl of bronchi and vessels curving towards the medial or lateral aspects of the pleural based mass. The lobar volume loss, usually substantial, is best detected by identifying fissural displacement. All of these features must be present for a confident diagnosis of rounded atel-

ectasis. Calcification and air bronchograms may sometimes be seen. Since lung cancer may occasionally coexist with the typical features of rounded atelectasis, careful follow-up by chest radiographs or by CT is important to ensure radiologic stability. Small benign pleural-based nodules, usually due to scars, are common in patients with asbestosis. These are usually wedge-shaped or irregular in outline. As with all other lung masses, the best index of benignity is lack of change over a two year interval.

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High-Resolution CT: Technique and Pitfalls

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Course Objectives

1. Summarize indications for high resolution CT (HRCT)
2. Review technical parameters utilized when performing HRCT
3. Describe technical pitfalls, and how to optimize scan technique.
4. Review interpretative pitfalls, and how to avoid them.

The clinical assessment of a patient who is known or suspected of having diffuse infiltrative lung disease (DILD) can be a difficult and perplexing problem. Unfortunately, this problem is far more common than generally perceived: As estimated by a 1972 Respiratory Diseases Task Force report from the National Institutes of Health, patients with diffuse infiltrative lung diseases (DILD) represent as many as 15% of all patients referred to pulmonologists for evaluation. In fact, diffuse interstitial lung diseases represent a strikingly heterogeneous group of diseases. Although sarcoid and pulmonary fibrosis usually account for between one third and one half of all cases, well over a hundred different causes of diffuse infiltrative lung disease have been described. As a consequence, a highly variable number of diagnostic studies are often obtained, with the final diagnosis or differential diagnoses based on a combination of laboratory tests, physiologic studies, radiographic examinations, and invasive procedures, including fiberoptic bronchoscopy with transbronchial biopsy and/or bronchoalveolar lavage, or open lung biopsy.

HRCT has emerged as one of the most powerful tools available in the noninvasive assessment of these patients. The diagnostic sensitivity and specificity of routine chest radiography is significantly augmented by HRCT, which is now accepted as highly accurate in assessing diffuse lung disease. In the appropriate clinical setting there are circumstances when information derived from HRCT is sufficiently characteristic to allow specific or presumptive diagnoses to be made in the absence of histologic verification. It cannot be overemphasized that the diagnostic evaluation of patients with suspected DILD should be considered a team approach involving pulmonologists, radiologists, and thoracic surgeons. Most important, optimal use of HRCT requires clinical correlation: only rarely is HRCT sufficiently characteristic in itself to

generate a specific diagnosis.

The remarkable accuracy of HRCT mandates, however, high quality examinations, with considerable attention paid to examination technique. With optimal scan technique the spatial resolution of HRCT is approximately 0.5 mm., although structures as small as 0.1-0.2 mm. may be visualized under certain circumstances. This talk will introduce the technical factors involved in HRCT, pointing out potential pitfalls, both interpretive and technical.

HRCT Technique

Collimation

In order to optimize image resolution the thinnest possible collimation should be used, usually 1 mm., 1.5 mm. or 2 mm. on most scanners. Such narrow collimation not only improves spatial resolution but also decreases partial volume averaging from adjacent structures.

Reconstruction Algorithm

Scan data should be obtained utilizing a high spatial frequency (sharp, or bone) algorithm, which will further improve image resolution. In comparison to standard algorithms high spatial frequency algorithms do not perform the smoothing function used to decrease image noise. Anatomic margins and tissue interfaces, therefore, appear sharper, however the payoff is increased image noise. Image interpretation isn't usually impaired, however, except in the case of very large patients. In such instances increasing the kVp and mAs can decrease excessive image noise (but the radiation dose to the patient will also be increased).

Image Spacing

HRCT is a sampling technique, based on the premise that in most diffuse interstitial lung diseases areas of representative disease will be present for analysis on at least some of the images obtained at staggered selected levels. As many DILDs are not uniform in distribution random sampling is usually performed. There is little uniformity in scan protocols. Some centers obtain a few images at selected levels; others space images evenly through the lungs. We obtain images at 10 mm. intervals throughout the lungs in our standard high-resolution examination.

Patient Position

Generally scans are obtained with the patient in a supine position. Not uncommonly subsegmental atelectasis will be present in dependent areas of the lung, typically the subpleural posterior mid and lower lungs, particularly in older patients and smokers. The appearance of this dependent atelectasis may be linear densities, or ill-defined areas of increased density. In either case it may be difficult to differentiate from true disease. Placing the patient in a prone position, and rescanning through the area after atelectasis has shifted to the newly dependent anterior lung, will allow differentiation of persistent true opacities from transient dependent atelectasis. This technique is easily and quickly performed if the abnormality is noted before the patient is off the scanner table. If HRCT scans are not routinely monitored some institutions include a few prone images to each scan protocol, in order to eliminate the possibility of mistaking atelectasis for abnormal opacities.

In selected situations when a known disease entity specifically targets the posterior lower lungs, such as in asbestosis, prone high-resolution images should be prospectively obtained.

Patient Respiration

Scans are routinely obtained at end inspiration, with the lungs fully expanded, and minimization of the confounding densities of superimposed subsegmental atelectasis. Occasionally end expiratory images are purposely obtained, usually to document air trapping in cases of small airway disease or emphysema. Normally lung increases in density and decreases in volume with the egress of air; failure by regions of lung to increase in density at expiration is taken as indicative of air trapping.

When small airway disease such as bronchiolitis obliterans are prospectively considered inspiratory and expiratory images should be obtained. Occasionally the inspiratory images will be normal, and the demonstration of air trapping on the expiratory images may be the only abnormality. Expiratory images are also effectively utilized in the evaluation of the patient noted to have a diffusely mosaic parenchymal attenuation pattern, in order to differentiate small airway disease from alveolitis or heterogeneous perfusion without airway disease.

Target Reconstructions

Retrospective target reconstructions of selected areas of interest allow further improvement in spatial resolution. These images are obtained from the raw scan data by using a small field of view to analyze a portion of the lung parenchyma, usually a single

lung. By applying this small field of view to the scan data from this isolated region the pixel size in the resultant image is smaller, and therefore the spatial resolution is increased. It is important to recognize that this result is not achieved by simply magnifying the image; in fact, magnification of an image degrades spatial resolution by enlarging the pixel size in the selected region, as the image is enlarged.

Target reconstructions are quickly and easily obtained, but are generally utilized only in limited selected cases requiring optimal resolution, because they require that the raw scan data be saved until the radiologist decides which images to reconstruct.

Specialized Techniques

Paradoxically, thinly collimated images providing optimal spatial resolution may result in interpretive challenges, because anatomic landmarks in the lung parenchyma may be harder to recognize. On a single 1 mm. thick section a small, round subcentimeter structure may represent a vessel on end or a lung nodule. On a thicker section the vessel will be recognized as such, by its linear and branching form. Similarly, small irregularly marginated nodules representing impacted bronchioles may not be recognized as organized in a classic “tree-in-bud” pattern on a single thin section. If multiple contiguous thin sections are “added”, and the image is viewed with a maximum intensity projection (MIP) technique, the “tree-in-bud” pattern may become evident, while the heightened spatial resolution is maintained. Inhomogeneous lung attenuation, due to emphysema, air-trapping, or heterogeneous perfusion, may be similarly accentuated by additive minimum intensity projection (MINIP) technique.

HRCT Pitfalls

Sampling

It is important to recognize that HRCT is a sampling technique, providing a small amount of image data for detailed analysis of the pattern and distribution of lung parenchymal features. It must be understood that the technique is inappropriate for the accurate detection of multifocal small abnormalities such as lung nodules. If HRCT is performed with 1 mm. sections at 10 mm. intervals a full 90% of the lung parenchyma is not included on the examination. Certainly limited disease such as a few small metastases could be missed with such a technique.

Similarly, there is a tendency towards assuming that greater sampling, by decreasing the image spacing, provides more data, thereby increasing the information provided. Actually, all diagnostic information necessary may be available on a single fortuitously

positioned, properly performed HRCT image. Beyond a certain point increasing the number of HRCT images by decreasing the image spacing fails to augment diagnostic accuracy, and simply increases time, cost, and radiation dose.

Inadvertent Expiratory Images

If unintended expiratory images are not recognized as such, because of language barriers or the patient’s inability to follow breathing instructions, abnormalities such as ground glass attenuation or inter- and intralobular septal thickening may be misinterpreted as disease. A clue suggesting a scan was obtained at expiration is collapse or deformity of the central airways, easily appreciated, for instance, as convex bowing of the membranous portion of the posterior trachea into the airway lumen.

Dependent Atelectasis

Proof of the nature of dependent densities in the posterior lungs can be achieved through prone imaging, as dependent atelectasis should shift to the now dependent anterior lung. Atelectasis should also be recognized as such in a few other common sites: anterior to the fissures, particularly in the posterior right upper lobe and the lingula, and adjacent to large osteophytes, hiatal hernias, and aortic aneurysms.

Motion

Motion artifact adjacent to the heart and aorta, secondary to cardiac pulsation, is unavoidable. It should, however, be easily recognized because it characteristically affects only the paracardiac lingula and lung adjacent to the transverse aorta. The appearance of disease in these areas, particularly if the remainder of the lungs are normal, should be viewed with suspicion.

If motion artifact is diffuse, from respiratory motion, it may be harder to recognize. When suspected the entire examination should be searched for cyclical variations in lung attenuation, reflecting repetitive inspiratory and expiratory images during the respiratory cycle. Misregistration of easily identified anatomic structures, such as the fissures, creating the appearance of a double fissure, is another easily recognized clue.

Subtle motion artifact can mimic disease. When misregistration “doubles” a pulmonary vessel the appearance is that of two parallel lines, which can be mistaken for the walls of a dilated bronchus. This false appearance of bronchiectasis is particularly problematic, as bronchiectasis is a process which may be focal, and may affect regions commonly subject to motion artifact, such as the lingula. Recognizing that actual bronchiectasis can usually be followed

on consecutive images, and the accompanying pulmonary artery branch is often identified, aids in differentiating these entities. A vessel subject to motion artifact when perpendicular to the plane of the section appears as a star or crescent moon shaped artifact. A low attenuation region immediately adjacent to the artifact can also be mistaken for an ectatic airway in cross-section.

Window Width and Level

If the window width is too wide (>1500 HU) variations in attenuation, or diseases characterized by low-density areas, such as emphysema, will be masked. If the window width is too narrow (<1000), or the level is too low, high contrast images will be subject to nonlinear preferential magnification, resulting in false thickening of small anatomic structures, such as reticular lines or bronchial walls. We prefer fairly narrow windows (approximately 1200 HU) and levels (approximately -700 HU). The actual values chosen are a matter of personal preference. It is strongly recommended, however, that consistency be used when viewing these cases. This will allow an understanding of normal and abnormal appearances to develop, will allow easy comparison of one case to another, and aid in comparing sequential examinations in the same patient.

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The Clinical Spectrum of Sarcoidosis

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At the time of publication, no abstract was available.

Thoracic Sarcoidosis: Patterns and Differential Diagnosis on CT

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Lecture Objectives

1. Become familiar with the variety of CT appearances of thoracic sarcoidosis
2. Learn key points in distinguishing sarcoidosis from other mimicking diseases, such as silicosis, eosinophilic granulomatosis, metastatic disease

Tuberculosis, an infectious granulomatous disease, has been labeled “the great mimic” for its ability to simulate a number of other disease processes. Sarcoidosis, a noninfectious granulomatous disease, is at least “a good mimic” of a variety of disease processes, both benign and malignant. In this exhibit, we demonstrate a collection of cases of sarcoidosis and their mimics. We suggest subtle differences and clinical correlations that may facilitate the correct CT diagnosis.

Sarcoidosis is a systemic granulomatous disease of unknown cause most commonly affecting young and middle aged patients. At initial diagnosis, 50% of patients are asymptomatic, 25% have respiratory symptoms (usually dyspnea), and 25% present with extrathoracic symptoms. The diagnosis is established when clinical and radiographic findings are supported by histologic evidence of non-caseating granulomas. Findings on chest radiographs include bilateral hilar and mediastinal lymphadenopathy with or without pulmonary parenchymal disease. CT of the chest is more sensitive than CXRs in the detection and characterization of both lymphadenopathy and pulmonary parenchymal involvement.

Staging System of Sarcoidosis

The value of the staging system is in predicting outcome. The majority of patients present with Stage 1 disease and are more likely to show complete resolution (CR) than patients with Stage 2 or 3 disease.

		% at dx	% with CR
Stage 0	Normal chest radiograph	8	
Stage 1	Hilar and mediastinal lymph node enlargement	51	65
Stage 2	Hilar and mediastinal lymph node enlargement associated with pulmonary abnormalities	29	49

Lymphadenopathy

Lymphadenopathy is seen in nearly 100% of patients and may show complete radiographic resolution in association with a benign clinical course, or may regress even as the parenchymal disease and clinical course worsen.

	% of patients with sarcoid lymphadenopathy	
	CXR	CT
Hilar	84%	88%
Right paratracheal	76	100
AP window	72	92
Subcarinal	12	64
Anterior mediastinal	12	48
Posterior mediastinal	0	16

Pulmonary Parenchymal Disease

CT is superior to chest radiography in the detection and evaluation of pulmonary parenchymal disease in patients with sarcoidosis. More than 90% of patients will have parenchymal disease demonstrated on CT that is not detected by chest radiography. Pulmonary parenchymal abnormalities are typically bilateral and symmetrical. There is predominant involvement of the upper lobes in 50 to 80% of patients.

Granulomatous involvement of the lung is frequently distributed along bronchovascular bundles that radiate from the hila.

Multiple granulomas in the periphery of the lung form nodules that may then coalesce to mimic masses and/or other alveolar processes.

Nodules with Upper Lobe Predominance

The distribution of abnormalities can provide significant clues to the correct diagnosis. Diseases that commonly have an upper lobe preponderance of pulmonary nodules include sarcoidosis, eosinophilic granulomatosis, tuberculosis, and both simple and complicated silicosis. Cavitation or necrosis within the small nodules is a clue to the correct diagnosis of eosinophilic granulomatosis. EG most commonly occurs in patients who are current cigarette smokers. Patients with reactivation tuberculosis may also have

cavity formation, and calcifications within hilar or mediastinal lymph nodes from prior infection. Silicosis may require an occupational history to exclude as a diagnosis.

Alveolar Opacities

In a more chronic setting, the differential diagnosis includes bronchioloalveolar cell carcinoma (BAC), pulmonary lymphoma, and pulmonary alveolar proteinosis (PAP). Lymphadenopathy may be seen in patients with either sarcoidosis or lymphoma, but is not usually seen in either bronchioloalveolar cell carcinoma or in pulmonary alveolar proteinosis. The patient with pulmonary lymphoma is likely to have more diffuse lymphadenopathy as well as abdominal disease.

Alveolar Opacities with a Peripheral Distribution

A strikingly peripheral pattern of bilateral pulmonary opacities can be seen in patients with sarcoidosis, producing a pattern that mimics embolic diseases, as well as chronic eosinophilic pneumonia. Enlarged lymph nodes, asymptomatic presentation, and absence of blood eosinophilia help to establish the correct diagnosis of sarcoidosis. A peripheral pattern of alveolar opacities can also mimic bronchioloalveolar cell carcinoma. The patient with BAC is more likely to complain of dyspnea, and in some cases, copious production of frothy white sputum (bronchorrhea).

Conglomerate Masses

As silicosis has an approximately 20 year latency period to reach this stage, the patient's age offers a clue to the correct diagnosis. Calcification may be seen within the masses or within lymph nodes in both sarcoidosis and silicosis. At times, occupational history may be the only way to reliably distinguish these two diseases in the older patient.

Bronchial Abnormalities

Lenique et al described bronchial abnormalities in 39/60 (65%) of sarcoid patients on CT. Bronchial walls were thickened in 39 patients, and the lumina were abnormal in 14. Luminal abnormalities included both regular and irregular/nodular narrowing. Traction bronchiectasis was present in 7 patients. Bronchial obstruction may also occur secondary to severe volume loss in the upper lobes in patients with fibrosis.

Air-trapping

Gleeson et al described air-trapping in three patients with sarcoidosis. A mosaic attenuation pattern may be seen on inspiratory images, but is often more clearly seen on expiratory images. Airflow limitation has been demonstrated on PFTs in patients with sarcoidosis.

This may be due to obstruction of airways by peribronchiolar granulomas, but Hansell et al has shown that a reticular pattern is the most common finding in patients with airflow obstruction.

Fibrosis and Distortion

Fibrosis within the lungs may be recognized by distortion of the interlobar fissures and crowding of central bronchi. This is typically most pronounced in the upper lobes. The pattern is mimicked by prior tuberculosis and by radiation-induced fibrosis.

Fibrosis and distortion are associated with the most significant deterioration in lung function.

Complications

Infection with *Aspergillus* can prove to be a serious complication in patients with sarcoidosis. Saprophytic colonization of the cavitary lung disease that occurs in patients with sarcoidosis by *Aspergillus* species can lead to hemoptysis. *Aspergillus* colonization may also occur in tuberculous cavities, emphysematous bulla, and cystic bronchiectasis.

Pneumothorax occurs in 2 - 4 % of patients, usually as a complication of fibrosis and bullae. Pneumothorax can occur earlier in the course of the disease due to necrosis of a subpleural granuloma.

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Radiation Injury of the Lung

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Objectives

1. To review the histologic and pathologic changes of the lung after radiation therapy.
2. To describe the radiographic patterns of lung injury secondary to conventional radiation therapy.
3. To demonstrate the method of 3-D conformal radiation therapy of the lung and the patterns of injury after this type of therapy.

The effects of radiation therapy on the lung parenchyma were first described in the 1920s, and have subsequently been well documented in the radiologic literature (1, 2, 3, 4, 5). The changes are categorized into early (pneumonitis) and late (fibrosis). Histologically, the early or acute phase is that of diffuse alveolar damage and the late phase is of end-stage fibrosis. Many factors affect the lung changes secondary to radiation injury. The most important factors are the dosage and time period of administration, the volume of lung irradiated, the field ports of therapy, and concomitant chemotherapy. Patient susceptibility is also important, but not a predictable factor.

Libshitz has categorized the CT appearance of radiation-induced changes of the lung into homogeneous, patchy consolidation, discrete consolidation, and solid consolidation. The acute (or early) changes are usually present at 8 weeks, but may be as early as 6 weeks, depending on dosage. This is usually referred to as radiation pneumonitis. The radiation pneumonitis will usually undergo a slow organization and condensation to yield a characteristic

radiation fibrosis. Most often this occurs at 9 - 12 months, but can further organize up to 24 months.

3-D conformal radiation therapy is becoming a common method of treating lung cancer. This method uses multiple ports focused on the tumor, that results in dispersing the radiation so that less normal lungs are damaged. The radiograph patterns of lung injury from 3-D conformal therapy are different than those of conventional therapy. We have classified these patterns as modified conventional, scar-like, and local.

This discussion will review the radiographic patterns of lung injury secondary to radiation therapy.

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The Use of Gallium 67 in Interstitial Lung Disease

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At the time of publication, no abstract was available.

Early Lung Cancer Action Project: Findings on Baseline and Annual Repeat Screening CT

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Purpose: The Early Lung Cancer Action Project (ELCAP) is designed to evaluate baseline and annual repeat screening by low radiation dose computed tomography (low-dose CT) in persons at high-risk for lung cancer.

Methods: Since starting in 1993, the ELCAP has enrolled 1000 asymptomatic persons, 60 years of age or older, with at least 10 pack-years of cigarette smoking, no prior cancer, and medically fit to undergo thoracic surgery. After a structured interview and informed consent, baseline chest radiographs (CXR) and low-dose CT were obtained on each subject. Low-dose CT was repeated on an annual basis as long as no malignancy was found. The diagnostic work-up of screen-detected noncalcified pulmonary nodules (NCNs) was guided by ELCAP recommendations which included short-term high-resolution CT (HRCT) follow-up for the smallest NCNs.

Baseline Screening Results: On low-dose CT at baseline as compared to CXR, NCNs were detected three times as commonly (23% vs 7%), malignancies four times as commonly (2.7% vs 0.7%), Stage I malignancies six times as commonly (2.3% vs 0.4%). Of the 27 CT-detected cancers, 96% (26/27) were resectable; 85% (23/27) were Stage I, 19 (83%) of the 23 were not seen on CXR. Following the ELCAP recommendations, biopsies were performed on 28 of the 233 subjects with NCNs; 27 had a malignant NCN and one had a benign one. Another three individuals underwent biopsy outside of the ELCAP recommendations, all had benign NCNs. No one had thoracotomy for a benign nodule.

Annual Repeat Screening Results: In the 1,184 repeat screenings, the test result was positive in 30 (3%). In two of these 30 instances, the subject died (of unrelated cause) before diagnostic work-up; the

nodule(s) resolved in another 12; and absence of further growth was documented by repeat CT in eight of the remaining 16. Further growth was documented in all of the remaining eight; all eight were biopsied and malignancy was diagnosed in seven of them. Six of the seven malignancies were non-small-cell carcinomas, five of Stage IA and one of Stage IIIA, and the one small-cell carcinoma was of limited stage. The median diameter of these malignancies was 8 mm. In another two subjects, symptoms prompted interim diagnosis of lung cancer, neither one of these nodule-associated (but endobronchial instead); one was a non-small cell carcinoma of Stage IIB and the other a small-cell carcinoma of limited stage.

Conclusion: Annual CT screening for lung cancer provides for detecting the disease at earlier and presumably more commonly curable stages in a cost-effective manner.

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Lung Cancer Screening: Low-Dose CT

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Lung Cancer: A Major Public Health Problem

Lung cancer is the most common fatal malignancy of both genders within the United States. Approximately 175,000 new cases are diagnosed in the United States each year, of which 75-80% were non-small cell lung cancer. In other words, one in 18 women and one in 12 men will develop bronchogenic carcinoma in their lifetimes. More than 50% of patients will have distant metastases at the time of diagnosis and only 20-25% will be localized and potentially resectable for cure (1).

The number of deaths from lung cancer exceeds the total combined number for the next three most common causes of cancer deaths: breast, colorectal, and prostate carcinomas. Routine screening for the next three most common causes of cancer deaths is recommended in selected populations. Survival rates for stage I lung cancer are in the same range as for breast cancer (2). However, screening for lung cancer is not recommended by the National Cancer Institute, American Cancer Society, American Medical Association or the American College of Radiology (3). Yet, over one million Americans will die of lung cancer in the next seven years if mortality rates remain stable. If mortality from lung cancer could be reduced by only 10% with screening, over 14,000 lives could be saved annually in the United States alone (4).

The treatment of early non-small cell lung cancer is actually quite effective. The five-year survival following resection of stage IA non-small cell lung cancer is in the range of 62-82% (5-15). However, detection of early non-small cell lung cancer has not been successful with chest radiography.

Screening is one form of early detection that involves applying a sensitive tool for disease identification, enabling more effective treatment. Two primary conditions need to be satisfied for effective screening. First, there must be a detectable pre-clinical phase of disease. That is, lung cancer must be recognizable prior to the onset of symptoms. This condition is satisfied. Stage I non-small cell lung cancers are usually asymptomatic. The estimated time that a stage I non-small cell lung cancer has been present before detection is at least four years (7). Lung cancer starts as cellular atypia progressing over time to

carcinoma in situ and eventually invasive carcinoma (16). Second, there must be an established means of intervention during the pre-symptom phase that alters the eventual outcome of the disease. Post-surgical survival of patients with stage I non-small cell lung cancer is 62-82%, implying that intervention at an early stage will be translated into prolonged survival and decreased mortality (9,17). It stands to reason that the smaller a non-small cell lung cancer is at detection, the more likely it is to be resectable for cure (16,18-22). On the other hand, a 1 cm lung cancer is actually late in the life cycle. At what point in life have most lung cancers metastasized? Despite the observation that lung cancer may be amenable to screening, no tool has been proven to be effective in reducing mortality.

Past Lung Cancer Screening Trials

Sputum cytology and chest radiography have been the most scrutinized methods of screening. In the 1970's, the National Cancer Institute (NCI) supported three mass screening programs involving Johns Hopkins, Memorial Sloan-Kettering, and the Mayo Clinic (23-25). Over 30,000 patients were involved in these three studies. All three studies involved men age 45 and older who smoked. The trial at Johns Hopkins and Memorial Sloan-Kettering investigated the addition of sputum cytology every four months to annual chest radiographs. The participants were randomly assigned to a dual-screened group involving annual chest radiographs and three-day sputum cytology every four months versus a group that only received an annual chest radiograph. These two trials showed that adding sputum cytology every four months to annual screening did not improve mortality rates of lung cancer when compared to use of annual chest radiography alone. Despite the absence of difference in lung cancer mortality in the two groups in these studies, the five-year survival was nearly 35 percent, well above the historical average of 13 percent (26).

The Mayo Lung Project was the only one of the three studies which compared careful assessment with chest radiography and sputum cytology every four months versus standard care which was a recommendation to have annual chest radiography and sputum cytology (25). Over 10,000 participants who smoked one pack or more of cigarettes per day received a

chest radiograph and sputum cytology assessment which led to the identification of 91 prevalence cancers. The participants were then randomized into one group offered chest radiography and sputum cytology every four months for six years while the other group received no scheduled intervention but was advised to have a yearly chest radiograph and sputum cytology. Two-hundred six cancers were detected in the screened group and one-hundred sixty in the control group (27). Compared to the control groups, screening found more cancers, a greater proportion of early stage cancers that were more resectable (46% vs. 32%) and a better 5-year survival (35% vs 15%) (27). However, the mortality from lung cancer in the screened group was 3.2 per 1000 person-years and was not statistically different from the control group. The lack of improvement in mortality in the three NCI-sponsored studies fails to prove that chest x-ray screening is appropriate. Could these seemingly contradictory findings be due to length and/or lead time biases? Could we find the same results with CT screening?

A number of organizations, including the American Cancer Society, American College of Radiology, and the NCI, do not recommend screening as a result of these and other studies (28).

Screening Biases

Use of survival from lung cancer as an end point is subject to bias (29). Bias inherent in screening includes lead time, length time, and over-diagnosis. Lead time bias occurs when a cancer is detected earlier, though intervention does not change the natural history of the disease. Someone with cancer would appear to live longer because the disease was detected earlier, even though survival had not changed. One would simply have had the disease recognized for a longer period. Length time bias involves showing an apparent improvement in survival when that improvement is actually due to detection of cancers with an indolent course which would have done well without intervention. Over-diagnosis is an extreme form of length time bias in which cases are detected that would not have altered the expected survival when compared to the normal population. Because of the inherent introduction of bias in a screening program, mortality is the only reliable measurement of effectiveness.

CT Screening Trials

Investigators have only recently considered the use of low-dose CT for screening (30,31). A Japanese study involved chest radiographs and CT scans twice a year for 1.5 years in 1,369 patients, most of

whom were men over age 50 with a greater than 20-pack-year history of smoking (32). Fifteen lung cancers were detected with spiral CT. Only four of these were demonstrated with chest radiography. The detection rate for spiral CT was 0.43% (15/3457); for chest radiography it was 0.12% (4/3457). The tumors detected with CT had an average diameter of 16 mm versus 30 mm for a group of patients screened with chest radiography alone in the period just before the spiral CT trial. Of the 15 non-small cell lung cancers detected, 14 were stage I tumors (93%).

Henschke, et al reported the prevalent CT findings in 1,000 asymptomatic high-risk volunteers. They found 27 cancers with CT and 7 with chest radiography. Eighty-five percent of the cancers found with CT were Stage I. (33)

In our ongoing, five-year National Cancer Institute study of 1,520 participants, we have found 19 prevalent and 2 incident lung cancers. One-half were Stage I.

False Positive Rates

Radiologically indeterminate benign lung nodules are considered a falsely positive finding of lung cancer. Scans falsely positive for lung cancer are a concern, because they generate patient anxiety and additional costs related to CT scans, radiologically- or bronchoscopically-guided biopsies, surgery, etc. The Japanese experience is that benign nodules are identified in approximately 8% (5-20%) of CT screening examinations (32,34-36). Henschke, et al found nodules in approximately 25% of screened participants (33). We found prevalent 1,368 uncalcified lung nodules in 51% of the 1,520 screened participants.

False positive cases are not new or unique to lung cancer screening. Approximately half of all solitary lung nodules resected are benign (37-40). Approximately two-thirds of all breast lesions biopsied are benign (41).

Our proposed lung nodule management algorithm (Table 1) is designed to expedite surgery for lung cancer and minimize intervention for benign nodules (42-45).

Cost and Radiation Issues

The effective radiation dose associated with the low-dose screening exam is 0.65 mSv (mRem). The approximate dose for "conventional" CT is 5.8 mSv, nearly ten fold higher.

CT Technique

Multislice Spiral Scanner Protocol

- 5mm collimation with 3.5mm reconstruction interval

- High speed mode
- Table feed; 30mm per second
- 120 kVp
- 40 mA

Single Slice Spiral Scanner Protocol

- Helical mode, 0.8 sec scan time
- Pitch 2:1
- 120 kVp
- 80 mA
- 7 mm collimation with 3.5 mm spacing

National Cancer Institute Study in Progress

Is there a relatively low-cost screening test with negligible risk that can demonstrate lung cancer early enough to change mortality from the disease?

Latest generation spiral CT scanners have the capacity to scan the entire chest during a single breath-hold with a radiation dose that is acceptable for mass screening. When used for screening purposes, hourly throughput on spiral scanners can be increased to over 12 patients per hour, allowing expenses to be reduced dramatically. Low-dose fast spiral chest CT has the capacity to consistently demonstrate lung cancers less than 1 cm diameter. These observations justify study of CT as a screening modality for non-small cell lung cancer.

Our primary objective is to show that screening patients at high risk (20 pack-years cigarette smoking history and 50 years of age) for non-small cell lung cancer with low-dose fast spiral chest CT has a reasonable likelihood of decreasing mortality from lung cancer.

We will accomplish our primary objective by testing the hypothesis that low-dose fast spiral chest CT screening of high-risk patients for non-small cell lung cancer will result in a significant downward shift to stage IA and IB tumors at diagnosis compared to historic controls of 40-50% in patients screened with chest radiography (5). We have designed the protocol to identify at least 27 incidence non-small cell lung cancers with 4,500 person-years of screening. Conservatively, we believe that screening for non-small cell lung cancer with low-dose fast spiral chest CT will result in detection of at least 75% of non-small cell lung cancers at the stage IA or IB levels (5,6,46). The five-year survival following resection of stage IA non-small cell lung cancers is in the range of 62-82% (5-15) so that if we can diagnose lung cancers earlier in their stage of development, we should be able to improve the overall lung cancer survival rate.

If screening with CT results in detection of 75% of lung cancers at an early stage there should be a concomitant downward shift in the percentage of patients with stage III and IV disease compared to historic controls of 40-50% (5). Conservatively, we estimate that screening with low-dose fast spiral chest CT will identify fewer than 25% of lung cancers at the stage III and IV levels. The five-year survival of stage III to IV disease ranges from 1-13% (6).

The results of phase II (single arm) studies out of Japan, New York City, and the Mayo Clinic are promising. They establish the basis for a large phase III (randomized controlled) study to determine whether there is a significant difference in mortality between patients screened with low-dose fast spiral chest CT and those not screened at all.

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Integration of Biomarkers and Imaging Studies for Tumor Detection

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Objectives

1. Briefly describe the current status of CT screening for lung cancer and potential difficulties with anatomic imaging.
2. Define biomarkers and potential role of biomarkers in early detection and characterization of lung cancer.

Background

Cancer remains a major health problem and diagnostic challenge. While current non-invasive radiologic studies and laboratory tests play an integral role in the evaluation of cancer patients, there are clear limitations in determining the etiology and biologic behavior of an anatomic abnormality. New, innovative strategies are essential if we are to have a significant impact on this disease.

Prior early detection efforts for lung cancer, even targeted at high risk individuals, were ineffectual. Cancers were detected at earlier stages in the screening groups as compared to the control groups, more cancers were resectable in the screened populations, and 5-year survival rates were significantly better in the screening versus control groups. Mortality rates from lung cancer and the number of unresectable cases, however, were not statistically different on final evaluation. Based on these data, screening for lung cancer with chest radiographs and/or sputum cytology has not been recommended.

More recently it has been suggested that these trials failed because plain films are too insensitive; by the time many lesions are detectable on chest radiographs, patients have advanced stage disease. Thus low-dose spiral CT has been proposed as an improved technique for lung cancer screening. Proponents of this method predict that the CT will detect smaller lesions than chest radiographs, and that this should translate into detection of earlier stage disease and, ultimately, a reduction in lung cancer mortality. At this time, the studies need to be complete and the data analyzed before it is known if CT screening will truly improve outcomes.

Prevalence screen data from these low-dose CT studies, however, again demonstrate several problems with using anatomic imaging. Many indeterminate

nodules are detected, and once a lung cancer is diagnosed, radiologic features can not predict the tumors biologic activity.

One possible approach to these imaging dilemmas is to incorporate biomarkers (*any measurable substance that reflects a biologic process*) into the diagnostic evaluation. To be clinically useful in lung cancer screening, these markers must be readily accessible (i.e., blood, sputum, and urine) and cost-effective.

While several interesting markers of lung cancer susceptibility have been identified, the search continues for the optimal marker or panel of tumor markers used to create a non-invasive molecular tumor profile. There are a number of recent technologic advances with the potential to identify novel RNA, DNA, and protein tumor markers, although none to date have been successfully integrated into screening trials.

For early detection and screening, biomarkers specifically can be used for the following purposes;

1. Determining high risk patients. They could be used to more efficiently suggest which patients might benefit from a screening study.
2. To distinguish benign from malignant pulmonary nodules on screening CT. This could be useful in determining which patients require further evaluation when an indeterminate nodule is detected.
3. To create a molecular profile once patients are diagnosed with lung cancer. This will be invaluable in suggesting the appropriate therapy and providing prognostic information as not all histologically similar or stages of lung cancer have the same biologic activity.

Summary

Biomarkers may be useful in complementing conventional imaging studies for early detection of lung cancer. The combination of tests could provide the requisite anatomic information and molecular characterization. These data will be invaluable in providing diagnostic, prognostic, and therapeutic information, which are essential if decreases in lung cancer mortality are to be realized.

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Staging Lung Cancer and the New Mountain Classification: Multimodality Approach

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Staging

Staging of any tumor consists of the determination of the extent of disease. Staging information is important for two reasons: (1) to determine prognosis and (2) to select patients for surgical intervention. The TNM system is widely used to classify lung tumors. In 1986 the staging system was revised based on epidemiologic evidence of improved survival following surgical resection in patients who had previously been classified as having unresectable disease. In the TNM classification, “T” indicates the features of the primary tumor, “N” indicates metastases to regional lymph nodes, and “M” refers to the presence or absence of distant metastases (Tables 1 & 2). In the old (pre 1985) lung cancer classification, stages I and II were considered amenable to surgical management, and stage III tumors were considered unresectable. The revised 1985 system and the current Mountain classification consists of four stages; stage IV includes only those patients with evidence of distant metastases (M1). Stage III has been redefined and divided into stages IIIA and IIIB. Of these two categories, stage IIIB is also considered inoperable disease. In the previous classification, tumors with limited invasion of the chest wall and mediastinum were included in this inoperable category, but under the new classification such tumors are considered to be potentially operable provided that vital structures in the mediastinum such as the great vessels, heart, and aerodigestive tract are not involved. The designation T4 is now used to describe lesions with extensive invasion of the mediastinum or diaphragm. In addition in the current system patients with ipsilateral nodal metastases are also considered operable. However, for the most part, only patients with limited ipsilateral mediastinal nodal disease fall into the operable category. These are usually cases in which tumor is contained within the capsule of the lymph nodes, and is limited to involvement of the lower mediastinal nodes. The category N3 was added to the TNM staging to refer to contralateral mediastinal or hilar lymph node or supraclavicular lymph node metastases. N3 disease is considered to be in the non-surgical or unresectable category.

In 1997 further revisions were introduced into the staging grouping of the TNM subsets in the International System for Staging Lung Cancer. This was adopted by the American Joint Committee on Cancer and the Union Internationale Contre le Cancer. There are very minor alterations in the previous classification. Stage I has been divided into two groups, IA and IB. T4 has also been slightly redefined to include satellite tumor nodule(s) within the ipsilateral primary lobe of the lung. Previously any additional nodules had been considered evidence of distant metastatic disease (M1). The definition of stages IIA, IIB, IIIA, and IIIB are included in Table 2. In regard to stage I, data has consistently shown a better outcome for patients with T1N0M0 lung tumors than for any other subsets. Survival is estimated to be approximately 60% in patients with clinical stage IA disease and only 38% for the those in clinical stage IB. Stage IB is designated as patients with T2 tumors. Regarding stage II, the survival rate for patients with T1N1M0 disease, that is, T1 lesions with involved hilar nodes is higher than those with T2N1M0 disease. However, the former is a small group and rather infrequent. In regard to stage III, definitions for stage IIIA and IIIB are provided in Table 2.

Computed Tomography

A number of different imaging modalities have historically been used in staging lung cancer. These have included standard and conventional tomography as well as computed tomography and magnetic resonance imaging. In some instances, accurate staging and the determination of appropriate treatment for patients with lung cancer can be made non-invasively with imaging modalities alone, although in most instances some degree of surgical staging is also necessary. Computed tomography has now become the major imaging modality of choice in the evaluation of patients with bronchogenic carcinoma. Computed tomography is not only useful for staging but also as a guide to surgical management and in the determination of appropriate methods for surgical staging.

Evaluation of the Primary Tumor (the T factor)

T3 tumors include tumors of any size with direct extension into the chest wall, diaphragm, the mediastinal pleura or pericardium without involvement of the heart, great vessels, trachea, esophagus, or vertebral body. T4 tumors are tumors of any size with invasion of the mediastinum or involvement of the heart, great vessels, trachea, esophagus, vertebral body, carina, or with associated malignant pleural effusion.

It is not always possible to distinguish T3 from T4 lesions with imaging studies. Lesions with chest wall invasion are classified as T3 lesions and are potentially resectable. Surgical resection, however, requires en bloc resection of the pulmonary malignancy and the contiguous chest wall and is associated with an operative mortality in the range of 8-15%. It is always desirable therefore to determine preoperatively if chest wall invasion is present, in order to select patients as operative candidates. The value of CT in the determination of chest wall invasion is somewhat limited. Although CT certainly provides incremental information over standard films, many of the findings described in the literature which are said to be associated with chest wall invasion have been shown to be neither sensitive nor specific. These include pleural thickening adjacent to the tumor, encroachment or increased density of pleural fat or an obtuse angle between the pulmonary mass and the pleural surface. Only the presence of a mass in the chest wall or definite rib destruction are helpful indicators of chest wall invasion. Magnetic resonance imaging has been shown to be more accurate than CT in defining the extent of chest wall invasion and particularly in the evaluation of superior sulcus carcinomas.

Similarly CT may be useful when extensive mediastinal invasion is present. Contrast enhanced images may show vascular encasement and involvement of major mediastinal organs. However, CT is unable to distinguish contiguity of tumor with the mediastinum in some instances from actual invasion of the walls of vital mediastinal structures. Again MR imaging has been shown to be more accurate than CT in delineating the extent of malignant invasion.

Evaluation of Nodal Metastases (the N Factor)

Computed tomography has become the method of choice for the assessment of mediastinal nodes in bronchogenic carcinoma. Previously patients with mediastinal nodal metastases from bronchogenic carcinoma were not considered to benefit from surgical

therapy. However, numerous studies have consistently documented improved survival of selected patients after resection of mediastinal nodal disease and in most cases adjuvant radiation therapy. The new American Joint Committee on Cancer Staging now considers patients with ipsilateral mediastinal lymph node metastases (N2) as potentially surgically resectable stage IIIA disease. Included in this group are patients with (a) intracapsular rather than extracapsular involvement and (b) positive nodes identified at thoracotomy after negative mediastinoscopy. In addition, early reports have indicated that even patients with gross and bulky ipsilateral nodal metastases (N2) may benefit from surgery if it is combined with neoadjuvant chemotherapy and radiation therapy. However, patients with contralateral mediastinal nodal involvement (N3) are considered to have nonoperable stage IIIB disease.

Several studies have addressed the accuracy of CT in the staging of mediastinal nodal metastases in lung cancer. Some early investigations reported a high sensitivity in the range of 88-94%, values that are equivalent to the sensitivity of mediastinoscopy. Opinions based on such data suggested that mediastinoscopy was unnecessary in cases in which the CT scan showed no evidence of enlarged nodes. However, the results in many of these early studies differed widely and are difficult to interpret for several reasons. The variant results may be explained by differences in size and nature of the patient group studied, the frequency of mediastinal lymph node involvement, the size criteria used to distinguish normal from abnormal nodes, and most importantly the method used for surgical correlation with radiographic findings. Surgical evaluation of mediastinal nodes was limited in most cases to node palpation rather than to complete nodal sampling and biopsy. In addition, lack of an adequate lymph node mapping scheme did not allow for strict correlation of abnormal nodes detected at CT with specific nodal groups sampled at thoracotomy and mediastinoscopy. More recent studies which have employed total nodal sampling and the ATS lymph node classification have shown a lower sensitivity for CT in the detection of nodal metastases. McLoud et al. reported that the sensitivity and specificity of CT were 64% and 62% respectively in a study which used 1 cm. as the upper limit of normal diameter for the short axis of lymph nodes and also employed extensive lymph node sampling that was correlated closely with CT nodal stations. The limitations of CT in the identification of N2 and N3 disease are now well accepted. MR imaging is constrained by similar limitations and there appears to be no clear advantage to MR imaging over

CT in identifying lymph node involvement by tumor.

Despite the limitations of CT in staging mediastinal lymph nodes, this imaging modality does provide important information concerning the nodal status of patients with lung cancer. Identification and localization of enlarged lymph nodes aids in the selection of the appropriate invasive procedure for surgical staging. Evidence of extensive lymphadenopathy with secondary signs such as obstruction of the superior vena cava or destruction of the vertebral bodies may preclude further need for staging procedures if the histologic characteristics of the primary lesion are known.

A negative CT scan for mediastinal adenopathy is a more controversial issue. It is the opinion of this author that such patients still merit mediastinoscopy because of the limitations of CT. However, in some institutions mediastinoscopy may not be available or preferred. If patients are selected immediately for thoracotomy without precedent mediastinoscopy careful nodal sampling must be done at the time of surgery. Because of the low specificity of CT, enlarged lymph nodes must be biopsied before surgery. Enlarged hyperplastic nodes occur frequently in the setting of central tumors associated with obstructive pneumonitis. Various procedures are available for such sampling, including mediastinoscopy, Wang needle biopsy, and percutaneous needle biopsy.

The issue of CT staging of the mediastinum in T1 lesions is controversial. T1 tumors are defined as lesions 3 cm. or less in greatest diameter surrounded by lung or visceral pleura without evidence of invasion proximal to the lobar bronchus. Several studies have suggested a low prevalence of mediastinal nodal metastatic disease with T1 cancers (5-15%). Because of such a low prevalence, it has been suggested that CT may not be necessary in such patients and that the preoperative staging should be limited to plain chest radiographs. However, Seely et al. in a study of 104 patients with T1 lesions found a higher prevalence of nodal metastases (21%). The sensitivity of CT in this study was 77%. The high prevalence of metastases to the mediastinum suggests the need for further careful preoperative staging in such patients which will include CT scanning.

Evaluation of Distant Metastases (the M Factor)

The role of imaging in the determination of extrathoracic metastases from bronchogenic carcinoma is somewhat controversial. CT and MR may be useful in the detection of silent brain metastases in patients with adenocarcinoma. Because the adrenal

glands are one of the most common sites for extrathoracic metastases, CT scans used in staging lung cancer should include the upper abdomen. In a study by Salvatierra et al., of 146 patients with lung cancer there was a 7.5% prevalence of adrenal metastases. Examination of the adrenal glands and in fact the liver can be done easily at the time of the CT examination of the chest. However, two-thirds of adrenal masses identified by CT in patients with lung carcinoma are non-neoplastic. Adrenal adenomas are quite common. Most adrenal adenomas are less than 3 cm. in diameter and often are of low attenuation (less than 10 Hounsfield Units) because of their fat content. However, in lesions not meeting these criteria, needle aspiration biopsy of the adrenal may be necessary.

Conclusion

Computed tomography remains the imaging method of choice in the staging of bronchogenic carcinoma. Despite its limitations, CT is still indicated in order (1) to determine the extent of the primary lesion; (2) to evaluate the mediastinum for the presence of nodal metastases; and (3) to screen for metastatic disease in the adrenal glands.

MR

Initial experience suggests that evaluation of the mediastinum with MR is approximately equal to that of CT with regard to the staging of bronchogenic carcinoma. These data, however, are somewhat limited. Webb et al. reported a series of 33 patients in which they compared staging with MR with staging done with computed tomography and surgery. They found that CT and MR provided comparable information regarding the presence and size of mediastinal lymph nodes. MR better discriminated mediastinal nodes from vascular structures when compared with non-contrast CT. However, in two of their 11 patients with multiple mediastinal lymph nodes that were normal in size at CT examination and surgery, MR suggested a confluent abnormal mass probably because of poorer spatial resolution. Musset et al. studied 44 patients with bronchogenic carcinoma prospectively by both computed tomography and magnetic resonance imaging. Both T1- and T2-weighted sequences and coronal and sagittal images were performed. They found no statistically significant differences between the two imaging methods in the evaluation of either tumor extent or nodal involvement. Their experience was similar to that of other investigators who reported that calculation of the relaxation times, T1 and T2 is not useful in distinguishing benign from

Table 1
TNM Descriptors

Primary Tumor (T)

- TX Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.
- T0 No evidence of primary tumor.
- Tis Carcinoma *in situ*.
- T1 Tumor ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus* (i.e., not in the main bronchus).
- T2 Tumor with any of the following features of size or extent:
 - > 3 cm. in greatest dimension.
 - Involves main bronchus, ≥ 2 cm. distal to the carina.
 - Invades the visceral pleura.
 - Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung.
- T3 Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus < 2 cm. distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung.
- T4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or tumor with a malignant pleural or pericardial effusion,[†] or with satellite tumor nodule(s) within the ipsilateral primary-tumor lobe of the lung.

Regional lymph nodes (N)

- NX Regional lymph nodes cannot be assessed.
- N0 No regional lymph node metastasis.
- N1 Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes involved by direct extension of the primary tumor.
- N2 Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s).
- N3 Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph nodes(s).

Distant metastasis (M)

- MX Presence of distant metastasis cannot be assessed.
- M0 No distant metastasis.
- M1 Distant metastasis present.[‡]

* The uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified T1.

[†] Most pleural effusions associated with lung cancer are due to tumor. However, there are a few patients in whom multiple cytopathologic examinations of pleural fluid show no tumor. In these cases, the fluid is nonbloody and is not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient's disease should be staged T1, T2, or T3. Pericardial effusion is classified according to the same rules.

[‡] Separate metastatic tumor nodule(s) in the ipsilateral nonprimary-tumor lobe(s) of the lung are also classified M1.

Table 2
Stage Grouping - TNM Subsets*

Stage	TNM Subset
0	Carcinoma <i>in situ</i>
IA	T1N0M0
IB	T2N0M0
IIA	T1N1M0
IIB	T2N1M0 T3N0M0
IIIA	T3N1M0 T1N2M0 T2N2M0 T3N2M0
IIIB	T4N0M0 T4N1M0 T4N2M0 T1N3M0 T2N3M0 T3N3M0 T4N3M0
IV	Any T Any N Any M1

*Staging is not relevant for occult carcinoma, designated TXN0M0.

malignant adenopathy. MR, however, may be useful in the assessment of T3 lesions, that is, lesions that directly invade the chest wall and mediastinum. In a recent report, Hagggar et al. reported that MR imaging was useful in the evaluation of chest wall invasion by carcinoma of the lung. They studied 19 patients, 13 of whom underwent surgery. MR findings indicative of chest wall invasion included a high signal focus within the chest wall and/or chest wall thickening on T2-weighted images. TR values at 2500 msec. and TE values at 50-100 msec. were employed. Contrast

differences between normal and invaded chest wall could be appreciated on these T2-weighted images, and coronal and sagittal imaging facilitated identification of tumor contiguity with extrathoracic structures.

Webb et al. in a study comparing results of CT with magnetic resonance imaging in 170 patients with bronchogenic carcinoma found little difference in the sensitivity, specificity, and accuracy of CT and MR in the evaluation of mediastinal adenopathy. However, he also reported an increased ability of MR to detect both chest wall and mediastinal invasion.

Superior sulcus carcinomas are defined as bronchogenic carcinomas occurring at the extreme apex of the lung. Such tumors may be considered resectable and are usually managed with radiation therapy followed by surgery with chest wall resection if there is no evidence of mediastinal or distant metastases. However, accurate assessment of the local extent of disease is an important aspect in the staging of these lesions. We have found MR to be useful in determining certain parameters of unresectability such as invasion of the vertebral body and involvement of the subclavian artery and brachial plexus. Sagittal and coronal images are particularly useful in imaging such lesions. T2-weighted images help to differentiate apical tumor from surrounding muscle and to define the extent of the tumor in the base of the neck.

MR is a useful technique in evaluating the mediastinum. It is most advantageous in the diagnosis of mediastinal vascular lesions. It is also useful in the evaluation of mediastinal masses, although the spatial resolution is less than that observed on CT scanning.

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The Solitary Pulmonary Nodule

Jeffrey S. Klein, MD

Objectives

At the completion of this presentation, the attendee will be able to:

1. understand the significance of accurate characterization of the solitary pulmonary nodule
2. describe the relative utility of noninvasive imaging modalities in the evaluation of the solitary pulmonary nodule
3. understand the role and utility of invasive diagnostic procedures for pathologic characterization of the solitary pulmonary nodule

Introduction

This presentation will review the definition of the SPN and detail the utility of various imaging modalities in characterizing these lesions, with a particular focus on newer techniques including contrast-enhanced computed tomography (CT), Single photon emission computed tomography (SPECT) nuclear medicine imaging, and positron emission tomography (PET).

Radiologic Characteristics of Solitary Pulmonary Nodules

The goal of assessing for various radiologic characteristics of a solitary pulmonary nodule is to determine whether or not the lesion can be accurately classified as almost certainly benign. Those lesions that do not meet specific benign criteria are considered indeterminate and will often require definitive pathologic characterization. While the conventional chest radiograph can provide information that allows definitive characterization of the SPN, the majority of patients with SPNs will undergo CT.

Size. The larger the SPN, the more likely it is to be malignant. In fact, the vast majority of lesions > 3 cm are malignant, and therefore identifying calcification in such lesions and characterizing the marginal characteristics of masses is not useful in differential diagnosis.

Growth. The absence of growth over at least a 2-year period is a reliable indicator of benignity. In order to firmly establish the absence of growth, films obtained with comparable radiographic technique are necessary. Limited thin-section CT should be performed for more accurate lesion measurement if there is any question whether a SPN has increased in size. The use of doubling time, which for spherical lesions is defined as a 25% increase in diameter, is based on the observation that benign lesions have doubling

times of less than 30 days or greater than 450 days. Therefore, SPNs with doubling times between 30 and 450 days require further evaluation.

The use of helical CT for evaluating SPN growth rates, particularly that small lesions, has received greater attention recently given advances in scanner technology, the ability to obtain nodule volumes using helical acquisition techniques and computer aided evaluation of data sets, and the increasing number of small lesions detected on CT performed for other indications or to screen for lung cancer presenting as a SPN. A recent paper describes the use of a software program that segments SPNs and calculates nodule volume to within a 3% accuracy. In a small series of patients with SPNs and a definitive diagnosis, the doubling time as determined by change in nodule volume on repeat CT scans was less than 177 days for all malignant nodules and greater than 396 days for all benign lesions. It is likely that computer-aided analysis of nodule volume will become an important part of the evaluation of small SPNs by helping determine growth rates that allow distinction of benign from malignant SPNs. The technique may prove useful for irregularly-shaped small lesions and lesions that grow in a cephalocaudal fashion that is difficult to discern on review of axial source images given differences in scan planes and patient positioning on follow-up CT exams.

Internal Density

Calcification. The presence of calcification in a specific pattern within a SPN is indicative of a benign lesion. These patterns include central, laminated, diffuse, or popcorn calcification. Eccentric or amorphous calcification can represent a calcified granuloma engulfed by a malignancy or dystrophic malignant calcification respectively and should not be taken as evidence of benignancy. While the presence and pattern of calcification can sometimes be determined on conventional radiographs, approximately 1/3 of noncalcified SPNs will have calcification on CT. For this reason, definitive identification of calcium usually requires thin-section CT using 1-3 mm collimated scans reconstructed with a high spatial frequency algorithm.

In lesions where calcification is not visibly evident on thin-section CT scans, CT densitometry should be performed by determining the attenuation value of the nodule. Most thoracic radiologists no longer use a

reference CT phantom for this purpose and calculate the average attenuation value through the central portion of the nodule. A value of 200 Hounsfield units (H.U.) or greater is reliable evidence of microscopic calcification and benignity.

Fat. The identification of fat within a SPN with smooth or lobulated margins is diagnostic of a pulmonary hamartoma. In lieu of pathologic confirmation, radiographic follow-up to confirm stability over a 2-year period is recommended.

Cavitation. Cavitation may occur in necrotic malignant SPNs but does not allow distinction of benign lesions as inflammatory lesions such as abscesses, infectious granulomatous lesions and Wegener's granulomatosis and pulmonary infarcts can cavitate. However, the thickness of the cavity wall is helpful in distinguishing benign from malignant lesions. Cavities with a greatest wall thickness < 5 mm are almost always benign, while the vast majority of those with a wall thickness > 15 mm are malignant.

Air bronchograms or "bubbly" lucencies. The presence of air bronchograms or cystic or "bubbly" lucencies within a SPN is highly suggestive of pulmonary carcinoma, although lymphoma and occasional benign lesions such as organizing pneumonia and mass-like sarcoidosis can have a similar appearance. Bubbly lucencies are particularly common in localized bronchioloalveolar cell carcinoma.

Margins. The margins of a SPN can provide important clues to the nature of the lesion. In general, smooth round nodules are benign while those with spiculated margins (corona radiata) are much more likely to be malignant. Satellite lesions surrounding the main (largest) nodule usually indicates a granulomatous process. A pleural tail, seen as a linear opacity extending from a lung nodule toward the peripheral pleural surface, can be seen in either benign or malignant lesions but when associated with malignancy is most often seen in pulmonary adenocarcinoma. Recognition of feeding and draining pulmonary vessels extending from the hilum towards the medial aspect of a round or lobulated nodule allows confident diagnosis of a pulmonary arteriovenous malformation most often associated with hereditary hemorrhagic telangiectasia (HHT). A bundle of curvilinear bronchi and vessels extending into the hilar aspect of a peripheral nodule or mass adjacent to pleural thickening is termed the comet tail sign and is characteristic of rounded atelectasis.

Enhancement. There are several imaging techniques that attempt to characterize SPNs based on the observation that malignant tumors are relatively hypervascular compared to benign lesions.

Nodule enhancement after intravenous contrast administration is now easily accomplished with the

use of power injectors and rapid scan acquisition with spiral CT. The technique involves thin-collimated (3-mm) spiral acquisitions through a SPN between 6 and 30 mm in diameter before and after intravenous contrast injection. Scans obtained each minute for 4 minutes after contrast injection are compared with baseline unenhanced scans. An enhancement value is then determined by calculating the mean attenuation value through the center of the nodule at peak contrast enhancement and subtracting the baseline value. A recent prospective multicenter study has shown that an enhancement value of less than 15 H.U. is virtually diagnostic of a benign lesion (i.e., the test has a high sensitivity for malignancy). Due to the rapid image acquisition with spiral CT, CT nodule enhancement can be performed following routine scanning of the chest without need for additional contrast administration and little additional time and radiation. However, the technique requires meticulous attention to detail and may be less accurate in larger SPNs (i.e., those > 2 cm) as these lesions are more often necrotic and may produce false negative exams. The technique may prove to be most useful for evaluation of probably benign SPNs when transthoracic needle biopsy is unavailable, cannot be performed, or is nondiagnostic and the patient is a poor surgical candidate.

^{99m}Tc Depreotide Scintigraphy

The affinity of malignant neoplasms including both small cell and non-small cell lung cancer for peptide analogs of somatostatin has led to at least two studies investigating the use of this agent in the non-invasive evaluation of SPNs. In a recent multicenter study using this agent commercially available as Neotect (Diatide, Inc, Londonderry, N.H.), 96.6% of malignant SPNs and masses were correctly identified although the specificity of the agent for distinguishing benign from malignant lesions was only 73%. Since cost and availability of SPECT is currently greater than that of FDG-PET, this agent may have some clinical utility in select settings, most typically nonsurgical candidates with irregularly-shaped lesions that are not amenable to CT nodule enhancement or percutaneous biopsy.

Positron Emission Tomography

There is a growing literature on the utility of PET using the radiopharmaceutical Fluoro-2-deoxy-D-glucose (FDG) in the evaluation of focal lung lesions including SPNs. FDG uptake in focal lesions is measured semiquantitatively by calculating a standardized uptake ratio (SUR). When assessing lesions >10 mm in diameter, FDG-PET has a sensitivity of 94-96% and a specificity of 87-88%. The low false negative rate of PET makes this a useful adjunct to thin-section CT in

excluding malignancy and allows clinical follow-up of probably benign lesions. False positive cases are usually seen in granulomas with active inflammation. The limited availability and high expense of FDG-PET are the main obstacles to widespread utilization in the evaluation of SPNs. Given the increasing availability of mobile PET scanners and the reimbursement for solitary nodule evaluation and lung cancer staging currently supported by Medicare, it is likely that the use of thoracic and whole body PET will expand well beyond academic research centers and become a mainstay of solitary nodule evaluation and lung cancer staging.

Techniques for Pathologic Diagnosis

Transthoracic needle biopsy (TNB). Image-guided TNB has become the semi-invasive procedure of choice for definitive characterization of SPNs. The procedure is most often performed under CT guidance and has been shown to have a sensitivity of over 90% for malignancy in most series, particularly when expert cytopathology is utilized. The ability of TNB to obtain a specific benign diagnosis for focal lung lesions is limited by difficulty aspirating diagnostic material from sclerotic granulomas. Recently, the use of small-gauge (< 20-gauge) cutting biopsy needles has provided histologic material from SPNs and can improve the yield for benign lesions from 60 to 80% or greater.

Bronchoscopy. In a patient with a SPN and findings suggesting central airway involvement (i.e., hemoptysis, bronchus entering hilar aspect of nodule on thin-section CT), bronchoscopy with brushings, washings, and endobronchial or transbronchial biopsy is the initial diagnostic procedure of choice, and in such situations can obtain a diagnosis in up to 80% of lesions. However, the diagnostic yield from bronchoscopy differs significantly with the size and location of the lesion and the experience of the bronchoscopist, with yields as low as 28% in one series. A cooperative bronchoscopic and transthoracic approach has been shown to be effective for peripheral nodules, and conventional or CT fluoroscopy help guide accurate placement of transbronchoscopic brushes and needles to improve diagnostic yield.

Video-assisted thoracoscopic surgery (VATS). This technique, usually performed by surgeons in the operating room under general anesthesia with single lung ventilation, can be used as both a diagnostic and therapeutic procedure for SPNs. The indications for VATS resection of SPNs differs considerably between institutions, but has been shown to have high diagnostic accuracy with less morbidity than thoracotomy.

Thoracotomy. Thoracotomy for resection of SPNs is usually limited to lesions with a high likelihood of malignancy when lobectomy and nodal resection will be necessary for definitive lung cancer staging and treatment. Additional indications include a deeply situated nodule or other lesion not amenable to thoracoscopic localization and resection or when limited pulmonary reserve necessitates limited lung resection to preserve pulmonary function.

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Pulmonary Metastases: Biology and Radiology

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Objectives

1. To review the pathways and biology of secondary neoplastic involvement of the lungs
2. To review technical advances that have contributed to the increased detection of pulmonary metastases

Introduction

The lungs are a common site of tumor metastases, with incidence rates cited between 20%-54% of all patients who died of malignancy. The rate of detection of pulmonary metastases for any tumor type throughout a patient's clinical course is lower than the incidence cited in autopsy series. The early detection of such metastases may affect both tumor stage and treatment planning.

Pathways of Metastases

Most commonly, metastatic disease to the lung is secondary to: (1) primary tumors that have a high propensity for pulmonary metastases or (2) primary tumors that are somewhat less likely to metastasize to the lung but occur with high prevalence within the population. These two categories may be explained by differences in the mechanisms of metastasis.

Spread via the Pulmonary or Bronchial Arteries

In the former situation, which is by far the most common, tumor cells are carried to the lungs in the blood stream in the inferior or superior vena. The initial event must be vascular invasion at the site of the primary neoplasm cells or fragments of tumor are dislodged and carried as tumor emboli to the lungs. The vast majority are too small to cause infarcts and lodge within pulmonary arteries or arterioles. Extension into the lung parenchyma follows with formation of a well defined nodule.

Much less commonly, pulmonary metastasis can also occur via the bronchial arteries, in a pathway analogous to the development of metastases in systemic visceral organs.

Spread via the Pulmonary Lymphatics

Hematogenous dissemination to small pulmonary arteries and arterioles is followed by invasion of the adjacent interstitial space and lymphatics with spread

along these pathways to the hilum and periphery of the lung.

A less common mechanism involves retrograde extension along lymphatic channels. Mediastinal lymph nodes are affected first, followed by retrograde extension to hilar and bronchopulmonary nodes and by involvement of pulmonary lymphatics and spread toward the lung periphery.

Spread via the Airways

Spread occurs after inoculation into the airways. This is an uncommon pathway for lung metastases, occurring in less than 2% of patients with solid tumors.

Generalizing Sites

1. Initial site for tumors with venous drainage primarily to the lung. This includes sarcoma, melanoma, choriocarcinoma, renal, testicular, adrenal gland, thyroid and head and neck tumors.

2. Tumors that involve the lung sequentially only after first metastasizing to other sites. The liver is the primary site for tumors of the gastrointestinal tract which includes stomach, pancreas and colon cancer. Either the lung or liver may be the generalizing site for esophageal or rectal tumors.

3. Simultaneous seeding of multiple organs including the lungs. Transitional cell carcinoma (bladder, ureter), uterine and cervical cancers. Renal cell and melanoma although listed under lung as the first site may involve other sites initially. Breast cancer has a complicated pattern of metastasis with simultaneous involvement of the lungs, bones or liver.

CT Imaging of Pulmonary Metastases

Conventional CT enables the demonstration of more pulmonary nodules than does chest radiography. Since the advent of helical CT scanning, even more pulmonary nodules are being detected due to elimination of respiratory misregistration. Helical CT also allows reconstruction of the acquired helical CT data set in overlapping sections, further improving detection of subcentimeter nodules. Thinner image sections obtained with the helical CT scans result in sharper images with less partial volume averaging effects.

At many facilities, radiologists are now interpreting CT studies on workstations rather than on radiographic film. Scrolling through helical CT images on a computer workstation in a sequential ciné mode has distinct technical and perceptual advantages. It has significantly increased the detection rate of pulmonary nodules 5 mm in diameter or smaller as compared to film-based viewing. No significant advantage has been demonstrated for lesions larger than 5 mm. On a perceptual level, ciné viewing facilitates differentiation of tubular structures (such as blood vessels) from spherical structures (such as pulmonary nodules).

Nodule Characteristics

The most common presentation of pulmonary metastatic disease to the lungs consists of multiple, sharply marginated nodules of varying sizes. Some metastases such as those from choriocarcinoma may present with a more spiculated appearance. A similar appearance may rarely be seen with other malignancies following chemotherapy presumably reflecting hemorrhage.

The number of pulmonary nodules is generally not helpful in distinguishing benign lesions from metastases. Although multiple nodules are more likely to represent metastases in younger patients, as granulomatous disease and intrapulmonary lymph nodes are less common.

Nodules larger than 1 cm are more likely to be malignant than are smaller nodules, regardless of whether an underlying malignancy is known; the likelihood of malignancy is even higher if the patient has a known malignancy. Nodules 1 cm or smaller are more likely to be benign in patients with no known malignancy compared to patients with a known malignancy.

Differentiation of Benign from Malignant Lesions

Unless fat or a characteristic pattern of calcification can be demonstrated within a lung nodule, or prior radiologic studies demonstrate stability of the nodule for at least 2 years - either of which would indicate the nodule is benign - the nature of the nodule remains obscure at imaging. However, calcification within a lung nodule in patients with sarcoma may be misleading, as metastatic lesions from osteosarcoma

or chondrosarcoma can contain radiologically demonstrable calcification.

Lung nodule enhancement has recently been proposed as an indicator of malignancy and vascularity in small solitary nodules (i.e., those measuring 5-40 mm). Malignant nodules were shown to enhance statistically significantly more than granulomas and benign neoplasms, with a sensitivity of 98%, specificity of 73%, and accuracy of 85%. Blood flow patterns at dynamic CT of malignant, benign and inflammatory solitary pulmonary nodules have recently also been evaluated.

Assessing growth of small nodules less than 1 cm with CT volumetric measurements has recently been reported in a preliminary study and may be a promising tool for evaluation of small nodules. Positron emission tomography (PET) is a powerful radiologic technique that can distinguish benign and malignant nodules in many cases. However, PET currently has limited ability to assess subcentimeter lesions.

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Postlobectomy Anatomy

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Postlobectomy anatomy resembles, but is distinct from that seen in severe lobar volume loss. In fact, in the ideal situation, lobectomy is the ultimate form of lobar collapse. Reorientation of the remaining lung after lobectomy is reflected by a pleural-mediastinal interface after left-sided lobectomy, and by the orientation of three neofissures after right-sided lobectomy (1).

Left-Sided Lobectomy

After left-sided lobectomy, the remaining lobe hyperexpands and produces pleural-mediastinal interfaces that can mimic lobar collapse. Postoperative clips/staples may be difficult to detect after lobectomy, and collapse associated with unresectable tumors may have biopsy clips/staples without removal of the lobe. In some cases, left lower lobectomy on lateral images may mimic left upper lobe collapse.

Routine radiographic signs of lobar collapse have been described (2). Some interesting signs observed in upper lobe collapse (juxtaphrenic peak) and lower lobe collapse (upper triangle sign, flat waist sign, and "top of the knob" sign) have also been described (3, 4). These signs can all be seen in lobectomy, often more prominent than observed with a collapsed lobe.

Computed tomography (CT) of lobar collapse has been described (5, 6). CT is an excellent modality for demonstrating the anatomic reorientation of mediastinal structures in left-sided lobectomy and in illustrating many of the signs seen on routine postlobectomy radiographs (1).

Right-Sided Lobectomy

Many of the signs observed in left-sided lobectomy can be seen with right-sided lobectomy, although to a lesser extent (e.g., upper triangle and juxtaphrenic peak signs). Removal of a lobe on the left produces pleural-mediastinal interfaces with the remaining lobe. Removal of a lobe on the right produces new fissural orientations (neofissures) between the remaining two lobes. These patterns can be seen on routine radiographs and CT (1). They are fairly constant in presentation but at times can be quite confusing.

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Benign Tumors of the Chest

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Objectives

1. To describe the various types of benign tumors that develop within the chest.
2. To summarize the chest radiographic and CT findings of these tumors.

Introduction

Benign tumors of the chest are uncommon, accounting for 2–5% of primary thoracic tumors. Many varieties are rare. They can involve the lung parenchyma, tracheobronchial tree, pleura and mediastinum. The symptoms experienced by the patient depend on the location of the tumor. Tumors arising in the tracheobronchial tree may produce wheezing, cough, hemoptysis or obstructive pneumonia. Those occurring in the lung parenchyma are usually asymptomatic. Some of these benign tumors have the potential to undergo malignant transformation.

Hamartoma

Hamartomas are the most common benign lung tumor. They are present in 0.2% of autopsies and account for 6–8 % of solitary nodules. They occur twice as common in men as women. They are usually solitary (98%) but can be multiple. They arise from bronchial wall tissue with 93 % being located peripherally and 7% occurring endobronchially. Central cartilage is present in virtually all hamartomas. Calcification may be present. Other tissues may be encountered within these tumors including; myxomatous, fibroelastic, adipose, muscle, bronchial glands and chronic inflammatory cells. These tumors are usually asymptomatic and are found incidentally on chest radiographs. Endobronchial hamartomas may be associated with hemoptysis or airway obstruction. On chest radiograph they usually appear as a solitary round nodule measuring less than 3 cm in diameter. They tend to have sharp margins that may be lobulated. They may demonstrate slow growth on serial chest radiographs. Calcification is seen in 10–15 % on chest radiograph. Mottled irregular calcification with an appearance similar to popcorn is characteristic of these tumors. Cavitation is very rare. On CT calcium and fat may be seen - no calcium or fat 35%, diffuse calcium 4%, areas of fat 40%, and both calcium and fat 21%.

Solitary Fibrous Tumor of the Pleura

Solitary fibrous tumor of the pleura is an uncommon tumor whose etiology is unknown. It occurs more commonly in women with an average age of 50 years. It is not related to smoking or asbestos exposure. It originates from the submesothelial connective tissue with 80% arising from the visceral pleura. The tumor may be pedunculated. Approximately 50% are asymptomatic. In the remainder the patients may complain of chest pain, cough or dyspnea. Hypertrophic pulmonary osteoarthropathy occurs in 34% and resolves following resection of the tumor. Hypoglycemia is seen in 5% of patients who tend to have large tumors. Hypoglycemia is much more common in women than men. Most of these tumors behave in a benign fashion (87%). A smaller number of tumors (13%) act aggressively. The appearance of the tumors on chest radiograph is a function of the size of the tumor. Large tumors tend to have acute angles and may opacify the chest. Pedunculated tumors may move on serial radiographs. Calcification is seen in 7%. In aggressive tumors, a pleural effusion may be present. On CT the tumors appear as a well-defined, often lobulated mass. They are of soft tissue attenuation, although in large tumors calcification and necrosis may be seen. Following contrast administration areas of intense enhancement may be present as well as areas of nonenhancement which represent areas of necrosis, hemorrhage or myxoid degeneration.

Inflammatory Pseudotumor

Inflammatory pseudotumors represent an unusual response to inflammation. The majority arise within the lung parenchyma but may occur within bronchi or the trachea. They are composed of varying amounts of fibroblasts, histiocytes, lymphocytes and plasma cells. They tend to be seen in individuals less than 40 years of age and are encountered equally in men and women. They are the most common solitary mass in children. Many patients are asymptomatic, but may complain of hemoptysis, cough, fever, dyspnea or chest pain. They may produce bronchial obstruction with resultant recurrent infections. On chest

radiograph they usually appear as a solitary nodule which may be lobulated and range in size from 2 to 5 cm in diameter. The majority of cases are single nodules but some may be multiple. They rarely involve the mediastinum or central airway. On CT the nodule may have homogeneous or heterogeneous attenuation. Contrast enhancement is varied being reported as none, homogeneous, heterogeneous and rim.

Sclerosing Hemangioma

Sclerosing hemangioma is an uncommon tumor derived from alveolar pneumocytes. It occurs four times more common in women than men and usually is encountered in patients between 30 and 50 years of age. Most patients are asymptomatic with some patients experiencing hemoptysis, cough or chest pain. On chest radiograph the tumor appears as a well-defined nodule. Calcification is uncommon and cavitation not reported. On CT Enhancement following contrast administration has been reported. The tumors tend to increase between 96–157 HU.

Laryngeal Papillomatosis

Laryngeal papillomatosis is a viral illness that involves the upper airways of children. In most cases the disease is confined to the larynx, but in 5% it spread to the trachea and proximal bronchi. In less than 1% of cases, pulmonary involvement occurs. Early onset of the disease and multiple surgical pro-

cedures done to treat the laryngeal lesions are associated with an increased incidence of lung involvement. In the lung, cavities may form that are lined with squamous epithelium. On chest radiographs round nodules may be seen as well as thin or moderately thick walled cavities. Air fluid levels may be seen in infected cavities. Atelectasis due to endobronchial nodules may occur. The nodules may undergo malignant transformation into squamous cell carcinoma. The enlargement of nodules or development of intracavitary nodules should suggest the development of squamous cell carcinoma.

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Neuroendocrine Tumors of the Thorax

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Objectives

To review the radiologic and pathologic features of neuroendocrine tumors of the thorax.

Introduction

Neuroendocrine differentiation is a relatively common histologic finding in pulmonary neoplasms. Some cases present with a clinical hormone syndrome; others reveal a neuroendocrine nature by their morphologic or immunohistochemical characteristics.

Thoracic tumors with neuroendocrine (NE) features include those involving the lung (typical bronchial carcinoid, atypical bronchial carcinoid, large cell NE carcinoma, small cell carcinoma) and thymus (thymic carcinoid). Thoracic NE neoplasms have ultrastructural and immunohistochemical features that resemble NE cells found in normal lung. Their neuroendocrine properties include the ability to synthesize, store and secrete chemical messenger substances such as neuroamines and neuropeptides.

In the normal lung, NE cells occur as solitary cells along the basement membrane of the bronchial and bronchiolar epithelium. They also occur as nodular cell clusters called neuroepithelial bodies and form part of the diffuse neuroendocrine system, a concept introduced by Feyrter in 1938. Despite extensive research efforts using electron microscopy, immunohistochemical studies, and molecular probes for analyses of gene expression, the physiologic roles of NE cells in pulmonary physiology remain unclear. Various concepts of pulmonary NE cell hyperplasia, dysplasia, and neoplasia have been proposed.

Some investigators propose that NE tumors derive from normal NE cells; others hypothesize that they arise from pluripotent stem cells which differentiate with neuroendocrine features. The classification and terminology of these tumors has generated considerable discussion and some confusion. Pulmonary NE lung tumors are often considered as forming a spectrum of differentiation, from the least malignant typical carcinoid, which follows a relatively indolent clinical course, to the most aggressive and malignant small cell carcinoma.

Carcinoid Tumors

The majority of carcinoid tumors occur in the gastrointestinal tract (90%). The respiratory tract is the

next most common site of involvement; carcinoids occur less commonly in the thymus.

Typical Bronchial Carcinoid

Typical bronchial carcinoids (TBC) are uncommon tumors, representing 1% - 2% of all lung tumors. They affect females slightly more often than males (52:48 in one large series), with an average age at presentation of 45.5 years. Affected patients may be asymptomatic or present with symptoms related to bronchial obstruction. Systemic hormonal manifestations are rare, even though hormonal products can be demonstrated within cellular neurosecretory granules in all carcinoids. Approximately 2% of cases of bronchial carcinoids develop Cushing syndrome. Carcinoid syndrome is less commonly seen, usually in patients with carcinoid metastases to the liver.

Macroscopically, bronchial carcinoids are well-defined nodules or masses that may be lobulated. They often involve central airways, but may be peripheral and subpleural. Tumors may grow within the bronchial lumen exclusively, but invasion through the bronchial wall is common. Often, the bulk of tumor is extraluminal, with a smaller intraluminal component a so-called "iceberg" tumor. Central tumors may partially or completely occlude the bronchial lumen and produce distal atelectasis and pneumonitis.

Radiographically, bronchial carcinoids manifest most frequently as a well-defined hilar or perihilar mass, with or without distal parenchymal disease, and without lobar predilection. In some cases, the tumor is obscured by distal effects of the tumor (atelectasis, obstructive pneumonitis, recurrent pneumonia, and mucoid impaction). CT demonstrates the well-defined tumor nodule or mass and often shows its bronchial relationship. Approximately 30% of bronchial carcinoids exhibit calcification that may be punctate or diffuse. Marked homogeneous contrast enhancement occurs frequently, reflecting the rich vascular stroma of bronchial carcinoids, and may help to differentiate the central enhancing carcinoid from adjacent atelectatic or consolidated lung. CT may demonstrate regional lymph node enlargement which may represent metastases or hyperplasia resulting from associated recurrent or chronic distal infection.

Carcinoids have numerous high-affinity, somatostatin-binding sites which may be useful in detecting occult tumors producing ACTH-dependent

Cushing syndrome. Octreotide, a somatostatin analogue, has been used for scintigraphic localization of carcinoids.

The treatment for bronchial carcinoids is complete surgical excision. Patients may require lobectomy, bilobectomy, or pneumonectomy because of long-standing distal obstructive changes in the parenchyma.

Atypical Bronchial Carcinoid

In 1972, Arrigoni and colleagues recognized the more malignant character of atypical bronchial carcinoids (ABC). ABC share some morphologic features of typical carcinoids but are distinguished by the presence of nuclear pleomorphism, increased cellularity and mitotic activity, and areas of coagulative necrosis. They affect patients over a wide age range, but patients with atypical lesions are, on average, ten years older than those with typical carcinoid neoplasms.

Atypical carcinoids are indistinguishable from typical carcinoids by their imaging features and by their gross pathologic appearance. Atypical lesions are larger, on average, than typical carcinoids and metastasize more frequently to regional lymph nodes.

Large-Cell Neuroendocrine Carcinoma

Large-cell neuroendocrine carcinoma (LCNEC) affects patients with a median age of 59 years (range, 35 to 75 years). The tumor is highly associated with cigarette smoking. Microscopically, LCNEC is characterized by large cells with a neuroendocrine appearance by light microscopy, a high mitotic rate (higher than seen in atypical carcinoid), necrosis, and neuroendocrine features by immunohistochemistry. They are commonly peripheral tumors greater than 3 cm in diameter. In the recent WHO International Histological Classification of Tumors, LCNEC is considered a variant of large cell carcinoma.

Small Cell Carcinoma

Small cell carcinoma (SCC) is the most aggressive pulmonary neuroendocrine tumor. Although commonly discussed as a type of bronchogenic carcinoma, it is also categorized as a neuroendocrine tumor of the lung. SCC is strongly associated with cigarette smoking and typically affects males more often than females. All SCC are high grade malignant lesions. Microscopically, SCC is characterized by small, uniform oval cells with scant cytoplasm. Most are located centrally within lobar or main stem bronchi. The tumor grows rapidly with early and widespread metastases. SCC typically manifests radiographically as a hilar or perihilar mass, often with associated mediastinal widening. The tumor may be obscured by hilar or mediastinal lymphadenopathy, by distal atelectasis or post-ob-

structive pneumonitis. SCC is the most common primary pulmonary malignancy causing superior vena cava obstruction. Approximately 10% of SCC are located peripherally and are usually associated with spread to hilar or mediastinal lymph nodes.

While neuroendocrine differentiation is a hallmark of SCC, it is not found in every case. SCC may cause a clinical hormone syndrome by secreting ectopic hormones. The most commonly seen syndromes are Cushing syndrome and inappropriate secretion of antidiuretic hormone.

Thymic Carcinoid

Thymic carcinoids are rare primary malignant neuroendocrine neoplasms that are histologically similar to atypical bronchial carcinoids. Necrosis and local invasion are common histologic findings. In general, thymic carcinoids are more aggressive than their bronchial counterparts.

Affected patients have a mean age of 53 years, but tumors occur across a wide age range with a male:female ratio of 3:1. Most patients are symptomatic (chest pain, cough, weakness, pulmonary infection). Approximately 20% of patients present with a clinical hormone syndrome (MEN-Type 1 or 2, Cushing, hypercalcemia).

Radiologically, thymic carcinoid manifests as an anterior mediastinal mass that mimics thymoma. Tumors are characteristically well-defined, lobulated, and heterogeneous on cross-sectional imaging. Lymphadenopathy is present in 30% of cases. Evidence of local invasion and mass effect are present in 69% of cases. Pleura effusion is uncommon.

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The Spectrum of Appearance of Lymphoma

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Objectives

This lecture will present the wide diversity of appearances which lymphoma can demonstrate in the chest, with an emphasis of integration of modern imaging findings with newer classification systems based on molecular and developmental biology of lymphatic malignancies. After attending this lecture, thoracic radiologists will be more aware of the newer methods of subdividing the complex types of lymphoma, will be refreshed in their clinical correlation of the various diseases, and will be able to make useful predictions about diagnoses and outcomes based on modern imaging techniques.

Introduction

The classification of lymphoma is a complex topic which has undergone vast change in recent years due to an improved understanding of the development and molecular biologic aspects of lymphocytes and their control mechanisms. Previous classification schemes did not always correlate well with clinical presentations and response to treatment. It is hoped that as the genetics and signal transduction systems which control lymphatic development and malignancies are better understood, a more rational classification system can be developed which will not depend entirely on histologic appearance. As new subtypes of lymphoma are discovered, an understanding of their imaging features becomes particularly important for chest radiologists, since the chest is a very common site of involvement by many types of lymphoma.

The REAL Classification System

One of the most exciting developments in lymphoma has been the introduction of the REAL classification system (Revised European and American Lymphoma). This is the first comprehensive classification system which has been based on genetic markers and an understanding of the cell biology of lymphatic cell lines. In a recent Medline search, there were twenty-nine different search categories for the topic of lymphoma. The traditional breakdown of cases into Hodgkin's and non-Hodgkin's lymphoma is no longer adequate. Many cases which were originally

classified into one of these two categories, with modern immunohistochemical and genetic analytic techniques, are now reclassified into totally different groupings.

Hodgkin's Disease

Hodgkin's disease is the classic type of lymphoma that most often is confined to the chest. The commonest sites of thoracic involvement are the superior and anterior mediastinum. In general, involvement by Hodgkin's disease is contiguous, with adjacent nodal groups being sequentially recruited as the disease progresses. Other very commonly involved nodal groups for Hodgkin's disease are the subcarinal space and the hilar regions. Hodgkin's disease rarely involves a single nodal group, but most often several adjacent groups, usually bilaterally symmetric. Nodes may be quite large, and can occasionally demonstrate necrosis. Calcification prior to therapy is rare, although it is common after radiation therapy. Residual masses after apparently successful treatment are rather common, and can sometimes be quite large. This may relate to the relatively large amount of fibrosis in the commonest subtype of Hodgkin's disease, nodular sclerosis, which may remain after treatment as fibrotic masses. Gallium and PET scanning can be helpful in determining whether residual masses after treatment of Hodgkin's disease represent active tumor or fibrotic residua. When the lungs are involved at presentation, HD generally spreads contiguously via bronchovascular bundles into parenchyma adjacent to nodal disease.

While the cell of origin of Hodgkin's disease has long been a mystery, recently it is becoming more clear that Hodgkin's disease may comprise at least two disparate groups of lymphoproliferative disorder: so-called "classic HD" and "nodular lymphocyte predominant" HD. The Reed-Sternberg cell appears to be a monoclonal B-cell population, with the other associated cells probably representing a reaction to the neoplastic cells. It is also becoming clear that many of the cases included in past studies of HD were actually misclassified, and actually represented newly-described variants of non-Hodgkin's lymphoma, such as anaplastic large cell (Ki-1) lymphoma or T-cell-rich B-cell lymphoma.

Non-Hodgkin's Lymphoma

In contrast to Hodgkin's disease, non-Hodgkin's lymphoma (NHL) involves the chest slightly less frequently overall than Hodgkin's disease. When the chest is involved, NHL can skip nodal groups and can involve non-contiguous regions. The commonest site is still the superior and anterior mediastinum, but other sites, such as posterior mediastinum, pleura, breast, chest wall or lung are slightly more common overall than with HD. A single nodal group, or unilateral disease is more commonly seen in the chest with NHL than HD. While some series list pulmonary involvement as being more common in HD than NHL, this is probably due to difficulties in distinguishing between atelectasis adjacent to bulky nodes vs. contiguous spread, which is the main mode of pulmonary involvement in HD. Pulmonary nodules, or clear non-contiguous pulmonary involvement is much more common in NHL than in HD.

Immunodeficiency-related Lymphoma

B-cell lymphomas develop in some patients after immune suppression for organ transplants, including cardiac and lung transplants, as well as in patients with congenital abnormalities of immunity. Multiple malignant clones may co-exist, which is markedly different from typical monoclonal NHL. The highest rate occurs in lung transplants, where the disorder may arise in as many as 8% of patients, particularly those receiving anti-T-cell immune suppression. Almost all such tumors are EBV positive, and the incidence of tumors is greatly increased if the transplant recipient was EBV negative prior to receiving the transplant. The patterns of disease are highly variable, and can range from multiple nodal and extranodal sites, which can be difficult to treat, to a single nodal site, which can sometimes be cured with surgical resection. In AIDS patients, lymphomas often involve unusual nodal groups or extranodal sites. The lung, when involved, most often has the appearance of multiple peripheral nodules without associated hilar or mediastinal adenopathy.

Body Cavity Lymphoma

Some NHL's preferentially involve body cavities, including the peritoneum and pleura. These "body cavity" lymphomas generally occur in the setting of AIDS, and may present with apparently simple pleural effusions without adenopathy. The disorder is generally associated with human Herpesvirus-8 infection, and there may be a causative relationship with this virus, which is also involved in the pathogenesis of Kaposi's sarcoma.

Anaplastic Large Cell Lymphoma

Anaplastic Large Cell Lymphoma (also called Ki-1 lymphoma for the presence of the Ki-1 antigen, also called CD-30 and positive in Reed-Sternberg cells of Hodgkin's disease) accounts for about 2% of all NHL's, and is either of T-cell or null-cell phenotype. Most cases have a typical translocation producing a potent oncogene. A wide variety of nodal and extranodal sites may be involved, including skin, bone, pancreas, and rarely lung or pleura. Ki-1 lymphomas can also arise in the immune-suppressed or after some other lymphoproliferative disorder, such as Hodgkin's disease, mycosis fungoides, or lymphomatoid papulosis.

T-cell-rich B-cell Lymphoma (TCRBCL)

A relatively newly described variant of NHL, TCRBCL is recognizable with immunocytologic methods, and was often in the past misclassified as HD, in particular the lymphocyte-predominant variant. In this disease, a small number of malignant B-cells are surrounded by a large number of non-malignant reactive T-cells. While it is possible that this disorder is closely related to HD, in some series it appears to be much more aggressive in its clinical course, particularly when compared to the lymphocyte-predominant variant of HD, which has the best prognosis of all types of HD. It often involves the skin, but can also involve the lung and including cavitory lesions and association with peripheral bronchiolitis obliterans and organizing pneumonia.

Mediastinal Large Cell Lymphoma

An entity which can mimic the appearance of Hodgkin's disease is mediastinal large B-cell lymphoma. These tumors may contain fibrotic bands similar to nodular sclerosing HD, and have been called "sclerotic" in the past. Tumor masses may be slightly larger overall than in HD, and more often are necrotic. Signs of aggressive behavior, such as chest wall invasion, SVC syndrome, or presence of pleural and/or pericardial effusions are not uncommon.

Mantle Cell Lymphoma

One of the areas where reclassification of NHL's has had the most impact is in the small B-cell tumors, most of which are indolent. These were previously all grouped together, but are now divided into mantle cell, follicular and marginal zone/MALT lymphomas. Of these, the mantle cell lymphomas are the most aggressive, acting more like large cell lymphomas clinically. They are derived from naive B-cells, and can be nodular or diffuse. They are the cell type associ-

ated with multiple lymphomatous polyposis in the intestines. Characteristic translocations yielding over-expression of cyclin D1 occur, and the BCL-1 gene is rearranged, allowing confident molecular diagnosis in most cases. The disease occurs with a strong male predominance.

Follicular Lymphoma

Follicular lymphoma is the classic indolent low-grade lymphoma, often with moderately large nodes at many sites in the chest and abdomen. In these cells, the BCL-2 gene is rearranged, and over time, the tumor may accumulate P53 mutations that can lead to evolution to a higher grade lymphoma, with rapid growth and spread after years of relatively stable disease. The cell of origin is thought to be a germinal center B-cell.

MALT and Marginal Zone Lymphoma

Marginal zone and MALT lymphomas also derive from germinal center B-cells, and have characteristic genetic alterations. The marginal zone lymphomas are thought to represent the nodal variant of the extranodal MALT and BALT lymphomas.

Newer Imaging Methods

Classic methods of imaging lymphoma such as CT have always been hampered by the poor correlation between the anatomic sites of disease, as measured by nodal size, and disease activity. Better functional imaging is needed, particularly in lymphomas which contain a large amount of fibrotic tissue. Positron emission tomography (PET) shows promise as a better method for assessing response to therapy, as well as possible conversion of lower grade disease to higher grade disease through transformation. There is also some interest in use of perfusion imaging with CT to try to assess nodal disease activity more accurately. Recognition of more specific findings using present methods, such as the “wrap-around” sign of spine involvement by lymphoma (allowing distinction between metastases and bone lymphoma since both will show abnormal marrow signal and associated soft tissue mass, but in lymphoma the bony cortex remains intact between the marrow and mass). Some studies have suggested that even with crude measurements limited to nodal size, important prognostic information may be obtained by following response to treatment closely, both during chemotherapy and during radiation treatment. However, better more reproducible measurement methods would probably yield better results (for example, measurement of tumor circumference, rather than

simple determination of one or two tumor dimensions, or the cardiothoracic ratio). This is counter to some recent research that has suggested that alternate 10 mm slices are identical to contiguous slices for initial staging of lymphoma. If we are to make precise measurements of disease, rather than crude estimates of stage, more complete imaging would be required.

Conclusion

The classification of lymphomas has undergone a revolution in recent years. A simple breakdown into Hodgkin’s disease and non-Hodgkin’s lymphoma will no longer suffice. As advances are made in our understanding of these diseases, our radiologic familiarity with the appearance of the various subtypes must keep pace if we are to serve as useful consultants for our oncologist colleagues.

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Notes

A large L-shaped line forming a frame for notes. The line starts at the top right, goes down, then turns left and goes across the page, ending at the bottom left. The corner is rounded.