

Grande Hall March 12, 2000

HRCT of Diffuse Lung Disease

Moderator: Poonam Batra, MD

- 1:00–1:20 International Consensus Classification of Idiopathic Interstitial Pneumonias
David A. Lynch, MB
- 1:20–1:40 High-Resolution CT: Inhomogeneous Lung Opacity
W. Richard Webb, MD
- 1:40–2:00 HRCT Assessment of Complications Associated to Chronic Infiltrative Lung Diseases
Tomás C. Franquet, MD
- 2:00–2:20 Pulmonary Drug Toxicity: Pathogenesis and Radiologic Manifestations
Jeremy J. Erasmus, MD
- 2:20–2:40 Thoracic Manifestations of Collagen Vascular Disease: Imaging Findings
Steven L. Primack, MD
- 2:40–3:00 HRCT of the Lungs: The Caveats
David M. Hansell, MD
- 3:00–3:10 Questions
- 3:10–3:25 Break

Pulmonary Infections

Moderator: Arfa Khan, MD

- 3:25–3:45 Emerging Infectious Diseases of the Chest
Loren H. Ketai, MD
- 3:45–4:05 Community-acquired and Nosocomial Pneumonia: The Role of Radiology Revisited
Christian J. Herold, MD
- 4:05–4:25 Histoplasmosis: The Spectrum of Disease
Jeffrey R. Galvin, MD
- 4:25–4:45 Pulmonary Tuberculosis
Ann N. Leung, MD
- 4:45–5:05 Atypical Mycobacteria: Expanding Spectrum of Disease
Thomas E. Hartman, MD
- 5:05–5:15 Questions

Sunday, cont.



International Consensus Classification of Idiopathic Interstitial Pneumonias

Co-Sponsored by American Thoracic Society and European Respiratory Society

Participating Radiologists: David A. Lynch, MB, David Hansell, MB, Jeff Galvin, MD
Philippe Grenier, MD, Nestor Müller, MD

The American Thoracic Society and European Respiratory Society have jointly sponsored a multidisciplinary panel of clinicians, pathologists and radiologists to standardize classification of the idiopathic interstitial pneumonias (IIPs). The purpose of this presentation is to summarize the radiology portion of the document developed by the committee, and to solicit comments from interested members of the Society of Thoracic Radiology.

Problems with Existing Classifications

In 1969 Liebow described a group of interstitial pneumonias including desquamative interstitial pneumonia (DIP), usual interstitial pneumonia (UIP), bronchiolitis obliterans interstitial pneumonia (BIP), lymphocytic interstitial pneumonia (LIP), and giant cell interstitial pneumonia (GIP) (Table 1). Since the etiology of the lung disease could not be identified in many patients, the term "idiopathic" began to be used for this group of disorders and ultimately the term IIP was used. There has been some evolution in the specific entities included in this group of disorders. LIP and GIP were dropped since many of the former turned out to be lymphoproliferative disorders and

many of the latter were found to be hard metal pneumoconioses. Also, several entities were subsequently recognized including bronchiolitis obliterans organizing pneumonia (BOOP), acute interstitial pneumonia (AIP) and non-specific interstitial pneumonia/fibrosis (NSIP). (Table 1).

Several problems have complicated the topic of IIP. First the term idiopathic implies the interstitial pneumonia lacks any etiology, when in fact, a specific cause may have been overlooked. (Tables 1-2). All of these interstitial disorders are also found in settings where the etiology is known, particularly in collagen vascular disease. There has also been variation in the terminology and underlying concepts between investigators in North America and Europe. Finally these conditions are rare and few physicians have substantial experience with them outside of referral centers.

The classifications proposed by Liebow and Katzenstein (Table 1) were primarily based on pathology. However, the concept of idiopathic pulmonary fibrosis (IPF) was largely founded on a clinical approach and IPF is often used as a clinical diagnostic term. In Europe, the clinical term cryptogenic fibrosing alveolitis (CFA) has been used rather than

TABLE 1: CLASSIFICATION OF IDIOPATHIC INTERSTITIAL PNEUMONIAS			
Liebow 1969	Katzenstein, 1997	Muller & Colby 1997	New Proposed Classification
Usual Interstitial Pneumonia	Usual Interstitial Pneumonia	Usual Interstitial Pneumonia	Idiopathic Usual Interstitial Pneumonia/ Idiopathic Pulmonary Fibrosis
Desquamative Interstitial Pneumonia	Desquamative Interstitial Pneumonia/Respiratory Bronchiolitis Interstitial Lung Disease	Desquamative Interstitial Pneumonia	Idiopathic Desquamative Interstitial Pneumonia
Bronchiolitis Obliterans Interstitial Pneumonia		Bronchiolitis Obliterans Organizing Pneumonia	Idiopathic Bronchiolitis Obliterans Organizing Pneumonia
	Acute Interstitial Pneumonia	Acute Interstitial Pneumonia	Acute Interstitial Pneumonia/ Idiopathic Diffuse Alveolar Damage
	Non-specific Interstitial Pneumonia	Non-specific Interstitial Pneumonia	Non-specific Interstitial Pneumonia
Lymphocytic Interstitial Pneumonia			Idiopathic Lymphocytic Interstitial Pneumonia
Giant Cell Interstitial Pneumonia			

NOS= Not otherwise specified





TABLE 2: RADIOLOGIC FEATURES AND DIFFERENTIAL DIAGNOSIS OF THE IDIOPATHIC INTERSTITIAL PNEUMONIAS

Histologic pattern	Usual radiographic features	Typical distribution on CT	Typical CT findings	CT differential diagnosis
DAD	Progressive diffuse ground glass density/consolidation	Diffuse	Consolidation and ground glass opacity, often with lobular sparing. Traction bronchiectasis later	Hydrostatic edema Pneumonia Acute eosinophilic pneumonia
OP	Patchy bilateral consolidation	Subpleural	Consolidation. Small or large nodules	Infection, Vasculitis Sarcoidosis, Alveolar carcinoma, Lymphoma Eosinophilic pneumonia NSIP
NSIP	Non-specific abnormalities. Normal in 7%	Peripheral, subpleural, basal, symmetric	Ground glass attenuation Irregular lines Consolidation Honeycombing	UIP, DIP, OP 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
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
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

IPF. In the absence of collagen vascular disease the term *lone CFA* is used. The concept of IPF included the belief that DIP and UIP represented the cellular and fibrotic spectrum of a single disease, respectively. This contrasted with Liebow's thinking that UIP and DIP were separate entities.

Idiopathic Usual Interstitial Pneumonia/Idiopathic Pulmonary Fibrosis

The terms UIP and IPF have become more narrowly defined since they were originally proposed several decades ago. As more histologic subsets of IIPs have been recognized and as the high resolution computerized tomography scanning appearance of the IIPs have become better recognized, the diagnostic criteria for UIP and IPF have become more restricted. Currently, it is recommended that the term IPF be used only for patients with a UIP pattern of pulmonary fibrosis.

Radiologic Features

Eighty-five to 90% of patients with IPF have an abnormal chest radiograph at presentation. The commonest radiographic abnormality is peripheral reticular opacity, most marked at the bases, and often associated with honeycombing and lower lobe volume loss (Table 2).

UIP is characterized on CT by the presence of reticular opacities, often associated with traction bronchiectasis (Table 2). Honeycombing is common. Ground glass attenuation is common, but is usually less extensive than reticular abnormality.

Architectural distortion, reflecting lung fibrosis, is often prominent. Lobar volume loss is seen with more advanced fibrosis. The distribution of UIP on CT is characteristically basal and peripheral, though often patchy. On serial scans in treated patients, the areas of ground glass attenuation may regress, but more commonly progress to fibrosis with honeycombing. Honeycomb cysts usually enlarge slowly over time.

Reticular abnormality on CT correlates with fibrosis on histopathologic examination. Honeycombing on CT correlates with honeycombing on biopsy. When ground glass attenuation is associated with reticular lines, traction bronchiectasis or bronchiolectasis, it usually indicates histologic fibrosis. Isolated ground glass attenuation may correlate with evidence of inflammation, or with patchy fibrosis.

The CT pattern of UIP due to IPF is commonly indistinguishable from that found in UIP due to asbestosis and to collagen vascular disease, though the rate of progression of abnormality may be slower in patients with collagen vascular disease. The presence of pleural plaques usually helps to distinguish asbestosis from IPF. Patients with chronic hypersensitivity pneumonitis, or with end-stage sarcoidosis, may uncommonly develop a CT pattern identical to that of UIP. Hypersensitivity pneumonitis should be considered if poorly defined fine micronodules are seen, or if there is sparing of the lung bases. Sarcoidosis should be suspected if the cysts are large, or if peribronchovascular nodules are present.



Desquamative Interstitial Pneumonia/ Respiratory Bronchiolitis-Associated Interstitial Lung Disease (RBILD)

DIP and RB-ILD have recently been grouped together as part of a single spectrum since they have overlapping histologic features and may be difficult to distinguish histologically. In addition, they are both strongly associated with cigarette smoking. There are some who feel that RB-ILD should be excluded from this statement because it is clearly not an idiopathic pneumonia.

Radiologic Features RB-ILD

The commonest chest radiographic abnormality in RB-ILD is thickening of the walls of central or peripheral bronchi, seen in about 75% patients. Ground glass opacity is seen in 57%. The chest radiograph is normal in 14%. The CT findings of RB-ILD include centrilobular nodules, patchy ground glass attenuation, and thickening of the walls of central and peripheral airways (Table 2). Upper lobe emphysema is often present. Patchy areas of hypoattenuation are thought to be due to air trapping. Similar findings are seen in many asymptomatic smokers, but the findings in patients with RB-ILD are usually more extensive. The CT findings of RB-ILD are commonly reversible in patients who stop smoking and are treated with corticosteroids. The extent of centrilobular nodules on CT correlates with the degree of macrophage accumulation and chronic inflammation in respiratory bronchioles. Ground-glass attenuation correlates with macrophage accumulation in the alveolar space and alveolar ducts.

The CT features of RB-ILD overlap with those of hypersensitivity pneumonitis, DIP, and NSIP. RB-ILD differs from DIP in that the ground glass attenuation of RB-ILD is usually less extensive, more patchy and more poorly defined than in DIP. Centrilobular nodules are uncommon in DIP. However, RB-ILD may be indistinguishable from DIP and NSIP. Other entities, which may appear similar to RB-ILD, include hypersensitivity pneumonitis.

DIP

The chest radiograph is relatively insensitive for detection of DIP, and has been reported to be normal in between 3 - 22% of biopsy proven cases. Radiographic signs of DIP include widespread patchy ground-glass opacification, with a lower zone predilection and sometimes a peripheral predominance (Table 2). A granular or nodular pattern has been reported.

Ground-glass opacification is present on CT in all cases of DIP. This has a lower zone distribution in the majority (73%) of cases, a peripheral distribution in 59% of cases, and is patchy in 23%. The distribution is diffuse and uniform in 18%. Irregular linear opacities and reticular pattern are frequent (59%) but limited in extent and usually confined to the lung bases. Honeycombing is seen in less than one third of cases, and is usually peripheral and very limited in extent. The ground glass attenuation which is the hallmark of this disease is presumed to be due to a combination of diffuse intra-alveolar cells, and diffuse mild septal fibrosis. Irregular linear opacities and honeycombing are presumed to correlate with evidence of lung fibrosis.

On follow-up HRCT, patients receiving treatment can be expected to show partial or near complete resolution of areas of ground-glass opacification. Progression of ground-glass opacification to a reticular pattern occurs infrequently (less than 20%). Conditions that may be radiologically indistinguishable from DIP include RB-ILD, acute or subacute hypersensitivity pneumonitis, sarcoidosis, and infections such as *Pneumocystis carinii* pneumonia.

Acute Interstitial Pneumonia/ Idiopathic Diffuse Alveolar Damage

The chest radiograph reveals bilateral airspace opacification with air bronchograms in essentially all patients with AIP (Table 2). 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, especially in patients with ARDS. As DAD moves from the exudative to the organizing stage the radiograph shows less consolidation and presents a ground glass appearance with irregular linear opacities.

The most common findings on CT in patients with AIP are areas of ground glass attenuation, bronchial dilatation and architectural distortion (Table 2). The extent of the areas of ground glass attenuation correlates with disease duration. In the early exudative phase the lung shows bilateral areas of ground glass attenuation that are most often bilateral and patchy, with areas of focal sparing of lung lobules giving a geographic appearance. The ground glass opacities are neither distinctly subpleural nor central. Consolidation is seen in the majority of cases but is not as common as ground glass attenuation. The distribution is most often basilar in patients with AIP but can oc-





asionally be diffuse or rarely have an upper lobe predominance. In patients with classic ARDS the areas of consolidation are most often in the dependent area of lung suggesting alveolar closure from the weight and hydrostatic pressure of the more superior lung tissue. Intralobular linear opacities and subpleural honeycombing are seen in a 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 attenuation and consolidation. The most common residual HRCT findings are areas of hypoattenuation, lung cysts, reticular abnormality and associated parenchymal distortion occurring mainly in the non-dependent lung.

The radiologic differential diagnosis of AIP depends on the stage but can include the following: widespread infection, hydrostatic edema, hemorrhage, alveolar proteinosis, bronchioloalveolar cell carcinoma and DIP.

On CT-pathologic correlation, consolidation and ground glass attenuation, when not associated with traction bronchiectasis correlate with the exudative or early proliferative phase of DAD. Ground glass attenuation or consolidation associated with traction bronchiectasis correlates with the proliferative and fibrotic phases of DAD. The focal areas of apparent sparing usually show mild exudative changes. Interlobular septal thickening usually correlates with juxta-septal alveolar collapse and organization during the proliferative and fibrotic phases.

Bronchiolitis Obliterans Organising Pneumonia (Cryptogenic Organising Pneumonia)

The most common radiographic findings in cryptogenic organizing pneumonia are unilateral or bilateral areas of consolidation, without a predilection for any particular lung zone (Table 2). The distribution is usually patchy but may be subpleural in a minority of cases. Small nodular opacities are seen in 10-50% of cases. A minority of patients present with a reticular interstitial pattern. Large nodular opacities (>1 cm) are the presenting radiographic appearance in less than 20% of cases. Lung volumes are normal in up to 75% of cases. The remainder demonstrate reduced lung volumes.

Areas of air-space consolidation are present on CT in 90% of patients with COP (Table 2). CT demonstrates a subpleural or peribronchial distribution in up

to 50% of cases. Air bronchograms are a consistent finding when consolidation is present. Mild cylindrical bronchial dilatation is commonly evident in areas of consolidation. Small nodules (<10 mm) are usually seen along bronchovascular bundles and are evident in up to 50% of cases. Pleural effusions are rare.

Approximately 15% of patients with COP 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%).

The majority of patients with COP demonstrate radiographic improvement with treatment. However, the parenchymal abnormalities may change even without treatment. Most patients who respond to steroids are left with small residual opacities. If reticular opacities are present on the chest radiograph of patients with COP, the patient is less likely to respond to steroids, and may progress to lung fibrosis.

On CT-pathologic correlation, the nodular pattern of COP correlates with localized organizing pneumonia, centered on obliterated bronchioles, while the consolidative pattern correlates with more diffuse organizing pneumonia.

The radiographic differential diagnosis of organizing pneumonia in patients with areas of consolidation includes alveolar cell carcinoma, lymphoma, vasculitis, sarcoidosis, and infection (particularly tuberculosis or atypical mycobacterial infection). When the consolidation is subpleural, then the diagnosis of chronic eosinophilic pneumonia should be considered.

Inclusion of BOOP as IIP?

The inclusion of idiopathic BOOP among the idiopathic interstitial pneumonias has been debated. Arguments against inclusion include the fact that air-space involvement (airspace organization) is a prominent feature of the syndrome, the lesion is not primarily interstitial in a histologic sense, and classic cases are unlikely to be clinically mistaken for patients with usual interstitial pneumonia (idiopathic pulmonary fibrosis).

Arguments in favor of inclusion of idiopathic BOOP among idiopathic interstitial pneumonias include the facts that a minority of cases do clinically and radiologically mimic cases of UIP, pathologists have mistaken BOOP for UIP, and older clinical series of IPF have frequently included cases that, in retrospect, are now recognized as idiopathic BOOP. Another reason to include BOOP in this document is that it has presented one of the greatest problems in confusion of terminology with its use as both an idiopathic entity and a nonspecific pathologic lesion that occurs in a wide variety of settings.



Nonspecific Interstitial Pneumonia

The recognition that lung biopsies from some patients with idiopathic interstitial disease do not fit into any well-defined histologic patterns of idiopathic interstitial pneumonia led proposals of the terms "unclassified interstitial pneumonia" by Kitaichi in 1990 and NSIP by Katzenstein in 1994. Katzenstein et al divided NSIP into three major subgroups based on the amount of inflammation and/or fibrosis in the lung biopsies: Group I, primarily with interstitial inflammation; Group II, with both inflammation and fibrosis, and Group III, primarily with fibrosis.

Radiologic Features

Of 97 reported cases, the chest radiograph was abnormal in 91 (94%). Patchy parenchymal opacity was the most common radiographic feature in one study, but interstitial abnormalities have also been described (Table 2).

The CT findings in NSIP are more heterogeneous than those of the other idiopathic pneumonias. Analysis of a total of 85 patients from three recent studies shows that ground-glass attenuation is the predominant finding, being seen in 80%, and is the sole abnormality in about one third of cases. It is most commonly bilateral and symmetrical with subpleural predominance. Irregular linear opacities are common (49%). Parenchymal consolidation was present in 27%, and was generally bilateral, subpleural and basal. Consolidation was the only abnormality in 4%. Some differences among the three studies in the prevalence of honeycombing, nodules and bronchovascular bundle thickening suggest that the centers may have had different study populations, or different criteria for diagnosis of NSIP.

In the limited number of cases of NSIP who have had follow-up CT examinations after treatment, the abnormalities of NSIP generally improve. However, as in other interstitial lung diseases, honeycombing is presumably irreversible.

Differential Diagnosis

The CT differential diagnosis of NSIP depends on the CT pattern, which it exhibits. In a study of 50 patients, experienced observers considered the CT pattern indistinguishable from UIP in 32%, hypersensitivity pneumonitis in 20%, BOOP in 14% and other diagnoses in 12%. The heterogeneity of the offered diagnoses indicates that NSIP does not have a consistent CT pattern (which is at variance with the suggestion that NSIP represents a distinct entity). The non-specific appearance of CT makes it difficult to distinguish NSIP from the other interstitial pneumonias. In one investigation, the authors assessed the value of

high resolution CT in the differential diagnosis of 129 patients with histologically proven idiopathic interstitial pneumonias. Two independent observers were able to make a correct first choice diagnosis in an average of 71% cases of UIP, 79% of cases of COP, 63% of DIP, 65% of AIP, and in only 9% of cases of NSIP. In this study, NSIP was confused most often with DIP, and less often with COP and UIP. This study was retrospective, and subject to significant selection bias, because patients with classic CT changes of UIP generally did not undergo biopsy. Therefore these figures cannot be used to determine the accuracy of CT for differential diagnosis of the interstitial pneumonias.

On CT-pathologic correlation, ground glass attenuation corresponds to interstitial thickening due to varying amounts interstitial inflammation and fibrosis. When irregular linear opacities, and bronchial dilatation were present in areas of ground glass attenuation, interstitial fibrosis and microscopic honeycombing were seen on histology. Areas of consolidation correspond to areas of bronchiolitis obliterans organizing pneumonia, with or without microscopic honeycombing.

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High-Resolution CT: Inhomogeneous Lung Opacity

W. Richard Webb, MD

In this presentation, the attendee will learn: 1) the types of disease associated with the HRCT finding of inhomogeneous lung opacity, 2) how to use image studies to help distinguish among these causes, and 3) the differential diagnosis of diseases resulting in these patterns.

The presence of inhomogeneous lung opacity on high-resolution CT (HRCT) can be a perplexing diagnostic problem for the practicing radiologist. This appearance, sometimes referred to as a “mosaic pattern” [1] can reflect 1) ground-glass opacity secondary to infiltrative lung disease, 2) obstructive airway disease with reduced lung attenuation occurring because of reduced lung perfusion, or 3) vascular obstruction with reduced lung attenuation occurring because of reduced lung perfusion. The differentiation of these three causes of inhomogeneous lung opacity is of obvious value in diagnosis, and can be accomplished in most cases by careful attention to inspiratory and expiratory HRCT findings.

Ground-Glass Opacity

“Ground-glass opacity” (GGO) is nonspecific term referring to a hazy increase in lung attenuation not associated with obscuration of underlying vessels. This finding can reflect the presence of a number of diseases, and can be seen in patients with either minimal interstitial thickening or minimal air-space filling [2].

Although “ground-glass” opacity is a nonspecific finding, its presence is very significant. This finding usually (80%) indicates an acute, active, and potentially treatable process [2,3], such as pulmonary edema, alveolitis, nonspecific interstitial pneumonia

(NSIP), desquamative interstitial pneumonia (DIP), active idiopathic pulmonary fibrosis (UIP), pneumonia (particularly pneumocystis carinii pneumonia), alveolar proteinosis, hypersensitivity pneumonitis, and sarcoidosis. Because of its association with active lung disease, the presence of this finding often leads to lung biopsy, depending of the clinical status of the patient.

When ground-glass opacity is associated with other findings of infiltrative disease such as interlobular septal thickening or other patterns of reticulation (i.e. “crazy paving”), or nodules, it can accurately be correctly identified as the cause of inhomogeneous lung opacity. Also, a pattern in which the areas of higher attenuation are centrilobular almost always represents ground-glass opacity with a centrilobular distribution. This pattern is uncommonly the result of vascular disease and mosaic perfusion, and in such cases it may actually reflect pulmonary edema (i.e. ground-glass opacity). GGO may also result in very ill-defined and poorly-marginated areas of increased opacity, lacking the sharply marginated and geographic appearance usually seen in patients with mosaic perfusion. In some patients, ground-glass opacity can be diagnosed simply because lung looks too dense, although this is quite subjective, and depends on using consistent window settings.

On expiratory scans, patients with patchy ground-glass opacity show a similar increase in opacity in both the relatively lucent and opaque lung regions. In other words, on expiratory scans, there is no accentuation of the inhomogeneity, although inhomogeneity persists.

In some patients with ground-glass opacity, air trapping may also be present. This combination often indicates mixed infiltrative and obstructive disease, and will be discussed below.

Mosaic Perfusion

Inhomogeneous lung attenuation may reflect “mosaic perfusion”, a term used to describe patchy lung attenuation resulting from patchy or abnormal lung perfusion. Since about 50% of lung density is blood, reducing lung perfusion results in a significant reducing in lung attenuation visible on HRCT.

Mosaic perfusion usually results from a) patchy airway obstruction with reduced ventilation of lung

FINDINGS OF GROUND-GLASS OPACITY

1. Associated findings of infiltrative disease (e.g. crazy paving, consolidation, or nodules)
2. Centrilobular opacities
3. Poorly marginated, non-anatomic, non-geographic opacities
4. No disparity in vascular size in regions of differing density
5. Absence of air-trapping on post-expiratory scans
6. Lung looks too dense (compared to what you are used to)



regions resulting in reduced perfusion on the basis of reflex vasoconstriction, or b) vascular obstruction, usually chronic. In patients having high-resolution CT, mosaic perfusion most often reflects obstructive airway disease such as cystic fibrosis or constrictive bronchiolitis [4,5]. In patients with chronic vascular obstruction, the diagnosis is usually suspected clinically, and spiral CT with contrast infusion is the imaging technique of choice.

The presence of smaller vessels in the blacker or less dense lung regions is exceedingly helpful in diagnosing mosaic perfusion as the cause of inhomogeneous lung attenuation; vessels are often reduced in size because of reduced blood flow in patients with this finding. For example, in a series of 48 patients with mosaic perfusion, primarily due to airway disease [5] observed smaller vessels in areas of low attenuation in 93.8% of cases. In patients with inhomogeneous lung attenuation due to vascular obstruction, decreased vessel size is also common [6,7]. On the other hand, this finding may be subtle and difficult to observe in some cases. In a blinded study by Arakawa et al [4] of patients with inhomogeneous lung opacity of various causes, only 68% of patients with airway or vascular disease were thought to show small vessels in areas of low attenuation.

Airways Disease with Mosaic Perfusion

In patients with mosaic perfusion resulting from airways disease, abnormal dilated or thick-walled airways may be visible in the blacker lung regions, an important clue to the correct diagnosis. In one study [8], abnormal airways were seen in 70% of patients with airways disease and mosaic lung attenuation. This appearance can be seen in a variety of airway diseases including bronchiectasis, cystic fibrosis, and constrictive bronchiolitis. In patients with mosaic perfusion secondary to airways disease, lobular areas of low attenuation are common. In patients with vascular disease as a cause of mosaic perfusion, areas of low attenuation are usually larger than lobules.

In a study of 70 patients with bronchiectasis [9], areas of decreased attenuation due to abnormal lung ventilation or air trapping were visible on inspiratory scans in 20% of lobes, and on expiration (air trapping) in 34%. Areas of decreased attenuation were more prevalent in lobes with severe bronchiectasis (59%), or localized bronchiectasis (28%), than in those without bronchiectasis (17%). The presence of decreased attenuation on expiration was also associated with mucus plugging; it was seen in 73% of lobes with large mucus plugs and in 58% of those with centrilobular mucus plugs. There was also a correlation ($r = 0.40$, $p < .001$) between the total bronchiectasis extent and severity and the extent of decreased attenuation shown on expiratory CT. In 55 patients who had pulmonary function tests, the extent of expiratory attenuation abnormalities were inversely related to measures of airway obstruction such as FEV_1 and FEV_1/FVC . In patients with constrictive bronchiolitis, inspiratory HRCT often shows patchy areas of mosaic perfusion. Bronchial or bronchiolar dilatation may be associated.

Vascular Disease with Mosaic Perfusion

Inhomogeneous lung attenuation is common in patients with chronic pulmonary thromboembolism (CPE), and decreased vessel size in less opaque regions is commonly visible. Findings of pulmonary artery hypertension may be of value in making this diagnosis and distinguishing it from airways disease.

In a study of pulmonary parenchymal abnormalities in 75 patients with chronic pulmonary embolism, 58 patients (77.3%) showed mosaic perfusion with normal or dilated arteries in areas of hyperattenuation [7]. In a study of patients with pulmonary hypertension due to chronic pulmonary thromboembolism, pulmonary hypertension of other causes, and a variety of other pulmonary diseases, HRCT was thought to show mosaic perfusion in all patients with CPE [6]. Considerably more variation in vessel size in different lung regions was also visible in the patients with CPE.

FINDINGS OF MOSAIC PERFUSION IN AIRWAYS DISEASE

1. Associated findings of airways disease (e.g. bronchiectasis)
2. Well marginated, segmental or lobular, geographic opacities
3. Areas of low attenuation may be lobular
4. Disparity in vascular size in regions of differing density
5. Air-trapping on post-expiratory scans
6. Lung looks too lucent (compared to what you are used to)

FINDINGS OF MOSAIC PERFUSION IN VASCULAR DISEASE

1. Associated findings of pulmonary hypertension (e.g. enlarged main PA)
2. Well marginated, segmental or lobular, geographic opacities
3. Lobular areas of low attenuation unusual
4. Disparity in vascular size in regions of differing density
5. No air-trapping on post-expiratory scans
6. Lung looks too lucent (compared to what you are used to)



Overall, HRCT had a sensitivity of 94-100% and a specificity of 96-98% in diagnosing CPE [6].

The frequency with which a mosaic pattern of lung attenuation is seen on CT in patients with various causes of pulmonary artery hypertension (PAH) has also been studied [10]. Twenty-one patients had PAH due to lung disease; 17 patients, due to cardiac disease; and 23 patients, due to vascular disease. Of the 23 patients with PAH due to vascular disease, 17 patients (74%) had a mosaic pattern of lung attenuation; 12 of these had chronic pulmonary embolism. Of the 21 patients with PAH due to lung disease, one patient (5%) had a mosaic pattern of lung attenuation.

Among the 17 patients with PAH due to cardiac disease, two patients (12%) had a mosaic pattern of lung attenuation [10]. Thus, a mosaic pattern of lung attenuation was seen significantly more often in patients with PAH due to vascular disease than in patients with PAH due to cardiac or lung disease.

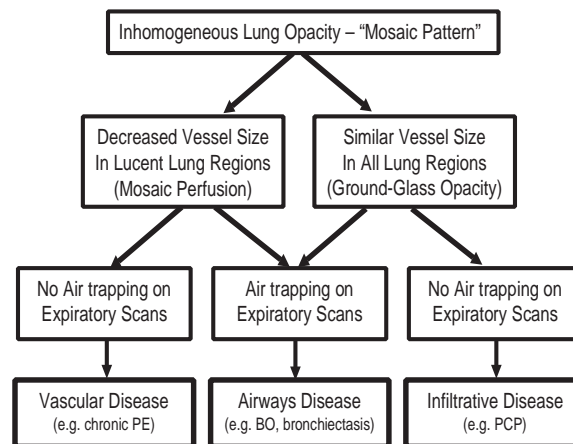
Use of Expiratory Scans in Patients with Mosaic Perfusion

In normal subjects, lung increases in attenuation on expiratory scans. In patients with air trapping, abnormal lung remains lucent on expiration, while normal lung regions increase in attenuation in a normal fashion.

Obtaining expiratory scans thus accentuates lung inhomogeneity in patients with mosaic perfusion due to air-trapping and airway disease [11,12] and is quite helpful in making this diagnosis. In a study by Arakawa et al [12], the accuracy of HRCT in diagnosing airways disease as a cause of inhomogeneous lung attenuation increased from 84% to 100% with the use of expiratory scans.

In patients with mosaic perfusion due to vascular disease, air trapping is not usually seen. However, in a recent study of patients with inhomogeneous lung attenuation of various causes [8], air trapping was thought to be present on expiratory scans in some patients with vascular disease when scans were viewed blindly.

In most patients with infiltrative disease and ground glass opacity, expiratory scans show a similar increase in opacity in both the relatively opaque and lucent regions. In patients with infiltrative disease and subtle GGO, expiratory scans can increase confidence and diagnostic accuracy. In a study by Arakawa et al [12], the accuracy of HRCT in diagnosing infiltrative disease as a cause of inhomogeneous lung attenuation increased from 81% to 89% with the use of expiratory scans. Furthermore, in some patients with inspiratory scans suggesting ground-glass opacity, expiratory scans sometimes show air trapping and mosaic perfusion to be the cause of the inhomogeneous lung opacity. Taking into account these various possi-



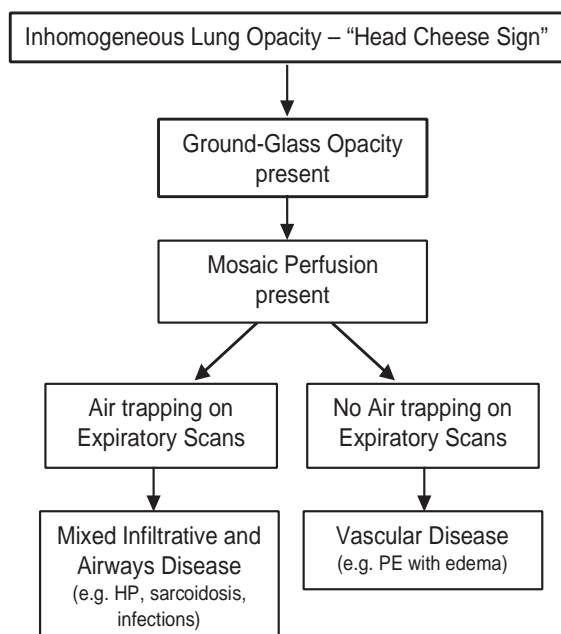
bilities, the following algorithm can be used to help diagnose patients with a mosaic pattern.

Using a combination of inspiratory and expiratory HRCT findings, most cases of inhomogeneous opacity can be correctly classified as mosaic perfusion due to vascular disease, mosaic perfusion due to airway disease, or ground-glass opacity. In two recent studies [4,8], it has been shown that infiltrative disease, airways disease, and vascular disease can be differentiated in a large majority of cases. In one study [8], the type of disease was identified correctly at CT in 81-83% of cases. In the second [4], a correct diagnosis was made in 79% of cases based on inspiratory scans alone, and 92% using both inspiratory and post-expiratory scans.

Mixed Disease and the “Head-Cheese Sign”

In occasional patients, inspiratory scans show a mixture of several types of abnormality, i.e. ground-glass opacity (or consolidation), normal lung, and mosaic perfusion. This combination has been termed the “head-cheese sign” because of its resemblance to a disgusting sausage [Chung MH, et al, STR 1998], and is usually indicative of mixed infiltrative and obstructive disease, usually associated with bronchiolitis. In patients with this appearance, the presence of GGO can usually be diagnosed on the inspiratory images, and obstruction can be confirmed on the expiratory scans [4]. The most common causes of this pattern are hypersensitivity pneumonitis, sarcoidosis, and, in our experience, infections with associated bronchiolitis.

Evidence of air-trapping in association with ground-glass opacity is a common HRCT finding in both the subacute and chronic stages of hypersensitivity pneumonitis [13]. In a series of 22 patients with hypersensitivity pneumonitis, HRCT scans with limited number of expiratory images were correlated



with pulmonary function tests [13]. Areas of decreased attenuation, mosaic perfusion, and air trapping were seen in 19 patients and were the most frequent finding. In addition, the extent of decreased attenuation correlated well with severity of functional index of air-trapping as indicated by increased residual volume ($r = .58, p < .01$).

Air Trapping in Patients with Normal Inspiratory Scans

In some patients, inhomogeneous lung attenuation is visible on expiratory scans in the presence of normal inspiratory scans. In one study [14], HRCT in 273 consecutive patients with suspected diffuse lung disease were reviewed. Forty-five patients showed air trapping on expiratory HRCT scans. Of these 45 patients, inspiratory high-resolution CT scans showed abnormal findings in 36 (bronchiectasis, bronchiolitis obliterans, asthma, chronic bronchitis, and cystic fibrosis). In the remaining 9 patients, inspiratory HRCT showed normal findings; conditions in these nine patients included bronchiolitis obliterans ($n = 5$), asthma ($n = 3$), and chronic bronchitis ($n = 1$). Results of pulmonary function tests in patients with air trapping and normal findings on inspiratory scans were intermediate, falling between those of patients with normal findings on inspiratory and expiratory HRCT scans and those of patients with air trapping

and abnormal findings on inspiratory scans. This appearance can also be seen in patients with hypersensitivity pneumonitis.

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HRCT Assessment of Complications Associated to Chronic Infiltrative Lung Diseases

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High-resolution computed tomography (HRCT) is currently the imaging modality of choice in the evaluation and diagnosis of chronic infiltrative lung diseases (CILD). HRCT can be used to confirm the pulmonary abnormality, to establish an specific diagnosis, and to diagnose possible associated complications. Complications associated to CILD are large and diverse and may affect pulmonary parenchyma, airways, mediastinum, or pleura. Accurate interpretation of HRCT findings and confident diagnosis of parenchymal complications relies heavily on pattern recognition. In certain disease entities the HRCT characteristics are diagnostic.

The aim of this presentation is to summarize the HRCT findings of a variety of complications associated with the most common CILD and to describe the characteristic findings of each involvement.

Parenchymal Complications

Diffuse alveolar hemorrhage (DAH) may complicate a variety of diffuse lung diseases including systemic lupus erythematosus, collagen vascular disorders, and lymphangioleiomyomatosis. The most typical CT findings in patients with diffuse alveolar hemorrhage is the presence of interlobular septal thickening and ground glass opacity. This pattern, in the correct clinical context, may be strongly suggestive of DAH.

Pulmonary infections are somewhat increased in CILD and its presence may be difficult or impossible to evaluate at radiography. Lung infection may complicate a variety of diffuse lung diseases such as systemic lupus erythematosus, IPF, alveolar proteinosis, coal worker's pneumoconiosis, and silicosis. Infection

Parenchymal Complications Associated with Chronic Infiltrative Lung Diseases

	Hemorrhage	Infection	Aspiration Pneumonia	Neoplasia	Ossification	Cavities and Bullae	Mycetoma
Rheumatoid Arthritis		+		+		++	
SLE	+++	+++					
PSS			+++	+++			
pSS	+			Lymphoma		+	
PM/DM			+++	++			
AS						+	+
IPF/UIP				+++	+		
Sarcoidosis						++	++
LAM	++	+					
Silicosis		Tuberculosis		+		+	+
Alveolar Proteinosis		+++					

SLE: Systemic Lupus Erythematosus; PSS: Progressive Systemic Sclerosis; pSS: Primary Sjögren's Syndrome; PM/DM: Polimyositis/Dermatomyositis; AS: Ankylosing Spondylitis; IPF/UIP: Idiopathic Pulmonary Fibrosis/Usual Interstitial Pneumonia; LAM: Lymphangioleiomyomatosis.



is the commonest pulmonary complication in SLE accounting for about 50% of pleuropulmonary manifestations. Patients under high dose of steroid administration, cytotoxic agents or with renal disease are especially susceptible to pulmonary infection. For unknown reasons, patients with silicosis have a particularly increased risk of tuberculosis. The frequency of tuberculosis increases with the more advanced silicosis stages. However, there are no definite radiographic features that help distinguish silicosis from intercurrent tuberculosis.

Esophageal dysmotility predisposes to aspiration pneumonitis and bronchiolitis. Aspiration pneumonia appears to be a serious pulmonary complication in patients with PSS, polymyositis and dermatomyositis being an important cause of morbidity in such patients. Aspiration bronchiolitis can be diagnosed by the presence of tubular or branched bronchioles distended with air or mucus. Patchy areas of consolidation may be observed in association with bronchiolitis due to transbronchial spread of aspirated material into peribronchial space.

Rounded atelectasis is a peripheral form of pulmonary collapse that is usually encountered incidentally on thoracic imaging studies. The disorder almost always occurs in patients with an underlying benign pleural inflammatory condition such as asbestosis, tuberculosis, trauma, pulmonary infarction, uremia, and chronic or organizing pleural effusion. Computed tomography has become the imaging technique of choice in the diagnosis of rounded atelectasis and, in the appropriate clinical setting, can avoid unnecessary interventional procedures. The essential radiologic features that suggest rounded atelectasis include the presence of pleural thickening adjacent to the mass and the comet-tail sign

Bronchogenic carcinoma. Adenocarcinoma is the most frequently diagnosed cell type (50% of all bronchogenic carcinomas). Adenocarcinoma has also been associated with concomitant lung disorders that produce focal or diffuse fibrosis such as IPF, connective tissue diseases, asbestosis, coal worker's pneumoconiosis, and silicosis. Although bronchioloalveolar cell carcinoma (BACC) accounts for less than 10% of primary lung tumors, up to 50% of BACC is associated with previous scarring in the lung. Idiopathic pulmonary fibrosis, rheumatoid lung, scleroderma, and lipoid pneumonia can develop either localized or diffuse BACC.

Lymphoid infiltration of extranodal sites are prominent features of Sjögren's syndrome (SS). For this reason, patients with SS have a high risk of developing primary non-Hodgkin lymphoma of the lung. Radiographically, pulmonary lymphoma associated with SS may present as a diffuse interstitial pro-

cess or as multiple nodular infiltrates. In our series of 50 patients with primary Sjögren's syndrome, one patient (2%) had multiple ill-defined pulmonary opacities with an associated air-bronchogram visible on CT. Lung biopsy obtained by thoracotomy demonstrated a low grade B-cell lymphoma.

Sarcoidosis is a systemic disease, of unknown etiology with protean thoracic manifestations. Uncommonly, sarcoidosis can cause bullae in the mid and upper lung zones that occasionally may harbour mycetomas. Sarcoidosis is the second commonest cause of mycetoma formation after tuberculosis.

Pulmonary hypertension occurs in approximately 10% of patients with the CREST variant of scleroderma. This is a primary form of pulmonary hypertension and occurs independent of the degree of pulmonary fibrosis.

Disseminated pulmonary ossification has been described in patients with end-stage pulmonary fibrosis.

Airway Complications

Small airways abnormalities are often associated with CILD. Bronchiectasis and bronchiolitis obliterans with airway obstruction is being increasingly recognized as a complication in rheumatoid arthritis (RA) and in other collagen vascular diseases. Thin-section CT is a sensitive technique in assessing pulmonary involvement in patients with primary Sjögren's syndrome. Interstitial lung disease and bronchiolar inflammatory changes are common abnormal findings in this disorder. Typical HRCT findings shows multiple scattered areas of air-trapping consistent with small airway obstruction reflecting the patchy ventilation and perfusion of lung which results from air trapping.

Bronchiolitis obliterans organizing pneumonia (BOOP) has also been reported in patients with rheumatoid arthritis under gold salts therapy.

In the chronic stage of CILD, traction bronchiectasis is a reliable indication of irreversible lung fibrosis.

Pleural Complications

Lymphangioleiomyomatosis (LAM) is a rare disease of women of child-bearing age characterized by widespread proliferation of atypical smooth muscle cells in the bronchial tree, alveolar septa, and pulmonary and lymphatic vessels. Such patients are at high risk for chylous pleural effusions and spontaneous pneumothoraces.

Langerhan's cell histiocytosis is HRCT findings in LCH include: peribronchial and centrilobular nodules, 1-5 mm in size; cavitary nodules; and thin walled lung cysts, with bizarre shapes, usually under 1 cm in size. Spontaneous pneumothorax occurs in 20% of adult cases.



Airway Complications Associated with Chronic Infiltrative Lung Diseases						
	Bronchiectasis	Bronchiolitis obliterans	Aspirative Bronchiolitis	BOOP	Traction bronchiectasis	Cysts
Rheumatoid Arthritis	++	++		++	++	++
PSS		+	+++			
PSS	+++	+++				+++
IPF/UIP					+++	+++
Sarcoidosis					+++	++
LAM						++

PSS: Progressive Systemic Sclerosis; pSS: Primary Sjögren's Syndrome; IPF/UIP: Idiopathic Pulmonary Fibrosis/Usual Interstitial Pneumonia; LAM: Lymphangiomyomatosis.

Pleural Complications Associated with Chronic Infiltrative Lung Diseases				
	Pneumothorax	Chylothorax	Pleural Calcification	Pleural effusion
pSS				++
SLE				+++
IPF/UIP	+++			
Sarcoidosis	++			
LAM	++	++		
Linfangiomyomatosis			++	++
LCH	++			

pSS: primary Sjögren's syndrome. SLE: Systemic Lupus Erythematosus. IPF/UIP: Idiopathic Pulmonary Fibrosis/Usual Interstitial Pneumonia; LAM: Lymphangiomyomatosis; LCH: Langerhan's cell Histiocytosis.

Mediastinal Complications Associated with Chronic Infiltrative Lung Diseases				
	Adenopathy	Egg-shell Calcification	Pneumo-mediastinum	Neoplasia
Rheumatoid Arthritis			+	
PSS	++		+++	
pSS	+++			Lymphoma Thymoma
IPF/UIP	++		+++	
Sarcoidosis		++	++	

PSS: Progressive Systemic Sclerosis; pSS: Primary Sjögren's Syndrome; IPF/UIP: Idiopathic Pulmonary Fibrosis/Usual Interstitial Pneumonia.

Pneumothorax, which is a common complication of both LCH and LAM, may also spontaneously occur in IPF. From a series of 78 patients with IPF, spontaneous extraalveolar air (pneumomediastinum and/or pneumothorax) was demonstrated at HRCT in 11.5% of cases. The process begins by rupture of weaker alveoli along the margins of the interlobular septa and vascular structures. Air dissects along the interlobular septae and perivascular spaces producing interstitial emphysema. Interstitial air may then rupture into the pleural space causing pneumothorax or into the mediastinum causing pneumomediastinum.

Diffuse pulmonary lymphangiomas is distinct from LAM, lymphangiectasis and pulmonary capillary hemangiomas. The main abnormalities seen on conventional and HRCT are smooth thickening of the interlobular septa and bronchovascular bundles, patchy bilateral areas of ground-glass attenuation, and a diffuse increased attenuation of the mediastinal fat. Bilateral pleural effusions, smooth thickening of the pleura, and calcified pleural thickening have been reported in association with this uncommon disease.

Mediastinal Complications

Etiologies of mediastinal lymphadenopathy include metastatic neoplasia, lymphoma, granulomatous disease, and lymphadenitis. Mediastinal lymph nodes are commonly visualized with CT in patients with chronic interstitial lung diseases. Several studies have reported enlarged mediastinal nodes in association with a variety of chronic interstitial lung disorders. The detection of lymphadenopathy in patients with idiopathic pulmonary fibrosis (IPF) can be the cause of considerable clinical concern. The risk of developing lung cancer in IPF patients has been documented in many reports. However, it should be emphasized that enlarged mediastinal lymph nodes in these patients not necessarily indicate the presence of an associated malignancy. Some authors have reported in their series that 13 (93%) of 14 patients with IPF had enlarged mediastinal nodes. Others, however, have found lymph node enlargement with a lower prevalence (41% of cases). The cause of enlargement of the mediastinal lymph nodes is not yet understood.



Eggshell calcification in mediastinal lymph nodes is commonly seen in silicosis. Other causes of mediastinal eggshell calcifications include sarcoidosis and amyloidosis.

Thymoma is the most common primary neoplasm of the thymus and the most common primary tumor of the anterior-superior mediastinum. Some thymomas are discovered during the evaluation of patients with associated systemic disorders such as myasthenia gravis, pure red cell aplasia, or hypogammaglobulinemia; thymoma is an infrequent complication of primary Sjögren's syndrome.

Summary

High-resolution CT has significantly improved understanding of the morphologic distribution and appearances of CILD. The radiologist plays an important role in detecting possible complications associated with CILD.

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Pulmonary Drug Toxicity: Pathogenesis and Radiologic Manifestations

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Introduction

Pulmonary drug toxicity is a common and possibly under-diagnosed cause of acute and chronic lung disease. There are numerous agents with potential pulmonary toxicity. These include cytotoxic drugs such as bleomycin, methotrexate and cyclophosphamide and non-cytotoxic drugs such as nitrofurantoin, sulfasalazine and amiodarone.

The histopathologic manifestations of pulmonary drug toxicity are protean, but often stereotypical. These reactions include diffuse alveolar damage (DAD), chronic interstitial pneumonia, bronchiolitis obliterans organizing pneumonia (BOOP), eosinophilic pneumonia (EP), obliterative bronchiolitis, and pulmonary hemorrhage, edema, hypertension or veno-occlusive disease. The clinical and radiologic manifestations of pulmonary drug toxicity generally reflect the underlying histopathologic processes. This talk will review the:

- (1) most common histopathologic manifestations of pulmonary drug toxicity and agents that typically cause these abnormalities (Table 1) and
- (2) radiographic and CT features of drug toxicity

Histopathologic Patterns with Radiologic Correlation

Diffuse Alveolar Damage (DAD)

Diffuse alveolar damage is a descriptive term for the sequence of events that occur after acute severe lung injury. It is one of the most common manifestations of drug-induced lung injury and results from necrosis of type I pneumocytes and alveolar endothelial cells. Histopathologically, DAD is divided into two phases, an acute exudative phase and a late reparative phase. The exudative phase is most prominent in the first week after lung injury and is characterized by intra-alveolar and interstitial edema and hyaline membranes composed of necrotic epithelial cells and protein-rich fluid. The reparative phase typically occurs after one or two weeks and is characterized by proliferation of type II pneumocytes and extensive interstitial fibrosis. Depending on the severity of the initial injury, fibrosis can improve, remain stable, or progress to honeycomb lung.

Table 1: Principal Histopathologic Manifestations of Pulmonary Drug Toxicity

MECHANISM OF INJURY	DRUGS
DIFFUSE ALVEOLAR DAMAGE (DAD)	Bleomycin, Busulfan, BCNU, Cyclophosphamide, Mitomycin, Melphalan, Gold Salts
CHRONIC INTERSTITIAL PNEUMONIA (CIP)	Amiodarone, Methotrexate, BCNU, Chlorambucil
BRONCHIOLITIS OBLITERANS ORGANIZING PNEUMONIA (BOOP)	Bleomycin, Gold Salts, Methotrexate, Amiodarone, Nitrofurantoin, Penicillamine, Sulfasalazine, Cyclophosphamide.
EOSINOPHILIC PNEUMONIA	Penicillamine, Sulphasalazine, Nitrofurantoin, Nonsteroidal Anti-inflammatory Drugs, Para-aminosalicylic Acid.
PULMONARY HEMORRHAGE	Anticoagulants, Amphotericin B, Cytarabine (Ara-C), Penicillamine, Cyclophosphamide.

Drugs that most commonly produced this type of lung injury are bleomycin, busulfan, carmustine (BCNU), cyclophosphamide, melphalan, mitomycin, and gold salts.

Affected patients usually present with dyspnea, cough and occasionally fever. Chest radiographs show bilateral heterogeneous or homogeneous opacities, often in a mid and lower lung distribution. Progression to diffuse opacification is common. Fibrosis typically develops within one week, but may not be evident on chest radiographs initially. With progressive fibrosis, however, marked architectural distortion and honeycomb lung can occur.

Chronic Interstitial Pneumonia

Although all forms of interstitial pneumonia have been reported as manifestations of pulmonary drug toxicity, the most commonly encountered form is termed chronic (or cellular) interstitial pneumonia (CIP). CIP is characterized by scattered areas of expansion of the interstitium by mononuclear inflammatory cells, mild interstitial fibrosis and reactive, hyperplastic type II pneumocytes. Interstitial inflammation is typically more homogeneous and more cellular than that seen in cases of usual interstitial pneumonia. CIP is histopathologically similar to non-specific interstitial pneumonia. However, the latter term is reserved for patients with collagen vascular disease or in whom the disease occurs idiopathically.



CIP occurs most commonly as a manifestation of amiodarone, methotrexate or carmustine (BCNU) toxicity. Gold salts and chlorambucil are less common causes.

Affected patients present with insidious onset dyspnea and nonproductive cough, usually within several months of initiating therapy. Low-grade fever and malaise are common constitutional complaints. Diffusing capacity for carbon monoxide (D_LCO) is characteristically decreased. Chest radiographs usually show diffuse heterogeneous opacities. Early HRCT scans may show only scattered or diffuse areas of ground glass opacity. Later, findings of fibrosis (traction bronchiectasis, honeycombing) predominate in a basal distribution.

Bronchiolitis Obliterans Organizing Pneumonia (BOOP)

Bronchiolitis obliterans organizing pneumonia (BOOP) is a non-specific histopathologic pattern of lung injury that can be a manifestation of pulmonary drug toxicity. BOOP is characterized by the proliferation of immature fibroblastic plugs (Masson bodies) within the respiratory bronchioles, alveolar ducts and adjacent alveolar spaces.

Bleomycin, gold salts, cyclophosphamide and methotrexate are most common causes of this form of lung injury. Amiodarone, nitrofurantoin, penicillamine, and sulfasalazine are less common causes of drug-induced BOOP.

Affected patients present with progressive dyspnea, non-productive cough and fever. Chest radiographs demonstrate bilateral scattered heterogeneous and homogeneous pulmonary opacities. The opacities are typically peripheral in distribution and are equally distributed between upper and lower lobes. CT often shows associated poorly defined nodular opacities, centrilobular nodules, branching tubular opacities and bronchial dilation. BOOP caused by pulmonary drug toxicity typically responds well to cessation of drug therapy but may also require the administration of corticosteroids.

Eosinophilic Pneumonia

Eosinophilic pneumonia is characterized by the accumulation of eosinophils and macrophages within the alveolar spaces. Alveolar septa are thickened and infiltrated by eosinophils, lymphocytes and plasma cells.

Causative drugs include penicillamine, sulfasalazine, nitrofurantoin, para-aminosalicylic acid and nonsteroidal anti-inflammatory drugs.

Affected patients typically present with progressive dyspnea, non-productive cough, and occasionally fever. Peripheral eosinophilia and elevated IgE

levels are common. Chest radiographs show homogeneous opacities that are typically peripheral and upper lobe in distribution. CT can be useful for demonstrating the peripheral nature of the pulmonary opacities. Eosinophilic pneumonia caused by drug therapy usually responds well to cessation of drug therapy but may also require the administration of corticosteroid therapy.

Pulmonary Hemorrhage

Diffuse pulmonary hemorrhage is an uncommon complication of drug therapy, with potentially significant morbidity and mortality. Typical causes include anticoagulants, amphotericin B, high dose cyclophosphamide, mitomycin, cytarabine (Ara-C), and penicillamine therapy. Affected patients can present with acute respiratory distress. Hemoptysis is uncommon. Chest radiographs typically show bilateral heterogeneous and homogenous opacities. Focal opacities are a less common finding. HRCT usually shows bilateral and diffuse ground glass opacities. Prognosis depends upon the causative agent.

Specific Agents

Although more than a 100 drugs are known to adversely affect the lungs, the most frequently encountered drugs manifesting with pulmonary toxicity are discussed below.

Cytotoxic Drugs

Cytotoxic drugs constitute the largest and most important group of agents associated with lung toxicity. Busulfan and cyclophosphamide are the most common drugs in this group to cause lung injury; chlorambucil and melphalan are uncommon causes of lung injury.

Busulphan is used to treat chronic myelogenous leukemia. Busulphan-induced lung disease is reported in up to 4% of patients and typically occurs in those who have received a total dose of more than 500 mg. Toxicity occurs from one month to 12 years (mean 3.5 years) after busulfan administration and is associated with a poor prognosis. DAD is the most common manifestation of busulphan-induced lung disease. Pulmonary fibrosis is less common and typically occurs only after prolonged administration of high doses of busulphan.

Cyclophosphamide is most commonly used to treat a variety of malignancies but is also used to treat non-malignant conditions such as glomerulonephritis and Wegener granulomatosis. Toxicity occurs from two weeks to 13 years (mean 3.5 years) after cyclophosphamide administration. There is no relationship between development of lung injury and dose or duration of administration. Discontinuation



of therapy is typically associated with a good prognosis. DAD is the most common manifestation of cyclophosphamide-induced lung disease. Pulmonary fibrosis and BOOP are much less common manifestations.

Carmustine (BCNU) is primarily used to treat CNS malignancies. Carmustine is one of the few drugs in which there is a clear relationship between cumulative dose and lung injury. Carmustine-induced lung injury occurs in 20-30% of treated patients overall, but the incidence increases to 50% if the cumulative dose is more than 1.5 gm/m². Lung injury can occur at low doses if the patient has had previous thoracic radiation therapy. DAD is the most common manifestation of carmustine-induced lung disease. Pulmonary fibrosis is less common.

Bleomycin-induced lung injury usually occurs in 3-5% of treated patients although there is a marked increased risk if the total cumulative dose is more than 450 units. The risk of developing lung injury is increased in the elderly, in patients receiving oxygen therapy or with a history of prior thoracic irradiation, and in patients in whom therapy is reinstated within six months after discontinuation. The prognosis is poor with most patients dying within three months of respiratory failure. DAD is the most common manifestation of bleomycin-induced lung disease. Pulmonary fibrosis and bronchiolitis obliterans with organizing pneumonia (BOOP) are less common manifestations. Unlike patients with DAD, patients with BOOP caused by bleomycin may be asymptomatic. Chest radiographs and CT may show nodular opacities in such cases. The nodules range in size from 5 mm to 3.0 cm in diameter, are usually subpleural in location and can be sharply or poorly marginated. Differentiation from metastases can be difficult and biopsy may be required.

Mitomycin induced lung injury occurs in approximately 8% of patients although the risk of injury increases if mitomycin is used in combination with vinca alkaloids. Although prognosis is poor (overall mortality 50%), early recognition of lung injury and discontinuation of mitomycin can result in complete recovery. DAD is the most common manifestation of mitomycin-induced lung disease. Bronchiolitis obliterans-organizing pneumonia, pulmonary hypertension and pulmonary veno-occlusive have also been reported.

Non-Cytotoxic Drugs

Amiodarone is commonly used to treat refractory ventricular tachyarrhythmias. Pulmonary toxicity occurs in approximately 5-10% of patients, usually within months of starting therapy. Although there is

no correlation between the development of drug toxicity and the duration of therapy or total accumulative dose, the risk is increased if the daily maintenance dose is greater than 400 mg and in elderly patients. The prognosis is good with most patients improving after discontinuation of therapy. Chronic interstitial pneumonitis is the most common manifestation of amiodarone-induced lung disease. Pleural inflammation is an accompanying feature and can manifest as a pleural effusion. Bronchiolitis obliterans pneumonia is less common and typically occurs in association with chronic interstitial pneumonitis.

A distinctive feature of amiodarone toxicity is the occurrence of focal, homogeneous pulmonary opacities. These opacities are typically peripheral in location and of high-attenuation on CT due to incorporation of amiodarone into the type-II pneumocytes. The combination of high attenuation abnormalities within the lung, liver and/or spleen are characteristic of amiodarone toxicity.

Gold salts are sometimes used to treat inflammatory arthritis. Gold-induced drug toxicity is uncommon, occurring in approximately 1% of patients. Toxicity occurs within two to six months after gold administration and is associated with mucocutaneous lesions in approximately 30% of patients. The prognosis is good with most patients improving after discontinuation of therapy. DAD and interstitial pneumonia are the most common manifestations of gold-induced lung disease. Bronchiolitis obliterans-organizing pneumonia is less common.

Methotrexate causes pulmonary toxicity in 5-10% of treated patients. Symptoms typically manifest within months of starting therapy. There is no correlation between the development of drug toxicity and the duration of therapy or total cumulative dose. The prognosis is good with most patients improving despite continuation of therapy. Chronic interstitial pneumonia is the most common manifestation of methotrexate-induced lung disease. Histopathologic changes resembling hypersensitivity pneumonitis and bronchiolitis obliterans-organizing pneumonia have been reported less commonly.

Nitrofurantoin-induced lung injury is uncommon and the large number of cases reported are mainly due to the widespread use of the drug. Acute and chronic drug-induced injury have been described. Acute toxicity is the more common presentation and usually occurs within two weeks of administration of nitrofurantoin. Clinical findings include fever, dyspnea, cough and peripheral eosinophilia. Prognosis is good with most patients recovering after discontinuation of nitrofurantoin. Acute pulmonary toxicity manifests radiologically as pulmonary edema with diffuse bilateral, predominantly basal interstitial opacities. Chronic



toxicity is less common and usually occurs after months or years of nitrofurantoin administration. Chronic pulmonary toxicity typically manifests clinically with an insidious onset of dyspnea and cough. Chronic interstitial pneumonia is the most common histopathologic and radiologic manifestation. Eosinophilic pneumonia is an uncommon manifestation of nitrofurantoin-induced lung injury.

New Agents

New anti-neoplastic agents are being added to the oncologist's armamentarium on almost a daily basis. Among these new agents are the taxoid derivatives paclitaxel and docetaxel, gemcitabine, topotecan and vinorelbine. These agents have demonstrated activity against malignancies of the breast, lung and ovary. Although experience is limited, it appears that many of these agents may have pulmonary toxicity. For instance, preliminary data suggests that paclitaxel may commonly cause pulmonary toxicity at doses higher than 100 mg/m². The histopathologic features of pulmonary toxicity caused by these agents are not well described.

Summary

The incidence of drug-induced pulmonary toxicity is increasing and more than 100 drugs are now known to cause lung injury. Because this lung injury can be progressive and fatal, early recognition is important. The diagnosis of pulmonary drug toxicity should be considered in any patient with a history of drug therapy who presents with new or progressive respiratory complaints. Although drug-induced pulmonary toxicity can be difficult to diagnose, knowledge of the drugs most frequently involved, together with an understanding of the typical histopathologic and radiologic manifestations of toxicity caused by those drugs, can be useful in the institution of appropriate treatment.

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Thoracic Manifestations of Collagen Vascular Disease: Imaging Findings

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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. Acute lupus pneumonitis is a diagnosis of exclusion. The chest radiographic findings, similar 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 tends 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 patients (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 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 (12). 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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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		+				+++



HRCT of the Lungs: The Caveats

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High resolution computed tomography (HRCT) is now a mature technique with an accepted place in the investigation of patients with suspected or known diffuse infiltrative lung disease [1-3]. Several studies have shown the basic superiority of HRCT over chest radiography in terms of sensitivity and specificity. However, as with any other diagnostic test, HRCT does have shortcomings and this presentation will concentrate on the following specific points:

- There are several artefacts which cause interpretive pitfalls by obscuring or mimicking diffuse lung disease [4].
- HRCT images provide a macroscopic, not microscopic, view of pathology, and inferences about the nature of lung disease are often based on indirect signs.
- Many factors need to be taken into account when considering the accuracy of HRCT as reported in the literature.

HRCT Artefacts and Interpretive Pitfalls

By comparison with other CT techniques (for example spiral CT for pulmonary embolism) there are relatively few technical parameters that can be altered when performing an HRCT examination of the lungs. Nevertheless, given an identical scanning protocol, the final appearance of the images obtained on two different CT scanners can be remarkably different. Such differences in image “look” may be problematic, particularly in the context of a follow-up HRCT examination to assess serial change of subtle parenchymal abnormalities, such as ground glass opacification.

Many studies have shown the substantial effect that a change in window settings has on the perception of object size, but there is less information about the effects of window settings on the detection of diffuse lung abnormalities. One study has shown that there is no diagnostic gain in allowing observers free rein in choosing window settings for the detection of diffuse interstitial lung disease [5]. However, there have been no systematic studies to identify which fixed window settings provide optimal conspicuity of diffuse lung abnormalities; the patterns of lung disease most affected by window settings are those characterized by regions of minor attenuation differences with poorly

defined margins (most obviously, a subtle mosaic attenuation pattern).

Once the basic mechanism behind the generation of ground glass opacification on HRCT is understood (essentially, nothing more or less than the displacement of air from voxels), the situations in which this pattern will be seen can be predicted [6]. More importantly, interpretation of the clinical significance of ground glass opacification will be better informed. The several pathophysiologic mechanisms that result in ground glass opacification on HRCT are summarized in the following, seemingly complex, definition:

Hazy increased attenuation of lung, but with preservation of bronchial and vascular margins; caused by partial filling of airspaces, interstitial thickening, partial collapse of alveoli, normal expiration, or increased capillary blood volume [7].

The main artefactual causes of apparent ground glass opacification on HRCT are: 1) normal end expiration, 2) inappropriate (wide) window settings, and 3) the appearance of the lung parenchyma on images obtained on an unfamiliar CT scanner. It has been recognized for some time that ground glass opacification is diagnostically non-specific and, furthermore, may result from many diverse pathologic processes [8]. Nevertheless, it is a common perception that ground glass opacification on HRCT invariably represents “active alveolitis”. An early study showed that ground glass opacification equated with reversible lung disease (whatever the pathologic diagnosis) in many cases [9]. However, ground glass opacification, as the dominant HRCT abnormality, is also encountered in irreversible conditions such as bronchioloalveolar cell carcinoma and fine intralobular fibrosis (most often the non-specific interstitial pneumonitis subtype of the interstitial pneumonias). The most frequent feature that suggests ground glass opacification represents fine interstitial fibrosis is the ancillary sign of distortion and dilatation of the airways within the areas of ground glass opacification [10,11].

Similar considerations apply at the other end of the scale of lung attenuation, namely at the “black lung” end of the spectrum. Apart from considerations of the technical factors (window settings etc.) that influence the detection of abnormal lung of decreased attenuation (most often under-perfused or





emphysematous lung), the basic interpretation of the pathologic nature of lung parenchyma of decreased attenuation deserves attention (see next section).

HRCT Provides Macroscopic, Not Microscopic, Information

HRCT provides a similar view of the lung as a low power scan of an autopsy or lung biopsy specimen. In many situations an experienced lung pathologist can make a confident diagnosis from such an inspection of the gross specimen, without resort to high power microscopy [12]. An example of this is provided by sarcoidosis, in which the appearances of the cut surface of an inflated lung (which mirror the appearances seen on HRCT) show the distribution of conglomerate granulomas, especially their relationship to the structures that make up the secondary pulmonary lobule. It is thus not surprising that the same level of confidence and accuracy can be achieved using HRCT, for conditions which have a distinctive macroscopic distribution. However, from the outset it was appreciated that HRCT does not depict microscopic detail: "...even at 200 microns the resolution of HRCT is still one to two orders of magnitude below what would be needed to match histologic resolution" [13]. Indeed, a normal HRCT does not necessarily exclude interstitial lung disease: a small proportion of symptomatic patients with biopsy proven pulmonary fibrosis have an apparently normal HRCT examination [14].

Nevertheless, it is not an overstatement to suggest that HRCT images often *reflect* histologic appearances and distribution of disease. For example, the fact that pulmonary sarcoidosis is seen as nodules on HRCT is because of the tendency of sarcoid granulomata to conglomerate. As another example, the retractile property of interstitial fibrosis is seen on HRCT as architectural distortion, with dilatation of bronchi in areas of ground glass opacification, well before there are macroscopic signs of fibrotic lung destruction. Nevertheless, it must be appreciated that *indirect* HRCT signs of fundamental pathologic processes are not wholly reliable. As a generalization, dilatation of the airways within areas of ground glass opacification reflects fine interstitial/intralobular fibrosis [10], but the clinical context is crucial: bronchial dilatation is also seen within areas of ground glass opacification in patients with acute respiratory distress syndrome, but whether these dilated airways within the milieu of acute lung inflammation and exudate, truly reflect "traction bronchiectasis" due to surrounding established fibrosis is not clear [11]. Another assumption relates to cases in which a reticular pattern is the dominant finding on HRCT. In this context, it may be assumed that when a reticular pat-

tern (excluding a reticular pattern comprising thickened interlobular septa alone) predominates, particularly when there is associated distortion of the lung architecture, that this pattern represents "irreversible fibrosis". However, there are a few situations in which this is not the case, for example subacute drug-induced lung disease, and these will be illustrated.

Areas of decreased attenuation of the lung parenchyma on HRCT in patients with severe obstructive airways disease due to constrictive obliterative bronchiolitis may sometimes be misinterpreted as "emphysema"; in this situation, the pulmonary vessels are attenuated within areas of areas of decreased attenuation, but are not distorted, as is the case in centrilobular emphysema. In one study of patients with bronchiectasis, it was assumed that the widespread areas of decreased attenuation on HRCT were caused by emphysema, accounting for the functional gas-trapping [15]. However, the "emphysema" seen in that study was not associated with decreased gas diffusing capacity, the functional hallmark of emphysema. In the majority of cases with bronchiectasis, in which there are areas of decreased attenuation, it seems probable that this reflects coexisting constrictive bronchiolitis, which is a usual accompaniment to bronchiectasis on pathologic study of resected specimens [16].

Reported Accuracy of HRCT in Diffuse Lung Disease

The studies in the literature have largely compared observer performance using HRCT versus chest radiography. Given the known problems with chest radiography in this particular clinical context, such studies in some respects exaggerate the superior performance of HRCT. In the specific context of idiopathic pulmonary fibrosis, the diagnostic advantages of HRCT over chest radiography may not be as great as early studies suggested. When the results of five studies comprising a total of 501 patients with a variety of interstitial lung diseases (145 of whom had a final diagnosis of idiopathic pulmonary fibrosis) are combined, a correct first choice diagnosis of idiopathic pulmonary fibrosis was made in 84% of cases on HRCT compared to 73% of cases on plain chest radiography. The relatively small diagnostic advantage of HRCT is sometimes overstated: a recent fact sheet circulated to chest physicians in the United Kingdom stated that "...the appearances on HRCT, which is much more accurate diagnostically than the chest x-ray, may avoid the need for invasive procedures in many cases" (Lung and Asthma Agency, fact sheet 97/1).

When interpreting the results of the various studies that have evaluated the diagnostic accuracy of HRCT, several factors need to be borne in mind: a) there is inevitably a selection bias with a relatively high



proportion of conditions which have distinctive HRCT appearances. In this respect, the study populations do not reflect the case mix encountered in “normal” clinical practice, in which there will be a higher frequency of smoking-related diffuse lung disease, interstitial pulmonary edema and normal individuals, b) such studies are retrospective and are usually undertaken by highly experienced observers, c) new or “difficult” conditions are under represented (e.g. the pathologic subtype of non-specific interstitial pneumonitis), and d) the reported accuracy of HRCT, when given as a single result cannot reflect the highly disease-dependent accuracy of HRCT; for example, the diagnostic accuracy of HRCT in cases of Langerhans cell histiocytosis is considerably higher than that for lymphocytic interstitial pneumonitis, which has a much wider spectrum of HRCT manifestations.

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Emerging Infectious Diseases of the Chest

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Attendees of this lecture will become be introduced to the definition of an emerging infectious disease and the epidemiology underlying its outbreak. Attendees will also become familiar with several examples of emerging infectious diseases, and learn the radiologist's role in suggesting the diagnosis of a novel infectious agent, or an infectious agent which has become newly prevalent or resistant to therapy.

What Is an Emerging Infectious Disease?

Emerging infections may be: 1) Known human pathogens that have become more virulent, more prevalent or resistant to antibiotics. Chest pathogens fitting this description include penicillin resistant pneumococcus and multi-drug resistant Tbc. 2) Zoonotic infections, infections spread from animals to humans but not establishing a life cycle in us. Epidemics often brought about by climatic or other environmental changes. Examples include malaria, dengue, and leptospirosis associated pulmonary hemorrhage. 3) Species jumping infections, infections derived from animals but subsequently establishing a new life cycle in humans. Herpes viruses probably are of this origin, derived from domesticated livestock. HIV virus, and very nearly the H5N1 influenza also belong in this category.

Yersenia Pestis

Includes bubonic plague, transmitted by flea bites or exposure to infected blood and pneumonic plague, transmitted by aerosol by humans and cats. Disease has 50% mortality untreated. Pneumonic form can be fatal in 24 hours.

Between 1919 and 1993 16,000 cases worldwide. 1994 outbreak in India, Mozambique and Malawi. Currently multi-drug resistant forms have been isolated. Epizootics (animal epidemics) are moving east and north from the traditional strongholds in the Southwest. Radiographic findings may be nonspecific. However, bubonic form may present with extensive mediastinal adenopathy. Yersinia pestis is in differential diagnosis of pneumonia with accompanying hilar/mediastal adenopathy. Other causes include endemic fungal infections, tuberculosis, tularemia, inhalational anthrax, underlying carcinoma etc.

Hantavirus Pulmonary Syndrome(HPS)

First described in the "Four Corners" area of the southwestern US in 1993, consists of a syndrome of rapidly progressive non-cardiogenic pulmonary edema and shock caused by a newly discovered Hantavirus. The characteristic presentation includes thrombocytopenia, severe hypovolemia, lactic acidosis, shock and death (mortality > 50%).

Hantaviruses cause asymptomatic infections in rodents and are excreted in their body fluids. Previously known Hantaviruses have been found to cause hemorrhagic fever renal syndrome in Asia and Europe. The hantavirus isolated in the Southwest is termed the "sin nombre" virus, but a number of other "New World" Hantaviruses have been discovered as causes of HPS. There have been between 400-500 cases of HPS reported in North and South America.

Early radiographic findings of HPS are remarkable for marked interstitial edema. These findings are atypical for ARDS. At this stage the chest radiograph (CR) may appear similar to other variants of non-cardiogenic edema in which alveolar damage is limited, e.g. IL-2 therapy and hyperacute drug reactions. The CR and clinical course follow one of two paths during the 24-48 hours after the initial abnormal CR. Patients may stabilize, in which case interstitial findings alone persist on the CR. Other patients progress to rapid alveolar flooding accompanied by shock. Treatment includes support with ECMO. Patients may develop CR findings of completely airless lung parenchyma while on ECMO for treatment of HPS, yet still survive.

Leptospirosis

Discovered in Central America and the Caribbean in the course of surveillance for Dengue Hemorrhagic fever. The disease is a spirochete infection that usually presents with renal and hepatic dysfunction and hemorrhage. Chest involvement often appears as small nodular opacities that progress to confluent consolidation or ground glass. Massive hemoptysis may be the terminal event. Lung pathology shows evidence of vascular involvement by spirochetes rather than diffuse alveolar damage (DAD).



Influenza A

Cause of 10-20 pandemics over the last two centuries, the worst in 1918-20 killing 20 million people. Usually presents as bronchiolitis with no CR findings, or findings of atelectasis. Alternatively, small patchy areas of consolidation may be present on CR, often associated with superinfection. Rapidly progressive form of Influenza A can occur causing DAD.

In Hong Kong in 1997 a new serotype, H5N1 was isolated, which caused this rapidly progressive form of disease associated with a mortality of > 50% in adults (non-immunocompromised). CR show rapidly progressive alveolar flooding without initial findings of localized opacities or focal atelectasis. The H5N1 strain was found to originate from birds, resulting in government authorized slaughter of all poultry. Subsequent work has shown the isolated H5N1 viruses to have retained all the RNA sequences from the avian source. If mixing with mammalian virus RNA had occurred, a severe pandemic would likely have resulted.

Multi-Drug Resistant Tuberculosis

Defined as tuberculosis resistant to INH and Rifampin. MDR is a worldwide problem with a prevalence of as great as 30% of TBc cases in some nations. Primary drug resistance (resistance in patients not previously treated) may more likely present with CR characteristic of primary TBc, particularly in HIV patients. Additionally, in HIV patients with TBc, development of adenopathy, new effusions, new or progressive infiltrates after two weeks of drug treatment suggests the presence of MDR. Secondary drug resistance is more likely to have the appearance of reactivation TBc, often with an extensive cavitory component.

Inhalational Anthrax

Anthrax is not truly an emerging disease, but deserves inclusion because of the threat of its use as a biological weapon. WHO reports that 50 kg of spores upwind of a city of 500,000 inhabitants could cause 95,000 deaths. Currently cutaneous and gastrointestinal anthrax outbreaks are occurring in Asia, but inhalation anthrax remains rare. Clinical course of inhalational anthrax is one of initial nonspecific symptoms for hours to days followed by a second stage of fever, dyspnea and shock. CR shows characteristic marked mediastinal widening (due to massive adenopathy) often with a pleural effusion but with remarkable lack of parenchymal lung disease. Treatment with antibiotics at this stage often fails, but the recognition of the diag-

nosis would be important to provide earlier life saving therapy to subsequent patients.

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Community-acquired and Nosocomial Pneumonia: The Role of Radiology Revisited

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Introduction

Pulmonary infections are among the most frequent causes of morbidity and mortality throughout the world. In the non-immunocompromised population, pneumonia is one of the two major infectious diseases. It is the most prevalent community-acquired infection and the second most common nosocomial infectious disorder. Despite advances in diagnosis and treatment, pneumonia remains the sixth leading cause of death in the United States, and mortality is particularly high in immunocompromised patients, in children, and in the elderly population.

Radiography plays a pivotal role in the detection and management of patients with pneumonia. Among all diagnostic tests, the chest x-ray has a unique position in confirming or excluding the diagnosis of pneumonia. Furthermore, it allows narrowing of the differential diagnosis, helps to direct additional diagnostic measures, and serves as an ideal tool for follow-up examinations. In this course, we will revisit the role of chest radiography in the diagnosis and management of patients with pneumonia and thereby attempt to increase the awareness of how radiologic methods may be used effectively in this infectious pulmonary disorder.

The Role of Radiology Revisited Detection and Exclusion of Pulmonary Infiltrates

The diagnosis of pulmonary infection poses a common problem in daily clinical practice. When a patient presents with symptoms such as fever, cough, and purulent tracheobronchial secretions, he or she may or may not suffer from pneumonia. In these cases, the diagnosis of pneumonia is based on the detection of a pulmonary infiltrate on the chest x-ray. This practice relies on the pathophysiologic events that lead to the development of a visible pulmonary infiltrate. Although some variation exists regarding the time frame between the onset of clinical symptoms and the development of a radiographically visible pulmonary infiltrate, it has been stated that the vast majority of infiltrates appears within the time period of 12 hours (1). This time frame allows detection or exclusion in most cases of community-

acquired pneumonia, where patients are generally seen by the radiologist within a few days following initial clinical presentation.

Caution, however, must be exercised in patients with nosocomial infections, i.e., in patients who develop pulmonary infections in a hospital setting. These patients may be seen in the radiology department within a matter of hours after the onset of clinical symptoms, - a time period in which a visible radiographic abnormality may not have developed. Moreover, in immunocompromised patients, the appearance of a detectable radiographic abnormality may be delayed, particularly when neutropenic (2, 3). Zornoza and coworkers investigated a series of 175 consecutive patients with gram-negative pneumonia who were neutropenic following anti-neoplastic chemotherapy. In these patients, 70 episodes of pneumonia were diagnosed only clinically, in the absence of radiographically detectable disease, after the onset of symptoms. In 27 of these 70 episodes, an infiltrate was subsequently found on follow-up chest radiography. In 25 of 57 patients with no radiographically detectable infiltrates, the diagnosis of pneumonia was established at autopsy. The radiographic appearance of a visible pneumonic infiltrate may not be delayed only in neutropenic patients but also in patients with functional defects of granulocytes due to diabetes, alcoholism, and uremia. Some controversy exists in the literature regarding the influence of the state of hydration on the development of pneumonia (4, 5). From a practical point of view, the radiologist must be aware that in the above-mentioned group of patients, pneumonia may exist without a visible pulmonary infiltrate.

The radiologic diagnosis of pneumonia may not be as straightforward in patients with underlying lung disease. In these patients, pre- or coexistent abnormalities may alter or disguise the appearance of a pneumonic infiltrate. Particularly in patients with widespread pulmonary abnormalities, such as end-stage fibrosing alveolitis, pulmonary edema or hemorrhage, and ARDS, the detection of a pneumonic infiltrate can be delayed or may not even be possible. Winer-Muram and co-authors analyzed 40 intensive



care patients with clinical signs and symptoms of pulmonary infection and new pulmonary abnormalities that were detected on chest radiography. In these patients, fiberoptic bronchoscopy with protected specimen brushing and bronchoalveolar lavage was performed and the findings were correlated with those of chest radiography. For the diagnosis of pneumonia, chest radiography provided an overall accuracy of 52%, and when ARDS coexisted with pneumonia, of 42%. When the radiologist was given clinical information, a further drop in accuracy resulted (6). Thus, it becomes clear that numerous disorders may obscure or alter the otherwise characteristic radiographic appearance of an infiltrate and may also render an etiologic approach difficult using pattern recognition.

Narrowing of the Differential Diagnosis

A second and quite important task for the radiologist is to aid the clinician in the narrowing of the etiologic differential diagnosis. The importance of this task relates to the fact that it is frequently impossible for the clinician to identify the causative organism of a pneumonic infiltrate. Reviewing the clinical literature on this topic, it becomes clear that with the full battery of microbiologic tests, only 30-70% of organisms can be identified. Moreover, sputum tests, which are commonly used to diagnose outpatient pneumonia, are frequently contaminated by upper respiratory tract colonization. This often results in the incorrect identification of organisms by sputum cultures in a high percentage of patients with community-acquired pneumonias (7, 8). On the other hand, the use of invasive procedures is frequently limited in nosocomial infections, especially in patients who are immunocompromised since coagulation disorders are not uncommon in this group of patients.

Narrowing of the etiologic differential diagnosis may be possible using radiologic pattern recognition and with the integration of clinical and laboratory information with the radiographic diagnosis. Pattern recognition is based on the categorization of radiographic abnormalities on chest x-ray and CT scans. Although with pattern recognition, specific etiologic diagnoses can hardly ever be established, patterns help to classify groups of potentially underlying organisms, especially in the analysis of community-acquired pneumonia. Levy and co-authors analyzed the value of initial noninvasive bacteriologic and radiologic investigations in 420 patients with community-acquired pneumonia (9). They demonstrated that (focal segmental or lobar) alveolar infiltrates were caused by bacterial agents in over 90% of cases, while the majority of diffuse interstitial or mixed abnormalities could be attributed to viral, atypical bacterial or tuberculous infections. Notably, a further

differentiation of radiographic patterns of typical bacterial pneumonia (caused by Hemophilus influenzae, Streptococcus pn, Staphylococcus aureus and aerobic gram-negative bacillae) and atypical bacterial pneumonia (caused by Mycoplasma pneumonia and Chlamydia species) is not possible. In a prospective study of 359 adults with community-acquired pneumonia, Fang and coworkers compared the radiographic, clinical and laboratory features of bacterial pneumonia with the findings of patients with atypical bacteria pneumonia and found no parameters that could reliably differentiate these groups (10).

As a general rule of thumb, localized segmental or lobar aveolar densities can be attributed to typical or atypical bacterial infections. Diffuse bilateral interstitial and/or interstitial alveolar infiltrates most commonly are caused by viruses, atypical bacteria, and protozoa. Micronodular disease is most often caused by miliary TB (miliary pattern), candidiasis, and histoplasmosis (small nodules), or viruses such as herpes or varicella zoster virus (diffuse nodules with hazy borders). Large, nodular lesions may represent bacterial abscesses, and in immunocompromised patients, may be caused by invasive aspergillosis and nocardia. In some cases, CT may help in identifying the underlying pattern.

The recognition of radiographic patterns can provide significant help to the clinician in designing a more targeted antibiotic therapy in cases where no underlying organisms can be identified. However, there are limitations to this approach. First, patterns overlap to a certain extent. Second, radiographic patterns may change with the immunologic status of the patient. For example, Ikezoe and associates evaluated the CT features of pulmonary tuberculosis in immunocompromised patients compared to other patients without underlying disease. They demonstrated that immunocompromised patients, who demonstrated a high prevalence of nonsegmental distribution of infiltrates and multiple small cavities within any given lesion, had a somewhat different presentation compared to patients without underlying disease who had a more segmental distribution of lesions in a single cavity within a given lesion (11). Finally, as already mentioned, patterns may be altered by pre- or coexisting lung disease.

Planning of Additional Diagnostic Procedures

In patients with community-acquired pneumonia, diagnosis and disease management most frequently rely on chest radiography and do not require the use of further diagnostic tests. In these patients, CT scanning and invasive diagnostic procedures are reserved only for cases in which treatment failure or complications, such as abscess formation, influence





the course of the disease. Conversely, in nosocomial infections, cross-sectional imaging techniques and invasive procedures such as needle or bronchoscopically guided biopsies are more often required. This is because nosocomial infections, i.e., pneumonias that develop in the hospital environment, are associated with a high mortality rate, ranging from 20-50%. Thus, identification of the causative organism is more intensively pursued, with the use of fiberoptic bronchoscopic lavage, brushing and/or biopsy. In many institutions, imaging methods such as CT scans are used for the guidance of invasive methods into areas of maximum disease.

The use of transthoracic CT aspiration needle biopsy in the diagnosis of pulmonary infection is controversial. Nevertheless, when noninvasive techniques used to identify the underlying organism such as sputum examination and cultures are non-diagnostic, a choice must be made between empiric therapy and an invasive diagnostic test. While the majority of patients is treated empirically, the nature and course of pneumonias in nosocomial infections and in immunosuppressed individuals frequently dictates a more aggressive approach. In such cases, transthoracic needle biopsy may help to identify the causative organism. Conces et al. reviewed a series of 441 transthoracic needle aspiration biopsies to evaluate the use of the procedure in the diagnosis of pulmonary infections (12). In 67 patients in whom pulmonary infection was suspected, a specific diagnosis was made with needle biopsy in 45 cases. In 46 cases in which infection was ultimately found to be present, aspiration biopsy identified the organism in 35 cases. Overall, clinically useful information was obtained in 81% of aspiration biopsies performed for pulmonary infection. Since other authors report similar results, needle biopsy should enrich the radiologist's armamentarium in diagnosing and managing pulmonary infections.

Patient Follow-up

The role of radiography in the follow-up of pulmonary infections is currently under debate. Because of increasing economic restrictions, imaging tests are used less routinely to monitor the resolution of pulmonary infiltrates. Many institutions now do not follow patients radiographically when the clinical course indicates successful treatment. In other institutions, with different healthcare systems, radiographic confirmation of the healing process is required for medicolegal reasons. As a general rule, most pneumonias resolve in a 2-4 week time period. However, complete resolution may take up to 8-12 weeks (13), especially in some bacterial infections, (including Chlamydia), in patients with underlying

lung disease, in immunocompromised patients, and in the elderly. In cases where continuous resolution of an inflammatory infiltrate cannot be demonstrated, differential diagnostic possibilities include suboptimal antibiotic therapy, noninfectious inflammation (bronchiolitis obliterans with organizing pneumonitis, acute alveolar sarcoid, eosinophilic pneumonia), as well as malignant lesions such as bronchoalveolar cell carcinoma, bronchogenic carcinoma with post-obstructive pneumonitis, and lobar lymphoma. The important role of the radiologist in these patients includes recognition of persistent infiltration and the planning of further diagnostic procedures, including CT scanning. The use of CT scanning before bronchoscopy has been advocated by many authors and, in our experience, is extremely helpful.

CT scanning is also the method of choice to evaluate patients with recurrent pulmonary infiltrates. Such recurrent infections may be triggered by congenital or acquired defects in the host's immune system, however, they may also be the result of underlying structural abnormalities such as bronchiectasis, large cavities, or architectural distortion. In these patients, CT scanning frequently helps to define the underlying disorder and to plan further therapeutic measures.

Conclusion

In patients with suspected pneumonia, the radiologist has an important role in the detection and exclusion of a pulmonary infiltrate, in the narrowing of the differential diagnostic spectrum, the planning of further diagnostic procedures, and in the follow-up. We have to be aware of the fact that chest radiography is the single most important test to perform the above tasks, and diagnosis and management of pneumonia is impossible without the use of the chest x-ray. Nevertheless, excellent communication between the radiologist and the clinician, and integration of clinical and radiographic information is necessary to ensure high quality care in patients with pneumonia.

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Histoplasmosis: The Spectrum of Disease

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Introduction

Histoplasmosis was first recognized in the medical literature in 1905 as an overwhelming illness with massive parasitization of the reticuloendothelial system. (1) In the 5 decades that followed it became clear that the majority of cases were asymptomatic and benign. (2) The disease is almost always the consequence of residence in an endemic area. Histoplasma capsulatum presents with a wide range of radiographic findings and can mimic, TB, carcinoma, lymphoma, sarcoidosis and metastases. An understanding of the pathophysiology and protean manifestations will help the radiologist with the recognition of this interesting and common organism. (3-8)

Objectives:

At the completion of this course the attendee will be able to:

1. summarize the pathophysiology of the lung disease caused by Histoplasma capsulatum;
2. describe the imaging findings that commonly occur in patients infected with Histoplasma capsulatum
3. apply this information in daily practice

Pathogenesis and Epidemiology

H. capsulatum is a fungus with septate branching hyphae of 1-2.5 microns. The organism exists as mycelia in the environment. The micronidia which is the smallest form of the organism measures 2-6 microns and therefore can easily reach the alveolus. Once the organism is at body temperature it converts to the more familiar yeast phase which is oval and measures 2-3 microns. In the normal host the yeast phase organisms are engulfed by macrophages where they proliferate until the host develops specific cellular immunity and delayed hypersensitivity which usually occurs 12-14 days after the initial infection. During that interval the infected macrophages migrate to regional lymph nodes where there is commonly dissemination to the reticulo-endothelial system. Once delayed hy-

persensitivity comes into play the infection is controlled. Eventually there is calcification at the site of original infection (Ghon focus) and draining lymph nodes (Ranke Complex).

H. capsulatum is a common soil contaminant in the central portion of the United States. Although the disease has been described worldwide the highest concentration of cases is seen in the fertile river basins of the Midwest. The organism grows best in a temperate climate where the soil is slightly acidic and enriched with bird droppings. The birds, however, do not harbor the organism because their body temperature is too high. Bats, on the other hand, are capable of carrying the organism. Those who live in endemic areas are continuously exposed and go through cycles of re-infection which are in most cases asymptomatic. This contrasts with M. tuberculosis in which infection is a single event with subsequent reactivation of quiescent organisms.

Histoplasmosis in Normal Hosts

The great majority of individuals (99%) who are infected with H. capsulatum acquire the organism by inhaling wind blown spores. The disease is self-limited and there are no reported symptoms. The chest radiograph in mild exposure is usually normal (75%). Occasionally, an area of lower lobe consolidation will be identified with regional lymph node enlargement. In less than 1% the individual will receive an intense exposure to the organism from a point source such as a chicken coop or construction site or while chopping wood. In this case the chest radiograph may show numerous nodules of consolidated lung that will eventually calcify when healed. These patients with heavy exposure may complain of fever, chest pain, cough and constitutional symptoms. A small number of patients may develop respiratory failure with intense exposure.

Late complications include: histoplasmosis, mediastinal granuloma and fibrosis and broncholithiasis.

Histoplasmosis is a common sequela to the primary infection and presents as a nodule that ranges from .5-3cm. Satellite nodules are typical but the lesion may be



solitary. The presence of central or diffuse calcification in a nodule of less than 3 centimeters is certainly a granuloma. This remnant of the primary focus may continue to enlarge with a doubling time of 14-113 months. The nodule grows through the addition of fibrous tissue in the periphery. The fibrous response is thought to be a response to the leakage of antigenic material from the *H. capsulatum*.

Mediastinal granuloma and fibrosis is a collection of lymph nodes varying from 3-10cm with a fibrous capsule. The pathogenesis is probably similar to that for histoplasmosis. The subcarinal and right paratracheal nodes are most commonly involved and may result in vascular or airway occlusion. Calcification can be identified within the areas of fibrosis in nearly all of the cases. The use of steroids or antifungal treatment has not shown significant efficacy.

Broncholithiasis results when calcified lymph nodes result in bronchial obstruction either eroding into the lumen of the bronchus or causing distortion from inflammation and fibrosis. The patient often presents with cough fever and hemoptysis. Chest pain and wheezing are less common. CT may demonstrate the lymph node within the bronchial lumen and atelectasis is common.

Chronic Histoplasmosis

This is a rare manifestation of *H. capsulatum* which has a superficial resemblance to postprimary tuberculosis. The disease is usually manifested in middle aged white males who have emphysema. The symptoms are similar to TB with malaise, cough and night sweats and presents in the apical-posterior segments of the upper lobes. However, true cavitation is rare in chronic histoplasmosis. The disease begins in emphysematous blebs. There are very few organisms and the inflammatory response renders the bleb walls more visible creating the appearance of true cavitation. It is thought

that chronic histoplasmosis is a hyperimmune response to a small amount of antigenic material. Approximately 30% of the cases resolve without treatment.

Disseminated Disease

The majority of individuals with disseminated disease have a deficit in cell mediated immunity and cannot control the primary fungemia. The common predisposing factors include: cytotoxic therapy, administration of corticosteroids and AIDS. The chest radiograph is normal in up to 50% of cases. Diffuse small nodules (less than 3mm) are the most common opacities in those with an abnormal radiograph. There may also be consolidation, however, adenopathy is rare. In a small number of cases there is no definable immune deficit. The patients present with low-grade fever, weight loss and fatigue. Adrenal involvement is present in the majority of cases and may lead to adrenal insufficiency.

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Pulmonary Tuberculosis

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The objective of this lecture is to review the radiologic findings of pulmonary tuberculosis (TB) in immunocompetent and immunocompromised patients with AIDS.

Screening

Radiographic screening is performed to identify persons with active pulmonary tuberculosis and is usually done in conjunction with tuberculin skin testing. A normal chest radiograph has a high negative predictive value for active disease; the frequency of false negative examinations is approximately 1% in immunocompetent adults and increases to 7%-15% in AIDS patients (1). On a single screening chest radiograph, detection of any parenchymal, nodal, or pleural abnormality with or without associated calcification should result in an assessment of indeterminate disease activity. Radiographic differentiation between active and inactive disease can only be made reliably on the basis of temporal evolution (2); lack of change over a 4 to 6 month interval usually is indicative of inactive disease (2).

Radiologic Manifestations

Primary Disease

Lymphadenopathy, most commonly involving the right paratracheal and hilar stations, is the radiologic hallmark of primary TB. Although enlarged nodes are present in approximately 90% of affected children, its prevalence declines with increasing age of infected individuals (3). On contrast-enhanced CT, tuberculous lymphadenitis often has a characteristic appearance with involved nodes demonstrating central areas of low attenuation and peripheral rim enhancement (4).

Parenchymal involvement in primary TB most commonly appears as an area of consolidation in a segmental or lobar distribution and typically affects the same side as enlarged nodes, if present. In contrast to the age-related trend observed with lymphadenopathy, a lower prevalence of radiographically detectable parenchymal disease has been identified in young children as compared to teenagers and adults (3). Because of these two opposing age-related trends in frequency of radiographic manifestations, parenchymal involvement in the absence of lymphadenopathy occurs in only approximately 1% of pediatric cases whereas this nonspecific pattern is observed in 40%-80% of adults with primary TB.

Pleural effusion is seen as a radiographic manifestation of primary TB in 6%-11% of affected children and 29%-38% of affected adults. An effusion usually develops on the same side as the site of initial infection and is typically unilateral; although usually present in association with either nodal or parenchymal abnormalities, pleural effusion may be the only radiographic finding indicative of the presence of primary TB.

Postprimary Disease

Parenchymal opacities located in the apical and posterior segments of the upper lobes and the superior segment of the lower lobes are the characteristic radiographic manifestations of postprimary TB and are associated with cavitation in approximately one-half of cases. Bronchogenic spread of disease occurs when an area of caseous necrosis communicates with the bronchial tree and manifests radiographically as multiple, ill-defined, 5-10 mm nodules distributed in a segmental or lobar distribution and typically involving the lower lung zones. The thin-section CT findings of bronchogenic spread of disease consist of 2-4 mm centrilobular nodules and sharply marginated linear branching opacities (5).

Pleural effusion occurs in approximately 20% of patients with postprimary TB and is typically unilateral in distribution. On contrast-enhanced CT, tuberculous effusions demonstrate smooth thickening of visceral and parietal pleural surfaces separated by a variable amount of fluid—the “split pleura” sign. Tuberculous effusions may remain stable in size for years; detection of persistent fluid within a calcified fibrothorax at CT should raise concern for a chronic tuberculous empyema (6).

Miliary Disease

Miliary spread of TB which results when a focal collection of tubercle bacilli discharges into a blood or lymph vessel may occur during either the primary or postprimary stages of disease. Normal radiographic findings in the early stages of miliary disease are well recognized; typical miliary lesions may not be visible until 3-6 weeks after hematogenous dissemination. Radiographically, the characteristic findings of miliary TB consist of innumerable, 1-3 mm noncalcified nodules scattered throughout both lungs with a mild basilar predominance. At thin-section CT, a mixture of both sharply and poorly defined, 1-4 mm nodules are seen in a



diffuse, random distribution often associated with septal thickening (7).

Findings Associated with AIDS

The radiographic manifestations of pulmonary tuberculosis in HIV-seropositive patients are dependent on the level of immunosuppression at the time of overt disease (8). Persons with relatively intact cellular immune function demonstrate radiographic findings similar to those of immunocompetent individuals. At severe levels of immune dysfunction, up to 20% of patients with AIDS and TB will have normal radiographs or exhibit radiographic findings usually associated with primary disease such as lymphadenopathy, regardless of prior TB exposure status. A miliary pattern of disease has also been associated with severe immunosuppression.

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Atypical Mycobacteria: Expanding Spectrum of Disease

Thomas E. Hartman, MD

Objectives:

- To describe the pulmonary manifestations of atypical mycobacterial infection.
- To recognize the influences that age, sex, underlying diseases and immunocompromise can have on the expected imaging findings for pulmonary manifestations of atypical mycobacterial infections.
- To discuss a new pulmonary manifestation of atypical mycobacterial disease and describe its imaging findings.

Non-tuberculous mycobacteria (NTMB) are a group of ubiquitous, low-grade pathogens which have been classified into four groups based on rate of growth, pigment production, and morphologic features. Table one lists the groups and the most common pulmonary pathogen(s) in each group.

Table 1

Group	Pulmonary pathogen(s)
I. —Photochromogens	<i>M. kansasii</i>
II. —Scotochromogens	<i>M. szulgai</i> , <i>M. xenopi</i>
III. —Nonphotochromogens	<i>M. avium-intracellulare</i> complex
IV. —Rapid growers	<i>M. fortuitum</i> , <i>M. chelonae</i>

Despite the high rates of exposure to those ubiquitous organisms, there is a low rate of clinical infection. Pulmonary manifestations of NTMB can be divided into five categories.

I—Classic infection

II—Non-classic infection

III—Achalasia associated infection

IV—Infection in immunocompromised patient

V—Hypersensitivity pneumonitis*

*New description

Classic Infection

- typically elderly men
- usually with underlying COPD or pulmonary fibrosis
- indistinguishable from postprimary TB

Nonclassic Infection

- typically elderly women
- usually without underlying lung disease

- characteristic findings are bronchiectasis and multiple small nodules or nodular infiltrates

Achalasia

- achalasia predisposes to NTMB infection
- usually *M. fortuitum* or *M. chelonae*
- findings resemble aspiration pneumonia radiographically

Immunocompromise

AIDS

- occurs late in clinical course
- CD₄ count < 100/mm³ (often < 50/mm³)
- often part of disseminated process
- adenopathy (mediastinal and/or hilar) may be only finding
- nodules, masses and miliary patterns may also be seen

Non-AIDS

- usually in lymphoproliferative disorders or in patients treated with immunosuppressive drugs
- imaging findings similar to AIDS although cavitation can be seen in this group

Hypersensitivity Pneumonitis

- newly described pulmonary manifestation
- “hot tub lung”
- hypothesized that contaminated water in hot tub is aerosolized and inhaled causing hypersensitivity reaction
- organisms cultured from lungs show genetic fingerprinting identical to organisms cultured from hot tub/spa or well water
- radiologic findings are typical of hypersensitivity pneumonitis
- radiographs show fine diffuse reticulonodular or miliary pattern
- CT shows patchy areas of ground glass attenuation and/or poorly formed nodules of ground glass attenuation. Expiratory images may show airtrapping indicating an associated bronchiolitis

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