High-Resolution CT of the Lung
High-Resolution CT of the Lung

FIFTH EDITION

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DEDICATION

To my father, who encouraged my curiosity and taught me to figure things out

—WRW

To my wife, Isabela, and my children—Alison, Phillip, and Noah Müller

—NLM

To Jocelyn, whose constant love and support has always been my greatest inspiration

—DPN
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Preface

During the past 25 years, high-resolution CT (HRCT) has become established as an indispensable tool in the evaluation of patients with diffuse lung disease. HRCT is now commonly used in clinical practice to detect and characterize a variety of lung abnormalities. In the approximately 5 years since our fourth edition was published, considerable progress has taken place in the understanding of diffuse lung diseases and the recognition of new entities and their nature, causes, and characteristics. Without doubt, HRCT has played a fundamental role in contributing to this progress and has become essential to the diagnosis of a number of diffuse diseases.

This fifth edition continues what the three of us, independently, in conjunction, and with each other’s encouragement and support, began some 30 years ago. The photograph of the three of us below was taken by a local resident at the 1989 Diagnostic Course in Davos, on a walk we took on the promenade above the Sweitzerhof on the day of our arrival, when as junior faculty, we were more than a little anxious about teaching along with such important and impressive chest radiologists as Fraser, Felson, Greenspan, Milne, Flowers, Heitzman, and many others.

At this meeting, we each spoke about the use of HRCT, which, at the time, was a little-known technique that was regarded with skepticism by many radiologists. We learned from each other as we spoke, compared slides in the speaker-ready room, and gained confidence from our shared opinions. At this meeting, we began thinking about a collaboration that would combine our experience and thoughts about this new modality and its potential uses. Our first edition of this book was published in late 1991, with a grand total of 159 pages. It was a quarter of an inch thick, and, to our knowledge, referenced every known paper on HRCT. From our perspective, it was the most important thing we had ever done.

That is how things start. Maybe that is the best way things should start. It was certainly fun and rewarding for each of us. And we three have stuck together over the years, out of our combined respect, admiration, friendship, and good humor. Each one of us believes that we learned more from our collaboration than we taught.

In this edition, we have incorporated an update and review of numerous recent advances in the classification and understanding of diffuse lung diseases and their HRCT features. Recent technical modifications in obtaining HRCT have also been reviewed, most notably the use of helical HRCT and dose-reduction techniques. We hope the reader will find these changes and updates helpful. As is our wont, we have reorganized our discussions into new sections and chapters, which we feel best presents the most important topics in HRCT diagnosis for reference and learning.

A new section has been added at the end of the book to provide a general review of HRCT, including an illustrated glossary of HRCT terms and a chapter providing a compilation of the common and typical appearances of the most common diffuse lung diseases encountered in clinical practice. These sections are intended to provide an illustrated index to the detailed descriptions of diseases found elsewhere in the book.

It is with a great deal of pride that we complete our fifth edition of this book, which has occupied so much of our thoughts, efforts, and time over the years. This task is accomplished in the hope that this book will encourage future generations of thoracic imagers to develop mutually productive relationships with friends and colleagues, in order to explore important questions in our understanding of the role of imaging in the assessment of thoracic disease.

To this end, we acknowledge the contributions of three esteemed colleagues, our former fellows, who have authored parts of this book. Their efforts have greatly inspired our own enthusiasm for the considerable task of bringing this edition to fruition.

W. Richard Webb  Nestor L. Müller  David P. Naidich
We wish to gratefully acknowledge the many colleagues who have provided us with insights and inspiration over the years, and allowed us to use their illustrations for this and prior editions of this book. Although they are too numerous to mention here, they are recognized throughout the following pages.
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The collagen-vascular diseases (CVDs) are acquired immunologically mediated inflammatory disorders that affect many organs (1–3). The CVDs that most commonly involve the lungs are rheumatoid arthritis (RA), progressive systemic sclerosis (PSS), systemic lupus erythematosus (SLE), polymyositis-dermatomyositis (PM-DM), mixed connective tissue disease (MCTD), and Sjögren syndrome (1–3). The CVDs can affect all components of the lung, including the interstitium, the large and small airways, the pleura, and the pulmonary vasculature (4). The most important manifestations are diffuse interstitial lung disease (ILD) and pulmonary hypertension, which together account for most of the morbidity and mortality in these patients (1,2).

The CVDs can cause a variety of ILDs, identical histologically to the idiopathic interstitial pneumonias (IIPs), including nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), organizing pneumonia (OP), and lymphoid interstitial pneumonia (LIP) (Table 10-1) (5–7). The ILD may precede the clinical and laboratory manifestations of the CVD for up to several years, present together with systemic manifestations at the time of diagnosis of CVD or, more commonly, manifest later in the course of the disease (2,8,9). It is estimated that up to 20% of patients who present with a chronic ILD either have an occult CVD or subsequently develop a clinically overt CVD (9,10). The most common pattern of interstitial fibrosis seen in CVDs is NSIP (6,7,11). Therefore, CVDs tend to be associated with a finer reticular pattern and less honeycombing than typically seen in patients who have idiopathic pulmonary fibrosis (IPF), and ground-glass opacity is more common as a predominant abnormality. Furthermore, pleural thickening or effusion may be present in patients who have collagen diseases, but neither is a feature of IPF. Also, CVD may be associated with other abnormalities, such as bronchiectasis, bronchiolitis obliterans, and follicular bronchiolitis, not seen in patients who have IPF and having distinct high-resolution computed tomography (HRCT) appearances. It is important to note that pulmonary abnormalities in these patients may be due to the underlying CVD or may result from complications of treatment, such as opportunistic infection and drug toxicity (2,12). Methotrexate, commonly used in the treatment of RA, may result in a variety of ILDs, most commonly NSIP (13). In recent years, there has been a major increase in the use of biologic disease-modifying agents in the treatment of CVDs.
CHAPTER 10  Collagen-Vascular Diseases

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+ uncommon; ++, common; ++++, most common pattern.

TABLE 10-1  Relative Frequency of Patterns of Abnormality in Collagen-Vascular Diseases

<table>
<thead>
<tr>
<th>Pulmonary disease</th>
<th>RA</th>
<th>PSS</th>
<th>SLE</th>
<th>PM-DM</th>
<th>MCTD</th>
<th>Sjögren syndrome</th>
<th>Ankylosing spondylitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSIP</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>++++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>UIP</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>++++</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>OP</td>
<td>+</td>
<td>Rare</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIP</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAD</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mosaic perfusion and air trapping</td>
<td>+++</td>
<td></td>
<td></td>
<td>+++</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural effusion or thickening</td>
<td>++</td>
<td>+++</td>
<td></td>
<td></td>
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</table>

+, uncommon; ++, common; ++++, most common pattern.

(14,15). These medications, particularly agents blocking tumor necrosis factor-α such as etanercept and infliximab, may result in interstitial pneumonia, sarcoid-like disease, and vasculitis (14) (see Chapter 15).

RA is commonly associated with thoracic abnormalities, including interstitial fibrosis, OP (bronchiolitis obliterans organizing pneumonia [BOOP]), bronchiectasis, bronchiolitis obliterans, necrobiotic nodules, and pleural effusion or pleural thickening (2,3,16). Other common complications include pulmonary infection and drug toxicity (12,17). The reported prevalence of ILD in patients with RA is highly variable, depending on the method of detection (e.g., pulmonary function test [PFT], radiograph, HRCT) and the population selected (asymptomatic, symptomatic, autopsy), ranging from as low as 4% and as high as 68% (18,19). Population-based studies have shown, however, that clinically significant ILD occurs in 5% to 10% of patients with RA (20,21) and fewer than 10% of patients die of respiratory failure (20,22). Findings consistent with ILD are detectable on the chest radiograph in approximately 10% of patients (23–25). The reported prevalence of ILD on HRCT in patients with RA ranges from 19% to 56% (26–29). In many of these cases, the ILD was not associated with any pulmonary symptoms. Asymptomatic ILD is common in patients with RA, and its significance and implications for therapy is not clear (12). Symptomatic ILD in RA usually follows the onset of joint symptoms by up to several years; however, it may occasionally precede joint disease (12).

There is controversy in the literature about the relative prevalence of UIP and NSIP on surgical biopsy in patients with RA. Some investigators have reported a greater prevalence of UIP (18,30), some a similar prevalence (31,32), and some a higher prevalence of NSIP (6). Lee et al. (30) reviewed the histologic findings in 18 patients with RA who underwent surgical biopsy for ILD using the American Thoracic Society/European Respiratory Society (ATS/ERS) consensus classification (15). Ten (55%) patients had a UIP pattern, six (33%) patients had an NSIP pattern, and two (11%) patients had an OP pattern. RA preceded ILD in 12 patients; in 3 patients, ILD preceded RA, and in 3 patients, both conditions were diagnosed simultaneously (30). Yoshinouchi et al. (31) reported the HRCT and histologic findings in 16 patients with RA and ILD. Seven patients had UIP, seven had NSIP, and two had both UIP and NSIP (31). In the study by Tansey et al. (6) of 15 patients with RA and ILD, 7 had NSIP, 6 had follicular bronchiolitis and a minor component of NSIP, and 2 had UIP. Despite this controversy, perhaps because of the greater prevalence of the UIP pattern on HRCT and the fact that patients with characteristic findings of UIP seldom undergo lung biopsy, most recent reviews and studies consider UIP to be the most common pattern of ILD seen in patients with RA (1–4,18).

High-Resolution Computed Tomography Findings

The HRCT findings of ILD in patients with RA are most commonly those of UIP (Figs. 10-1 to 10-3, Table 10-2) and less frequently NSIP (Fig. 10-4) or OP pattern. The HRCT shows reticular pattern and mild honeycombing in the subpleural lung regions.
FIGURE 10-2  A–C: Prone HRCT at three levels in a patient with RA and lung disease. Subpleural opacities in the mid-lung (A and B) have a small nodular or branching appearance, consistent with that of follicular bronchiolitis. At a lower level (C), findings of intralobular interstitial thickening and traction bronchiectasis are typical of fibrosis.

FIGURE 10-3  RA and end-stage UIP with honeycombing.  A: HRCT at the level of the tracheal carina shows subpleural honeycombing and interlobular septal thickening indistinguishable from IPF.  B: HRCT through the right lung base shows diffuse honeycombing and septal thickening.
TABLE 10-2 HRCT Findings in Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Finding(s)</th>
<th>Most common finding(s).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis without fibrosis</td>
<td></td>
</tr>
<tr>
<td>Findings of fibrosis (i.e., traction bronchiectasis and bronchiolectasis, intralobular interstitial thickening, irregular interlobular septal thickening, irregular interfaces)</td>
<td></td>
</tr>
<tr>
<td>Honeycombing</td>
<td></td>
</tr>
<tr>
<td>Ground-glass opacity</td>
<td></td>
</tr>
<tr>
<td>Peripheral and subpleural predominance of fibrosis or ground-glass opacity</td>
<td></td>
</tr>
<tr>
<td>Lower lung zone and posterior predominance</td>
<td></td>
</tr>
<tr>
<td>Pleural thickening or effusion</td>
<td></td>
</tr>
<tr>
<td>Small centrilobular nodules (follicular bronchiolitis)</td>
<td></td>
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<tr>
<td>Large (rheumatoid) nodules</td>
<td></td>
</tr>
<tr>
<td>Findings of bronchiolitis obliterans (i.e., air trapping, mosaic perfusion)</td>
<td></td>
</tr>
</tbody>
</table>

*Most common finding(s).  
Finding(s) most helpful in differential diagnosis.

(27,33,34). Tanaka et al. (33) reviewed the HRCT findings in 63 patients with RA seen at an ILD clinic. The most common abnormalities evident on HRCT were reticulation (98% patients) and ground-glass opacities (90% patients). The authors identified four major CT patterns: UIP (41%), NSIP (30%), bronchiolitis (17%), and OP (8%). The UIP pattern was characterized by the presence of irregular linear opacities (100% of patients) and honeycombing (96%), involving predominantly the basal and subpleural lung regions with mild associated ground-glass opacities (92%) (Figs. 10-1 to 10-3). Traction bronchiectasis and architectural distortion, when present, were always observed concomitantly with reticulation and honeycombing. NSIP was characterized by bilateral ground-glass opacities (100%), with some predominance of subpleural and basal regions, associated with fine reticulation (100%) and minor honeycombing (53%) (Fig. 10-4). OP was characterized by the presence of multiple patchy areas of airspace consolidation (80%) and ground-glass opacities (100%), usually with subpleural or peribronchial distribution (33). In all but 2 of the 16 patients who underwent lung biopsy, the CT findings reflected the pathologic findings (33). Biederer et al. (34) correlated HRCT and PFTs in 33 patients with suspected ILD associated with RA. The most common finding was reticulation seen in 40 of 53 (75%) patients, presenting as a mixed pattern with ground-glass opacities in 15 of 40. A pure reticular pattern was most common in patients with long-standing ILD. The extent of interstitial abnormalities was highly variable and correlated with a decrease in carbon monoxide diffusing capacity (DLCO) (34). Patients with a definite UIP pattern on HRCT seldom undergo lung biopsy, but patients with RA and an NSIP pattern or indeterminate findings on HRCT may have UIP or NSIP on surgical biopsy. Kim et al. (35) reviewed the HRCT findings in 82 patients with RA who had ILD. The HRCT scans were interpreted as definite UIP in 20 (24%), likely NSIP in 19 (23%), and indeterminate in 43 (52%). Definite UIP was considered present when there was basilar predominant reticulation, traction bronchiectasis, and honeycombing, with limited ground-glass opacity. Predominantly bibasilar ground-glass opacities with limited (or no) reticulation and absent honeycombing was interpreted as likely NSIP. Of the 19 patients with a likely NSIP pattern on HRCT, 6 underwent surgical lung biopsy, which showed UIP in 4 and NSIP in 2 patients. Six out of 43 patients with an indeterminate pattern on HRCT underwent surgical lung biopsy, which showed UIP in 5 patients and NSIP in 1 (35).

Overall, patients with CVD-related ILD, including patients with RA-related ILD, have a better prognosis than patients with IPF (4,36,37), but patients with RA and a definite UIP pattern on HRCT have a prognosis similar to that seen in patients with IPF (35,37). In one study of 362 patients (269 with IIP and 93 with interstitial pneumonia associated with CVD), the patients with interstitial pneumonia associated with CVD survived longer (mean, 177 months) than patients with IIP (mean, 66.9 ± 6.5 months; p = 0.001) (36). A multivariate analysis showed that younger age, better pulmonary function, and the presence of a CVD were independent prognostic factors. No significant differences were found between CVD-associated NSIP and idiopathic NSIP in survival, clinical features, or lung function. The mean survival of patients with UIP associated with CVD was 177 months compared to 70 months in patients with IPF (36). However, the study showed a trend toward worse survival in RA-UIP patients than in RA-ILD patients with an NSIP pattern (p = 0.08) (36). Kim et al. (35) compared the prognosis in 82 patients with RA-associated ILD with that in 51 patients with IPF. Twenty (24%) out of 82 patients with RA had HRCT findings interpreted as definite UIP. These patients showed worse survival than those without this pattern (median survival, 3.2 vs. 6.6 years), and a survival similar to that shown by those with IPF. Analysis of specific HRCT features demonstrated that traction bronchiectasis...
bronchiectasis on HRCT (48). Perez et al. (46) reviewed the prevalence and characteristics of airways involvement in 50 RA patients who did not have ILD. They found HRCT to be more sensitive in detecting airway abnormalities than were PFTs. HRCT demonstrated bronchial or lung abnormalities, or both, in 35 cases (70%), consisting of air trapping ($n = 16; 32\%$), cylindrical bronchiectasis ($n = 15; 30\%$), and mild heterogeneity in lung attenuation (i.e., mosaic perfusion) ($n = 10; 20\%$). In contrast, PFTs demonstrated airway obstruction (i.e., reduced forced expiratory volume in 1 second/forced vital capacity [FVC]) in only nine patients (18%) and evidence of small airways disease in only four (8%).

Patients with RA-associated UIP or NSIP may occasionally develop acute exacerbation, i.e., rapid deterioration of respiratory symptoms without any identifiable cause and new parenchymal opacities due to diffuse alveolar damage (DAD) or, less commonly, OP superimposed on the ILD (Fig. 10-5) (38–41). The HRCT findings of acute exacerbation consist of extensive bilateral ground-glass opacities with or without associated dependent areas of consolidation superimposed on a background of UIP or NSIP (38,42). The prognosis of acute exacerbation in ILD in CVD is better than that of acute exacerbation of IPF (43). In one study (43), the 90-day mortality of acute exacerbation in 15 patients with CVD-associated interstitial pneumonias, including 6 with RA, was 33% compared to 69% in 13 patients who had acute exacerbation of IPF (43). Rarely, DAD may be the initial pulmonary manifestation of RA (44).

The most common abnormalities seen on HRCT in patients with RA are bronchiectasis and findings consistent with bronchiolitis (Fig. 10-6, Table 10-2). Bronchiectasis has been reported on HRCT in approximately 30% of patients with RA (45,46). In one study of 84 patients with RA, 38 (49%) had abnormal HRCT scans (45). The findings included (a) bronchiectasis and/or bronchiolectasis (30%), (b) pulmonary nodules (22%), (c) subpleural micronodules and/or pseudoplaques (17%), (d) nonseptal linear attenuation (18%), (e) areas of ground-glass attenuation (14%), and (f) honeycombing (10%) (45). Bronchiectasis and airways disease in RA can be associated with chronic infection, which has an increased incidence in rheumatoid patients, or bronchiolitis obliterans (46,47). For example, in a study of 20 nonsmoking RA patients who had normal chest radiographs, 5 (25%) were found to have unsuspected basal and honeycomb fibrosis were associated with worse survival. Female sex and a higher baseline DLCO were associated with better survival (35).

FIGURE 10-5 Acute exacerbation of ILD in rheumatoid arthritis. A: HRCT shows mild peripheral reticulation, irregular thickening of the interlobular septa, and minimal ground-glass opacities. The findings are consistent with UIP. B: HRCT 6 months later when the patient developed acute respiratory failure demonstrates extensive bilateral ground-glass opacities with associated linear opacities (crazy-paving pattern) and traction bronchiectasis consistent with DAD. The diagnosis of acute exacerbation of UIP was made after exclusion of other potential causes of DAD.

FIGURE 10-6 Bronchiectasis and obliterative bronchiolitis in RA. HRCT shows extensive bilateral bronchiectasis and areas of decreased attenuation and vascularity (mosaic perfusion), mainly in the left lung.
Utility of High-Resolution Computed Tomography

HRCT is more sensitive than chest radiography in the diagnosis of lung disease in patients who have RA. Fujii et al. (57) reviewed the chest radiographic and HRCT findings of 91 patients who had RA. On HRCT, 43 patients had findings of UIP with fibrosis, 5 had findings consistent with bronchiolitis obliterans, and 43 had a normal HRCT. In approximately half of these 91 patients, chest radiographic findings were similar to those shown on HRCT. However, 17 of 46 (37%) patients believed to have normal chest radiographs had HRCT abnormalities consistent with rheumatoid lung disease. Furthermore, 14 of 43 (33%) patients believed to have abnormal chest radiographs had no evidence of significant lung disease on HRCT (57). Also, HRCT can be useful in demonstrating lung disease in RA patients who have normal chest radiographs but have pulmonary function abnormalities (59,60). Some HRCT findings are more frequent in symptomatic patients who have rheumatoid lung disease (45). These include honeycombing, bronchiectasis, nodules, and ground-glass opacity.

PROGRESSIVE SYSTEMIC SCLEROSIS (SCLERODERMA)

PSS has a higher prevalence of pulmonary involvement than the other CVDs. The most common manifestations and leading causes of death are interstitial fibrosis, which occurs eventually in up to 75% of patients, and pulmonary arterial hypertension (61,62). ILD most often complicates the diffuse cutaneous form of PSS but can also be associated with the limited form of the disease or with PSS without cutaneous involvement (20,61). Initial studies using echocardiography suggested a prevalence of PA hypertension of up to 49% in PSS, but more recent prospective studies using cardiac catheterization as the gold standard for diagnosis have shown a prevalence of 8 to 12% (61,63,64). Approximately 80% of patients with PSS and ILD have a histologic pattern of NSIP (11,65). Bouros et al. (11) reviewed the histologic findings in 80 patients with PSS and ILD. Approximately 78% had NSIP, 8% had UIP, 7% had end-stage lung disease, and the remaining had other patterns. The most common abnormality on chest radiography is a symmetric basal reticulonodular pattern. The chest radiograph, however, may be normal in patients with abnormal PFTs and abnormal HRCT (66). The incidence of radiographically recognizable interstitial disease is probably around 25%, although various studies quote an incidence ranging from 10% to 80% (67).

High-Resolution Computed Tomography Findings

The HRCT findings of interstitial fibrosis in PSS usually resemble those of idiopathic NSIP and consist mainly of ground-glass opacities frequently with superimposed fine...
section iii

High-Resolution CT Diagnosis of Diffuse Lung Disease

FIGURE 10-8  NSIP in progressive systemic sclerosis. A: HRCT performed on a multidetector CT scanner shows extensive bilateral ground-glass opacities and mild superimposed reticulation. B: Coronal reformation demonstrates predominantly peripheral and lower lung zone distribution of the ground-glass opacities and reticulation.

Reticulation and traction bronchiectasis (Figs. 10-8 and 10-9, Table 10-3) (5,65). Associated focal areas of consolidation are seen in some cases (Fig. 10-10) (68). Desai et al. (65) compared the HRCT findings in 225 patients with ILD associated with PSS with the findings in 40 consecutive patients with IPF and 27 patients with idiopathic NSIP. Approximately two-thirds of patients with PSS had predominant ground-glass opacities or a mixed pattern with ground-glass opacities and reticulation, and one-third of patients had a predominant reticular pattern. This was similar to patients with idiopathic NSIP. The only difference was the overall extent of abnormalities, which was smaller in patients with PSS (median extent of ILD was 13% of the lung parenchyma compared to 30% for idiopathic NSIP). Although NSIP is the most common pattern of abnormality seen in patients with PSS, reticulation may sometimes be the predominant abnormality on HRCT and result in an appearance similar to that of IPF (Figs. 10-11 and 10-12).

Remy-Jardin et al. (69) reviewed the HRCT, PFT, and bronchoalveolar lavage results of 53 patients who had PSS, emphasizing the frequency of ground-glass opacity and honeycombing in these subjects. Among the 32 patients who had abnormal HRCT findings, 26 (81%) had ground-glass opacities and 19 (59%) had honeycombing. The honeycombing in PSS is usually of limited extent and associated with areas of ground-glass opacity. In the study by Remy-Jardin et al. (69), all patients who had honeycombing also showed ground-glass opacity. These abnormalities had a distinct basal, posterior, and peripheral predominance. Goldin et al. (70) reviewed the HRCT scans in 162 patients with symptomatic PSS-related ILD. The main findings consisted of ground-glass opacities (90%) including areas of ground-glass attenuation without evidence of fibrosis (49%), evidence of fibrosis (93%), and honeycombing (37%). All findings involved mainly the lower lung zones. The authors concluded that in the majority of cases the findings were consistent with NSIP but that the presence of honeycombing in 37% of HRCT scans suggests that some patients may have a mixture or overlap of NSIP and UIP patterns (70). The extent of pulmonary fibrosis seen on HRCT scans was significantly negatively correlated with FVC and TLC, i.e., associated with restrictive physiologic impairment, and negatively correlated with DLCO, i.e., associated with impairment.

FIGURE 10-9  A and B: Subpleural ground-glass opacity in a young patient with scleroderma. A subtle but distinct increase in opacity is visible in the posterior lungs on prone scans.
FIGURE 10-10  Subpleural ground-glass opacity and consolidation in a patient with scleroderma. Before treatment (A–C), subpleural opacities are the predominant abnormality. Traction bronchiectasis (C) seen within areas of opacity in the posterior costophrenic sulcus indicates some evidence of fibrosis. After treatment, scans at similar levels (D–F) show considerable reduction in opacity. Persistent abnormalities in the posterior lungs and at the lung bases, including irregular reticulation and traction bronchiectasis, likely represent fibrosis.

TABLE 10-3  HRCT Findings in Progressive Systemic Sclerosis (Scleroderma)

<table>
<thead>
<tr>
<th>Finding(S)</th>
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<tbody>
<tr>
<td>Ground-glass opacity</td>
</tr>
<tr>
<td>Findings of fibrosis (i.e., honeycombing, traction bronchiectasis and bronchiolectasis, intralobular interstitial thickening, irregular interlobular septal thickening, irregular interfaces)</td>
</tr>
<tr>
<td>Peripheral and subpleural predominance of fibrosis or ground-glass opacity</td>
</tr>
<tr>
<td>Lower lung zone and posterior predominance</td>
</tr>
<tr>
<td>Pleural thickening or effusion</td>
</tr>
<tr>
<td>Small centrilobular nodules (follicular bronchiolitis)</td>
</tr>
<tr>
<td>Esophageal dilatation</td>
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</table>

*Most common finding(s).  
Finding(s) most helpful in differential diagnosis.

The extent and severity of fibrosis on HRCT also correlate with the peak PA pressures and may be helpful in screening for pulmonary hypertension in patients with PSS.

Small nodules with or without associated honeycombing have also been reported in patients who have PSS and are presumed to represent focal lymphoid hyperplasia (follicular bronchiolitis), a common histologic finding in PSS. However, nodules are not a prominent HRCT feature of this disease.

Other findings on CT in patients who have PSS include diffuse pleural thickening, seen in one-third of cases; asymptomatic esophageal dilatation, present in 40% to 80% of cases (Fig. 10-12); and enlarged mediastinal nodes, seen in approximately 60% of cases. The presence of esophageal dilatation may be
High-Resolution CT Diagnosis of Diffuse Lung Disease

PSS and severity of ILD. Overall, the pattern and distribution of abnormalities were similar to those seen in adults. However, whereas in adults honeycombing predominates in the lower lung zones, in children the honeycombing was most severe in the upper lung zones (75).

Follow-up of patients with PSS and ILD may show initial improvement (Fig. 10-10), but in the majority of cases the fibrosis progresses on long-term follow-up (Fig. 10-13). Kim et al. (68) reviewed the findings on serial HRCT scans in 40 patients with PSS and ILD over a mean follow-up period of 39 months. On the initial HRCT, all patients had ground-glass opacities (mean extent 18%), 36 (90%) had irregular linear opacities (mean extent 4%), 13 (33%) had consolidation (mean extent 1.9%), and 12

**FIGURE 10-11** A and B: Findings of fibrosis in a patient with scleroderma. Subpleural honeycombing, traction bronchiectasis, and some irregular interlobular septal thickening are the predominant features. These abnormalities closely mimic the appearance of IPF.

**FIGURE 10-12** A and B: Prone HRCT in a patient with scleroderma with mild interstitial fibrosis and esophageal dilatation. Irregular reticular opacities are visible in the peripheral lung, consistent with fibrosis. The esophagus (e) is dilated and contains an air-fluid level.
ILD may also represent fibrosis particularly when there is admixed reticulation or traction bronchiectasis (76–78). The current evidence in the literature is that ground-glass opacities in patients with PSS-associated NSIP are most commonly associated with irreversible disease (79,80). Shah et al. (79) performed sequential HRCT in 41 patients with PSS over a mean follow-up period of 27 months (range, 6–60 months). Ground-glass opacity was the most common imaging finding, present in 66% of patients, and usually associated with other signs of interstitial disease, including nonfibrotic interstitial opacities in 27% and fibrotic interstitial opacities in 32%. Improvement was only documented in two (5%) patients with ground-glass opacities and nonfibrotic interstitial opacities (79).

The prognosis of NSIP associated with PSS is similar to that of idiopathic NSIP and considerably better than that of IPF (36). The prognosis of ILD in PSS is influenced more by the severity of lung involvement than the pattern of parenchymal disease. Bouros et al. (11) correlated the initial histologic findings with prognosis in 80 patients with PSS-associated ILD. The histologic appearances included cellular NSIP (n = 15), fibrotic NSIP (n = 47), UIP (n = 6), end-stage lung disease (n = 6), and other patterns (n = 6). Five-year survival differed little between NSIP (91%) and UIP/end-stage lung disease (82%); mortality was associated with lower initial DLCO and FVC levels (p = 0.004 and p = 0.007, respectively). Survival and serial FVC and DLCO did not differ between cellular and fibrotic NSIP. Increased mortality in NSIP was associated with lower initial DLCO (p = 0.04) and deterioration in DLCO levels during the next 3 years (p < 0.005). The authors concluded that outcome in PSS-associated ILD is linked more strongly to disease severity at presentation and serial DLCO than to histopathologic findings (11).

Utility of High-Resolution Computed Tomography

HRCT plays a major role in the detection and characterization of lung involvement in PSS patients (70,76). HRCT is commonly performed to identify the presence of ILD in patients with PSS because the clinical symptoms and PFTs are nonspecific and the chest radiographic findings are often equivocal or falsely negative (76). Dyspnea may result from ILD, pulmonary vascular disease, or cardiac impairment and PFTs are limited by the wide range of normal, typically 80% to 120% of normal values (76). Schurawitzki et al. (66) studied 23 patients who had PSS using chest radiographs and HRCT. Chest radiographs were abnormal in only 15 (65%), but HRCT showed evidence of ILD in 21 (91%); the authors concluded that HRCT was clearly superior to chest radiographs for detecting minimal lung disease.

Wells et al. (77) assessed the potential role of HRCT as a predictor of lung histology on open-lung biopsy specimens in patients who had PSS. In this study, CT discriminated correctly between inflammatory and fibrotic histologic appearances in 16 of 20 (80%) biopsy specimens. Predominant ground-glass opacities often correlated with the presence of inflammation, and the presence of a predominantly reticular pattern on HRCT correlated closely with the presence of fibrosis on the pathologic specimens (77). However, ground-glass on HRCT in patients with (30%) had honeycombing (mean extent 2%). Follow-up HRCT showed increase in overall extent of disease in 24 patients and showed no change in 16 patients. The worsening was due mainly to an increased extent of ground-glass opacity and honeycombing. The increase in the extent of honeycombing on CT correlated significantly with the decrease in DLCO (68). There was no significant difference in the extent of ground-glass opacity, irregular linear opacity, and honeycombing on the initial HRCT between patients who showed progression of disease or remained stable.

**FIGURE 10-13** Disease progression in PSS. A: HRCT shows bilateral ground-glass opacities, reticulation, traction bronchiectasis, and minimal honeycombing. B: HRCT 2 years later demonstrates progression of fibrosis with more extensive reticulation and honeycombing. Also noted is a fluid level within the dilated esophagus.
thickening or architectural distortion), pulmonary fibrosis (i.e., reticular intralobular interstitial thickening, traction bronchiectasis, and bronchiolectasis), and honeycomb cysts. HRCT scan findings included evidence of pulmonary fibrosis (93% of patients), areas of pure ground-glass opacity (49%) and areas of honeycombing (37%). The extent of pulmonary fibrosis on baseline HRCT scans was predictive of the progression rate in the absence of active immunosuppressive therapy as well as the response to cyclophosphamide therapy, which was greatest in those with the most extensive pulmonary fibrosis seen on baseline HRCT scans (70). Pure ground-glass opacity and the extent of honeycombing at the baseline HRCT did not significantly affect the FVC at 12 months (70).

Densitometry may be more reproducible than visual assessment of lung changes on HRCT and may correlate better with functional impairment in patients with PSS. Camiciottoli et al. (81) assessed the intra- and interobserver reproducibility of visual and densitometric lung CT analysis in 48 PSS patients. The intra- and interobserver reproducibility of mean lung attenuation (intraobserver weighted kappa = 0.97; interobserver weighted kappa = 0.96) were higher than those of visual assessment (intraobserver weighted kappa = 0.71; interobserver weighted kappa = 0.69). In univariate analysis, only densitometric measurements correlated with exercise and quality of life questionnaire parameters. In multivariate analysis, mean lung attenuation, skewness, and kurtosis correlated significantly with FRC, FVC, DLCO, exercise test, and quality of life questionnaire parameters, while visual assessment was associated only with FRC and FVC (81).

The best estimate of prognosis in PSS-ILD is probably obtained by using a semi-quantitative assessment of extent of disease on CT, integrated, if necessary, with lung function. Goh et al. (82) evaluated the prognostic value of baseline HRCT and PFT variables in 215 patients with PSS-ILD. Increasingly extensive disease on HRCT was a powerful predictor of mortality ($p < 0.0005$), with an optimal extent threshold of 20%. Patients with disease extent less than or equal to 10% on HRCT were classified as having limited disease and those with extent greater than or equal to 30% as having extensive disease. In patients with HRCT extent of 10% to 30% (termed indeterminate disease), a FVC threshold of 70% was an adequate prognostic substitute. On the basis of these observations, Systemic sclerosis associated interstitial lung disease (SSc-ILD) was staged as limited disease (minimal disease on HRCT or, in indeterminate cases, FVC $\geq 70\%$) or extensive disease (extensive disease on HRCT or, in indeterminate cases, FVC $< 70\%$). This system (hazards ratio [HR], 3.46; 95% confidence interval [CI], 2.19–5.46; $p < 0.0005$) was more discriminatory than an HRCT threshold of 20% (HR, 2.48; 95% CI, 1.57–3.92; $p < 0.0005$) or an FVC threshold of 70% (HR, 2.11; 95% CI, 1.34–3.32; $p = 0.001$). The system was evaluated by four trainees and four practitioners, in PSS patients with minimal and severe disease on HRCT defined as clearly less than 20% or clearly more than 20%, respectively, and the use of an FVC threshold of 70% in indeterminate cases. The staging system was predictive of mortality for all scorers. The authors concluded that that discriminatory prognostic information in PSS-associated ILD can be obtained using a staging system based on combined evaluation with HRCT and PFTs (82).

**SYSTEMIC LUPUS ERYTHEMATOSUS**

SLE is a multisystem autoimmune CVD that typically affects young women (female-to-male ratio of 9:1) (83,84). The age at diagnosis is usually between 15 and 45 years (84). SLE is commonly associated with pleural and pulmonary abnormalities. An autopsy study of 90 patients with SLE found pleuropulmonary involvement in 98%, the most common being pleuritis (78%), bacterial infections (58%), primary and secondary alveolar hemorrhages (26%), followed by distal airway alterations (21%), opportunistic infections (14%), and pulmonary thromboembolism, both acute and chronic (8%) (85). Sepsis was considered the major cause of death (85). Pleural effusion is seen on chest radiographs in 30% to 50% of patients during the course of disease (3,84). The pleural effusion may be uni- or bilateral, and is usually small to moderate in size. Pleural involvement may be the first manifestation of SLE and is commonly associated with pericarditis (86).

More than 50% of patients who have SLE have lung disease at some time (87). Pulmonary parenchymal complications of SLE include pneumonia, acute lupus pneumonitis, diffuse pulmonary hemorrhage, and ILD (86). The most common pulmonary complication of SLE is pneumonia (86,87). Patients with SLE are more susceptible to bacterial and opportunistic infections due to immunosuppressive therapy with corticosteroids or other agents as well immunologic dysfunction related to SLE (86). Acute lupus pneumonitis occurs in 1% to 4% of patients with SLE and usually manifests with sudden onset of fever, cough and dyspnea (86). It is characterized histologically by a combination of DAD, edema, and alveolar hemorrhage (5,86). Diffuse alveolar hemorrhage is an uncommon but severe manifestation of SLE, with a prevalence ranging from 0.5% to 6% (86).

Clinically significant chronic ILD develops in 3% to 8% of patients with SLE, there being a progressive increase in prevalence with disease duration (86,88,89). Trivial interstitial abnormalities have been reported on HRCT in up to 38% of patients with SLE and no clinical evidence of lung involvement (4,90). Because significant ILD is uncommon in SLE, there is limited data on the pathologic pattern. However, as with other CVDs, the most common pattern appears to be NSIP followed by UIP (4,6,86). OP (BOOP) is also seen with increased frequency in patients who have SLE (86,91) and LIP has been described in a few patients (86).

**High-Resolution Computed Tomography Findings**

HRCT findings in patients who have SLE include (a) findings of fibrosis, although they are less common than in patients...
who have RA or scleroderma; (b) ground-glass opacity; (c) small nodules; (d) bronchial wall thickening or bronchiectasis; and (e) pleural thickening or effusion (Table 10-4).

The most common HRCT findings of interstitial fibrosis in patients with SLE include interlobular septal thickening, intralobular interstitial thickening, ground-glass opacities, and architectural distortion (Figs. 10-14 and 10-15) (90,92,93). These findings tend to be mild involving a small percentage of the lung parenchyma and usually are not associated with clinical symptoms or abnormal pulmonary function (4,90,92). Diffuse interstitial disease with a pattern characteristic of NSIP or UIP is considerably less common being seen in approximately 4% of patients (Figs. 10-14 and 10-15) (94).

Ground-glass opacity and consolidation in patients with SLE may be associated with pneumonia, lupus pneumonitis (Fig. 10-16), pulmonary hemorrhage (Fig. 10-17), or, occasionally organizing pneumonia (BOOP) (5,94). Pulmonary infection, acute lupus pneumonitis, and diffuse alveolar hemorrhage may result in clinical and radiologic findings of ARDS (84,95). Occasionally, hazy or fluffy centrilobular perivascular opacities may be seen, likely related to vasculitis (96).

Findings of airways disease such as bronchial wall thickening and bronchiectasis have been reported in 18% to 20% of patients who have SLE (90,92). Pleuroperticardial abnormalities were seen in 15% to 17% of cases in two studies (92,93).

### Utility of High-Resolution Computed Tomography

Several studies have shown that interstitial fibrosis is seen more frequently on HRCT than on chest radiographs (90,92,93,97). Bankier et al. (90) performed a

<table>
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<tr>
<th>TABLE 10-4 HRCT Findings in Systemic Lupus Erythematosus</th>
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<tr>
<td>Ground-glass opacity&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Findings of fibrosis (i.e., interlobular interstitial thickening, irregular interlobular septal thickening, irregular interfaces, bronchiectasis and bronchiolectasis)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Honeycombing (less common than with IPF)</td>
</tr>
<tr>
<td>Peripheral and subpleural predominance of fibrosis or ground-glass opacity&lt;sup&gt;c,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lower lung zone and posterior predominance&lt;sup&gt;c,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>Pleural thickening or effusion&lt;sup&gt;c,b&lt;/sup&gt;</td>
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<sup>a</sup>Most common finding(s).
<sup>b</sup> Finding(s) most helpful in differential diagnosis.
Polyomyositis and dermatomyositis are chronic autoimmune disorders characterized by weakness in the proximal limb muscles (98,99). Approximately 50% of patients have a characteristic skin rash, which enables distinction of dermatomyositis from polymyositis. PM-DM is a rare disease, with an overall incidence ranging from 2 to 10 new cases per million persons at risk per year (99). Pulmonary complications occur in more than 40% of patients, and are associated with significant morbidity and mortality (99). Common complications include ILD, aspiration, pneumonia, and drug-induced lung diseases (99). The risk of malignancy is also increased, particularly in DM, the standardized index ratio for lung cancer being 5.9 for DM and 2.8 for PM (100).

It is estimated that 35% to 40% of patients with PM-DM develop ILD during the course of their disease (101). The pattern of involvement is most commonly NSIP (6,101–103). Other histologic patterns are OP, UIP, and DAD. LIP is uncommon (99,101). Patients with PM-DM may have more than one pattern of abnormality on lung biopsy, the most common combination being NSIP and OP (6). The radiographic findings of PM-DM-associated ILD usually consist of reticular opacities and/or areas of
consolidation. In one study of 57 patients with PM-DM-associated ILD, reticular opacities were seen in 95% of cases and areas of consolidation in 25% (102). In more than 90% of patients, the findings involved mainly the lower lobes (102).

**High-Resolution Computed Tomography Findings**

HRCT findings of PM-DM include (a) ground-glass opacity; (b) findings of fibrosis, although honeycombing is uncommon; and (c) consolidation (Figs. 10-18 to 10-20, Table 10-5). These findings are consistent with NSIP being the most common histologic pattern followed by OP, UIP, and DAD. Ikezoe et al. (104) reviewed the HRCT findings in 25 patients who had PM-DM; 23 had abnormal HRCT scans. The most common findings seen in these 23 patients included ground-glass opacities (92%), linear opacities (92%), irregular interfaces (88%), airspace consolidation (52%), parenchymal micronodules (28%), and honeycombing (16%). A relatively high prevalence of airspace consolidation (52%) and a low prevalence of honeycombing (16%) were observed. Correlation of HRCT with pathologic findings showed that 2 patients who had extensive consolidation had DAD; 8 patients who had subpleural bandlike opacities or airspace consolidation, or both, had OP; and 4 patients who had honeycombing had UIP (104). Cottin et al. (103) assessed the HRCT and histologic findings in 17 patients with PM-DM. The most common HRCT findings were reticular and ground-glass opacities. Histologic patterns included NSIP in 11 (65%) patients, UIP in 2, OP (BOOP) in 2, LIP in 1, and unclassifiable interstitial pneumonia in 1 patient (60). Survival at 5 years was 50%. Douglas et al. (102) reviewed the HRCT findings in 30 patients with PM-DM-associated ILD. The findings included irregular linear opacities seen in 19 of 30 (63%) patients, consolidation in 16 of 30 (53%), and ground-glass opacities in 13 of 30 (43%). In the majority of patients the findings had a lower lobe predominance. None of the patients had honeycombing (102). Surgical lung biopsies available in

<table>
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<th>TABLE 10-5 HRCT Findings in Polymyositis-Dermatomyositis</th>
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<tr>
<td>Ground-glass opacity&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Honeycombing (less common than with IPF)</td>
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<tr>
<td>Peripheral and subpleural predominance of fibrosis or ground-glass opacity&lt;sup&gt;a,b&lt;/sup&gt;</td>
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<sup>a</sup>Most common finding(s).

<sup>b</sup>Finding(s) most helpful in differential diagnosis.
22 patients showed NSIP in 18, organizing DAD in 2, BOOP in 1, and UIP in 1 patient.

Mino et al. (105) assessed the HRCT findings before and after treatment with corticosteroids and immunosuppressants in 19 patients who had PM-DM. Findings on the initial HRCT scans included pleural irregularities and prominent interlobular septa ($n = 19$), ground-glass opacity ($n = 19$), patchy consolidation ($n = 19$), parenchymal bands ($n = 15$), irregular peribronchovascular thickening ($n = 15$), and subpleural lines ($n = 7$). Honeycombing was not detected on any CT images. These findings were more severe in the basal and subpleural regions of the lungs. In 16 of the 17 patients who underwent sequential CT, areas of consolidation, parenchymal bands, and irregular peribronchovascular thickening improved, becoming pleural irregularities and prominent interlobular septa, ground-glass opacity, and subpleural lines on follow-up CT scans (105).

Akira et al. (106) performed sequential HRCT scans in seven patients who had PM-DM, five of whom had histologic confirmation of pulmonary involvement. The predominant finding on the initial CT scans in four patients was subpleural consolidation, which was shown to be due to OP (BOOP). One patient with bilateral patchy areas of ground-glass opacity and consolidation was shown to have DAD. In most cases, consolidation improved with use of corticosteroid or immunosuppressive therapy, or both; in two patients, however, consolidation evolved into honeycombing. In one patient with subpleural linear opacities, parenchymal abnormalities slowly progressed, and linear opacities had evolved into honeycombing at the patient’s 8-year follow-up.

Bonnefoy et al. (107) assessed the changes in the pattern, distribution, and extent of ILD on HRCT in 20 patients with PM-DM after a mean follow-up of 38 months. The patients were classified into four groups according to the dominant pattern of abnormality on the initial HRCT: ground-glass opacity and reticulation (45%), airspace consolidation (20%), honeycombing (20%), and normal or almost normal lung (15%). Under medical treatment, the ground-glass opacities and consolidation most commonly improved, while the extent of honeycombing usually increased. Some patients showed marked clinical deterioration with development of extensive consolidation on HRCT and DAD histologically, regardless of the initial pattern on HRCT (107). In another follow-up study of 19 patients who had PM-DM and HRCT, the initial HRCT showed findings consistent with predominant inflammation in 11 patients, mixed inflammation and fibrosis in 2, fibrosis in 2, and was normal in 4 (108). All patients were treated with high-dose glucocorticoids and other immunosuppressive agents. Follow-up examination 12 to 238 weeks after the initial examination was performed in 15 patients. None of the patients with changes consistent with ILD in the initial HRCT experienced a complete resolution at follow-up investigation. Of the 11 patients with predominantly inflammatory findings at the first examination, 3 had developed fibrotic changes, 2 had mixed inflammatory and fibrotic changes, and 4 remained unchanged at the last examination; 1 patient had died and 1 had no follow-up examination. Three of the 4 patients with normal HRCT at the first examination underwent follow-up investigation; 1 had developed fibrotic changes, 1 inflammatory changes, and 1 linear opacity changes. The authors concluded that the course of ILD in patients with PM-DM could not be predicted on the first examination (108).

**MIXED CONNECTIVE TISSUE DISEASE**

MCTD is a condition characterized by clinical and laboratory findings overlapping those of PSS, SLE, and PM-DM (109). A prerequisite for diagnosis is the presence of high titers of circulating autoantibodies to uridine-rich small nuclear ribonucleoprotein (anti-U1 RNP) (4,109). MCTD is much more common in women (female-to-male ratio about 9:1) (110). Pulmonary abnormalities occur in 25% to 85% of MCTD patients during the course of the disease (111,112). The most common pulmonary complication is ILD, which has been reported in 21% to 67% of patients (3,112). The most frequent interstitial pattern in MCTD is NSIP; less common patterns include UIP, LIP, and OP (3,94). HRCT is superior to the chest radiograph in demonstrating the presence of ILD in MCTD and in distinguishing ILD from other parenchymal abnormalities (112). Other common complications of MCTD are pulmonary hypertension and pleural effusion. Pulmonary arterial hypertension occurs in 10% to 45% of patients and is associated with a poor prognosis (3). Pleural effusions, frequently transient in nature, are seen in approximately 50% of patients (109,113). Less common complications associated with MCTD include aspiration due to esophageal dysmotility; diffuse pulmonary hemorrhage and pulmonary thromboembolism (3,109).

**High-Resolution Computed Tomography Findings**

HRCT findings of MCTD include (a) ground-glass opacities, (b) subpleural micronodules, (c) reticulation, (d) septal lines, and (e) honeycombing (Figs. 10-21 to 10-23, Table 10-6). Kozuka et al. (114) reviewed the HRCT findings in 41 patients with MCTD-associated ILD. The predominant abnormalities included ground-glass opacities seen in all patients, subpleural micronodules seen in 98%, and nonseptal linear opacities seen in 80%. Other findings included intralobular reticular opacities (61%), architectural distortion (49%), and traction bronchiectasis (44%), and, less commonly, interlobular septal thickening, ill-defined centrilobular nodules, and honeycombing. The abnormalities usually had a peripheral distribution and lower lobe predominance (114). Saito et al. (115) reviewed the HRCT scans of 35 patients with MCTD and ILD. Septal thickening was seen in 100% of patients, subpleural micronodules in 94%, honeycombing in 51%,...
subpleural linear opacities in 37%, and ground-glass opacities in 11%. The predominant HRCT pattern was interlobular septal thickening in 83% of patients, honeycombing in 11%, subpleural micronodules in 3%, and consolidation in 3% (115). The differences between the results of the study by Saito et al. (115) and the one by Kozuka et al. (114) are presumably related to different patient populations and the different interval between onset of disease and the HRCT. The patients in the report by Kozuka et al. (114) underwent HRCT of the chest within 1 year (mean, 4.5 months) of the diagnosis of MCTD, compared to a mean interval of 49.5 months in the study...

**FIGURE 10-21** MCTD with pulmonary fibrosis. A and B: HRCT at two levels shows a fine reticular pattern posteriorly, which reflects septal thickening and intralobular interstitial fibrosis.

**FIGURE 10-22** A–C: HRCT in a 26-year-old woman with MCTD, basilar crackles on physical examination, and restrictive disease on PFTs. Intralobular interstitial thickening results in a very fine reticular pattern in the subpleural lung and lower lobes. Traction bronchiectasis (A, arrows) is also visible.
SJÖGREN SYNDROME

Sjögren syndrome is an autoimmune disease characterized by the clinical triad of keratoconjunctivitis sicca, xerostomia, and recurrent swelling of the parotid gland caused by lymphocytic infiltration of the exocrine glands (116). The prevalence (annual incidence) of primary Sjögren syndrome in North America is 320 per 100,000 population (117), which is greater than that of SLE. It has a female-to-male ratio of 9:0. Secondary Sjögren syndrome occurs in association with other autoimmune diseases, most commonly RA (116,118). More than half the patients have respiratory symptoms, most commonly hoarseness (from dry larynx) and cough (from xerotrachea) (4). However, clinically significant respiratory disease was present in only 11% of patients in a study of 1,010 Spanish patients with primary Sjögren syndrome (119). The majority of patients with ILD have a histologic pattern of NSIP (4,120,121). Less common patterns include LIP, UIP, and OP (BOOP) (4,121). Occasionally, the interstitial disease may represent primary pulmonary lymphoma or diffuse interstitial amyloidosis (121). Airway abnormalities include bronchiectasis, chronic bronchiolitis, and follicular bronchiolitis (6,52,94). A relatively common finding in patients with Sjögren syndrome is the development of lymphoma, the prevalence being 40 times that in the general population (116). The prevalence of primary pulmonary lymphoma is estimated to be 1% to 2% in patients with Sjögren syndrome (118). The most common type is non-Hodgkin lymphoma, most frequently mucosa-associated lymphoid tissue (MALT) lymphoma (118).

The frequency of reported radiographic abnormalities ranges from 2% to 34% (122). The most common radiographic finding consists of a reticular or reticulonodular pattern, usually with a basal predominance (122,123). This pattern may be caused by LIP, interstitial fibrosis, or, occasionally, lymphoma (123,124).
High-Resolution Computed Tomography Findings

Common HRCT findings in Sjögren syndrome include (a) ground-glass opacity, (b) findings of fibrosis, (c) centrilobular nodular opacities, and (d) lung cysts (Figs. 10-24 and 10-25, Table 10-7). Franquet et al. (122) assessed the HRCT findings in 50 patients who had Sjögren syndrome for a mean of 12 years (range, 2–37 years) after the onset of disease. Abnormalities were detected in 17 patients (34%) on HRCT compared with 7 (14%) on chest radiographs. The most common findings consisted of bronchiolectasis and poorly defined centrilobular nodular or branching linear opacities (seen in 11 patients), areas of ground-glass opacity (in 7), and honeycombing (in 4). The latter was bilateral, asymmetric, and present almost exclusively in the periphery of the lower lobes (122). A tree-in-bud appearance related to infection or follicular bronchiolitis was visible in 3.

Uffmann et al. (125) performed HRCT in 37 consecutive patients with primary Sjögren syndrome and normal chest radiographs. Abnormal HRCT findings were seen in 24 of 37 patients (65%) and consisted mainly of interlobular septal thickening (n = 9), micronodules (n = 9), lung cysts (n = 5), and ground-glass opacities (n = 4). Intralobular opacities, honeycombing, and bronchiectasis were less frequent.

Lohrmann et al. (126) reviewed the HRCT scans of 24 patients with primary Sjögren syndrome. Nineteen patients (79%) had abnormal HRCT findings, including bronchiectasis, thin-walled cysts, and small pulmonary nodules (seen in 46% of patients), ground-glass opacities and emphysema (38%), interlobular septal thickening (29%), honeycombing (25%), tree-in-bud pattern (21%), and mosaic perfusion (17%) (126).

Ito et al. (120) correlated the HRCT and histologic findings in 33 patients with primary Sjögren syndrome. The most common histologic pattern was NSIP, seen in 61% of patients; less common findings included bronchiolitis, LIP, MALT lymphoma, and amyloidosis. A characteristic HRCT pattern of NSIP was defined according to the ATS/ERS classification of IIPs as consisting predominantly of ground-glass opacities, usually with associated irregular linear opacities in a predominantly peripheral and basal distribution (120,127). HRCT-pathologic correlation resulted in a 94% positive predictive value of this

<table>
<thead>
<tr>
<th>TABLE 10-7 HRCT Findings in Sjögren Syndrome</th>
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<tbody>
<tr>
<td><strong>Ground-glass opacity</strong></td>
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<tr>
<td>Findings of fibrosis (i.e., traction bronchiectasis or bronchiolectasis, intralobular interstitial thickening, irregular interlobular septal thickening, irregular interfaces)</td>
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<tr>
<td>Honeycombing</td>
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<td>Peripheral and subpleural predominance of fibrosis or ground-glass opacity</td>
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<td>Lower lung zone and posterior predominance</td>
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<td>Small centrilobular nodules (follicular bronchiolitis)</td>
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<td>Cysts or small subpleural nodules (LIP)</td>
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* Most common finding(s).
* Finding(s) most helpful in differential diagnosis.
HRCT pattern for a pathologic diagnosis of NSIP; however, the diagnostic value of HRCT was low (15%) for patterns other than NSIP (120).

Parambil et al. (121) correlated the histologic patterns with the radiographic and HRCT features in 18 patients with primary Sjögren syndrome and ILD. The main HRCT findings in NSIP were ground-glass and reticular opacities distributed peripherally in both lower lung zones. HRCT in patients with OP (BOOP) showed bilateral patchy consolidation, mainly in the subpleural and peribronchovascular regions, and patchy ground-glass opacities. UIP was characterized by reticular opacities and traction bronchiectasis in a predominantly basal and peripheral distribution and commonly associated with subpleural honeycombing. The main findings in LIP and primary pulmonary lymphoma consisted of patchy areas of consolidation, ground-glass opacities, and nodules. Multiple cysts were seen in all three patients with LIP and one of the two patients with primary pulmonary lymphoma. Prominent interlobular septal thickening with small randomly distributed nodules were present in the patient who had diffuse interstitial amyloidosis (121).

The HRCT manifestations of LIP in Sjögren syndrome are similar to those seen in LIP associated with other conditions (see Chapter 9) (128,129). The predominant findings consist of extensive areas of ground-glass opacity and randomly distributed thin-walled cysts (Fig. 10-25) (128,129). The presence of cystic lesions and focal regions of air trapping on expiratory HRCT have been associated with follicular bronchiolitis in a patient with this disease (130). Other common findings in LIP include interlobular septal thickening, intralobular linear opacities, areas of consolidation, centrilobular nodules, and subpleural nodules (129). Amyloidosis occurring in relation to Sjögren syndrome may appear as multiple nodules and cystic lesions (131) or as septal thickening with small randomly distributed nodules; the nodules may calcify (see Fig. 9-38) (121).

Lymphoma in patients who have Sjögren syndrome may result in patchy areas of consolidation, ground-glass opacities, and multiple nodules (Fig. 10-26) (118,121). The prevalence of bronchiectasis was evaluated in a cohort of 507 patients with primary Sjögren syndrome (132). Forty one (8%) patients were classified as having bronchiectasis associated with primary Sjögren syndrome (40 women, mean age of 64 years). The bronchiectasis was cylindrical and, in 29 cases (71%), located in the lower lobes. During follow-up, patients with bronchiectasis had a higher frequency of respiratory infections (56% vs. 3%, p < 0.001) and pneumonia (29% vs. 3%, p = 0.002) than did patients without (132).

**ANKYLOSING SPONDYLITIS**

Ankylosing spondylitis is a spondyloarthropathy characterized by sacroiliitis, spinal stiffness, and loss of spinal mobility (133). It is estimated to affect approximately 0.1% of the population and to have a male-to-female ratio ranging from 10:1 to 15:1 (134). The most characteristic pulmonary complication is upper-zonal fibrosis, which usually manifests 15 years or more after the onset of arthritic manifestations (134). Occasionally, however, pulmonary involvement may occur before any skeletal symptoms, or in asymptomatic persons with early-stage ankylosing spondylitis (134,135). An early review of the records of 2,080 patients with ankylosing spondylitis disclosed 28 (1.3%) who had pleuropulmonary manifestations, including 25 with apical fibrobulous lesions, 2 with pleural effusions, and 1 with apical fibrosis and pleural effusion (136). A more recent study of 1,028 ankylosing spondylitis patients seen over a 10-year period found 22 (2.1%) with apical lung fibrosis detected on chest radiography (137). Radiologically, the process begins as apical pleural involvement, and then apical opacities develop and progress to cyst formation. Generally, the disease begins unilaterally and becomes bilateral. The chest radiographic findings may closely mimic those of tuberculosis. Symptoms are usually absent, unless the cavities become secondarily infected. The histologic lesions consist of nonspecific inflammation and fibrosis. Mycobacterial or fungal superinfection of the upper lobe cysts and cavities, most commonly by Aspergillus fumigatus with formation of fungus balls, has been reported in up to one-third of the patients (134). Such infection may lead to recurrent and sometimes massive hemoptysis (134). Since the advent of HRCT several studies have shown that upper lobe fibrosis is more common than previously evident on the radiograph and that ILD, beyond apical fibrosis, is also a feature of ankylosing spondylitis (138). The cause of ILD in ankylosing spondylitis is unclear and the histologic findings have rarely been described.

**High-Resolution Computed Tomography Findings**

Common HRCT findings in ankylosing spondylitis include (a) apical fibrosis, (b) septal lines, (c) bronchiectasis, and (d) pleural thickening (Fig. 10-27, Table 10-8). Apical fibrosis in ankylosing spondylitis is frequently associated
with apical bullae and cavities and may be complicated by aspergilloma formation or necrotizing *Aspergillus* pneumonia (Fig. 10-27) (139–141). Fenlon et al. (142) prospectively assessed the chest radiographic and HRCT findings in 26 patients who had ankylosing spondylitis. Abnormalities were evident on the radiograph in 4 (15%) patients and on HRCT in 18 (69%). The most common findings on HRCT consisted of ILD, seen in 4 patients; bronchiectasis, seen in 6; mediastinal lymphadenopathy, seen in 3; paraseptal emphysema, seen in 3; tracheal dilatation, seen in 2; and apical fibrosis, seen in 2 (87). Chest radiography failed to identify any of the patients who had ILD.

Turetschek et al. (143) reviewed the HRCT findings in 25 patients with ankylosing spondylitis who had a normal chest radiographs and no history of smoking. Fifteen of 21 patients (71%) had abnormalities on HRCT, including interlobular septal thickening (33%), mild bronchial wall thickening (29%), and pleural thickening and pleuropulmonary irregularities (both 29%). Eight of 15 patients (53%) with abnormal CT and 4 of 6 patients (67%) with normal CT findings had mild restrictive lung function. Senocak et al. (144) reviewed the HRCT findings in 18 patients with ankylosing spondylitis. The most common findings in nonsmokers were septal and pleural thickening seen in 40% of nonsmokers. Apical fibrosis was present in 15% of patients; the fibrosis was unilateral and right sided in all cases and was associated with emphysema even in nonsmokers. Souza et al. (140) assessed the chest radiographs and inspiratory and expiratory HRCT features in 17 patients with ankylosing spondylitis, 8 of which were smokers. Pulmonary abnormalities were seen on chest radiography in 2 (12%) patients and on CT in 15 (88%) patients. The abnormalities on CT included evidence of airway disease in 14 (82%), interstitial abnormalities in 11 (65%), and emphysema in 6 (35%) patients. Airway abnormalities included bronchial wall thickening in 7 (41%), mosaic perfusion pattern in 3 (18%), centrilobular nodules in 3 (18%), bronchiolectasis in 2 (12%), and air trapping on expiratory HRCT in 7 (41%) patients. Interstitial abnormalities included parenchymal bands in 7 (41%), intralobular linear opacities in 2 (12%), and 1 patient each with irregular thickening of interlobular septa, subpleural lines, and honeycombing. Two (12%) patients had coarse irregular linear opacities predominantly in the upper lobes associated with focal luencies consistent with bullae or thin-walled cavities. One of the patients had an intracavitary soft-tissue mass consistent with an aspergilloma. Two of the six patients with emphysema were lifetime nonsmokers (140).

Sampaio-Barros et al. (145) performed a prospective study of 52 consecutive asymptomatic patients with ankylosing spondylitis, using chest radiography, PFTs, and

<table>
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<th>TABLE 10-8 HRCT Findings in Ankylosing Spondylitis</th>
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<td>Apical fibrosis Tender to firm, mobile, rubbery in consistency.</td>
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<tr>
<td>Septal lines</td>
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<tr>
<td>Bronchiectasis</td>
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<td>Mosaic perfusion and air trapping</td>
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- Most common finding(s).
- Finding(s) most helpful in differential diagnosis.
HRCT. Of the 52 patients, 33 (63%) had never smoked, 14 (27%) were current smokers, and 5 (10%) were ex-smokers. The chest radiograph showed pulmonary abnormalities in four patients (8%) and the PFT presented a restrictive pattern in 52% of the patients. Thoracic HRCT demonstrated abnormalities in 21 patients (40%), consisting predominantly of linear parenchymal opacities (19%), lymphadenopathy (12%), emphysema (10%), bronchiectasis (8%), and pleural involvement (8%). The authors concluded that nonspecific subclinical pulmonary involvement is frequent in AS.

In one study, the authors performed HRCT and PFTs in 20 patients with ankylosing spondylitis, including 10 with less than 10 years’ disease duration and 10 with 10 or more years’ disease duration. HRCT revealed abnormalities in 14 patients (70%) (146). The most common findings were apical fibrosis (45%) and emphysema (25%). HRCT findings were more prominent in late ankylosing spondylitis patients (disease duration ≥ 10 years) (p = 0.015). PFTs were considered as abnormal in four patients (20%). Three of these patients had concomitant HRCT abnormalities. On the other hand, 10 patients with normal PFTs had abnormalities on HRCT. The authors concluded that HRCT is superior to PFTs in detecting lung abnormalities in patients with ankylosing spondylitis.

REFERENCES


**Chapter 10** Collagen-Vascular Diseases

Cystic Lung Diseases

As defined by the Fleischner Society glossary of terms, lung cysts are round parenchymal lucencies or low-attenuation areas with well-defined interfaces with normal lung. Cysts are characteristically thin-walled structures with walls less than 3 mm in size, usually containing air, although occasionally containing fluid or solid material (1). This is in distinction to lung cavities, which, by definition, demonstrate thicker walls, and have a distinctly different differential diagnosis.

A wide variety of disease states, ranging from common to rare, can result in diffuse lung cysts (Table 19-1) (2,3). Of these, Langerhans cell histiocytosis (LCH) (4), lymphangiomyomatosis (LAM) and tuberous sclerosis complex (TSC), lymphoid interstitial pneumonia (LIP) and follicular bronchiolitis, and different types of emphysema represent those entities most likely to be encountered in routine clinical practice. Cystic lung disease is also reviewed in Chapter 6, and emphysema is discussed in the next chapter.

Other causes of lung cysts include Birt-Hogg-Dubé (BHD) syndrome (Fig. 6-13) (5–7), amyloidosis (which may be associated with lymphoproliferative disease in Sjögren syndrome) (Chapter 16) (8,9), light chain deposition disease (LCDD) (Chapter 16) (Fig. 6-14) (10,11), cystic metastases, benign metastasizing leiomyoma (12), tracheobronchial papillomatosis (3), neurofibromatosis, barotrauma in deep sea divers (Fig. 6-15), and Proteus syndrome (Fig. 6-16) (13). Cysts may also be seen in association with other high-resolution computed tomography (HRCT) abnormalities in hypersensitivity pneumonitis (HP), desquamative interstitial pneumonia (DIP), interstitial pneumonias with honeycombing (e.g., idiopathic pulmonary fibrosis [IPF]), and small airways disease (14).

### PULMONARY LANGERHANS CELL HISTIOCYTOSIS

Collectively, LCH refers to a group of diseases of unknown etiology often recognized in childhood, in which there is a proliferation and infiltration of CD1+ histiocytes or Langerhans cells (LCs) in one or more body systems, including bone, lung, pituitary gland, mucous membranes, skin, lymph nodes, and liver (4,15–19). LCs are specialized immune cells belonging to a family of dendritic cells derived both from CD34+ bone marrow stem cells and CD11c+ blood precursor cells. These form a network of antigen-presenting sentinel migratory cells throughout the body, typically including...
Cystic Lung Diseases

Pathology

Although PLCH in adults typically occurs in heavy smokers, its etiology remains unknown. The typical peribronchiolar location of lesions is consistent with a response to inhaled antigens; however, PLCH occurs in only a small minority of smokers, and little improvement occurs with smoking cessation. It has been suggested that this disease may represent a response to an unknown viral infection (19).

In its earliest stages, PLCH is characterized histologically by a cellular interstitial infiltrate composed of LCs, lymphocytes, macrophages, eosinophils, plasma cells, and fibroblasts (15,19,20). The infiltrate typically extends into the adjacent lung, resulting in a stellate lesion. With progression, the infiltrate evolves into granulomatous nodules that subsequently cavitate (Fig. 19-1). Unlike other causes of LCH, PLCH nodules are typically nonclonal (4,15–19). Recently, it has been shown by Kambouchner et al. (23) that PLCH primarily involves the respiratory bronchioles with disease subsequently extending proximally to involve terminal bronchioles and distally to involve alveolar ducts; this results in linear rather than spherical lesions, and accounts for the macroscopic appearance of nodules that are irregular in shape.

In its later stages, the cellular granulomas and cavitary nodules are replaced by fibrosis and the formation of lung cysts (Figs. 19-2 and 6–5) (4,15–19). Cystic lung lesions may be either thick or thin walled, appearances that have been attributed, respectively, to the presence of cavitary nodules or peribronchiolar, cicatricial emphysema. It has been suggested that cavitary nodules result from bronchiolar dilatation resulting from inflammation and fibrosis of the bronchiolar wall (23).

Histologic findings are marked by temporal heterogeneity with nodules in varying stages of development found in association with cystic fibrotic scars (24). As cystic spaces evolve, it is not unusual for pigmented macrophages to fill the resulting airspaces, resulting in a so-called DIP-like reaction (25). In fact, given the underlying association between LCH and smoking, it is not uncommon for other smoking-related diseases to be simultaneously identified. This includes, in particular, respiratory bronchiolitis/respiratory bronchiolitis-interstitial lung disease (RB/RB-ILD) and DIP (26–28).

It should also be emphasized that as many as 80% of patients who have late-stage PLCH develop a form of pulmonary vasculitis leading to severe pulmonary hypertension (19,25). In one study of 21 patients with end-stage PLCH and severe pulmonary hypertension, histopathologic evaluation in 60% of the cases revealed a proliferative vasculopathy involving muscular arteries and veins, with evidence of medial hypertrophy and intimal and subintimal fibrosis with resulting arterial obliteration (29). Strikingly, these findings occurred in regions unaffected by LCs. Furthermore, follow-up histologic evaluation showed progression of vascular lesions in the absence of progression of granulomatous disease. In comparison

| TABLE 19-1 Causes of Diffuse Thin-Walled Lung Cysts |
|----------------|----------------|
| **Common**    | **Less Common** |
| Emphysema (e.g., bullae) | PLCH |
| Cystic bronchiectasis | LAM (isolated LAM or associated with the TSC) |
| Honeycombing | LIP |
| **Rare** | Follicular bronchiolitis |
| BHD syndrome | PLCH |
| Amyloidosis and LCDD | LAM (isolated LAM or associated with the TSC) |
| Cysts associated with DIP | LIP |
| Benign metastasizing leiomyoma | Follicular bronchiolitis |
| Cystic pulmonary metastases | PLCH |
| Tracheobronchial papillomatosis | LAM (isolated LAM or associated with the TSC) |
| Proteus syndrome | LIP |
| Neurofibromatosis | Benign metastasizing leiomyoma |

the skin, lymph nodes, bronchial mucosa, and the thymus, which primarily function to facilitate antigen-specific immune reactions (15,19,20). Although studies have shown that LCH represents a clonal proliferation of cells (21), it is not believed that this disease is neoplastic. It is more likely that LCH in adults represents an uncontrolled or abnormal immune response initiated in situ by LCs in response to an unidentified antigenic stimulus (19,22). Evidence that the lesions in LCH result from cellular recruitment rather than neoplastic cell proliferation include a lack of cellular atypia, absence of focal tissue invasion, and near-complete absence of LCs in late lesions. LCH is classified as resulting either in single-organ disease, as occurs in patients with pulmonary Langerhans cell histiocytosis (PLCH), or in multigang or multisystem disease, as occurs in patients with Hand-Schüller-Christian disease or Letterer-Siwe disease, respectively (19).

PLCH is an uncommon disorder typically occurring in young adults between the ages of 20 and 40 years, although it may occur at any age (15). Previously referred to as pulmonary eosinophilic granuloma or pulmonary histiocytosis X, PLCH typically presents with isolated, single-organ involvement, although it may also be a manifestation of both multigang and multisystemic disease (15,19,20). In a review of 314 patients who had histologically proven LCH, PLCH was identified in 129 (40.8%) patients, with isolated pulmonary involvement occurring in 87 (28%) patients (4). In patients who had multisystem disease in addition to pulmonary involvement, sites most often affected included the skeleton and the pituitary gland (4).
with patients who have pulmonary hypertension due to end-stage IPF or emphysema, pulmonary hypertension in patients with PLCH is significantly worse despite better expiratory function; this suggests that pulmonary hypertension in PLCH represents a specific entity and not simply the result of chronic hypoxemia. In addition to arterial disease, patients who have severe LCH are also predisposed to develop pulmonary veno-occlusive disease (30).

**Clinical Findings**

PLCH is an uncommon disease. Gaensler and Carrington (31) found LCH in only 3.4% of 502 patients who had open-lung biopsy for chronic, diffuse infiltrative lung disease. More than 90% of patients who have PLCH are smokers, and this disease is considered to be related to smoking in most patients (25,32–37). In a review of 87 patients who had isolated pulmonary involvement by LCH, only 3 were nonsmokers (4). The majority of patients who have pulmonary LCH are young or middle-aged adults (average age, 32 years). Although previous reports have stressed a male preponderance, studies confirm that men and women are equally affected, likely the result of increasing tobacco use by women. Common presenting symptoms include cough and dyspnea (38,39). Up to 20% of patients present with pneumothorax (36). Pulmonary function tests (PFTs) in patients with PLCH prove to be highly variable, with obstructive, restrictive, and mixed patterns all being described (40).

Compared with patients who have multisystem disease, the prognosis in patients who have isolated pulmonary involvement is good; the disease regresses spontaneously in 25% of patients and stabilizes clinically and radiographically in 50%. In the remaining 25% of cases, the disease follows a progressive downhill course, resulting in diffuse cystic lung destruction. In a small minority of cases, death results from respiratory insufficiency, pulmonary hypertension, or both (4,18). For example, in a review of 87 patients who had isolated pulmonary disease, 74 (85%) patients ultimately became disease free, and 3 patients had progressive disease resulting in severe pulmonary fibrosis and pulmonary hypertension (4).

Although spontaneous regression of disease is common, disease recurrence has been documented to occur up to 7.5 years after the initial presentation (41). Furthermore, there is no clear correlation between smoking history and recrudescence of disease, with nodules recurring in some patients after smoking cessation. PLCH may also recur...
following lung transplantation. Although it is considered a nonneoplastic disorder, PLCH has been noted to develop following treatment for Hodgkin disease. There is also an apparent association with non-small cell lung cancer, which has been reported to occur prior to, simultaneous with, and following the development of PLCH (15,19).

Radiographic Findings

The radiographic findings of LCH include reticular, nodular, and reticulonodular patterns, and honeycombing, often in combination (32,33,35,36,42). Abnormalities are usually bilateral, predominantly involving the middle and upper lung zones, with relative sparing of the costophrenic angles (35,36). Lung volumes are characteristically normal or increased. Nodules when present have irregular borders and vary from 1 to 10 mm in size (15). With progression, PLCH results first in a predominantly reticulonodular pattern, with subsequent development of cystic lung disease. Pneumothoraces occur and are frequently the initial presentation of recurrent disease. Additional findings that have been reported include mediastinal adenopathy, pulmonary consolidation, and a solitary pulmonary nodule (15).

High-Resolution Computed Tomography Findings

HRCT findings of pulmonary PLCH have been reported by a number of authors (26–28,43–45). In almost all patients, HRCT demonstrates cystic airspaces, which are...
Usually less than 10 mm in diameter (Figs. 6-5 to 6-8 and 19-2 to 19-4); these cysts are characteristic of PLCH (43,46–48) and were seen in 17 of 18 patients studied by Brauner et al. (44) and all 12 patients studied by Giron et al. (46) (Table 19-2).

On HRCT, the lung cysts have walls that range from being thin and barely perceptible (Figs. 6-5, 6-7, and 19-4) to being several millimeters in thickness (Figs. 6-6, 19-2, and 19-3). In a study by Grenier et al. (49), 88% of 51 patients who had LCH showed thin-walled (less than 2 mm) cysts.
Cysts on HRCT, whereas 53% of patients showed thick-walled (greater than 2 mm) cysts. The presence of distinct walls allows differentiation of these cysts from areas of emphysema, which can also be seen in some patients. Although many cysts appear round, they can also have bizarre shapes, being bilobed, cloverleaf shaped, or branching in appearance (Figs. 6-5 to 6-7 and 19-2 to 19-4) (26–28,43–45). These unusual shapes are postulated to occur because of fusion of several cysts, or perhaps because the cysts sometimes represent ectatic and thick-walled bronchi (36); in the series reported by Brauner et al. (43), confluent or joined cysts with persisting septations were seen in more than two-thirds of patients. Upper lobe predominance in size and number of cysts is common (Figs. 6-5 and 19-2 to 19-4). Large cysts or bullae (larger than 10 mm in diameter) are also seen in more than half of cases; some cysts are larger than 20 mm (26–28,43–45).

In some patients, cysts are the only abnormality visible on HRCT, but in the majority of cases, small nodules (usually smaller than 5 mm in diameter) are also present (Figs. 4-20, 19-1, 19-5, and 19-6) (43,48); nodules were seen in 14 of 18 patients in Brauner’s series, and in 14 of 17 patients in Moore’s series (43,48). Larger nodules, sometimes exceeding 1 cm, may also be seen, but they are less common. In the study by Grenier et al. (50), 47% of 51 patients who had LCH showed nodules smaller than 3 mm in diameter, whereas 45% of patients showed nodules ranging between 3 mm and 1 cm in diameter, and 24% of patients showed nodules exceeding 1 cm in size. Nodules can vary considerably in number in individual cases, probably depending on the activity of the disease; nodules can be few in number or myriad (43,48). The margins of nodules are often irregular, particularly when there is surrounding cystic or reticular disease. On HRCT, many nodules can be seen to be peribronchial or peribronchiolar and therefore centrilobular in location; in this disease, there is a tendency for granulomas to form around the bronchioles (43). HRCT may be valuable in directing lung biopsy to areas showing lung nodules (43).

The nodules are usually homogeneous in appearance, but some nodules, particularly those larger than 1 cm in diameter, may show lucent centers, presumably corresponding to small cavities (51). These cavities, however,
High-Resolution CT Diagnosis of Diffuse Lung Disease

may sometimes represent a dilated bronchiole surrounded by granulomas and thickened interstitium (43). In the study by Grenier et al. (50), 25% of 51 patients who had PLCH showed cavitory nodules. In some patients, progression of cavitory nodules to cystic lesions has been observed (44,46); this progression is characteristic as later described.

In many patients who have cysts or nodules, the intervening lung parenchyma appears normal on HRCT, without evidence of fibrosis or septal thickening (26–28,43–45). However, in a small percentage of cases, irregular interfaces (the interface sign) are present, or a fine reticular network of opacities is visible (Fig. 19-7) (26–28,43–45). These fine reticular opacities may correlate with intralobular fibrosis or early cyst formation, or with the progression and confluence of cysts (46). Ground-glass opacity is also sometimes seen but is not a prominent feature of this disease. This appearance needs to be differentiated from typical findings of basilar subpleural reticulation and fibrosis characteristic of usual interstitial pneumonitis, a disorder that has also been associated with smoking history (26–28,45).

HRCT shows no consistent central or peripheral predominance of lesions (43,50), but in nearly all cases, the lung bases and the costophrenic sulci are relatively spared (42,52). In Brauner’s series (43) of 18 patients, 2 had abnormalities localized to the upper lobes and 9 had disease that was predominant in the upper or middle lung zones; 2 patients had diffuse disease, but no patient had disease with a lower lung predominance. An upper lobe predominance was reported in 57% of Grenier’s 51 patients (50), whereas a middle lung or basal predominance was never observed.

The evolution of lesions has been assessed using CT. As documented by Brauner et al. (44) in a study of 212 patients who had PLCH, although nodular lesions were twice as frequent as cysts on initial CT studies, follow-up CT examinations showed cystic lesions twice as often as nodular disease. Nodular opacities and thick-walled cysts typically underwent regression with time, while thin-walled cysts, linear densities, and emphysema either remained unchanged or progressed. These data support the previously noted conjecture that lesions in LCH undergo a predictable pathologic and radiologic evolution, beginning with centrilobular nodules (Fig. 19-1) and followed by cavitation (Figs. 19-5 and 19-6), the formation of thick-walled cysts (Figs. 6-6 and 19-3), and, finally, the development of thin-walled cysts (Figs. 6-5, 19-2, 19-4, and 19-8). Whereas nodular lesions may regress spontaneously or be replaced by cysts, once formed, cystic lesions persist, eventually becoming indistinguishable from diffuse emphysema.

Evidence of mosaic attenuation on inspiratory scans and air trapping on expiratory scans may also be seen in patients who have LCH and show nodular opacities or lung cysts (Fig. 19-8) (53). This may reflect the presence of bronchiolar obstruction or air trapping in cystic lung regions.

**FIGURE 19-7** Pulmonary Langerhans cell histiocytosis. A: Volumetric HRCT shows numerous thin-walled cysts (straight arrows) and small nodules (curved arrows) in the upper lobes. Also noted are irregular linear opacities consistent with fibrosis, focal ground-glass opacities, and emphysema (arrowheads). B: Coronal reformation demonstrates the characteristic distribution of disease mainly in the upper and middle lung zones with relative sparing of the lung bases. On both the cross-sectional and coronal images, it is difficult to distinguish some of the cysts due to LCH from emphysema. The patient was a 30-year-old woman. (Courtesy of Dr. Eduardo Sabbagh, Santiago, Chile.)
Utility of High-Resolution Computed Tomography

HRCT is superior to chest radiographs in demonstrating the morphology and distribution of lung abnormalities in patients who have PLCH (26–28,43–45) and in making a specific diagnosis of this disease (50). In fact, in many patients who have PLCH and plain radiographic findings of reticular abnormalities, HRCT shows that the plain film findings reflect the presence of numerous superimposed lung cysts. As compared with chest radiographs, HRCT is significantly more sensitive in detecting small and large cysts and nodules smaller than 5 mm in diameter (43,50).

As previously noted, PLCH is not associated with any consistent pattern of PFT abnormalities, although airways obstruction is common (54) and probably related to peribronchiolar and bronchiolar luminal fibrosis (25). In a study by Moore et al. (48), the extent of disease on HRCT correlated better with impairment in gas exchange, as assessed by the percent predicted carbon monoxide diffusing capacity (DLCO) \( r = -0.71 \), than did plain radiographic findings \( r = -0.57 \). In another study (54), significant correlation \( r = 0.8 \) between HRCT and reduced diffusing capacity was also found. However, no correlation has been shown between CT findings and PFT findings of obstruction (48,54). Air trapping in association with lung cysts has been reported on expiratory HRCT in a patient who had LCH, despite the absence of evidence of airways obstruction on PFT (53).

Although HRCT may allow an accurate diagnosis of this disease when typical findings are present (15,19,26–28,43–45), HRCT is limited in its ability to predict histopathologic activity. As documented by Soler et al. (55), there is excellent correlation between the extent of nodules identified by HRCT and the density of nodules identified histopathologically. In distinction, in patients with a predominant pattern of cystic disease, histologic correlation is less accurate. As reported in this study of 13 patients with documented PLCH, inflammatory granulomas could still be identified in most patients with a predominant cystic pattern on HRCT; these investigators thus advise continued long-term follow-up in patients with findings otherwise suggestive of inactive fibrotic disease (55).

It is interesting to note that in a recent survey of pulmonologists, regarding the role of HRCT in obviating lung biopsy in patients with diffuse interstitial lung disease, most of the 237 responders would not accept a diagnosis of PLCH, despite the presence of characteristic HRCT findings (56). As is discussed in the following section, in this same study, a similar reluctance was also expressed by most responders for accepting HRCT findings as diagnostic in patients with suspected LAM.

**Differential Diagnosis**

In patients who show nodules as the only HRCT abnormality, the differential diagnosis is extensive; differentiation from sarcoidosis, silicosis, metastatic tumor, and tuberculosis may be impossible, although a typical distribution of the nodules can be valuable in diagnosis (57). Nodules in LCH tend to be centrilobular (Figs. 4-20, 19-1, and 19-5 to 19-7), whereas perilymphatic (septal, subpleural, and peribronchovascular) nodules are typically seen in sarcoidosis, silicosis, and lymphangitic carcinomatosis (57). Sparing of the costophrenic angles should raise the possibility of pulmonary LCH, but this finding can be seen in other nodular diseases as well.

Centrilobular emphysema and DIP, two diseases also related to smoking, can result in HRCT appearances
similar to those of PLCH. Centrilobular emphysema results in focal rounded lucencies, typically with an upper lobe predominance. However, in most patients who have centrilobular emphysema, focal areas of lung destruction lack visible walls, distinguishing them from the lung cysts typical of PLCH. On the other hand, in some patients with centrilobular emphysema, areas of emphysema show thin walls on HRCT, mimicking the appearance of PLCH; furthermore, in patients with late-stage PLCH, cyst walls may sometimes be very thin or imperceptible, closely mimicking centrilobular emphysema (Fig. 6-5). In the latter case, there would be little clinical significance in a misdiagnosis, as treatment would be similar.

In patients with DIP, the presence of underlying emphysema or focal areas of air trapping may result in an appearance of multiple thin-walled cysts associated with patchy ground-glass opacity (Fig. 19-9). Although the presence of cysts may cause confusion between PLCH and DIP, the finding of patchy ground-glass opacity seen in DIP usually allows an accurate differentiation (58). However, as noted previously, patients with documented PLCH may also develop DIP or RB-ILD.

Cystic lesions in PLCH, in contrast, can be easily distinguished from honeycombing and larger air cysts in end-stage IPF (26–28,43–45). Pulmonary LCH characteristically involves the upper two-thirds of the lungs, with relative sparing of the costophrenic angles (Figs. 6-5, 19-1, 19-2, 19-4, 19-7, and 19-8) (16,17). IPF and other causes of honeycombing primarily involve the subpleural lung regions and the lung bases. Also, in patients who have IPF, the honeycomb cysts are surrounded by abnormal parenchyma, which shows findings of extensive fibrosis, whereas most of the cysts in LCH are surrounded by normal lung. Lung volumes are normal or increased in cystic LCH, whereas they are generally reduced in patients who have IPF and show honeycombing.

In a woman with LAM, or patients with tuberous sclerosis, cystic lesions identical to those seen in pulmonary LCH can sometimes be identified (2,3). However, in distinction to the parenchymal changes identified in patients with LCH, the lung bases are characteristically involved in patients with LAM or TSC.

The cysts in pulmonary LCH, when adjacent to blood vessels, can mimic the signet ring sign of bronchiectasis. However, distinction from bronchiectasis is straightforward because the cysts in LCH lack the characteristic continuity of dilated bronchi seen on contiguous slices in patients who have airways disease (48).

As discussed in Chapter 6 and in this chapter, multiple thin-walled lung cysts are also seen in some patients who have LIP (Fig. 6-12) (59–61). These tend to have a lower lobe predominance. Other findings in patients who have LIP include small subpleural nodules, centrilobular nodules, interlobular septal thickening, and ground-glass opacity (61).

Despite the similar appearances of various cystic lung diseases, the accuracy of HRCT in distinguishing the most common causes of cystic lung disease (PLCH, pulmonary LAM, and emphysema) has been well documented (62). Recently, in a retrospective study of 92 patients with chronic cystic lung disease, including 18 patients with PLCH, 18 with pulmonary LAM, 17 with usual interstitial pneumonia, 16 with LIP, 15 with emphysema, and 8 with RB-ILD, two readers made a correct first-choice diagnosis in 148 of 184 (80%) readings. Although the correct diagnosis of PLCH was made in just 72% of patients, in those cases in which the diagnosis was suggested with a high degree of certainty, a correct diagnosis was established in 88% (58).

LYMPHANGIOMYOMATOSIS AND TUBEROUS SCLEROSIS COMPLEX

LAM, also known as lymphangioleiomyomatosis, is a rare multisystem disease characterized by infiltration of immature-appearing smooth muscle cells (LAM cells) into the lungs, airways (Fig. 19-10), and along axial lymphatic
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CHAPTER 19

vessels in the chest and abdomen (63–68). The hallmark of this disease is cystic destruction of the lung parenchyma (Fig. 19-11). Spindle cell infiltration can also involve the hilar, mediastinal, and extrathoracic lymph nodes, sometimes resulting in dilatation of intrapulmonary lymphatics and the thoracic duct. Involvement of the lymphatics can lead to chylous pleural effusions or ascites. Infiltration of cells in the walls of pulmonary veins may rarely cause venous obstruction and lead to pulmonary venous hypertension with resultant hemoptysis.

Pathology

LAM occurs either in association with tuberous sclerosis complex (TSC-LAM) or in a sporadic form (sporadic lymphangiomyomatosis [S-LAM]). Both TSC-LAM and S-LAM are linked to tuberous sclerosis gene (TSC1 and TSC2) mutations involving both TSC1 or TSC2 in the case of TSC-LAM, or TSC2 in the case of S-LAM, located on chromosomes 9q34 and 16p13 (68). LAM appears to result from the metastatic dissemination of LAM cells bearing mutations that result in inactivation or loss of heterozygosity in TSC1 and TSC2, leading to hyperactivation of the mammalian (or mechanistic) target of rapamycin (mTOR). mTOR is a serine/threonine protein kinase that regulates cell growth, motility, and survival; protein synthesis and transcription.

The result of these mutations is inappropriate proliferation of LAM cells, migration, and tissue invasion. In patients with TSC-LAM, mutations are identified in all cell lines, whereas in patients with S-LAM, mutations are identified only in the lung, kidney, and lymph nodes. LAM cells have been shown to disseminate either through hematogenous or lymphatic pathways, raising the possibility that S-LAM actually represents a form of metastatic disease with cells arising from angiomylipomatosis tissue, akin to benign metastasizing leiomyoma (66,68). In distinction to S-LAM, TSC is an autosomal-dominant disorder with highly variable expressivity, most often occurring as a result of sporadic mutations.

The lesions of pulmonary LAM can be divided into early (active) and late phases (69,70). In its early phases, LAM results in a proliferation of cells primarily in terminal bronchioles and alveolar walls (Fig. 19-10). Findings of proximal acinar and irregular emphysema adjacent to the periphery of smooth muscle infiltrates, findings due to the destructive effects of metalloproteinases expressed by the LAM cells. Similar changes may be seen from more distal smooth muscle proliferation with normal-appearing proximal bronchioles (71). Evidence of fibrogenesis, including the presence of abundant fibronectin, may also be identified.
These changes result in dilated emphysema-like spaces, within which may be identified hyperplastic type II pneumocytes and hemosiderin-laden macrophages, presumably the result of hemorrhage (70,71). Later in the course of disease, cellular infiltrates regress, leaving markedly dilated alveolar spaces associated with smooth muscle hyperplasia and diffuse collagen deposition.

Proliferation of spindle cells causes circumferential narrowing and obstruction of bronchioles, leading to airways obstruction and air trapping. Airways obstruction has also been shown to result from loss of alveolar support occurring in association with lung cysts. Using detailed morphometric analysis of postmortem lungs obtained from two patients who had LAM, Sobonya et al. (72) showed that of these two mechanisms, it is likely that the loss of parenchymal interdependence resulting from diffuse cystic disease and consequent loss of alveolar support may be the more important.

The smooth muscle cells found in LAM have been shown to be phenotypically heterogeneous, smooth muscle, actin and desmin-positive cells derived from myoid precursors. Immunohistochemical studies show that approximately 80% of proliferating cells in LAM patients stain positively for estrogen receptors, whereas nearly all stain positively for progesterone receptors, in distinction to normal smooth muscle cells (71). LAM cells also differ from normal smooth muscle cells because they react with HMB-45, a monoclonal antibody that identifies a 100-kDa glycoprotein (gp 100) that is located in premelanosomes antigens in the cytoplasm of melanoma cell lines (63,70–72). HMB-45 staining is also found in patients who have angiomyolipomas of the kidney, multifocal micronodular pneumocyte hyperplasia (73,74), and clear cell tumors of the lung (75). Although the significance of immunohistochemical staining with HMB-45 remains uncertain, this finding has proved useful in improving the accuracy of transbronchial biopsy for diagnosing LAM. More recently, it has also been shown that LAM cells express lymphatic endothelial markers, including vascular endothelial growth factors of which VEGF-D has been shown to be elevated in the serum of patients with LAM, representing a potentially useful means for monitoring response to therapeutic interventions (76).

**Clinical Findings**

LAM is thought to occur almost exclusively in women of childbearing age, but recent data have shown that increasing numbers of older women are being diagnosed with this disease (77). Using data recently derived from two large patient registries, Cohen et al. (77) found that the mean age of diagnosis was 46.7 years, with 50% of older women presenting without a history of pneumothorax. This likely reflects a growing awareness of LAM occurring in women with the TSC and the increasing use of HRCT to diagnose otherwise unexplained pulmonary symptoms (77).

While the incidence of LAM has been estimated to be between 1 and 2.6 cases per 100,000 women worldwide (63,68), this likely represents an underestimation, as many cases are at least initially misdiagnosed as either asthma or chronic obstructive pulmonary disease. S-LAM affects approximately 1 in 400,000 women (78), while TSC-LAM affects 30% to 40% of adult female patients with TSC. TSC-LAM is five to tenfold more common than the isolated form of LAM (2,66).

The prevalence of LAM occurring in male TSC patients remains controversial. In one study of 186 patients with TSC having undergone abdominal CT, while pulmonary cysts were identified in 40 of 95 (42%) female patients, cysts were considerably less common in male patients, seen in only 12 of 91 (13%) patients (p < 0.001), and cysts were less numerous and smaller in men (79). In distinction, recent data based on whole lung imaging suggests that LAM may occur with equal frequency in both sexes, being identified in 11 of 29 (38%) men with documented TSC (80). In this study, the diagnosis of cystic lung disease required that only four discrete cysts be identified (80,81).

The majority of patients with LAM present with dyspnea, pneumothorax, and/or cough (63,66,68,81). Patients with S-LAM are more likely to develop signs and symptoms than patients with TSC-LAM (81).

As documented in a cohort of 230 LAM patients, evidence of airway obstruction was the most common spirographic abnormality, occurring in 57% of individuals, with an average forced expiratory volume in 1 second (FEV1) of approximately 70%. About one-fourth of patients with obstructive airway disease exhibit reversible airflow obstruction after bronchodilator inhalation. In one-third of patients, spirometric results proved normal (81).

In this same population, pneumothorax was documented to have occurred in 55.5% of patients, with a mean of 4.4 pneumothoraces occurring in subjects with at least one prior episode (81). As a result, pleurodesis is now recommended with the initial episode of pneumothorax (66). Not surprisingly, a history of prior pleurodesis affects both pulmonary function and the appearance of the pleura on CT (82).

The disease follows an insidious course with a variable rate of progression and is generally first diagnosed because of pneumothoraces or chylosus effusions in a woman of childbearing age. The mean time interval from the onset of symptoms to diagnosis is typically between 3 and 5 years (51,63). Sixty percent develop chylosus pleural effusions, up to 80% develop pneumothorax, and 30% to 40% develop blood-streaked sputum or frank hemoptysis at some time in the course of the disease (64,65,83). In select cases, biopsy confirmation may be required for diagnosis, with adequate tissue generally available by transbronchial biopsy, with immunohistochemical staining for actin, desmin, and HMC-45; however, open-lung biopsy remains the gold standard (68). In one recent study of 80 women with LAM, the diagnosis was established by open-lung biopsy in 50, transbronchial biopsy in 14, retroperitoneal lymph node biopsy in 6, and characteristic HRCT findings in 10 (84).

Traditional therapy has relied on hormonal manipulation by oophorectomy or administration of progesterone with high dose medroxyprogesterone, tamoxifen, or luteinizing hormone-releasing hormone analogs. Unfortunately,
there is little evidence of consistent efficacy. For example, in one study, Taviera-DaSilva et al. (85) showed that progestosterone therapy failed to slow the progression of lung function decline. In patients with reversible airway obstruction, treatment with bronchodilators is of value, and in patients with angiomyolipomas larger than 4 cm in size, treatment with embolization is indicated. Unfortunately, mortality still occurs in 10% to 20% of patients with symptoms and 30% having lung biopsy (66). As a consequence, LAM is now listed as an indication for lung transplantation (70). This may be performed safely, despite a history of prior pleurodesis (66). Disease recurrence in transplanted lungs has been reported (86).

Although lung transplantation is currently the only definitive treatment, it is reserved for individuals with advanced disease. It is anticipated that a role for HRCT screening will follow the advent of treatment methods focused on specific molecular targets (66). These include, among others, metalloproteinase inhibitors, statins, interferon, VEGF inhibitors, and rapamycin (sirolimus). Of these, rapamycin (sirolimus), an mTOR inhibitor has shown the greatest promise in stabilizing pulmonary function and potentially decreasing the size of renal angiomyolipomas, although drug resistance has proved potentially problematic (87–90).

**Radiographic Findings**

The plain radiographic manifestations of LAM include reticular, reticulonodular, miliary, and honeycomb patterns (68,83,91). More than 50% of patients have radiographic evidence of pneumothorax at the time of first presentation (70). Lung volumes can be increased in patients who have this disease. Radiologic abnormalities may precede, accompany, or postdate other manifestations of the disease, such as pneumothorax and chyloous pleural effusion. Not infrequently, radiographs often fail to reveal the presence of diffuse lung cysts subsequently verified surgically (83). As documented by Chu et al. (63), chest radiographs were interpreted as normal in 9 of 35 (26%) patients who had proven LAM.

**High-Resolution Computed Tomography Findings**

On HRCT, patients with LAM characteristically show numerous thin-walled lung cysts, surrounded by relatively normal lung parenchyma (Figs. 6-9 to 6-11 and 19-12 to 19-16, Table 19-3) (2,3,63,68,92–101). These cysts usually range from 2 mm to 5 cm in diameter, but they can be larger. Their size tends to increase with progression of the disease (98). In patients who have mild disease, the cysts usually measure smaller than 5 mm in diameter. In patients who have more extensive disease, in which 80% or more of the lung parenchyma is involved, the cysts tend to be larger, most being larger than 1 cm in diameter. The walls of the lung cysts are usually thin and faintly perceptible, but they may range up to 4 mm in thickness (96,98). Irregularly shaped lung cysts, as are seen in patients who have LCH, are uncommon. Lung cysts seen on HRCT correlate with the presence of the lung cysts that are common pathologically in this disease; these cysts are partially surrounded by the abnormal spindle cells typical of LAM.

LAM occurring in patients with TSC has the same appearance as seen in individuals with isolated LAM. In one retrospective study of 186 adult TSC patients, including 91 (49%) male subjects, in whom as a minimum evaluated with abdominal CT including the lung bases, cysts were identified in 52 of 186 (28%) cases, with the size of lesions varying from 2 mm to greater than 2 cm (79).

Some patients with TSC have small lung nodules, ranging from a few millimeters to 8 mm in diameter, with a random distribution, representing micronodular pneumocyte hyperplasia (Fig. 19-17) (102,103), an entity never seen in patients with S-LAM. Franz et al. (103) performed genotyping and CT in 23 asymptomatic women with

**FIGURE 19-12** Lymphangiomyomatosis. A and B: HRCT targeted to the left lung shows multiple cystic airspaces of varying sizes. These have walls ranging from being barely perceptible to 2 mm in thickness. The lung parenchyma between the cystic airspaces is normal. The cysts are primarily round in shape, but a few appear confluent.
FIGURE 19-13  Tuberous sclerosis complex/lymphangioleiomyomatosis. A and B: Targeted HRCT sections through the left lung in a patient with documented tuberous sclerosis show typical appearance of diffuse thin-walled cysts randomly distributed throughout the lungs nearly replacing normal lung. Note that this appearance is indistinguishable from the diffuse cystic changes seen in isolated cases of LAM.

FIGURE 19-14  Lymphangiomyomatosis. A and B: HRCT images through the upper and lower lobes, respectively, show the characteristic appearance of similar size, thin-walled cysts, uniformly distributed throughout both lungs. Note that in this case there is a small left-sided pneumothorax. C: Coronal reformatted image shows to good advantage the uniform distribution of cysts characteristic of LAM. Note the left-sided basilar pneumothorax.
**FIGURE 19-15** LAM with tuberous sclerosis. A–C: LAM in a 35-year-old woman with tuberous sclerosis. HRCT shows numerous discrete, round, thin-walled lung cysts. Cysts are thinner walled and more regular in size and shape than those seen in patients who have LCH. Intervening lung parenchyma appears normal. Cysts are diffusely distributed, and cysts at the lung bases (C) are similar in size and number to those seen at the lung apices (A). These abnormalities were associated with adenoma sebaceum, shortness of breath, airway obstruction on PFTs, and low diffusing capacity.

**FIGURE 19-16** LAM in a patient with tuberous sclerosis. A–D: Select sections in a young woman with documented tuberous sclerosis show diffuse thin-walled cysts throughout both lungs, typical of patients with LAM. Note the presence of a left-sided chest tube, being used to treat an associated pneumothorax. E: Contrast-enhanced CT through the upper abdomen in this patient shows the characteristic appearance of a fat-containing angiomylipoma in the right kidney (arrow). A left renal mass is also seen.
Thin-walled lung cysts, usually round in shape\textsuperscript{a, b}
Diffuse distribution, costophrenic angles involved\textsuperscript{a, b}
Mild septal thickening or ground-glass opacity
Lymph node enlargement
Small nodules in patients with TSC
Pleural effusion\textsuperscript{b}
Pneumothorax\textsuperscript{a}

\textsuperscript{a}Most common findings
\textsuperscript{b}Findings most helpful in differential diagnosis

**TABLE 19-3** HRCT Findings in Lymphangiomyomatosis

**FIGURE 19-16** (Continued)

**FIGURE 19-17** Micronodular pneumocyte hyperplasia in TSC. A–D: Target-reconstructed HRCT images through the middle and lower lungs show innumerable tiny lung nodules in a patient with tuberous sclerosis and micronodular pneumocyte hyperplasia. A few scattered lung cysts are present. E: Non-contrast CT image through the upper abdomen shows a fat-containing angiomyolipoma in the right kidney.
TSC. Pulmonary cysts consistent with LAM were found in nine (39%) patients. Ten (43%) patients had pulmonary parenchymal nodules. Pulmonary nodules were more common in women with cysts (78% vs. 21%, \( p < 0.05 \)), and 52% of all patients had either cysts or nodules. TSC2 mutations were identified in all cyst-positive patients who were tested (\( n = 8 \)), whereas both TSC1 and TSC2 mutations were found in patients with nodular disease.

In the majority of patients, the cysts are distributed diffusely throughout the lungs, and no lung zone is spared (Figs. 19-12 to 19-16); diffuse lung involvement is seen even in patients who have mild disease. In reported series (96,98), there is no evidence of lower lung zone, central, or peripheral predominance on CT scans. Thus, the HRCT findings do not support the previous impression that the lesions initially have a predominantly basal distribution (65).

In most patients, the lung parenchyma between the cysts appears normal on HRCT (Figs. 19-12 to 19-15). In some cases, however, a slight increase in linear interstitial markings (94,99), interlobular septal thickening (94,96), or patchy areas of ground-glass opacity (98) are also seen. The latter probably represent areas of pulmonary hemorrhage. Pneumothorax may be seen to be associated with cysts in patients who have this disease (Figs. 19-14, 19-16, and 19-18).
Other features of LAM include hilar, mediastinal, retrocrural lymph node enlargement and lymphedema. In one review of 228 patients with documented LAM, 8 (3.5%) had LAM-associated peripheral lymphedema, with lymphedema representing the initial presenting feature in 5 (104). Adenopathy was visible in four of the seven patients who had complete chest CT scans reported by Sherrier et al. (100). Air trapping on expiratory scans may also be seen (53).

Not surprisingly, pleural effusion, pneumothorax, or both are frequently identified and can be helpful in distinguishing LAM from PLCH. In one large series, they were identified in five (14%) and two (6%) patients, respectively (63). It should be emphasized that the appearance of the pleura on HRCT will vary, depending on whether there is a history of prior pleurodesis. As documented by Avila et al. (105), pleural abnormalities are more likely to be identified in patients following pleurodesis. Of 258 patients with documented LAM, pleural abnormalities were present in 76% of patients following pleurodesis, as compared with 38% of cases without prior pleurodesis, with marked differences in the occurrence of pleural thickening (65% vs. 26%), loculated effusions (11% vs. 2.4%), pneumothoraces (10% vs. 1.6%), foci of high attenuation (23% vs. 1.6%), and masses (14% vs. 0.8%), respectively (105). In this same study, although pleural masses were noted to enhance following intravenous contrast administration, they were characterized by a lack of interval growth.

Even though pulmonary and pleural findings clearly predominate, abdominal and pelvic findings are also frequent. In one study of 80 patients with LAM, 61 (76%) had positive findings at abdominal/pelvic CT, including renal angiomyolipomas in 54%, enlarged abdominal lymph nodes in 39%, and lymphangioleiomyomas in 16%, respectively (Fig. 19-16) (84). Angiomyolipomas are especially frequent, occurring in more than 90% of patients with TSC-LAM and 30% to 50% of patients with S-LAM (66). Chu et al. (63) detected a total of 31 solid renal masses in 18 of 35 (51%) patients, including 6 (17%) patients who had multiple angiomyolipomas and 4 (11%) who had bilateral involvement. Typically asymptomatic when small, these have a well-known tendency to cause retroperitoneal hemorrhage, hematuria, and loss of renal function, resulting when greater than 4 cm in diameter. Once this size, periodic screening with CT or ultrasound is generally recommended. Therapeutic options include embolization, radioablation, or nephron-sparing partial nephrectomy (66). Patients with TSC-LAM are more likely to develop hepatic and renal angiomyolipomas, while patients with S-LAM are more likely to develop pleural effusion, ascites, and abdominal lymphangioleiomyomas (81).

Utility of High-Resolution Computed Tomography

HRCT is superior to chest radiography in determining the extent and distribution of air cysts in this disease, and it can demonstrate extensive abnormalities in patients who have normal radiographic findings (96,98,100). Also, cysts are commonly visible in asymptomatic patients with TSC (103). The cystic abnormalities of LAM are also much easier to assess and are better defined on HRCT than on conventional CT. Cysts visible on HRCT were rarely seen on chest radiographs, unless they were larger than 1 cm. Because HRCT findings closely mirror the gross pathologic appearances of this disease, HRCT constitute a major diagnostic criterion for establishing LAM (Table 19-4).

Disease extent as assessed on CT correlates better than do radiographic findings with clinical and functional impairment in patients who have LAM (70). Typically, PFTs reveal decreased diffusing capacity, and, less commonly,
airflow obstruction with reduced FEV\textsubscript{1} and FEV\textsubscript{1}/FVC ratio, accompanied by a reduction in elastic recoil. Significant correlations have been documented between a reduced FEV\textsubscript{1}/FVC ratio, increased total lung capacity, and prognosis (106). On CT, the best correlations have been observed between the extent of disease and impairment in gas transfer as assessed by the DLCO (92,96,98). Although significant correlations have also been demonstrated between extent of cystic disease and severity of airways obstruction (92,96,98), this has proved more controversial. In the study by Aberle et al. (92), for example, good correlation was reported between CT scores and measures of airways obstruction, in particular, the FEV\textsubscript{1}/FVC ratio (\(r = -0.92; p < 0.002\)). Similarly, Lenoir et al. (96), in a study of 11 patients who had LAM (\(n = 9\)) and tuberous sclerosis (\(n = 2\)), found good correlation between CT findings and FEV\textsubscript{1}/FVC ratios and DLCO. In distinction, although good correlations between CT scores and DLCO have also been reported by Müller et al. (98) in their study of 14 patients who had LAM, similar good correlation was not seen with lung volumes or airflow parameters.

In an early study, Crausman et al. (107,108) assessed the use of quantitative computed tomography (QCT) measurements as a means to predict prognosis in LAM patients. Using two end-expiratory HRCT images (at the carina and just above the diaphragm), these authors used a density mask program with a threshold of -900 Hounsfield units to obtain a QCT index in 10 patients who had documented LAM. Defined as the amount of cystic lung expressed as a percent of total lung area for the two slices combined, a good correlation was found between the QCT index and the FEV\textsubscript{1} (\(r = -0.9; p = 0.0005\)), residual volume (\(r = 0.7; p = 0.02\)), DLCO (\(r = -0.76; p = 0.01\)), and exercise performance measured as maximum workload (\(r = -0.84; p = 0.002\)), among other measurements (108). These data are significant given previously noted correlations between measurements of airflow obstruction and prognosis (106).

As shown by Avila et al. (82) in a study of 37 patients with LAM, qualitative ratings of the severity of cystic lung disease compared favorably with quantitative evaluation over a wide range of pulmonary dysfunction, with good agreement noted between two observers (\(k = 0.75\)). More recently, CT has been used to grade the severity of LAM using advanced textural analysis and feature correlation to identify and quantify cystic areas as well as to assess lung distal to obvious cysts. On the basis of this approach, these investigators could identify damage in the form of emphysema-like spaces in portions of the lung separate from cysts, with declined lung function correlating with these features (109).

Although quantitative assessment of HRCT data provides good correlation with spirometric measures of lung function, in fact, quantitative CT is rarely obtained in clinical practice.

Given the characteristic nature of imaging findings, it has been proposed by several investigators that a specific diagnosis of LAM can be established by HRCT (66,110). As a consequence, the LAM Foundation has suggested that annual HRCT screening be performed in all women with unexplained recurrent pneumothoraces or emphysema in the absence of a history of tobacco use, as well as women older than 18 years with tuberous sclerosis (66). The potential for HRCT to identify otherwise asymptomatic women with TSC, in particular, may allow identification of a subset of patients with early disease (78,111–113). In one recent retrospective study of 101 female women with TSC in whom CT studies were available for review, 48 (47.5%) had CT evidence of cystic lung disease (114). In this study the risk of LAM increased with age, with a prevalence of 27% in women below 21 years of age, increasing to 81% in women over the age of 40. Ultimately, 63% of subjects developed symptoms, while a total of 12.5% died of LAM.

Important for the potential use of CT to screen patients with TSC, among asymptomatic subjects with LAM, 84% had cysts identified on a single CT section at the level of the carina. This suggests a possible role for acquiring a limited, low-dose CT screening study to minimize radiation exposure (114). Also, a limited number (3 to 10) of CT slices has been reported as an effective means of screening patients with TSC, both men and women (80).

Patients who have lung transplantation for LAM have increased morbidity and mortality due to complications related to their underlying disease (Fig. 19-18) (115);
these LAM-related complications can be diagnosed or suggested using CT. In a review of 13 patients who had unilateral ($n=8$) or bilateral ($n=5$) lung transplantation for LAM, complications found during and after transplantation included excessive pleural adhesions ($n=4$), native lung pneumothorax ($n=3$), chylous effusion ($n=1$), chylous ascites ($n=3$), complications from renal angiomylipomas ($n=4$), and recurrent LAM ($n=1$). One patient died as a result of complications of LAM (115).

**Differential Diagnosis**

A number of entities may be confused with LAM (Table 19-1). For example, lung cysts very similar to those seen in LAM have also been described in patients who have pulmonary PLCH (43,48). However, three findings usually allow the differentiation of these two diseases. In many patients who have pulmonary PLCH, a nodular component is also present (Figs. 19-5 and 19-6); this is less uncommon with LAM. However, it should be noted that in patients with tuberous sclerosis, similar micronodular opacities may be the result of micronodular pneumocyte hyperplasia (Fig. 19-17). This entity may also be associated with airflow obstruction and mosaic attenuation (116).

Irregularly shaped cysts commonly seen in patients who have PLCH (Figs. 19-2 and 19-3) are much less frequent with LAM. Furthermore, PLCH characteristically involves the upper two-thirds of the lungs and spares the costophrenic angles (Fig. 19-4), whereas LAM involves the lungs diffusely (2,3,68). Finally, it should be emphasized that PLCH is one of a number of diseases characteristically associated with tobacco use, while no such connection between cigarette smoking and LAM has been demonstrated.

Additional entities that may be mistaken for LAM include LIP (Figs. 9-36, 9-37, and 6-12), follicular bronchiolitis, subacute HP with cyst formation, amyloidosis (Fig. 16-17), LCDD (Figs. 6-14, 16-19, and 16-20), low-grade leiomyosarcomas and benign metastasizing leiomyoma, and BHD syndrome (66). Randomly distributed thin-walled lung cysts with similar morphology to those seen in LAM, for example, have been reported to occur in up to 13% of patients with subacute HP, although this entity is typically associated with a range of additional findings including poorly defined centriflobular nodules and later in the course of disease, extensive lung fibrosis (117).

Of those entities most likely to present with similar appearing thin-walled cysts, two entities in particular stand out as differential possibilities: LIP and the BHD syndrome.

**LYMPHOID INTERSTITIAL PNEUMONIA**

LIP is a rare interstitial lung disease that typically occurs in association with either underlying dysproteinemia or autoimmune diseases. It is also discussed in Chapters 6, 9, and 11. LIP is most often associated with Sjögren syndrome or other collagen diseases, but LIP has also been reported in patients’ immunosuppression, such as those with AIDS, especially children, as well as in patients with common variable hypogammaglobulinemia (118); it is also frequently idiopathic. Previously classified as an idiopathic interstitial pneumonia, LIP is now considered a lymphoproliferative disorder.

LIP results in diffuse infiltration of the lung interstitium by monotonous sheets of polyclonal lymphocytes in association with type II pneumocyte hyperplasia and the accumulation of mononuclear cells that result in the development of noncaseating granulomas and well-formed lymphoid germinal centers. HRCT findings include a variety of abnormalities, including patchy ground-glass opacity, bibasilar reticulation, scattered parenchymal nodules frequently subpleural in location, and thickened interlobular septae.

Thin-walled lung cysts have been described in up to two-thirds of patients with LIP and appear randomly distributed (Figs. 6-12, 9-36, 9-37, 11-26, and 19-19 to 19-21) (119). In one study of 22 patients with LIP, CT findings most commonly identified included areas of ground-glass opacity and poorly defined centriflobular nodules in all 22 patients. Cystic airspaces were seen in 15 of 22 (68%) (61). Except for lung cysts, all CT findings in patients with LIP are potentially reversible (60).

Cysts in LIP are thin walled, up to 3 cm in diameter, often predominate in the lower lobes, and are usually limited in number. In many cases, they tend to be associated with vessels, seen in relation to the cyst walls. A history of collagen-vascular disease, and particularly Sjögren syndrome, is very helpful in differential diagnosis.

**BIRT-HOGG-DUBÉ SYNDROME**

A number of review articles have described the range of features associated with BHD (120–122). BHD is a rare autosomal-dominant disorder clinically characterized by diffuse thin-walled lung cysts, cutaneous fibrofolliculomas predominantly involving the face, neck, and upper trunk, and most importantly, renal tumors, ranging from benign oncocytomas to malignant renal cell carcinomas. The latter occur in up to 70% of patients by age 70.

The underlying defect in patients with BHD consists of mutations in the folliculin (FLCN) gene located on chromosome 17p11.2, leading to a loss of the tumor suppressor, FLCN. FLCN, in turn, interacts with signaling molecules such as 5’-AMP activated protein kinase and similar to LAM, and mTOR (123). FLCN occurs in normal cells of the skin, kidney and lungs, among others: there is no gender predilection.

**Clinical Findings**

Cysts may appear in isolation without the other stigmata of the syndrome and may be identified in patients as young as 20 to 30 years. In distinction, renal carcinoma tends to occur in older patients, typically those over 40 years of age. Given concerns over the development of renal cancer, it has been suggested that screening with MRI should be performed in patients with known BHD over the age of 20 (122).
FIGURE 19-19  Lymphoid interstitial pneumonia. A–D: Select axial HRCT sections from the upper lobes to the lung bases, respectively in a patient with Sjögren syndrome and documented LIP show variable size, thin-walled randomly distributed cysts, in the absence of lung nodules or reticulation. E and F: Coronal maximum and minimum intensity images in the same case as A–D. Note that the maximum intensity projection is of value by confirming a lack of nodules in this case, while the maximum intensity projection shows the extent and severity of cystic changes to good advantage. In this case, a combination of clinical history and involvement of the lower lobes allows differentiation of this appearance from LCH.
FIGURE 19-20 Lymphoid interstitial pneumonia. High-resolution images through two different patients with documented LIP showing the range of cystic changes that may be identified, from a few scattered thin-walled cysts (arrows in A) to a diffuse profusion of tiny cysts superficially mimicking the appearance of LAM (B).

FIGURE 19-21 Lymphoid interstitial pneumonia. A and B: Sections through the lower lobes in a patient with Sjögren syndrome and documented LIP show variable size, thin-walled cysts, some of which appear coalescent, resulting in bizarre shapes. In this case, a combination of clinical history and involvement of the lower lobes allows differentiation of this appearance from LCH. (Case courtesy of Dr. Ami Rubinowitz, Yale-New Haven Hospital, New Haven, CT.)
Overall, multiple pulmonary cysts occur in 80% of members of affected families. Clinically up to 75% of patients with BHD present with spontaneous, frequently recurrent pneumothorax. Thin-walled cysts are nearly ubiquitous in patients with BHD, although, as documented by Toro et al. (124) in a study of 198 patients with BHD, while 178 (89%) proved to have lung cysts, pneumothoraces occurred in only 24% of cases. Pneumothoraces tend to occur more often in younger patients, the incidence decreasing with age. Not surprisingly, the diagnosis is often delayed, with pneumothoraces mistakenly attributed most often to underlying emphysema. In distinction to LAM, most patients with BHD and cystic lung disease have near-normal pulmonary function (125).

The cause of pulmonary cysts in BHD is unclear, and their histology have been incompletely characterized. However, cysts predominate in the medial and subpleural lung, and in the mid- and lower lung zones. In one study, cyst walls have been shown histologically to be partially incorporated into the pleura and interlobular septa (123). Cyst walls are lined by alveolar cells without evidence of atypia or neoplastic transformation (123). While unruptured cysts show no evidence of inflammation, histologic evaluation of ruptured cysts shows evidence of inflammation, making these lesions indistinguishable from emphysematous bullae or blebs.

**High-Resolution Computed Tomography Findings**

Cysts in BHD appear thin walled; they can often be distinguished from those of LCH and LAM by appearance and distribution (Table 19-5). In a study (6) of 17 patients with BHD syndrome, CT showed cystic lung disease in 15; the cysts varied in size up to 7.8 cm; such large cysts are uncommon with LCH and LAM. In another study, although most cysts (76%) were less than 1 cm in diameter, 6% were larger than 2 cm (7). Large cysts were frequently multiseptated (6).
Cysts may be limited in number in some patients, but in a study by Agarwal et al. 6 of 15 patients, 33% had more than 20 cysts (6); Tobino et al. (7) found that cysts numbered from 29 to 407 in a study of 12 patients with BHD.

Bilateral cysts are typical (6,7). In distinction to LCH and LAM, cysts predominate at the lung bases; 85% and 87% of cysts in two studies were in the lower lungs (6,7), and cysts tend to be largest in this location. Tobino et al. (7) found the majority of cysts to be visible in the medial (58%) rather than lateral (27%) lower lungs (Figs. 6-13 and 19-22).

Cysts often contact a pleural surface, and in some cases may appear to be within or related to a fissure. Tobino et al. (7) found that 40.5% of cysts were subpleural in location. Cysts can be round, oval, lenticular, or irregular in shape; in one study, 77% of cysts were irregular in shape, rather than round or oval. Cysts in the medial lower lobes, those subpleural in location, and those with irregular shapes tended to be larger than cysts in other locations (p = 0.001) (7).

Differences between the appearance and distribution of cysts associated with BHD and LAM have recently been reported. In a study of 14 patients with BHD syndrome and 52 with LAM, the extent, number, size, and circularity of cysts were calculated, and the distribution of cysts within six separate lung zones was also evaluated (125). As compared to LAM, BHD showed fewer cysts, which were more limited in extent, and more often had non-rounded shapes. Cysts associated with BHD more frequently involved the lower and medial lung, and were larger than those seen in patients with LAM (both p < 0.001). A family history of pneumothorax also predicted BHD (p < 0.001) (125).

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TABLE 19-5 HRCT Findings in Birt-Hogg-Dubé Syndrome

| Thin-walled lung cysts, usually round, oval, lenticular or irregular in shape | Lower lung predominance of cysts |
| Medial predominance in shape | Subpleural (and fissural) cysts common |
| Cysts often large (and less uniform in size than LAM) | Pneumothorax |

aMost common findings.
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