CHEST

Diffuse Cystic Lung Disease

A Clinical Guide to Recognition and Management

Alessandro N. Franciosi, PhD; Nishant Gupta, MD; David J. Murphy, MD; Kathryn A. Wikenheiser-Brokamp, PhD; and Cormac McCarthy, PhD

TOPIC IMPORTANCE: Diffuse cystic lung diseases (DCLDs) represent a group of pathophysiologically heterogeneous entities that share a common radiologic phenotype of multiple thin-walled pulmonary cysts. DCLDs differ from the typical fibroinflammatory interstitial lung diseases in their epidemiology, clinical presentation, molecular pathogenesis, and therapeutic approaches, making them worthy of a distinct classification. The importance of timely and accurate identification of DCLDs is heightened by the impact on patient management including recent discoveries of targeted therapeutic approaches for some disorders.

REVIEW FINDINGS: This article offers a practical framework for evaluating patients with DCLD, indicating the most appropriate and current diagnostic and management approaches. We focus on the DCLDs that are most likely to be encountered by practicing pulmonologists: lymphangioleiomyomatosis, pulmonary Langerhans cell histiocytosis, Birt-Hogg-Dubé syndrome, and lymphoid interstitial pneumonia. Chest CT scan is the most informative noninvasive diagnostic modality to identify DCLDs. Thereafter, instituting a structured approach to high-yield associated factors (eg, medical, social, and family history; renal and dermatologic findings) increases the likelihood of identifying DCLDs and achieving a diagnosis.

SUMMARY: Although the individual diseases that comprise the DCLD family are rare, taken together, DCLDs can be encountered more frequently in clinical practice than commonly perceived. An increased eagerness among general pulmonary physicians to recognize these entities, coupled with a practical and systematic clinical approach to examinations and investigations, is required to improve case findings, allow earlier intervention, and reduce morbidity and mortality.

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KEY WORDS: Birt-Hogg-Dubé syndrome; diffuse cystic lung disease; follicular bronchiolitis; lymphangioleiomyomatosis; lymphoid interstitial pneumonia; pneumothorax; pulmonary Langerhans cell histiocytosis; Sjögren disease; tuberous sclerosis complex

ABBREVIATIONS: AML = angiomyolipoma; BHD = Birt-Hogg-Dubé syndrome; DCLD = diffuse cystic lung disease; D_{LCO} = diffusion capacity of the lung for carbon monoxide; FB/LIP = follicular bronchiolitis/lymphoid interstitial pneumonia; ILD = interstitial lung disease; LAM = lymphangioleiomyomatosis; mTOR = mechanistic target of rapamycin; PLCH = pulmonary Langerhans histiocytosis; SP = spontaneous pneumothorax; TSC = tuberous sclerosis complex

AFFILIATIONS: From the Department of Respiratory Medicine (A. N. F. and C. M.), St. Vincent's University Hospital, Dublin, Ireland; the School of Medicine (A. N. F., D. J. M., and C. M.), University College Dublin, Dublin, Ireland; the Division of Pulmonary, Critical Care, and Sleep Medicine (N. G.), University of Cincinnati, Cincinnati, OH; the Department of Radiology (D. J. M.), St. Vincent's University Hospital, Dublin, Ireland; the Division of Pathology & Laboratory Medicine (K. A. W.-B.), Division of Pulmonary Medicine, and Perinatal Institute Division of Pulmonary Biology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; and the Department of Pathology & Laboratory Medicine (K. A. W.-B.), University of Cincinnati, Cincinnati, OH.

CORRESPONDENCE TO: Cormac McCarthy, MD, PhD, FRCPI; email: cormac.mccarthy@ucd.ie

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Diffuse cystic lung diseases (DCLDs) represent a heterogeneous group of distinct pathophysiologic entities that share a common phenotype of multiple thin-walled cysts within the lung parenchyma. A cyst is characterized as a round parenchymal lucency with a thin appreciable wall (typically ≤ 2 mm) and a well-defined interface with normal lung.[1] The presence of up to three to four cysts may be considered normal, especially in older adults, whereas > four cysts are generally suggestive of an underlying abnormality.[2-4] We propose a threshold of > 10 cysts to further subdivide DCLDs into paucicystic (≤ 10 cysts) and multicystic (> 10 cysts) diseases. Identification and timely diagnosis of DCLDs requires an in-depth assessment of chest CT scan. Although the individual diseases that comprise the DCLD family are rare, taken together, DCLDs can be encountered more frequently in clinical practice than commonly perceived.

DCLDs are generally classified under the umbrella of interstitial lung diseases (ILDs).[5] However, there are fundamental differences between DCLDs and typical fibroinflammatory ILDs regarding epidemiology, clinical manifestations, natural history of disease progression, underlying pathophysiologic mechanisms, and therapeutic approaches. For instance, DCLDs typically affect younger age groups compared with the typical fibrotic ILDs and are often associated with recurrent spontaneous pneumothoraces (SPs). The etiopathogeneses of DCLDs range from one-way check valve formation (ie, progressive focal air trapping, terminal airway dilatation) due to small airway inflammation to protease-mediated cystic lung destruction, that contrasts with the epithelial senescence, repeated microinjury, and aberrant repair mechanisms that characterize fibrotic ILDs. As a group, DCLDs tend to have a better long-term prognosis than fibrotic ILDs, with available targeted therapies that meaningfully alter the natural history of disease progression of some DCLDs. As such, we submit that DCLDs deserve an independent classification[6] based on the underlying etiopathogenic mechanisms highlighting the unique differential diagnosis, disease manifestations, and patient management.

In this article, we present an integrated clinical, radiologic, and histopathologic overview of DCLDs with a focus on the disorders that are most likely to be encountered in clinical practice. Additionally, we provide a practical framework for evaluating suspected cases to guide the most efficient approach toward achieving the right diagnosis, and highlight some key recent developments and future directions for the most commonly seen entities.

Search Strategy and Selection Criteria

References for this review were identified through PubMed search for articles published from January 1980 to August 2023. Search terms included the following: diffuse cystic lung disease, LAM, lymphangioleiomyomatosis, BHD, Birt-Hogg-Dube, pulmonary Langerhans histiocytosis, PLCH, lymphocytic interstitial pneumonitis, lymphoid interstitial pneumonia, and LIP. Relevant articles published between 1980 and 2023 were identified in the authors' personal files, Google Scholar, ResearchGate, and Springer Online Archives Collection. Articles retrieved from these searches and relevant references cited in those articles were reviewed. Articles published in English, French, Spanish, and German were included.

Classification and Epidemiology

DCLDs may arise from a single identifiable cause, or complex interplay between social, genetic, and environmental factors. Consequently, a wide range of etiologies have been recognized, resulting in a broad and overlapping proposed classification structure (Table 1). Some of the most common DCLDs represent low-grade monogenic neoplasms (lymphangioleiomyomatosis [LAM], pulmonary Langerhans histiocytosis [PLCH]), whereas others represent a genetic/developmental defect (Birt-Hogg-Dubé syndrome [BHD]) or an abnormal lymphoproliferative disorder (follicular bronchiolitis/lymphoid interstitial pneumonia [FB/LIP]).

The exact population prevalence of DCLDs is not well established and likely to be significantly underestimated due to frequently delayed and missed diagnosis. LAM is almost exclusively seen in women with a previous estimated prevalence of 3.4 to 7.8 per 1 million women.[7] Recent reports have suggested that the prevalence of LAM is significantly higher than these estimates, and is closer to approximately 20 cases per 1 million adult women.[8,9] The prevalence of BHD is reported to be approximately 2 per 1 million people with no difference in sex distribution[10]; however, this may be a significant underestimate because approximately 5% to 10% of patients presenting with apparent primary SP have been estimated to have underlying BHD.[11] The prevalence of PLCH is thought to be similar (approximately 5 per 1 million), although without a gender predilection. FB/LIP is rare, and the prevalence is unknown.[12-16] However, Sjögren disease is relatively common with an estimated

TABLE 1] Proposed Classification Structure for Differential Etiologies of Cystic Lung Disease

Classification	Diseases
Neoplastic	Lymphangioleiomyomatosis
	Pulmonary Langerhans cell histiocytosis, non-Langerhans cell histiocytosis
	Primary and metastatic neoplasms, including sarcomas, adenocarcinomas, pleuropulmonary blastoma
Genetic/developmental/congenital	Birt-Hogg-Dubé syndrome
	Proteus syndrome, neurofibromatosis, Ehlers-Danlos syndrome
	Congenital pulmonary airway malformation, bronchopulmonary dysplasia, etc
Associated with lymphoproliferative disorders	Lymphoid interstitial pneumonia
	Follicular bronchiolitis
	Sjögren disease
	Amyloidosis
	Light chain deposition disease
Infectious	*Pneumocystis jirovecii*
	Staphylococcal pneumonia
	Recurrent respiratory papillomatosis
	Endemic fungal diseases, especially coccidioidomycosis
	Paragonimiasis
Associated with interstitial lung diseases	Hypersensitivity pneumonitis
	Desquamative interstitial pneumonia
Smoking-related	Pulmonary Langerhans cell histiocytosis
	Desquamative interstitial pneumonia
	Respiratory bronchiolitis
Other/miscellaneous	Posttraumatic pseudocysts
	Fire-eater's lung
	Hyper-IgE syndrome
Mimics of cystic lung diseases	Emphysema: in those who do not smoke, consider α1-antitrypsin deficiency, occupational exposures, HIV, hypocomplementaemic urticarial vasculitis syndrome, Marfan syndrome, Williams-Beuren syndrome
	Bronchiectasis
	Honeycombing seen in late-stage scarring interstitial lung diseases

prevalence of 430 per 1 million people with a strong female predominance. DCLD has been reported to occur in 7.4% to 46.2% of patients with Sjögren disease.[17-22] Conservatively assuming that DCLD arises in 5% to 10% of patients with Sjögren disease, the prevalence of Sjögren-related cystic lung disease would be 21 to 43 patients per 1 million. Sjögren-related cystic lung disease most commonly manifests as FB/LIP with less frequent presentations including amyloidosis, light chain deposition disease, and lymphoma. Increased awareness and vigilance in diagnosing DCLDs when evaluating chest imaging together with screening of appropriate at-risk populations (eg, adult women with tuberous sclerosis complex [TSC], patients presenting with an apparent primary SP) will aid in establishing timely diagnosis and guiding disease-specific management strategies.

Identification of DCLD

Clinicians can arrive at an accurate DCLD diagnosis using a noninvasive approach in most instances by combining critical radiologic evaluation of cyst morphology and distribution with consideration of key demographic variables (eg, sex, focused medical history and physical examination, identification of extrapulmonary imaging abnormalities, evaluation for the presence of disease-specific laboratory biomarkers).

Excluding the possibility of common cyst mimics (emphysema, cystic bronchiectasis, or cavitary disease) is the initial recommended diagnostic decision point followed by distinguishing between paucicystic (≤ 10 cysts) entities and the more diffuse, bilateral, and multilobar changes typical of multicystic DCLDs to further refine the diagnostic decision-making process.[6,23]

Clinical History and Physical Examination

Comprehensive, systematic clinical assessment provides invaluable information to ascertain the underlying etiology in patients presenting with DCLD. Although the typical age of presentation of the major DCLDs tends to be in early to middle adulthood, presentations can occur across wide age ranges, making age a less reliable indicator of disease etiology. Patient demographics can be valuable for identifying the underlying DCLD. For example, LAM is almost exclusively seen in women and Sjögren disease has a strong female preponderance. Most patients with PLCH have concomitant exposure to cigarette smoke. Detailed review of systems aids in identifying diagnostic clues such as the presence of sicca symptoms or other signs and symptoms of connective tissue disorders that point toward FB/LIP as the underlying DCLD. Family history of skin lesions, renal tumors, and/or SP can suggest a diagnosis of BHD.[24]

Although the pulmonary examination findings are not sufficiently specific to differentiate the distinct DCLDs, extrapulmonary findings, especially dermatologic manifestations, can provide valuable information. Careful skin examination can reveal features suggestive of TSC, an inherited systemic disorder that is associated with LAM. Typical skin findings in TSC include facial angiofibromas, subungual fibromas, hypomelanotic macular (ash-leaf) lesions, and connective tissue hamartomas typically found on lumbar skin (shagreen patches).[25] In contrast, white, domed papules composed of benign tumors of the hair follicle (fibrofolliculomas) on the face, scalp, and upper trunk are pathognomonic for BHD.[26]

Laboratory Evaluation

Laboratory testing should include tests to rule out entities in the differential diagnosis including cyst mimics such as emphysematous changes due to low alpha-1 antitrypsin levels, connective tissue disease indicated by elevated autoimmune serologic biomarkers including antinuclear antibodies and extractable nuclear antigens, immunodeficiencies with altered immunoglobulin levels, light chain deposition disease evidenced by elevated serum light chains, and DCLDs with disease-specific serum biomarkers (eg, elevated vascular endothelial growth factor-D levels in LAM) (Table 2).[27,28]

Radiologic Evaluation

Chest CT scan is the most valuable noninvasive diagnostic modality to differentiate among the distinct DCLDs. Radiologic patterns are either diagnostic or substantially narrow the differential diagnosis. CT scan provides the most comprehensive assessment with excellent spatial resolution, 3-dimensional isotropic imaging, and fast acquisition speed. Chest CT scan images of patients with suspected or confirmed DCLD should be acquired as volumetric data sets with full coverage from lung apices to base at full inspiration. An acquisition protocol should be used to reconstruct images with thin sections and high spatial frequency algorithms.[29] Axial images should be reconstructed with thin slices (< 1.5 mm) and a high spatial frequency kernel to evaluate the lungs together with separate soft tissue kernel reconstruction to evaluate the mediastinum and pleura. Coronal and sagittal multiplanar reformats are useful to evaluate zonal cyst distribution. Minimum intensity projection reconstructions are valuable for identifying the presence of cysts, particularly in paucicystic cases. Contrast enhancement is not necessary for pulmonary parenchymal evaluation, but the administration of contrast if required for another reason (eg, in a CT pulmonary angiogram for suspected pulmonary embolus) does not reduce the effectiveness of CT scan for identifying cysts. Expiratory imaging is useful to assess for the presence of air trapping but is not a key element of DCLD evaluation. Thin-slice CT imaging is the most important component of a CT scan performed for DCLD evaluation, with low-dose CT imaging generally being sufficient for follow-up imaging of patients with a confirmed diagnosis.

The Fleischner Society[1] glossary of thoracic radiology defines a cyst as a round parenchymal lucency with a well-defined interface with normal lung. Cysts have a thin, appreciable wall (that is usually < 2 mm) (Fig 1). The cysts are predominantly air filled but can occasionally contain fluid or solid material. Accurately recognizing the presence of pulmonary cysts on CT scan can be challenging, even for experienced thoracic radiologists. Centrilobular emphysema represents the chief cyst mimic but can be differentiated from cysts by the centrilobular location, absence of distinct cyst walls,

TABLE 2] Summary of the Major Diffuse Cystic Lung Diseases

Disease	Pulmonary Manifestations	Cyst Features	Distribution	Gender Predilection and Other Associations	Extrapulmonary Manifestations	Diagnosis	Complications	Management Considerations
LAM	Dyspnea, pneumothorax, chylothorax.	Round, thin-walled, uniform size and shape.	Diffuse with no geographic predilection.	Females > males Typically diagnosed in the reproductive age group; however, can be seen from teenagers to octogenarians. Can occur sporadically or in patients with underlying TSC.	Renal AMLs, chylous effusions (chylothorax, chylous ascites) Abdominopelvic lymphadenopathy Retroperitoneal lymphangioleiomyomas. Other systemic manifestations of TSC in patients with TSC-LAM (eg, Shagreen patches, ash leaf lesions, facial angiofibromas, subungual fibromas, SEGAs, cortical tubers, epilepsy).	Characteristic cysts plus one of the following: TSC, renal AML, chylous effusions, lymphangioleiomyoma, Elevated VEGF-D ≥ 800 pg/mL. Lung biopsy may be needed if none of these are present.	Recurrent spontaneous pneumothorax, progressive respiratory failure.	Serial lung function monitoring. Bronchodilators. mTOR inhibitors for moderate to severe or progressive lung disease, or problematic chylous effusions, or large AML(s). Early pleurodesis for pneumothorax. Lung transplantation for end-stage disease.
BHD	Spontaneous pneumothorax, often recurrent.	Variable size small (< 1 cm) or large (> 2 cm), round to elliptical or lentiform in shape, thin-walled.	Peripheral, basal-predominant, perivascular, subpleural.	Female = male. Positive family history of pneumothorax, skin lesions and/or renal tumors. *FLCN* gene mutation.	Renal tumors: can be multiple and/or bilateral. Skin fibrofolliculomas: typically on face, neck, and upper torso.	Characteristic cysts plus skin biopsy confirming fibrofolliculomas. *FLCN* gene mutation.	Recurrent spontaneous pneumothorax, renal cancer.	Early pleurodesis for pneumothorax. Longitudinal renal cancer monitoring. Family screening.
PLCH	Cough, dyspnea, chest pain, pneumothorax.	Variable size and shapes ranging from round to bizarre, can be associated with nodules and thick-walled cavities.	Upper-to-midzone predominant, spares costophrenic angles, reticulonodular changes in late stages.	Female = male. Cigarette smoking. *BRAF* and other MAPK pathway mutations (NRAS, MAP2K1, etc). Typically diagnosed in third to fifth decade of life.	Skin rash, lytic bone lesions, diabetes insipidus.	Characteristic radiologic findings with history of cigarette smoking. Histopathologic confirmation with $CD1a^{+}$ / $CD207^{+}$ cell aggregates, often with other smoking-related changes. Sequencing for MAPK pathway mutations.	Pneumothorax, progressive respiratory failure, pulmonary hypertension.	Smoking cessation. Serial lung function monitoring. Bronchodilators ± ICS if airflow obstruction. *BRAF* and/or *MEK* inhibitors. Cladribine.
FB/LIP	Cough, dyspnea, less commonly pneumothorax.	Smooth, round, thin-walled, variable size ranging from 1 to 30 mm; often have eccentric vessels and internal septations.	Diffuse with slight lower-lobe predominance, may also have coexistent ground glass or nodular infiltrates.	Females > males. Immune-dysregulatory states such as autoimmune disorders (Sjögren disease, RA, SLE), CVID, HIV.	Features of associated underlying conditions such as sicca, arthralgias, Raynaud, history of infections.	Autoimmune serologies or other corroborative testing to identify underlying condition. Lung biopsy may be needed in some cases.	Progressive respiratory impairment, pneumothorax, rarely transforms to lymphoma.	Serial lung function monitoring. Treatment aimed at underlying disease (eg, immunosuppression for autoimmune disorders, antiretrovirals in HIV, immunoglobulin replacement in CVID).

AML = angiomyolipoma; BHD = Birt-Hogg-Dubé syndrome; CVID = common variable immune deficiency; FB = follicular bronchiolitis; ICS = inhaled corticosteroid; LAM = lymphangioleiomyomatosis; LIP = lymphoid interstitial pneumonia; MAPK = mitogen-activated protein kinase; mTOR = mechanistic target of rapamycin; PLCH = pulmonary Langerhans cell histiocytosis; RA = rheumatoid arthritis; SEGA = subependymal giant cell astrocytoma; SLE = systemic lupus erythematosus; TSC = tuberous sclerosis complex; VEGF = vascular endothelial growth factor.

TABLE 3] General Recommendations Applicable to All Patients With DCLD

Recommendation
1. Counsel to avoid smoking.
2. Stay up-to-date on vaccinations against common respiratory pathogens (eg, influenza, pneumococcal pneumonia, respiratory syncytial virus, COVID-19)
3. Patients should be educated about the typical signs and symptoms of pneumothorax and instructed to seek medical attention if they have new-onset symptoms suggestive of a pneumothorax
4. The risk of in-flight pneumothorax is approximately 1 per 100 flights, and air travel is considered safe for most patients with DCLDs
5. Advise against scuba diving due to the potential risk of spontaneous pneumothorax
6. Patients presenting with spontaneous pneumothorax should undergo pleurodesis after the first episode of pneumothorax; prior pleurodesis is not a contraindication for future lung transplantation

DCLD = diffuse cystic lung disease.

and nonuniform distribution of enlarged airspaces (Fig 2).[30] The presence of central vessels traversing the airspace is characteristic of centrilobular emphysema, and can be a useful discriminator when present.[31] Other potential mimics of pulmonary cysts include cystic bronchiectasis, honeycombing, and cavities which are defined as a gas-filled space developing in a focal consolidation or mass. These mimics can usually be confidently distinguished from cysts by careful image evaluation, including multiplanar reformats.[32] Cyst distribution and shape are the most valuable discriminating CT features among distinct DCLD entities. Cases with a small number of scattered cysts are often the most difficult to diagnose accurately on CT scan. In these paucicystic cases, the presence of ancillary, noncystic features (eg, lung nodules, ground glass

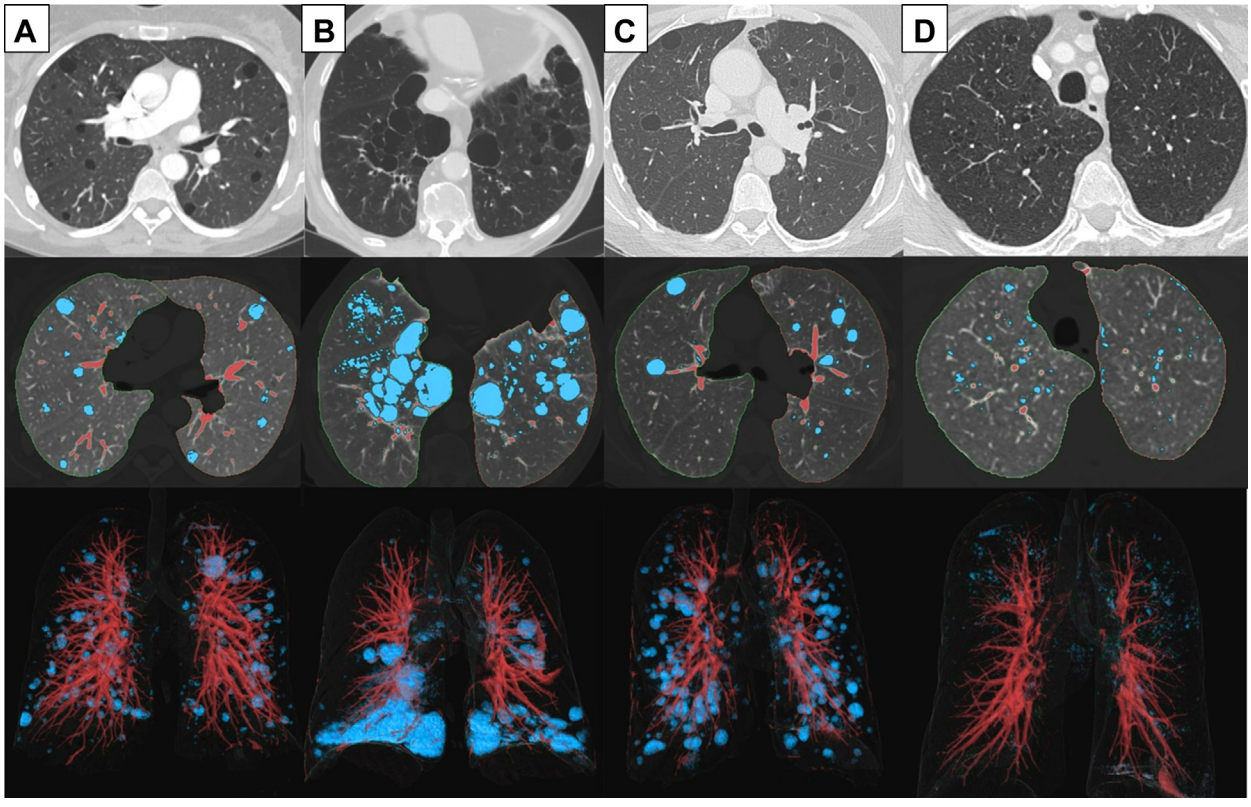

Figure 1 – *A-D, Cyst distribution in diffuse cystic lung diseases. CT thorax imaging showing cysts (in blue) in (A) lymphangioleiomyomatosis (LAM), (B) Birt-Hogg-Dubé syndrome (BHD), (C) lymphoid interstitial pneumonia (LIP), and (D) pulmonary Langerhans histiocytosis (PLCH). Notice the uniform distribution in LAM; subpleural, lower-lobe predominance of elliptical cysts in BHD; perivascular cysts in LIP; and upper lobe predominant cysts in PLCH.*

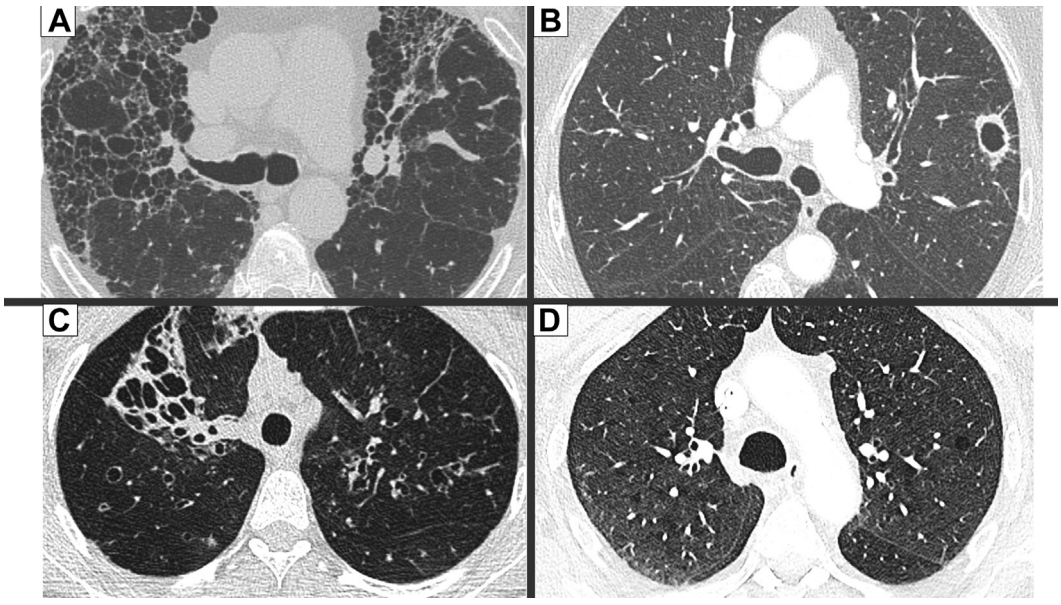

Figure 2 – *A-D, Common mimics of cystic lung disease identified on CT scan. (A) Honeycombing typical of pulmonary fibrosis. (B) Lung cavity/abscess, demonstrating a thick, well-described wall, not typical of a cyst. (C) Cystic bronchiectasis, best appreciated by identifying continuity of the airway on contiguous CT slices. (D) Subtle centrilobular emphysema, usually differentiated by the absence of a definite cyst wall, and the presence of vessels running through the airspace.*

opacification) are important for narrowing the differential diagnosis[33] (Fig 3). Significant diagnostic information can also be gleaned by careful examination of the visualized abdominal organs, with particular attention to identifying renal anomalies such as angiomyolipomas (AMLs) or tumors, which suggest an underlying diagnosis of LAM or BHD, respectively. Radiologic analysis of chest CT scan features using machine learning approaches offers promise for improved future detection of DCLDs but requires further validation.[34]

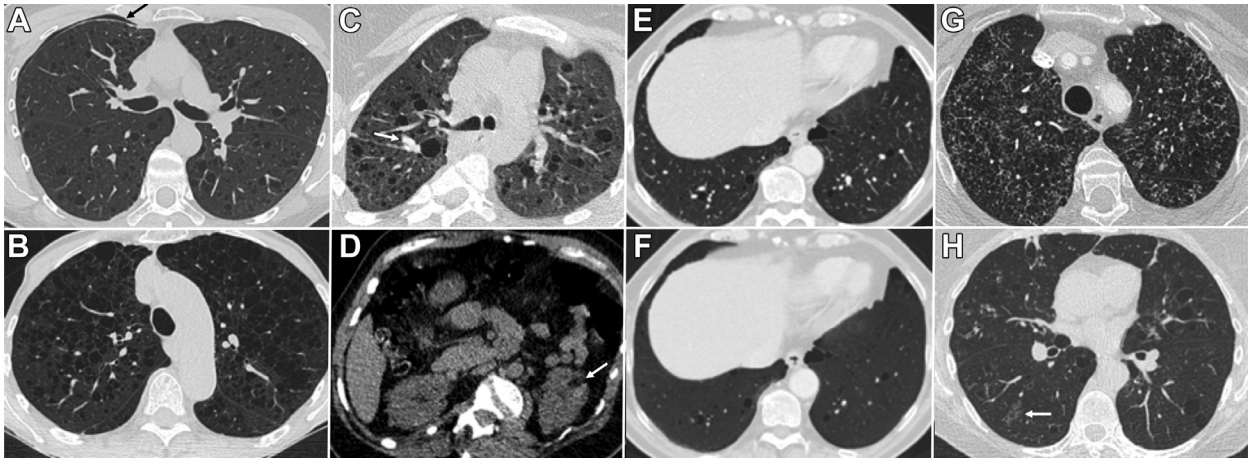

Figure 3 – *A-H, Diffuse cystic lung disease features identified on CT scan. (A) Axial CT thorax scan on lung windows demonstrates multiple, scattered, thin-walled pulmonary cysts in an adult woman with lymphangioleiomyomatosis (LAM), with a small right spontaneous pneumothorax (arrow). (B). Severe LAM in an older adult female patient with extensive bilateral pulmonary cysts, almost completely replacing normal lung parenchyma. (C) CT thorax scan in an adult female patient with tuberous-sclerosis associated LAM demonstrates extensive bilateral pulmonary cysts, with high-density thickening along the right oblique fissure secondary to prior talc pleurodesis. (D) Corresponding noncontrast CT abdomen scan in the same patient with an approximately 2-cm fat density lesion in the anterior interpolar region of the left kidney (arrow) consistent with angiomyolipoma. (E) CT thorax image from an adult male patient with Birt-Hogg-Dubé syndrome shows scattered, bibasal pulmonary cysts with a paramediastinal and perivenular distribution. (F) Minimum intensity projection (MinIP) CT image in the same patient. MinIP reconstructions can be useful in increasing cyst conspicuity by emphasizing low attenuation voxels. (G) Adult woman with pulmonary Langerhans histiocytosis with extensive irregular upper lobe pulmonary cysts with wall thickening and associated tiny centrilobular nodules. (H) CT thorax scan in an adult woman with Sjögren syndrome-lymphoid interstitial pneumonia with pulmonary cysts, patchy ground glass opacification (arrow), and heterogenous bronchial wall thickening.*

The combined radiologic and clinical findings should be integrated to identify the most appropriate diagnosis. Usually, clinicoradiologic correlation points toward one of the major DCLDs, and confirmatory diagnostic testing establishes the diagnosis, with further pathologic evaluation being required to strengthen or confirm the clinical diagnosis in a subset of cases (Fig 4).

Pathologic Evaluation

Pathologic diagnosis of DCLD is typically made by video-assisted thoracoscopic surgery-guided surgical lung biopsy. Diagnostic histologic features can be present in transbronchial forceps or cryobiopsies in some cases, with the diagnostic yield of transbronchial biopsies dependent on the specific disease entity and the technical feasibility of targeting the lesion for biopsy. Cysts are pathologically defined as dilated spaces within the tissue lined by epithelial cells which can be accentuated by cytokeratin immunohistochemical staining to highlight cysts in cases with rare or small cysts and when airspaces are collapsed.[35] Dilated spaces that lack an epithelial lining are termed pseudocysts and can mimic lung cysts. Emphysema is the most common cyst mimic and can be distinguished from cysts by the lack of a distinct wall and evidence of tissue destruction. It is important to carefully evaluate for features of DCLD within the background of emphysema given that some DCLDs are smoking-related, namely PLCH. Enlarged cystically dilated distal airspaces can also be seen in pediatric lung biopsies due to congenital growth abnormalities associated with preterm birth, genetic alterations, and congenital lung disease (eg, trisomy 21, proteus syndrome, Filamin A deficiency).[36] Pulmonary interstitial emphysema resulting from air dissecting into the interstitial space can also mimic cysts with these spaces lacking an epithelial lining and occasionally being associated with a foreign body type response in chronic cases.

The cellularity associated with cysts provides valuable clues for establishing a specific DCLD diagnosis. For example, scant LAM cells may be found adjacent to the cysts and a preponderance of histiocytes associated with a mixed inflammatory infiltrate should raise consideration for PLCH or other non-Langerhans cell histiocytoses (eg, Erdheim-Chester disease). Like the radiologic evaluation, the location of the cysts and cellular infiltrates may provide additional diagnostic clues. For example, prominent lymphocytic infiltrates should raise the differential diagnosis of FB/LIP, immunodeficiency, lymphoma, and connective tissue diseases, particularly Sjögren disease. The histopathologic findings in the adjacent lung may also provide valuable insights into the etiology. If the surrounding lung is normal, LAM, BHD, and metastatic lesions[37] should enter the differential diagnosis. A background of smoking-related lung changes should alert one to the possibility of PLCH.

A systematic pathologic evaluation of the biopsy is required to arrive at the diagnosis of a specific DCLD entity. It is important to determine whether the biopsy is representative of the overall lung disease by comparing the histopathologic findings with the radiologic features. Recognizing collapsed cystic structures, distinguishing true cysts from cyst mimics, and evaluating the cyst wall and adjacent lung tissue for pathologic clues to the disease entity are key to establishing the correct pathologic diagnosis. Many DCLD cases are diagnosed based on typical clinical and radiologic findings; thus, lung biopsy is performed only when patients lack typical presentations for a distinct entity. Integrating the pathologic features with the salient clinical, serologic, and radiologic features is thus critical for establishing the correct pathologic diagnosis. Additionally, this multimodal correlation is valuable in confirming a presumptive histologic diagnosis in cases of early stage disease with subtle histopathologic features or if only rare disease-related cell types are present in the biopsy.

General Recommendations Applicable to All Patients With DCLDs

Management approaches vary among the distinct DCLDs; however, in general, patients with DCLD should be counseled on smoking cessation, the importance of vaccination against common respiratory pathogens, the signs and symptoms of SP and an action plan for the management of SP, and the overall risks and safety of air travel. Several studies have estimated that patients with DCLDs have an approximate 1% risk of developing SP related to atmospheric pressure changes associated with air travel, with specific risk estimates of 1.1% to 2.6% in LAM, 0% to 0.63% in BHD, and 0.37% in PLCH.[38-43] In general, air travel is considered safe for most patients with DCLDs; however, individualized recommendations for patients should take into account the extent of cyst profusion and the underlying cardiorespiratory reserve to handle an SP. Patients should be counseled to seek medical advice prior to flying in the event of sudden new-onset dyspnea and/or chest pain (Table 3).[44]

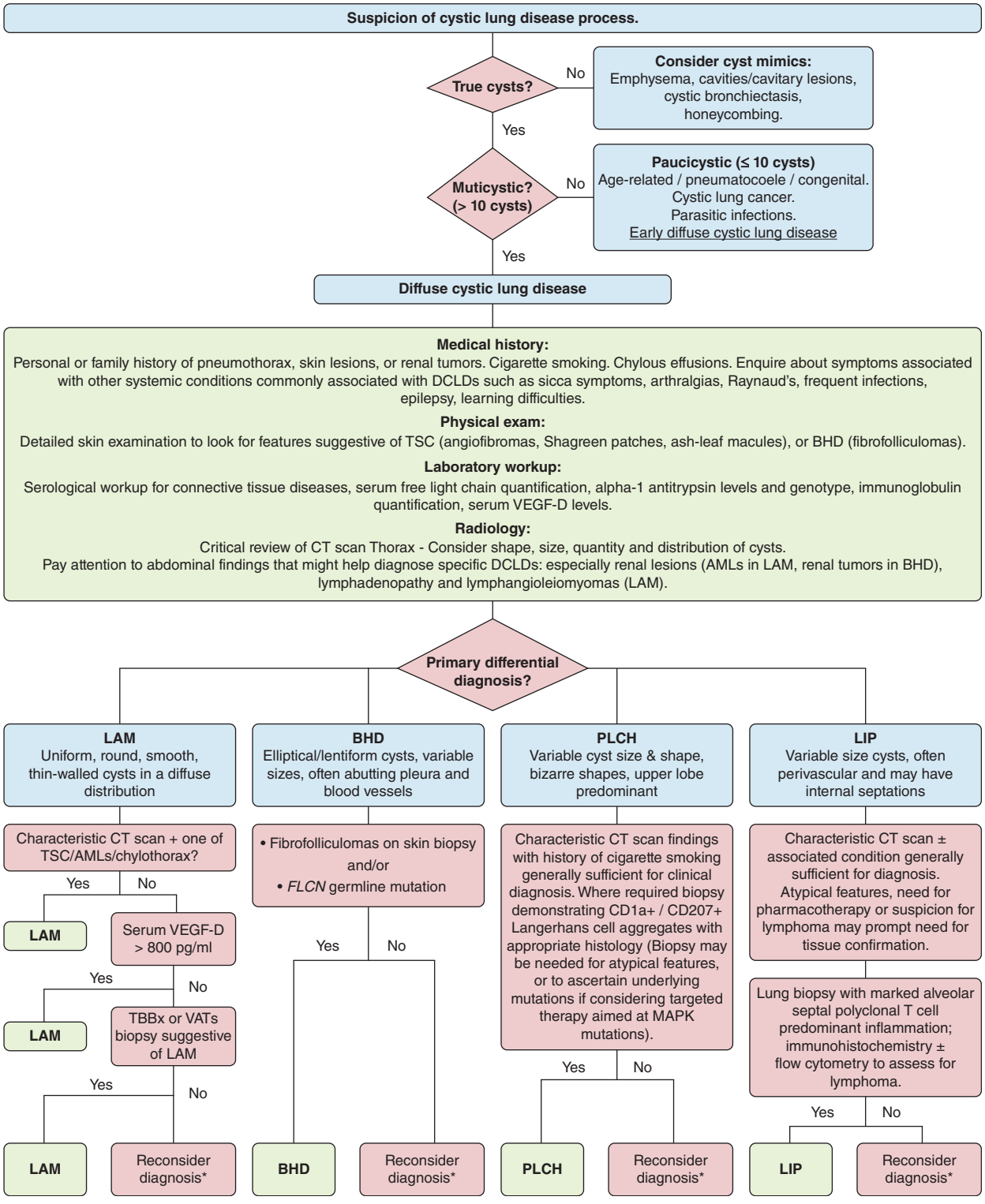

Figure 4 – *Algorithm to approach a patient with cystic lung disease. *Consider atypical presentation of one of the major DCLDs or another cause (eg, amyloidosis, light chain deposition disease). AML = angiomyolipoma; BHD = Birt-Hogg-Dubé syndrome; DCLD = diffuse cystic lung disease; LAM = lymphangioleiomyomatosis; LIP = lymphoid interstitial pneumonia; MAPK = mitogen-activated protein kinase; PLCH = pulmonary Langerhans histiocytosis; TBBx = transbronchial biopsy; TSC = tuberous sclerosis complex; VAT = video-assisted thoracoscopy; VEGF = vascular endothelial growth factor.*

Major DCLDs

Lymphangioleiomyomatosis

LAM is the prototypical DCLD. LAM is a progressive, female-predominant, low-grade pulmonary neoplasm caused by constitutive activation of the mechanistic target of rapamycin (mTOR) pathway driven by mutations in one of the two known *TSC* genes.[28,45-48] Activated mTOR signaling drives unchecked growth and proliferation of abnormal smooth muscle-like cells that arise from an external source,[49] evade detection by the immune system,[50-52] gain access to blood and lymphatics through secretion of lymphangiogenic growth factors such as vascular endothelial growth factors (vascular endothelial growth factor-C and vascular endothelial growth factor-D),[53,54] and metastasize to the lungs where they drive a program of matrix remodeling leading to cystic destruction of pulmonary parenchyma.[47,48] LAM occurs in patients with known TSC or sporadically in patients without the inheritable condition (sporadic LAM).[55,56] The prevalence of cysts in women with TSC is approximately 40% with a lower (approximate 13%) prevalence of cysts in men with TSC,[57] and sporadic LAM is almost exclusively restricted to women. Additionally, men with TSC even in the presence of pulmonary cysts rarely have any clinical manifestations.[58-60]

The average age of diagnosis in LAM is in the mid-30s to mid-40s with the two most common modes of presentation being progressive dyspnea on exertion or SP, which is often recurrent.[61] Other modes of presentation include chylous effusions such as chylothorax or chylous ascites,[61] cyst detection on chest CT scan performed as a screening test in women with TSC or in patients with renal AML,[25,62] or incidental discovery of pulmonary cysts by chest CT scan performed for unrelated reasons.[63]

The characteristic chest CT scan findings of LAM are diffuse, multiple, bilateral, spherical, uniform, thin-walled cysts without any geographic predilection (Figs 1, 3).[64] Although most commonly the intervening pulmonary parenchyma appears normal on chest CT scan, occasionally chylous pleural effusion, ground glass opacification suggestive of chylous congestion, or renal AML(s) are present. Although the cyst features in LAM are unique, current guidelines suggest not using cyst features alone to establish a confirmed diagnosis of LAM.[65] In a patient with chest CT scan showing cysts typical of LAM, the diagnosis can be confirmed with the added presence of one of the following features: concomitant TSC, renal AML, serum vascular endothelial growth factor-D $\geq$ 800 pg/mL, or lymphatic involvement as suggested by the presence of lymphangioleiomyomas or chylous effusions. In the absence of any of these confirmatory features, tissue confirmation may be needed and is most often obtained by transbronchial or video-assisted thoracoscopic surgery-guided lung biopsy.[65] The diagnostic histopathologic features of LAM are cysts combined with LAM cells characterized as spindled and cuboidal epithelioid cells with a smooth muscle phenotype and expressing melanocytic markers, most commonly glycoprotein-100 that is detected with the human melanoma black-45 antibody which is valuable in confirming the pathologic diagnosis (Fig 5).[28,66-68]

The mainstay of treatment for LAM is pharmaceutical approaches aimed at stabilizing or slowing the pace of lung function decline and managing other disease-related complications. In a randomized, placebo-controlled, double-blind clinical trial, an oral mTOR inhibitor, sirolimus, was shown to stabilize lung function decline and improve some measures of quality of life in patients with LAM.[69] Based on these results, sirolimus has now been approved by the US Food and Drug Administration, the EU European Medicines Agency, and regulatory authorities in multiple other countries for the treatment of LAM. Sirolimus is now considered the first-line treatment for patients with both sporadic LAM and tuberous sclerosis associated-LAM who meet one of the following criteria: abnormal lung function (FEV_1 < 70% predicted), chylous complications, rapidly declining lung function (FEV_1 loss $\geq$ 90 mL/y), or substantial disease burden as suggested by impaired diffusion capacity of the lung for carbon monoxide (D_{LCO}), need for supplemental oxygen, air trapping, or hyperinflation.[45,56] In addition to stabilizing lung function decline, treatment with sirolimus has also been shown to improve long-term survival in women with LAM.[70] Sirolimus is generally well tolerated in women with LAM; the most common treatment-related adverse effects include mucositis, acneiform rash, nausea, diarrhea, lower extremity edema, and hyperlipidemia. Sirolimus is a potent inhibitor of wound healing and should be held in the perioperative period to allow optimal healing of incisions. The adverse effects tend to be more common in the initial 3 to 6 months after treatment initiation and reduce over time.[71,72] Treatment with low-dose sirolimus (approximately 1 mg daily) can further mitigate the risk of adverse effects while maintaining similar efficacy.[73,74]

SP is commonly seen in women with LAM and is associated with a very high risk of recurrence.[65,75,76] Patients with LAM should be educated about the common signs and symptoms of SP, and pleurodesis should be performed after the sentinel event to reduce the recurrence risk.[65,77] Treatment with sirolimus might also help reduce the risk of future SP.[76,78,79] Lung transplantation remains a viable option for patients with end-stage disease with posttransplant outcomes better for patients with LAM than with other chronic lung diseases.[80]

Future Directions

Treatment with sirolimus is suppressive rather than remission-inducing, and durable disease control requires long-term drug administration. Future investigations in LAM need to better define the long-term safety and efficacy of sirolimus use in LAM, optimize the dosing strategies and timing of treatment initiation, improve prognostication and predictive models to help individualize treatment decisions, and develop novel remission-inducing therapies for LAM, either in isolation or in combination with sirolimus. The role of low-dose sirolimus in treating patients with LAM with early disease and preserved lung function is currently under investigation.[81]

Birt-Hogg-Dubé Syndrome

BHD is a rare, autosomal-dominant disorder characterized by the development of hair follicle tumors (fibrofolliculoma), pulmonary cysts, and renal tumors. BHD results from loss of function mutations in the tumor suppressor gene, *FLCN*, which encodes the protein folliculin. The exact function of *FLCN* is unknown; however, evidence suggests it is involved in the regulation of cell growth, proliferation, and survival through interactions with the mTOR signaling pathway and others.[82-84] In contrast to LAM, there is no known gender predilection in BHD.

Pulmonary cysts are seen in > 80% of patients with BHD. Although reported in all age groups, cystic lung disease in BHD is often detected in the fourth to fifth decade of life.[85,86] Characteristic CT findings include round to lentiform, variably sized, thin-walled pulmonary cysts in a basilar and subpleural distribution and often abutting the mediastinal pleura and pulmonary vessels.[87-89] The cysts are histologically nondescript spaces surrounded by normal, sometimes compressed, lung parenchyma without significant inflammation, fibrosis, or a distinct disease-identifying cell population or feature.[90,91]

Detailed family history and skin examination are vital in the diagnosis of BHD. It is important to note, however, that there is marked phenotypic variability in patients with BHD and that the absence of skin or renal findings is not sufficient to exclude the presence of BHD. Diagnosis of BHD can be achieved by the confirmation of fibrofolliculomas in a patient with compatible chest CT findings or by genetic testing revealing a pathogenic *FLCN* mutation.

The natural history of lung disease progression in BHD is poorly understood. Typically, lung cysts in BHD occupy a small proportion of the pulmonary parenchyma and generally do not progress to respiratory failure[92-94]; however, a very gradual increase in cyst progression over time has been reported in case reports and small case series.[95,96] SP has been reported to variably occur in 23% to 76% of patients with BHD and has a high risk (> 70%) of recurrence, forming the basis for consideration of pleurodesis after the first SP episode.[38,92] Interestingly, SP in BHD has been reported in the absence of radiologic evidence of cysts on chest CT scan.[97]

Renal cancer is the most severe manifestation of BHD, being seen in up to one-third of patients and most commonly in individuals > 50 years of age.[98] Chromophobe adenomas and oncocytomas are the most common renal tumors in BHD, presenting as bilateral and multifocal tumors in > 50% of patients.[98] Once the diagnosis of BHD is confirmed, patients should be followed with long-term screening for renal tumors, beginning from the 20 years of age.[27] Given the need for multiple scans over time, noncontrast MRI scan roughly every 3 years is preferred because of its sensitivity to detect small lesions and the avoidance of ionizing radiation exposure.[99] However, these screening recommendations represent expert opinion rather than being derived from controlled evidence. In general, renal tumors from BHD tend to be indolent, and the exact benefit of screening in reducing mortality or the cost-effectiveness of frequent scans has not been systematically assessed.

Future Directions

In addition to ascertaining the exact role of renal tumor screening in patients with BHD, other investigative goals for BHD include improved understanding of the

mechanisms of pulmonary cyst formation and the natural history of disease progression, to help develop future targeted therapeutics.

Pulmonary Langerhans Histiocytosis

PLCH is an inflammatory myeloid neoplasm characterized by the abnormal accumulation of dendritic cells harboring activating mutations in the mitogen-activated protein kinase pathway.[100-104] A strong association exists between PLCH and cigarette smoke exposure with > 90% of patients with PLCH having active tobacco use or previously using tobacco.[105-107] A murine model of PLCH provides evidence that cigarette smoke exposure can promote the accumulation of myeloid cells harboring mitogen-activated protein kinase mutations in the lungs. Secondary immune cell recruitment then drives the release of cytotoxic mediators and matrix degrading enzymes leading to the characteristic pulmonary changes seen in PLCH.[102]

In adults, PLCH most commonly manifests as a single system disorder affecting the lungs; however, lung involvement may also be present as a component of systemic LCH or with extrapulmonary involvement typically in the form of lytic bone lesions, diabetes insipidus, or cutaneous involvement. Multiorgan involvement is seen in about 15% of patients with PLCH.[105,108,109] PLCH is most commonly diagnosed in the mid-20s to mid-30s; however, it can be seen at any age and there is no known gender predilection.[100,106,107] The most common symptoms in patients with PLCH include dyspnea on exertion, fatigue, and dry cough.[42,105,107] A small proportion of patients present with SP (approximately 15%-20%)[110] or exhibit constitutional symptoms (eg, malaise, fever, night sweats, weight loss [approximately 10%-15%]).[42,105,107] Incidental detection of PLCH due to chest imaging performed for other reasons is another common scenario for PLCH diagnosis.[109]

The characteristic chest CT scan findings of PLCH include nodules, thin-walled cysts, and/or thick-walled cavities with the disease features dependent on the stage at which the disease is detected. In the initial phases, chest imaging is composed primarily of multiple nodules that evolve over time into thick-walled cavities, and finally thin-walled cysts. The cysts in PLCH are often irregularly shaped, with the appearance of tubular or branching structures. The radiologic findings in PLCH are more prominent in the mid to upper lung zones with sparing of the costophrenic sulci (Figs 1, 3).[27,28] Diagnostic histopathologic findings in PLCH include bronchiolocentric accumulation of S100 and CD1+ Langerhans cells, often accompanied by variable numbers of eosinophils, macrophages, plasma cells, and lymphocytes (Fig 5). In later stages, pericicatricial airspace enlargement and stellate fibrosis can occur (Fig 5). Although a definitive diagnosis of PLCH requires histopathologic confirmation, either by lung biopsy (most common) or biopsy of other extrapulmonary locations, typically skin or bone, in most cases, characteristic CT scan findings in combination with a compatible clinical history may be sufficient to establish a clinical diagnosis of PLCH, especially in patients with a history of exposure to cigarette smoke.[100,108]

The mainstay of management in PLCH involves cigarette smoke cessation which can lead to disease stabilization or even regression.[108,111-113] In patients with progressive disease, pharmacotherapy with cladribine or targeted therapy with B-Raf proto-oncogene, serine/threonine kinase and/or mitogen-activated protein kinase inhibitors is a reasonable next step.[108,114-119] SP is seen in 15% to 20% of patients with PLCH with a high risk of recurrence. Early pleurodesis can substantially reduce the recurrence risk and is recommended after the first pneumothorax episode.[42,78,110] Lung transplantation remains a viable option for patients with end-stage lung disease with posttransplant outcomes similar to those in patients with other chronic lung diseases.[120]

Future Directions

Knowledge of the underlying mitogen-activated protein kinase pathway mutations in the pathogenesis of PLCH has suggested the possibility of targeted treatment with B-Raf proto-oncogene, serine/threonine kinase and/or mitogen-activated protein kinase inhibitors in patients with progressive and/or high-risk disease. Randomized controlled trials assessing the safety and efficacy of this approach and early identification of the ideal subset of patients who should be enrolled in these trials are high priority areas for future investigation.

Follicular Bronchiolitis/Lymphoid Interstitial Pneumonia

LIP is a rare idiopathic interstitial pneumonia first described in 1969.[5,16,121] LIP is characterized by prominent lymphocytic infiltration of the lung parenchyma with marked widening of the alveolar septa often with nodular lymphoid aggregates (Fig 5).[5,13,122] FB, in contrast, is characterized by peribronchiolar lymphoplasmacytic inflammation with prominent

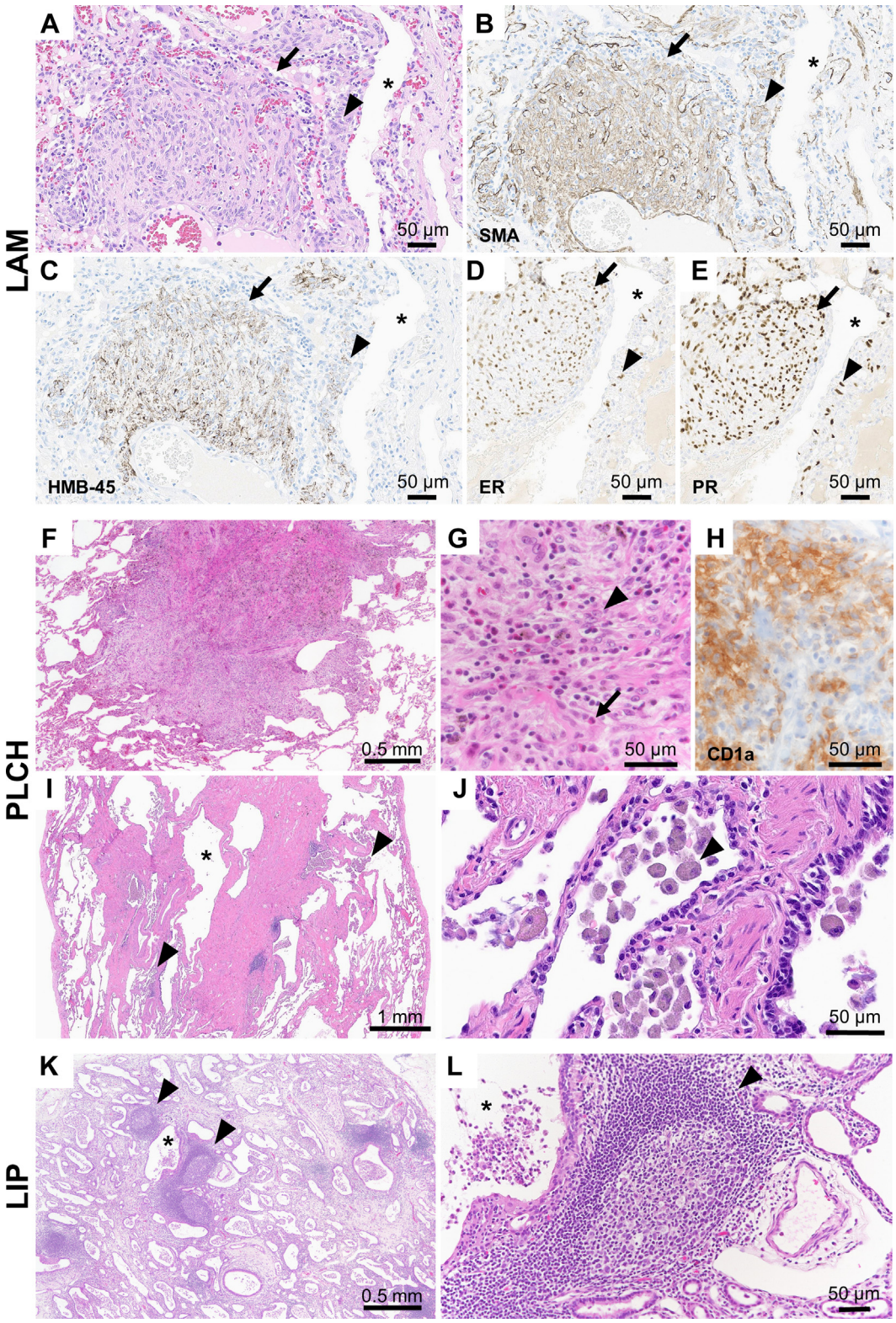

Figure 5 – *A-L, Histopathologic features of diffuse cystic lung diseases to correlate with radiologic findings. A-E, Diagnostic features of lymphangioleiomyomatosis (LAM) (A) including cysts (*) and spindled and epithelioid LAM cells adjacent to the cysts (arrowheads) and forming nodules (arrows). LAM cells have smooth muscle and melanocytic phenotypes evidenced by expression of smooth muscle actin (SMA) (B, brown) and positive immunostaining with the human melanoma black-45 antibody (HMB-45) against the premelanosomal marker, glycoprotein 100 (C), respectively. LAM cells also frequently express estrogen receptor (ER) (D, brown) and progesterone receptor (PR) (E, brown). F-J, Features of pulmonary Langerhans histiocytosis (PLCH) at the cellular stage include nodules (F) composed of clusters of Langerhans cells with characteristic folded or kidney bean shaped nuclei (G, arrowhead) admixed with other*

lymphoid follicles and relatively normal pulmonary parenchyma.[123] FB and LIP can be thought of as a pathophysiologic continuum with FB representing an early stage of disease that can progress to LIP. FB/LIP can be seen in association with autoimmune disease, most classically Sjögren disease, but also in association with other autoimmune diseases (eg, systemic lupus erythematosus, rheumatoid arthritis[67,124-126]) and immune dysregulatory syndromes including HIV/AIDS and common variable immunodeficiency.[121,127,128] Cyst formation in FB/LIP is multifactorial due to possible ischemia caused by vascular obstruction, postobstructive bronchiolar ectasia, and/or bronchiolar compression by lymphoid tissue.[15,129]

Patients most commonly present with chronic cough[12] or progressive dyspnea.[14] Infrequently, patients present with systemic symptoms including fever, night sweats, arthralgias, and weight loss or evidence of an underlying disease such as symptoms of an associated autoimmune disorder.[13,16,121,130] Many cases of LIP are identified incidentally and can precede diagnosis of the underlying associated condition. LIP is twice as common in women as men[5,131] and typically presents in the fifth decade, especially in those with autoimmune disease, most classically Sjögren disease.[16,132] Pulmonary function testing usually reveals a restrictive ventilatory defect[13,16] and a decrease in the D_{LCO}[15] in patients with advanced disease. Conversely, FB is characterized by obstructive spirometry with air trapping and reduced D_{LCO}.[133]

Pulmonary cysts can be seen in 60% to 80% of patients[31] with LIP and generally account for $<$ 10% to 20% of the total lung parenchymal volume.[134] The cyst distribution is predominantly in the lower lung fields.[135,136] Typically, the cysts are thin-walled, of varying size and morphology, and are often associated with eccentric vessels and internal septations (Figs 1, 3).[31,136,137] Other CT scan findings in LIP may include poorly defined centrilobular[31] and subpleural micronodules, bilateral diffuse areas of ground glass opacification,[31] bibasilar reticulation, and peribronchovascular interstitial thickening.[134,136-141] CT scan findings in FB usually correlate with the peribronchovascular distribution of lymphoid infiltration and follicles seen on histopathology.[127] Lung biopsy is required to establish the diagnosis of LIP/FB with certainty; however, characteristic DCLD pattern in patients with known associated underlying diseases is often considered sufficiently diagnostic to obviate the need for pathologic confirmation.

Management of LIP/FB is largely based on case series and case reports and typically dictated by the underlying disease[13,131] (eg, immunosuppressive agents for autoimmune diseases or antiretroviral therapy for HIV).[16] However, it is unclear if immunosuppression has any effect on cyst progression or development. A small proportion of patients with FB/LIP (approximately 5%) may transform to lymphoma; hence, consideration should be given to periodic surveillance imaging every 3 to 5 years, with consideration of PET scan $\pm$ biopsy in case of atypical or enlarging ground glass or nodular lesions.[27,67]

Future Directions

Immunosuppression using novel biologic agents, especially those targeting the B cells, have been reported to have clinical efficacy in patients with Sjögren disease.[142-144] The effect of these therapies on the natural history of progression of lung disease needs further investigation and offers promise for being able to treat patients with advanced or progressive lung disease.

Other DCLDs

Several other less common causes of DCLDs should be considered in the diagnostic workup with an awareness of their important features. The most important alternate diagnoses to consider are amyloidosis and light chain deposition disease. Amyloidosis may present as a systemic condition or be confined to the lung where it occasionally presents as a DCLD.[145] An associated malignancy (eg, mucosa-associated lymphoid tissue lymphoma) may be found in up to one-third of amyloid-associated DCLD cases.[146,147] Some cases of LIP, especially when associated with Sjögren disease, may have amyloid deposits in the lung biopsy.[13,131,141] Light chain deposition disease is a monoclonal immunoglobulin deposition disease typically associated

*inflammatory cells often including eosinophils (G, arrow). Langerhans cells are highlighted by positive immunostaining for CD1a (H, brown). Later PLCH stage with stellate collagenous fibrosis (I) associated with cystically dilated air spaces (I, *). Features of cigarette smoke exposure are often present including accumulation of pigmented macrophages within airspaces (I-J, arrowheads) as seen in respiratory bronchiolitis. K, L, Diagnostic features of lymphoid interstitial pneumonia with marked widening of the alveolar septa by an inflammatory infiltrate with distortion of alveolar spaces (K). Lymphoid follicles with germinal centers (K, L, arrowheads) are present within the alveolated lung parenchyma as well as around bronchioles (*). LIP = lymphoid interstitial pneumonia. Hematoxylin and eosin (A, F-G, I-L) and immunohistochemically (B-E, H) stained histologic images are shown. Magnification is indicated by scale bars in each image. ER = estrogen receptor; HMB-45 = human melanoma black-45; PR = progesterone receptor.*

with lymphoplasmacytic proliferative diseases such as multiple myeloma and monoclonal gammopathy of unknown significance, or occasionally with autoimmune diseases such as Sjögren disease.[148-150] Isolated pulmonary light chain deposition disease mimicking the other more common DCLDs is rare but has been reported.[151]

Certain connective tissue disorders including Ehlers-Danlos syndrome, Marfan syndrome, and neurofibromatosis should also be considered as underlying genetic causes of DCLD.[152-154] Congenital conditions such as congenital pulmonary airway malformation may also present as DCLD in childhood[155] or adulthood.[156] Additional rare causes of DCLD include hyper-IgE syndrome, a rare primary immunodeficiency condition characterized by elevated serum IgE levels and sinopulmonary and cutaneous infections.[157,158] Fire-eater's lung can also present as diffuse cysts on CT scan due to multiple pneumatoceles.[159] Certain malignancies can mimic DCLD including primary lung cancer, metastatic adenocarcinomas, bladder cancer, and metastatic sarcomas among others. Thus, malignancies should be carefully considered in the diagnostic workup.[160] Other rare conditions that have been reported to cause pulmonary cysts include coatomer protein complex subunit alpha syndrome and inherited C-C chemokine receptor type 2 deficiency.[161,162]

Interpretation

DCLDs are a fascinating family of unique disorders that are pathophysiologically, morphologically, and clinically distinct from the typical ILDs. Careful integration of clinical, radiologic, serologic, and histopathologic features in a logical stepwise manner can result in the correct diagnosis of DCLDs in most cases (Fig 4, Table 2).[27,126,163] Advances in our understanding of the molecular pathways underlying the various DCLDs has resulted in the development of specific diagnostic biomarkers and targeted therapeutics leading to improved patient outcomes.

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