CHEST

Smoking-Related Diffuse Cystic Lung Disease

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Exposure to cigarette smoke can lead to a variety of parenchymal lung diseases, including diffuse cystic lung diseases (DCLDs). Lymphangioleiomyomatosis (LAM) is the prototypical DCLD and has a characteristic appearance on high-resolution CT (HRCT). We present a series of four patients with DCLD on HRCT who were referred to our institution with a presumed diagnosis of LAM and who were found instead to have smoking-related injury of the small airways on histopathological analysis. We submit that cigarette smoke–induced small airway injury can present as DCLD on HRCT in a pattern that can mimic LAM. A detailed history of cigarette smoke exposure should be obtained in patients presenting with DCLD, and imaging features should not be used in isolation to establish a firm diagnosis of LAM.

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Exposure to cigarette smoke has been associated with a variety of diffuse parenchymal lung diseases, such as respiratory bronchiolitis-associated interstitial lung disease, desquamative interstitial pneumonia, pulmonary Langerhans cell histiocytosis (PLCH), acute eosinophilic pneumonia, and idiopathic pulmonary fibrosis.[1,2] Of these, PLCH most commonly manifests as a diffuse cystic lung disease (DCLD) on high-resolution CT (HRCT), and cystic changes have been reported in desquamative interstitial pneumonia.[3] The differential diagnosis of DCLDs is broad and, in addition to smoking-related diseases, includes diseases caused by a variety of pathophysiological mechanisms.[3,4]

ABBREVIATIONS: DCLD = diffuse cystic lung disease; HRCT = high-resolution CT; LAM = lymphangioleiomyomatosis; PLCH = pulmonary Langerhans cell histiocytosis

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Materials and Methods

We performed a retrospective chart review of four patients presenting to our institution with DCLD and a presumed diagnosis of lymphangioleiomyomatosis (LAM) who underwent surgical lung biopsy for diagnostic confirmation. Histopathological examination in all cases revealed changes consistent with smoking-related small airway damage including distal bronchioloectasis with mucostasis, emphysema, and cyst formation. Some of the results from this study have been previously reported in the form of an abstract.[5]

Results

All four patients were women with a mean age of 43.5 years (range, 31-53 years), which is a typical demographic in our LAM referral clinic. Dyspnea on exertion was the major presenting symptom in all four subjects, with two of the four also having chronic cough. None of the patients had a history of pneumothorax. Three of the four patients were active smokers with an average smoke exposure of 18 pack-years (range, 5-32), and one patient was largely homebound and had significant, near-constant secondhand exposure to cigarette smoke. Alpha-1 antitrypsin levels were normal in all patients. Other pertinent history and clinical findings included absence of sicca or serological findings to support the diagnosis of Sjögren syndrome, absence of skin lesions or family history of pneumothorax or renal neoplasms to support the diagnosis of Birt-Hogg-Dubé syndrome, and absence of tuberous sclerosis or renal angiomyolipomas to support the diagnosis of LAM. Serum vascular endothelial growth factor-D level was obtained on one patient and was nondiagnostic at 348 pg/mL. The remaining three patients were evaluated before the availability of serum vascular endothelial growth factor-D as a diagnostic biomarker for LAM.[6] A review of the HRCT images revealed the presence of multiple, round, thin-walled cysts of variable sizes distributed diffusely throughout the lung parenchyma. Some of the cysts were perivascular or contained internal structures, including septations or blood vessels (Fig 1). Centrilobular emphysema was present on HRCT in two of the four patients (Table 1, Fig 1).

All four patients had wedge biopsies from at least two lung lobes. Histopathologic analysis showed loss of alveolar density with multiple cystic spaces in all patients, corresponding to the diffuse cystic change seen radiographically (Fig 2). Alveolar walls of normal thickness surrounded and traversed the cystic spaces. Many of the cystic spaces were associated with small airways, with some of the spaces representing dilated distal bronchioles and alveolar ducts. Vessels were present in many of the walls of the cystic spaces,

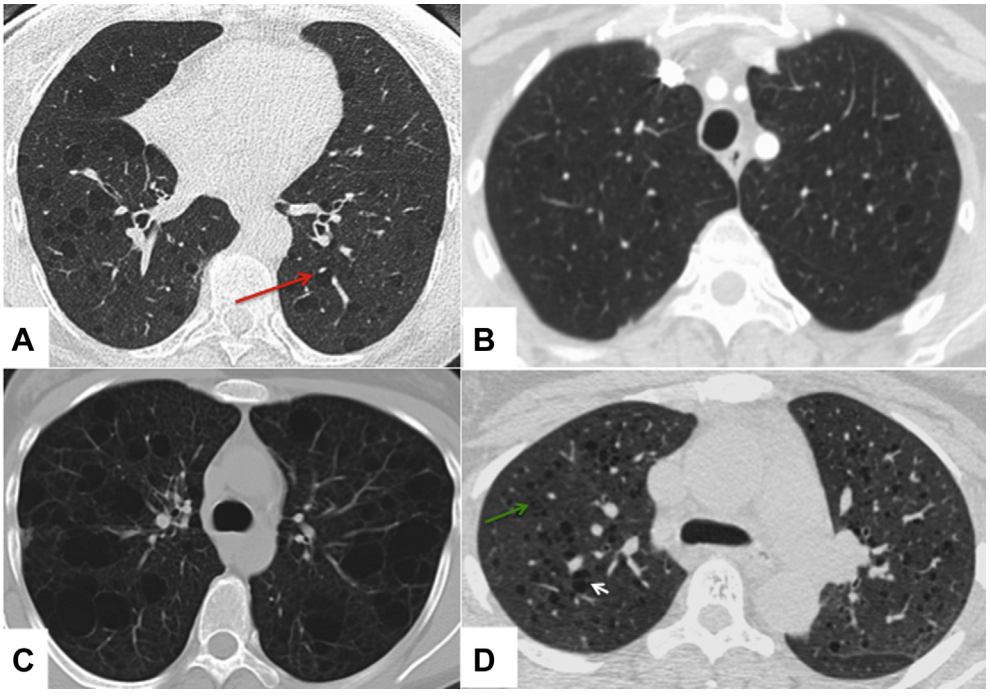

Figure 1 – *High-resolution chest CT scan images. A-D, Notice the presence of diffuse cystic change in all cases. Some of the cysts are perivascular (red arrow). Typical centrilobular emphysema is also seen in some instances (green arrow), as is thin internal septation (white arrow).*

TABLE 1] Clinical and Radiological Features of the Patients in Study

No.	Sex	Age (y)	Smoking	Sjögren Serologies	HRCT Findings			
					Cyst Size	Cyst Features	Distribution	Other Findings
1	F	49	32 py	Negative	2 mm-1 cm	Majority of cysts with eccentric vessels	Peribronchovascular	Centrilobular emphysema
2	F	41	17 py	Negative	3-5 mm	Very uniform smooth, round cysts; some with eccentric vessels and septations	Diffuse	NA
3	F	31	Secondhand	ND	5 mm-2 cm	Round to oval cysts; some with eccentric vessels and septations	Diffuse	Centrilobular emphysema with subpleural bullae
4	F	53	5 py and secondhand	Negative	3 mm-1.5 cm	Smooth, round cysts; some with eccentric vessels and septations	Diffuse	NA

F = female; HRCT = high-resolution CT; NA = not available; ND = not done; py = pack-year.

consistent with the bronchiolocentric localization and HRCT findings. All four patients had focal alveolar destruction consistent with emphysema and chronic bronchiolitis with features of respiratory bronchiolitis characterized by accumulations of pigmented macrophages within the lumen of small bronchioles and surrounding alveolar spaces (Fig 2). Other features of small airway disease were also present, including mild focal bronchiolar mural fibrosis, goblet cell metaplasia, and luminal mucostasis with admixed foamy macrophages, as are often seen in association with small airway obstruction. Complete luminal obliteration of airways was absent in all cases. Focal interstitial fibrosis with chronic inflammation was noted around some of the cystic spaces, but the fibrosis lacked the distinct peribronchiolar stellate configuration of late stage fibrotic PLCH and was not associated with residual Langerhans cell clusters as assessed morphologically and by immunohistochemical staining for CD1a or S100. No LAM cells were identified by morphological analysis or immunohistochemical staining for human melanoma black-45 and smooth muscle actin. Taken together, the histopathological features were those of cystic change on a background of various smoking-related lung changes in the absence of typical DCLDs such as PLCH and LAM. We conclude that the cystic change is an unusual manifestation of smoking-related lung injury.

Discussion

We have shown that exposure to cigarette smoke can be associated with a cystic appearance mimicking other prototypical DCLDs. The exact mechanism of cyst formation and its relationship to emphysema in these cases remains unclear. Rowan et al[7] described five patients with non–smoking-related small airway damage presenting as cystic changes on chest CT scan mimicking LAM and/or PLCH; they proposed that bronchiolitis-induced narrowing of small airway lumens resulted in the development of check-valve–mediated distal airspace dilation and cyst formation. Matrix remodeling resulting from expression of elastases, metalloproteinases, and other enzymes is also a plausible mechanism,[4] although the factors that might favor a cystic phenotype rather than the much more common emphysema-like presentation are not clear. Additional cases of bronchiolitis-associated cystic lung disease, including both respiratory[8] and constrictive bronchiolitis,[9] have been reported. Regardless of the mechanism of cyst formation, it is tempting to speculate

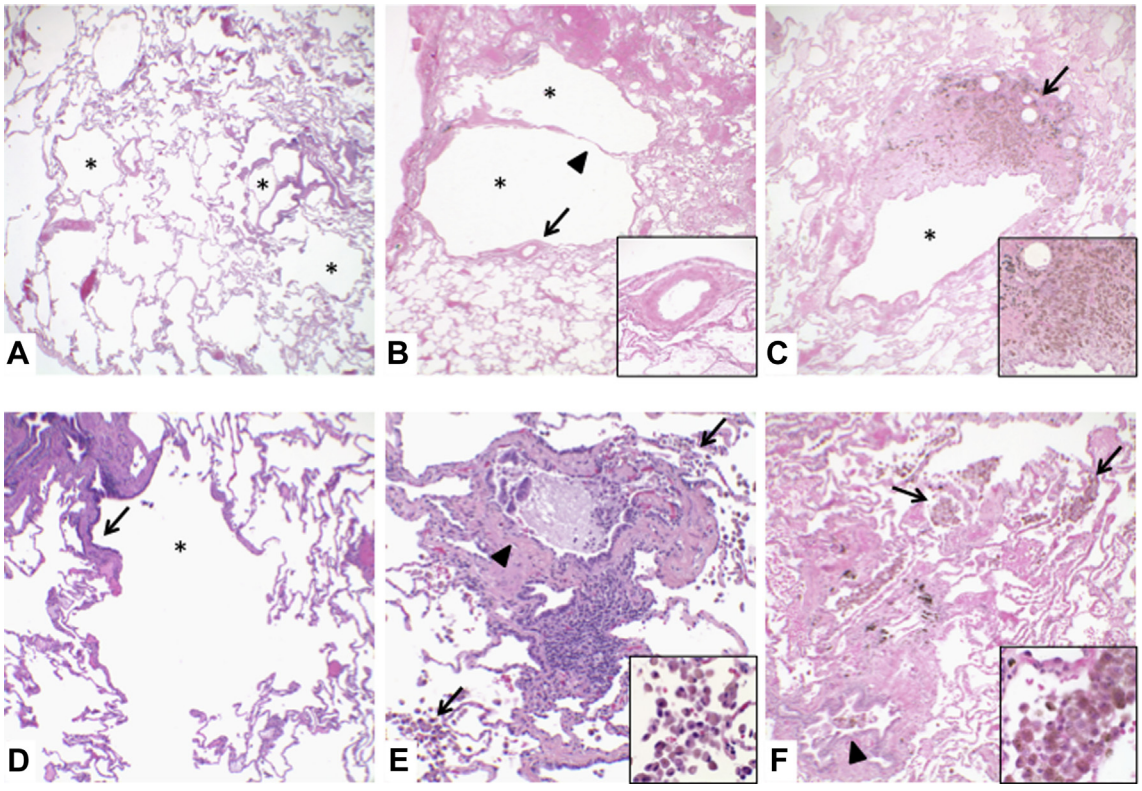

Figure 2 – *Histopathological images highlighting characteristics of cystic spaces and small airway injury. A-D, Multiple cystic spaces were present in biopsies from all four patients. A-B, Many cystic spaces were surrounded by alveolar walls of normal thickness with alveolar septae traversing some cysts (arrowhead) corresponding to the septations seen radiographically. Vessels were frequently present within the walls of the cystic spaces (arrow and inset) consistent with the HRCT findings. C, Fibrosis with chronic inflammation and anthracotic and smoking-related pigment deposition were present around some cysts, (arrow and inset) but no Langerhans cells were present. D, Some cystic spaces represented dilated terminal airways (arrow) and alveolar ducts. E-F, Biopsies from all four patients had small airway disease with histopathologic features including small bronchioles (E, arrowhead) with luminal mucostasis, mild mural fibrosis and chronic inflammation, and respiratory bronchiolitis characterized by accumulation of pigmented macrophages in small airways (F, arrowhead) and surrounding alveolar spaces (arrows and insets). A and E, Representative images from patient 1 corresponding to the Fig. 1A HRCT. D, Patient 3 corresponding to the Fig 1C HRCT. B, C, F, Patient 4 corresponding to Fig 1D HRCT. B-C, Note cystic spaces with differing characteristics occurred in individual patients. Original magnifications: B, ×20; A, C, ×40; D, F, ×100; E, B inset, C inset, ×200, and E-F insets, ×1,000.*

that the concurrent findings of small airway damage of diverse etiologies and cystic change consistent with DCLD suggest a causative relationship. This case series provides further support of a role for cigarette smoke exposure in DCLD.

The cases in this study were referred because of the suspicion of LAM. With the advent of sirolimus as an effective suppressive treatment for LAM[10,11] and the prospect of adverse effects associated with long-term therapy, the need to obtain a definite diagnosis of LAM before initiating treatment has become a clinical imperative. Diagnostic confirmation of LAM can be achieved in >70% of patients without lung biopsy.[11,12] The current study demonstrates that smoking-related DCLD can mimic LAM radiologically and highlights the importance of not basing DCLD diagnoses on HRCT appearance alone, as recommended in the recent American Thoracic Society/Japanese Respiratory Society LAM Guidelines.[13] We submit that radiologic cyst characteristics such as the presence of internal structures or septations within the cysts should prompt an evaluation of alternative (non-LAM) etiologies of DCLD, especially in patients with a history of exposure to cigarette smoke.

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