Smoking-Related Interstitial Lung Diseases

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KEYWORDS

- Desquamative interstitial pneumonia • Respiratory bronchiolitis
- Acute eosinophilic pneumonia • Pulmonary Langerhans cell histiocytosis
- Combined pulmonary fibrosis and emphysema

KEY POINTS

- Smoking is associated with several forms of interstitial lung disease (ILD), including pulmonary Langerhans cell histiocytosis, respiratory bronchiolitis-associated ILD, desquamative interstitial pneumonia, acute eosinophilic pneumonia, and combined pulmonary fibrosis and emphysema; some are diagnosed almost exclusively in smokers.
- High-resolution computed tomography shows various patterns depending on the specific type of smoking-related ILD.
- Although histopathologic confirmation via lung biopsy may be indicated in some situations, it is not always necessary.
- Smoking cessation is a major component of the management strategy for patients with smoking-related ILDs.

INTRODUCTION

Cigarette smoke is associated with the development of several diffuse parenchymal lung diseases, known collectively as smoking-related interstitial lung diseases (ILDs) **Box 1**.[1,2] These disease entities include (a) pulmonary Langerhans cell histiocytosis (PLCH), (b) respiratory bronchiolitis (RB) ILD, (c) desquamative interstitial pneumonia, (d) acute eosinophilic pneumonia (AEP), and (e) combined pulmonary fibrosis and emphysema (CPFE). This review describes the characteristics of the diseases mentioned above, their clinical manifestations, pathogenesis, diagnosis, and treatment strategies.

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PULMONARY LANGERHANS CELL HISTIOCYTOSIS

Langerhans cell histiocytosis (LCH) is a rare disease characterized by tissue infiltration of CD1a + myeloid cells that share many features with Langerhans cells and can present with a broad spectrum of clinical manifestations, from a self-limited process localized to a single organ to severe, life-threatening multiorgan involvement.[3] It commonly affects bone, skin, pituitary, spleen, and liver.[3,4] Most cases of PLCH involve the lung alone, but coexistence with extrapulmonary sites of involvement can also occur.[5–7] Initially, the pathogenesis was mainly attributed to a reactive process secondary to tobacco smoke exposure. However, the paradigm shifted with the description of mutation BRAF V600E and mutations in other genes resulting in constitutive activation of the MAPK (mitogen-activated protein kinase) pathway.[8,9] A combination of cigarette smoke and MAPK signaling pathway mutations results in a PLCH-like process in animal models.[10] Although the precise role of smoking in disease pathogenesis remains to be determined, it is likely that smoking acts as a pro-inflammatory trigger in susceptible individuals.[11]

PLCH is typically diagnosed in young adults, and over 90% of patients are current or former smokers at the time of diagnosis.[6,7,12] Occasionally, patients are asymptomatic and present with incidental radiographic changes.[6] Common respiratory symptoms include chronic dry cough and dyspnea; less commonly, patients report wheezing or hemoptysis. Systemic symptoms, such as asthenia, chest pain, fever, and weight loss can also be present.[7,12] Fifteen to twenty percent develop pneumothorax related to cystic lung process,[13,14] with recurrence in about half of the affected patients.[15]

Pulmonary function tests (PFTs) reveal a decreased diffusing capacity in approximately 90% of patients, and both restrictive and obstructive patterns are seen.[6,16] Chest radiography typically shows a micronodular, reticular, or cystic pattern involving both lungs with basilar sparing.[17] The classic description of PLCH on high-resolution computed tomography (HRCT) scans is the coexistence of nodules and cysts in the upper and middle lobes, with relative sparing of the lung bases (**Fig. 1**).[18] However, nodular opacities alone (including cavitating nodules) are more common in early disease.[6,16] Bronchoscopy with bronchoalveolar lavage (BAL) can help establish the diagnosis, with more than 5% of CD1a + cells being consistent with PLCH.[19] According to current consensus guidelines, histopathologic confirmation is recommended, accompanied by analysis for mutations in the BRAF or MAPK-ERK pathways.[20] Typical cases, with characteristic HRCT features of PLCH, in the appropriate clinical context, may be an exception.[20] Bronchoscopic or surgical lung biopsies provide a definitive diagnosis, with increased diagnostic yield with surgical biopsies.[21,22] Alternatively, a positive biopsy

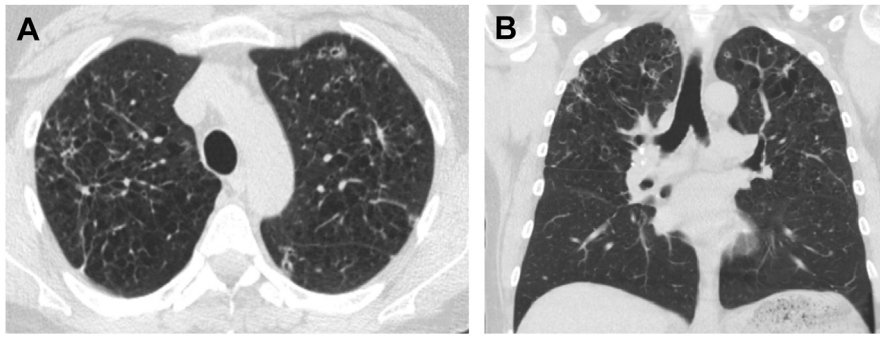

Fig. 1. PLCH. (*A*) Axial CT image showing nodules, cavitating nodules, and cysts in both upper lungs. (*B*) Coronal CT image showing predominantly upper lung distribution of abnormalities with relative sparing of the lower lungs.

of an extrapulmonary site, accompanied by compatible imaging, is diagnostic of PLCH. Echocardiography is helpful in screening for pulmonary hypertension (PH), a prevalent complication.[23] Histopathology shows multiple nodules with abundant Langerhans cells, which stain positive for S100 protein and the more specific markers CD1a and Langerin (CD207) (**Fig. 2**). In early disease, there is a predominance of cellular inflammation, with destructive bronchiolitis.[24] In advanced cases, scarring, such as stellate scars, is more common, and Langerhans cells might not be detectable.[24] Vascular medial thickening is commonly reported.[12,24]

The natural history of the disease is variable. Two years after diagnosis, 40% of patients have evidence of worsening pulmonary function.[5] Ongoing tobacco use and lower PaO2 are associated with the risk of lung function deterioration.[5] A recent study reported an estimated ten-year survival of 93%,[25] implying an improvement compared to the median survival of 12.5 years reported previously.[6,26] The presence of PH, abnormal diffusion capacity for carbon monoxide (DLCO), air trapping, decreased forced expiratory volume in one second (FEV1), and persistent smoking are markers of poor prognosis.[6,23,26] Therefore, counseling patients with PLCH about smoking cessation is essential. Oral glucocorticoids, immunosuppressive and chemotherapeutic agents are options in progressive disease, albeit with limited evidence. Cladribine has been reported to improve symptoms and spirometry in several small case series, and it is recommended as first-line systemic therapy in cases of progressive disease or persistent respiratory dysfunction, including those patients unable to quit smoking.[20,27] In patients with pulmonary arterial hypertension, PH-targeted therapy has been shown to improve hemodynamics.[28] Finally, lung transplantation should be considered in advanced disease when appropriate.[29]

RESPIRATORY BRONCHIOLITIS-INTERSTITIAL LUNG DISEASE

RB is a histopathologic term used to describe the presence of brown-pigmented macrophages in the respiratory bronchioles and was initially described as an incidental finding on autopsies of smokers.[30] It is a finding present in virtually all lung biopsies of smokers and many former smokers and is not necessarily a marker of clinical disease.[30–33] On the contrary, when there is clinical and radiological evidence of ILD associated with RB, it is classified as RB-ILD.[34] Myers and colleagues[34] described RB-ILD in 1987, with cases of heavy cigarette smokers presenting with respiratory symptoms and abnormal chest radiographs. Surgical-lung biopsy showed a mild

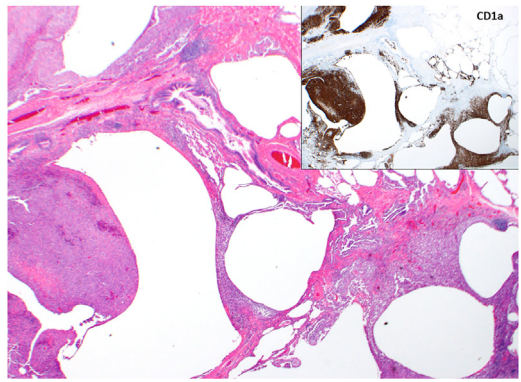

Fig. 2. PLCH. Lung biopsy showing cystic changes associated with collections of Langerhans cells highlighted by CD1a immunohistochemical staining (*inset*).

chronic inflammatory cell infiltration and thickening of the alveolar septa, in addition to RB. The initial report was followed by several case series describing similar findings[1,35–37]

Typically, patients with RB-ILD present in the third to the sixth decade of life (**Table 1**). Almost all the cases correspond to smokers or former smokers.[35,37,38] Symptoms include dyspnea, cough, and chest pain, and about half complain of sputum production.[34,35,37] On auscultation, patients often present with crackles and wheezing. Examination of the extremities reveals clubbing in 10% to 30% of cases.[1,35,39] Pulmonary function is variable, with normal PFTs in 10% to 20%.[35,39] The most consistent finding is a decrease in the DLCO, but it can be normal in up to 30%.[35,39]

Chest radiography shows reticular or reticulonodular interstitial patterns.[34,38] The most common findings on high-resolution computerized tomography (HRCT) are bronchial wall thickening, ground-glass opacities, and centrilobular nodules in both upper and lower lobes (**Fig. 3**). Two-thirds of patients also have centrilobular emphysema with upper lobe predominance.[40] A reticular pattern is identified in close to 30%: however, significant fibrosis, traction bronchiectasis, and honeycombing are typically absent.[40] Of note, hypersensitivity pneumonitis (HP) may present with similar radiologic findings, but a history of smoking makes the diagnosis of RB-ILD more likely, as smoking is associated with a lower incidence of HP compared to the general population.[41]

Findings on BAL are nonspecific and can yield the pigment-laden macrophages associated with smoking, with no abnormal increase of other leukocyte types suggestive of an alternative diagnosis.[34,42] A biopsy is not always needed for the diagnosis. However, when obtained, surgical lung biopsy is the method of choice, given the patchy distribution of the disease, which could result in sampling error with bronchoscopic biopsies. Histopathology reveals pigmented macrophages in alveolar ducts, alveoli, and respiratory bronchioles, interstitial inflammation, and mild fibrosis of the alveolar septa. There is a patchy, peribronchiolar, and periarterial distribution of the interstitial abnormalities[34,37,38] (see **Fig. 3**). Whether RB and RB-ILD can be separated based on histopathological criteria alone is controversial.

Table 1
Clinical characteristics of respiratory bronchiolitis-associated interstitial lung diseases and desquamative interstitial pneumonitis

	RB-ILD	Desquamative Interstitial Pneumonitis
Demographics	Age: 30 to 60 years old	Age: 40 to 50 years old Slight male predominance
Associations	Smoking >95%	Smoking 80% Occupational exposures Connective tissue Infection
Imaging	Centrilobular nodules Bronchial wall thickening	Ground glass opacities, lower lobe predominant. Reticular pattern
Pulmonary function tests	Variable. May be normal Decreased diffusion capacity (mild)	Restriction is more common, although other patterns can be present. Decreased diffusion capacity (moderate-severe)
Treatment	Smoking cessation	Smoking cessation Corticosteroids

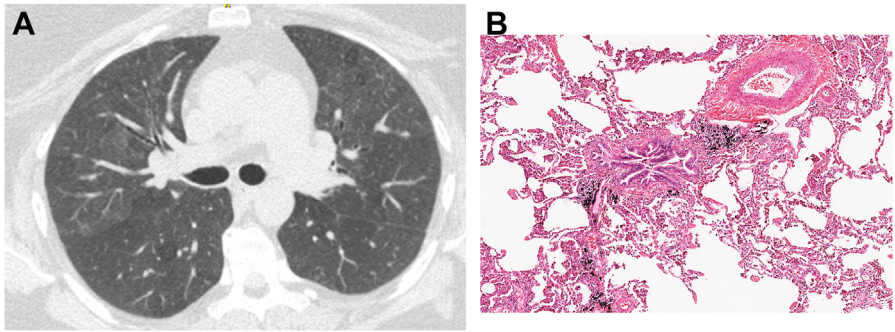

Fig. 3. RB-ILD. (*A*) Axial CT image showing hazy ground-glass opacities involving anterior portions of the upper lobes. (*B*) RB-ILD shows less prominent collections of alveolar macrophages than in DIP, mainly localized to bronchiolar lumens and adjacent centriacinar alveolar spaces, with little or no interstitial fibrosis.

Smoking cessation is the mainstay of treatment of RB-ILD and may bring on stability or improvement of symptoms after a few years.[34,37] A small series showed improvement in centrilobular ground-glass opacities and DLCO in all patients (n = 5) after quitting smoking, with a mean follow-up of 46 months.[43] However, many patients experience worsening symptoms despite smoking cessation.[39] Therefore, clinicians often prescribe oral glucocorticoids or immunosuppressant drugs to treat RB-ILD, but the evidence is limited. In general, the prognosis of RB-ILD is good, and mortality is rare.[39]

DESQUAMATIVE INTERSTITIAL PNEUMONIA

Liebow first described desquamative interstitial pneumonia (DIP) in 1965.[44] It was initially thought that the characteristic lesions corresponded to the desquamation of the alveolar cells into the distal air spaces. However, in reality, the lesion is caused by the accumulation of pigment-laden macrophages in the alveoli. In 2001, the American Thoracic Society and European Respiratory Society discussed changing the name to "alveolar macrophage pneumonia", but they elected to preserve the historic nomenclature.[45] There is a significant clinical and histopathologic overlap between RB-ILD and DIP, and although the pathogenesis has not been entirely elucidated, they likely share some common mechanisms. Approximately 20% of cases are encountered in never-smokers, as opposed to RB-ILD, which virtually always presents in tobacco users.[46] Approximately one-third of patients have a history of environmental exposure to dust and fumes, and high levels of inorganic particles have been found on biopsies of patients with DIP,[46,47] suggesting that occupational exposures may play a role in the development of the disease. Indeed, DIP has been reported from exposure to copper, beryllium, fire extinguisher powder, diesel fumes, solder fumes and nylon filaments[48] Additional possible associations include connective tissue disorders such as scleroderma and rheumatoid arthritis, drugs such as sirolimus, nitrofurantoin, tocainide, sulfasalazine, and viral infections.[46,49–54]

On average, patients are middle-aged at presentation, although cases in children have also been described.[55,56] Most series report a male predominance.[35–37,46,57] The most common symptom in DIP is dyspnea (86%), followed by cough (65%), which is usually nonproductive. Chest pain and constitutional symptoms, such as weight loss, fatigue, and weakness, can also occur.[46] One-fifth of patients have a normal

physical exam, whereas crackles and clubbing are common findings. The predominant pattern on PFTs is restrictive in 70% of cases, with impaired gas exchange, as evidenced by a decreased diffusion capacity.[35,46] The functional abnormalities tend to be more severe in DIP than in RB-ILD (**Table1**).[37]

Chest radiography generally shows bilateral interstitial markings. HRCT is characteristic for ground glass opacities with lower lobe and slight peripheral predominance; consolidative opacities are less commonly seen (**Fig. 4**). Reticular opacities are present in half of the cases, but findings of fibrosis like architectural distortion and honeycombing are unusual. In some, thin-walled cysts may be noted in the parenchyma and are usually small.[58,59] BAL can show eosinophilia (mean eosinophil count of 18% in one study) in a minority of cases.[60] As in other ILDs, confirmation of the diagnosis often requires a surgical lung biopsy, although cryobiopsy is an emerging option.[22] The cardinal feature of DIP is the uniform filling of the alveolar spaces with mononuclear cells (see **Fig. 4**), as opposed to the patchy, bronchiolocentric distribution of RB-ILD.[61] However, the distinction between these processes is not always clear and may represent a continuous spectrum of smoking-related reactions. Lymphoid follicles, interstitial fibrosis, and eosinophils are more common in DIP compared to those with RB.[36] Varying degrees of fibrosis have been reported, but typically not as prominent as in usual interstitial pneumonia (UIP),[62] the histopathologic pattern seen in idiopathic pulmonary fibrosis and fibrotic forms of connective tissue-associated ILD, hypersensitivity pneumonitis, and drug-induced lung disease.

DIP may manifest fibrotic changes when progressive, although the proportion of patients with progression of their disease is much smaller than with UIP.[58] Smoking and other inhalational exposures should be avoided. Most patients are treated with corticosteroids or immunosuppressants with variable responses, although with scarce evidence supporting their therapeutic efficacy. Two-thirds of patients have clinical improvement, whereas close to 25% decline.[46] Without treatment, the proportion of clinical worsening is higher.[57] A minority of patients require lung transplantation.[50]

ACUTE EOSINOPHILIC PNEUMONIA

AEP is an acute respiratory illness presenting with hypoxemia, diffuse pulmonary infiltrates, and a markedly elevated eosinophil count on BAL.[63,64] Typically, it presents in young males in the third to fifth decades of life, especially in those initiating or

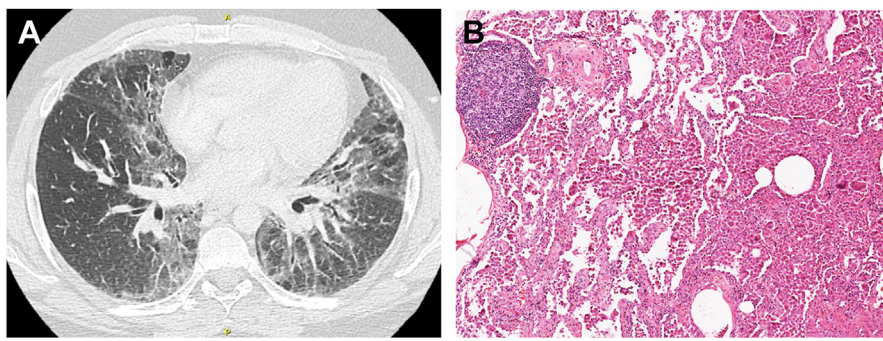

Fig. 4. DIP. (*A*) Axial CT image showing bilateral ground-glass opacities along with some reticular opacities and few regions of hyperlucency (air-trapping). (*B*) Diffuse accumulation of pigmented alveolar macrophages with mild interstitial thickening due to fibrosis. Lymphoid follicles with a prominent germinal center (shown in the upper left field) are often present in DIP.

increasing the amount of tobacco smoked.[65] Secondhand smoke, electronic cigarettes, recreational drugs, dust, and other occupational exposures have also been reported to precipitate this disorder.[66–70] AEP can also be associated with medication use, including daptomycin, minocycline, mesalamine, and other antimicrobials, antidepressants, and anti-inflammatory and chemotherapeutics.[71–73]

In patients with smoking-related AEP, an acutely evolving (days to few weeks) presentation occurs with cough, fever, chest pain, and dyspnea. Peripheral eosinophilia is often absent on initial presentation and develops later in the course.[74,75] Chest radiography shows alveolar and interstitial opacities, Kerley B-lines; bilateral pleural effusions are seen in approximately half of patients.[75] CT typically shows ground-glass, nodular and consolidative opacities, interlobular septal thickening, and pleural effusions (**Fig. 5**A).[76] A BAL with an eosinophil count of >25% is usually diagnostic in the appropriate clinicoradiologic setting (**Fig. 5**B). Interestingly, eosinophilia on BAL has been reported to be associated with less hypoxemia.[75] If a biopsy is performed, it shows interstitial edema and infiltration of alveolar, bronchiolar, and interstitial spaces by eosinophils and diffuse alveolar damage (**Fig. 5**C).[77]

Although the presentation can be severe, including respiratory failure requiring mechanical ventilation, the prognosis is generally good, and most patients experience complete resolution with steroid treatment when diagnosed promptly.[78,79] Typically, the treatment includes intravenous or oral steroids in the acute setting, followed by a taper over 2 to 4 weeks.[78] Review of potential exposures and subsequent avoidance of the offending agent is crucial.

COMBINED PULMONARY FIBROSIS AND EMPHYSEMA

CPFE is a clinical syndrome that classifies a subgroup of patients with emphysema with coexistent pulmonary fibrosis (**Fig. 6**).[80–83] It remains controversial whether CPFE is a distinct entity or merely the coexistence of two separate processes. **Box 1** presents a summary of the clinical, physiologic, and radiologic characteristics associated with CPFE. PFTs may show normal lung volumes and spirometry despite the profoundly abnormal physiology due to two opposing pathophysiologic processes. Reduced gas exchange capacity occurs with both emphysematous and fibrotic disorders; therefore, decreased DLCO may be the sole abnormality on PFTs.[82,83]

Unfortunately, CPFE is associated with a high mortality rate, with a clinical course characterized by frequent exacerbations and gradual progression to chronic respiratory failure.[84–87] In addition, the incidence of lung cancer and PH is high.[85,88,89] The outcomes of patients with CPFE are worse than in COPD alone but comparable to idiopathic pulmonary fibrosis when adjusting for the degree of fibrosis.[81] There is no specific treatment of CPFE other than optimizing the treatment of the emphysema and fibrosis. Management includes general measures such as smoking cessation, supplemental oxygen if required, and pulmonary rehabilitation. Bronchodilators may be useful in patients with airflow limitations. Antifibrotics can be considered in cases with progressive fibrosis. However, patients with significant emphysema have been generally excluded from clinical trials assessing the efficacy of antifibrotic therapy.[81] Identification of PH and specific treatment thereof can be considered for these patients.[88,90]

OTHER INTERSTITIAL LUNG DISORDERS

There is growing recognition of parenchymal abnormalities in smokers that do not meet the criteria for distinct smoking-related ILDs described above. With the

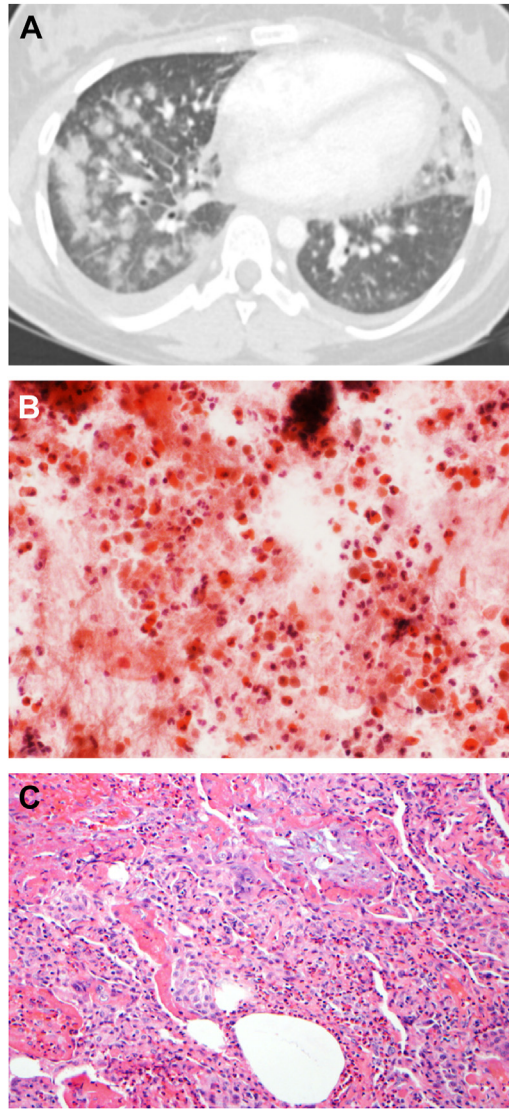

Fig. 5. AEP. (*A*) Axial CT image showing patchy consolidative opacities bilaterally with small pleural effusions, right greater than left. (*B*) Cytology specimen showing numerous eosinophils with occasional Charcot Leyden crystals (right middle field). (*C*) Lung biopsy with numerous intraalveolar eosinophils accompanied by features of diffuse alveolar damage including hyaline membranes and alveolar fibrinous exudates.

implementation of lung cancer screening for smokers, it has been reported that many have interstitial lung abnormalities (ILAs), even in the absence of respiratory symptoms.[91,92] Although the clinical significance is unclear, ILAs have been associated with decreased functional capacity, lung function, quality of life, and increased mortality.[93–95] In addition, the histopathologic term "smoking-related interstitial fibrosis" (SRIF) describes a common finding in smokers' lungs, with interstitial fibrosis in the subpleural lung tissue showing prominent collagen deposition.[96] Some patients may

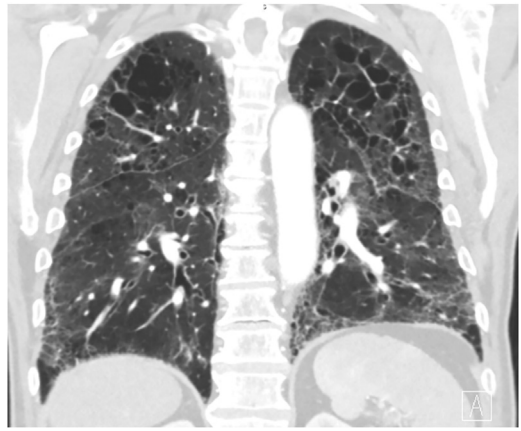

Fig. 6. CPFE. Coronal CT image showing emphysematous changes predominantly in the upper lungs with a bibasilar and peripheral distribution of fibrotic changes.

manifest mild-moderate changes in lung function measurement, but long-term follow-up data are lacking.[96,97] In contrast, hypersensitivity pneumonitis is less prevalent in smokers for reasons that are still not fully defined but may involve the effect of nicotine on immune responses to inhaled antigens.[98] Sarcoidosis also has a decreased prevalence in tobacco smokers, and some studies suggest that smoking could modify the effect of genetic predisposition.[99,100]

Box 1
Clinical characteristics of combined pulmonary fibrosis and emphysema (CPFE)

Clinical characteristics of combined pulmonary fibrosis and emphysema (CPFE)

Demographics
- Age: Commonly 60 to 80 years old
- Sex: Over 70% male

Symptoms
- Dyspnea on exertion
- Cough
- Recurrent exacerbations

Associated comorbidities
- Pulmonary hypertension
- Lung cancer

Physical examination
- Inspiratory basal crackles
- Clubbing

Radiographic findings
- Fibrotic changes: honeycombing, reticular opacities, traction bronchiectasis, ground-glass opacities, and architectural distortion; more prominent in lower lung zones
- Emphysema and bullae, more prominent in upper lung zones (see **Fig. 6**)

Pulmonary function tests
- Severely reduced diffusion capacity
- FEV1/FVC ratio is normal or slightly reduced
- Spirometry and lung volumes may be normal or near normal

Data from Refs.[81,82]

SUMMARY

Smoking-related ILDs encompass a heterogeneous group of pulmonary diseases diagnosed in association with tobacco use, including RB-ILD, DIP, PLCH, AEP, and CPFE. Their pathogenesis is not entirely understood, and the contribution from cigarette smoke itself versus other environmental and genetic factors is a current area of investigation. Prognosis varies among these disorders, but smoking cessation is a major component of management for affected patients.

CLINICS CARE POINTS

- Smoking induces a broad spectrum of pathologic processes in the lung and includes interstitial lung diseases (ILDs).
- Currently recognized forms of smoking-related ILDs include pulmonary Langerhans cell histiocytosis, respiratory bronchiolitis-interstitial lung disease, desquamative interstitial pneumonia, acute eosinophilic pneumonia, and combined pulmonary fibrosis and emphysema.
- Smoking cessation is an essential component of management for patients with smoking-related ILDs.
- The coexistence of emphysema and pulmonary fibrosis often escapes clinical recognition but is frequently associated with the occurrence of pulmonary hypertension and lung cancer.

DISCLOSURE

The Authors declare nothing to disclose.

REFERENCES

1. Moon J, du Bois RM, Colby TV, et al. Clinical significance of respiratory bronchiolitis on open lung biopsy and its relationship to smoking related interstitial lung disease. Thorax 1999;54(11):1009–14.
2. Ryu JH, Colby TV, Hartman TE, et al. Smoking-related interstitial lung diseases: a concise review. Eur Respir J 2001;17(1):122.
3. Emile JF, Abla O, Fraitag S, et al. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. Blood 2016;127(22):2672–81.
4. Kobayashi M, Ando S, Kawamata T, et al. Clinical features and outcomes of adult Langerhans cell histiocytosis: a single-center experience. Int J Hematol 2020;112(2):185–92.
5. Tazi A, de Margerie C, Naccache JM, et al. The natural history of adult pulmonary Langerhans cell histiocytosis: a prospective multicentre study. Orphanet J Rare Dis 2015;10:30.
6. Vassallo R, Ryu JH, Schroeder DR, et al. Clinical outcomes of pulmonary langerhans'-cell histiocytosis in adults. N Engl J Med 2002;346(7):484–90.
7. Colby TV, Lombard C. Histiocytosis X in the lung. Hum Pathol 1983;14(10):847–56.
8. Badalian-Very G, Vergilio J-A, Degar BA, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. Blood 2010;116(11):1919–23.
9. Roden AC, Hu X, Kip S, et al. BRAF V600E expression in Langerhans cell histiocytosis: clinical and immunohistochemical study on 25 pulmonary and 54 extrapulmonary cases. Am J Surg Pathol 2014;38(4):548–51.

10. Liu H, Osterburg AR, Flury J, et al. MAPK mutations and cigarette smoke promote the pathogenesis of pulmonary Langerhans cell histiocytosis. JCI Insight 2020;5(4). https://doi.org/10.1172/jci.insight.132048.
11. Vassallo R, Harari S, Tazi A. Current understanding and management of pulmonary Langerhans cell histiocytosis. Thorax 2017;72(10):937–45.
12. Travis WD, Borok Z, Roum JH, et al. Pulmonary Langerhans cell granulomatosis (histiocytosis X). A clinicopathologic study of 48 cases. Am J Surg Pathol 1993; 17(10):971–86.
13. Mendez JL, Nadrous HF, Vassallo R, et al. Pneumothorax in pulmonary Langerhans cell histiocytosis. Chest 2004;125(3):1028–32.
14. Radzikowska E, Błasińska-Przerwa K, Wiatr E, et al. Pneumothorax in Patients with Pulmonary Langerhans Cell Histiocytosis. Lung 2018;196(6):715–20.
15. Le Guen P, Chevret S, Bugnet E, et al. Management and outcomes of pneumothorax in adult patients with Langerhans cell Histiocytosis. Orphanet J Rare Dis 2019;14(1):229.
16. Tazi A, Marc K, Dominique S, et al. Serial computed tomography and lung function testing in pulmonary Langerhans' cell histiocytosis. Eur Respir J 2012; 40(4):905.
17. Lacronique J, Roth C, Battesti JP, et al. Chest radiological features of pulmonary histiocytosis X: a report based on 50 adult cases. Thorax 1982;37(2):104–9.
18. Brauner MW, Grenier P, Mouelhi MM, et al. Pulmonary histiocytosis X: evaluation with high-resolution CT. Radiology 1989;172(1):255–8.
19. Auerswald U, Barth J, Magnussen H. Value of CD-1-positive cells in bronchoalveolar lavage fluid for the diagnosis of pulmonary histiocytosis X. Lung 1991; 169(6):305–9.
20. Goyal G, Tazi A, Go RS, et al. International expert consensus recommendations for the diagnosis and treatment of Langerhans cell histiocytosis in adults. Blood 2022;139(17):2601–21.
21. Baqir M, Vassallo R, Maldonado F, et al. Utility of bronchoscopy in pulmonary Langerhans cell histiocytosis. J Bronchology Interv Pulmonol 2013;20(4): 309–12.
22. Barata M, Caetano Mota P, Melo N, et al. Transbronchial lung cryobiopsy in smoking-related interstitial lung diseases. Sarcoidosis Vasc Diffuse Lung Dis 2020;37(4):e2020013.
23. Chaowalit N, Pellikka PA, Decker PA, et al. Echocardiographic and clinical characteristics of pulmonary hypertension complicating pulmonary langerhans cell histiocytosis. Mayo Clinic Proc 2004;79(10):1269–75.
24. Roden AC, Yi ES. Pulmonary langerhans cell histiocytosis: an update from the pathologists' perspective. Arch Pathol Lab Med 2016;140(3):230–40.
25. Benattia A, Bugnet E, Walter-Petrich A, et al. Long-term outcomes of adult pulmonary Langerhans cell histiocytosis: a prospective cohort. Eur Respir J 2022; 59(5). https://doi.org/10.1183/13993003.01017-2021.
26. Delobbe A, Durieu J, Duhamel A, et al. Determinants of survival in pulmonary Langerhans' cell granulomatosis (histiocytosis X). Groupe d'Etude en Pathologie Interstitielle de la Société de Pathologie Thoracique du Nord. Eur Respir J 1996;9(10):2002–6.
27. Grobost V, Khouatra C, Lazor R, et al. Effectiveness of cladribine therapy in patients with pulmonary Langerhans cell histiocytosis. Orphanet J Rare Dis 2014; 9:191.

28. Le Pavec J, Lorillon G, Jaïs X, et al. Pulmonary Langerhans cell histiocytosis-associated pulmonary hypertension: clinical characteristics and impact of pulmonary arterial hypertension therapies. Chest 2012;142(5):1150–7.
29. Dauriat G, Mal H, Thabut G, et al. Lung transplantation for pulmonary langerhans' cell histiocytosis: a multicenter analysis. Transplantation 2006;81(5): 746–50.
30. Niewoehner DE, Kleinerman J, Rice DB. Pathologic changes in the peripheral airways of young cigarette smokers. N Engl J Med 1974;291(15):755–8.
31. Fraig M, Shreesha U, Savici D, et al. Respiratory bronchiolitis: a clinicopathologic study in current smokers, ex-smokers, and never-smokers. Am J Surg Pathol 2002;26(5):647–53.
32. Wright JL, Lawson LM, Pare PD, et al. Morphology of peripheral airways in current smokers and ex-smokers. Am Rev Respir Dis 1983;127(4):474–7.
33. Cosio MG, Hale KA, Niewoehner DE. Morphologic and morphometric effects of prolonged cigarette smoking on the small airways. Am Rev Respir Dis 1980; 122(2):265–71.
34. Myers JL, Veal CF Jr, Shin MS, et al. Respiratory bronchiolitis causing interstitial lung disease. A clinicopathologic study of six cases. Am Rev Respir Dis 1987; 135(4):880–4.
35. Ryu JH, Myers JL, Capizzi SA, et al. Desquamative interstitial pneumonia and respiratory bronchiolitis-associated interstitial lung disease. Chest 2005; 127(1):178–84.
36. Craig PJ, Wells AU, Doffman S, et al. Desquamative interstitial pneumonia, respiratory bronchiolitis and their relationship to smoking. Histopathology 2004; 45(3):275–82.
37. Yousem SA, Colby TV, Gaensler EA. Respiratory bronchiolitis-associated interstitial lung disease and its relationship to desquamative interstitial pneumonia. Mayo Clin Proc 1989;64(11):1373–80.
38. Yousem SA. Respiratory bronchiolitis-associated interstitial lung disease with fibrosis is a lesion distinct from fibrotic nonspecific interstitial pneumonia: a proposal. Mod Pathol 2006;19(11):1474–9.
39. Portnoy J, Veraldi KL, Schwarz MI, et al. Respiratory bronchiolitis-interstitial lung disease: long-term outcome. Chest 2007;131(3):664–71.
40. Park JS, Brown KK, Tuder RM, et al. Respiratory bronchiolitis-associated interstitial lung disease: radiologic features with clinical and pathologic correlation. J Comput Assist Tomogr 2002;26(1):13–20.
41. Solaymani-Dodaran M, West J, Smith C, et al. Extrinsic allergic alveolitis: incidence and mortality in the general population. QJM: An Int J Med 2007; 100(4):233–7.
42. Agius RM, Rutman A, Knight RK, et al. Human pulmonary alveolar macrophages with smokers' inclusions: their relation to the cessation of cigarette smoking. Br J Exp Pathol 1986;67(3):407–13.
43. Nakanishi M, Demura Y, Mizuno S, et al. Changes in HRCT findings in patients with respiratory bronchiolitis-associated interstitial lung disease after smoking cessation. Eur Respir J 2007;29(3):453–61.
44. Liebow AA, Steer A, Billingsley JG. Desquamative Interstitial Pneumonia. Am J Med 1965;39:369–404.
45. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Resp Crit Care 2002;165(2):277–304.

46. Hellemons ME, Moor CC, von der Thusen J, et al. Desquamative interstitial pneumonia: a systematic review of its features and outcomes. Eur Respir Rev 2020;29(156). https://doi.org/10.1183/16000617.0181-2019.
47. Abraham JL, Hertzberg MA. Inorganic particulates associated with desquamative interstitial pneumonia. Chest 1981;80(1 Suppl):67–70.
48. Godbert B, Wissler MP, Vignaud JM. Desquamative interstitial pneumonia: an analytic review with an emphasis on aetiology. Eur Respir Rev 2013;22(128):117–23.
49. Ishii H, Iwata A, Sakamoto N, et al. Desquamative interstitial pneumonia (DIP) in a patient with rheumatoid arthritis: is DIP associated with autoimmune disorders? Intern Med 2009;48(10):827–30.
50. Ong S, Levy RD, Yee J, et al. Successful lung transplantation in an HIV seropositive patient with desquamative interstitial pneumonia: a case report. BMC Pulm Med 2018;18(1):162.
51. Hasegawa H, Nakamura Y, Kaida Y, et al. [A case of desquamative interstitial pneumonia associated with hepatitis C virus infection]. Nihon Kokyuki Gakkai Zasshi 2009;47(8):698–703.
52. Sung SA, Ko GJ, Kim JY, et al. Desquamative interstitial pneumonia associated with concurrent cytomegalovirus and Aspergillus pneumonia in a renal transplant recipient. Nephrol Dial Transpl 2005;20(3):635–8.
53. Schroten H, Manz S, Köhler H, et al. Fatal desquamative interstitial pneumonia associated with proven CMV infection in an 8-month-old boy. Pediatr Pulmonol 1998;25(5):345–7.
54. Iskandar SB, McKinney LA, Shah L, et al. Desquamative interstitial pneumonia and hepatitis C virus infection: a rare association. South Med J 2004;97(9):890–3.
55. Buchino JJ, Keenan WJ, Algren JT, et al. Familial desquamative interstitial pneumonitis occurring in infants. Am J Med Genet Suppl 1987;3:285–91.
56. Stillwell PC, Norris DG, O'Connell EJ, et al. Desquamative interstitial pneumonitis in children. Chest 1980;77(2):165–71.
57. Carrington CB, Gaensler EA, Coutu RE, et al. Natural history and treated course of usual and desquamative interstitial pneumonia. N Engl J Med 1978;298(15):801–9.
58. Hartman TE, Primack SL, Kang EY, et al. Disease progression in usual interstitial pneumonia compared with desquamative interstitial pneumonia. Assess serial CT. Chest 1996;110(2):378–82.
59. Akira M, Yamamoto S, Hara H, et al. Serial computed tomographic evaluation in desquamative interstitial pneumonia. Thorax 1997;52(4):333–7.
60. Kawabata Y, Takemura T, Hebisawa A, et al. Eosinophilia in bronchoalveolar lavage fluid and architectural destruction are features of desquamative interstitial pneumonia. Histopathology 2008;52(2):194–202.
61. Konopka KE, Myers JL. A Review of Smoking-Related Interstitial Fibrosis, Respiratory Bronchiolitis, and Desquamative Interstitial Pneumonia: Overlapping Histology and Confusing Terminology. Arch Pathol Lab Med 2018;142(10):1177–81.
62. Carrington CB, Gaensler EA, Coutu RE, et al. Usual and desquamative interstitial pneumonia. Chest 1976;69(2 Suppl):261–3.
63. Allen JN, Pacht ER, Gadek JE, et al. Acute eosinophilic pneumonia as a reversible cause of noninfectious respiratory failure. N Engl J Med 1989;321(9):569–74.

64. Badesch DB, King TE Jr, Schwarz MI. Acute eosinophilic pneumonia: a hypersensitivity phenomenon? Am Rev Respir Dis 1989;139(1):249–52.
65. Uchiyama H, Suda T, Nakamura Y, et al. Alterations in smoking habits are associated with acute eosinophilic pneumonia. Chest 2008;133(5):1174–80.
66. Chaaban T. Acute eosinophilic pneumonia associated with non-cigarette smoking products: a systematic review. Adv Respir Med 2020;88(2):142–6.
67. Rom WN, Weiden M, Garcia R, et al. Acute eosinophilic pneumonia in a New York City firefighter exposed to World Trade Center dust. Am J Respir Crit Care Med 2002;166(6):797–800.
68. Cherian SV, Sardinas G, Al Salihi SA, et al. A 62-year-old man with cough and dyspnea after crack cocaine inhalation. Ann Am Thorac Soc 2016;13(8):1416–8.
69. De Giacomi F, Vassallo R, Yi ES, et al. Acute eosinophilic pneumonia. causes, diagnosis, and management. Am J Respir Crit Care Med 2018;197(6):728–36.
70. Oh P, Balter M. Cocaine induced eosinophilic lung disease. Thorax 1992;47(6):478–9.
71. Bartal C, Sagy I, Barski L. Drug-induced eosinophilic pneumonia: a review of 196 case reports. Medicine (Baltimore) 2018;97(4):e9688.
72. De Giacomi F, Decker PA, Vassallo R, et al. Acute eosinophilic pneumonia: correlation of clinical characteristics with underlying cause. Chest 2017;152(2):379–85.
73. Higashi Y, Nakamura S, Tsuji Y, et al. Daptomycin-induced eosinophilic pneumonia and a review of the published literature. Intern Med 2018;57(2):253–8.
74. Buelow BJ, Kelly BT, Zafra HT, et al. Absence of Peripheral Eosinophilia on Initial Clinical Presentation Does Not Rule Out the Diagnosis of Acute Eosinophilic Pneumonia. J Allergy Clin Immunol Pract 2015;3(4):597–8.
75. Choi JY, Lim JU, Jeong HJ, et al. Association between peripheral blood/bronchoalveolar lavage eosinophilia and significant oxygen requirements in patients with acute eosinophilic pneumonia. BMC Pulm Med 2020;20(1):22.
76. Daimon T, Johkoh T, Sumikawa H, et al. Acute eosinophilic pneumonia: Thin-section CT findings in 29 patients. Eur J Radiol 2008;65(3):462–7.
77. Tazelaar HD, Linz LJ, Colby TV, et al. Acute eosinophilic pneumonia: histopathologic findings in nine patients. Am J Respir Crit Care Med 1997;155(1):296–302.
78. Rhee CK, Min KH, Yim NY, et al. Clinical characteristics and corticosteroid treatment of acute eosinophilic pneumonia. Eur Respir J 2013;41(2):402–9.
79. Philit F, Etienne-Mastroianni B, Parrot A, et al. Idiopathic acute eosinophilic pneumonia: a study of 22 patients. Am J Respir Crit Care Med 2002;166(9):1235–9.
80. Cottin V. Combined pulmonary fibrosis and emphysema: bad and ugly all the same? Eur Respir J 2017;50(1). https://doi.org/10.1183/13993003.00846-2017.
81. Cottin V, Selman M, Inoue Y, et al. Syndrome of Combined Pulmonary Fibrosis and Emphysema: An Official ATS/ERS/JRS/ALAT Research Statement. Am J Respir Crit Care Med 2022;206(4):e7–41.
82. Cottin V, Nunes H, Brillet PY, et al. Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. Eur Respir J 2005;26(4):586–93.
83. Nemoto M, Koo CW, Ryu JH. Diagnosis and Treatment of Combined Pulmonary Fibrosis and Emphysema in 2022. JAMA 2022;328(1):69–70.
84. Mejia M, Carrillo G, Rojas-Serrano J, et al. Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension. Chest 2009;136(1):10–5.

85. Hage R, Gautschi F, Steinack C, et al. Combined Pulmonary Fibrosis and Emphysema (CPFE) Clinical Features and Management. Int J Chron Obstruct Pulmon Dis 2021;16:167–77.
86. Kim HJ, Snyder LD, Neely ML, et al. Clinical Outcomes of Patients with Combined Idiopathic Pulmonary Fibrosis and Emphysema in the IPF-PRO Registry. Lung 2022;200(1):21–9.
87. Ryerson CJ, Hartman T, Elicker BM, et al. Clinical features and outcomes in combined pulmonary fibrosis and emphysema in idiopathic pulmonary fibrosis. Chest 2013;144(1):234–40.
88. Cottin V, Le Pavec J, Prevot G, et al. Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome. Eur Respir J 2010; 35(1):105–11.
89. Goh NSL. Pulmonary hypertension in combined pulmonary fibrosis and emphysema: a tale of two cities. Respirology 2018;23(6):556–7.
90. Jacob J, Bartholmai BJ, Rajagopalan S, et al. Likelihood of pulmonary hypertension in patients with idiopathic pulmonary fibrosis and emphysema. Respirology 2018;23(6):593–9.
91. Chung JH, Richards JC, Koelsch TL, et al. Screening for lung cancer: incidental pulmonary parenchymal findings. AJR Am J Roentgenol 2018;210(3):503–13.
92. Tanner NT, Thomas NA, Ward R, et al. Association of cigarette type with lung cancer incidence and mortality: secondary analysis of the national lung screening trial. JAMA Intern Med 2019;179(12):1710–2.
93. Doyle TJ, Washko GR, Fernandez IE, et al. Interstitial lung abnormalities and reduced exercise capacity. Am J Respir Crit Care Med 2012;185(7):756–62.
94. Ash SY, Harmouche R, Putman RK, et al. Clinical and genetic associations of objectively identified interstitial changes in smokers. Chest 2017;152(4):780–91.
95. Washko GR, Hunninghake GM, Fernandez IE, et al. Lung Volumes and Emphysema in Smokers with Interstitial Lung Abnormalities. N Engl J Med 2011; 364(10):897–906.
96. Katzenstein AL, Mukhopadhyay S, Zanardi C, et al. Clinically occult interstitial fibrosis in smokers: classification and significance of a surprisingly common finding in lobectomy specimens. Hum Pathol 2010;41(3):316–25.
97. Katzenstein AL. Smoking-related interstitial fibrosis (SRIF), pathogenesis and treatment of usual interstitial pneumonia (UIP), and transbronchial biopsy in UIP. Mod Pathol 2012;25(Suppl 1):S68–78.
98. Blanchet MR, Israël-Assayag E, Cormier Y. Inhibitory effect of nicotine on experimental hypersensitivity pneumonitis in vivo and in vitro. Am J Respir Crit Care Med 2004;169(8):903–9.
99. Douglas JG, Middleton WG, Gaddie J, et al. Sarcoidosis: a disorder commoner in non-smokers? Thorax 1986;41(10):787–91.
100. Rivera NV, Patasova K, Kullberg S, et al. A gene-environment interaction between smoking and gene polymorphisms provides a high risk of two subgroups of sarcoidosis. Sci Rep 2019;9(1):18633.