REVIEW ARTICLE

Smoking-Related Interstitial Lung Disease

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SUMMARY

Background: Smoking-related interstitial lung diseases (SR-ILDs) are a heterogeneous group of diseases with major clinical significance. Reliable epidemiological data are not yet available.

Method: Review of pertinent literature retrieved by a selective search in PubMed.

Results: The available data on many aspects of SR-ILDs are sparse, but recent studies on the pathophysiology and targeted treatment of these conditions have revealed ways in which clinical outcomes can be improved. High-resolution computerized tomography should be used for differential diagnosis; lung biopsy is often unnecessary. Oncogenic mutations play a role in the pathogenesis of pulmonary Langerhans-cell histiocytosis (PLCH). In the future, cladribine and vemurafenib may be treatment options for PLCH. Desquamative interstitial pneumonia (DIP) may be difficult to distinguish from respiratory-bronchiolitis—associated interstitial lung disease (RB-ILD); DIP is treated with steroids and sometimes with immune suppressants. In idiopathic pulmonary fibrosis (IPF), the antifibrotic drugs pirfenidone and nintedanib can delay disease progression. Smoking is also a risk factor for combined pulmonary fibrosis and emphysema (CPFE), rheumatoid-arthritis—associated interstitial lung disease (RA-ILD), pulmonary alveolar proteinosis (PAP), acute eosinophilic pneumonia (AEP), and diffuse alveolar hemorrhage (DAH) in Goodpasture syndrome.

Conclusion: In smokers with exertional dyspnea and/or a nonproductive cough, SR-ILDs must be considered in the differential diagnosis. If an SR-ILD is suspected, the patient should be referred to a pulmonary specialist. Early treatment and smoking cessation can improve clinical outcomes, particularly in the acute and chronically progressive types of SR-ILD.

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Inhalation of tobacco smoke is a risk factor for various diseases of the lungs and respiratory tract. Besides chronic obstructive pulmonary disease, pulmonary emphysema, and lung cancer, this group of diseases includes smoking-related interstitial lung disease (SR-ILD).

The term “interstitial lung disease” (ILD) is used for a category of diseases characterized by damage to the pulmonary interstitial tissue (sometimes involving alveolar epithelium and pulmonary blood and lymph vessels). Smoking is a risk factor for the development and unfavorable course of a number of ILD (1, 2). Conventionally, “smoking-related interstitial lung disease” embraces the entities known to have a strong epidemiological association with smoking:

- Pulmonary Langerhans cell histiocytosis (PLCH)
- Respiratory-bronchiolitis—associated interstitial lung disease (RB-ILD)
- Desquamative interstitial pneumonia (DIP) (e1)

However, smoking may also be a risk factor for other ILD:

- Idiopathic pulmonary fibrosis (IPF)
- Combined pulmonary fibrosis and emphysema (CPFE)
- Acute eosinophilic pneumonia (AEP)
- Rheumatoid-arthritis—associated interstitial lung disease (RA-ILD)
- Diffuse alveolar hemorrhage (DAH) in Goodpasture syndrome
- Pulmonary alveolar proteinosis (PAP) (2–5, e2).

The group of SR-ILD are among the less common pulmonary diseases, with no reliable data on incidence and prevalence. Despite their rarity, these diseases are of great importance for the medical care of smokers who present with dry cough and/or exercise-induced dyspnea. Diagnostic and therapeutic nihilism on the part of patients with SR-ILD is no longer justified, for several reasons: First, there are new specific treatment options for various SR-ILD entities. Second, if the prognosis is poor the indications for lung transplantation should be determined early. Finally, particularly in acute forms of ILD (AEP, DAH in Goodpasture syndrome), the prognosis will be improved if the specific treatment is accompanied by the patient giving up smoking.

Apart from clinical examination and determination of lung function, the most important instrument in the diagnosis of ILD is high-resolution computer tomography. Bronchoalveolar lavage can also yield valuable additional information. Surgical lung biopsy is seldom necessary. The *Table* lists the distinctive

Figure 1: High-resolution computer tomography in pulmonary Langerhans cell histiocytosis. Late stage with irregular cystic formations

features of the entities PLCH, RB-ILD, DIP, IPF, and CPFE as identified in a selective survey of the literature (PubMed). Our understanding of SR-ILD has grown in recent years. New insights into the pathophysiology of various entities of SR-ILD have paved the way for specific treatments.

Pulmonary Langerhans cell histiocytosis

More than 98% of patients who develop PLCH are active or former smokers (e3). In contrast to other forms of histiocytosis, smoking seems to represent the central trigger for the disease (6, 7). Exposure to tobacco smoke results in proliferation of the Langerhans cells as seen in lung tissue samples and bronchoalveolar lavage fluid (e4). Oncogenic mutations of the BRAF-V600E gene have recently been demonstrated in the pulmonary lesions, speaking for underlying clonal proliferation (8).

Treatment and prognosis

Overall the prognosis of PLCH is good. If the patient stops smoking at an early stage, reversal of the pulmonary changes may ensue (*eFigure*) (e5). In advanced stages, however (*Figure 1*), a progressive disease course may become apparent; pulmonary hypertension is observed in > 75% of symptomatic patients (e6, e7). Systemic corticosteroids may be a treatment option in patients with significant impairment, and if the disease continues to progress immunosuppressants and cytostatics can be used. However, the evidence for these approaches is confined predominantly to retrospective analyses of small case series (e8, e9). Interestingly, early case reports (9, e10) describe a positive effect for treatment with cladribine (2-chlorodeoxyadenosine, 2-CdA), a purine analog that induces apoptosis in lymphocytes and monocytes and thus exerts a cytostatic and immunosuppressant effect (e11). To date,

however, there are no prospective studies on the treatment of PLCH with cladribine. In cases of systemic histiocytosis a treatment response has been shown for the substance vemurafenib, a BRAF kinase inhibitor, in the presence of an oncogenic mutation of the BRAF-V600E gene (10). It remains to be investigated whether vemurafenib is also suitable for the treatment of patients with PLCH who display this mutation.

Lung transplantation may be indicated in patients with treatment-resistant disease. Recurrence of PLCH may occasionally be found (e12).

Respiratory bronchiolitis-associated interstitial lung disease

Respiratory bronchiolitis is an expression of the chronic inflammatory response to inhalation of tobacco smoke and can be demonstrated in all smokers (e13, e14). The recovery time after cessation of smoking ranges from 1 to 30 years (e14). The respiratory bronchiolitis itself seldom becomes symptomatic.

If the changes are sufficiently pronounced to be discernible on diagnostic imaging, then the respiratory bronchiolitis is accompanied by interstitial lung disease, which may become symptomatic (*Figure 2*) (11). A patient with RB-ILD usually has a smoking history of over 30 pack-years.

Treatment and prognosis

Beyond giving up smoking, no specific treatment is required, because the prognosis is very good. The disease typically has a stable course and patients who stop smoking may show a tendency towards recovery (e15). No severely progressive or fatal cases of RB-ILD have been described in the literature (e15). Small retrospective observational studies have shown occasional cases of improvement with steroids, but treatment should be considered only in the presence of significant functional impairment (11).

Desquamative interstitial pneumonia

Desquamative interstitial pneumonia is related to smoking in over 90% of cases (*Figure 3*). Forms of DIP associated with other external noxae, autoimmune disease, infection, or drug intake are much rarer (12, e16–e19). Some characteristics of smoking-related DIP are reminiscent of RB-ILD; clear differentiation may be difficult. Nevertheless, the observed differences in disease course and prognosis preclude the understanding of RB-ILD and DIP as different stages or degrees of severity of the same disease.

DIP in childhood is not associated with tobacco smoke. The reader is referred to the relevant literature (e20).

Treatment and prognosis

Untreated, around two thirds of patients with DIP show disease progression; however, spontaneous improvement has also been described (12).

The mortality of DIP ranges from around 6 to 28% (12, 13). The patient should be strongly advised to stop

TABLE

Differential diagnosis of smoking-related interstitial lung disease

	Pulmonary Langerhans cell histiocytosis (PLCH)	Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD)	Desquamate interstitial pneumonia (DIP)	Idiopathic pulmonary fibrosis (IPF)	Combined pulmonary fibrosis and emphysema (CPFE)
Symptoms	Frequently dry cough and exertional dyspnea, rarely asymptomatic. Occasionally fever, weight loss, and functional deficit. Pneumothorax is first manifestation in 15% of cases. Age at onset: 20 to 40 years Distribution ♂/♀: ca. 1:1 (e8, e9, e44)	Frequently asymptomatic, occasionally cough and exertional dyspnea Age at onset: 20 to 50 years Distribution ♂/♀: almost 2:1 (11)	Exertional dyspnea, dry cough, occasionally weight loss and fatigue (12) Age at onset: 20 to 50 years Distribution ♂/♀: ca. 2:1 (12, 13)	Exertional dyspnea, dry cough Age at onset: over 50 years Distribution ♂/♀: ca. 1:1 to 2:1 (17, 18)	Exertional dyspnea Age at onset: 50 to 70 years Distribution ♂/♀: ca. 9:1 (29)
Clinical findings	Usually no indicative findings; clubbed finger in occasional cases (e8)	Frequently rates on auscultation (ca. 50%), occasionally clubbed finger (e45)	Frequently rates on auscultation (60%), frequently clubbed finger (up to 50%) (12, 13)	Rates on auscultation; frequently clubbed finger (50–70%) (17, 18)	On auscultation: quiet breathing noises with occasional rhonchi (13%), frequently rates (87%); frequently clubbed finger (43%) (28)
Lung function	Obstructive, restrictive, or mixed ventilation disorders Impaired diffusion capacity (e44)	Frequently restrictive ventilation disorder, less often mixed obstructive-restrictive findings or no abnormality (11). Impaired diffusion capacity (11).	Restrictive ventilation disorder, impaired diffusion capacity (12, 13)	Restrictive ventilation disorder, impaired diffusion capacity (17, 18)	Typically, formally slight impairment on spirometry with severe restriction of diffusion capacity (28)
High-resolution computer tomography (HRCT)	Early stage: Small irregular or star-shaped nodules, accentuated in the upper and middle part of the lung (eFigure). Advanced stage: Ring shadows (round foci with central liquefaction, at the same time irregular, partly merged nodular and cystic formations (Figure 1) (e46). Definitive diagnosis is possible on the basis of the typical radiomorphology together with the history of smoking and possibly previous pneumothorax. Further invasive measures are seldom required.	Wall accentuation of the terminal bronchioles associated with centrilobular nodules and with a diffusely distributed patchy ground-glass pattern, often strikingly accentuated bilaterally in the upper part of the lung (Figure 2) (e47).	Bilateral ground-glass pattern, often peripheral and accentuated in the lower part of the field, frequently with geographic distribution (Figure 3). Increasing traction bronchiectases and cyst formation as the disease progresses. The latter findings are not exclusively subpleural in location and therefore cannot be confused with honeycombing.	The typical finding is the pattern of UIP with bilateral, subpleural reticular patterns and honeycombing, accentuated in the lower part of the lung (Figure 4) (17, 18).	Bullous, paraseptal, or centrilobular pulmonary emphysema, accentuated in the upper part of the lung, coexistent with pulmonary fibrosis predominantly in the lower part of the lung (Figure 5a, b) (28, e30). Honeycombing and reticular fibrosis are typical, occasionally accompanied by ground-glass opacifications (28).
Bronchoalveolar lavage (BAL)	Increase in Langerhans cells to > 4% is highly specific for the presence of histiocytosis (e48); smoker's macrophages regularly seen.	Increased total cell count and high number of smoker's macrophages, occasionally accompanied by mild neutrophil proliferation (11)	High total cell count, sometimes pronounced eosinophilia and neutrophilia (e49). Smoker's macrophages regularly seen.	Mild neutrophilia and eosinophilia (pronounced lymphocytosis is atypical and widely rules out IPF) (17, 18).	Frequently non-specific, mild neutrophilia. Smoker's macrophages regularly seen (28).
Histology	Distribution of Langerhans cells in bronchial walls and alveolar septa (e8). In small-diameter airways, development of numerous nodules (with Langerhans cells, eosinophils and smoker's macrophages.) Increasing pulmonary fibrosis, irregular star-shaped nodules; later, cystic formations (e50)	Picture of respiratory bronchiolitis with adjacent chronic inflammatory-fibrosing alveolar segments. Smoker's macrophages predominantly in the centrilobular areas. Differentiation of RB-ILD from DIP on pathological criteria may be difficult (11–13).	Accumulation of smoker's macrophages with diffuse distribution in the alveolar spaces; typical interstitial inflammatory and fibrosing changes (e49, e51, 52).	UIP-pattern with the picture of fibrosis and/or architectural destruction with or without honeycombing; predominantly subpleural and/or paraseptal distribution. Patchy pattern of fibrosis. Foci of fibroblasts are typical (17, 18).	Pulmonary emphysema is accompanied by fibrotic segments of lung (typical fibrosis pattern: UIP, fibrotic NSIP, RB-ILD, DIP or unclassifiable fibrosis) (39).

UIP, usual interstitial pneumonia; NSIP, nonspecific interstitial pneumonia

Figure 2: High-resolution computer tomography in respiratory bronchiolitis-associated interstitial lung disease. Bronchiocentric interstitial ground-glass opacifications, accentuated in the upper part of the lung.

Figure 3: High-resolution computer tomography in desquamative interstitial pneumonia. Increased interstitial ground-glass and partly reticular patterns with geographical distribution

smoking. Administration of systemic corticosteroids usually achieves stabilization, rarely improvement (12, e21). In the case of long-term treatment, reduction of steroid consumption by combination with cyclophosphamide or azathioprine can be considered. Overall, however, the evidence on the effect of drug treatment for DIP is scanty and based essentially on retrospective observational studies and case reports (12, e21, e22). Provided all the criteria are fulfilled, lung transplantation may represent an option. One case report describes recurrent DIP in the transplanted organ after single-lung transplantation (14).

Idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis does not occur preferentially in smokers and is therefore not, strictly speaking, one of the SR-ILD. Overall, however, active or former smokers have a 1.6 times greater risk of developing IPF than non-smokers (15, 16). The prevalence of IPF is around 2 to 43 per 100 000 persons; predominantly older adults are affected (e23).

IPF is defined as a particular form of chronic, progressive fibrosing interstitial pneumonia of unknown origin. It is confined to the lung and is associated with the histopathological and/or radiological pattern of “usual interstitial pneumonia” (UIP) (Figure 4) (17, 18). IPF is thus a diagnosis of exclusion, because the UIP pattern can also be present in other ILD (pulmonary asbestosis, chronic exogenous-allergic alveolitis, and ILD triggered by medications or associated with an underlying rheumatological disease).

The mechanism of IPF is unknown. The current opinion is that damage to the alveolar epithelium leads to primary fibrotic remodeling processes. Besides tobacco smoke, many other inhaled noxae have been described as risk factors for the development of IPF (e.g., metal or wood particles, stone dust, particles of vegetable or animal origin) (17, 18). Not all cases of IPF are sporadic; rare familial forms have also been described (e24, e25).

High-resolution computer tomography occupies a central position in the diagnostic algorithm. Histology (surgical biopsy) is considered only if the previous findings are incongruent. The diagnosis should be determined by an interdisciplinary team (pneumology, radiology, pathology) (17, 18).

Treatment and prognosis

On the whole the prognosis of IPF is unfavorable; however, the disease course can differ considerably from patient to patient depending on various risk factors (17). In a retrospective multicenter study the 1-year mortality ranged from 6% to 39%, depending on the risk profile, and the 3-year mortality lay between 16% and 77% (19).

Lung transplantation is the sole curative treatment for IPF. The results of all studied drug treatments have been disappointing. The IFIGENIA study, published in 2005, indicated a positive treatment effect for high-dose N-acetylcysteine (NAC) (20). The recent

PANTHER study demonstrated no such effect for NAC monotherapy, however, and so-called triple therapy (prednisolone, azathioprine, NAC) was associated with increased mortality (21).

In 2011 the antifibrotic substance pirfenidone was licensed as the first specific drug for treatment of mild and moderate IPF in Europe. According to the results of the CAPACITY and ASCEND studies, pirfenidone can slow the progress of the disease (22, 23). The recently published ASCEND study showed a significant treatment effect with regard to the outcome “decline in forced vital capacity (FVC) $\geq 10\%$ or death” (pirfenidone 16.5% vs placebo 31.8%) (23). The pooled study data (CAPACITY and ASCEND) showed a significant reduction in mortality (pirfenidone 3.5%, placebo 6.7%). The most adverse effects of pirfenidone treatment are found particularly in the gastrointestinal tract (nausea 32.8%, dyspepsia 16.8%, diarrhea 21.7%) and the skin (rash 28.7%, photosensitivity reaction 12.2%). (22).

The studies INPULSIS-1 and INPULSIS-2 showed that the progress of IPF was slowed significantly by treatment with the multikinase inhibitor nintedanib (rate of decline in FVC $\leq 10\%$ with nintedanib 70.1%, with placebo 60.5%) (24). Moreover, fewer patients suffered an acute exacerbation of IPF (nintedanib 1.9%, placebo 5.6% after central case review). The observed adverse effects mainly involved the gastrointestinal tract (diarrhea: INPULSIS-1 61.5%, INPULSIS-2 63.2%; nausea: INPULSIS-1 22.7%, INPULSIS-2 26.1%); however, treatment was discontinued due to diarrhea in $< 5\%$ of cases. Nintedanib has recently been licensed in the USA, and approval in Europe is under review. Further new substances for the treatment of IPF are currently under investigation (e26).

Acute exacerbations have particular significance for the prognosis of IPF. Acute exacerbation is defined as rapid deterioration of unknown cause in which the progression of the disease, normally slow and steady, suddenly accelerates, possibly to the point of acute respiratory distress syndrome (ARDS). The 1-year and 3-year rates of incidence for acute exacerbation of IPF are 14% and 21% (25). The probability of death in the acute phase is $> 50\%$, rising to 90 to 100% in cases where ventilation becomes necessary (e27). Bolus treatment with high-dose intravenous steroids can be tried (17, 18).

Further factors relevant to the prognosis are development of pulmonary hypertension and occurrence of lung cancer (4 to 20% of all patients with IPF) (26). Recent studies have identified gastroesophageal reflux as a risk factor for an unfavorable course of IPF (27, e28); however, the effect of antacid treatment has to be investigated in further prospective studies.

Combined pulmonary fibrosis and emphysema

Combined pulmonary fibrosis and emphysema probably cannot be viewed as an independent disease entity. Rather, it is a syndrome resulting from simultaneous occurrence of pulmonary fibrosis and pulmonary emphysema, two diseases whose prevalence is elevated

Figure 4: High-resolution computer tomography in idiopathic pulmonary fibrosis. Predominantly basal and subpleural reticular fibrosis with honeycombing

in smokers (28). Nevertheless, the two diseases in combination show typical characteristics that justify separate consideration of patients with CPFE (*Figure 5*) (e29). Almost exclusively active and former smokers are affected (98%) (29). With regard to lung function, spirometry is broadly normal but gas exchange is severely impaired (28). High-resolution computer tomography is the principal diagnostic modality. Harvesting of tissue for histology is rarely necessary and can be hazardous in advanced CPFE.

Treatment and prognosis

There is no specific treatment for CPFE. In analogy to the treatment of patients with either pulmonary emphysema or pulmonary fibrosis alone, the patient should stop smoking, the indication for long-term oxygen treatment should be assessed, and suitable patients should be listed for lung transplantation (29).

The prognosis of patients with CPFE is comparable to that of patients with IPF alone (e30, e31). The prognosis cannot be adequately estimated from the development of lung function parameters. Above all the prognosis is determined by pulmonary hypertension, which occurs in 47% of patients with CPFE and is associated with 1-year mortality of 60% (28, e32).

Other ILD with high prevalence in smokers

Acute eosinophilic pneumonia

Inhalation of tobacco smoke can trigger AEP. The disease can arise both in new smokers and in those who resume smoking after a period of abstinence or increase their consumption (5, 30, 31). Manifestations have also been described after combined smoking of tobacco and marijuana or cannabis (e33). No robust data on the incidence of AEP are available. A retrospective study in US military personnel found an incidence of 9.1 per 100 000 person-years (31). The response to systemic

Figure 5: High-resolution computer tomography in combined pulmonary fibrosis and emphysema.

- a) Pulmonary emphysema, accentuated in the upper part of the lung
- b) Predominantly basal and subpleural fibrosis with largely reticular and less pronounced ground-glass components.

corticosteroid treatment is very good; complete remission can be attained (30). Retrospective studies have documented the necessity for short-term supportive ventilation in 2 to 67% of cases, depending on the risk constellation (30, 31); in occasional cases extracorporeal procedures are required (e33).

Rheumatoid arthritis-associated interstitial lung disease

Smoking represents a risk factor for the development of RA-ILD (3, 32, e34). The time of onset and the course of the RA-ILD are independent of the underlying disease. The manifestations of this disease are heterogeneous, and the treatment plan should be drawn up on an individual basis in close cooperation with the

patient's rheumatologist. For details of the treatment concept the reader is referred to the relevant literature (e35–e37).

Diffuse alveolar hemorrhage in Goodpasture syndrome

A case series of 51 patients with glomerulonephritis and anti-glomerular basal membrane antibodies showed a clear association (100%) between smoking status and the likelihood of the occurrence of DAH (4). Inhalation of tobacco smoke must therefore be viewed as a risk factor for the occurrence of DAH in Goodpasture syndrome. The acute treatment must be managed by an interdisciplinary team. The options for treatment comprise medicinal immune suppression, plasmapheresis, and, in the presence of renal failure, hemodialysis (33, e38).

Alveolar proteinosis

The estimated prevalence of PAP is 0.1 per 100 000 persons. The proportion of active or former smokers among patients with PAP is 56 to 79% (34, e2). In the presence of significant impairment of lung function the treatment of choice is whole-lung lavage (e39, e40). If there is no satisfactory response to treatment and anti-GM-CSF antibodies are demonstrated (GM-CSF = granulocyte-macrophage colony-stimulating factor), the patient's suitability for inhalation therapy with GM-CSF can be assessed (35).

Smoking-related interstitial lung disease: general treatment principles

Smoking cessation

From the pathophysiological viewpoint, stopping smoking is plausible and advisable in all of the above-mentioned diseases. Several case series on individual entities of SR-ILD have reported improvement following cessation of smoking (12, e5, e14, e15). There are no robust data, however, on how the prognosis changes in patients who have given up smoking. DAH in Goodpasture syndrome and AEP are acute conditions that require immediate specific treatment. Both of these diseases have also been reported in patients who have stopped smoking but then started again, reinforcing the importance of smoking cessation (4, 5).

Rehabilitation

Pneumological rehabilitation is particularly important for the preservation of quality of life and functional capacity in patients with chronic progressive disease (36, e41, e42).

Oxygen treatment

In the presence of significant hypoxia long-term oxygen treatment is indicated and should be prescribed according to the current guidelines (37).

Transplantation

Patients under 65 with refractory progressive disease and without contraindications can be considered for lung transplantation listing, particularly in the presence

KEY MESSAGES

- The possible presence of smoking-related interstitial lung disease must be considered in patients with a positive smoking history and unspecific respiratory symptoms (dyspnea, dry cough).
- Measures for diagnosis and treatment must be planned in cooperation with a pneumologist; if required, a tertiary pulmonary clinical department can also be consulted.
- The most important diagnostic tool is high-resolution computer tomography. There is often no need to obtain a tissue sample for histology.
- The availability of novel treatment options necessitates early establishment of the definitive diagnosis.
- Cessation of smoking may have an immediate positive effect on the prognosis.
- In progressive disease, listing for lung transplantation must be considered in good time.

of a high lung allocation score (LAS), a rapid decline in forced vital capacity of > 10% within 6 months, requirement for oxygen, and decreased oxygen saturation on exercise (oxygen saturation < 89%) (38, e43). Patients considered suitable for transplantation should be assigned to a specific transplantation center at an early stage.

Conflict of interest statement

Dr Hagmeyer has received consulting and speaking honoraria from Intermune and Boehringer.

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REVIEW ARTICLE

Smoking-Related Interstitial Lung Disease

Lars Hagmeyer, Winfried Randerath

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eFigure: High-resolution computer tomography in in pulmonary Langerhans cell histiocytosis (PLCH). Early stage with typical bronchiolocentric star-shaped nodules.