What is the impact of tobacco on the lungs? Smoking-related interstitial lung disease: radio-pathological correlation.

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Learning objectives

To describe and illustrate the radiologic findings in the different types of interstitial lung diseases related to smoking. To point out the most important radiologic criteria for the diagnosis of the different types of interstitial lung diseases and to relate these criteria to the histologic findings.
Background

Interstitial diseases are a heterogeneous group of entities with known or unknown etiology. They are characterized by dyspnea, diffuse changes in the lung parenchyma, restrictive lung function, and reduced gas interchange.

Tobacco smoking is related with the development of different types of interstitial diseases such as respiratory bronchiolitis, pulmonary Langerhans cell histiocytosis, desquamative interstitial pneumonia, and interstitial pneumonia combined with emphysema.

High-resolution computed tomography (HRCT) enables these diseases to be characterized into different individual entities. However, the clinical, radiologic, and pathologic findings of the different interstitial lung diseases can overlap, and mixed patterns often coexist in the same patient. Here we try to illustrate the HRCT and histologic findings of the different interstitial diseases related with tobacco smoking, but we must emphasize that the clinical, radiologic, and histologic findings must be integrated to obtain an accurate diagnosis in these patients.
Findings and procedure details

We reviewed the radiologic findings in these types of interstitial diseases related with tobacco smoking. We present representative cases of each entity, describing the radiologic and histologic findings and the most relevant clinical information and discussing the differential diagnosis.

RESPIRATORY BRONCHIOLITIS ASSOCIATED WITH INTERSTITIAL LUNG DISEASE (RB-ILD):

Respiratory bronchiolitis is a common incidental finding in the lungs of asymptomatic smokers (Fig. 1 on page 9). Less frequently, heavy smokers develop respiratory bronchiolitis associated with interstitial lung disease, characterized by altered lung function and radiologic abnormalities; bronchiolitis is the underlying histologic lesion.

• Clinical and epidemiologic findings:
  • Heavy smokers (> 30 pack-years).
  • Slightly more common in men.
  • Mild cough and dyspnea are the most common symptoms.
  • Impaired pulmonary function.

• Radiologic findings:
  • Chest X-rays: often normal, although it is also common to find nonspecific thickening of the bronchial wall seen as thin bilateral reticular opacities, usually in the upper lobes.
  • HRCT: Respiratory bronchiolitis presents as centrilobular nodules located predominantly in the upper lobes. RB-ILD may be associated with the centrilobular nodules, ground-glass opacities, and thickening of the bronchial walls. Emphysema in the upper lobes is a common finding. Emphysema can also be associated with fibrosis, seen on HRCT as a reticular pattern in areas of centrilobular emphysema (Fig. 2 on page 9).

• Differential diagnosis: hypersensitivity pneumonitis, desquamative interstitial pneumonia, and nonspecific interstitial pneumonia.

• Histologic findings: pigmented macrophages around the respiratory bronchiole and slight interstitial inflammatory changes, predominantly in the respiratory bronchioles and adjacent alveoli. No fibrosis (Fig. 3 on page 10).
• Quitting smoking results in significant improvement.

DESQUAMATIVE INTERSTITIAL PNEUMONIA:

This is a severe/end-stage type of RB-ILD. The term "desquamative" continues to be used even though it is erroneous because histology reveals that this condition is characterized by the accumulation of pigmented macrophages within the alveoli rather than of desquamative epithelial cells as was originally thought.

• Clinical and epidemiologic findings:
  • Smokers (90%) in the 4th or 5th decades of life; male predominance. Passive smokers or nonsmokers with systemic disorders (e.g., infections) or occupational, environmental, or drug exposure.
  • Dyspnea and dry cough are the usual symptoms. Insidious onset.
  • Pulmonary function tests show decreased DLCO and a restrictive pattern.

• Radiologic findings:
  • Chest X-rays: normal findings or ground-glass opacities, predominantly in the periphery or bases of the lung.
  • HRCT: bilateral peripheral ground-glass opacities, although they may also be patchy or diffuse, predominantly in the bases. Emphysema may also be present. A reticular pattern and small cysts are indicative of fibrotic changes (Fig. 4 on page 11, Fig. 5 on page 12).

• Differential diagnosis: RB-ILD, hypersensitivity pneumonitis, nonspecific interstitial pneumonia, and atypical infections such as Pneumocystis jirovecii pneumonia.

• Histologic findings: increased number of pigmented macrophages diffusely distributed throughout the alveolar spaces and thickening of the alveolar septa with a variable degree of fibrosis and mild interstitial inflammation. The key to differentiating between RB-ILD and desquamative interstitial pneumonia is the distribution of the lesions: bronchiolocentric in RB-ILD and diffuse in desquamative interstitial pneumonia (Fig. 6 on page 13).

• The prognosis is good if the patient quits smoking; corticoids can also help.

PULMONARY LANGERHANS CELL HISTIOCYTOSIS:
Unlike Langerhans cell histiocytosis in children, which is a systemic disease, pulmonary Langerhans cell histiocytosis is a disease in adults that normally involves only the lungs.

• **Clinical and epidemiologic findings:**
  - > 90% of patients are smokers.
  - The incidence peaks between the ages of 20 and 40 years; men and women are affected in equal proportions.
  - The most common symptoms are nonproductive cough and dyspnea, although 25% of patients are asymptomatic at the time of diagnosis.
  - 1/3 of patients have constitutional symptoms (weight loss, fever, night sweats).
  - 10% debut with spontaneous pneumothorax.
  - Findings at pulmonary function tests are normal or show decreased DLCO.

• **Radiologic findings:**
  - Chest X-rays: nodular and/or reticular opacities, predominantly in the upper lobes.
  - HRCT: sensitive and specific for the diagnosis of pulmonary Langerhans cell histiocytosis; the characteristic finding is nodules and cysts, predominantly in the upper and medial fields, sparing the bases (Fig. 7 on page 14, Fig. 8 on page 15 and Fig. 9 on page 16):
    1. Cysts in thin walls, some of which are confluent or have unusual irregular shapes.
    2. Cysts in thick walls.
    3. Centrilobular or peribronchial nodules (normally 1 mm - 5 mm), some of which are cavitated, in association with cysts.
    4. Predominance (of nodules and cysts) in the upper fields, sparing the costophrenic angles.
    5. Discrete reticular opacities.

• **Differential diagnosis:** in the right context, the radiologic findings are very specific. If only nodules are found, the differential diagnosis can be very wide, including sarcoidosis, silicosis, metastatic disease, and tuberculosis. Cystic lesions must be differentiated from lymphangioleiomyomatosis, emphysema, and idiopathic pulmonary fibrosis.

• **Histologic findings:** the key finding is the presence of peribronchiolar nodules containing Langerhans cells and inflammatory cells in the initial phases. With time, these nodules progress to fibrotic nodules that form stellate peribronchiolar scars separated by relatively normal lung parenchyma and cysts (Fig. 10 on page 17).
• The disease usually stabilizes on quitting smoking, but in some cases it continues to progress anyway.

INTERSTITIAL PNEUMONIA COMBINED WITH EMPHYSEMA:

The combination of emphysema in the upper lobes with fibrosis in the lower lobes has become increasingly recognized as a distinct entity in smokers.

• **Clinical and epidemiologic findings:**
  - Men in the sixth and seventh decades of life.
  - Severe decrease in DLCO, with relatively conserved lung volume.
  - High prevalence of pulmonary hypertension.

• **Radiologic findings:**
  - **HRCT:** Honeycomb pattern, reticular opacities, and traction bronchiectasis are the most common findings in the lower lobes; paraseptal and centrilobular emphysema predominate in the upper lobes (Fig. 11 on page 18, Fig. 13 on page 19, Fig. 12 on page 20 and Fig. 14 on page 21).

These radiologic patterns are typical of idiopathic pulmonary fibrosis, although in some series there is greater prevalence of ground-glass opacities with a pattern similar to that seen in fibrosing nonspecific interstitial pneumonia.

• **Differential diagnosis:** occasionally, fibrosis and emphysema can involve the same area of lung; the resulting low attenuation of the emphysematous foci can appear to have margins due to the adjacent reticular pattern (thickening of the interlobular septa). This HRCT pattern can be mistaken for a cystic lung disease such as lymphangioleiomyomatosis or pulmonary Langerhans cell histiocytosis. Correlation with clinical findings and paying attention to other findings such as the nodules in pulmonary Langerhans cell histiocytosis or diffuse cystic changes in lymphangioleiomyomatosis can be helpful.

• **Histologic findings:** surgical biopsy often results in a pattern similar to that of usual interstitial pneumonia, although pigmented alveolar macrophages may be present, distributed in a pattern similar to that seen in RB-ILD or desquamative interstitial pneumonia in some areas. In isolated cases, ground-glass opacities similar to those seen in nonspecific interstitial pneumonia are present (Fig. 15 on page 22).
• The prognosis is poor; median survival is 6.1 years.

OVERLAPPING AND RELATION AMONG THE DIFFERENT INTERSTITIAL DISEASES ASSOCIATED WITH SMOKING:

The clinical, radiologic, and histologic features of the different interstitial diseases associated with tobacco smoking overlap.

The overlapping is most evident between RB-ILD and desquamative interstitial pneumonia. In fact, these entities are different stages of the same disease, corresponding to different degrees of severity of the same process caused by chronic smoking, and the two entities can coexist in the same patient. On the other hand, desquamative interstitial pneumonia is more clinically aggressive than RB-ILD, and, as mentioned above, can also affect nonsmokers.

Histologically, the key for differentiating between RB-ILD and desquamative interstitial pneumonia is the distribution of the lesions: bronchiolocentric in RB-ILD and diffuse in desquamative interstitial pneumonia.

The histologic changes found in RB-ILD or interstitial lung disease are also very common in patients with Langerhans cell histiocytosis, as they correlate with the cumulative exposure to tobacco smoke and are often accompanied by areas of ground-glass attenuation on HRCT.

Smokers who develop emphysematous disease and/or fibrosis often have the same radiologic and histologic alterations as seen in RB-ILD or desquamative interstitial pneumonia, and patients with desquamative interstitial pneumonia can also develop a pattern of nonspecific interstitial pneumonia with fibrosis.
**Fig. 1:** Respiratory bronchiolitis in an asymptomatic 45-year-old man with a 15-pack-year history of smoking. (a) HRCT image of the upper lobes shows bilateral centrilobular nodules. (b) Enlargement of a segment of the previous image.

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**Fig. 2:** A 37-year-old man with a 20-pack-year history of smoking presented with cough and dyspnea. (a) HRCT image shows mild diffuse parenchymal involvement with ill-defined centrilobular nodules, suggesting inflammatory disease of the small airways. (b) MiniMIP (3mm) shows the centrilobular nodules with better definition.

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**Fig. 3:** Respiratory bronchiolitis. Pigmented alveolar macrophages distributed around the lumen of the bronchiole and in the adjacent alveolar spaces. Slight fibrosis and discrete associated chronic inflammatory infiltrates.

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**Fig. 4:** Desquamative interstitial pneumonia and emphysema in a 50-year-old man with a smoking habit who presented with cough together with gradually developing dyspnea; pulmonary function tests showed reduced DLCO and a restrictive pattern. HRCT shows areas of centriacinar and paraseptal emphysema in the upper lobes (arrow) with a few small cysts and bilateral patchy areas of ground-glass attenuation, predominantly in the subpleural and basal regions (*).
Fig. 5: Desquamative interstitial pneumonia in a 55-year-old man with a 20-pack-year history of smoking. HRCT shows bilateral areas of ground-glass opacities with a patchy distribution predominantly affecting the left lung and upper fields.

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**Fig. 6:** Desquamative interstitial pneumonia. Accumulation of pigmented macrophages in the alveolar spaces, associated with minimal interstitial thickening.

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Fig. 7: Pulmonary Langerhans cell histiocytosis. A 53-year-old man with a 30-pack-year history of smoking presented with cough and dyspnea. HRCT shows walled radiolucent structures that suggest small cysts in the upper fields. Small centrilobular nodules compatible with respiratory bronchiolitis are also seen in the upper fields.

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Fig. 8: Pulmonary Langerhans cell histiocytosis. A 62-year-old woman with a four-to-five-month history of chronic cough, HRCT shows multiple irregular nodules of varying sizes in both lungs, many of which are cavitated, sparing nearly all of the costophrenic sinuses. Some septal thickening can also be appreciated.

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**Fig. 9:** Pulmonary Langerhans cell histiocytosis. A 68-year-old man with a 100-pack-year history of smoking. HRCT shows extensive diffuse parenchymal involvement in the upper and medial fields of both lungs with a predominantly cystic pattern, together with areas of emphysema and small ill-defined centrilobular nodules. The spiculated pulmonary nodule in the left upper lobe corresponds to a primary lung tumor (circle).

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Fig. 10: Lung biopsy specimen from a patient with pulmonary Langerhans cell histiocytosis. (a) Multiple nodular infiltrates due to the accumulation of Langerhans cells in the alveolar spaces. (b, c, and d) Cells with abundant eosinophilic cytoplasm and grooved nuclei with indented nuclear membranes; on immunohistochemistry, they are positive for S-100 and CD1a.

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Fig. 11: A 74-year-old man with a 20-pack-year history of smoking before quitting two years prior. HRCT shows paraseptal and centrilobular emphysema and findings suggestive of interstitial disease (idiopathic pulmonary fibrosis) with a reticular pattern, honeycomb lung, and traction bronchiectasis, predominantly in the bases and periphery.

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**Fig. 13:** An 80-year-old man with a 100-pack-year history of smoking presented with dyspnea developing progressively over a few months. HRCT shows interstitial involvement predominantly affecting the subpleural and basal regions, with honeycomb lung, reticular pattern, and traction bronchiectasis (idiopathic pulmonary fibrosis). There is extensive emphysema in paraseptal areas and in the upper fields.

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**Fig. 12:** A 47-year-old man with a 48-pack-year history of smoking before quitting 3 years prior presented with a 6-year history of chronic cough and dyspnea (currently occurring after minimal activity). HRCT shows subpleural parenchymal involvement, more evident in the bases, with ground-glass opacities, reticular pattern, and traction bronchiectasis; no honeycombing is seen. Paraseptal and centriacinar emphysema, predominantly in the upper fields.

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**Fig. 14:** A 61-year-old man with a 40-pack-year history of smoking presented with dyspnea and reduced DLCO. HRCT shows extensive changes resulting from centrilobular and paraseptal emphysema, predominantly in the upper lobes. In the lower lobes, cystic-appearing structures correspond to areas of emphysema associated with a reticular pattern due to fibrosis.

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Fig. 15: Emphysema and idiopathic pulmonary fibrosis. (a and b) Emphysema and fibrosis. Subpleural fibrosis and fibroblastic foci, respectively. Focal architectural distortion due to dense, predominantly subpleural and paraseptal fibrosis, with fibroblastic foci, forming areas of honeycombing with associated foci of emphysema. (c) Nonspecific interstitial pneumonia with a cellular pattern in which moderate chronic interstitial inflammation and mild hyperplasia of type II pneumocytes are seen. (d) Nonspecific interstitial pneumonia with a fibrotic pattern in which we can see homogeneous loose or dense interstitial fibrosis and mild chronic interstitial inflammation.

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Conclusion

The spectrum of interstitial lung diseases related with tobacco smoking is broader than generally appreciated, and the various forms often coexist. HRCT enables us to evaluate the type, severity, and extension of these diseases, overlap among them, and the changes they bring about over time. Nevertheless, it is important to remember that an integrated clinical, radiologic, and histologic approach is necessary to ensure the accurate diagnosis of these diseases.
References


