Langerhans Cell Granulomatosis and Smoking-Related Interstitial Lung Diseases

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Introduction

Cigarette smoke contains a mixture of thousands of chemicals, including nicotine, chemical poisons, toxic gases, small particles, and carcinogens. This complex mixture of substances is a leading cause of preventable deaths, causing approximately 650,000 premature deaths each year in the European Union [1]. Inhalation of the toxic particles associated with cigarette smoking and the subsequent immune response leads to a variety of pathological manifestations. Cardiovascular diseases, Chronic Obstructive Pulmonary Disease (COPD), and lung cancer are the most frequent causes of smoking-related deaths [2]. Cigarette smoking has also been implicated as a major cause of interstitial lung diseases (ILDs). ILDs such as respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) and desquamative interstitial pneumonia (DIP), although considered by the current ATS/ERS classification to be idiopathic forms of ILD [3], are clearly associated with cigarette smoking and may be more appropriately defined as "smoking-related interstitial lung diseases" (SR-ILD). Another clinical entity causatively associated with smoking is Pulmonary Langerhans Cell Histiocytosis (PLCH) [4]. More than 90% of all PLCH reported cases and 85–90% of RB-ILD and DIP patients are smokers [4, 5]. In addition, several epidemiological studies have shown evidence for disease remission when smoking ceases [6]. In spite of that, the pathogenic mechanism(s) explaining the association between these diseases and tobacco smoke exposure have not been completely elucidated. Respiratory Bronchiolitis (RB) is a common histopathological finding in smokers, characterized by the accumulation of pigmented macrophages in respiratory bronchioles and alveoli. It has been postulated that a small proportion of smokers may develop an excessive response to smoke provoking interstitial and airspace inflammation as well as fibrotic thickening of the alveoli. These events can eventually lead to symptoms such as cough and dyspnea and to impaired lung function. RB-ILD is usually associated with a good prognosis with radiological and clinical resolution often occurring after smoking cessation; some cases with severe clinical involvement are often treated with corticosteroid therapy, albeit with unknown benefits. Similarly, DIP is characterized by macrophage accumulation in bronchioles and alveoli, although it is much more diffuse than seen in RB-ILD. DIP has a worse prognosis than RB-ILD, and is more often treated with corticosteroid therapy, despite the absence of controlled studies evaluating the efficacy of this approach. PLCH is characterized by the presence of bronchiolocentric interstitial lesions which form nodules that ultimately cavitate and evolve to form cysts, the predominant feature of the disease. PLCH has a good prognosis with smoking cessation alone, though chronic progressive disease or rapid clinical deterioration may sometimes require the use of chemotherapeutic agents. Although SR-ILDs have several distinctive histopathological and radiological features, mixed patterns of SR-ILDs may frequently coexist in the same patient. These observations support the concept that RB-ILD, DIP, and PLCH form a spectrum of interstitial patterns of lung injury related to cigarette smoke [7].

Acute Eosinophilic Pneumonia (AEP) has also been included in the SR-ILD group. Smoking may precipitate AEP in young adults with a recent onset of heavy tobacco use, as occurred among US military personnel deployed in Iraq. AEP is considered a rare disorder with only a few cases reported in the medical literature. It is a severe acute illness usually found in younger adults, although patients of any age can be affected. It is characterized by acute febrile respiratory failure, diffuse bilateral lung infiltrates on chest X-rays,

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and pulmonary eosinophilia. AEP mimics pulmonary edema on chest radiographs, with reticular opacities and interlobular septal thickening appearing in the earlier stages of the disease. These changes are apparent on HRCT, and patchy ground glass and consolidation appear as the disease progresses [8]. Idiopathic pulmonary fibrosis (IPF) and combined pulmonary fibrosis with emphysema (CPFE) are other diseases with a strong association with cigarette smoking. Of 607 patients with CPFE observed in different studies, 592 (98%) were either current or former smokers, whereas in IPF the prevalence of smokers or former smokers varies from 41% to 83% [9]. Although new studies are needed to better clarify the role of smoking in AEP, CPFE, and IPF, it is reasonable to list these diseases among those with a common etiologic factor, cigarette smoke.

Pulmonary Langerhans' Cell Histiocytosis

History and Classification

Langerhans' cells (LCs) belong to the family of dendritic cells but can be distinguished from other myeloid cells in this lineage by their tissue location, morphological features, and functional properties [10]. A medical student, Paul Langerhans, was the first to describe these cells in 1868 during his studies of tactile corpuscles in human skin [11]. Almost 100 years after Langerhans' original observations, LCs were linked to a heterogeneous group of disorders and clinical syndromes currently known as Langerhans' cell histiocytosis (LCH). In 1941, Farber recognized histologic similarities in three different diseases: Hand–Schuller–Christian disease, characterized by the triad of skeletal lesions, exophthalmos, and diabetes insipidus, Letterer–Siwe disease, a multiorgan disease of children affecting the liver, spleen, lymph nodes, lungs, and bones and eosinophilic granuloma defined as a solitary or multiple histiocytoses of bone [12]. In 1953, Lichtenstein gathered these three conditions under the term histiocytosis X, where "X" was referred to the unknown cause and pathogenesis of these diseases [13]. Many terms have been used to define histiocytosis X and its related conditions beyond the three above, including Hashimoto–Pritzker syndrome, self-healing histiocytosis, pure cutaneous histiocytosis, Langerhans' cell granulomatosis, Langerhans' cell granulomatosis, type II histiocytosis, and non-lipid reticuloendotheliosis. In 1961, Birbeck et al. studying the electron microscopic features of basal melanocytes and LCs in patients with vitiligo observed distinctive granules (Birbeck granules) in the cytoplasm of epidermal LCs, which remain among the most specific markers for these cells [11]. Langerhans cell histiocytosis (LCH) is part of a spectrum of other histiocytic disorders, characterized by aberrant accumulation of cells thought to be derived from dendritic cells or macrophages of different organs, often involved in granuloma formation.

The first classification of histiocytosis, published in 1987 by the Working Group of the Histiocyte Society, consisted of three categories: Langerhans cell (LC), non-LC-related, and malignant histiocytoses [14]. In light of recent insights, a new classification has been proposed for histiocytic disorders, dividing them into five groups based on clinical, radiographic, pathological, genetic, and/or molecular features [15]. These include: (1) the Langerhans family of Langerhans cells histiocytosis, Erdheim–Chester Disease and extracutaneous juvenile xanthogranuloma; (2) cutaneous and mucocutaneous histiocytoses, such as xanthogranuloma family, characterized by the presence of non-LCH localized to skin and/or mucosal surfaces; (3) the malignant histiocytoses, tumors with anaplastic histology and negativity for specific differentiation markers such as keratins, EMA, Melan-A, HMB45, B, and T lymphocyte markers; (4) Rosai–Dorfman disease and miscellaneous noncutaneous non-Langerhans cell histiocytoses; (5) hemophagocytic lymphohistiocytosis, a rare, often-fatal syndrome of intense immune activation characterized by fever, cytopenias, hepatosplenomegaly, and hyperferritinemia and macrophage activation syndrome, which often occurs in the setting of an underlying rheumatic condition. The first classification of the histiocytoses, published in 1987 by the Working Group of the Histiocyte Society, endorsed the term "Langerhans cell histiocytosis" to replace the term histiocytosis X and presented a new classification of histiocytic disorders divided into groups according to organ involvement [14]. This classification was made possible by the advent of high-resolution computed tomography (HRCT) that improved imaging and characterization of histiocytic lesions. Depending on the organs involved, LCHs may be categorized into a localized form, defined as "single-system disease," and a disseminated form known as "multisystem disease." Single-system disease is characterized by isolated involvement of lung, bone, or skin. Multisystem disease is subdivided into low-risk and high-risk groups, according to clinical course and response to treatment. This distinction is made because prognosis and treatment are closely linked to the extent of disease at presentation and whether or not "risk" organs (liver, spleen, lung, bone marrow) are involved. Isolated Pulmonary Langerhans' cell histiocytosis that primarily affects adult smokers, was categorized as an LCH variant, different from the severe and lethal pulmonary involvement seen in multisystem disease [16, 17].

Epidemiology

Precise data regarding the prevalence of PLCH are not available. Alston et al. estimated an incidence of five cases per

1,000,000 children aged 0–14 [18]. In a 5-year prospective study in 20 pulmonology centers in Belgium, 360 patients with interstitial pneumonia were identified, of whom 3% had PLCH [19]. During a 6-year period, Colby et al., identified 15 cases of PLCH compared with 274 cases of sarcoidosis among patients evaluated at a referral center [20]. A large epidemiological study was conducted by Aricò et al. with the aim to detect the incidence of LCH in a 1-year period among 13 countries. They found 274 adult patients with an LCH diagnosis: 31.4% (86 patients) were single-system LCH, including isolated pulmonary involvement in 44 patients; and 68.6% (188 patients) had multisystem disease [16]. A Japanese study of discharge diagnoses from a group of hospitals with more than 200 beds found 160 cases of PLCH over a 1-year period, with the prevalence of the disease estimated at 0.27 and 0.07 per 100,000 persons in males and females, respectively [21]. The widespread use of HRCT is increasingly identifying incidental cases of PLCH in asymptomatic patients, suggesting the prevalence of the disease is likely underestimated. The fact that many patients experience spontaneous remission and that histological findings are not always entirely diagnostic for PLCH also contribute to under-recognition. Accurate epidemiological data are not currently available regarding racial differences [17]. PLCH predominantly affects young adults, with a peak frequency between 20 and 40 years of age [22]. Although a marked male predominance was initially reported, more recent studies reveal similar proportions of males and females, or even a slight predominance of females, particularly in series from the USA. These differences probably reflect changing smoking habits over time. Abundant data support a causal relationship between cigarette smoke and PLCH in adults, revealing that at least 90% of adult patients who develop PLCH smoke tobacco or marijuana or were exposed to substantial second-hand smoke exposure. In addition, there is clear evidence of partial or complete resolution of the disease after smoking cessation [17, 23]. In current smokers, cigarette smoke induces macrophage recruitment and accumulation around small airways, interstitium, and distal airspaces in the lungs. One unresolved question relates to the observation that only a very small proportion of smokers develop PLCH, thus implying an involvement of endogenous host factors or additional exogenous factors. It is tempting to speculate that PLCH develops due to an amplified inflammatory response caused by tobacco smoke that induces activation of multiple inflammatory cells in the lung, resulting in a vicious cycle of inflammation, tissue injury, and tissue remodeling. It is still unknown whether failure of endogenous anti-inflammatory mechanisms or additional exogenous insults like viral infections plays a role in promoting smoking-induced PLCH and this continues to be an important area for future investigation [24]. It is important to note that PLCH has been reported in adult nonsmokers. In addition, epidemiological data reveal interesting differences in the incidence of isolated PLCH in children and adults. Isolated PLCH is less frequent in children than multisystem disease suggesting it is a different form of PLCH with no obvious correlation to cigarette smoke.

Pathogenesis

Despite decades of study, the pathogenesis of PLCH remains poorly understood and may be different from that of other LCHs. A central question concerning LCH is whether it represents a neoplastic process or is reactive process due to an as yet unidentified stimulus. According to Wilman et al., LCH has been shown to be a monoclonal proliferation of histiocytes, supporting a neoplastic origin [25]. However, another study suggests polyclonal expansion of LCs in the lungs of patients with PLCH. Yousem et al. [26] state that PLCH, in contrast to other forms of LCH, is characterized by a nonmalignant clonal evolution of LCs after being stimulated by smoking. In order to investigate clonality in PLCH, the X-linked polymorphic human androgen receptor assay (HUMARA) was applied in lung biopsies from female PLCH patients. LCs from pulmonary nodules were studied for differential methylation patterns at the HUMARA locus: 29% were clonal and 71% were non-clonal. The authors concluded that the smoking-induced form of PLCH is a biologically distinct histiocytosis variant that is more consistent with a reactive rather than a clonal proliferative process initiated by cigarette smoking in certain predisposed individuals [24]. In this model, the primary event induced by cigarette smoke is probably the recruitment and activation of LCs in the small airways. LCs are dendritic cells produced in the bone marrow, whose main function is antigen presentation to T-cells. LCs are morphologically different from other dendritic cells due to the presence in their cytoplasm of specific organelles involved in the internalization of exogenous substances, the Birbeck granules, which are visible by electron microscopy. In the normal lung, LCs are confined to the tracheobronchial epithelium and are only activated by danger signals. Their function is antigen presentation and migration to regional lymphoid tissues where adaptive immune responses are induced. They also play an important role in mediating tolerance toward inhaled antigens and in preventing unnecessary inflammation of the airways by innocuous antigens. It is important to note that increased numbers of LCs are found in other smoking-related lung diseases such as chronic obstructive pulmonary disease (COPD), other interstitial lung diseases, and lung cancer. These observations suggest that cigarette smoke may alter the physiologic turnover of dendritic cells in the lung, or may facilitate recruitment of LCs precursors. Cigarette smoke is also known to induce the production of a number of cytokines involved in

the recruitment and activation of LCs. One of the most important cytokines induced by cigarette smoke and studied in PLCH lesions is transforming growth factor-beta (TGF-β). This cytokine is produced by epithelial cells and macrophages and is involved in the processes that lead to tissue remodeling, fibrosis, and scar formation. Immunohistochemical studies show that TGF-β is overexpressed in PLCH lung biopsies. Tumor necrosis factor-alpha (TNFα) is also produced by epithelial cells and macrophages and has a critical role in activating LCs [24]. Granulocyte macrophage colony stimulating factor (GM-CSF) is another cytokine produced by epithelial cells and fibroblasts that modulates the distribution and differentiation of LCs. Tazi et al. showed that GM-CSF is abundantly expressed in the epithelium of bronchioles of patients affected by PLCH [27]. It is plausible that smoking-induced production of the three above-mentioned cytokines, in proximity to lung dendritic and LCs, results in continuous stimulation of these cells and their precursors, facilitating their local expansion in peribronchiolar regions. The relationship between smoking and PLCH was recently confirmed by gene expression studies on LCs obtained from tissues and bronchoalveolar lavage cells (BAL) of PLCH patients that spontaneously produce increased amounts of osteopontin. Osteopontin is a glycoprotein involved in cell-mediated immunity and pro-chemotactic activity for macrophages, monocytes, LCs, and dendritic cells. Prasse et al. demonstrated an augmented production of osteopontin in BAL cells from SR-ILD patients and not from other ILDs such as sarcoidosis or IPF, with the highest levels in PLCH and DIP. On the contrary, very low or undetectable osteopontin levels were observed in healthy smokers and healthy nonsmoking volunteers, suggesting that an increase in osteopontin production is not common to all inflammatory lung diseases but may instead be an indicator of a specific form of macrophage activation due to cigarette smoke. Cigarette smoke constituents may in fact stimulate the epithelium, increase the production of proinflammatory cytokines, including osteopontin, hence inducing the recruitment of alveolar macrophages and the differentiation of LCs. Differences in the concentration of cytokines and osteopontin in BAL cells from DIP-PLCH patients and healthy smokers remain incompletely understood [28]. Taken together, these data suggest that cigarette smoke acts as a direct stimulant of airway factors that promote the differentiation, activation, and survival of dendritic and LCs, supporting the hypothesis that cigarette smoke may directly promote pro-survival dendritic/LCs pathways [24].

The recent identification of an oncogenic BRAF-V600E mutation in more than half of all LCH cases represented a major advance in our understanding of the pathogenesis of LCH lesions [29], including PLCH lesions. BRAF-V600E mutations have been detected in circulating cell-free DNA extracted from peripheral blood plasma of PLCH patients using allele-specific real-time PCR or digital droplet PCR [30], a procedure called "liquid biopsy." Many other BRAF mutations, other than V600E, have more recently been identified in patients with PLCH [31–33].

The BRAF protein is a member of the serine/threonine kinase RAF family, and is a key component of the MAPK (RAS-RAF-MEK-ERK) signaling pathway that leads to the activation of transcription factors involved in cell growth and proliferation. BRAF V600E, the most common mutation in PLCH, is a major driver of human malignancies that result from downstream constitutive activation of MEK and ERK, including malignant melanomas and hairy cell leukemia [34]. However, BRAFV600E somatic mutation does not necessarily mean that LCH is a malignant disease because this mutation has also been observed in benign nevi [35]. Recent studies demonstrated BRAF V600E mutation in 38–57% of extrapulmonary LCH cases [29, 36]. Some studies have reported that BRAF-V600E mutation is more commonly observed in multisystem disease than in isolated disease. The presence of this mutation in children with LCH is associated with an increased risk of recurrence of systemic LCH, a high-risk disease (with risk organs) with increased resistance to first-line therapy [36, 37]. The second-most common mutated gene in LCH is MAP2K1, a member of the MAPK pathway, identified in ~50% of LCH patients with wild-type BRAF [38, 39]. Recently, activating NRASQ61K/R mutations have been described in PLCH, in some cases occurring concurrently with BRAFV600E mutations in different cell clones from the same patient [40]. A significant expression of the programmed cell death PD-1/PDL-1 immune checkpoint inhibitors and T-regulatory cells was shown to be present in the microenvironment of LCH lesions, and these markers were correlated with the presence of the BRAFV600E mutation [41].

In conclusion, it is possible to consider LCH as an inflammatory myeloid neoplasm with a variable clinical expression. Smoking probably plays a role in recruitment of circulating mutant myeloid cells and/or a triggering role in the development of lung inflammation by these cells.

Diagnosis

Clinical Features

Establishing a diagnosis of PLCH requires a high index of clinical suspicion. Physical examination findings are generally nonspecific and despite widespread involvement of the lung, symptoms can be relatively minor or absent, and patients often attribute their symptoms to smoking. In up to 25% of cases, the disease causes no symptoms and is only detected on routine chest radiography [42]. The most common respiratory symptoms are dry cough and, less frequently, dyspnea on exertion, that can be associated with

constitutional manifestations such as asthenia, fever, night sweats, and weight loss. Spontaneous pneumothorax resulting in chest pain leads to diagnosis in 10–20% of cases [43]. Pneumothorax is more common in young males, occurs at any time during the course of the disease, and may be bilateral and recurrent [17]. Hemoptysis is uncommon and should not be attributed to PLCH until other causes such as bronchogenic carcinoma or aspergilloma within a cystic cavity have been ruled out. Physical examination of the chest is usually normal, except in patients with pneumothorax, rib lesions, or advanced disease. Rales and/or digital clubbing are rarely present [24].

Extrathoracic Lesions

Although PLCH in adults generally presents as a single-system disease, symptoms due to extra-pulmonary localizations may be present in up 10–15% of patients. According to Tazi et al., bone lesions (20% of patients), diabetes insipidus with polyuria and polydipsia, resulting from infiltration of the posterior pituitary (5% of patients), and skin lesions are the most common extrapulmonary manifestations in PCLH (Fig. 18.1) [17]. History and physical examinations are essential to search for extrathoracic LCH involvement, as are skeletal radiographs including a dental panoramic, complete blood chemistry analysis to detect liver involvement and morning urine osmolality to screen for diabetes insipidus. Adult LCH commonly involves bones and may occur as a bone-limited disease (38%) or as a component of a multisystem disease (66%) [44]. Bone lesions manifest as pain or as a "mass" or "swelling" of the involved site.

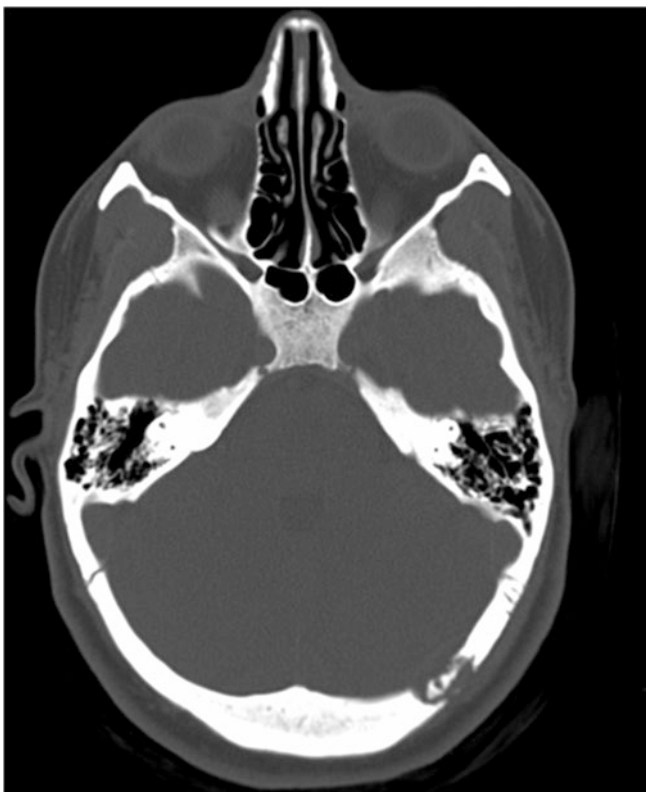

Fig. 18.1 Skull CT scan of a patient affected by PLCH. It shows two osteolytic bone lesions in the parietal bones and a bigger one in the occipital bone

Islinger et al. reviewed a series of LCH patients with bone lesions over a 58-year period which included 211 LCH adults. It was estimated that in adults, lesions of the skull occurred in 28% of cases, of the rib in 25%, of the pelvis in 8%, and of the spine in 3%. However, other sites can be involved in long bones and mandible [45]. The radiological appearance of bone lesions and clinical manifestations depends on the site involved and on the disease stage. Typically bone lesions are lytic or may have poorly defined borders, and in early stages are characterized by a more aggressive pattern of osteolysis. Chronic lesions may resolve completely with or without therapy, or develop a sclerotic appearance due to periosteal new bone formation. Bone lesions of the skull are lytic, round with defined margins and sometimes may contain a residual bone fragment. They may extend across suture lines, increase in number, or extend into adjacent soft tissue. Osseous lesions may evolve into epidural or epicranial soft tissue masses. Skull lesions can be asymptomatic or can cause headache and tenderness in the skull region involved while those of the mandible can destroy alveolar bone producing the radiological appearance of "floating teeth." Rib involvement is demonstrated by osteolytic areas, periostitis, and fractures. Sometimes, it is possible to find an extrapleural mass resulting from soft tissue extension, which causes pain. Pelvic involvement is characterized by poorly defined areas of osteolysis that develop well-defined sclerotic margins over time. Spine lesions are osteolytic and can cause the collapse of the vertebral body. In long bones, lesions are frequently intramedullary and diaphyseal and may appear aggressive. Treatment regimens differ widely and are often based on empiric observations. Surgical interventions such as curettage or total excision, radiotherapy, and chemotherapy have all been reported. Although treatment options for adults have never been validated by a clinical trial, studies in the literature compare the efficacy of different chemotherapeutic treatments. Cantu et al. studied 58 adult LCH patients with bone lesions at a site or as a component of a multisystem disease and described improvement or resolution of bone lesions in a majority of patients treated with radiotherapy, surgery, or chemotherapy (vinblastine/prednisone, 2-chlorodeoxyadenosine, and cytosine arabinoside) in comparison with corticosteroids alone [46]. Lair et al. also reported that radiotherapy is a safe and effective means for providing local control of LCH involving bones [47].

Another important extrapulmonary complication of LCH is pulmonary hypertension. It tends to be more severe in

PLCH than in other interstitial lung diseases, often characterized in later stages by dyspnea at rest and features of right-ventricular circulatory failure. Histopathologically, PH in PLCH is associated with intimal fibrosis and remodeling of both venous and arterial systems [48]. Dauriat et al. estimated that pulmonary hypertension is present in 92% of 36 patients evaluated for lung transplantation [49]. Because pulmonary hypertension is a poor prognostic indicator in PLCH, it is important to screen all patients, especially those with excessive dyspnea and normal lung function tests, by echocardiography [48]. In selected cases, cardiac catheterization is necessary to confirm PH. Once the diagnosis is made, therapy with vasodilators including phosphodiesterase inhibitors or endothelin receptor antagonists may be considered. Improved exercise capacity can be achieved with these agents, often with an objective reduction in pulmonary pressures, but arterial oxygenation can also worsen as a result of a greater imbalance in ventilation/perfusion due to the inhibition of hypoxic pulmonary vasoconstriction. Prostacyclin can cause severe pulmonary edema and should be used very cautiously in these patients because of the venous involvement. Le Pavec et al. reported their experiences with a group of 29 PH-PLCH patients treated with the usual pulmonary hypertension therapies: endothelin receptor antagonists, phosphodiesterase 5 inhibitors, or prostanoids demonstrating improvement in hemodynamics without oxygen worsening or pulmonary edema in most patients. Supplemental oxygen should be administered to maintain saturations greater than 90% with rest, exercise, and sleep, based on extrapolation from other diseases where the benefits of the therapy have been demonstrated. However, more studies are needed to evaluate safety and efficacy of all pulmonary hypertension treatments and management approaches in PH-PLCH [50].

The reported prevalence of central nervous system (CNS) complications ranges widely from 3.4% to 57% [51, 52] and can be subdivided clinically into two groups: the "mass lesion" forms presenting as space occupying lesions anywhere in the CNS; the "neurodegenerative" forms which are characterized by neural cell loss and pyramidal syndrome.

Typical LCH mass lesions may contain CD1a+ LCH cells, lymphocytes, and macrophages with histology similar to extracranial lesions, and usually involve the anterior and posterior hypothalamic pituitary regions, resulting in diabetes insipidus, growth hormone deficiency, and thyroid function abnormalities. Radiological findings include thickening and enhancement of the pituitary stalk with loss of the posterior pituitary bright spot; enlargement and enhancement of the pineal gland; thickening and enhancement of the choroid plexus; and intraparenchymal masses, usually characterized by a nodular pattern after contrast administration. A variable degree of atrophy of the cerebellum and midbrain has also been described [51]. Magnetic resonance imaging (MRI) may show tissue expansion or cystic changes in either the pituitary stalk or the pineal gland in up to 63% of patients [53].

"Neurodegenerative CNS LCH" is a syndrome of variable severity characterized by progressive clinical and radiological abnormalities that can occur at any point in the LCH disease course from the initial diagnosis to greater than 5 years later. The only histopathologic study available reported the absence of CD1a+ histiocytes, an inflammatory collection of CD8+ lymphocytes associated with neuronal and axonal degeneration [54]. Magnetic resonance imaging (MRI) may show increased T2-weighted MRI signal in the dentate nucleus of the cerebellum, basal ganglia, and pons and PET scanning may reveal decreased or increased FDG uptake in affected regions of the brain [55]. Clinically, ataxia, and tremors may be a consequence of cerebellar involvement. Rarely, patients may develop a progressive cerebellar syndrome, with spastic tetraparesis, pseudobulbar palsy, and cognitive deterioration [56].

LCH patients should be carefully evaluated for cerebellar, pyramidal, and bulbar deficits. Several rating scales have been proposed but not yet broadly approved for LCH patients, such as the Brief Ataxia Rating Scale (BARS) which includes a subset of five tests focusing primarily on coordination of gait, arm, leg, speech, and eye movements [57].

Very few studies are present in the medical literature and an optimal treatment for CNS localization of the disease has not been defined. Tin et al. have described a good response to vinblastine, used in other aggressive forms of LCH, in patients with CNS mass lesions with response rates of up to 70%. No effect of this therapy has been described on neurodegenerative lesions [58].

Pulmonary Function Tests

Pulmonary function test findings are variable in PLCH and the disease can be associated with a restrictive, obstructive, or mixed pattern. According to Tazi et al., the obstructive pattern is the most common. In this study, flow–volume curve alterations were present in 50% of patients, and the ratio of forced expiratory volume in 1 s (FEV1) to vital capacity (VC) was diminished in 20–30% of patients with recent onset of PLCH [17]. This pattern may be related to the bronchial involvement characteristic of smokers, or to bronchiolar obstruction due to peribronchiolar fibrosis or inflammatory infiltrates [17]. On the contrary, Crausman et al. described a restrictive pattern in 11 patients of a cohort of 23 patients with an early PLCH diagnosis. However, in advanced stages, a restrictive pattern usually predominates as lung fibrosis progresses [18, 59]. At the time of diagnosis, up to 20% of patients may have normal pulmonary function tests, while approximately 60–90% of patients have low diffusing capacity for carbon monoxide (DLCO). Blood gas values at rest may remain normal even in advanced disease, although increased A-a gradient and hypoxemia can occur in early

stages [17]. Canuet et al. correlated lung function with HRCT findings and found that the extent of cysts was closely associated with the impairment of both lung function and gas exchange. Interestingly, a predominantly nodular pattern, suggestive of an active inflammatory disease, has only moderate functional consequences [60].

Tazi et al. similarly described the correlation between lung function and HRCT lesions. They studied a group of 49 PLCH patients who experienced a deterioration of lung function in 60% of cases, including a decline of FEV1 in 40% of patients and a decline of DLCO in 50% of the patients. The DLCO reduction can herald the presence of pulmonary hypertension. However, according to other studies, the main lung function defect is airway obstruction and this finding is consistent with the bronchiolar localization of pulmonary LCH lesions. Increased profusion of cysts on HRCT scans correlated with a deterioration in lung function parameters. Serial lung function tests are the preferred method to monitor progression of disease to limit exposure to radiation [61].

Chest Radiography

Most patients with PLCH exhibit chest radiographic abnormalities. In the earlier stages of the disease, it is common to find small nodules that typically range from 1 to 10 mm in diameter and have a bilateral and symmetric distribution on chest radiography. These nodules are characterized by irregular borders and may be single or coalescent. The distribution of nodules is typically limited to upper/middle lung zones with sparing of the lung bases, especially in the costophrenic sulci. As the disease progresses, reticulonodular abnormalities and cystic changes may predominate. As cysts become more numerous, nodules tend to diminish in number [11]. End-stage PLCH is characterized by reticular areas of opacity that may progress to honeycomb lung and contiguous cystic cavities up to 2 cm diameter resulting in patterns that can mimic the radiographic appearance of advanced emphysema or LAM. LAM and end-stage PLCH are the two forms of ILD that can produce hyperinflation rather than reduced lung volumes on CXR and PFTs [62]. Pneumothorax is known to be a complication of PLCH and may occur in the absence of other radiographic pulmonary abnormalities. Chest radiography has limited sensitivity and specificity for the detection and characterization of interstitial lung diseases, and in some cases of PLCH, chest X-ray may even appear to be normal. Khoor et al. reported a rare presentation of PLCH in a 45-year-old male cigarette smoker on chest radiography as a solitary pulmonary nodule. Biopsy showed the histologic and immunophenotypic characteristics of PLCH [63]. Twenty-one years after excision of the sentinel nodule, a new contralateral lung nodule appeared which remained unchanged during 36 months of observation. Another notable radiographic finding in PLCH is pulmonary artery prominence, due to pulmonary hypertension that may occasionally complicate PLCH [63].

High-Resolution Computed Tomography (HRCT)

HRCT is superior to routine chest radiography in demonstrating the morphology and distribution of lung abnormalities. Patterns differ widely based on the stage of PLCH. In the early stages of the disease, a pattern defined by the presence of multiple nodular opacities measuring 1–5 mm in diameter or larger is often found [64]. Nodule sizes greater than 10 mm in diameter are unusual [65]. These small nodules, which are not typically apparent on chest X-rays, are characterized by irregular margins surrounded by normal lung parenchyma (Fig. 18.2). They may be profuse and are generally solid, although cavitation may occur over time.

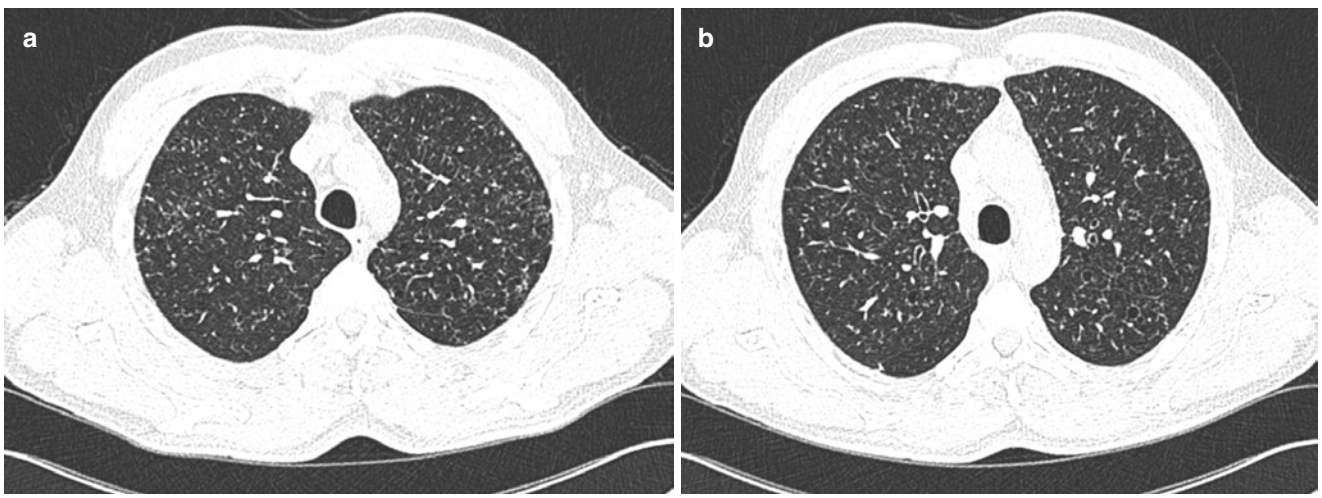

Fig. 18.2 HRCT of the lungs of a patient affected by PLCH, showing a predominant nodular pattern. Centrilobular and peribronchiolar nodules and present (**a**), some of which are cavitated (**b**)

However, the predominant characteristic of lung nodules is their distribution, with a topographical predominance in the upper and middle lung zones with relative sparing of the lung bases. Most nodules show a centrilobular or peribronchial distribution, reflecting the bronchiole-centered localization of PLCH lesions in histopathologic studies. Brauner et al. has proposed a temporal progression of these pulmonary nodules into cavitary nodules and then into cysts [64], with serial scans revealing a decreasing preponderance of nodules and an increasing number of thin-walled cysts. Cystic lesions tend to be small and thick walled initially, with diameters of less than 10 mm, and then become larger and thinner walled, with diameters up to 20 mm. Conceptually, cyst formation can develop due to cavitation within a centrilobular nodular lesion or to increasing bronchiolar dilatation from granulomas destruction and fibrosis at the lesion margin. Cyst distribution is most prevalent in upper lung zones where they can appear as round or ovoid spherical spaces or with bizarre shapes that result from coalescence of adjacent cysts (Fig. 18.3a–c). Some of these cystic spaces reach diameters of up to 80 mm. Advanced disease is characterized by architectural distortion by cysts with few nodules [66], while late-stage disease is marked by the presence of large areas of honeycombing, predominantly in the upper lung zones. Some studies have described full or partial resolution of lesions occurring in patients with nodular lesions, indicative of reversibility, while cystic lesions remain unchanged or worsen with time [67]. Soler et al. compared the nature of the findings on CT scans with those of lesions on biopsy samples in PLCH patients. They found that early-stage PLCH histopathological lesions consisted of florid granulomas that were composed of typical LCs associated with macrophages and inflammatory cells, particularly lymphocytes and eosinophils. In more advanced disease, necrotic granulomas were found in pulmonary samples, characterized by a prominent central cavity and few fibrotic changes, but still numerous LCs and inflammatory cells in their walls. In these cases, few cavitated nodules or thin-walled cysts were seen on CT scans. In late-stage PLCH, fibrous cysts of variable size, demarcated by a

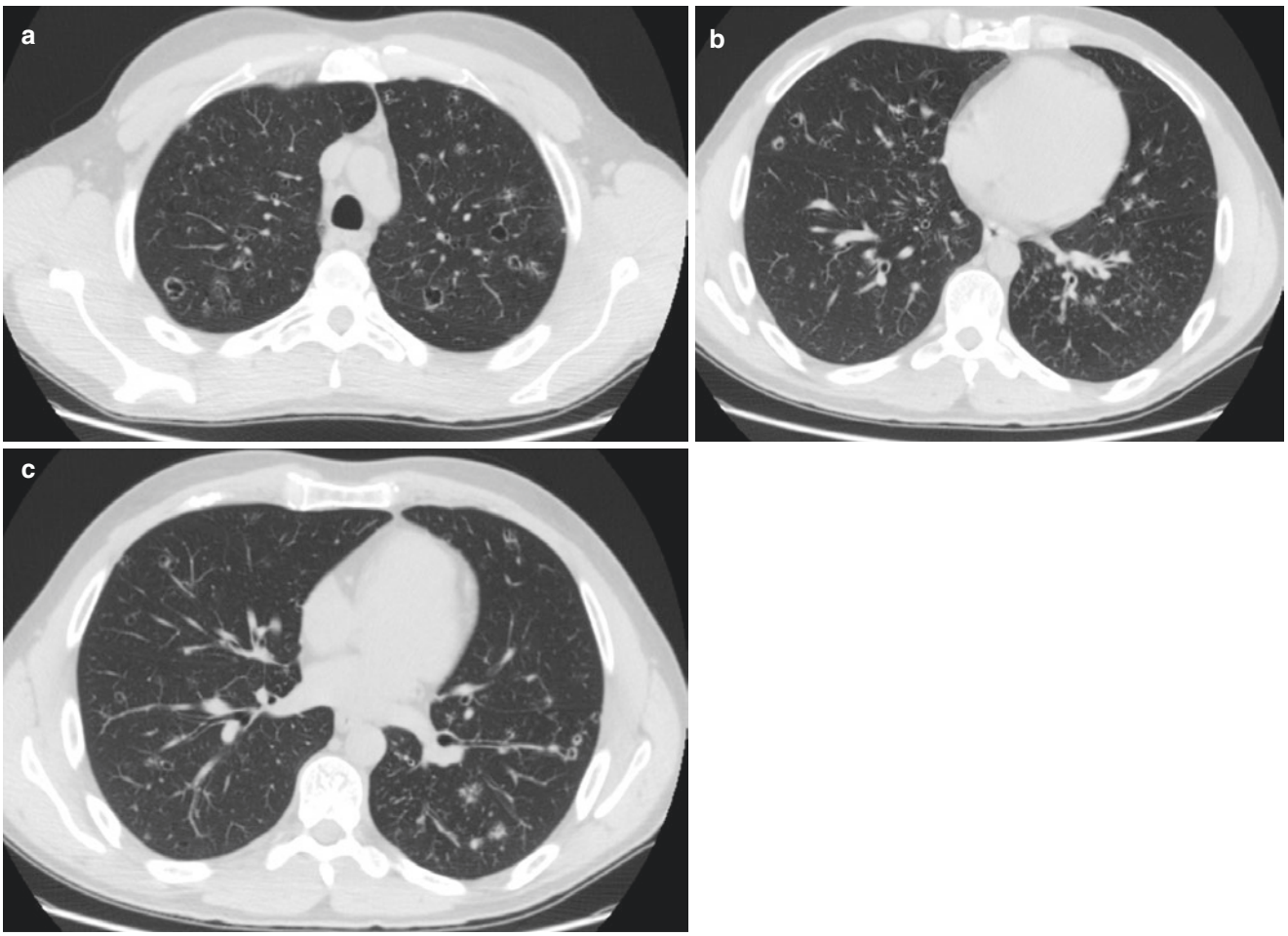

Fig. 18.3 HRCT of the lungs of a patient affected by PLCH showing a predominant cystic pattern. The cysts are characterized by variable wall thickness and bizarre shapes (**a**). Centrilobular and bronchiolocentric nodules are present, some of which are starting to cavitate (**b**, **c**)

fibrous ring of variable thickness, and containing no LCs and few or no inflammatory cells, were usually found [68]. Kim et al. studied a cohort of 27 PLCH biopsy-proven patients, evaluating HRCT and histopathological findings at the time of surgical lung biopsy. The predominant CT pattern was represented by centrilobular nodules (ten patients) corresponding to peribronchiolar granulomas with LCs on biopsy. Nodules were typically present on upper lung zones with a random distribution. Thick- and thin-walled cysts and bizarre-shaped cysts were present in four, eight, and five patients, respectively, most with a predominant distribution in the upper lung zones and characterized by a central cavity surrounded by a thin wall of LCs and eosinophils. These studies suggest that while it is possible to conclude that a nodular pattern on CT scans reflects histopathologically active PLCH disease, no correlation is possible between histological and radiological findings in cyst predominant disease because HRCT cannot differentiate between fibrous cysts and cavitary granulomas [67]. Canuet et al. reported that the distribution of cysts was closely associated with an impairment of both lung function and gas exchange. A dominant nodular pattern suggestive of active inflammatory disease has only moderate functional consequences, while a cyst predominant pattern was strongly correlated with lung function parameters [60]. Nodular changes may be present in several other lung diseases including sarcoidosis, silicosis, tuberculosis, RB-ILD, hypersensitivity pneumonitis, or metastatic disease [68], which can represent a dilemma. Although all of these conditions are associated with a centrilobular nodular pattern on CT scans, the relationship of nodules to other pulmonary structures and their distribution can be an aid to a correct diagnosis. A perilymphatic distribution with nodules in interlobular septa, peribronchovascular and subpleural spaces is typical of sarcoidosis. A random distribution of nodules within secondary pulmonary nodules is characteristic of miliary tuberculosis and hematogenous metastases. In some cases, a halo of ground glass attenuation characteristic of metastatic nodules can be useful to differentiate them from PLCH nodules. In other cases, only lung biopsy can discriminate between them [69]. When only cysts are seen on the CT scan, the differential diagnosis includes idiopathic pulmonary fibrosis (IPF), emphysema, bronchiectasis, and lymphangioleiomyomatosis (LAM). When honeycombing is present, defined as the presence of air-filled cystic spaces that often predominate in a peripheral subpleural location, the primary differential is between IPF and PLCH. These cysts can be of different sizes with wall thicknesses between 1 and 3 mm, consisting of fibrous tissue lined by bronchiolar epithelium, which is shared by adjacent cysts. This radiographic pattern is most typical for honeycombing and is not seen in cysts that are found in PLCH. In addition, honeycombing is often associated with other findings of pulmonary fibrosis such as reticular opacities, irregular subpleural and peribronchovascular thickening, and traction bronchiectasis, while PLCH cysts are surrounded by normal lung zones. The most important difference between the two entities remains the sparing of lower lung zones in PLCH, while IPF is characterized by a predominantly basilar distribution of the cysts. Pulmonary emphysema is defined as a permanent, abnormal enlargement of airspaces distal to the terminal bronchiole accompanied by the destruction of the alveolar walls. It is usually easy to differentiate PLCH from emphysema by the walled off focal areas of low attenuation that are found in PLCH, contrasting with hyperlucent regions without walls surrounded by normal lung parenchyma in emphysema [64]. Bronchiectasis is localized, irreversible bronchial dilatation, bordered by a thickened bronchial wall that may be mistaken for cystic airspace disease when viewed in cross-section. It can be differentiated from cystic lung disease by the presence of an adjacent blood vessel suggesting a bronchovascular unit rather than a cystic air space, and by stepping through adjacent HRCT sections that demonstrate continuity of the cystic space with an airway [70]. LAM is characterized by the presence of thin-walled cysts of variable size from 2 to 40 mm diameter on HRCT. Vessels can be seen at the periphery of the cysts, unlike emphysema where vessels may be found in the center of the lesion. The most important difference between LAM and PLCH lies in the distribution of cysts, with LAM cysts involving all regions of the lungs in a uniform pattern without sparing the costophrenic angles [70, 71].

Positron emission tomography with ^{18}F-fluorodeoxyglucose has a limited value in the assessment of patients with PLCH. Only 20–25% of patients show higher ^{18}F-fluorodeoxyglucose uptake in the lungs, particularly in thick-walled cysts and nodular lesions. Krjicek et al. reported in a small series that PET scan imaging cannot reliably distinguish between the benign inflammatory nodular lesions of PLCH and malignant lesions [72–74].

Bronchoscopy and Bronchoalveolar Lavage (BAL)

Bronchoscopy is a well-tolerated procedure that can provide useful information for the correct diagnosis of PLCH. In PLCH, the bronchial tree is usually either normal on gross examination or reveals signs of nonspecific inflammation due to smoking and the bronchoalveolar lavage fluid of may exhibit an increased number of cells with a marked predominance of alveolar macrophages, a decreased CD4/CD8 ratio or increased levels of eosinophil cells. These features are also often present in the BAL fluid of smokers where there is no evidence of interstitial lung disease. LCs identified by staining with antibodies against CD1a and S-100 antigens on the cell surface have been proposed as PLCH markers. Casolaro et al. have demonstrated the presence of LCs in the bronchoalveolar lavage of smokers without interstitial lung

diseases, concluding that cigarette smoking is associated with an expansion in the population of LCs on the epithelial surface of the lower respiratory tract [75]. In addition, Tazikawa et al. have described the presence of LCs in patients affected by idiopathic pulmonary fibrosis, sarcoidosis, and other fibrotic lung disorders so it would seem that LCs in bronchoalveolar lavage are not specific for diagnosing PLCH [48]. However, Tazi et al. demonstrated that even if an increased level of LCs may be present in other pulmonary diseases, a threshold of 5% LCs ensures adequate specificity, although the sensitivity remains quite low (<25%) [17]. Smetana et al. demonstrated the presence of another cell surface marker in the BAL fluid of PLCH patients named Langerin (CD207), which is specific for LCs present in the skin and in the epithelia of small airways and bronchioles. They compared the percentage of CD1a and Langerin positive cells in PLCH with other fibrotic lung disorders such as sarcoidosis and IPF, and found they were almost identical in all the tested cases. This result highlights the potential utility of Langerin for improving the usefulness of BAL in the diagnosis of PLCH [76], although the true diagnostic potential has yet to be assessed in clinical studies. Bronchoalveolar lavage rarely establishes a definitive diagnosis of PLCH in adults with ILD, but can be helpful in the differential diagnosis of infectious diseases characterized by the presence of excavated nodules, such as *Pneumocystis jiroveci* pneumonia.

Lung Biopsy

Transbronchial lung biopsy has a limited role in the diagnostic workup for PLCH as confirmed by Vassallo et al. in a study of 102 patients with histological diagnoses of PLCH. Among 29 patients who underwent transbronchial lung biopsy, the findings were diagnostic only in six patients [77]. However, transbronchial lung biopsy remains useful for differential diagnosis by excluding other disorders, such as sarcoidosis. Even if the HRCT is suggestive of PLCH in the great majority of patients with typical clinical manifestations, some cases are difficult to interpret. In patients with systemic symptoms and cavitated pulmonary nodules, patients with suspected pulmonary metastases or in female patients in differential diagnosis with LAM, a definitive diagnosis often requires pulmonary biopsy. In cases in which the diagnosis is uncertain, surgical biopsy may permit a diagnosis of PLCH demonstrating the presence of the characteristic lesions. However, lung biopsy should not be performed in patients with extensive destructive lesions given the increased procedural risk in patients with limited pulmonary reserve [17]. In a patient with suspected PLCH and an extrapulmonary lesion with compatible HRCT findings, a diagnosis may be provided by a biopsy of the lesion. However, a majority of adults have isolated PLCH, which requires a surgical lung biopsy using video-assisted thoracoscopy or open thoracotomy for a definitive diagnosis. Since the lesions are focal, the specimens should be sufficiently large to avoid sampling error, preferably from 2 to 3 different areas of the lung. Lung biopsy is not considered necessary when HRCT findings are characteristic and concordant with the clinical history [68]. With the discovery of BRAF mutations and their evolving role in the prognosis and treatment of LCH, the importance of lung biopsy is now being reconsidered, even for those for whom a confident clinical diagnosis is possible through noninvasive means.

Pathology

Gross lung tissue specimens in PLCH may exhibit different features according to the stage of the disease at the time of biopsy. In the earlier stages, nodules appear as focal lesions with irregular and stellate borders. In advanced disease phases, the predominant finding is a hyperinflated lung with cysts and honeycomb formation [68]. On microscopic examination, the characteristic early lesions in PLCH are localized to terminal and respiratory bronchioles and are composed of activated LCs organized into loose granulomas containing lymphocytes and inflammatory cells including eosinophils and macrophages (Fig. 18.4a, b) [10]. The morphology of LCs found in these inflammatory nodular lesions is generally similar to that of LCs in normal tissues: they are medium sized cells with elongated nuclei, and display multiple cytoplasmic extensions and pale cytoplasm which contains few phagocytic vacuoles. A definitive identification of LCs in these inflammatory lesions is possible by immunohistochemical staining with monoclonal antibodies directed against the membrane antigen, CD1a (Fig. 18.5), or by the identification of Birbeck granules, identifiable through electron microscopic visualization. Birbeck granules are intracytoplasmic organelles that may be involved in the intracytoplasmic transport of antigens captured by LCs. The histology of PLCH granulomas varies according to the particular stage of the disease, even if lesions of different ages can be found in the same lung biopsy specimen. The lesions are focal, poorly demarcated, and separated by apparently normal lung parenchyma. They are centered on the terminal and respiratory bronchioles and destroy the airway walls, giving the impression that PLCH pathogenesis is more closely aligned with a bronchiolitis than a diffuse infiltrative lung disease. At this stage, LCs form a compact central granuloma surrounded by variable numbers of lymphocytes, eosinophils, and macrophages, which extend to adjacent alveolar structures. This lesion may evolve forming a cavity

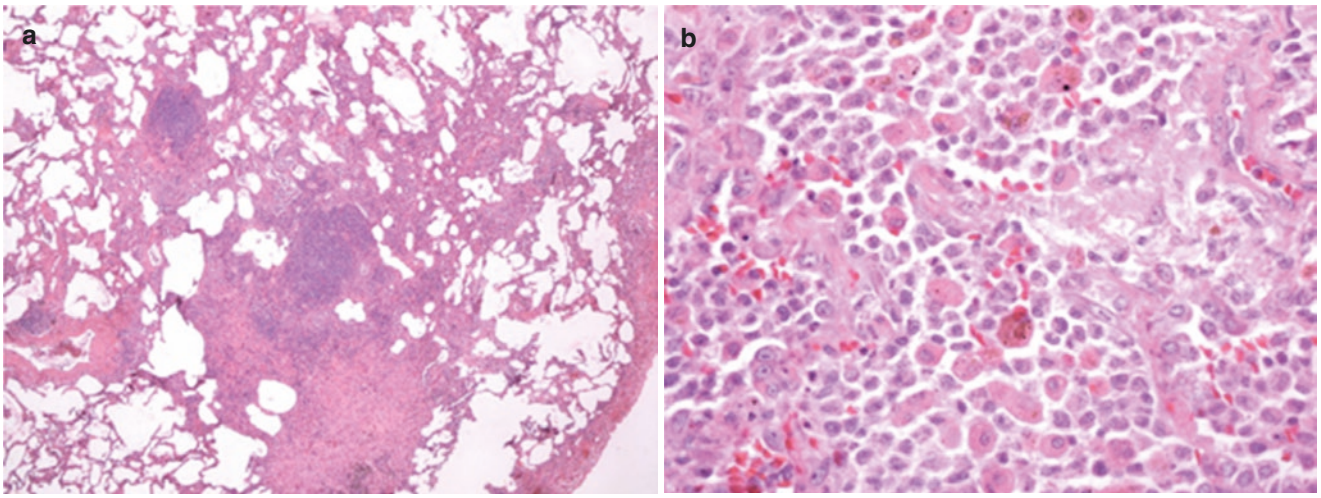

Fig. 18.4 LCH with centrilobular nodules with irregular margins (**a**) and aggregates of Langerhans cells together with golden macrophages and eosinophils (**b**). (Courtesy of Professor G. Rossi. University of Modena-Reggio Emilia, Italy)

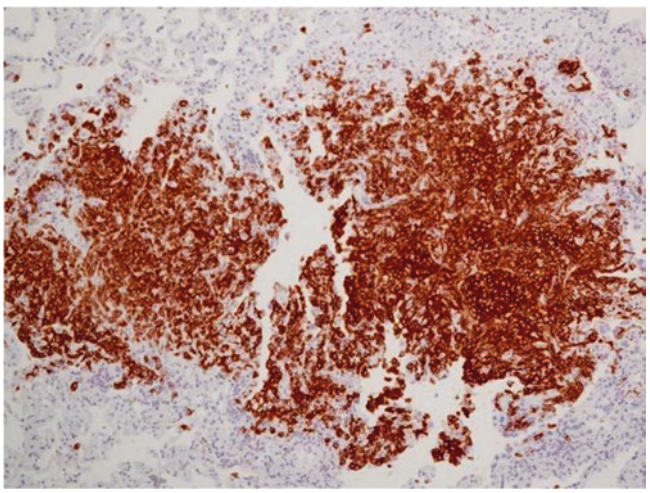

Fig. 18.5 Immunohistochemistry for CD1a highlights Langerhans cells. (Courtesy of Professor G. Rossi. University of Modena-Reggio Emilia, Italy)

that results from the expansion of the lumen of a bronchiole damaged by granulomatous reaction. PLCH granulomas are poorly demarcated and extend in adjacent alveolar structures that often contain pigmented macrophages, producing RB-ILD-like changes or a desquamative interstitial pneumonia-like pattern. In lesions of intermediate age, there are few LCs, while lymphocytes, macrophages, and neutrophils are still present in LCH granulomas. In late-stage lesions, LCs are almost absent and there are more macrophages containing pigment or lipid inclusions [10]. The lesions are then replaced by stellar fibrotic scars or by confluent adjacent cysts. Interestingly, in uninvolved areas, the lung structure seems to be normal or characterized by common smoking-related abnormalities, such as respiratory bronchiolitis and increased levels of pigmented macrophages infiltrating the bronchiole walls [17].

Treatment

The recruitment of a sufficient number of patients for controlled therapeutic trials has been hampered by the low incidence of PLCH and its relative clinical stability. To date, no randomized trials of therapy for adult PLCH have been reported. All data regarding the effectiveness of PLCH treatment are derived from observational studies, case reports, and expert opinions. The association between PLCH and smoking suggests that cigarette smoke plays a role in the pathogenesis of the disease. Therefore, it is imperative that patients stop smoking and this should be encouraged by clinicians, especially in heavy smokers, through smoking cessation programs, tobacco replacement therapy, and other means [17]. Some case reports have shown that interventions that eliminate smoke exposure can lead to an improvement in the clinical and radiographic findings or even in the resolution of the disease [50]. Mogulkoc et al. described two cases of PLCH in smokers characterized by the presence of nodules, some of which were cavitated or formed small cysts on CT scans and by a reduced DLCO. After smoking cessation, there was an objective radiological improvement with reduction of nodules and functional improvement with an increase in DLCO [23]. Similarly, Negrin-Dastis [78] described a PLCH case with total regression of radiological lesions after 12 years of smoking cessation. Because of the rarity of PLCH and the unpredictable course of the disease, there are

no reliable data regarding the efficacy of smoking cessation on disease resolution. Tazi et al. [79] reported four smokers with biopsy-proven PLCH who experienced disease regression after smoking cessation but who subsequently developed reactivation with the appearance of new nodules on CT scans that were empirically treated with corticosteroid therapy. However, other studies provide contrasting data, describing cases where the disease has worsened despite smoking cessation [79, 80] and recently Tazi et al. have reported that smoking cessation did not modify the pulmonary LCH outcomes in a group of 49 LCH adult patients [61]. Finally, it is well established that the disease can improve spontaneously and there is, as yet, no definitive proof that smoking cessation affects the outcome of the disease. Nonetheless, smoking cessation is considered as a first step in the treatment of PLCH. Failure to prevent the progression of the disease by this means is generally followed by a trial of steroid treatment. The rationale of using corticosteroids, especially in the early stages of the disease in which nodular lesions are the predominant features, is based on the possibility of accelerating the resolution of the associated granulomatous and inflammatory processes. In advanced stages, the presence of fibrosis may explain the lack of response to therapy that is often observed with steroids. On this basis, it has been suggested that corticosteroid therapy is promising for treatment of symptomatic PLCH with a predominant nodular pattern on HRCT scans. Usually prednisone or prednisolone are administered at a starting dose of 0.5–1 mg/kg/day tapered over 6–12 months [17]. In a group of 42 PLCH patients treated with corticosteroids, Schonfeld and coworkers demonstrated clinical and radiographic improvements, although they did not observe any significant changes in respiratory function [81]. If disease progression occurs in spite of a 6-month period of steroid treatment, chemotherapy may be considered. The cytotoxic agents that have been used for treatment of PLCH include vinblastine, mercaptopurine, cyclophosphamide, or more recently, cladribine (2-chlorodeoxyadenosine).

In the 1960s, chemotherapy was used to treat LCH in children because it was thought to be a malignant process. Single agents such as methotrexate, 6-mercaptopurine, vinblastine, and vincristine were initially and successfully used in pediatric patients and these encouraging results led to new trials. Different perspectives were explored in randomized trials conducted by the Histiocyte Society: in the first study, the efficacy of vinblastine or etoposide in combination with prednisolone was compared. For 24 weeks, patients were treated vinblastine (6 mg/m^2) intravenously every week, or etoposide (150 mg/m^2/day) intravenously for 3 days every 3 weeks, followed by a single initial dose of corticosteroids. There was no difference in survival or disease reactivation rates with this regimen, but the absence of response after 6 weeks of treatment was presumed to be related to poor prognosis with increased mortality. The second trial conducted by the Histiocyte Society was carried out on 193 randomized LCH children divided into two groups, the first group receiving vinblastine, prednisolone, and mercaptopurine, the second receiving the same therapy with the addition of etoposide. The dosage was as follows: first group, initial treatment of continuous oral prednisone (40 mg/m^2 daily in 3 doses for 4 weeks tapering over 2 weeks) and vinblastine (6 mg/m^2 intravenous bolus weekly for 6 weeks); while the second group received the same therapy with the addition of etoposide (150 mg/m^2/day, 1-h infusion weekly for 6 weeks). At the sixth week, the maintenance therapy was 6-mercaptopurine (50 mg/m^2 daily orally) and pulses of oral prednisone (40 mg/m^2 daily in 3 doses, Days 1–5) and vinblastine (6 mg/m^2/day once every 3 weeks) in the first group, while the second group received vinblastine in addition every 3 weeks. The total duration of treatment was 24 weeks. This trial demonstrated that more intensive treatment increases response rates and reduces mortality from LCH [82]. The Histiocyte Society conduced its third clinical trial with the aim of assessing whether the addition of methotrexate to prednisolone and vinblastine and increasing treatment duration to 12 months could reduce relapse rates. Even though all of these studies were performed on pediatric populations, they suggest that these agents may have a role in the treatment of LCH in adults with pulmonary and/or multisystemic involvement (considering PLCH as a single-system disease with a "risk organ" involvement) [83]. In multisystem LCH, which is often refractory to treatment and characterized by frequent relapse, there is no standard salvage regimen. Recently, however, cladribine has been used as a second-line treatment for both children and adults with good response. Cladribine is a purine nucleoside analogue with selective toxicity to lymphocytes and monocytes, which acts by interfering with single-stranded DNA repair and synthesis in lymphocytes and monocytes. Aerni et al. described a case of LCH with pulmonary involvement that responded well to cladribine treatment, suggesting the possibility of its use in selected cases [84].

Similarly, Grobost et al., in a small series of five patients reported cladribine efficacy, as a single agent, in the treatment of PLCH patients with nodular lung lesions and/or thick-walled cysts providing that a diffuse hypermetabolism on positron emission tomography (PET)-scan was observed [85].

Other therapies have been proposed for LCHs, including oral acitretin, which is a Vitamin A analogue. Derenzini et al. treated a group of seven patients, three suffering from multisystem and four from single-system LCH, with MACOP-B. This chemotherapy regimen is used for non-

Hodgkin lymphoma and consists of a combination of prednisolone, vincristine, bleomycin, methotrexate, doxorubicin, and cyclophosphamide. A 100% response rate in all seven adult patients was reported [86].

Bisphosphonate therapy can also be effective for treating LCH bone lesions [87, 88]. A nationwide survey from Japan described 16 children treated with bisphosphonates for bone LCH. All children had bone disease; none had risk-organ disease. Most patients received six cycles of pamidronate at 1 mg/kg per course given at 4-week intervals. In 12 of 16 patients, all active lesions including skin and soft tissues resolved. Although bisphosphonates are used for bone LCH, some publications report response in other organs, such as skin [29]. The discovery of BRAF and MAP2K1 mutations in LCH has led to targeted therapies acting upon the RAS/RAF/MEK/ERK pathway. Approximately, 60% of LCH cases harbor the somatic mutation that produces the oncogenic BRAF V600E variant [29]. Most of the 40% of cases not expressing BRAF V600E have other genetic alterations including those that result in structural rearrangements of BRAF, and mutations in other components of the pathway, such as MAP2K1 [38]. The pathogenetic role played by these alterations in LCH is confirmed by the clinical responses to targeted inhibitors of BRAF or MEK1 (the product of the MAP2K1 gene) seen in LCH cases carrying activated mutations of those targets [89].

Resistance to BRAF inhibitors has been reported commonly in malignancies in adults but only very rarely in the histiocytoses. The approach of combining a BRAF inhibitor with a MEK inhibitor has been investigated in adult malignancies and may be a future consideration for treatment of LCH. An ongoing international trial is addressing this by testing the combination of dabrafenib and a MEK inhibitor, trametinib, in adults and children with refractory or relapsed LCH. *BRAF* V600E mutations can be targeted in different ways by BRAF inhibitors (vemurafenib and dabrafenib) or by the combination of BRAF inhibitors plus MEK inhibitors (dabrafenib/trametinib and vemurafenib/cobimetinib). These combinations are already approved in different contexts such as melanoma [90, 91].

Small series and anecdotal case reports of refractory and relapsed BRAFV600E-mutated LCH have shown responses to the BRAF inhibitors, vemurafenib, and dabrafenib [92].

Vemurafenib (VMF), a BRAF (v-RAF murine sarcoma viral oncogene homolog B) inhibitor originally approved for metastatic melanoma [93], was approved by the European Medicines Agency as an orphan drug for refractory LCH [94]. VMF monotherapy is administered orally (10 mg/kg twice a day) for at least 8 weeks. The main adverse events include severe cutaneous toxicity, cardiac toxicity, squamous cell carcinoma and, more rarely, secondary pancreatic cancer.

Bhatia reported about 11 patients with Erdheim–Chester disease (ECD) or ECD/LCH harboring the *BRAF*V600E mutation treated with the single-agent dabrafenib following the failure of chemotherapy or radiation, or following discontinuation of vemurafenib therapy because of toxicity or intolerance. Surprisingly, responses were observed in the central nervous system, a site of disease often refractory to other treatments [95].

It is important to note that PLCH treatment is not yet standardized, and to date the data regarding the effectiveness of treatment are derived from observational studies, case reports, and expert opinions. More studies are needed regarding more effective and less toxic treatments.

Another important treatment to be considered is pleurodesis in cases of recurrent pneumothorax due to rupture of cystic lesions. Mendez et al., demonstrated the superiority of pleurodesis to tube thoracostomy alone in preventing ipsilateral recurrence of pneumothorax [96].

Lung transplantation is performed in selected patients with progressive disease that is refractory to other forms of treatment, including patients with severe pulmonary hypertension unresponsive to vasodilator therapy, and when severe respiratory failure develops. Etienne et al. performed lung transplantation in seven adult LCH patients and observed resolution in five of these patients, while the other two have suffered recurrence of LCH in the grafted lung. These two patients resumed smoking after transplantation and had extrapulmonary localization of the disease at baseline [97]. A retrospective multicenter study of 39 patients who underwent lung transplantation for end-stage PLCH described a recurrence rate in the allograft as high as 20.5%. The presence of extrapulmonary disease before transplantation and a resumption of smoking post transplantation have been described as risk factors for recurrent disease. These risk factors for recurrence should be considered in evaluating candidacy for transplant [49].

Course and Prognosis

PLCH is has an unpredictable natural history in the individual patient ranging from an asymptomatic and stable course to a progressive debilitating disease that leads to respiratory failure and death over a period of months. The ability to identify patients with poor prognosis would facilitate difficult decisions regarding the benefit of aggressive treatment early in the course of disease.

Established prognostic factors in LCH include disease extent at diagnosis, the presence of risk organ dysfunction, and early response to therapy. According to Delobbe et al., older age, lower FEV1/FVC ratio at diagnosis and prolonged corticosteroid therapy suggest an adverse prognosis [98]. However, in this study, the diagnosis of PLCH was not

confirmed by lung biopsy and some patients included were children. Other studies in literature suggest that PLCH patients are at increased risk of developing bronchogenic carcinoma and hematological malignancies, although such occurrences may be merely coincidental [99]. In a more recent study, Vassallo et al. studied a cohort of 102 PLCH patients and reported a median survival of 12.5 years, demonstrating that adult patients affected by PLCH have a shortened survival compared to the general population. Reduced DLCO or severe COPD due to concomitant cigarette smoking were considered as possible negative prognostic factors [77]. Pulmonary hypertension is an unrecognized complication of PLCH that is associated with poor prognosis [100]. Thus, it is important to estimate pulmonary hypertension by echocardiography at the time of diagnosis and afterwards in follow-up controls. When pulmonary hypertension is suspected on the basis of echocardiography, and especially when the estimated PAP is higher than 40 mmHg, a cardiac catheterization is warranted to confirm and define the severity of pulmonary hypertension [24]. Multiorgan involvement may be characterized by poor prognosis and for correct management of PLCH is necessary to investigate other possible organs involvement. The diagnostic approach to these patients should include skeletal X-rays to show possible bone disease and gadolinium-enhanced magnetic resonance imaging of the brain to identify potential involvement of the hypothalamic region. In recent years, fluorodeoxyglucose (FDG) PET scan imaging has been proposed to differentiate malignant pulmonary nodular lesions from benign ones. However, false-positive FDG-PET scan has been demonstrated in other conditions such as active infections, noninfectious inflammatory processes, benign neoplasms, and interstitial lung diseases such as sarcoidosis. In a cohort of 11 patients with PLCH diagnosis, PET-scan-positive patients had predominantly nodular lung disease, while PET-scan-negative patients had mainly cystic lung changes. However, it was not possible to distinguish between the benign inflammatory nodular lesions of PLCH and malignant lesions because the pulmonary nodules, and some cystic lesions, can demonstrate standardized uptake value (SUV > 2.5) similar to malignant lesions [72]. Phillips et al. compared both the capacity of different imaging techniques to determinate the extent of LCH and the effectiveness of therapy. A decreased FDG uptake following therapy suggested a role for FDG-PET in detecting disease activity and early response to therapy with greater accuracy than other imaging modalities in patients with LCH affecting bones and soft tissues [101]. However, it is necessary to have more prospective data to guide the clinical use of FDG-PET in the diagnosis and follow-up of LCH. After PLCH diagnosis is made, it is important to follow the course of the disease carefully, evaluating clinical parameters, chest radiography or (better yet) HRCT, and pulmonary function, initially at intervals of no more than 6 months. HRCT scanning has proven to be useful in understanding the evolution of the pathological lesions, as confirmed by the study of Soler et al. in which a correlation between the extent of nodular abnormalities and the density of florid granulomatous lesions in lung tissue was demonstrated. Long-term follow-up of PLCH patients is recommended because even after years of apparent quiescence, lung function can deteriorate and new nodular lesions can occur, due to reactivation of the disease [68]. Case reports of PLCH in pregnant women have been reported. Pregnancy does not seem to influence the course of the disease, except for the appearance of exacerbations of LCH-related diabetes insipidus. Pregnancy is not contraindicated in PLCH women unless there is a severe respiratory failure [10].

Case Report I

An 18-year-old woman with a 2-year history of tobacco smoking went to her doctor complaining of chest pain for 2 months. The patient was previously healthy and was not taking regular medication of any kind. She denied a prior history of dyspnea on exertion, cough, or fever. A chest radiograph revealed a right pneumothorax, and an HRCT revealed evidence of nodules, some of which were cavitary, and cysts that extended throughout the lungs sparing only the costophrenic angles (Fig. 18.6a–c). Pulmonary function tests showed normal spirometric values, normal walking test, and a decreased DLCO value (56% of predicted). A bronchoscopy with BAL was performed showing that CD1a+ cells were 8% of total cells. Nevertheless, a lung biopsy was performed and the histological diagnosis was compatible with PLCH. CD1a and S100 positive cells were found. No extra-pulmonary manifestations of the disease were found. The patient quit smoking soon after the diagnosis was made and was monitored with clinic visits every 3 months that demonstrated stability of disease based on symptoms. Thanks to the frequent follow-up, assessment of the clinical-radiological and functional trajectory of disease was possible at the 1 year visit. On CT scans many new cysts were found, some formed by the confluence of smaller cysts, ranging in size up to 6–7 cm of diameter. Total parenchymal loss was estimated at 30% in 1 year. The patient, began to complain of dyspnea on exertion and coughing. Considering the progression of the disease and the patient's young age, therapeutic intervention was felt to be indicated. In line with the Histiocyte Society study, the patient was treated with prednisolone + vinblastine + 6mercaptopurine for 6 months. Since completion of the therapy, functional and clinical improvement have been observed. Symptoms gradually disappeared and DLCO increased to 70%. Six years after therapy lung function is back to normal, symptoms are absent and CT scan shows stability of the disease.

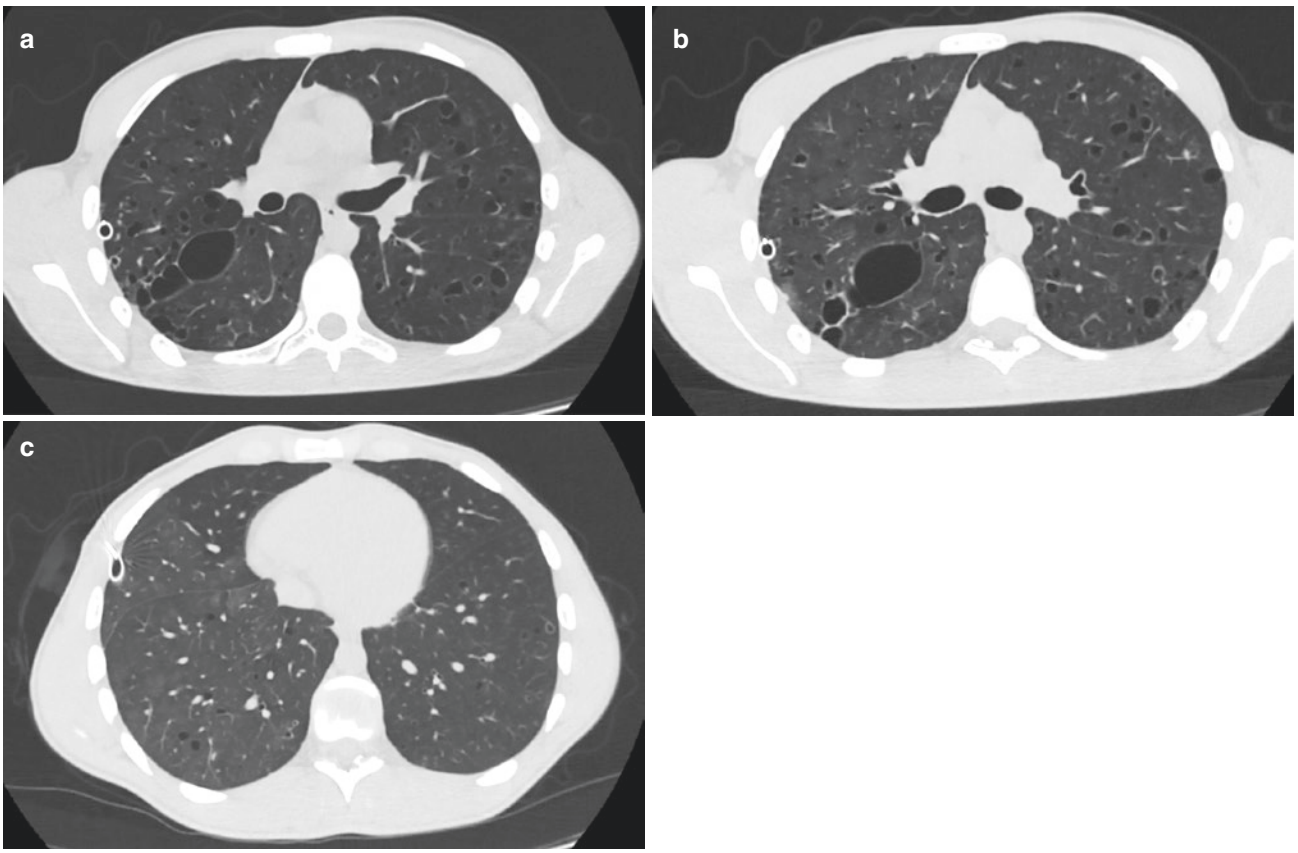

Fig. 18.6 (**a**) High-resolution CT scan demonstrates a small left pneumothorax with chest drainage and bilateral irregular cysts, with thin walls. (**b**) Some of these cysts appear to coalesce into larger and irregular structures with bizarre shapes. (**c**) Image depicting the typical lesion distribution with relative sparing of lower lobes

Respiratory Bronchiolitis-associated Interstitial Lung Disease (RB-ILD)

Introduction

Bronchiolitis is a generic term used to describe an inflammatory process involving the small airways that may be the consequence of cigarette smoke exposure, infections, aspiration, environmental agents, drugs or underlying systemic disorders such as connective tissue diseases and transplantation rejection [102]. In 1974, Niewoehner described the presence of inflammatory changes in the peripheral airways of a group of young smokers who had died of sudden death. The postmortem findings showed the presence of clusters of pigmented macrophages in respiratory bronchioles and neighboring alveoli [103]. These changes, termed respiratory bronchiolitis (RB), is used to describe this form small airways inflammation that occurs in virtually all smokers. In 1987, Myers et al. studied six smokers with clinical, functional, and radiological features suggestive of interstitial lung disease who underwent lung biopsy. The major pathologic findings were the presence of respiratory bronchiolitis, characterized by clusters of pigmented alveolar macrophages within respiratory bronchioles, and, in addition, a mild chronic interstitial inflammatory infiltrate of bronchiolar walls associated with hyperplasia of alveolar epithelial cells [104]. These were the first cases described in literature of respiratory bronchiolitis associated with an inflammatory and fibrotic involvement of the interstitium. The term "respiratory bronchiolitis with associated interstitial lung disease" (RB-ILD) appeared in 1989 in a study by Yousem et al. describing the histopathological differences between this new entity and other interstitial lung diseases. These and other studies, looking at the histopathological differences between RB and RB-ILD, have concluded that RB-ILD is usually associated with a greater extension of fibrosis, even though lungs of smokers affected by RB may also show mild alveolar fibrosis. The result is that differential diagnosis between RB and RB-ILD, exclusively based on histopathological and/or radiological findings, can be very difficult [105], and should also be based on clinical presentation. RB is usually asymptomatic while in RB-ILD symptoms such as dry cough and dyspnea are more often present [103].

Cottin et al. studied a population of 79 smokers affected by spontaneous pneumothorax who underwent surgical biopsy. RB and RB-ILD were found in 88.6% and 67.1% of patients, respectively [106]. Emphysematous lesions were also present in a third of patients, collectively demonstrating the high incidence of these three pathologies in patients with spontaneous pneumothorax. However, explaining the mechanism by which tobacco induces change in small airways and the development of emphysema and bullae, remains an ongoing challenge.

The occurrence of RB is uncommon in the absence of smoke exposure. Fraig et al. studied a population of 109 patients affected by RB of whom 98% were smokers (current or former smokers). and only 2% were nonsmokers [107]. Woo et al. described a case of a nonsmoking woman with radiological and histological features of RB–ILD, who was continuously exposed to cigarette smoke because of her job. This study highlights the limitation of focusing on the incidence of RB in smokers and nonsmokers, as second-hand smoke and environmental exposure can also result in respiratory bronchiolitis [108].

BAL findings in RB-ILD patients usually do not differ from those seen in normal "healthy" smokers and include an increased total number of cells or an increase in the percentage of macrophages that contain black tobacco pigment inclusions. A modest increase in neutrophils may also be present [109, 110].

Epidemiology

In a study performed on lung biopsy of smokers, Fraig et al. described the presence of RB in all smokers and about 50% of former smokers [107]. They also found an interesting correlation between the degree of pigmentation of macrophages and peribronchial fibrosis with the number of pack-years of cigarettes. In other studies, the relationship between RB and total smoke exposure is less obvious, although the percentage of smokers developing RB is consistently very high, ranging from 70% to 90%. RB-ILD is also closely related to smoking; different studies have shown that more than 90% of patients affected by RB-ILD are current smokers. RB-ILD typically affects smokers of 40–50 years of age with a slight male predominance and a history of cigarette smoking of 30 or more pack-year [5].

Clinical Features

The most common symptoms of RB-ILD are cough and dyspnea, and the typical physical exam findings include inspiratory crackles and, more rarely, digital clubbing. Lung function tests are nonspecific, and they can even be normal, but more commonly will reveal obstructive, restrictive, or mixed obstructive/restrictive patterns. An obstructive pattern is a typical sign of smoking exposure and RB, while mixed patterns suggest a diagnosis of RB with interstitial lung disease. Diffusing capacity is usually decreased and may be a useful guide of severity of disease. DLCO values are not diagnostically useful, however, since they may be affected by other conditions related to cigarette smoking such as emphysema [42].

Histopathological Findings

According to Myers et al., who first described the disease, RB-ILD and RB share many histological similarities [104]. The histological hallmark of both disorders is the accumulation of pigmented alveolar macrophages within respiratory bronchioles. RB macrophages are identified by abundant eosinophilic cytoplasm, with brown granular pigmentation representing constituents of cigarette smoke. A chronic inflammatory cell infiltrate within bronchiolar walls is seen in RB-ILD, without honeycomb change or fibroblastic foci (Fig. 18.7). Myers and colleagues suggested that the main difference between RB and RB-ILD is based on the extent of the fibrosing and inflammatory process, which in RB-ILD also involves adjacent alveolar walls in addition to airways [104]. Nakanishi et al. correlated the histopathological findings of RB-ILD patients with radiological features. Accumulation of macrophages within bronchioles was associated with centrilobular micronodules (<3 mm), while the association of peribronchiolar inflammation, fibrosis, and amassment of macrophages within the alveolar spaces corresponded to larger nodules (>3 mm). Ground glass opacities were the result of mild alveolar fibrosis accompanied by inflammation and accumulation of macrophages. In more advanced stages of the disease, HRCT showed areas of linear and reticular opacity that histologically corresponded to alveolar and subpleural microcystic fibrosis [111]. Craig et al. compared the histological features of DIP and RB-ILD, studying their clinical and radiological correlation [112]. They studied 24 patients with RB-ILD and 25 with DIP. The typical histological feature of the two entities is the presence of intra-alveolar macrophages characterized by pigmented cytoplasm and associated with variable interstitial fibrosis and chronic inflammation. RB-ILD lesions usually have a bronchiolocentric distribution, while DIP lesions are diffuse involving the entire pulmonary acinus. They also described a significantly greater extent of interstitial fibrosis, eosinophilic infiltration, and lymphoid follicle formation in DIP compared to RB-ILD. Yousem and coworkers examined nine cases of smokers with dyspnea, a mixed obstructive/restrictive pattern on lung function, reduced DLCO, and radiographic features of RB-ILD showing centrilobular nodules,

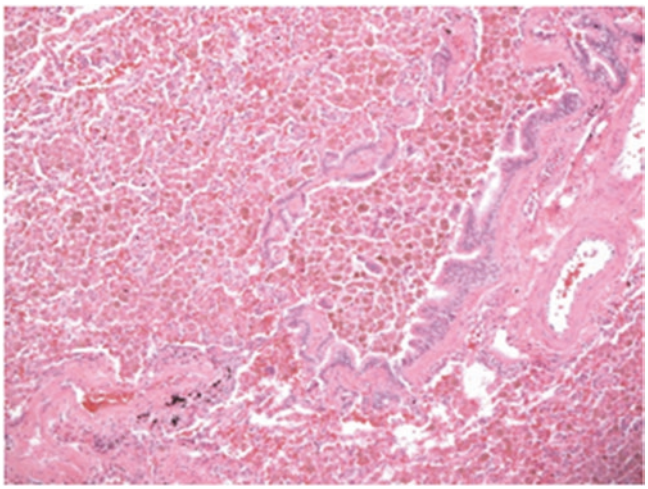

Fig. 18.7 RB consisting of distorted bronchioles with aggregates of "golden" macrophages into and around the bronchioles. (Courtesy of Professor G. Rossi. University of Modena-Reggio Emilia, Italy)

ground glass opacities, and emphysema. Surprisingly, lung biopsy revealed an extensive collagenous thickening of the alveolar septa with a patchy and subpleural distribution characteristic of nonspecific interstitial pneumonia (NSIP). This study confirms how difficult the differential diagnosis of these diseases may be, and highlights the critical role that smoking plays in fibrotic lung diseases [113].

Radiologic Findings

Chest X-ray is normal in up to 20–30% of cases of RB-ILD, and in other cases may show nonspecific thickening of the central and peripheral bronchial walls, bilateral reticular-nodular opacities with diffuse distribution or upper lobe predominance [42]. The most common HRCT findings are thickening of the bronchial walls, centrilobular nodules in the upper lung zones, and ground glass opacities (Fig. 18.8). Heyneman et al. compared the predominant HRCT features in a cohort of patients affected by RB, RB-ILD, and DIP, observing that in all of these conditions centrilobular nodules and ground glass opacities represent the most common radiological pattern [114]. In RB-ILD, these abnormalities are more profuse compared to RB and are characterized by the presence of areas of reticulation suggesting underlying interstitial fibrosis, albeit in the absence of honeycombing or traction bronchiectasis. There is no radiological cutoff that defines the boundary between RB and RB-ILD. The radiological differential diagnosis may become even more complicated considering that HRCT findings of RB-ILD may be very similar to those described for DIP [2]. DIP is characterized on CT scans by the presence of large areas of ground glass attenuation, which are usually bilateral, largely symmetrical, and peripheral and lower zone predominant. Basal,

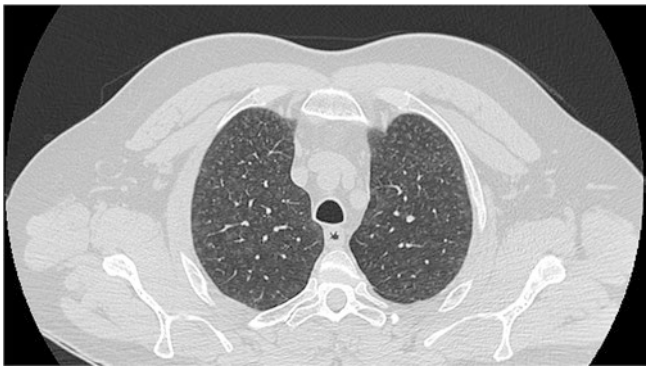

Fig. 18.8 HRCT of a patient affected by RB-ILD showing poorly defined centrilobular nodules

interlobular opacities can be associated with small peripheral cystic spaces with traction bronchiectasis. NSIP is marked by ground glass opacities, with irregular linear or reticular opacities and scattered micronodules in a subpleural distribution. In advanced disease, the presence of traction bronchiectasis and subpleural small cysts defined as "microcystic honeycombing" may be helpful in making the correct diagnosis of NSIP [115].

Prognosis and Therapy

A number of studies that have linked smoking with the development of RB-ILD have demonstrated a clear improvement of the disease after smoking cessation. Nakanishi et al. have shown that smoking cessation alone, without any other treatment, leads to clinical, functional, and radiographic improvement. Symptoms and DLCO values were both improved after smoking cessation, as were ground glass opacities and centrilobular nodules on CT scans. A significant correlation between the change in DLCO and the reduction of centrilobular nodules and ground glass opacities was observed [111]. Sadikot et al., described two patients with biopsy-proven RB-ILD with dyspnea, severe lung function involvement, and respiratory failure who had significant clinical and functional improvement after smoking cessation [116]. Mavridou et al. reported a case of acute RB-ILD in which smoking cessation alone was not adequate, requiring steroid treatment. Gradual clinical, functional, and radiological improvement was reported, although it was necessary to continue high dose of corticosteroids for a longer period of time because of clinical deterioration following corticosteroid tapering [117]. Similarly, Woo et al. described a case of RB-ILD occurring in a patient exposed to second-hand cigarette smoke. The patient was treated with high dose of corticosteroids which resulted in improvement of ground glass opacities and centrilobular nodules on HRCT [108]. However, some other studies have not confirmed the effectiveness of smoking cessation and

have also questioned the role of steroid treatment. Moon et al. retrospectively studied a group of ten patients with pathological features typical of RB-ILD. All patients were smokers except one, who was instead exposed to solder smoke. Most of them were symptomatic and nine patients had quit smoking either before or at the time of the diagnosis. Lung function tests showed both restrictive and obstructive patterns and severe DLCO reduction. Seven patients were treated with steroids, together with cyclophosphamide or azathioprine in six cases. The patients who received only steroids reported DLCO and FVC improvement, while in the six patients treated with corticosteroids and cyclophosphamide, FVC was unchanged in five cases and worsened in one. DLCO improved just in one patient, deteriorated in two, and remained unchanged in three cases. The three patients who quit smoking without any additional treatment reported unchanged FVC and DLCO values in the follow-up period [5]. In another study of RB-ILD patients, Portnoy et al. described clinical and functional decline in 32 patients in spite of smoking cessation and steroid treatment. These studies suggest that the prognosis of RB-ILD is not as good as usually believed. Even though mortality secondary to smoking-related interstitial lung disease is quite rare [109]. Due to the lack of clinical trials, the choice of treatment in RB-ILD is often based on expert opinions or case series. While some studies have shown disease improvement following corticosteroid treatment, the benefit of this therapy is unproven, and patients with RB-ILD should be strongly encouraged to enroll in a smoking cessation program and stop smoking. However, the true effectiveness of smoking cessation, corticosteroids or immunosuppressants in the treatment of RB-ILD remain unanswered clinical question that require further studies.

Desquamative Interstitial Pneumonia

The term "desquamative interstitial pneumonia" was originally coined by Liebow et al. who believed that intra-alveolar cells, typical of this disease, were reactive alveolar pneumocytes that had "desquamated" from the alveolar surface [118]. Later, electron microscopy demonstrated that these cells were alveolar macrophages. Early studies proposed that DIP was the cellular phase of usual interstitial pneumonia (UIP), because of some similarities in histopathological features [119]. This idea was not sustained by Carrington et al., who highlighted the poor prognosis for UIP and the absence of response to corticosteroid therapy in comparison with DIP. It has since been concluded that the pathogenesis and natural history of DIP and UIP are distinct [120]. Currently, DIP is included in the American Thoracic Society/European Respiratory Society classification as a form of idiopathic interstitial pneumonia characterized by the presence of diffuse exudation of pigmented macrophages in the alveolar spaces [3].

Epidemiologic and Clinical Features

Although classified as idiopathic, DIP has a number of radiological and histopathological similarities to RB-ILD and is also related to cigarette smoking. Different studies have supported this correlation, showing that almost 90% of patients affected by DIP are current or former smokers. Based on a comprehensive evaluation of HRCT findings, Heyneman et al., hypothesized that DIP and RB-ILD may be considered different degrees of severity of reaction of small airways and lung parenchyma to cigarette smoke [113]. In another study, Craig et al. showed that only 60% of DIP patients have a history of cigarette smoking [114]. It is in fact important to note that DIP has been also associated with a variety of other conditions including drug reactions and connective tissue diseases. Schartz et al. described a case of scleroderma with pulmonary involvement where a lung biopsy confirmed a diagnosis of DIP [121]. Similarly, Esmaeilbeigi et al. reported a case of lupus, with interstitial lung disease on CT scans, suggestive of NSIP pattern, while lung biopsy confirmed the diagnosis of DIP [122]. Ishii et al. reported the association between rheumatoid arthritis and interstitial lung disease with DIP pattern, supporting the possible correlation between autoimmune diseases and DIP [123]. It has been also reported one case of DIP characterized by increased serum levels of angiotensin-converting enzyme (ACE) and lysozyme that are known to be elevated in sarcoidosis. These findings are likely related to the involvement of macrophages and neutrophils in the pathogenesis of DIP and may suggest a possible role for ACE as a diagnostic tool for DIP. Obviously, more studies are necessary to prove the correlation between ACE serum levels and DIP [124]. Very few epidemiological data regarding DIP are present in literature. According to Carrington et al., DIP accounts for less than 3% of interstitial lung diseases. Its low incidence is probably linked to the poor knowledge of the disease and to the objective difficulties in making a correct diagnosis. It commonly affects patients in their third to fifth decade, with a preference for males who are affected nearly twice as often as females [120]. Patients usually complain of dyspnea on exertion and productive or dry cough. It is also possible to observe a variety of nonspecific symptoms such as weight loss, fatigue, and fever. Digital clubbing may be present while on chest auscultation it is possible to identify crackles. In the two largest case series reported in literature [114, 120] almost 90% of DIP patients were smokers or had a cigarette smoke exposition, even if, as described above, DIP can be the radiological and histological pattern of presentation in autoimmune disorders or in drug reactions. Lung function tests can show restrictive, obstructive, or mixed patterns together with a marked reduction in DLCO that is common and typical of DIP [42]. In any case, DIP is characterized by a more marked reduction

of DLCO in comparison to RB-ILD and by a more serious impairment of gas exchange [125].

Histopathological Findings

Histopathological diagnosis of DIP can be difficult to distinguish from RB-ILD. According to Wells, DIP is histologically characterized by hyperplasia of type II pneumocytes, accumulation of dusty macrophages within alveoli and diffuse alveolar septa thickening. These features are very similar to those observed in RB-ILD [126]. Nonetheless, the criteria to differentiate histological patterns of DIP from RB-ILD are well defined by consensus in the ATS/ERS classification for idiopathic interstitial pneumonias [3]. According to this classification, DIP is characterized by macrophage accumulation in the distal airspaces with alveolar pneumocyte proliferation along the alveolar septa. The alveolar septa thickening is also due to a chronic inflammatory infiltrate that includes plasma cells, occasional eosinophils, and lymphoid aggregates (Fig. 18.9). However, histological differential diagnosis between DIP and RB-ILD is based not only on the typology of lesions but also on their extent: DIP affects the lung in a more uniform, diffuse manner and rather than the more limited bronchiolocentric distribution observed in RB and RBILD. Despite these differences, it has been hypothesized that RBILD and DIP represent extremes of a spectrum of reactions of small airways and alveoli to cigarette smoking [114]. Other authors, consider DIP and RBILD as distinct entities, characterized by different presenting features and clinical courses. Wells et al. maintained that DIP and RB-ILD are separate entities that can be distinguished by radiological features (predominance of centrilobular nodules in RB-ILD and ground glass opacities with fibrosis in DIP); prognosis (better in RB-ILD than in DIP) and therapeutic indication (marginal in RB-ILD and necessary in DIP) [126]. However, in the differential diagnosis of DIP, other ILDs should be considered because many ILD patients are current smokers and often show, on lung biopsy, intra-alveolar macrophage accumulation as a consequence of smoking. In these cases, clinical and anamnestic information may be helpful for the diagnosis.

Radiological Findings

The radiologic pattern is nonspecific and includes ground glass areas and reticular or nodular opacities with a basal predominance as described by Liebow [118]. The prevailing abnormality at HRCT is represented by ground glass attenuation that may be peripheral, patchy, or diffuse and often with a basal subpleural predominance (Fig. 18.10) [42]. Hartman et al. studied a cohort of patients with biopsy-proven diagnosis of DIP, and described the presence of ground glass attenuation as the predominant finding. These lesions involved mainly the middle and lower lung zones with a peripheral distribution in 60% of patients, a patchy distribution in 25% of patients, and a diffuse distribution in 15%. The distribution of lesions on CT scans is very similar to that seen in usual interstitial pneumonia, but differential diagnosis should be easy because of the prevalence of ground glass opacities in DIP [127]. Craig et al. reported that HRCT appearances were suggestive for DIP just in 4 of 13 DIP patients, while the most prevalent appearance (7–13 cases) was represented by NSIP pattern. Also CT scans performed in follow-up period were characterized by a NSIP pattern

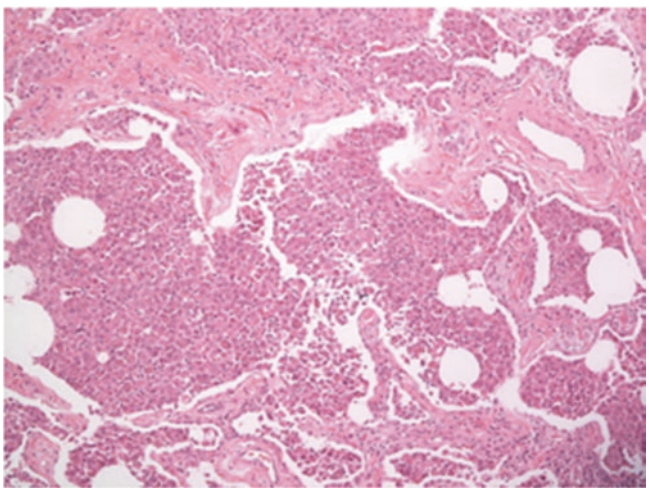

Fig. 18.9 DIP is characterized by homogeneous interstitial fibrosis with pools of golden histiocytes in dilated alveolar spaces. (Courtesy of Professor G. Rossi. University of Modena-Reggio Emilia, Italy)

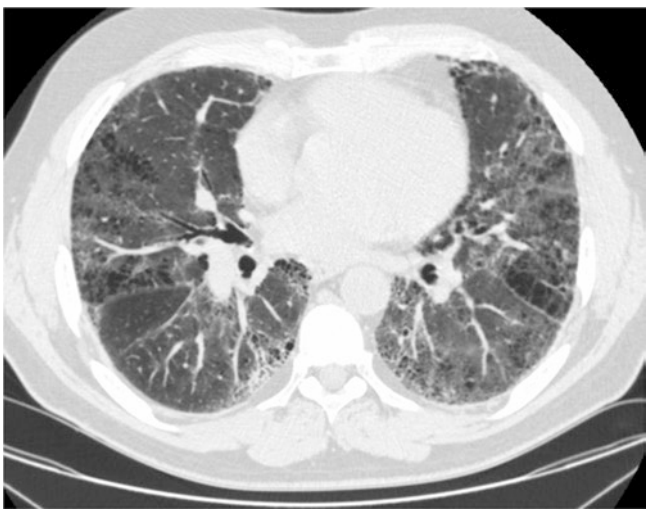

Fig. 18.10 High-resolution CT image obtained through the mid lungs showing peripheral reticulation and bilateral patchy ground glass in a patient with DIP

suggesting a possible evolution of DIP in NSIP [112]. Ground glass opacities described on CT scans of DIP patients are also present in RB-ILD, although in this disease centrilobular nodules are the predominant feature. The distribution of ground glass opacities is diffuse, symmetrical, and patchy in DIP, while peribronchiolar distribution prevails in RBILD [128]. Heyneman et al. also confirmed that ground glass opacities represent the predominant pattern in 100% of DIP patients, localized in mid to lower lung zones and with a subpleural distribution. They also described the presence of fibrosis with intralobular lines and honeycombing associated to traction bronchiectasis. Minor findings revealed on CT scans were subpleural nodules, emphysema, and areas of consolidation [114].

Prognosis and Therapy

The objective difficulties in making the correct diagnosis of DIP and the low incidence of the disease have contributed to the absence of studies large enough to obtain reliable data concerning the course of the disease. Carrington et al. compared mortality in UIP and DIP in a 1-year follow-up period, showing 87% of mortality in UIP and 16% in DIP [120]. Baloira et al. estimated a 10-year survival rate of 70%, while no death occurred in RB-ILD patients in the same period of follow-up [125]. A 27.5% mortality rate has been described in a group of 40 patients with DIP who had been followed up for a mean duration of 9 years. Similarly, Yousem et al. reported a 32% mortality rate in 36 patients with DIP, while no deaths were observed in 18 patients with RB-ILD [105]. Although the correlation between DIP and cigarette smoke has not been conclusively demonstrated, spontaneous remission has been reported after smoking cessation with no recurrence of disease in up to 4 years of follow-up [129, 130]. In those cases where smoking cessation alone does not stop disease progression, empiric steroid treatment has been attempted. The dose of prednisone used is 40–60 mg daily with a gradual tapering over a 6- to 9-month period [131]. Akira et al. reported a case series of DIP patients treated with prednisolone at the initial daily dose of 40–60 mg and described CT changes in a 12-month follow-up period. All DIP patients presented with ground glass opacities in mid and lower lobes with a subpleural distribution on the initial CT. After stopping smoking and following corticosteroid therapy, a decrease in the extent of ground glass opacities was described in the majority of patients. When DIP does not respond to corticosteroids immunosuppressive agents are often considered, although data supporting this approach are limited [132]. Unfortunately, DIP can progress to end-stage disease and lung transplantation may become necessary because of severe functional and clinical decline. DIP recurrence has been reported after lung transplantation.

Conclusion

It is widely known that tobacco smoke may cause pulmonary diseases such as COPD or cancer, but its role in causing smoking-related interstitial lung diseases, including RB-ILD, DIP, and PLCH, is under-recognized. The correlation between cigarette smoke and these diseases is supported by solid epidemiological data demonstrating a preponderance of smokers in cases of SR-ILD. It has been also been shown that smoking cessation may represent an effective therapy, even if pulmonary abnormalities can persist for long periods after smoking cessation. The pathogenic mechanisms underlying the relationship between smoke and SR-ILD have not been elucidated, but it has been postulated that cigarette smoke in susceptible individuals may cause an excessive inflammatory and/or fibrotic response at the bronchiolar and alveolar level. Because of the common etiologic agent, SR-ILDs share many clinical and functional aspects and, to some extent, radiological and histopathological patterns. DIP and RB-ILD, for instance, are both characterized by poorly defined centrilobular nodules and ground glass opacities; in these circumstances, only the extent of the lesions may help to discriminate the two diseases. In PLCH, the presence of nodules, cysts, and the characteristic sparing of lower lung lobes may greatly simplify the diagnostic process. It is obvious that radiological findings should be interpreted in an appropriate clinical context that must account for smoking history, symptoms, signs, and pulmonary function tests. Nevertheless, in some cases, where all these elements are nonspecific and diagnosis remains vague, a lung biopsy should be considered. Sometimes not even the histological features allow the correct diagnosis because DIP and RB-ILD may have very similar histopathological patterns. The incidence of SR-ILDs is probably underestimated because of the problematic diagnostic approach that requires integration of complex pulmonary, radiological, and pathological features. Furthermore, many issues regarding pathogenesis, clinical evolution, and treatment strategies remain unresolved. New and larger studies are needed to better define the factors that define susceptibility and the clinical course of SR-ILDs and their responses to smoking cessation, corticosteroid, and immunosuppressant treatment.

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