Lymphoproliferative lung disorders: clinicopathological aspects

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Lymphoproliferative disorders of the lung can be reactive lesions, malignant diseases or post-transplant disorders http://ow.ly/onfxh

Lymphoproliferative disorders are rarely observed as primary lesions in the lung, representing only 0.3% of all primary pulmonary malignancies, <1% of all the cases of non-Hodgkin lymphoma and 3–4% of all the extra nodal manifestations of non-Hodgkin lymphoma. The earliest comprehensive studies of pulmonary lymphomas were those of SALTZSTEIN [1] and PAPIOANNOU and WATSON [2], which were published in the 1960s. These investigators made important observations: low-grade neoplasms were more frequent than higher grade lymphomas (reticulum cell sarcomas) and both tumours had better clinical outcomes than their nodal-based counterparts. The authors also concluded that the majority of neoplasms with a low-grade cytological appearance should be considered as reactive proliferations, introducing the term ''pseudo-lymphoma''. This hypothesis showed significant weak points and, approximately 20 years later, ADDIS et al. [3] concluded that ''most if not all the cases of pseudo-lymphoma can be classified, when re-evaluated, as malignant lymphoma''. Knowledge of these entities expanded rapidly after the advent of new investigative tools such as immunohistochemistry and molecular biology techniques. The World Health Organization (WHO) classification of lymphoid neoplasm recently emphasised the importance of clinical features [4]. Table 1 provides an overall classification of lymphoproliferative disorders, which are described as: reactive/non-neoplastic lymphoid lesions, malignant parenchymal lymphoproliferative lesions (primary or secondary) and post-transplant lymphoproliferative disorders.

Pathological aspects

Reactive pulmonary lymphoid diseases

Three rare forms of benign hyperplasia of pulmonary lymphoid tissue, namely follicular bronchiolitis, pulmonary nodular lymphoid hyperplasia and lymphocytic interstitial pneumonia, are regarded as part of the spectrum of lymphoid hyperplasia of the bronchus-associated lymphoid tissue (table 1) [5, 6]. Follicular bronchiolitis is characterised by lymphoid follicular hyperplasia, often with reactive germinal centres, in the walls of bronchioles with narrowing of the lumen. Pulmonary nodular lymphoid hyperplasia (pulmonary pseudo-lymphoma) is a distinct form of reactive lymphoid proliferation with links to the family of IgG4-related sclerosing diseases, characterised by a dense nodular infiltration of mature, polyclonal lymphocytes and plasma cells, which are well-circumscribed and mainly sub-pleural, with some dense fibrosis between

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TABLE 1 Classification system for the pulmonary lymphoproliferative disorders
Spectrum of pulmonary lymphoproliferative disorders
Reactive pulmonary lymphoid diseases
Follicular bronchiolitis
Nodular lymphoid hyperplasia (pulmonary pseudo-lymphoma)
Lymphocytic interstitial pneumonia
Castleman's disease
Localised (hyaline-vascular, plasma cell type)
Multicentric
Primary pulmonary lymphoma
B-cell primary pulmonary non-Hodgkin lymphoma (MALT lymphoma)
Primary pulmonary diffuse large B-cell lymphoma
Lymphomatoid granulomatosis
Follicular lymphoma
Mantle cell lymphoma
Extra-osseous plasmacytoma
Intravascular large B-cell lymphoma
Large B-cell lymphoma
Plasmoblastic lymphoma
T-/NK-lymphoma
Anaplastic large cell lymphoma
Hodgkin lymphoma
Post-transplantation lymphoproliferative disorders

MALT: mucosa-associated lymphoid tissue; NK: natural killer cell.

the follicles. The dominant feature of lymphocytic interstitial pneumonia is a diffuse lymphoid infiltrate within the alveolar interstitium consisting of T-cells and variable numbers of polyclonal plasma cells; follicular hyperplasia is evident along the bronchiolo-vascular bundles and at the periphery of the secondary lobules (interlobular septa and sub-pleural interstitium), and loosely formed epithelioid granulomas are commonly seen [7]. Castleman's disease is classified, according to the clinical profile, as localised or multicentric (table 1) [8, 9]. The histopathogenetic classification distinguishes a hyaline vascular type and a plasma cell type, with a mixed type of Castleman's disease characterised by the occurrence in the same patient of hyaline vascular and plasma cell features. The hyaline vascular type shows numerous follicles with a concentric layering of small B-cells around an onion-skin appearance, depleted, abnormal germinal centres with penetrating hyalinised capillaries in a ''lollipop'' appearance, and large dysplastic cells with vesicular nuclei consistent with follicular dendritic cells. In fact, Castleman's disease has been recognised as a neoplasm of follicular dendritic cells as clonal cytogenetic abnormalities have been reported [10, 11]. The plasma cell type is characterised by diffuse polyclonal or monoclonal (more frequently IgM) plasma cell proliferation, often in sheets, in the inter-follicular stroma. Castleman's disease is rarely associated with HIV and human herpes virus (HHV)-8 infection, or Kaposi's sarcoma herpes virus and Epstein–Barr virus (EBV) infections [12, 13].

Primary pulmonary lymphomas

These are defined as a clonal lymphoid proliferation affecting one or both lungs (parenchyma and/or bronchi) in patients with no detectable extrapulmonary involvement at the time of diagnosis or during the subsequent 3 months (table 1). However, this definition is not precise because indolent extra-nodal lymphoma may present clinically and radiologically as primary pulmonary lesions [14–16], and aggressive lymphoid tumours may initially manifest as disorders mainly involving the respiratory tract. Therefore, primary pulmonary lymphomas should be defined as lymphoid neoplasms that become manifest as respiratory diseases. The WHO classification of tumours of the lung [4] categorises primary pulmonary lymphomas into: B-cell primary pulmonary non-Hodgkin lymphomas (as marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type); primary pulmonary diffuse large B-cell lymphoma; and lymphomatoid granulomatosis. Nevertheless, the lung may be the primary site of presentation of most types of usually lymph node based lymphomas, such as: follicular lymphoma; intravascular large B-cell lymphoma; mantle cell lymphoma; extra-osseous plasmacytoma; large B-cell lymphoma arising in HHV-8-associated multicentric Castleman's disease; plasmoblastic lymphoma; T-/natural killer cell (NK)-lymphoma; anaplastic large-cell lymphoma; and Hodgkin lymphoma. Primary pulmonary MALT lymphoma is a rare extra-nodal lymphoma that is usually of the low-grade B-cell type and is considered to arise from the MALT of the bronchus. Low-grade B-cell lymphomas represent 50–90% of all the primary

lung lymphomas. On histological analysis, the pulmonary structure is effaced by abnormal lymphocyte infiltration, predominantly localised along broncovascular bundles, interlobular septa and visceral pleura, in a lymphangitic pattern [17, 18]. Like MALT lymphomas arising in other sites, pulmonary MALT lymphomas are formed by the accumulation of clonal lymphoid cells characterised by the morphological and biological features of marginal zone B-cells [4]; small, round, centrocyte-like monocytoid cells characterised by small and irregular nuclei, inconspicuous nucleoli and abundant clear cytoplasm. Neoplastic lymphocytes typically accumulate around non-neoplastic lymphoid follicles, forming poorly defined sheets of cells at the periphery of the mantle zones, which extend into the lung parenchyma. The presence of reactive follicles, which can be particularly abundant and are presumably pre-existing to the lymphoma development, can pose diagnostic problems on morphological and immunophenotypical analysis. Histologically, the differential diagnosis includes all pulmonary diseases characterised by the accumulation of lymphoid follicles and, in particular, the spectrum of follicular hyperplasia, follicular bronchiolitis and lymphocytic interstitial pneumonia, as well as, more rarely, hypersensitivity pneumonitis, inflammatory pseudotumor, intraparenchymal thymoma and Castleman's disease. In a consistent proportion of cases, it is possible to demonstrate lymphoplasmacytic differentiation with a significant plasma cell component exhibiting immunoglobulin light chain restriction. It is possible that some cases of primary plasmacytoma of the lung (a rare low-grade tumour of unclear aetiopathogenesis presenting as isolated or diffuse nodules) can be included in the clinical–pathological spectrum of MALT lymphomas, together with localised pulmonary amyloidosis. A heterogeneous pattern of cytogenetic abnormalities has been demonstrated, including aneuploidy (observed in nearly 40% of cases with trisomy 3 and 18 being the most common) and specific chromosomal translocations. Translocation t (11; 18) (q21; q21) characterises about one-third of extra-nodal marginal MALT lymphomas (3–41%) [19–22]. Primary high-grade large pulmonary B-cell lymphoma represents a minority of cases of primary pulmonary lymphomas (11–19%) [4]. Morphologically, in the lung, it forms confluent sheets of tumour cells and tends to destroy the normal lung parenchyma. The tumour is composed of large, dyscohesive tumour cells with coarse chromatin, distinct nucleoli and abundant amphophilic cytoplasm. It is usually described as centroblastic or immunoblastic. Lymphomatoid granulomatosis is an extra-nodal angiocentric and angio-destructive lymphoproliferative disorder [23, 24]. Data indicate that lymphomatoid granulomatosis is an EBV positive B-cell proliferation associated with an exuberant T-cell reaction [25]. The term lymphomatoid granulomatosis includes a group of related lesions characterised by the infiltration of pulmonary parenchyma by a heterogeneous cell population composed of a large number of reactive T-cells, a variable proportion of large EBV-infected B-cells (as defined by the expression of B-cell related antigens CD20 and CD79a), and EBV markers such as latent membrane protein-1 and EBV-encoded RNA [26, 27]. The lymphoid infiltrate often surrounds muscular pulmonary arteries and veins, and typically invades the walls of these vessels, with frequent necrosis. Lymphomatoid granulomatosis lesions are heterogeneous, and have been graded depending on the proportion of neoplastic B-cells and surrounding reactive T-cells, the degree of lymphocytic atypia and the heterogeneity of the infiltrate distinguishing three grades characterised by a varying proliferation index and prognostic differences. Grade 1 lesions contain few or no EBV-infected cells (less than five per high-power field). They are usually lack necrosis and are polymorphous. Grade 2 lesions have scattered EBV-infected cells (five to 20 per high-power field) and foci of necrosis, but they remain polymorphous. Grade 3 forms can be considered as diffuse large B-cell lymphomas. Foci of necrosis are evident and sheets of markedly atypical cells (resembling immunoblasts or with double nuclei resembling Reed–Sternberg cells) infiltrate the lung parenchyma in an angiocentric fashion. The T-cell component exhibits an activated cytotoxic phenotype and can be considered as a reactive response to infected/neoplastic B-cells. Lymphomatoid granulomatosis needs to be distinguished histologically from other diseases characterised by polymorphous lymphoid infiltration (IgG4-related sclerosing disorders, angio-immunoblastic lymphoadenopathy, EBV infection, acute and fibrinous organising pneumonia, inflammatory sarcomatoid carcinoma, and other malignant lymphomas, in particular enteropathy-associated T-cell lymphoma and acute T-cell lymphoblastic leukaemia), and/or by local coagulative necrosis and prominent angioinvasion (including extra nodal T-/NK- (nasal type) lymphoma, polyangioitis and granulomatosis).

Follicular lymphoma is generally an indolent B-cell lymphoproliferative disorder of transformed follicular centre B-cells [4]. Immunohistochemical staining is positive in virtually all cases for cell surface CD20 and CD10, nuclear bcl-6 and monoclonal immunoglobulins, as well as membrane expression of the bcl-2 protein. The overwhelming majority of cases involve the characteristic translocation t (14; 18) (q32; q21), involving the IgH/bcl-2 genes. Intravascular large B-cell lymphoma is a rare subtype of B-cell lymphoma with an estimated frequency of <1% of all lymphomas and is characterised by an intravascular proliferation of clonal lymphocytes with little or no parenchymal involvement, usually without the involvement of lymphoid tissues and, occasionally, peripheral blood [28, 29]. A variant may be the primary large cell lymphoma of the splenic sinuses. Single cases of aggressive T-cell lymphoma with an angiotropic growth

pattern have also been reported. Proliferation of lymphoma cells in the blood vessels of parenchymal organs results in vessel obliteration and ischaemia. Histology shows subtle changes and it is characterised by small pulmonary vessels and dilated capillaries showing intraluminal infiltration of medium sized cells with ovoid hypercromatic nuclei. When occurring in the lung, nasal type NK-/T-lymphomas can present many similarities with lymphomatoid granulomatosis [4, 30, 31], including angioinvasion, expression of markers of EBV infection, necrosis, immune disturbances and a rich T-cell infiltrate exhibiting cytotoxic immunophenotype, as defined by the expression of CD8, TIA-1 (T-cell-restricted intracellular antigen 1), granzyme-B and perforin. The occurrence of EBV marker expression is heterogeneous in pulmonary T-cell lymphomas. Anaplastic large cell lymphoma T-cell type was previously recognised as Ki-1 lymphoma for the strong expression of the activation antigen CD30/Ki-1 [4]. Mycosis fungoides, in its rare granulomatous variant, may primarily involve the lungs. Due to its rarity and lack of clinical–radiological specificity, the diagnosis is always difficult and requires accurate histopathological analysis [32]. Primary pulmonary Hodgkin lymphoma is characterised by neoplastic nodules, formed by a heterogeneous cell population including many inflammatory cells (macrophages, T-lymphocytes, plasma cells and granulocytes), and isolated atypical cells characterised by the cytological features of Reed–Sternberg/Hodgkin cells of the classic-type Hodgkin lymphoma (as defined in the WHO classification) [4, 33–35]. Immunophenotypic analysis can be highly useful in characterising Reed–Sternberg/Hodgkin cells. Various modifications can be observed in the parenchyma adjacent to the neoplastic nodules of Hodgkin lymphoma, including focal organising pneumonia, endoalveolar accumulations of foamy macrophages and interstitial lymphoid infiltration. Differential diagnoses for classic Hodgkin lymphoma include solitary fibrous tumour with extensive inflammation and inflammatory myofibroblastic tumour [36].

Post-transplantation lymphoproliferative disorders

These develop in organ or bone marrow transplant recipients and range from benign lymphoid hyperplasia to frank malignant lymphoma, which is a potentially life threatening complication that occurs in ∼1.7–3.5% of solid organ transplantation recipients (table 1). The pathological features follow benign plasmacytic hyperplasia and infectious mononucleosis-like post-translational lymphoproliferative disorder (PTLD; polyclonal diseases arising in the oropharynx or lymph nodes), polymorphic lymphoproliferative disorder (nodal or extra-nodal monoclonal disease), monomorphic PTLD (predominantly B-cell neoplasm or less often T-cell neoplasm, widely disseminated and monoclonal), Hodgkin lymphoma and Hodgkin-like PTLD. In plasmacytic hyperplasia and infectious mononucleosis-like lesions there is a mixture of polyclonal B-cells, plasma cells and T-cells [4], evidence of multiple EBV infectious events and no oncogene or tumour-suppressor gene alterations. Polymorphic PTLD are composed of immunoblasts, plasma cells and intermediate-sized lymphoid cells that form destructive masses in the lung parenchyma. Monomorphic PTLD consists of areas of necrosis surrounded by a dense monomorphic lymphoid infiltrate (angioinvasive and destructive infiltrate); cells appear to be transformed (large, blastic cells with prominent nucleoli and basophilic cytoplasm).

Clinical profiles and laboratory syndromes: red flags for clinicians

Primary lymphoprolipherative diseases in the lung may present characteristic clinical profiles that, when associated with peculiar laboratory syndromes, represent "red flags" for diagnosis (table 2). A practical classification of these addressing clinical/laboratory aspects are briefly described as: asymptomatic lesions detected by accident possibly associated to the presence of serum paraproteins and/or increased lactate deydrogenase (LDH) (MALT lymphomas) [37]; neoplasm arising in specific clinical contexts (MALT lymphomas in collagen vascular disease, mainly Sjögren syndrome, lymphomatoid granulomatosis in HIV positive patients or subjects with Wiskott–Aldrich syndrome, and post-transplant lymphoproliferative processes); neoplasm manifesting with respiratory symptoms associated with lymphopenia and/or eosinophilia (T-cell lymphomas not otherwise specified, granulomatous mycosis fungoides, and Hodgkin lymphoma); thromboembolic or acute pulmonary hypertension-like onset associated with a significant increase of LDH and/or hypercalcaemia (intravascular lymphomas); haemophagocytic syndrome characterised by abrupt onset, coagulation abnormalities, elevated triglycerides, ferritin, transaminases and LDH, decreased levels of fibrinogen, and usually cytopenias or even pancytopenia (nasal type T-/NK-cell lymphomas, T-cell lymphomas not otherwise specified); rarely organising pneumonia (lung infiltrates that have organising pneumonia as morphological background responding to steroids) may be the presenting and confounding clinical manifestation of pulmonary lymphomas, mainly lymphomatoid granulomatosis or Hodgkin lymphoma [37]; and differential diagnosis can include conditions arising in patients treated with methotrexate, natalizumab or other drugs [38–40]. Furthermore, indolent neoplasms have a chronic course but aggressive neoplasm may have a rapidly progressive course due to the disease itself or to infections complicating the immunodeficiency related to the tumour.

TABLE 2 Clinical profile and laboratory syndromes: red flags for clinicians

Asymptomatic lesions	MALT lymphoma
Serum para-proteins and/or increased LDH	
Collagen-vascular disease	MALT lymphoma in collagen-vascular disorders (*e.g.* Sjögren)
Immunodeficiency	Lymphomatoid granulomatosis in HIV
	Lymphomatoid granulomatosis in Wiskott–Aldrich syndrome
Transplantation	Post-transplant lymphoproliferative processes
Respiratory symptoms	T-cell lymphomas
Lymphopenia and/or eosinophilia	Granulomatous mycosis fungoides
	Hodgkin lymphoma
Thromboembolism	Intravascular lymphoma
Acute pulmonary hypertension-like onset	
Increased LDH and/or hypercalcaemia	
Haemophagocytic syndrome[#]	NK-/T-cell lymphoma, nasal type
	T-cell lymphoma
Organising pneumonia	Hodgkin lymphoma
	Lymphomatoid granulomatosis
Treatment with methotrexate, natalizumab or other drugs	Atypical lymphoproliferative processes

MALT: mucosa-associated lymphoid tissue; LDH: lactate dehydrogenase; NK: natural killer cell. [#]: abrupt onset, increased triglycerides, increased ferritin, coagulation abnormalities, increased transaminases, and decreased fibrinogen and cytopenia/pancytopenia.

Specific entities

Primary pulmonary lymphomas

About half of the patients with primary pulmonary MALT lymphoma are asymptomatic at presentation, and nearly half of these cases are identified accidentally on the basis of abnormal radiological findings [41]. The pulmonary symptoms are nonspecific, like cough, dyspnoea, chest pain and occasional haemoptysis, but are more common than constitutional symptoms, such as weight loss, fever, night sweats or fatigue. These symptoms may present for several weeks to months before diagnosis. This indolent behaviour can explain why many cases of pulmonary MALT lymphoma have been previously defined as pseudo-lymphoma. Laboratory findings are nonspecific and usually normal; only a few patients have increased levels of LDH and/or β_2-microglobulin in the serum. Also, less frequently, a monoclonal band is found in serum immunoelectrophoresis. Radiological features of MALT lymphoma are solitary, well-delineated soft-tissue masses with air bronchogram. Although hilar and mediastinal lymphadenopathy is not a prominent radiological finding, nodal involvement is documented on pathologic analysis in ~30% of cases. High-resolution computed tomography (HRCT) findings include: areas of alveolar consolidation more frequently centred on dilated bronchi, ground-glass attenuation, the presence of the "halo sign", peribronchovascular nodules, the "tree-in-bud pattern", peribronchovascular thickening and septal lines (table 3) [42–44]. Radiographic findings may remain unvaried for several years. Cases of endotracheobronchial MALT lymphoma with polypoid features, even causing unilateral lung hypertransparency or of pleural MALT lymphoma, have been reported [45]. MALT lymphomas have generally been reported not to show increased fluorine 18-fluorodeoxyglucose (^{18}FDG) accumulation on positron emission tomography (PET), but this was not confirmed in recent studies [46]. The outcome of MALT-type primary pulmonary lymphoma is generally favourable. More than 80% of the cases have a 5-year survival rate, and the median survival rate has been reported as >10 years [46]. Clinical features associated with poor prognosis in a study of primary pulmonary lymphoma included patients >60 years of age with elevated serum LDH and elevated serum β_2-microglobulin levels [37, 47]. High-grade primary large pulmonary B-cell lymphomas often occur in patients with underlying immunological disorders such as immunosuppression in solid organ transplantation, HIV infection and Sjögren syndrome [17, 48]. Patients are usually symptomatic with respiratory symptoms (cough, dyspnoea and haemoptysis), fever and weight loss. Common radiological and computed tomography findings include a single pulmonary mass, not infrequently excavated (mostly in HIV patients or in other immunosuppressed hosts), and atelectasis; pleural effusion may be present. Median survival time is 8–10 years, but relapse and progression occur early and survival is dramatically poorer in patients with underlying immunological disorders such as AIDS and transplantation. Lymphomatoid granulomatosis may affect virtually any organ, it is most frequently characterised by pulmonary, skin and central nervous system involvement. This condition usually affect adults (average age 50 years) with a predilection for males (male to female ratio 2:1) and patients with underlying immunodeficiency (HIV positive patients and Wiskott–Aldrich syndrome) [48]. However, occurrence in childhood has been documented. In lymphomatoid granulomatosis, the lung is the most frequently involved site, while the

Lymphoproliferative lung disorders	Computed tomography features
MALT lymphoma	Nodules or consolidation
	Peribronchovascular
	Multiple/bilateral (70%)
	Hilar/mediastinal nodes (30%)
	Ground-glass attenuation (halo sign)
	Rarely cysts, pleural effusion, tree-in-bud
High-grade primary large pulmonary B-cell lymphomas	Nodule or mass cavitation in 50%
	Rarely pleural effusion
Lymphomatoid granulomatosis	Bilateral nodules/masses
	Peribronchovascular
	Coalescence and/or cavitate
	Pleural effusion (30%)
	Hilar adenopathies (<25%)
	Migratory
	Uncommon: single nodules, alveolar opacities and reticulonodular diffuse lesions
Follicular lymphoma	Ground-glass opacities (crazy paving)
	Nodules
Intravascular large B-cell lymphoma	Bilateral reticular shadows
	Reticulonodular or nodular shadows
	Ground-glass opacities
	Wedge-shaped subpleural opacities
	Pleural effusion
Nasal-type T-/NK-lymphomas	Nodules or excavated masses
	Pleural effusion
Anaplastic large cell lymphoma, T-cell type	Masses or single nodules
Mycosis fungoides	Nodules with halo signs
	Peripheral consolidation
	Crazy paving pattern
Primary pulmonary Hodgkin disease	Solitary mass or multinodular disease
	Air bronchograms or cavitation
	Pleural effusion, lymphadenopathy

MALT: mucosa-associated lymphoid tissue; NK: natural killer cell.

upper respiratory tract is less commonly involved. Ulceration of the upper airways has been described in 10–30% of cases. Other sites of involvement are the brain, kidney, liver, skin, soft tissues, bladder and gastrointestinal tract. Few subjects are asymptomatic. Nearly 90% of patients report chronic respiratory symptoms, mainly cough, chest pain and dyspnoea, accompanied by B-symptoms such as fever, weight loss and sweating. Haemoptysis or acute respiratory distress syndrome rarely occur. Laboratory findings are characterised by increased erythrocyte sedimentation rate (ESR) and, in a minority of cases, by lymphopenia, leukocytopenia and low CD4$^+$ lymphocyte count. Lung nodules are the most common feature on chest radiographs and occur in ~80% of cases. Cavitations may be noted in 20% of cases. Pulmonary nodules are the most common findings on computed tomography images (fig. 1), along with bronchovascular distribution [49, 50]. In ~30% of patients, pleural effusion is present at the beginning and hilar adenopathies are found in <25% of cases (table 3). Differential diagnosis in patients with lymphomatoid granulomatosis is a real challenge. Granulomatosis with polyangiitis (Wegener's) other necrotising vasculitis, necrotising nodular sarcoidosis, infections, bronchogenic carcinoma and metastatic tumours, organising pneumonia, IgG4-related sclerosing disorder [51] and, very rarely, acute lung injury are at the top of the list. The clinical course is highly variable. Patients may show waxing and waning of their disease; in grade 1 forms and when the lesions are localised to the lungs, spontaneous resolution may be observed in up to 27% of cases [52]. One-third of patients with grade 1 lesions progress to malignant lymphoma, whereas two-thirds of patients with grade 2 lesions develop lymphoma. Patients affected by the aggressive form of disease die within 2 years, despite polychemotherapy. Death is often caused by a progressive pulmonary involvement.

Follicular lymphoma is characterised by diffuse lymphoadenopathy, bone marrow involvement, splenomegaly and, less commonly, other extranodal sites of involvement, such as the gastrointestinal
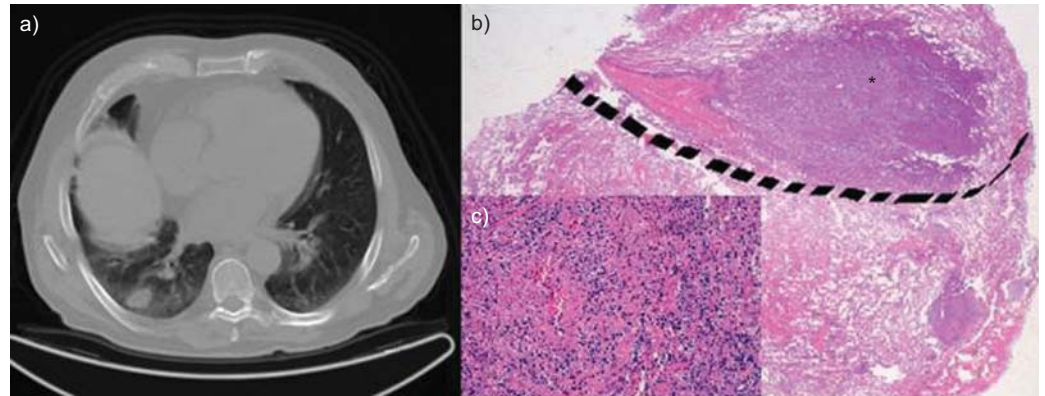
FIGURE 1 a) 18-fluorodeoxyglucose positron emission tomography-computed tomography in a 72-year-old male revealed pulmonary nodules in the lower lobes. Surgical lung biopsy of the consolidation in the right lower lobe revealed lymphomatoid granulomatosis. b) Lymphomatoid granulomatosis histopathological specimen in the same patient showing a well-demarcated cellular nodule with a central area of necrosis (asterisk). The preserved alveolar parenchyma is shown in the lower part of the image, below the dashed line. c) The angiocentric nature of the lesion.

tract, lung, skin and other sites [4]. Primary lung involvement is usually asymptomatic. HRCT scans show ground-glass opacities, sometimes with a "crazy paving" pattern or nodules (table 3). Intravascular large B-cell lymphoma usually shows rapid progression and short survival with, at best, transient remissions; the clinical presentation is highly variable, ranging from no or limited organ involvement to multiple organ failure. Therefore, the diagnosis is often difficult. The very poor prognosis in these patients reflects, in part, frequent delays in diagnosis and initiation of therapy due to their extraordinary presentation. A case of pulmonary arterial hypertension and a case of respiratory insufficiency with air trapping have been previously reported [53]. LDH, soluble interleukin-2 receptor and ESR are usually elevated. Pulmonary function tests show a markedly decreased diffusing capacity. Chest radiographs may be normal or show reticulonodular or pleural effusion. Computed tomography findings may include bilateral reticular shadows, reticulonodular or nodular shadows, ground-glass opacities, wedge-shaped sub pleural opacities and pleural effusion (table 3) [54]. [18]FDG-PET shows increased [18]FDG uptake [55]. A ventilation/perfusion scan may show a mismatched segmental defect identical to that observed in pulmonary thromboembolism. Splenomegaly, pancytopenia, erythroblastosis, massive elevation of LDH levels and, rarely, hypercalcaemia urgently suggest the presence of a haematological neoplasm, in particular, a myeloproliferative syndrome or aggressive lymphoma. Nasal-type T-/NK-lymphomas in the lung show clinical–radiological features similar to lymphomatoid granulomatosis. CD4^{+} lymphopenia and systemic symptoms such as fever, malaise, weight loss and haemophagocytic syndrome are not infrequent [31]. Lung involvement may show nodules or excavated masses (table 3) [56]. Anaplastic large cell lymphoma of the T-cell type has been rarely described as a primary pulmonary presentation; masses or single nodules are the features observed on computed tomography (table 3). Patients usually present with B-symptoms. Mycosis fungoides usually presents with fever, lymphopenia, eosinophilia, and increased ESR and LDH [32]. Computed tomography features include nodules with halo signs, peripheral consolidation and a crazy paving pattern (table 3). Primary pulmonary Hodgkin disease is a rare entity and has to be distinguished from the more common intrathoracic nodal Hodgkin disease secondarily involving the lung [33–35]. Due to its rarity, epidemiological data of primary pulmonary Hodgkin disease are scarce. In a review of 60 recorded cases, primary pulmonary Hodgkin disease was shown to affect females more frequently than males and showed a bimodal age distribution (<35 years and >60 years) with no significant correlation with smoking. Dry hacking cough is the most common presenting symptom. Radiologically, it appears as a solitary mass or multinodular disease (fig. 2). Dishomogeneity or cavitation of these lesions is common (table 3). Since the presentation of this disease is nonspecific and as noninvasive tests are rarely revealing, diagnosis often requires open thoracotomy and lung biopsy.

Post-transplantation lymphoproliferative disorders
Incidence varies depending on organ recipient (renal recipients <1%, hepatic and cardiac allografts 1–2%, heart–lung or liver–bowel allografts 5%); marrow allograft recipients have a low risk of PTLD (1%), with those receiving human leukocyte antigen-mismatched/T-cell depleted bone marrow or receiving immunosuppressive therapy for graft *versus* host disease being at higher risk for development of lymphoma (up to 20%). High values of ESR and C-reactive protein are common; plasmacytic hyperplasia and polymorphic lymphoproliferative disorder are usually asymptomatic, and generally regress spontaneously
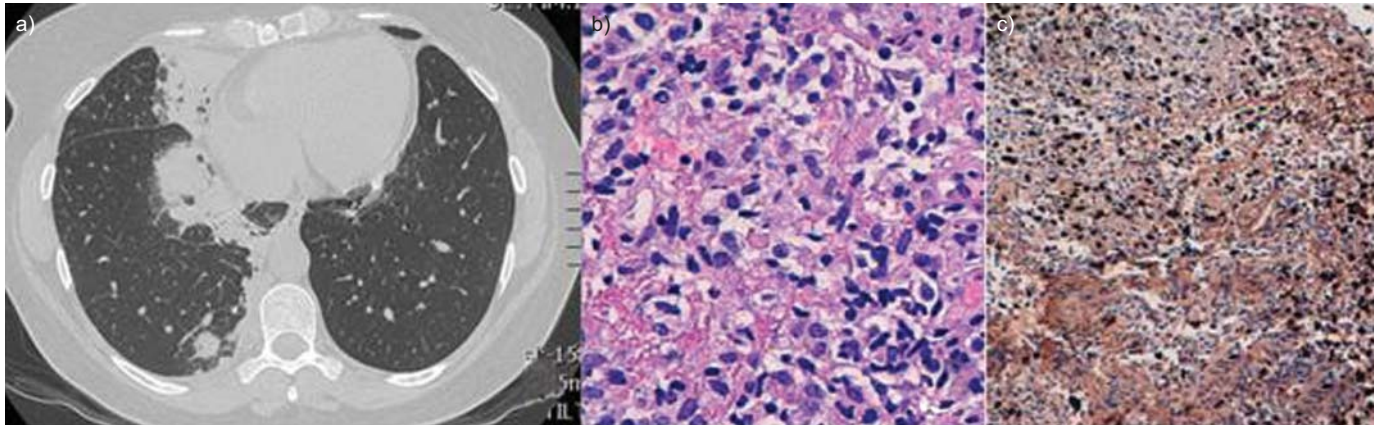
FIGURE 2 a) An axial multidetector computed tomography scan in a 43-year-old female, demonstrating consolidations with air bronchograms. b) Transbronchial biopsy of the consolidation revealed Hodgkin lymphoma. c) Immunophenotypic analysis revealed strong expression of activation markers (CD30).

following withdrawal of immunosuppression. The majority of PTLD are associated with EBV infection, but most patients have a negative serology for EBV and cytomegalovirus before transplantation. The median (range) time interval from transplantation to diagnosis is ~8 (1–97) months (*i.e.* shorter in patients receiving heart, lung or stem cell/bone marrow transplants). Typical radiological findings are single or multiple nodules with hilar or mediastinal adenopathy, interlobular septal thickening and air space consolidation. Nodules with peripheral ground-glass attenuation (halo sign) may imitate invasive mycoses. They can also involve serous surfaces and can develop pleural effusions from which tumour cells can be recovered.

Diagnosis and staging of lymphoproliferative lung disorders

Due to their rarity and heterogeneity, diagnosis of lymphoproliferative lung disorders can occasionally be problematic if solely based on histological analysis; therefore, the use of more sensitive and precise techniques is recommended, including immunophenotypic analysis by immunohistochemistry and/or flow cytometry and molecular biology.

Differential diagnosis of pulmonary lymphoma includes viral, bacterial or opportunistic pneumonia, radio- and drug-induced pneumonitis, tuberculosis, sarcoidosis, cryptogenic organising pneumonia, alveolar proteinosis, lipidic pneumonia, alveolar haemorrhage, bronchoalveolar cell cancer, hypersensitivity pneumonitis, eosinophilic pneumonia, vasculitis, and primary or metastatic lung tumours. Diagnosis is primarily based on clinical, radiological and histological findings, and different procedures may be used to obtain diagnostic tissue. Bronchoalveolar lavage (BAL) is usually not sufficient for a complete morphological analysis, but can be useful when molecular and immunophenotypic studies are available [57, 58], particularly to exclude an alternative diagnosis. In about two-thirds of patients affected by MALT lymphoma, and in particular in those cases in which computed tomography scans shows alveolar and/or ground-glass opacities, BAL shows lymphocytic alveolitis (lymphocytes >20% total cells), a high percentage of cells expressing a B-phenotype and, in some cases, cytological features consistent with low-grade malignant lymphoma (medium sized lymphoid cells with lymphoplasmocytoid differentiation and irregular nuclear borders). Flow cytometry and immunocytochemical analysis could reveal a monotypic expression of surface light chains (indicating a clonal B-cell proliferation). Recent studies report that genotyping investigation on BAL fluid can contribute to the diagnosis of MALT lymphoma with an even higher sensitivity and sensibility [59]. In different lymphomas, BAL is less sensitive and specific; infrequently, Reed–Sternberg/Hodgkin cells may also be detected.

Endoscopic bronchial or transbronchial biopsies and percutaneous computed tomography-guided core needle biopsies are the most frequently used techniques. Computed tomography imaging plays an important role in directing the bronchoscopist to the appropriate biopsy site and the diagnostic yield of transbronchial biopsy is higher when it targets visible radiographic abnormalities [57]. Fluoroscopy and endobronchial ultrasonography are valuable tools to detect pulmonary masses or consolidations, increasing the diagnostic yield of transbronchial biopsy. However, a histological diagnosis is possible in only 30–50% of patients undergoing transbronchial biopsy due to the absence of specific signs in a large number of those sampled. When a pleural effusion is present, medical thoracoscopy may be diagnostic. When less invasive procedures fail (mostly in non-MALT lymphomas), a definitive diagnosis can be obtained from surgical samples (mostly by video-assisted thoracoscopy and less so by open lung thoracotomy).

Immunohistochemical analysis is mandatory in diagnosing all types of pulmonary lymphomas [4, 48]. Neoplastic lymphocytes are characterised by distinct molecular profiles useful to distinguish pulmonary MALT lymphoma from reactive processes and other lymphomas. The analysis of immunoglobulin light chains (κ and λ) can occasionally provide evidence of clonal expansion, especially in cases with increased secretory differentiation. Neoplastic marginal-zone cells can be characterised by either positive markers (*e.g.* the abnormally expressed CD43 antigen) or by the absence of a variety of relevant markers, including those expressed by follicular lymphoma (CD10$^+$ and bcl-6$^+$), mantle cell lymphoma (CD5$^+$ and cyclin D1$^+$) and lymphocytic leukaemia (CD5$^+$ and CD23$^+$) [59]. Flow cytometry can provide relevant information by revealing the presence of clonal B-cell populations characterised by immunoglobulin light chain restriction, as well as illustrating an antigenic profile compatible with the diagnosis. PCR molecular genetic analysis can provide information regarding the presence of clonal lymphocyte population by investigating rearrangements in either immunoglobulin or T-cell receptor genes. This analysis can be performed, due to its extraordinary sensitivity, on a very small amount of tissue but the possible occurrence of false-negative and false-positive results must be taken into account.

Staging procedures to evaluate the extension of the disease will include a complete physical examination of the patient, laboratory tests (β$_2$-microglobulinaemia, LDH, lymphocytic total count, lymphocyte subsets analysis, and serology for HIV, cytomegalovirus and EBV infection), thoracic, abdominal and pelvic computed tomography scan and bone marrow biopsy. Computed tomography-PET provides morphological and metabolic information increasing the diagnostic accuracy in the initial staging and follow-up of lymphomas, although in low-grade lymphomas, the PET result might be negative; *vice versa*, PET can be positive in lung inflammatory lesions (drug-related lung injury, infections, *etc.*).

References

1   Saltzstein S. Pulmonary malignant lymphomas and pseudolymphomas. Classification, therapy and prognosis. *Cancer* 1963; 16: 928–955.
2   Papaionnaou AN, Watson W. Primary lymphoma of the lung. An appraisal of its natural history and a comparison with other localized lymphomas. *J Thorac Cardiovascular Surg* 1965; 49: 373–387.
3   Addis BJ, Hyiek E, Isaacson PG. Primary pulmonary lymphoma. A re-appraisal of its hystogenesis and its relationship to pseudo lymphoma and lymphoid interstitial peumonia. *Histopathology* 1988; 13: 1–17.
4   Swerdlow SH, Campo E, Harris NL, *et al.*, eds. WHO Classification of Tumours of Hematopoietic and Lymphoid tissues. Lyon, IARC Press, 2008.
5   Nicholson AG, Poletti V, Semenzato G. Lymphoproliferative lung disease. *In:* Gibson J, Geddes D, Costabel U, *et al.*, eds. Respiratory Medicine. 3rd Edn. London, Harcourt Health Sciences, 2003; pp. 1694–1707.
6   Ahmed S, Kussick SJ, Siddiqui AK, *et al.* Bronchial-associated lymphoid tissue lymphoma: a clinical study of a rare disease. *Eur J Cancer* 2004; 40: 1320–1326.
7   Guinee DG, Franks TJ, Gerbino AJ, *et al.* Pulmonary nodular lymphoid hyperplasia (pulmonary pseudo-lymphoma): the significance of increased numbers of IgG4-positive plasma cells. *Am J Surg Pathol* 2013; 37: 699–709.
8   Castleman B, Iverson L, Menendez VP. Localized mediastinal lymphnode hyperplasia resembling thymoma. *Cancer* 1956; 9: 822–830.
9   Herrada J, Cabanillas F, Rice L, *et al.* The clinical behavior of localized and multicentric Castleman disease. *Ann Intern Med* 1998; 128: 657–662.
10   Oksenhendler E, Boulanger E, Galicier L, *et al.* High incidence of Kaposi sarcoma-associated herpes virus-related non-Hodgkin lymphoma in patients with HIV infection and multicentric Castleman disease. *Blood* 2002; 99: 2331–2336.
11   Izumi M, Mochizuki M, Kuroda M, *et al.* Angiomyoid proliferative lesion: an unusual stroma-rich variant of Castleman's disease of hyaline-vascular type. *Virchows Arch* 2002; 44: 400–405.
12   Chadburn A, Abdul-Nabi AM, Teruya BS, *et al.* Lymphoid proliferations associated with human immunodeficiency virus infection. *Arch Pathol Lab Med* 2013; 137: 360–370.
13   Dossier A, Meignin V, Fieschi C, *et al.* Human herpes virus 8-related Castleman disease in the absence of HIV infection. *Clin Infect Dis* 2013; 56: 833–842.
14   De Boer JP, Hiddink RF, Raderer M, *et al.* Dissemination patterns in non-gastric MALT lymphoma. *Haematologica* 2008; 93: 201–206.
15   Zinzani PL, Martelli M, Poletti V, *et al.* Practice guidelines for the management of extranodal non-Hodgkin lymphomas of adult non-immunodeficient patients. Part I: primary lung and mediastinal lymphomas. *Haematologica* 2008; 93: 1364–1371.
16   Thieblemont C, Berger F, Dumontet C, *et al.* Mucosa-associated lymphoid tissue lymphoma is a disseminated disease in one third of 158 patients analyzed. *Blood* 2000; 95: 802–806.
17   Li G, Hansmann ML, Zwingers T, *et al.* Primary lymphomas of the lung: morphological, immunohistochemical and clinical features. *Histopathology* 1990; 16: 519–531.
18   Kurtin PJ, Myers JL, Adlakha H, *et al.* Pathologic and clinical features of primary pulmonary extranodal marginal zone B-cell lymphoma of MALT type. *Am Surg Pathol* 2001; 25: 997–1008.
19   Remstein ED, Dogan A, Einerson RR, *et al.* The incidence and anatomic site specificity of chromosomal translocations in primary extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) in North America. *Am J Surg Pathol* 2006; 30: 1546–1553.
20   Kido T, Yatera K, Noguchi S, *et al.* Detection of MALT1 gene rearrangements in BAL fluid cells for the diagnosis of pulmonary mucosa-associated lymphoid tissue lymphoma. *Chest* 2012; 141: 176–182.
21   Bertoni F, Zucca E. Delving deeper into MALT lymphoma biology. *J Clin Invest* 2006; 116: 22–26.
22   Isaacson PG, Du MQ. MALT lymphoma: from morphology to molecules. *Nat Rev Cancer* 2004; 4: 644–653.

23   Colby TV. Current histological diagnosis of lymphomatoid granulomatosis. *Mod Pathol* 2012; 25: Suppl. 1, S39–S42.
24   Hoshida Y, Tomita Y, Zhiming D, *et al.* Lymphoproliferative disorders in autoimmune diseases in Japan. Analysis of clinicopathological features and Epstein-Barr virus infection. *Int J Cancer* 2004; 108: 443–449.
25   Ochi N, Yamane H, Yamagishi T, *et al.* Methotrexate-induced lymphoproliferative disease: Epstein-Barr virus-associated lymphomatoid granulomatosis. *J Clin Oncol* 2013; 31: e348–350.
26   Dunleavy K, Roschewski M, Wilson WH. Lymphomatoid granulomatosis and other Epstein-Barr virus associated lymphoprolifetive processes. *Curr Hematol Malig Rep* 2012; 7: 208–215.
27   Katzenstein AL, Doxtader E, Narendra S. Lymphomatoid granulomatosis: insights gained over 4 decades. *Am J Surg Pathol* 2010; 34: e35–e48.
28   Yu H, Chen G, Zhang R, *et al.* Primary intravascular large B-cell lymphoma of the lung: a report on one case and review. *Diagn Pathol* 2012; 7: 70–74.
29   Ponzoni M, Ferreri AJ, Campo E, *et al.* Definition, diagnosis, and management of intravascular large B-cell lymphoma: proposals and perspectives from an international consensus meeting. *J Clin Oncol* 2007; 25: 3168–3173.
30   Rodriguez J, Romaguerra JE, Manning J, *et al.* Nasal-type T/NK lymphomas: a clinicopathologic study of 13 cases. *Leuk Lymphoma* 2000; 39: 139–144.
31   Ren YL, Nong L, Zhang S, *et al.* Analysis of 142 Northern Chinese patients with peripheral T/NK-cell lymphomas: subtype distribution, clinicopathologic features, and prognosis. *Am J Clin Pathol* 2012; 138: 435–447.
32   Sverzellati N, Poletti V, Chilosi M, *et al.* The crazy-paving pattern in granulomatous mycosis fungoides: HRCT-pathologic correlation. *J Comput Assist Tomogr* 2006; 30: 843–845.
33   Yousem SA, Weiss LM, Colby TV. Primary pulmonary Hodgkin's disease. *Cancer* 1986; 57: 1217–1224.
34   Radin AI Primary pulmonary Hodgkin's disease, *Cancer* 1990; 65: 550–563.
35   Cartier Y, Johkoh T, Honda O, *et al.* Primary pulmonary Hodgkin's disease: CT findings in three patients. *Clin Radiol* 1999; 54: 182–184.
36   William J, Variakojis D, Yeldandi A, *et al.* Lymphoproliferative neoplasms of the lung. A review. *Arch Pathol Lab Med* 2013; 137: 382–391.
37   Daniels CE, Myers JL, Utz JP, *et al.* Organizing pneumonia in patients with hematologic malignancies: a steroid-responsive lesion. *Respir Med* 2007; 101: 162–168.
38   Wang H, Wu D, Xiang H, *et al.* Pulmonary non-Hodgkin's lymphoma developed during long-term methotrexate therapy for rheumatoid arthritis. *Rheumatol Int* 2012; 32: 3639–3642.
39   Ebeo CT, Girish MR, Byrd RP, *et al.* Methotrexate-induced pulmonary lymphoma. *Chest* 2003; 123: 2150–2153.
40   Jois RN, Gaffney K, Cane P, *et al.* Methotrexate-associated lymphoproliferative disorder masquerading as interstitial lung disease. *Histopathology* 2007; 51: 709–712.
41   Borie R, Wislez M, Thabut G, *et al.* Clinical characteristics and prognostic factors of pulmonary MALT lymphoma. *Eur Respir J* 2009; 34: 1408–1416.
42   Bae YA, Lee KS, Han J, *et al.* Marginal zone B-cell lymphoma of bronchus-associated lymphoid tissue: imaging findings in 21 patients. *Chest* 2008; 133: 433–440.
43   Wislez M, Cadranel J, Antoine M, *et al.* Lymphoma of pulmonary mucosa-associated lymphoid tissue: CT scan findings and pathologic correlations. *Eur Respir J* 1999; 14: 423–429.
44   Watanabe Y, Koyama S, Miwa C, *et al.* Pulmonary mucosa-associated lymphoid tissue (MALT) lymphoma in Sjogren syndrome showing only the LIP pattern radiologically. *Intern Med* 2012; 51: 491–495.
45   Motta G, Conticello C, Amato G, *et al.* Pleuric presentation of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue: a case report and a review of the literature. *Int J Hematol* 2010; 92: 369–373.
46   Zhang WD, Guan YB, Li CX, *et al.* Pulmonary mucosa-associated lymphoid tissue lymphoma: computed tomography and ^{18}F fluorodeoxyglucose-positron emission tomography/computed tomography imaging findings and follow-up. *J Comput Assist Tomogr* 2013; 35: 608–613.
47   Cordier J, Chailleux E, Lauque D, *et al.* Primary pulmonary lymphomas. A clinical study of 70 cases in non-immunocompromised patients. *Chest* 1993; 103: 201–208.
48   Addis BJ. Pulmonary lymphoproliferative diseases. *In:* Hasleton P, Flieder DB, eds. Spencer's Pathology of the Lung. Vol. 2. Cambridge, Cambridge University Press, 2013; pp. 1316–1374.
49   Hare SS, Souza CA, Bain G, *et al.* The radiological spectrum of pulmonary lymphoproliferative disease. *Br J Radiol* 2012; 85: 848–864.
50   Lee JS, Tuder R, Lynch DA. Lymphomatoid granulomatosis: radiologic features and pathologic correlations. *AJR Am J Roentgenol* 2000; 175: 1335–1339.
51   Matsui S, Hebisawa A, Sakai F, *et al.* Immunoglobulin G4-related lung disease: clinicoradiological and pathological features. *Respirology* 2013; 18: 480–487.
52   Rossi G, Marchioni A, Guicciardi N, *et al.* A rare cause of fever and PET-positive nodules in the lungs. *Clin Respir J* 2009; 3: 118–120.
53   Kotake T, Kosugi S, Takimoto T, *et al.* Intravascular large-B cell lymphoma presenting pulmonary arterial hypertension as an initial manifestation. *Intern Med* 2010; 49: 51–54.
54   Souza CA, Quan K, Seely J, *et al.* Pulmonary intravascular lymphoma. *J Thorac Imaging* 2009; 24: 231–233.
55   Wagner T, Brechemier D, Dugert E, *et al.* Diffuse pulmonary uptake on FDG-PET with normal CT diagnosed as intravascular large B-cell lymphoma: a case report and a discussion on the causes of diffuse FDG uptake in the lungs. *Cancer Imaging* 2012; 12: 7–12.
56   Lee BH, Kim SY, Kim MY, *et al.* CT of nasal-type T/NK cell lymphoma in the lung. *J Thorac Imaging* 2006; 21: 37–39.
57   Poletti V, Romagna M, Gasponi A, *et al.* Bronchoalveolar lavage in the diagnosis of low-grade, MALT type, B-cell lymphoma in the lung. *Monaldi Arch Chest Dis* 1995; 50: 191–194.
58   Poletti V, Chilosi M, Olivieri D. Diagnostic invasive procedures in diffuse infiltrative lung diseases. *Respiration* 2004; 71: 107–119.
59   Zompi S, Couderc LJ, Cadranel J, *et al.* Clonality analysis of alveolar B lymphocytes contributes to the diagnostic strategy in clinical suspicion of pulmonary lymphoma. *Blood* 2004; 103: 3208–3215.