

# Primary pulmonary lymphoma

**Author: Professor Jacques Cadranel<sup>1</sup> and Professor Jean-François Cordier**

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<sup>1</sup>Service de Pneumologie et de Réanimation Respiratoire, Hôpital Tenon, 4 Rue de la Chine, 75020 Paris, France. [jacques.cadranel@tnn.ap-hop-paris.fr](mailto:jacques.cadranel@tnn.ap-hop-paris.fr)

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## Abstract

*Primary pulmonary lymphoma (PPL) is defined as a clonal lymphoid proliferation affecting one or both lungs (parenchyma and/or bronchi) in a patient with no detectable extrapulmonary involvement at diagnosis or during the subsequent three months. This definition includes: multifocal mucosa-associated lymphoid tissue (MALT) non Hodgkin lymphoma (NHL); pulmonary lymphoma with satellite nodes (hilar or mediastinal); low-grade B-cell PPL; high-grade B-cell PPL. Nearly half of the patients are asymptomatic at diagnosis and are identified incidentally on the basis of a radiological pulmonary anomaly. When present, symptoms are non specific, such as cough, mild dyspnea, chest pain and occasionally hemoptysis. At pulmonary auscultation crackles are present in less than 20% of cases. No triggering antigens have so far been identified in the lung. PPL is very rare. While extranodal forms represent 24 to 50% of cases of NHL, PPL represents only 3 to 4% of extranodal NHL, less than 1% of NHL, and only 0.5 to 1% of primary pulmonary malignancies. There is no consensus on treatment. Current treatment options are surgery, chemotherapy and radiotherapy. Surgical resection is commonly preferred for localized tumors. Exclusive chemotherapy is generally used for patients with bilateral or extrapulmonary involvement, relapse or progression; combination regimens such as CHOP (cyclophosphamide, adriamycin, vincristine and prednisone) have not proven more effective than single-agent regimens with chloraminophene, cyclophosphamide, azathioprine or steroids.*

## Keywords

primary pulmonary lymphoma, mucosa-associated lymphoid tissue (MALT), lymphomatoid granulomatosis

## Diagnosis criteria and definition

Primary pulmonary lymphoma (PPL) is defined as a clonal lymphoid proliferation affecting one or both lungs (parenchyma and/or bronchi) in a patient with no detectable extrapulmonary involvement at diagnosis or during the subsequent three months (1). When the lung is the principal tumor site, this definition also includes:

- i) multifocal mucosa associated lymphoid tissue (MALT) non Hodgkin lymphoma (NHL)
- ii) pulmonary lymphoma with satellite nodes (hilar or mediastinal).

The current definition of PPL covers:

- 1) low-grade B cell PPL [PPL-B], it is the most frequent form,
- 2) high-grade PPL-B.

**Disease name and synonyms**

Low-grade PPL-B corresponds to lymphoma and also to most disorders formerly called "pseudolymphoma" as routine use of sensitive immunohistochemical techniques (2-9) and molecular biology-based methods (9) in fact showed their lymphomatous nature. These lymphomas are subdivided as follows: lymphocytic, diffuse with small lymphocytes, mixed diffuse, or diffuse with small cleaved cells in the Working formulation; lymphocytic, lymphoplasmocytic, centrocytic, centroblastic/centrocytic diffuse in the Kiel classification (2-9) ; and MALT lymphoma in the REAL classification (10). In the latest classification (WHO classification) (11) MALT lymphomas belong to the marginal zone lymphomas but are distinguished from nodal and splenic forms by their different clinical behavior and cytogenetic characteristics (11). However, some cases of low-grade PPL-B do not correspond to the definition of MALT-type NHL and high-grade PPL-B has also been described (1).

**Prevalence**

PPL is very rare. While extranodal forms represent 24 to 50% of cases of NHL (1), PPL represent only 3 to 4% of extranodal NHL, less than 1% of NHL, and only 0.5 to 1% of primary pulmonary malignancies (1, 2).

**Low-grade PPL-B****Prevalence**

Low-grade NHL-B accounts for 58 to 87% of cases of PPL in pathology series (2,4,7,9); nearly 90% of these cases correspond to MALT-type NHL (4,7,9). Age of onset is approximately 50 to 60 years, with subjects under 30 rarely affected (2,3,5,8,13). The two sexes are equally affected (2,3,5,6,8,13).

**Clinical description**

Nearly half of the patients are asymptomatic at diagnosis, and are identified incidentally on the basis of a radiological pulmonary anomaly (2,3,5,6,13). When present, symptoms are non specific, such as cough, mild dyspnea, chest pain and occasionally hemoptysis. At pulmonary auscultation crackles are present in less than 20% of cases (13). By definition, extra-pulmonary manifestations are limited to general signs (fever and weight loss) and occur in less than one quarter of patients (2,3,5,6,13). The usual radiological aspect is a localized alveolar opacity, with an air bronchogram (5,6,13) in nearly 50% of cases. Computed tomography,

which is more sensitive than standard radiography, has demonstrated that the lesions are usually bilateral and multiple (14,15). Nearly all these lesions contain an air bronchogram or clear areas corresponding to an intact bronchial lumen. Less than 10% of patients have bilateral diffuse reticulonodular opacities, atelectasia or pleural effusion (5,6,13); computed tomography can reveal hilar and mediastinal adenopathies (13).

**Diagnostic methods**

The diagnosis of MALT-type NHL is based on histological examination of surgical samples or less frequently bronchial, transbronchial or transthoracic biopsy material.

Bronchial endoscopy is usually normal (13), although abnormalities ranging from mucosal inflammation to bronchial stenosis can be observed (13). The value of bronchoalveolar lavage (BAL) for the diagnosis of PPL has not been adequately assessed. B-cell lymphocytic alveolitis is particularly valuable when its clonal nature can be demonstrated by the detection of immunoglobulin (Ig) gene clonal rearrangements using molecular biology-based methods (Southern blot or RT-PCR) (16-20). Screening for monoclonal Ig in the BAL supernatant by immunoelectrophoresis (13), and restricted membranous or intracytoplasmic Ig light-chain expression by slide immunohistochemistry or flow cytometry (21) may be useful for diagnosis. Microscopically, MALT-type PPL is defined as a lesion containing (3,5,7,9):

- 1) proliferation of small lymphoid cells analogous to marginal zone cells of Peyer's patches or spleen follicles, centrocyte-like cells and small lymphocytes, plasmocytes or monocytoid cells;
- 2) a lymphoepithelial lesion showing lymphoid cell migration from the marginal zone to the bronchiolar epithelium;
- 3) reactive follicular hyperplasia;
- 4) rare blastic cells. More unusual features include amyloid deposits and granulomatous foci. Various degrees of fibrosis can be found.

Lymphomatous infiltration causes smooth or nodular interstitial thickening with a peribronchovascular distribution (4).

Immunohistochemical analysis shows the B-cell phenotype (CD19, CD20) (2-9) and clonal nature (7,9) of the lymphoid infiltrate. Immunohistochemical tests can rule out low-grade lymphoma (centrofollicular NHL-B, mantel NHL-B and LLC-type lymphoma) by showing the lack of CD5 and CD10 surface antigens (4,9,22). Using an Ig heavy-chain gene target sequence

(Fr3/JH), the monoclonal nature of the proliferation was shown in 12 out of 20 samples of MALT-type PPL (9). The absence of a dominant B-cell clone detection in BAL fluid could help to dismiss invasive investigations of pulmonary lesions. The detection of a dominant B-cell clone would lead to the performance of a pulmonary biopsy to get histologic diagnosis in primary pulmonary lymphoma and, by contrast, would avoid the need for biopsy in the setting of a secondary pulmonary lymphoma (32).

### **Differential diagnosis**

Radiological identification of a chronic localized or diffuse alveolar or interstitial opacity covers a wide range of etiologies (especially bronchiolo-alveolar carcinoma, organizing pneumonia). Histologically, especially when the sample is small, the main difficulty is to distinguish MALT-type NHL from diffuse lymphoid hyperplasia or interstitial lymphoid pneumonia, and follicular bronchitis (23). Occasionally extrinsic allergic alveolitis may be considered. Some other nodular pulmonary lesions may also have a lymphoid contingent, such as plasmacyte granuloma, inflammatory pseudotumors, fibrous histiocytoma, pulmonary hyalinizing granuloma, intrapulmonary adenopathies, and Castleman's disease (23).

### **Management and treatment**

Nodal lymphoma is ruled out by physical examination and abdominal and thoracic CT with contrast enhancement. Bone marrow biopsy is also crucial, excluding bone marrow involvement in the majority of patients (24-26). The search for other mucosal sites includes ophthalmological and ENT (ear, nose, throat) examinations (with MRI or CT of the salivary and lacrimal glands if necessary), plus upper gastrointestinal endoscopy (and coloscopy plus small-intestinal transit, according to some authors) (24-26). The only useful laboratory tests in the pretreatment work-up are serum electrophoresis and immunoelectrophoresis (24-26).

The outcome of MALT-type PPL is favorable in most series, with a 5-year survival rate exceeding 80% and a median survival time of more than 10 years (2,3,5,7,13). Long-term follow-up is necessary, owing to the frequency of late local or extrathoracic relapse after surgical resection (almost 50% of patients after more than 2 years) (2,3,8,13). No clear prognostic factors have been identified in MALT lymphoma. Some authors have suggested that low-grade PPL may transform into high-grade proliferation, based on the existence of mixed forms or transitional forms identified by serial biopsy

(2,4,7,9). This conflicts with recent studies showing differences between the cytogenetic abnormalities of low-grade and high-grade PPL (27).

There is no consensus on treatment. Current treatment options are surgery, chemotherapy and radiotherapy. The respective efficacy of these treatments cannot be analyzed, however, owing to a lack of comparative series; some authors even propose simple clinical monitoring (3). Nevertheless, surgical resection is commonly preferred for localized tumors (2,3,6-8). Exclusive chemotherapy is generally used for patients with bilateral or extrapulmonary involvement, relapse or progression; combination regimens such as CHOP have not proven more effective than single-agent regimens with chloraminophene, cyclophosphamide, azathioprine or steroids (3,6). Radiotherapy is little used (2,3,6,7).

### **Etiology and unresolved question**

The stomach which is the most frequent site of MALT lymphoma might serve as a model for pulmonary MALT lymphoma. As in the stomach, MALT is absent from the lung in physiological circumstances. During chronic antigenic stimulation (by *Helicobacter pylori*, for example), MALT can develop in the stomach and undergo secondary lymphomatous transformation arising from marginal zone B cells. In order to develop, the malignant B cell clone requires the presence of T cells specifically directed against *Helicobacter pylori* antigens. *Helicobacter pylori* eradication can lead to lengthy complete remission of gastric lymphoma (28). However, no triggering antigens have so far been identified in the lung, but chronic antigenic stimulation in certain autoimmune disorders (systemic lupus erythematosus, multiple sclerosis, Hashimoto's thyroiditis and especially Sjögren's syndrome) might play a role in the onset of pulmonary MALT lymphoma (28).

To date, three recurrent structural chromosomal abnormalities have been described in MALT lymphoma. The first, t(11;18)(q21;q21), is thought to be the most common being present in 20-50% of cases. t(11;18) has been shown to be prognostically and therapeutically significant in gastric MALT lymphomas, being associated with tumors that extend deeply into the gastric wall and/or disseminate beyond the stomach, and also being associated with gastric MALT lymphomas that are *Helicobacter pylori*-negative or fail to respond to *H. pylori* eradication therapy. Aneuploidy, particularly trisomy 3, 7, 12, and/or 18, is also common in MALT lymphoma but is rarely associated with t(11;18), suggesting that

MALT lymphomas with t(11;18) and those with aneuploidy develop along different pathogenetic pathways. Two other chromosomal structural abnormalities were recently identified: t(14;18)(q32;q21) and t(1;14)(p22;q32). It has been suggested that all they potentiate MALT lymphoma progression by upregulating the NF-kappa B signal transduction pathway (34). These abnormalities are more frequently observed in lung MALT lymphomas than in stomach that suggests two different diseases triggered by different factors.

### Other forms of B-cell PPL

#### **Other low-grade forms of B-cell PPL**

In less than 10% of cases, low-grade PPL-B does not meet the histologic criteria of MALT-type NHL. According to the WHO classification (10), these cases can correspond to follicular or mantle lymphocytic NHL or LLC. The clinical and pulmonary radiological aspects are similar to those of MALT-type PPL (4,7).

#### **High-grade PPL-B**

High-grade NHL-B represents 11 to 19% of cases of PPL in published series (4,7,9). High-grade NHL-B often occurs in patients with underlying disorders, such as solid organ (heart/lung) transplantation (29), HIV infection (30) and Sjögren's syndrome (31). Epstein-Barr virus has been implicated in the onset of some of these high-grade NHL affecting the lung (29). The incidence of high-grade B-cell PPL may have been underestimated as they spread rapidly into mediastinal and extra-thoracic locations. It has been observed that in 50% of cases they can coexist with MALT, B-cell lymphomas (33). Patients are usually symptomatic, with respiratory manifestations, fever and weight loss (2,7,13). Radiological investigations usually show a single pulmonary mass or atelectasia; pleural effusion is often present too (2,7,13). When a radiographic image shows cavitated pulmonary mass, the possibility of a high-grade B-cell primary PPL has to be considered in the differential diagnosis whether or not there is an underlying disease involving autoimmunity or immunodepression (33). Bronchial endoscopy is often abnormal, with budding or infiltrative stenosis with a tumoral aspect (2,13). The histologic diagnosis is generally easy, even with very small samples (bronchial, transbronchial or transthoracic biopsy). Most cases are immunoblastic and centroblastic NHL (2,4,7,9,13).

Survival is much poorer in high-grade PPL than in low-grade PPL, and survival is lower in

patients with underlying disorders (HIV infection, transplantation...). Treatment after surgical resection is usually based on the combination chemotherapy regimens used for high-grade nodal NHL (2,13).

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