

# Primary Pulmonary Lymphoma: Current Status

Luciano Wannesson, Franco Cavalli, Emanuele Zucca

## Abstract

Primary pulmonary lymphoma (PPL) is a rare disease with a favorable prognosis compared with lung cancer. Although a number of histologic variables of B- and T-cell lymphoma were reported as PPL, marginal zone lymphoma of the mucosa-associated lymphoid tissue type is by far the most frequent diagnosis. This review summarizes the present knowledge of histopathology, molecular biology, diagnosis, prognosis, and treatment of this heterogeneous entity.

*Clinical Lymphoma & Myeloma*, Vol. 6, No. 3, 220-227, 2005

**Key words:** Extranodal lymphoma, Indolent lymphoma, Marginal zone lymphoma, Mucosa-associated lymphoid tissue

## Introduction

Primary pulmonary lymphoma (PPL) is a rare disease that encompasses a histologic spectrum of lymphomas. It accounts for < 1% of all pulmonary neoplasms and all extranodal non-Hodgkin's lymphomas (NHLs) as well.<sup>1,2</sup> The peak incidence is in the sixth decade of life, with a slight predominance in men.<sup>3</sup> The prognosis of most PPLs is favorable in comparison with other lung tumors and does not depend on disease resectability. Therefore, it is important that clinicians and pathologists consider the possibility in the diagnostic workup of any new pulmonary tumor in order to avoid unnecessary invasive procedures.

The purpose of this review is to define PPL as NHL involving the parenchymal lung tissue and describe most relevant issues related to lymphoma of the lung as histologic variants, molecular biology, diagnostic approaches, prognosis, and treatment results.

## Histopathology

The most common histologic type of PPL is constituted by lymphomas arising from the mucosa-associated lymphoid tissue (MALT). Mucosa-associated lymphoid tissue is normally present in the intestine in the form of Peyer's patches, but it does not exist in the normal bronchial mucosa. Nevertheless, lymphoid aggregates can develop in the lung, and the condition is known as follicular bronchiolitis, often found in association with Sjögren syndrome.<sup>4</sup> Analogous to the stomach (*Helicobacter pylori gastritis*) and the salivary gland (myoepithelial sialadenitis), acquired

MALT can be present in the lung under certain conditions. The World Health Organization classification of tumors of lymphoid tissues assigns MALT lymphoma the term "Extranodal Marginal Zone Lymphomas of MALT-type."<sup>5</sup> In 2 retrospective surveys on 48 and 70 cases of PPL, respectively, this histology was found in 73% of the patients.<sup>3,6</sup> Herbert et al first described this entity in the lung in 1984.<sup>7</sup> The tumor cells can resemble germinal center centrocytes or small lymphocytes, or they can assume a monocytoid appearance. Scattered transformed blasts are common and can cause problems in the grading. An important feature of MALT lymphomas is the presence of lymphoepithelial lesions formed by the invasion of mucosal individual glands by aggregates of lymphomatous B-cells. The presence of scattered blasts, plasma cell differentiation, nonneoplastic reactive follicles, and follicular colonization suggests that these cells might be participating in an immune response. Mucosa-associated lymphoid-tissue lymphoma immunoglobulin (Ig) heavy- and light-chain genes are rearranged and show somatic mutation of their variable regions consistent with a postgerminal center memory B-cell derivation.<sup>8</sup> These lymphomas share the cytologic features and immunophenotype CD20, CD21, CD35, CD79a, and Igs (usually IgM) of marginal zone B cells, considering their normal counterpart.<sup>9</sup> CD43 and CD11c could have a weak expression, whereas CD5, CD10, CD23, and IgD are negative.<sup>10</sup> Histologic transformation of pulmonary MALT lymphomas into high-grade tumors has been reported in approximately 15% of cases.<sup>6</sup> A variable rate of scattered large cells represents a common feature in MALT-type lymphomas; nevertheless, when large cells are disposed in clusters or sheets, it suggests the emergence of the transformation into high-grade histology. Different steps of transformation can be found ranging from sheets and clusters of blasts in a small lymphocytic background to a diffuse infiltrate of large B cells that can be difficult to distinguish from primary diffuse large B-cell lymphoma (DLBCL).<sup>10</sup>

Department of Medical Oncology, Institute of Southern Switzerland, Bellinzona, Switzerland

Submitted: Apr 29, 2004; Revised: Aug 12, 2004; Accepted: Aug 16, 2004

Address for correspondence: Emanuele Zucca, MD, Department of Medical Oncology, Institute of Southern Switzerland, Ospedale San Giovanni, CH-6500 Bellinzona, Switzerland  
Fax: 419-1811-9182; e-mail: IELSG@ticino.com

Electronic forwarding or copying is a violation of US and International Copyright Laws. Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Cancer Information Group, ISSN #1526-9655, provided the appropriate fee is paid directly to Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923 USA 978-750-8400.

A number of other B-cell histologies were occasionally found in PPL, including DLBCL,<sup>6,11</sup> follicular lymphoma (FL),<sup>6</sup> lymphoplasmacytic lymphoma,<sup>6,12</sup> and mantle cell lymphoma.<sup>12</sup> In 1 case of plasmablastic PPL, a histologic subtype that usually arises in the oral cavity in patients who are positive for human immunodeficiency virus (HIV) was described. This rare entity had a diffuse growth pattern strongly expressed in CD138 and VS38c and was predominantly IgG-positive. A subpopulation of neoplastic cells was stained positive for CD43 and epithelial membrane antigen, whereas other B- or T-cell markers, Bcl-2, cyclin D1, IgM, IgD, and keratin were negative.<sup>13</sup>

Rush et al reported a series of 5 patients with primary pulmonary anaplastic large-cell lymphoma.<sup>14</sup> All cases were CD30+ and CD15-. The immunophenotypes were T cells in 3 cases and null phenotypes in 2 cases. Unfortunately, the authors of this report were not able to assess the presence of the nucleophosmin-anaplastic lymphoma kinase fusion protein. Unilateral lung lesions were present in 3 cases, whereas diffuse bilateral involvement was evident in 1 patient with an underlying symptomatic HIV infection. The fifth case had an intratracheal mass as the sole site of involvement. The behavior of this disease is aggressive, but it can be cured with chemotherapy or chemoradiation therapy in approximately 60% of cases. In addition, peripheral T-cell PPL and natural killer (NK) cells derived from large granular lymphocyte lymphomas were also described in the medical literature as case reports or as part of a case series.<sup>6,15-17</sup>

## Pathophysiology

Because PPL is a heterogeneous disease, the description of the pathophysiologic mechanisms leading to every histologic subtype would be very extensive, exceeding the purpose of this review. For practical reasons we will focus this section on the pathophysiology of pulmonary MALT lymphoma.

### Molecular Biology of MALT-Type Pulmonary Lymphomas

Most B-cell lymphomas are associated with single, specific nonrandom chromosomal translocations involving definite oncogenes. Usually, the coding domains of these genes are not affected by the translocations, but their pattern of expression is deregulated by the juxtaposition of regulatory sequences from the partner chromosomes, most often the Ig heavy-chain loci in 14q32 (Table 1).

Curiously, the extranodal marginal zone lymphomas represent the unique condition in which 3 different chromosomal translocations involving different mechanisms of oncogene deregulation appear to lead to the same disease.<sup>18</sup>

### Structural Chromosomal Abnormalities: Translocations and Fusion Proteins

Three chromosomal translocations were found to be specific of MALT lymphoma with different incidences depending on primary organ involvement: t(11;18), t(14;18), and t(1;14); they appear to be mutually exclusive (Figure 1). Rare cases carrying other translocations have also been described.

**t(11;18)(q21;q21).** The t(11;18)(q21;q21) translocation is

**Table 1 Nonrandom Translocations in B-Cell Non-Hodgkin's Lymphoma**

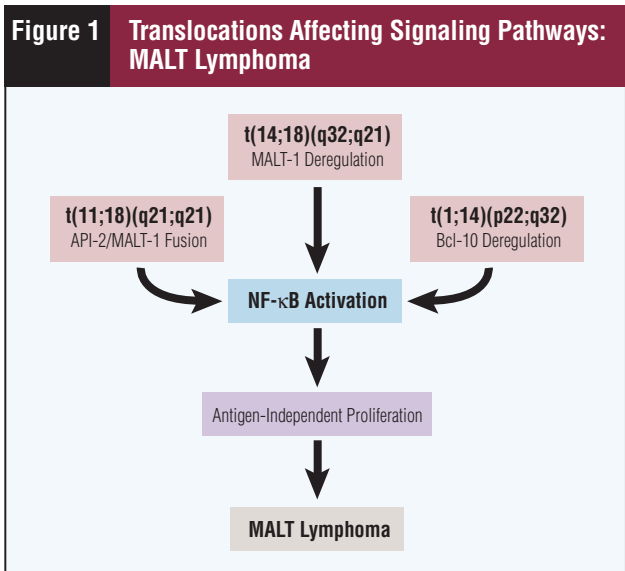
Lymphoma Type	Chromosomal Alteration	Oncogene Involved	Mechanism of Oncogene Activation
Lymphoplasmacytic	t(9;14)(p13;q32)	<i>PAX-5</i>	Transcriptional deregulation
Follicular	t(14;18)(q32;q21)	<i>bcl-2</i>	Transcriptional deregulation
MALT	t(11;18)(q21;q21)	<i>API-2/MALT-1</i>	Fusion protein
	t(14;18)(q32;q21)	<i>MALT-1</i>	Transcriptional deregulation
	t(1;14)(p22;q32)	<i>bcl-10</i>	Transcriptional deregulation
Mantle Cell	t(11;14)(q13;q32)	<i>bcl-1</i>	Transcriptional deregulation
DLBCL	3q27 Translocations	<i>bcl-6</i>	Transcriptional deregulation
Burkitt's	t(8;14)(q24;q32)	<i>c-MYC</i>	Transcriptional deregulation

the most common chromosomal aberration found in MALT lymphoma, with approximately 50% of incidence in cases presenting an abnormal karyotype.<sup>19,20</sup> In a survey that screened 417 cases of MALT lymphoma for t(11;18), its incidence was the highest in the lung (38%), followed by the stomach (24%), conjunctiva (19%), and orbit (14%).<sup>21</sup>

This translocation generates the fusion of *API-2* at 11q21 (a gene that belongs to the family of inhibitors of apoptosis proteins) with *MALT-1* at 18q21 (a gene of the paracaspases family that contains Ig-like domains). It codifies the chimeric gene *API-2/MALT-1* that was initially considered to contribute to lymphomagenesis through increased inhibition of apoptosis (deregulation of the *API-2* component), and, on one hand,<sup>22,23</sup> it was demonstrated that the fusion protein activates the nuclear factor-κB (NF-κB), leading to antigen-independent B-cell proliferation. The induction of NF-κB by the *MALT-1* component was described by Lucas et al and implies a gain-of-function of the caspase-like domain of the *MALT-1* gene product, otherwise unable to activate NF-κB in its wildtype.<sup>24</sup> Indeed, *MALT-1* under physiologic conditions binds Bcl-10. An association of t(11;18) with a pattern of moderate Bcl-10 nuclear overexpression by immunohistochemistry has been described and could be used as a surrogate marker of the presence of t(11;18).<sup>21,25</sup>

In the great majority of cases in which t(11;18) is present, it constitutes the only karyotype aberration, thus suggesting a likely relevant pathogenic role.

An interesting observation was made by Rosenwald et al, who screened 106 patients with NHL by interphase cytogenetics using yeast artificial chromosome and probes to determine the prevalence of t(11;18). The translocation was observed in 9 of 33 patients (27%) with MALT lymphomas, but none of the 32 primary and secondary high-grade extranodal lymphomas studied suggested that MALT lymphomas presenting the t(11;18) were at least unlikely to transform into high-grade tumors.<sup>26</sup>



Translocations are mutually exclusive. All of them lead to abnormal activation of the NF-κB in an antigen-independent manner by different pathophysiologic mechanisms. B-cell proliferation overwhelms apoptosis, resulting in neoplastic growth. The t(11;18) is the only example of a fusion protein (API-2/MALT-1) involved in the pathogenesis of a B-cell lymphoma.

Okabe et al screened 51 cases of pulmonary MALT lymphoma in archival paraffin sections for API-2/MALT-1 fusion by reverse-transcriptase (RT) polymerase chain reaction (PCR), and the transcript was detected in 41% of the samples. Its presence appeared associated with the absence of underlying autoimmune diseases, a normal lactate dehydrogenase (LDH) level, a typical histology without plasmacytic differentiation or increased number of large cells, and a moderate nuclear Bcl-10 expression.<sup>27</sup>

To explain the higher incidence of t(11;18) at specific organ sites, it has been hypothesized that the nature of premalignant disease preceding MALT lymphoma might influence the process of lymphomagenesis. In gastric MALT lymphoma, the t(11;18) is significantly associated with infection by a CagA-positive *H. pylori* strain that is very potent in inducing inflammatory responses, including the activation of neutrophils.<sup>21</sup> This suggests that substances with genotoxic potential, such as bacterial toxins or the oxidative products of neutrophils, are implicated. Follicular bronchiolitis is a disease often characterized by suppurative exudates in the bronchiolar lumina and neutrophils in the adjacent alveoli. It is frequently associated with acquired MALT lymphoma in the lung parenchyma and could constitute a premalignant lung condition in which genotoxic factors might well be involved in the lymphocyte neoplastic transformation.<sup>21,22,28</sup>

**t(14;18)(q32;q21).** The great majority of translocations between chromosomes 14 and 18 are detected in FL and DLBCL, in which they are characterized by a juxtaposition of the *IgH* gene on 14q32 with the antiapoptotic *bcl-2* gene on 18q21. The translocation of Bcl-2/IgH, is directly implicated in the pathogenesis of both types of lymphoma. Nevertheless, *bcl-2* is not the sole gene present in 18q21; *MALT-1* shares the same location in a site closer to the centromer. A t(14;18)(q32;q21) translocation in which MALT-1 appears to be deregulated by its

juxtaposition to the *IgH* locus has recently been independently reported by 3 groups.<sup>11,29,30</sup> This is identical to the t(14;18) involving *IgH* and Bcl-2 in FLs at conventional cytogenetic analysis, becoming evident only by fluorescence in situ hybridization (FISH) and PCR. In the report by Streubel et al, 12 patients were positive for the *IgH/MALT-1* fusion.<sup>29</sup> The distribution was in the liver (4 of 4), ocular adnexa (3 of 8), skin (3 of 12), and salivary gland (2 of 11), with no cases among 7 pulmonary MALT lymphomas. In all t(14;18)-positive cases, the t(11;18) was negative by RT-PCR, but 3 and/or 18 trisomy were associated in 4 of them. In a recent series of 28 cases with primary pulmonary MALT-type lymphoma by Remstein et al, 75% of patients presented with a cytogenetic abnormality.<sup>30</sup> One quarter of them had API-2/MALT-1 fusion without any concomitant aneuploidy. Three patients (11%) had *IgH/MALT-1* fusion, with 2 of them also showing 3 and 12 trisomy. A total of 11 patients (39%) had aneuploidy only, with 3 and 18 trisomy being the most common. Of the 3 cases carrying this *IgH/MALT-1* translocation reported by Sánchez-Izquierdo, all showed complex karyotypes with additional abnormalities, and, in 2 of them, the lymphoma was disseminated at multiple extranodal sites, including the lung.<sup>11</sup> It can be concluded that API-2/MALT-1 and *IgH/MALT-1* are mutually exclusive, and additional karyotype anomalies can be present in the latter but are rare in the former.

**t(1;14)(p22;q32) and Bcl-10 Mutations.** The incidence of t(1;14) in MALT lymphomas is low but recurrent and was described in primary lung cases as well. It involves the *bcl-10* gene locus in 1p22 upstream to the promoter. Wildtype Bcl-10 is a protein of 233 amino acids with caspase-recruiting domains that weakly promote apoptosis by activating caspase-9. More recently, it has been shown that this protein promotes cell proliferation by the activation of NF-κB. Bcl-10 mediates the oligomerization of the MALT-1 caspase-like domain, and it is this event that permits the activation of NF-κB. When t(1;14) occurs, it generates a truncated Bcl-10 in its carboxyl terminal domain; this mutation can activate NF-κB but is unable to induce apoptosis.<sup>24,31,32</sup>

#### Other Karyotype Abnormalities

A case of MALT lymphoma showing t(1;2)(p22;p12) was reported by Achuthan et al.<sup>33</sup> The translocation was shown to involve the *bcl-10* gene and the immunoglobulin-κ light-chain locus by FISH. A complex variant of t(11;18) was reported in a single case of primary pulmonary MALT lymphoma involving chromosomes 11, 12, and 18 [t(11;12;18)(q13;q13,q12)].<sup>34</sup>

**Numeric Chromosomal Aberrations.** Numeric chromosomal aberrations are common but not specific for MALT lymphoma and are the genetic aberration first described as being recurrent and associated with the disease. A survey that analyzed 70 archival cases (paraffin-embedded tissue) of MALT lymphomas from various sites by FISH included 7 cases of pulmonary primary site.<sup>35</sup> Among the entire population, 60% had trisomy of chromosome 3 (+3), 21% had trisomy 18 (+18), 13% had trisomy 12 (+12), and

**Table 2** Clinical Findings and Diagnostic Procedures for Primary Pulmonary Lymphoma<sup>3,6,14,38,39</sup>

Lymphoma Type	Number of Patients (%)				
	Cordier et al <sup>3</sup> (1993; N = 70)	Ferraro et al <sup>6</sup> (2000; N = 48)	Rush et al <sup>14</sup> (2000; N = 5)	Turner et al <sup>38</sup> (1984; N = 47)	Zinzani et al <sup>39</sup> (2003; N = 12)
<b>Lymphoma Type</b>					
MALT-type	51 (73)	28 (58)	–	47* (100)	12 (100)
Other low-grade	10 (14)	2 (4)	–	–	–
High-grade	9† (13)	17 (36)	5 (100)	–	–
<b>Mode of Presentation</b>					
Pulmonary	9 (13)	16 (33)	–	14 (30)	6 (50)
Systemic	26 (37)	10 (21)	1 (20)	2 (4)	–
Pulmonary and systemic	8 (11)	4 (8)	4 (80)	–	–
Asymptomatic	27 (39)	18 (38)	–	25 (53)	6 (50)
<b>Radiographic Pattern</b>					
Solitary nodules	43 (61)	6 (13)	1 (20)	16 (34)	5 (42)
Multiple nodules	16 (23)	20 (42)	4 (80)	11 (23)	–
Mass	‡	29 (60)	–	§	–
Infiltrates/consolidation	7 (10)	41 (86)	–	15 (32)	7 (58)
Thoracic nodes	–	15 (31)	–	–	–
Pleural effusion	6 (9)	7 (15)	–	2 (4)	–
Atelectasis	3 (4)	–	–	–	–
<b>Tissue Sampling</b>					
Transbronchial biopsy	2 (3)	7 (15)	NS	NS	6 (50)
Transthoracic biopsy	1 (1.4)	–	NS	NS	1 (8)
Thoracoscopic biopsy	–	4 (8)	NS	NS	–
Open Thoracotomy	62 (89)	43 (90)	NS	NS	5 (42)

Abbreviation: NS = not specified

\*Number not specified.

†All patients were symptomatic.

‡No distinction between mass and nodule was established.

§Described in the article as well-differentiated lymphocytic lymphoma.

3% had trisomy 7 (+7). All 7 cases of pulmonary primary had trisomies: 4 had trisomy 3, 3 had trisomy 18, and 2 had trisomy 12. These specific abnormalities and their frequency of occurrence were confirmed in other studies performed in gastric and nongastric extranodal MALT lymphomas.<sup>36,37</sup>

**Gene Amplifications.** Genomic amplification of MALT-1 has been reported as a possible additional mechanism of MALT-1 activation in MALT lymphomas, but it has not yet been described in pulmonary cases.<sup>11</sup>

## Diagnosis

### Clinical Findings

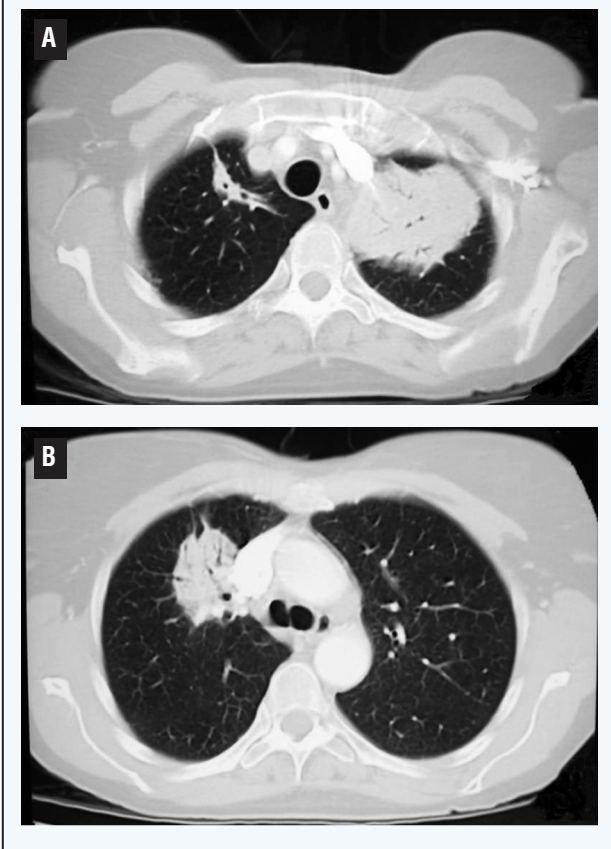
Primary pulmonary lymphoma exhibits 2 major modalities of clinical presentation: one is the incidental detection of a pulmonary lesion on a screening chest radiograph performed for a routine health examination of an asymptomatic patient; the other is with pulmonary and/or systemic symptoms. Although low-grade lymphomas can present in both fashions, the more aggressive

histologies do so with symptoms in the great majority of cases. In fact, in a series of 5 patients, the fifth patient had symptoms related to an underlying HIV infection.<sup>14</sup> Furthermore, several cases of PPL with a range of high-grade histologies published in the literature (angiocentric T-cell, NK-derived large granular lymphocyte, plasmablastic, and diffuse large B-cell lymphomas) presented almost exclusively with pulmonary and/or systemic symptoms.<sup>15-17</sup> On the other hand, if we analyze 2 case series that included 47 patients and 12 patients with exclusively low-grade PPL, the rate of asymptomatic presentations increased to 50% in both studies, with the remaining 50% evidencing nonspecific pulmonary symptoms.<sup>38,39</sup> In a series with a mixed population of 48 patients (low-grade lymphomas 62% and high-grade 36%), the initial symptoms were pulmonary in 33% of patients, systemic in 21%, or both in 8% of cases.<sup>6</sup> The remaining 38% of patients were asymptomatic at diagnosis. In order of frequency, these symptoms were cough, fatigue, weight loss, fever, dyspnea, hemoptysis, diaphoresis, and chest pain (Table 2).<sup>3,6,14,38,39</sup>

Sometimes the detection of a concomitant paraprotein can



**Figure 2** Computed Tomography Scan of a Patient with Multifocal Pulmonary MALT Lymphoma



Staging chest CT scan of a 69-year-old woman with MALT lymphoma of the left conjunctiva showing 2 asymptomatic lung masses. Mucosa-associated lymphoid-tissue lymphoma was confirmed in tissue samples from both lesions obtained by transbronchial biopsy. (A) A solid mass with an air bronchogram in the left apex and the upper extension of a lesion in the right lung, with the typical pattern of peribronchovascular thickening. (B) The lower portion (parahilar) of the right lung mass, also showing an air bronchogram.

suggest a lymphoproliferative origin of the pulmonary disease before a biopsy is preformed. An IgM monoclonal gammopathy is the most commonly found; IgG and IgA monoclonal gammopathies are the next most common.<sup>3,38</sup>

### Imaging

The disease presentation pattern in chest radiographs is somewhat variable and can show a mass, a solitary nodule, multiple nodules, and localized or diffuse bilateral infiltrates. A pleural effusion can be found (Table 1).<sup>3,6,14,38,39</sup>

Computed tomography (CT) scans confirm the findings of chest radiographs and, in this case of MALT-type PPL, allow a better characterization of a typical pattern—the peribronchial thickening (Figure 2). Hilar or mediastinal lymphadenopathy of variable size can also be found on CT scans.<sup>40</sup>

In accordance with these concepts are the results of a retrospective survey by King et al that assessed the imaging features of MALT-type PPL.<sup>41</sup> The chest radiographs (n = 18) and CT scans (n = 17) of 24 patients with a known diagnosis of MALT-type PPL were reviewed. Multiple pulmonary lesions were

identified in 19 of 24 patients (79%), solitary lesions in 4 of 24 patients (17%), and diffuse pulmonary infiltration was present in 1 patient. Lesions included masses or mass-like areas of consolidation (n = 21) and pulmonary nodules (n = 18). Associated findings were air bronchograms, airway dilatation, a positive angiogram sign, and a halo of ground glass shadowing at lesion margins. Peribronchovascular thickening was also observed, as were hilar or mediastinal lymph node enlargement and pleural effusions or thickening.

**Positron Emission Tomography.** Positron emission tomography (PET) is a functional imaging technique that uses the glucose-analogue radio-labeled positron emitter fluorine-18 to evaluate glycolytic activity, which is greater in malignancies than in normal tissues.<sup>42</sup> For diagnostic and staging purposes PET has only intermediate efficacy in cases of MALT lymphoma (50%-90% positive results rate); therefore, this tool has no role in the majority of cases of PPL at present. Moreover, PET scans have not been determined as useful for the assessment of prognosis of this histologic variant.

The case of aggressive lymphoma is different because PET is a reliable technique for diagnosis and staging purposes (> 90% positive results rate). In addition, in the setting of the assessment of prognosis, the use of PET scans is increasing because the progression-free survival (PFS) rate correlates with PET scans after the completion of 1 cycle of chemotherapy in this group of patients.<sup>43</sup> In other words, a negative PET scan after the first course (or completion) of chemotherapy is associated with a statistically significant better PFS. In conclusion, as for lymphomas of other locations, the actual role of PET in PPL is highly dependent on the histologic variant.

### Definitive Diagnosis

As for other lung lesions, the available tools for tissue sampling are transthoracic needle biopsy, transbronchial biopsy, open thoracotomy, and wedge resection by thoracoscopy. The selection of the diagnostic procedure is made essentially upon disease location but also depends on the patient's performance status and single-center experiences (Table 1). An innovative tool considered in the assessment of the clonality of the B cells present in the fluid from a bronchoalveolar lavage can help for the diagnostic workup of undiagnosed patients with pulmonary opacities and could be especially useful in avoiding more invasive procedures when there is suspicion of a relapse. Samples from 106 consecutive patients exhibiting a clinical suspicion of primary or secondary lymphoma of the lung were analyzed for B-cell clonality by PCR. The detection of a strong B-cell clonal population on bronchoalveolar lavage fluid was clearly associated with a histologic diagnosis of pulmonary NHL ( $P = 0.0001$ ), with 97% specificity and 95% negative predictive value.<sup>44</sup>

### Is There a Prognostic Model for Primary Pulmonary Lymphoma?

Because PPL is a heterogeneous disease, the known prognostic factors and the prognostic models developed for the

individual histologic subtypes can be helpful in the management of primary lung localization.

For pulmonary MALT lymphoma, there exist a few case series that have failed to find variables with a significant association, with survival rates a result of their small number of patients.<sup>3,6,39</sup>

Nevertheless, some useful information can be drawn from a retrospective survey by the International Extranodal Lymphoma Study Group (IELSG) that analyzed 180 patients with nongastric MALT-type marginal zone B-cell lymphomas from different locations.<sup>45</sup> A panel of pathologists revised all cases, and only nontransformed MALT-type lymphomas were accepted ( $\leq 20\%$  of scattered blast). At univariate analysis, Ann Arbor stage IV, increased LDH level, extranodal involvement of  $\geq 2$  sites, presence of nodal involvement, International Prognostic Index (IPI) intermediate/high risk or high risk, and the pattern of dissemination (MALT sites only vs. other stage IV) were associated with a worse overall survival (OS), cause-specific survival (CSS), and PFS (Table 3).<sup>45</sup> It is interesting to highlight some details, including an increased number of large cells was not significantly associated with worse OS, but the median PFS (8 years vs. 4 years) has a tendency to be shorter for patients with tumors containing scattered blasts ranging between 10% and 20%; within the subgroup of patients with stage IV disease, those with involvement of multiple MALT sites only had a better survival ([a 5-year OS] 100% vs. 70%) than patients with stage IV involving non-MALT organs (including bone marrow and lymph-nodes) or multifocal involvement of a single organ; and transformation into high-grade lymphoma was reported in 6 patients (3%), and there were 3 variables associated with this event, including the primary hepatic location ( $P = 0.005$ ), an advanced disease stage ( $P = 0.03$ ), and a serologic evidence of previous Hepatitis C virus infection ( $P = 0.002$ ). Paradoxically all the cases experiencing transformation had a low percentage of blasts at diagnosis ( $< 10\%$ ). The multivariate analysis was limited by a restricted number of events (10% death rate at 5 years); however, statistically significant variables were revealed, including Ann Arbor stage that retained its prognostic significance for OS, nodal involvement that was associated with a shorter CSS, and a favorable IPI score that was associated with a better PFS (Table 2). The 5-year estimated survival rates for the 15 cases (8%) of MALT-type PPL included in this trial were 100% for OS and CSS, and 75% for PFS (CI 95%, 41%-91%). Zinzani et al published similar results in a series of 12 patients with PPL of MALT-type.<sup>39</sup> All patients were alive at a median survival time of 34.5 months, with 9 of them (75%) exhibiting a CR, 2 (17%) in their second CR, and the remaining patient with a PR after second-line chemotherapy.

Among 48 patients with PPL from the series by Ferraro et al, 28 patients (58%) had MALT lymphoma, and 7 additional patients (15%) presented a MALT lymphoma transformed into a diffuse large-cell lymphoma.<sup>6</sup> The survival rates for the whole MALT lymphoma group (with and without histologic transformation) were 68% at 5 years (CI 95%, 51%-83%) and 53% at 10 years, respectively (CI 95%, 39%-73%). Although

**Table 3** Adverse Prognostic Factors: International Extranodal Lymphoma Study Group Trial<sup>45</sup>

Adverse Prognostic Factors by Univariate Analysis for OS, CSS, and PFS
Ann Arbor stage IV
Increased LDH levels
Involvement of $\geq 2$ extranodal sites
Involvement of non-MALT sites
Nodal involvement
IPI intermediate/high-risk or high-risk group
Adverse Prognostic Factors Retaining Significance by Multivariate Analysis
Ann Arbor stage IV (for OS)
Presence of nodal involvement (for CSS)
IPI intermediate/high-risk or high-risk group (for PFS)

Statistically significant adverse prognostic factors in terms of OS, CSS, and PFS in an IELSG series of 180 patients with nongastric MALT lymphoma.

this was a surgery-based therapy group, the addition of adjuvant chemotherapy or radiation therapy to some patients failed to demonstrate a survival advantage in univariate analysis.

In the French multicenter retrospective study on 70 cases of PPL, the subgroup of patients with low-grade lymphoma showed a 5-year OS of 93.6%.<sup>3</sup> This low-grade group consisted of 51 patients with MALT lymphoma (73%), 2 patients with FL, 1 patient with lymphoplasmacytic lymphoma, and 7 patients with unclassifiable low-grade lymphoma. There were also 9 patients with high-grade lymphoma that had a poorer outcome because 7 of them had died before the closing of the survey. The only statistically significant prognostic variable in this study was tumor histology. Low-grade cases presented a better survival than their high-grade counterpart ( $P = 0.001$ ).

In summary, the prognosis of PPL depends on histology. Specific prognostic models for PPL are lacking. Lung MALT-type lymphomas usually behave as an indolent disease.

## Treatment

The treatment choice for PPL should be based on histology, stage, biologic characteristics, and performance status. We will discuss the treatment outcomes for pulmonary MALT-type lymphomas. For practical reasons we will not describe the treatment of the other histologies.

Based on the concept that nongastric extranodal MALT lymphomas from different primary sites join together into a single disease, we analyzed the series from the IELSG on 180 patients with MALT lymphomas from various extranodal sites. In this series, 97% of patients (174) received a lymphoma-directed treatment, and, in the remaining 3%, a wait-and-see policy was adopted.<sup>45</sup> Chemotherapy was the primary treatment for 78 patients, with 36 of them receiving an anthracycline-based regimen. Radiation therapy alone was delivered to 41 patients. Surgery alone was performed in 68 patients. Forty-one additional

patients underwent tumor resection and received adjuvant chemotherapy, radiation therapy, or chemoradiation therapy. A total of 139 patients exhibited a CR (77%), and 29 patients exhibited a PR (16%) after initial therapy, with an overall response rate (ORR) of 93%. In the subgroup of patients with stage IV disease, 57% exhibited a CR, and 35% exhibited a PR (ORR, 92%). Among the patients receiving chemotherapy, the ORR was 92%, with a 72% of CR rate. The use of an anthracycline-containing regimen did not significantly improve the response rate, OS, CSS, and PFS in comparison with a single alkylating agent or the CVP regimen (cyclophosphamide/vincristine/prednisone) or in localized or advanced-stage disease. In light of these results, we can conclude that whatever therapy is given to the patient, it will produce similar outcomes; therefore, the physician must consider the less toxic option for every single situation.

The results of the French multicenter retrospective survey support these observations.<sup>3</sup> In the subgroup of low-grade PPL, prognosis did not differ significantly according to the treatment modalities. Chlorambucil alone was as good as the more aggressive chemotherapy regimens (including anthracycline-containing regimens) and other approaches such as surgery or radiation therapy, alone or in combination with chemotherapy. The treatment groups were constituted as follows: 3 patients (5%) received no treatment, 11 patients received only chlorambucil, 4 patients received more aggressive combinations, 1 patient received chemoradiation therapy, 21 patients underwent surgery only, 16 patients underwent surgery and chemotherapy, and 3 patients were treated with surgery and radiation therapy.

In the Mayo Clinic series cited previously, 48 patients with PPL of various histologies and a surgery-based treatment approach had a 5-year OS of 67% and a 10-year OS of 56% for the whole group.<sup>6</sup> No statistically significant advantages in survival were found for patients who underwent a complete resection or received adjuvant chemotherapy.

In the Zinzani et al series of 12 patients with MALT-type PPL, 8 patients were treated with chemotherapy alone (6 of them with anthracycline-containing regimens), 3 patients underwent surgery (1 of them with adjuvant chemotherapy), and 1 patient was treated with chemotherapy plus radiation therapy. The CR rate was 100%, with 9 patients (75%) remaining in first CR after a median follow-up of 65 months, 2 patients (17%) in second CR at 32 and 88 months, and 1 patient in PR after relapse at 92 months.<sup>39</sup>

The data available from the 3 retrospective studies analyzed suggest that none of the therapeutic modalities that included chemotherapy, radiation therapy, surgery, or their combinations are superior in terms of outcome. Moreover, among patients receiving chemotherapy, the same retrospective studies suggest that the outcome of the patients treated with an anthracycline-containing regimen is not superior to the outcome of those treated with CVP or even chlorambucil alone. In consequence, the choice of the less toxic treatment is mandatory and should be patient-tailored. Randomized prospective studies are necessary to confirm this observation.

## Role of Rituximab

Conconi et al conducted a phase II study to test the activity of this anti-CD20 monoclonal antibody as monotherapy in untreated or relapsed extranodal MALT lymphomas (including 4 patients with PPL).<sup>46</sup> Treatment consisted of the standard 4-weekly doses of 375 mg/m<sup>2</sup>. This survey showed a high ORR in stomach (n = 15) and extragastric origin (n = 20) disease sites. The ORR was 73%, and the median time to treatment failure was 14.2 months in the whole series, but it was significantly longer in chemotherapy-naïve patients compared with those who had previous chemotherapy treatments (22 months vs. 12 months, respectively; *P* = 0.001). The treatment toxicity was mild to moderate and was related in general to first infusion reactions. As a consequence of these results, the IELSG is now conducting a randomized study that compares chlorambucil alone versus chlorambucil in combination with rituximab in extranodal MALT lymphoma.

## Conclusion

Primary NHL of the lung is a heterogeneous disease. A variety of histologic subtypes have been reported including B- and T-cell lymphomas. Most cases appear to derive from acquired MALT lymphoma developed in the lung as a consequence of chronic inflammatory conditions. They are relatively rare, but the diagnostic procedure of lung opacities should take them into account because their management is different from lung cancer. Histology (MALT-type lymphoma and other less-frequent indolent lymphomas vs. aggressive histologies) is the main prognostic factor that directs the treatment choice. Therapy of the aggressive subtypes must be based on aggressive chemotherapy. There are several therapeutic options for the management of MALT lymphomas, including single-agent chemotherapy, anti-CD20 antibodies, radiation therapy, and surgery. The choice should be patient-tailored, keeping in mind that the disease most often has an indolent course, and the literature is sparse, with no data from randomized studies to help the decision.

## Acknowledgement

We thank all the investigators who contributed to the IELSG study of nongastric MALT lymphoma for their commitment to improve our understanding of extranodal lymphomas.

## References

1. Miller DL, Allen MS. Rare pulmonary neoplasms. *Mayo Clin Proc* 1993; 68:492-498.
2. Sutcliffe SB, Gospodarowicz MK. Localized extranodal lymphomas. In: Keating A, Armitage J, Burnet A, et al, eds. *Haematological Oncology*. Cambridge, UK: Cambridge Medical Reviews; 1992:189-222.
3. Cordier JF, Chailleux E, Lauque D, et al. Primary pulmonary lymphomas. A clinical study of 70 cases in nonimmunocompromised patients. *Chest* 1993; 103:201-208.
4. Hansen LA, Prakash UB, Colby TV. Pulmonary lymphoma in Sjogren's syndrome. *Mayo Clin Proc* 1989; 64:920-931.
5. Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. *J Clin Oncol* 1999; 17:3835-3849.
6. Ferraro P, Trastek VF, Adlakha H, et al. Primary non-Hodgkin's lymphoma



- of the lung. *Ann Thorac Surg* 2000; 69:993-997.
7. Herbert A, Wright DH, Isaacson PG, et al. Primary malignant lymphoma of the lung: histopathologic and immunologic evaluation of nine cases. *Hum Pathol* 1984;15:415-422.
  8. Qin Y, Greiner A, Trunk MJ, et al. Somatic hypermutation in low-grade mucosa-associated lymphoid tissue-type B-cell lymphoma. *Blood* 1995; 86:3528-3534.
  9. Cavalli F, Isaacson PG, Gascoyne RD. MALT Lymphomas. *Hematology (Am Soc Hematol Educ Program)* 2001; 241-258.
  10. Isaacson PG, Müller-Hermelink HK, Piris MA, et al. Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). In: Jaffe ES, Harris NL, Stein H, et al, eds. *Tumours of haematopoietic and lymphoid tissues. World Health Organization Classification of Tumours*. Lyon, France: IARC Press; 2001:157-160.
  11. Sánchez-Izquierdo D, Buchonnet G, Siebert R, et al. MALT1 is deregulated by both chromosomal translocation and amplification in B-cell non-Hodgkin lymphoma. *Blood* 2003; 101:4539-4546.
  12. Begueret H, Vergier B, Parrons M, et al. Primary lung small B-cell lymphoma versus lymphoid hyperplasia: evaluation of diagnostic criteria in 26 Cases. *Am J Surg Pathol* 2002; 26:76-81.
  13. Lin Y, Rodrigues GD, Turner JF, et al. Plasmablastic lymphoma of the lung: report of a unique case and review of the literature. *Arch Pathol Lab Med* 2001; 125:282-285.
  14. Rush WL, Andriko JA, Taubenberg JK, et al. Primary anaplastic large cell lymphoma of the lung: a clinicopathologic study of five patients. *Mod Pathol* 2000; 13:1285-1292.
  15. Maejima S, Kitano K, Ichikawa S, et al. T-cell non-Hodgkin's lymphoma of the lung. *Intern Med* 1993; 32:403-407.
  16. Mizuki M, Ueda S, Tagawa S, et al. Natural killer cell-derived large granular lymphocyte lymphoma of lung developed in a patient with hypersensitivity to mosquito bites and reactivated Epstein-Barr virus infection. *Am J Hematol* 1998; 59:309-315.
  17. Karakus S, Yalcin S, Gulen N, et al. Angiocentric T-cell lymphoma of the lung mimicking metastatic carcinoma. Case report. *J Exp Clin Cancer Res* 1998; 17:371-373.
  18. Zucca E, Bertoni F, Cavalli F. Pathogenesis and treatment of extranodal lymphomas: the fascinating model of mucosa-associated lymphoid tissue lymphoma. *Haematologica* 2003; 88:841-844.
  19. Auer IA, Gascoyne RD, Connors JM, et al. t(11;18)(q21;q21) is the most common translocation in MALT lymphomas. *Ann Oncol* 1997; 8:979-985.
  20. Ott G, Katzenberger T, Greiner A, et al. The t(11;18)(q21;q21) chromosome translocation is a frequent and specific aberration in low-grade but not high-grade malignant non-Hodgkin's lymphomas of the mucosa-associated lymphoid tissue (MALT-) type. *Cancer Res* 1997; 57:3944-3948.
  21. Ye H, Liu H, Attygalle A, et al. Variable frequencies of t(11;18)(q21;q21) in MALT lymphomas of different sites: significant association with CagA strains of H pylori in gastric MALT lymphoma. *Blood* 2003; 102:1012-1018.
  22. Dierlamm J, Baens M, Wlodarska I, et al. The apoptosis inhibitor gene API2 and a novel 18q gene, MLT, are recurrently rearranged in the t(11;18)(q21;q21) associated with mucosa-associated lymphoid tissue lymphomas. *Blood* 1999; 93:3601-3609.
  23. Uren AG, O'Rourke K, Aravind LA, et al. Identification of paracaspases and metacaspases: two ancient families of caspase-like proteins, one of which plays a key role in MALT lymphoma. *Mol Cell* 2000; 6:961-967.
  24. Lucas PC, Yonezumi M, Inohara N, et al. Bcl10 and MALT1, independent targets of chromosomal translocation in malt lymphoma, cooperate in a novel NF-kappa B signaling pathway. *J Biol Chem* 2001; 276:19012-19019.
  25. Maes B, Demunter A, Peeters B, et al. Bcl10 mutation does not represent an important pathogenic mechanism in gastric MALT-type lymphoma, and the presence of the API2-MLT fusion is associated with aberrant nuclear Bcl10 expression. *Blood* 2002; 99:1398-1404.
  26. Rosenwald A, Ott G, Stiglbauer S, et al. Exclusive detection of the t(11;18)(q21;q21) in extranodal marginal zone B cell lymphomas (MZBL) of MALT type in contrast to other MZBL and extranodal large B cell lymphomas. *Am J Pathol* 1999; 155:1817-1821.
  27. Okabe M, Inagaki H, Ohshima K, et al. API2-MALT1 fusion defines a distinctive clinicopathologic subtype in pulmonary extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. *Am J Pathol* 2003; 162:1113-1122.
  28. Travis WD, Galvin JR. Non-neoplastic pulmonary lymphoid lesions. *Thorax* 2001; 56:964-971.
  29. Streubel B, Lamprecht A, Dierlamm J, et al. t(14;18)(q32;q21) involving IGH and MALT1 is a frequent chromosomal aberration in MALT lymphoma. *Blood* 2003; 101:2335-2339.
  30. Remstein ED, Kurtin PJ, Einerson RR, et al. Primary pulmonary MALT lymphomas show frequent and heterogeneous cytogenetic abnormalities, including aneuploidy and translocations involving API2 and MALT1 and IGH and MALT1. *Leukemia* 2004; 18:156-160.
  31. Willis TG, Jadayel DM, Du MQ, et al. Bcl10 is involved in t(1;14)(p22;q32) of MALT B cell lymphoma and mutated in multiple tumor types. *Cell* 1999; 96:35-45.
  32. Wotherspoon AC, Pan LX, Diss TC, et al. Cytogenetic study of B-cell lymphoma of mucosa-associated lymphoid tissue. *Cancer Genet Cytogenet* 1992; 58:35-38.
  33. Achuthan R, Bell SM, Leek JP, et al. Novel translocation of the bcl10 gene in a case of mucosa associated lymphoid tissue lymphoma. *Genes Chromosomes Cancer* 2000; 29:347-349.
  34. Kubonishi I, Sugito S, Kobayashi M, et al. A unique chromosome translocation, t(11;12;18)(q21;q13;q21) [correction of t(11;12;18) (q13;q13;q12)], in primary lung lymphoma [published erratum in *Cancer Genet Cytogenet* 2002; 134:91]. *Cancer Genet Cytogenet* 1995; 82:54-56.
  35. Wotherspoon AC, Finn TM, Isaacson PG. Trisomy 3 in low-grade B-cell lymphomas of mucosa-associated lymphoid tissue. *Blood* 1995; 85:2000-2004.
  36. Schreuder MI, Hoeve MA, Hebeda KM, et al. Mutual exclusion of t(11;18)(q21;q21) and numerical chromosomal aberrations in the development of different types of primary gastric lymphomas. *Br J Haematol* 2003; 123:590-599.
  37. Remstein ED, Kurtin PJ, James CD, et al. Mucosa-associated lymphoid tissue lymphomas with t(11;18)(q21;q21) and mucosa-associated lymphoid tissue lymphomas with aneuploidy develop along different pathogenetic pathways. *Am J Pathol* 2002; 161:63-71.
  38. Turner RR, Colby TV, Doggett RS. Well-differentiated lymphocytic lymphoma. A study of 47 patients with primary manifestation in the lung. *Cancer* 1984; 54:2088-2096.
  39. Zinzani PL, Tani M, Gabriele A, et al. Extranodal marginal zone B-cell lymphoma of MALT-type of the lung: single-center experience with 12 patients. *Leuk Lymphoma* 2003; 44:821-824.
  40. Lewis ER, Caskey CI, Fishman EK. Lymphoma of the lung: CT findings in 31 patients. *AJR Am J Roentgenol* 1991; 156:711-714.
  41. King LJ, Padley SP, Wotherspoon AC, et al. Pulmonary MALT lymphoma: imaging findings in 24 cases. *Eur Radiol* 2000; 10:1932-1938.
  42. Friedberg JW, Chengazi V. PET Scans in the staging of lymphoma: current status. *Oncologist* 2003; 8:438-447.
  43. Kostakoglu L, Coleman M, Leonard JP, et al. PET predicts prognosis after 1 cycle of chemotherapy in aggressive lymphoma and Hodgkin's disease. *J Nucl Med* 2002; 43:1018-1027.
  44. 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.
  45. Zucca E, Conconi A, Pedrinis E, et al. Nongastric marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. *Blood* 2003; 101:2489-2495.
  46. Conconi A, Martinelli G, Thieblemont C, et al. Clinical activity of rituximab in extranodal marginal zone B-cell lymphoma of MALT type. *Blood* 2003; 102:2741-2745.