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Primary pulmonary lymphoma

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ABSTRACT: Three distinct entities are now covered by the definition of primary pulmonary clonal lymphoid proliferation. The aim of this review is to describe the pathophysiological, diagnostic, prognostic and therapeutic aspects of these three entities.

Low-grade pulmonary B-cell lymphoma is the most frequent form of primary pulmonary clonal lymphoid proliferation. It arises from mucosa-associated lymphoid tissue. It is usually indolent and appears in the form of a chronic alveolar opacity. The prognosis is excellent, but treatment is controversial (simple monitoring, surgery or single-agent chemotherapy). High-grade pulmonary B-cell lymphoma is far rarer and usually occurs in individuals with an underlying disorder (e.g. immunodeficiency). The prognosis is poor and therapeutic options depend on the underlying disorder.

The inclusion of lymphomatoid granulomatosis in the definition of primary pulmonary lymphomas is controversial. The clonal nature of the proliferation is very rarely demonstrated and extrapulmonary involvement is frequent (upper airways, skin, kidneys, central nervous system, etc.). The prognosis is extremely variable, with some authors reporting complete remission with steroids and cyclophosphamide and others reporting failure of combination chemotherapy.

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Lymphomatous proliferation can involve the lungs in three ways: 1) by haematogenous dissemination of non-Hodgkin's lymphoma (NHL) or Hodgkin's disease (HD); 2) by contiguous invasion from a hilar or mediastinal site of nodal lymphoma; and 3) by primary pulmonary involvement. The first two situations involve progression or relapse of a known lymphomatous disorder, and treatment focuses on the haematological disorder. The third situation, the focus of this review, poses a number of diagnostic and therapeutic problems for pneumologists.

Primary pulmonary lymphoma (PPL) is defined as 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 3 months [1, 2]. When the lung is the principal tumour site, this definition also includes: 1) multifocal mucosa-associated lymphoid tissue (MALT) NHL; 2) pulmonary involvement

with satellite nodes (hilar or mediastinal); and 3) multiorgan involvement by lymphomatoid granulomatosis, the clonal nature of which is controversial.

PPL is very rare. While extranodal forms represent 24–50% of cases of NHL [1–3], PPL represent only 3–4% of extranodal NHL, <1% of NHL, and only 0.5–1% of primary pulmonary malignancies [1, 4, 5]. The current definition of PPL [1, 6] covers: 1) low-grade B-cell PPL (PPL-B), the most frequent form; 2) high-grade PPL-B; and 3) lymphomatoid granulomatosis (LG), a rare disorder.

Primary pulmonary B-cell non-Hodgkin's lymphoma: MALT non-Hodgkin's lymphoma

Evolution of concepts and terminology

Low-grade PPL-B corresponds to what was formerly called "pseudolymphoma". The term pseudolymphoma

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was chosen because of doubts over the malignant nature of these slowly progressive lesions and their relatively benign histological aspect [7–10]. Routine use of sensitive immunohistochemical techniques [5, 11–17] and molecular biology-based methods [17] in fact showed that most pseudolymphomas contained clonal proliferation, thus demonstrating their lymphomatous nature. The term pseudolymphoma was therefore abandoned and these lymphomas were 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 [5, 11–17]; and MALT lymphoma in the Revised European-American Classification of Lymphoid Neoplasms (REAL) classification [18]. In the latest classification (World Health Organization (WHO) classification) [19], MALT lymphomas belong to the marginal zone lymphomas but are distinguished from nodal and splenic forms by their different clinical behaviour and cytogenetic characteristics [19–22]. 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].

Mucosa-associated lymphoid tissue lymphoma

Bronchial mucosa-associated lymphoid tissue. MALT is a lymphoid tissue specialising in mucosal defence [1]. It was first described in the gastrointestinal tract of animal models, then in the human ileum. It comprises of Peyer's patches, a lamina propria, intra-epithelial lymphocytes and mesenteric lymph nodes. Peyer's patches are lymphoid nodules with an architecture similar to that of lymph node follicles, except that the marginal B zone is more highly developed in the former. The lamina propria contains immunoglobulin (Ig) A-secreting plasmocytes and T lymphocytes. Phenotypically, intra-epithelial lymphocytes are CD8+ T-cells. The stomach is the most frequent site of MALT lymphoma and serves 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 *H. pylori* antigens. Thus, *H. pylori* eradication can lead to lengthy complete remission of gastric lymphoma [23]. 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 particularly Gougerot-Sjögren's syndrome) are considered to affect the onset of pulmonary MALT lymphoma [23].

Epidemiology. Low-grade NHL-B accounts for 58–87% of cases of PPL in pathological series [5, 12,

15, 17]. Nearly 90% of these cases correspond to MALT-type NHL [12, 15, 17]. Age of onset is ~50–60 yrs (12–79 yrs) and subjects <30 yrs are rarely affected [5, 9, 11, 13, 14, 16, 24]. The two sexes are equally affected [5, 9, 11, 13, 14, 16, 24].

Clinical and radiological signs. Nearly half these patients are asymptomatic at diagnosis and are identified fortuitously on the basis of a radiological pulmonary anomaly [5, 11, 13, 14, 24]. When present, symptoms, such as cough, mild dyspnoea, chest pain and occasionally haemoptysis, are nonspecific [5, 9, 11, 13, 14, 16, 24]. Pulmonary auscultation reveals crackles in <20% of cases [24]. By definition, extrapulmonary manifestations are restricted to general signs (fever and weight loss) and occur in less than one quarter of patients [5, 11, 13, 14, 24]. The usual radiological aspect (50–90% of cases) is a localised alveolar opacity, with a diameter of <5 cm and blurred or well-defined contours (according to the series); it is associated in nearly 50% of cases with an air bronchogram (fig. 1a) [13, 14, 24]. Computed tomography (CT) (figs. 1b and c), which is more sensitive than standard radiography, has demonstrated that the lesions are usually bilateral (60–70%) and multiple (70–77%) [25, 26]. Nearly all these lesions contain clear areas corresponding to an intact bronchial lumen (fig. 2). The presence of distended bronchi within the lesions is a good diagnostic sign, although the underlying mechanism is unexplained [26]. Less than 10% of patients have bilateral diffuse reticulonodular opacities, atelectasia or pleural effusion [13, 14, 24]. CT can reveal hilar and mediastinal adenopathies [9, 24]. The interval between the first clinical or radiological manifestations and diagnosis ranges from 5 months to 8 yrs [5, 11, 13, 14, 24].

Contribution of bronchial endoscopy. Bronchial endoscopy usually shows a normal macroscopic aspect [24], although abnormalities ranging from mucosal inflammation to bronchial stenosis can be observed [24]. The diagnostic yield of bronchial, and especially transbronchial, biopsy is higher when it targets visible endobronchial lesions or radiographic abnormalities [24]. However, the absence of specific signs in most of these samples necessitates further diagnostic investigations [5, 9, 11, 13, 14, 16, 24]. Bronchoalveolar lavage (BAL) is very useful for differential diagnosis of chronic alveolar opacities [27]. In contrast, its value for the positive diagnosis of PPL is inadequately assessed. BAL has proven useful in isolated cases of PPL [28–38], while its use is not always mentioned in large published series [5, 9, 11, 13, 14, 16]. BAL appears to be particularly valuable if it shows lymphocytic alveolitis (lymphocytes >20% of total cells), which is found in about two-thirds of these patients [24, 27, 29, 31]. This lymphocytosis, which is usually composed principally of T-cells, is only a specific sign when >10% of B lymphocytes are present [24, 29, 32]. B-cell alveolitis is particularly valuable when its clonal nature can be demonstrated by the detection of Ig gene clonal rearrangements using molecular biology-based methods (Southern blot

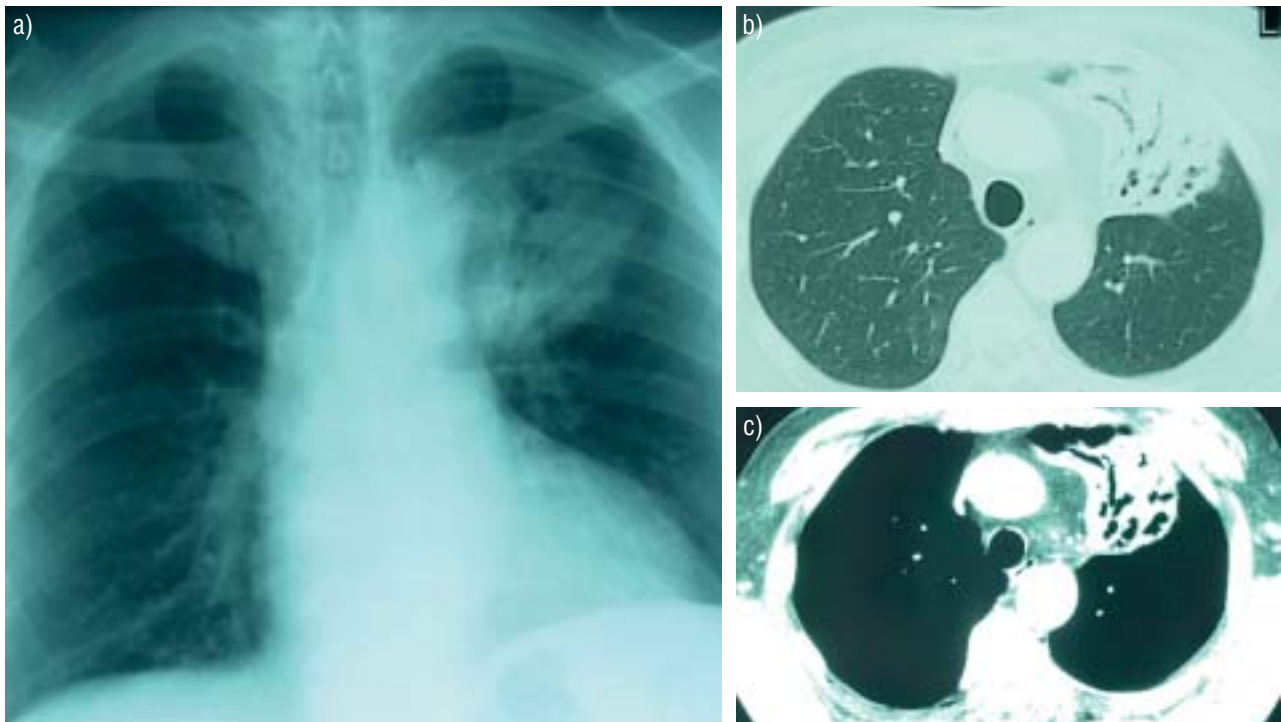


Fig. 1.—Pulmonary mucosa-associated lymphoid tissue (MALT) lymphoma. a) Standard face-on radiography showing a mass in the upper left lobe containing an air bronchogram. Computed tomography sections (b) parenchymatous and (c) mediastinal window) showing the upper left lobe containing an air bronchogram.

or reverse transcriptase-polymerase chain reaction) [35–37, 39, 40]. However, these methods are not widely used in routine practice and require further evaluation of their sensitivity and specificity. They can already be used to diagnose a recurrence of histologically proven PPL. Screening for monoclonal Ig in the BAL supernatant by immunoelectrophoresis [24, 33, 38, 41] and restricted membranous or intracytoplasmic Ig light-chain expression by slide immunohistochemistry or flow cytometry [29–32, 38] have been used but have been replaced by molecular biology-based methods.

Diagnostic criteria. The diagnosis of MALT-type NHL is based on histological examination of surgical samples or bronchial, transbronchial or trans-thoracic biopsy material.

Results of conventional histology. The macroscopic aspect is that of a whitish, soft and poorly-defined mass. Microscopically, MALT-type PPL is defined as a lesion [11, 13, 15, 17, 42] containing: 1) proliferation of small lymphoid cells analogous to the marginal zone cells of Peyer's patches or spleen follicles, centrocyte-like cells and small lymphocytes, plasmocytes or monocytoïd cells; 2) a lymphoepithelial lesion showing lymphoid cell migration from the marginal zone to the bronchiolar epithelium; 3) reactive follicular hyperplasia; and 4) rare blastic cells. More unusual features include amyloid deposits [10, 43] and granulomatous deposits [10, 12, 43]. Various degrees of fibrosis can be found. Lymphomatous infiltration causes smooth or nodular

interstitial thickening with a peribronchovascular distribution [12] (fig. 3).

Contribution of immunohistochemistry. Immunohistochemical analysis contributes to the differential and positive diagnosis of MALT-type PPL. It shows the B-cell phenotype (CD19, CD20) [5, 11–17] and clonal nature [15, 17] of the lymphoid infiltrate invading follicular structures and invading the bronchial/bronchiolar epithelium (fig. 3). It also reveals, by the persistence of dendritic cells (CD21, CD35), the presence, within the tumoural proliferation, of destroyed follicles, together, in most cases, with small reactive T lymphocytes (CD3) in the alveolar wall infiltrate and around peribronchiolar nodules [12, 17]. Above all, immunohistochemical tests can rule out low-grade lymphoma (centrofollicular NHL-B, mantel NHL-B and chronic lymphocytic leukaemia (CLL)-type lymphoma) by showing the lack of CD5 and CD10 surface antigens [12, 17, 44, 45].

Contribution of molecular biology. Southern blotting is performed on frozen samples. 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 [17].

Differential diagnosis. Differential diagnosis of MALT-type PPL is based on clinical and histological grounds. Clinically, the problem boils down to diagnosing MALT-type PPL after radiological identification of a chronic localised or diffuse alveolar or

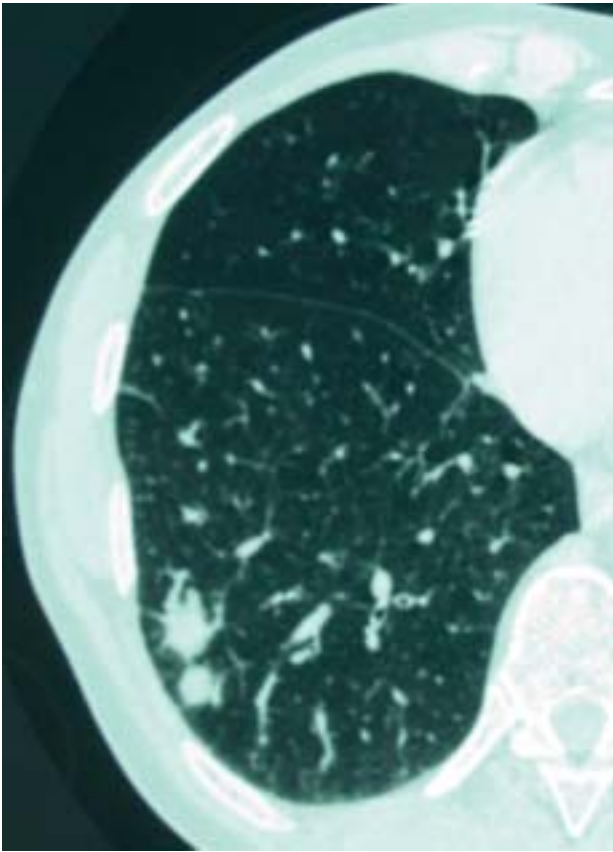


Fig. 2. – Pulmonary mucosa-associated lymphoid tissue (MALT) lymphoma. Computed tomography section (parenchymatous window) showing two joined peripheral nodules with blurred contours located in the lower right lobe. One of the nodules is bronchocentric.

interstitial opacity, which can have a wide range of aetiologies (table 1).

Histologically, especially when the sample is small, the main difficulty is distinguishing MALT-type NHL from diffuse lymphoid hyperplasia or interstitial lymphoid pneumonia (ILP), and follicular bronchitis (FB). This distinction may seem irrelevant to the clinician, because the radiological and clinical features of these disorders often differ from those of MALT-type PPL [47]. Other histological entities, such as extrinsic allergic alveolitis, can be considered, owing to their similar radiological expression and the presence of a lymphoid lesion. Some other nodular pulmonary lesions also have a lymphoid contingent, such as plasmocyte granuloma, inflammatory pseudotumours, fibrous histiocytoma, pulmonary hyalinising granuloma, intrapulmonary adenopathies, and Castleman's disease [48].

Pretreatment extension work-up. Nodal lymphoma is ruled out by abdominal and thoracic CT with contrast enhancement. Although bone marrow involvement is far more frequent in lymphoma of the nodal or splenic marginal zone [21], bone marrow biopsy is crucial, showing signs of invasion in $\leq 20\text{--}30\%$ of patients in recent series of MALT lymphoma [49, 50]. Similarly,

these series showed concomitant involvement of other mucosal lymphoid sites in 25–35% of cases [47–51], and even more frequently in patients with MALT lymphoma not involving the gastrointestinal tract. The search for other mucosal sites must include ophthalmological and ear, nose and throat (ENT) examinations (with magnetic resonance imaging (MRI) or CT of the salivary and lacrimal glands in suspect cases), plus upper gastrointestinal endoscopy (and colonoscopy plus small-intestinal transit, according to some authors). The only useful laboratory tests in the pretreatment work-up are serum electrophoresis and immunoelectrophoresis. Monoclonal gammopathy (IgM in eight out of 10 cases) is found in 20–60% of cases, especially in forms with plasmocyte differentiation [5, 9, 14, 24]. A recent study showed that an elevated β_2 microglobulin level is an independent predictor of poor survival [50].

Course, prognosis and treatment. Course and prognostic factors. The outcome of MALT-type PPL is generally favourable in most series, with a 5-yr survival rate of $>80\%$ and a median survival time of >10 yrs [5, 9–11, 13, 15, 24]. The overall survival of these patients is longer than that of patients with lymphoma of the nodal or splenic marginal zone [21]. In contrast, it has not yet been demonstrated that the survival of patients with MALT-type PPL is equivalent to that of the general population [10, 52]. The median survival of patients with gastrointestinal MALT-type PPL does not differ from that of patients with other localisations, but progression-free survival appears to be shorter in the latter, especially in patients with pulmonary forms [53]. Long-term surveillance is necessary, owing to the frequency of late local or extrathoracic relapse after surgical resection (almost 50% of patients after >2 yrs) [5, 10, 11, 16, 24]. No clear prognostic factors have been identified in MALT lymphoma. In univariate analysis, some all-comer series of MALT lymphoma have shown a pejorative influence of age over 60 yrs, elevated β_2 microglobulin and failure to enter a complete response during first-line treatment [50]. The only prognosticator in multivariate analysis is elevated β_2 microglobulin. According to other authors, intratumoural amyloid deposition is a factor of poor prognosis, while lymphoepithelial lesions are associated with a good prognosis [52]. A recent series of 48 patients with PPL identified no prognostic factors among the following: presentation, bilaterality, tumour/nodes/metastasis (TNM) stage, surgical resection, adjuvant chemotherapy and several histological criteria [54].

Some authors have suggested that low-grade PPL can transform into high-grade proliferation, based on the existence of mixed forms or transitional forms identified by serial biopsy [5, 9, 12, 15, 17]. This conflicts with recent studies showing differences between the cytogenetic abnormalities of low-grade and high-grade PPL. For example, the t(11;18) translocation is only present in low-grade PPL [55]. For this reason, the latest revision of the WHO classification recommends the use of the term "large B-cell lymphoma" rather than "high-grade MALT lymphoma" [19].

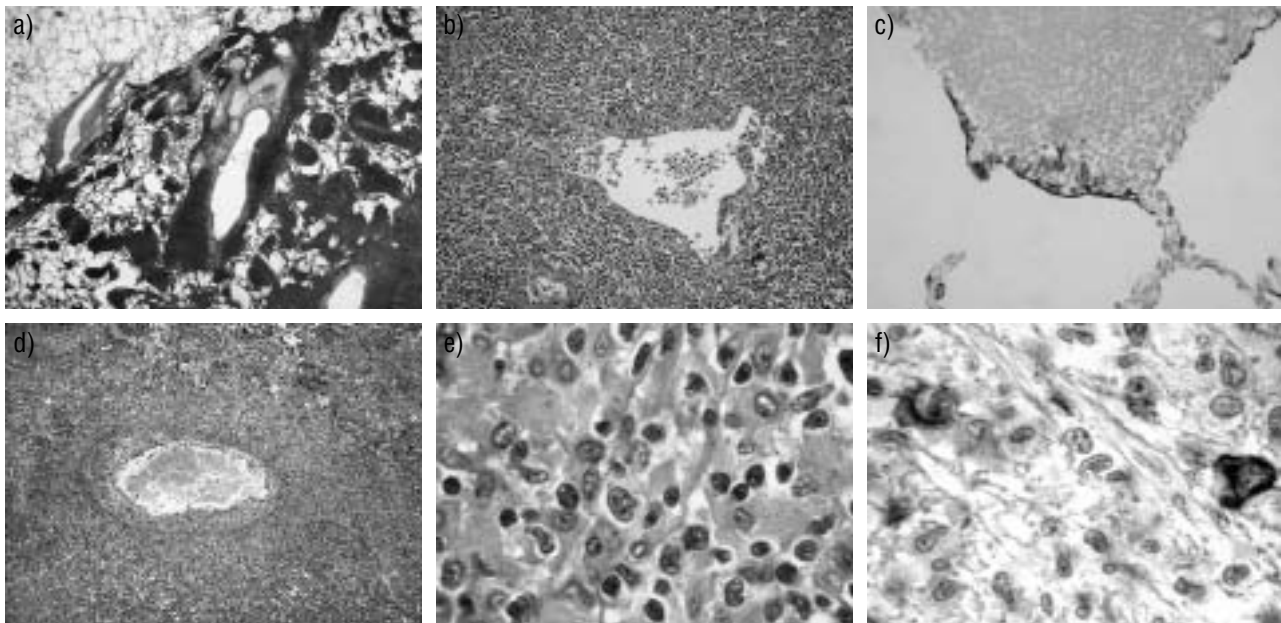


Fig. 3.—Pulmonary mucosa-associated lymphoid tissue (MALT) lymphoma (a–c). a) Interstitial proliferation with peribronchovascular tropism (HES $\times 25$). b) Lymphoepithelial lesion, with the bronchiolar epithelium masked or partially destroyed by the lymphoid infiltrate (HES $\times 200$). c) Residual epithelial cells are revealed with an anticytokeratin antibody (immunohistochemistry, avidin-biotin peroxidase $\times 100$). Pulmonary lymphomatoid granulomatosis (d–f). d) Lymphoid proliferation with vascular parietal invasion (HES $\times 100$). e) Mixed cell population with large atypical lymphoid cells and small lymphoid cells (HES $\times 1000$). f) Large atypical lymphoid cells are revealed with an anti-CD20 antibody (immunohistochemistry, avidin-biotin peroxidase $\times 1000$).

Principles of treatment. There is no consensus on treatment. The lack of an identified culprit antigen in the lung, contrary to the stomach (*H. pylori*), means that antibiotics effective on low-grade localised gastric lymphoma are inappropriate. Current treatment options are surgery, chemotherapy and radiotherapy [5, 9–11, 14–16]. The respective efficacy of these treatments cannot be analysed, however,

Table 1.—Principal aetiologies of chronic solitary or multiple alveolar opacities

Frequent causes

Viral or bacterial pneumonia, slowly resolving[#]
 Organising pneumonia (BOOP)[#]
 Tuberculosis
 Pulmonary infarction
 Pulmonary contusion
 Localised pulmonary oedema

Less frequent causes

Bronchioloalveolar cancer[#]
 Pseudo-alveolar sarcoidosis[#]
 Pulmonary hypersensitivity[#]
 Lymphoma[#]
 Alveolar proteinosis[#]
 Oily pneumonia[#]
 Radio-induced pneumonitis[#]
 Eosinophilic pneumonia
 Alveolar haemorrhage
 Atypical *Pneumocystis carinii* pneumonia
 Opportunistic bacterial pneumonia (nocardiosis, actinomycosis, etc.)

BOOP: bronchiolitis obliterans with organising pneumonia.
[#]: the most frequent tentative diagnoses (owing to their clinically subacute presentation) [46].

owing to a lack of comparative series, and some authors even propose simple clinical monitoring [11]. Nevertheless, surgical resection is commonly preferred for localised tumours [5, 9–11, 14–16]. Exclusive chemotherapy is generally used for patients with bilateral or extrapulmonary involvement, relapse or progression. Combination regimens, such as cyclophosphamide, adriamycin, oncovin and prednisone (CHOP), have not proven more effective than single-agent regimens with chloraminophene, cyclophosphamide, azathioprine or steroids [9, 11, 14]. Radiotherapy is rarely used [5, 9, 11, 14, 15].

Other forms of B-cell primary pulmonary lymphoma

Low-grade B-cell primary pulmonary lymphoma. In <10% of cases, low-grade PPL-B does not meet the histological criteria of MALT-type NHL. According to the WHO classification [18], these cases can correspond to follicular or mantle lymphocytic NHL or CLL. The clinical and pulmonary radiological aspects are similar to those of MALT-type PPL [12, 15].

High-grade primary pulmonary lymphoma-B. High-grade NHL-B represents 11–19% of cases of PPL in published series [12, 15, 17]; MALT-type NHL coexists in ~50% of cases. High-grade NHL-B often occurs in patients with underlying disorders, such as solid organ (heart/lung) transplantation with cyclosporine A or OKT3 immunosuppression [56–60], human immunodeficiency virus (HIV) infection [60–63] and Gougerot-Sjögren's syndrome [64]. It is reminiscent of high-grade pleural NHL in acquired immune deficiency syndrome

(AIDS) patients [60, 65] and in patients with pleural sequelae of collapse therapy. Epstein-Barr virus (EBV) has been implicated in the onset of some of these high-grade NHL affecting the lung [62, 63, 65–68].

Excluding HIV-infected subjects, mean age at onset is ~60 yrs (30–80 yrs) [5, 9, 10, 15, 24]. Patients are usually symptomatic, with respiratory manifestations, fever or weight loss [5, 9, 10, 15, 24]. Radiological investigations usually show a single pulmonary mass or atelectasia. Pleural effusion is also often present [5, 9, 10, 15, 24]. In the current authors' experience, multiple and/or excavated opacities are frequently found in HIV-infected patients [61–63]. Bronchial endoscopy is often abnormal, with budding or infiltrative stenosis with a tumoural aspect [5, 9, 24]. The histological diagnosis is generally easy, even with very small samples (bronchial, transbronchial or transthoracic biopsy), owing to the presence of blast-like lymphoid cells with strong mitotic activity, clearly indicative of malignancy [5, 9, 24, 69]. The lymphoid infiltrate aggresses the bronchial, vascular (endoluminal invasion) or pleural structures, and necrosis is usually found. Most cases are immunoblastic and centroblastic NHL [5, 9, 12, 15, 17, 24]. Histology has a limited role in differential diagnosis [48]. The highly atypical cytological aspect means that immunohistochemistry is required to rule out carcinoma, melanoma or sarcoma if there is a marked fibroblastic reaction, and especially extension of a nodal lymphoma or leukemic involvement. Markedly angiotropic lesions raise the possibility of lymphomatoid granulomatosis.

Survival is poorer in high-grade PPL than in low-grade PPL. Overall, the median survival time is ~8–10 yrs [5, 9, 24], but it is far lower in patients with underlying disorders (HIV infection, transplantation, collapse therapy). Progression and local or distant relapse occur earlier and are more frequently [5, 9, 24]. Treatment after surgical resection is often based on the combination chemotherapy regimens used for high-grade nodal NHL [5, 9, 24].

Primary pulmonary plasmocytoma. Primary pulmonary plasmocytoma is extremely rare. Less than 50 cases have been reported in the literature [70, 71]. Age at onset is ~40 yrs, although cases have been described in children and older patients [70, 71]. The two sexes are equally affected. Patients are usually asymptomatic, but fever, weight loss, chest pain, dyspnoea, cough and even haemoptysis have occasionally been described [70, 71]. The most common radiological aspect is that of an isolated pulmonary nodule, but a case of bilateral diffuse lung disease has been reported [72]. A hilar adenopathy is observed in <10% of cases [70]. Bronchial endoscopy is always normal and the diagnosis is almost always based on thoracotomy findings [70]. Histologically, the lesions are composed solely of plasmocytes with variable degrees of cytological anomalies [70, 71]. Amyloid lesions can be present [73]. By definition, immunohistochemical studies show monoclonal intracytoplasmic immunoglobulin expression [70, 71, 73]. This differentiates these cases from low-grade lymphoma, which always

contains small lymphocytes and reactive plasmocytes expressing polyclonal Ig [70, 71, 73].

In patients with suspected primary pulmonary plasmocytoma, myeloma must be ruled out by normal bone marrow and skeletal examination [70]. Treatment is mainly based on surgical excision of the plasmocytoma. If surgery is contraindicated, most plasmocytomas are radiosensitive. The overall 2- and 5-yr survivals of primary pulmonary plasmocytoma are 66% and 40%, respectively [71]. Despite complete tumour excision, 15–30% of patients develop multiple myeloma within a few years [70].

Pulmonary intravascular lymphoma. Pulmonary intravascular lymphoma is due to proliferation of atypical lymphoid cells within the lumen of capillaries, arterioles, venules and lymph ducts, with little or no invasion of the adjacent parenchyma. It is usually located in the central nervous system and skin. The underlying mechanism appears to be the loss of certain surface receptors on lymphoid cells, preventing their extravascular migration. Pulmonary involvement is rare [74, 75], with about 15 cases reported in the literature. Usually, the clinical and radiological picture is that of diffuse interstitial lung disease with hypoxemia and fever [75, 76]. There is no mediastinal node involvement. There is frequently an altered general state and a lactate dehydrogenase elevation [77], and cerebral, renal or cutaneous involvement is almost always present [74, 75]. A case of pulmonary arterial hypertension [76] and a case of respiratory insufficiency with air trapping [77] have been reported. Transbronchial biopsies can assist with the diagnosis [77], as can cytological analysis of pulmonary capillary blood cells [78]. Combination chemotherapy regimens used in high-grade NHL have some efficacy, giving a complete response rate of ~50%.

Lymphomatoid granulomatosis: immunoproliferative angiocentric pulmonary lesions

Evolution of concepts and terminology

Lymphomatoid granulomatosis (LG) was initially described within the framework of pulmonary angiitis and granulomatosis. It was first recognised as a clinical and anatomical entity distinct from Wegener's granulomatosis (and probably linked to EBV) by LIEBOW and co-workers in 1972 [79, 80]. Patients generally have an altered general state, with pulmonary nodules and extrathoracic involvement (usually cutaneous and neurological) [79, 80]. The histological lesion is an "atypical, angiocentric, angi-destructive and granulomatous lymphoreticular infiltrate" [79, 80]. Several questions have been raised since this initial description:

Is lymphomatoid granulomatosis a lymphoid malignancy? Clinically, LG is characterised by the absence of node, hepatosplenic or bone marrow involvement evocative of NHL. Its natural course is extremely variable. Spontaneous remissions have been reported [34, 81, 82] and prolonged complete remissions have

been obtained in nearly 50% of patients with steroids and cyclophosphamide [83, 84]. However, in most published series the prognosis is grim, with death occurring in >50% of cases, despite combination chemotherapy [34, 79, 81, 84, 85]. Histologically, the lesions sometimes have a lymphomatous aspect, with areas of large atypical lymphoid cells. Authentic high-grade NHL is diagnosed during the course of the disease or at autopsy in from 10% to nearly 50% of patients. Immunohistochemical and molecular biology-based analyses performed in two series showed evidence of clonality in five out of 11 and six out of nine cases of LG [86, 87]. Given this variable clinical course and lesional aspect, some authors grade the lesions from 1 (minimal anomalies) to 3 (maximal anomalies), based on the proportions of atypical and inflammatory cells [81, 85, 88, 89]. A recent study showed a correlation between lesional grade and the B-cell proliferation index, but not the T-cell, macrophage or natural killer-cell proliferation index. The proliferation index of grade-3 lesions appears to be identical to that of large B-cell NHL [90].

Is lymphomatoid granulomatosis a lymphoid lesion of the T or B phenotype? The definition of LG as an immunoproliferative T-cell disorder is now being challenged. The T-lymphomatous nature of some cases of LG had been suggested on the basis of an aberrant T-cell phenotype or a chromosomal abnormality, but clonal rearrangement of T-cell receptor genes has never been demonstrated [83, 87, 91–94]. Other studies based on immunohistochemistry and molecular biology showed, in fact, that most LG correspond to the definition of B-cell NHL. In these studies, the large atypical cells expressed B-cell markers (CD20) and showed restricted Ig light-chain expression (K or L) [87, 91, 92, 95, 96]. Molecular biology studies usually show clonal rearrangement of Ig genes [86, 87, 91, 96].

Is lymphomatoid granulomatosis induced by Epstein-Barr virus? A large number of studies point to a role of EBV in the pathogenesis of LG, as in post-transplant and HIV-related lymphoproliferative syndromes [86, 87, 97, 98]. Viral proteins (lysosome-associated membrane protein (LMP) and EBV-associated nuclear antigen (EBNA)) or viral genomic sequences (EBR1 and EBR2) have been found within the lymphoid infiltrate in 59–72% of cases of LG studied so far [86, 87, 97, 98]. A recent study showed that EBV-infected tumour cells bear B-cell markers [98]. Viral proteins (LMP1 and EBNA2) normally induce a cytotoxic T-cell response, which appears to be deficient in LG [98].

Lymphomatoid granulomatosis

Epidemiology. LG is rare. Between 500–600 cases have been reported in the literature, in the form of case reports and series of 10–150 patients [34, 79, 82, 84, 85, 88, 99–101]. Age at onset is ~30–50 yrs (2.5–85 yrs) [34, 79, 80, 84, 85, 88, 99–101]. Males seem to be more susceptible than females, with a sex ratio of between 1–6.5 males per female [34, 79, 82, 84, 85, 88, 99–101].

No geographical or ethnic susceptibility factors have been found.

Clinical and radiological pulmonary signs. Nearly 90% of patients are symptomatic at diagnosis and present with a 4- to 8-month history of general and respiratory symptoms [34, 79, 82, 84, 85, 88, 99–101]. Respiratory symptoms are found in 54% to >80% of cases, and mainly consist of cough and dyspnoea. Chest pain and potentially life-threatening haemoptysis can occur [79, 82, 99]. Fever, weight loss or sweating occur in 30–70% of cases. Cases of acute respiratory distress have been reported. In one series, the average oxygen tension in arterial blood was 8.9 kPa (67 mmHg (40–100 mmHg)) and there was a restrictive, obstructive or mixed syndrome in 40%, 20% and 15% of cases, respectively [34].

The radiological aspect in >80% of cases is that of multiple poorly-defined nodular opacities measuring 1–8 cm in diameter. They are bilateral and predominate in the lower lobes [34, 79, 81, 82, 84, 85, 88, 99, 102–104]. The nodules have a peribronchovascular distribution and tend to converge to form pseudotumoural masses and excavate, and can disappear or migrate spontaneously ("wax and wane") [82, 88, 103] (fig. 4). Anatomical-radiological correlation studies have shown that excavated masses correspond to infarcted granulomatosis lesions [104, 105]. Unilateral or single nodules, alveolar opacities, and bilateral reticulonodular involvement are more unusual. Mild pleurisy is observed in 40% of cases [34, 79, 82, 85, 99, 102, 106] and pneumothorax has only been described in patients with excavated nodules [82]. Hilar adenopathies are found in 25% of cases [81, 82, 102].

Extrapulmonary manifestations. Extrapulmonary manifestations mainly affect the skin, nervous system or ENT sphere. They can precede, coincide with or follow the onset of respiratory manifestations [34, 79, 81, 82, 84, 85, 88, 99]. Cutaneous involvement is observed in 36–53% of cases, and consists of erythema, nodules and, more rarely, mucosal ulceration [85].

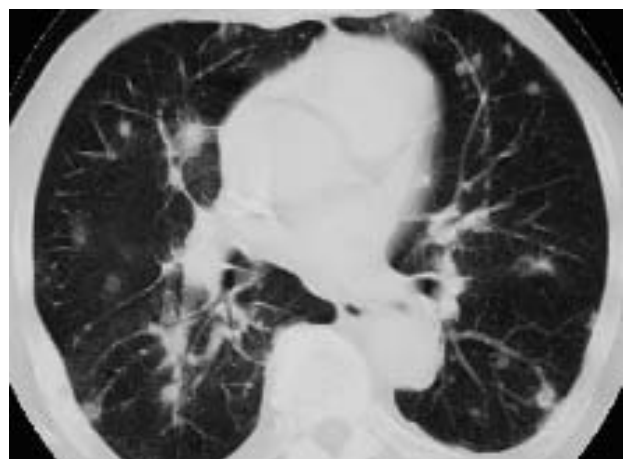


Fig. 4.—Pulmonary lymphomatoid granulomatosis. Computed tomography section (parenchymatous window) showing multiple nodules with peribronchovascular distribution predominating in the lower lobes.

Neurological involvement takes the form of central deficits (blindness, hemiparesis, ataxia, convulsions, coma, headache, confusions, *etc.*), sensory-motor neuropathies affecting the limbs or cranial nerves, and, far more rarely, hypothalamic-pituitary involvement, and occurs in 10–35% of cases [34, 79, 81, 82, 84, 85, 88, 99]. Ulceration of the upper airways is described in 10–30% of cases [34, 81, 84, 85]. The frequency of renal involvement is variously reported; it is ~0–10% at diagnosis and increases during the course of the disease, reaching 30–40% in some autopsy series [79, 81, 84]. It is almost always due to a mass syndrome; creatinemia and the urinary sediment are usually normal. Specific peripheral adenopathies are also infrequent, being observed in 5–8% of cases [34, 79, 81, 84]. Other extrapulmonary manifestations, such as arthralgia and ocular or gastrointestinal involvement, were observed in ~10% of cases in some series [34, 79, 81, 84]. There have been anecdotal reports of involvement of numerous other organs [34, 79, 81, 84, 85], including muscle, thyroid, liver, spleen, testicle, bone marrow, adrenal glands, heart, prostate, ovaries, *etc.*

Diagnostic criteria. The diagnosis of LG is based on histological examination of surgical pulmonary samples. Endoscopic samples are rarely positive [34]. Other histological samples of adequate size can sometimes be obtained by biopsy of skin lesions (positive in 44% of cases) or ENT tissues (86%) [34]. It is recommended to biopsy all accessible sites, owing to the variable proportions of atypical cells found at a given time in the different lesions.

Results of standard histological analysis. Macroscopically, these lesions are relatively well-defined nodules of variable size, grey, white or yellowish, and sometimes necrotic and cavitated. The infiltrate is polymorphous, being composed of lymphocytes (small or medium size, sometimes irregular, but with a mature-looking chromatin and nucleolus), associated with more immature activated lymphoid, plasmacytoid or immunoblastic cells and with large, more or less irregular, blastic cells [81–83, 86, 95]. Cell numbers are variable, and clumps of cells can occur. Mitotic activity is also variable (at least one mitosis per low-power field) according to LIEBOW *et al.* [79]. Mitoses are usually found alongside zones of necrosis or around vessels [85]. Mature plasmacytes or macrophages are also present. There are no Sternberg cells. Polymorphonuclear neutrophils and eosinophils are generally absent [79, 82, 92]. Similarly, there is no epithelioid or giant-cellular granuloma tissue [79, 82].

The vascular tropism of this infiltrate affects vessels of all types (fig. 3), but particularly muscle veins and arterioles. The cellular infiltrate is mainly parietal, raising the endothelium and restricting the lumen [79, 87]. Endoluminal invasion and vessel thrombosis are rarer [79]. The angiocentrism is sometimes only visible after staining the slides for vascular elastin, especially when the vessel is masked by a dense cellular infiltrate. The adjacent pulmonary tissue can harbour organising alveolar lesions [79, 82]. The bronchioles are

sometimes ulcerated or obliterated by granulation tissue [79, 82].

Contribution of immunohistochemistry. Immunohistochemistry helps to confirm the lymphoid nature of the lesion and its high cellularity (predominantly CD4+ T lymphocytes) [83, 91, 92, 96]. In particular, on paraffin sections suitable for morphological analysis, it shows that the atypical large cells are also lymphoid (CD45) and usually bear B-cell markers (fig. 3) [83, 86, 87, 91–94, 96]. CD30 antigen expression is sometimes found [107]. The search for clonality must focus on these cells, with the aim of demonstrating either an aberrant phenotype of the B-cell lineage (CD20+/CD43+) [87] or restricted Ig light-chain expression [86, 87, 92]. In a number of cases these cells also express EBV LMP protein [107].

Contribution of molecular biology. Molecular biology shows the lymphomatous nature of a number of these lesions by demonstrating clonality, especially in the case of B-cell proliferation [86, 87]. In addition, coupled to immunohistochemical methods, it can show EBV infection of these cells.

Differential diagnosis. Clinically, the main difficulty is in diagnosing LG in patients with multiple excavated nodular opacities and subacute general and respiratory signs (table 2). An infectious cause must be ruled out in localised forms, by histochemical staining (Ziehl, Grocott, Gram). Some aetiologies are more difficult to identify, owing to radiological-clinical and/or histological features resembling those of LG. These aetiologies include Wegener's granulomatosis, necrotising sarcoidosis, and benign granulomatous and lymphocytic angiitis [6, 34, 79, 80, 85, 88, 108]. Other histological entities can also be discussed, owing to their clinical expression and the possibility of lymphoid

Table 2.—Principal aetiologies of multiple, possibly excavated nodular opacities

Frequent causes
Metastasis (ENT, uterine, testicular cancer, choriocarcinoma) [#]
Septic metastases (endocarditis) [#]
Tuberculosis [#]
Postembolic pulmonary infarction [#]
Less frequent causes
Wegener's granulomatosis [#]
Sarcoidosis (possibly necrotising) [#]
Rheumatoid arthritis [#]
Benign granulomatous and lymphocytic angiitis [#]
Lymphomatoid granulomatosis, lymphoma [#]
Opportunistic bacterial pneumonia (nocardiosis, actinomycosis, <i>etc.</i>) [#]
Invasive or semi-invasive aspergillosis, other mycoses [#]
Multiple hamartochondromas
Multiple hydatid cysts
Amyloidosis
Pneumoconiosis

ENT: ear, nose and throat. [#]: the most frequent tentative diagnoses (extra-pulmonary signs and radiological excavation) [46].

lesions. Given the therapeutic implications, it is essential to rule out Hodgkin's disease and high-grade angiotropic NHL before diagnosing LG.

Pretreatment extension work-up. The extension work-up comprises a search for cutaneous and especially neurological involvement, by cerebral MRI. Owing to their relative frequency, renal and ENT lesions should also be sought. Finally, node and bone marrow involvement must be searched for, as it makes the diagnosis of LG/diffuse NHL highly probable [81].

No particular laboratory test is required for diagnosis or prognostication in this setting. Anaemia, a biological inflammatory syndrome, hyperleukocytosis or, on the contrary, leucopenia or lymphopenia are often present [34, 81, 82, 84, 85, 88]. The immunological work-up shows only nonspecific abnormalities [85, 88]. Antinuclear antibodies and rheumatoid factor are very rarely positive [81, 82]. Hypogammaglobulinaemia or hypergammaglobulinaemia with circulating immune complexes have been described [34, 81, 82]. Cutaneous anergy to recall antigens or dinitrochlorobenzene is observed in >50% of cases [84, 88]. Lymphocyte proliferation to antigens or mitogens is also subnormal.

Course, prognosis and treatment. Course and prognostic factors. Although the boundaries between "malignancy and benignity" and "monoclonality and polyclonality" remain poorly defined in LG, the prognosis is generally poor. The median survival time among patients with LG is ~4 yrs [34]. Death ensues in 38–88% of cases [34, 79, 81, 82, 84]. The median of survival time of patients who die is 6.5–19 months [34, 81, 82, 84, 99]. Death is usually due to asphyxia or haemoptysis (44–89% of cases) [34, 79, 81, 82, 84, 99], neurological complications (7–31% of cases) or infections (23–38% of cases), which may or may not be treatment related [34, 82, 85, 99]. In a number of cases, death is associated with nodal or visceral lymphoma (5–47% of cases) [34, 81, 82, 84, 85] or carcinoma (11%) [34]. Among survivors, the median survival time is 2–4 yrs (≤ 10 yrs) in the series with the longest follow-up [34, 81, 82, 84, 99]. Survival is better among patients who enter complete remission, although late relapses occur in ~10% of cases [34, 82].

Very few studies have identified predictors of survival. Factors of good prognosis appear to include advanced age, lack of symptoms and unilateral radiological lesions. Factors of poor prognosis include onset before age 25, neurological lesions and hepatosplenomegaly [81, 82]. Sex, race and cutaneous involvement do not appear to influence the vital prognosis. Leucopenia, persistent fever or anergy appear to be associated with progression to more aggressive forms of LG [84]. Histologically, the presence of large numbers of large atypical cells and a high degree of necrosis may be pejorative factors [81, 82]. However, the latter were not confirmed in a recent study, in which none of the histological classifications was predictive of survival among patients with LG [87]. Owing to the variety of treatments used to treat

LG, their impact on outcome is difficult to deduce from survival curves.

Principles of treatment. There is no consensus on treatment. It is usually based on steroid therapy, alone or combined with cyclophosphamide (CPM), and combination chemotherapy [34, 79, 81, 82, 84, 99]. FAUCI *et al.* [84] obtained prolonged complete remissions in seven out of 13 (54%) patients treated for LG with the combination of CPM ($2 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$) and prednisone (PDN) ($1 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$, tapering doses) for an average of 37 and 28 months, respectively. Nevertheless, eight patients (61%) died of LG, including seven of associated high-grade NHL resistant to chemotherapy escalation. LIPFORD *et al.* [83] also obtained complete responses in nine (50%) out of 18 patients treated with CPM and PDN for LG of histological grades I (5 out of 9), II (2 out of 6) and III (2 out of 3). Nevertheless, nine of these 18 patients (50%) subsequently died of high-grade NHL refractory to different chemotherapy regimens. In this series, five of the eight patients with grade III LG who were initially treated with intensive combination chemotherapy remained in complete remission after a mean follow-up of nearly 7 yrs (1–12 yrs). Other groups have reported similar results with intensive combination chemotherapy [34]. These data suggest: 1) equivalent efficacy of the CPM/PDN combination and more intensive chemotherapies; 2) poor prognosis of patients who do not enter remission; and 3) the need for clinical, cytological or genetic criteria to detect NHL or anticipate its onset.

Localised pulmonary forms have been successfully treated with surgery and/or radiotherapy [81, 85, 88]. Radiotherapy has also been used to treat more diffuse and/or extrathoracic forms (especially cerebral involvement) [23, 53, 82, 84]. Simple monitoring may also be appropriate, as spontaneous complete remissions have been observed [34, 81, 82].

Conclusion

A good deal of progress has been made in understanding the pathophysiology of primary pulmonary lymphoma. The role of Epstein-Barr virus, for example, is now well documented in some cases of high-grade B-cell lymphoma and lymphomatoid granulomatosis. Similarly, it is possible that an infectious agent plays a role in the emergence of pulmonary mucosa-associated lymphoid tissue lymphoma (analogous to *Helicobacter pylori* in the stomach). The diagnosis of these clonal lymphoid proliferations has also benefited from advances in immunohistochemistry and molecular biology. These techniques must now be more thoroughly assessed in this setting, especially on small endoscopic biopsy samples, so as to avoid unnecessary, purely diagnostic thoracotomy. Treatment of these rare tumours is poorly standardised and patient registers must be created to define the best therapeutic strategies.

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