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About a general approach of primary lung lymphomas

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Abstract

Primary pulmonary lymphomas are very rare accounting for 0.5 to 1% of the primary malignant tumors of the lung. They are dominated by the mucosa-associated-lymphoid tissue lymphoma, high grade B cell lymphoma and lymphomatoid granulomatosis. The diagnosis and the management of these tumors remain debated and challenging. We target to assess the pathogenesis, clinical, microscopic and radiologic characteristics of these tumors. In the other hand, we target to highlight the main treatment modalities and to emphasize on the necessity of a standardization of the management of these tumors.

Keywords

MALT Lymphoma, High Grade B Cell Lymphoma, Lymphomatoid Granulomatosis, Primary Lung Lymphoma

1. Introduction

Primay lung lymphomas are defined as lymphoid monoclonal proliferation developed in one or both lungs without extra-pulmonary localization at the time of diagnosis or within a delay of three months [1, 2]. This definition includes clinically multifocal non-Hodgkin lymphomas if their distribution is similar to the distribution of the mucosa-associated lymphoid tissue, lung lesions with satellite lymph nodes if the lung lesions are the main localization and multi-visceral localizations of lymphomatoid granulomatosis (LG). Primary lung lymphomas include 3 histological entities which are low grade B lymphoma developed in 90% of the cases upon the mucosa-associated lymphoid tissue (MALT), high grade B lymphoma and lymphomatoid granulomatosis.

MALT lymphomas develop upon the MALT. Initially, they were considered as pseudo-lymphomas because of their good behavior [3, 4, 5, 6]. The development of immunohistochemical techniques and molecular biology proved that these pseudo-lymphomas corresponded to a monoclonal proliferation [7, 8]. In 1983, Isaacson grouped all low grade lymphomas (gastric, pulmonary, of the sweat glands…) in the group of malignant lymphomas of the MALT [9]. In 1994, MALT lymphomas were integrated into the REAL classification by Harris. Then, the WHO classification which was published in 2001 and 2008 included them in extra-lymph node B lymphomas of the marginal zone [10, 11].

LG was initially included in the group of vascular and granulomatous lung lesions. In 1972, Liebow considered it as a particular entity related to the Epstein Bar Virus (EBV [12, 13]. Since this description, the malignant character of this lesion has been proved based on histologic features and clinical behavior. Since 1984, it has been considered as a T immuno-proliferative lesion despite of the absence of genetic rearrangement of the T receptor [14, 15]. More recently, in 1994, Guinee and Myers have shown a minor B population expressing CD20 antibody. These cells were infected by the EBV [16]. The LG has been integrated in the 2001 WHO classification using a grading system from 1 to 3 which was proposed by Lipford in 1989. This grading system is based on the number of the infected cells by EBV, the extension of the necrosis and the degree of

polymorphism. Grade 3 lesions are considered as diffuse large B cell lymphoma [16].

In less than 10% of the cases, low grade B cell lymphomas don't meet the diagnostic criteria of MALT non Hodgkin lymphomas. These tumors may correspond to lymphocytic lymphoma, follicular lymphoma or mantle cell lymphoma. Hodgkin lymphomas have been exceptionally reported but their primary pulmonary localization remains debated [1].

High grade B non Hodgkin lymphomas account for 11 to 19% of primary lung lymphomas. They are associated in 50% of the cases to a MALT lymphoma. This finding suggests that B high grade lymphomas can appear de novo or secondary to a transformation of a MALT lymphoma [8, 17]. The transforming potential of primary lung lymphoma from low grade to high grade has been supposed facing mixed forms. These findings are debated based on recent studies that showed different cytogenetic abnormalities in both lymphomas. For this reason, the revised WHO classification recommended the use of large B cell lymphoma instead of high grade MALT lymphoma [18].

2. Pathogenesis

The causes of PLL remain debated. An infectious agent may play a key role in MALT lymphoma like Helicobacter Pylori (HP) in the stomach or EBV in LG. The implication of smoking hasn't been demonstrated [1, 18]. According to *Richmond and coworkers*, smoking plays no role in the genesis of these tumors [19].

2.1. Immune Theory

The dysimmune affections that are more frequently associated to PLL are disseminated lupus erythematosus, multiple sclerosis, rheumatoid polyarthritis, rhizomelic polyarthritis, hashimoto's thyroiditis and mainly Sjögren syndrome [20]. This fact, made some authors stipulate about the immune origin of PLL.

2.2. Infectious Theory

HIV is associated to a high risk of high grade lymphomas of the lung in less than 10% of the cases [1, 21, 22]. In LG, the infection by the EBV is consensual [16]. The expression of some viral proteins such as LMP or the presence of viral genome sequence (EBR1, EBR2) has been found within the lymphoid infiltrate in 59 to 72% of the cases of LG.

2.3. Chromosomal Abnormalities

Today, 4 chromosomal abnormalities have been identified in MALT lymphoma: chromosome 3 trisomia observed in 60% of MALT lung lymphomas, the translocation t (11;18) (q21 ;q21) and the translocation (1;14) (p22;q32). The translocation t(11;18) has been noted in 25 to 55% of PLL [23, 24]. It is very specific of MALT lymphoma and hasn't been observed in splenic or lymph node lymphomas of the marginal zone. It corresponds to the fusion of 2 genes IAP2 (*Inhibitor of apoptosis protein 2*) situated in the chromosome 11q21 and MALT1 (*MALT lymphoma-associated translocation*) situated in chromosome 18q21. This fusion encodes for a protein that plays a key-role in the oncogenesis by the activation of NF-κ B. The translocation t (1; 14) (p22 ; q32) is rare in MALT lymphoma. It corresponds to the juxtaposition of the Bcl10 gene situated in the chromosome 1p22 and the promoting region IGH in the chromosome 14q32 which induces an excessive production of bcl-10 protein which is likely to be linked to MALT1 and can enhance NF- κ B, like for the translocation t (11; 18). The translocation t (14; 18) (q32; q21) is rare [25].

Concerning the LG, many studies have shown a direct relationship with EBV by demonstrating the presence of 2 viral proteins LMP-1 and EBNA-2. LMP-1 induces the expression of the Bcl2 genes which causes the immortality of the cells and induces their transformation into fibroblasts. EBNA-2 induces the expression of numerous cellular and viral oncogenes [26].

3. Epidemiology

3.1. Frequencies

Extra-lymph node lymphomas account for 24 to 48% of the non Hodgkin lymphomas. The primary lung localization is rare representing only 3 to 4% of non Hodgkin extra-lymph nodes lymphomas, less than 1% of non Hodgkin lymphomas and only 0.5 to 1% of the primary malignant tumors of the lung [1]. Secondary lung localizations of lymphomas are more common accounting for 25 to 40% of the cases. In less than 10% of the cases, low grade B lymphomas don't meet the criteria of MALT non Hodgkin lymphomas. They may correspond to lymphocytic lymphoma, follicular lymphoma or mantle cell lymphoma [2]. High grade primary lung lymphomas account for 11 to 19% of PLL [8]. They are associated to a MALT lymphoma in 50% of the cases. LG is very rare with about 500 observations reported in the literature [27, 28].

3.2. AGE

The mean age of presentation is about 50 to 60 years. Patients aged under 30 years were exceptionally described [29]. In MALT lymphomas, the mean age is about 50 years. In high grade lymphomas, the mean age is 60 years. In LG, the mean age is between 30 to 50 years. Some cases of pediatric LG have been identified by *Karnak* and *Le Sueur* who discussed its association with Wiskott-Aldrich syndrome [30].

3.3. Sex

In the majority of the studies, like the studies of *Cordier* and *Hoste*, the distribution of MALT and high grade lymphomas is equal between men and women [1, 7]. Some authors like *Koss* and *Kennedy* reported an increased

incidence in men. Others reported an increased incidence in women (*Ferraro*, *Graham*,*Kurtin*) [31, 32, 33, 34].

In LG, men seem to be more concerned than women with a sex ratio of 1 to 6.5 [6, 12].

4. Clinical Study

4.1. Signs and Symptoms

4.1.1. MALT Lymphomas and High Grade B cell Lymphomas

In more than 50% of the cases, the patients are asymptomatic and the diagnosis is incidental [34]. In symptomatic patients, the symptoms are non specific evoking more frequently a lung infection. Respiratory symptoms are the most frequent. In their studies, *Ferraro* and *Kurtin,* reported respiratory symptoms in 26 to 33% of the patients and general signs in 6 to 21% [32, 34].

4.1.2. Lymphomatoid Granulomatosis

In LG, about 90% of the patients are symptomatic. Symptoms consist mainly in respiratory signs and general symptoms [6, 12]. Pulmonary and general signs are observed in 50 to 80% of the cases. They are dominated by cough and dyspnea. Chest pain and hemoptysia are less frequent [12].

b- Extra pulmonary manifestations

Extra-pulmonary manifestations are mainly cutaneous and neurologic. These symptoms may be synchronous, may precede or succeed respiratory symptoms [28].

Cutaneous manifestations are observed in 36% to 53% of the cases. Neurologic symptoms are observed in 10 to 35% of the cases [12, 28]. Ulcerated lesions of the upper airway are described in 10 to 30% of the cases [28]. Renal symptoms are observed in 0 to 10% of the cases at the time of diagnosis and 30 to 40% of the cases during the evolution [12, 28].

4.2. Associated Affections

The frequency of PLL seems to be increased in patients with auto-immune or systemic diseases [6].

5. Biology

5.1. Protein Immunoelectrophoresis

This exam can help to assess the diagnosis when showing a monoclonal pick of immunoglobulins in 20 to 60% of the cases particularly in forms with plasmocytoid differentiation [7, 17, 34]. The monoclonal immunoglobulin pick is mainly of IgM type (80%) and in the majority of the cases with kappa light chains [31, 34]. *Kurtin* reported the presence of a monoclonal immunoglobulin in 28 PLL within 35 PLL [34]. *Kurtin* and *Thieblemon*t considered that the presence of increased levels of beta-2microglobulin is a predictive factor of low survival [34].

5.2. Lacto.Deshydrogenase (LDH)

Its level is increased in 20 to 60% of the cancers and it indicates a global elevation of the 5 iso.enzymes present in the blood. It is used as an indicator of the tumoral mass in non Hodgkin lymphomas. The level of LDH in the blood may be useful in the follow up of the patients. *Kim* noticed higher levels in high grade lymphomas stipulating its possible prognostic significance [35].

6. Bronchial Endoscopy

It is useful in performing bronchial and transbronchial biopsies. Few reports have mentioned endoscopic aspects of these tumors. Bronchial fibroscopy is normal in 50% of the cases [1].

7. Radiologic Findings

7.1. Chest X-ray

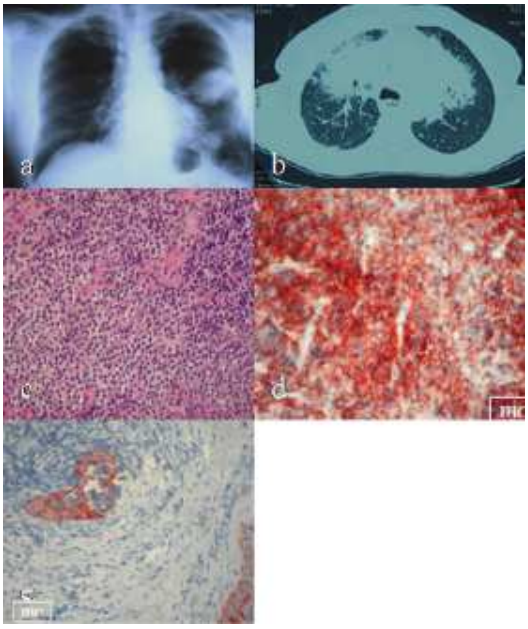

Figure 1. *a/ Chest-x-ray showing two alveolar opacities of the left lung in a patient with MALT lymphoma, b/ CT-scan showing a bilobular alveolar condensation containing an irregular aeric bronchogram, c/ microscopic findings showing multiple tumor cells centrocyte-like (arrow) with irregular nuclei and clear cytoplasm (HE x 400), d/ Immunohistochemical findings showing the exptression of CD20 by tumor cells (HE x 400), e/ Immunohistochemical findings highlighting lympho-epithelial lesions using cytokeratin antibodies (HE x 400).*

In MALT lymphomas, 50 to 90% of the patients present with alveolar opacities (Figure 1a) [1]. These opacities are secondary to the obliteration of the alveolar spaces by the lymphomatous infiltration and the thickening of the interstitium [36]. They consist in a nodule or a mass of less than 5 cm. These images may be multiple in 25 to 30% of the cases and bilateral in about 20% of the cases. Diffuse radiologic forms are mainly symptomatic [1]. A

bronchogram is observed in 50% of the cases and is related to the thickening of the broncho.vascular tissue secondary to a lymphomatous infiltration [36, 37, 38].

In LG, radiologic findings consist mainly in multiple nodular opacities in 68 to 95%, measuring between 1 to 8 cm (Figure 2a). These nodules correspond to the angiocentric granulomatous infiltration. They tend to be confluent or to form pseudo.tumoral masses in 13 to 38% of the cases, to excave or disappear or migrate in 5 to 30% of the cases. Mediastinal adenomegalies are absent or of little size [37].

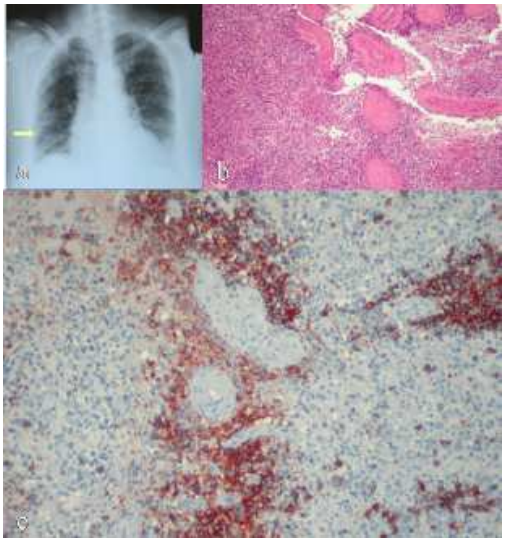

Figure 2. *a/ chest-x-ray showing interstitial syndrome with multiple alveolar opacities in a patient with lymphomatoid granulomatosis, b/ Microscopic findings showing polymorphic lymphomatous proliferation which is angiocentric and angiodestructive (HE x 250).*

7.2. CT.Scan

CT.scan plays a key.role in revealing the primary lung localization and in evaluating the extension of the tumor. It allows the study of the mediastinum and the adjacent structures. It is also useful in the radiologic follow up of the patients. In the literature, we notice the absence of difference between low grade and high grade lymphomas (Figure 1b, Figure 3a). In LG, multiple micro.nodules are observed in 2/3 of the cases.

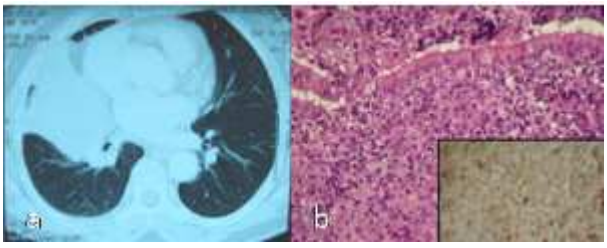

Figure 3. *a/ CT-scan showing a tumor mass with a collapse of the middle lobe in a patient with high grade B cell lymphoma, b/ Microscopic findings of high grade B cell lymphoma showing blastic cells (HE x 400),/ Immuno-histochemical findings showing the expression of CD20 antigen by the blastic cells (HE x 400).*

7.3. Magnetic Resonance Imaging

It is of low interest but it may be useful in cases of sub.pleural condensations when differentiating between pleural and parenchymal origin may be challenging. Pulmonary lymphoma appears as a large homogeneous mass in T1.weighed images and a homogeneous mass in T2 enhanced.weighed images [36, 38].

7.4. Positron Emission Tomography

It may show small lymphadenopathies. It can be useful to differentiate a residual tumor from necrosis or fibrosis [36, 38].

8. Pathology

8.1. Means of Study

8.1.1. Cytology

a. Bronchial cytology

It seems to be inefficient [1]. Some authors tried to report cytologic characteristics of MALT lymphoma and showed that pathologists are able to recognize lymphoepithelial lesions that represent a diagnostic key of MALT lymphomas (39). Broncho.alveolar lavage (BAL) contributes to assess a chronic alveolar opacity [40]. It can be useful for the diagnosis when it shows a lymphocytic alveolitis with more than 20% of B lymphocytes [40]. The diagnostic value of this exam appears when the clonal nature of the lymphocytes is identified by the detection of a membranous expression or intra.cytoplasmic light chains by immunocytochemistry on slides or DNA flow cytometry and the demonstration of the immunoglobulin gene clonality using molecular techniques. In a study about 106 patients Zompi suspected a PL based on the BAL findings with a specificity of 97% and a sensitivity of 95% using a prospective analysis of monoclonality of lymphocytes using PCR technique [41].

b. Pleural puncture

Inspite of the rarity of the pleural localization, pleural puncture may be useful in the follow up of pulmonary lymphomas with pleural localizations [1, 33].

8.1.2. Biopsies

a. Bronchial biopsy

Bronchial biopsy enables the diagnosis of low grade lymphoma in 10% to 20% of the patients [1, 32]. The samples must be multiple and of sufficient size. The interpretation may be difficult because of the artifact that makes the normal lymphocytes look like centrocyte.like or monocytoid cells. When the samples are too small, the infiltrating character, the destruction of the cartilage or lympho.epithelial lesions may be absent. In case of high grade lymphoma, the diagnosis on small biopsies is easier when blastic cells are observed [1].

b. Transparietal puncture or biopsy

Initially, it has been used to determine the stage and the

evolution of the residual tissue after the treatment of PLL. Nowaday, it is indicated when the bronchial biopsy is insufficient or the thoracotomy contra.indicated. Nevertheless, this method hasn't been used frequently because of its limited diagnostic efficiency and its complications (heamorrhage, pneumothorax) [42].

c. Pleural biopsy

It has been reported to be useful when guided by ultra.sound or CT.scan examination [1].

8.1.3. Surgical Biopsies and Samples

In 70 to 100% of the cases, the diagnosis of PLL is made on surgical specimen. Surgical biopsy enables to obtain a sufficient material to make the diagnosis and to perform total surgical resection in case of a unique localized lesion [1, 32,43, 44].

8.2. Gross Findings

In low grade lymphomas, the most frequent feature is a well limited mass white.grey, homogeneous, ranging from 2 to 11 cm [7]. In some cases, it can be ill.defined invading the peripheral parenchyma without necrosis. High grade lymphomas are characterized by foci of necrosis and endobronchial, vascular and pleural infiltration [1].

LG is characterized by variable types of nodules that may be well.limited, grey.white and sometimes excavated with foci of necrosis [1].

8.3. Microscopic Features

The diagnosis of lymphoma is based on microscopic findings. The presence of a lymphomatous parenchymal infiltrate, the size of the cells, the aspects of the nuclei, the extension and the topography of the infiltrate, its relation with the bronchial structures, the vessels and the associated lesions can help to assess the diagnosis. In many cases, morphologic features may be insufficient and immunohistochemistry is compulsory to assess the diagnosis [1].

8.4. Immunohistochemistry

In lymphomas, immunohistochemistry is necessary to confirm the lymphomatoid nature of the proliferation, to prove the monoclonality and to assess the B or T nature of the tumor cells. Thus, immunohistochemistry helps to distinguish between malignant proliferation and other reactive lymphoid lesions.

In B lymphomas, the monoclonality is demonstrated by diagnosing a monotypic immunoglobulin either in the surface cell or in the cytoplasm with one type of light chain and usually one type of heavy chain [1].

8.5. Molecular Biology

It can shows a rearrangement of the gene of a heavy chain of an immunoglobulin using the target Fr 3/ JH in B lymphomas or the rearrangement of the gene receptors γ.δ in T lymphomas [1]. Techniques of molecular biology have many applications including the assessment of the lymphoid nature of a proliferation when the immunohistochemical study is insufficient, in case of a lymphomatous proliferation with a few B cells and within a polyclonal B lymphoid hyperplasia where it can isolate a monoclonal population with more sensitivity than the immuno.histochemical techniques.

8.6. Main microscopic types

8.6.1. MALT lymphoma

a. Morphology

Microscopic features are similar to all MALT lymphoma despite of their localization. They mimic payer plaques and contain a characteristic association of a tumoral component and a reactive component [1,8]. Characteristic features consist in:

• B lymphomatous cells of small to medium size with irregular nuclei and a relatively abundant cytoplasm, usually clear mimicking centrocytes called: "centrocyte.like cell " (CLC). Others cells are observed such as monocytoïd B cells and small lymphocytes that may present a plasma cell differentiation.

• Lympho.epithelial lesions defined by the presence of nests of CCL (more than 3 CCL) in the epithelium of glands with usually a partial or total epithelial destruction. Contiguous epithelial cells show usually pseudo.oncocytic feature.

• Monotypic plasmocytic differentiation may be observed in the third of the cases but it is usually masqueraded by a reactive plasmocytosis

• Reactive hyperplasia of the lymphoid follicles (Figure 1c)

In its pulmonary localization, MALT lymphoma is characterized in its early forms by a peri.tumoral infiltrate with nodular distribution. It becomes diffuse in advanced stages. Peri.bronchiolar topography is usually observed. This peribronchiolar distribution and the thickening of the peri.bronchovascular tissue explain the absence of alveolar infiltration and the aeric bronchogram observed in CT.scan.

In some cases, amyloid deposits or granulomatous reaction may be observed [6, 41].

b. Immunohistochemistry

The immuhistochemistry (IHC) allows specifying the phenotype B of the infiltrate by the showing the expression of CD 20 and CD79a. The monoclonal nature is demonstrated by revealing a monotypical immunoglobulins or a monoclonal light chain. In the majority of the cases, they are IgM, more rarely IgA or IgG. The lympho.epithelial lesions are well detected using cytokeratin (CK) and EMA antibodies [1, 8] (Figure 1d). In very rare cases, tumor cells express CD5 antibody (45).

c. Molecular biology / genetic abnormalities

In 60% of MALT lymphomas, a genetic clonal rearrangement may be showed using Southern Blot or PCR techniques. In addition to their diagnostic value, these techniques are helpful in the interpretation of lymphoid infiltrates and in the follow up of the patients. In fact, the

comparison of the genetic rearrangement between the primary tumor and the metastases may be helpful in the diagnosis of a recurrence. Bcl2 oncogene is rearranged in MALT lymphomas and in 80% of the lymph node follicular lymphomas. Chromosome 3 trisomia is observed in 60% of the cases and a translocation t (11; 18) is noticed in one third of the cases. This translocation isn't observed in high grade B cell lymphomas. P53 is partially inactivated in MALT lymphoma, whereas, it is completely inhibited in high grade B cell lymphomas [1, 7].

8.6.2. High grade B cell lymphoma

a. Microscopic features

We distinguish 2 types of high grade B cell lymphomas:

• De novo lymphomas that are classified according to the WHO classification. They are characterized by a proliferation of blastic lymphoid cells with numerous mitoses. The lymphoid infiltrate invades the bronchial and vascular structures. It corresponds mainly to an immunoblastic or centroblastic lymphoma.

• Transformed MALT lymphoma: In addition to the characteristic features of MALT lymphoma, it is characterized by the presence of blastic cells, of lymphoid follicles largely invaded, of vascular invasion, of necrotic foci or a pleural infiltration. These criteria are characteristic of a high grade transformation. The frontier between large cell and small cell lymphomas is sometimes debated. For the majority of the authors, the distinction between the de novo and the transformed lymphomas has no prognostic or therapeutic impact [1, 7] (Figure 3b)

b. Immunohistochemistry

Tumor cells are of B phenotype expressing CD20 and CD79a antigens. There is also an expression of light monotypic chains [1, 7] (Figure 3c).

c. Molecular biology / genetic abnormalities

The presence of a genetic rearrangement of immunoglobulin is observed in 20% of the cases

[1, 7]. Genetic abnormalities aren't known very well in pulmonary diffuse large B cell lymphomas.

8.6.3. Lymphomatoid Granulomatosis

a. Morphology

LG is considered as a large B cell lymphoma that is frequently associated to the EBV infection. It is an angiocentric and angiodestroying lymphoproliferation with an important reactive lymphocyte T cell component. Microscopically, it is nodular and polymorphous surrounding the muscle wall of the arteries and pulmonary veins in early stages. It is composed of small lymphocytes, histiocytes, plasmocytes and rarely neutrophils and eosinophils associated to atypical large lymphoid cells, mimicking in some cases immunoblasts or Reed Sternberg cells. A central necrosis is observed [42]. Tumor cells are polymorphous forming joined nests mainly surrounding necrotic foci or organized around the vessels. Mitotic activity is variable [42]. The angiotropism may be sometimes difficult to prove because of the density of the infiltrate and can be viewed only when using special stains for assessing elastic fibers of the vascular wall. In the adjacent pulmonary parenchyma, we can see features of pneumonia (Figure 2b) [12, 42].

b. Histologic grades

The different studies showed that the presence of numerous tumor cells is correlated to a bad prognosis. A microscopic grading system is proposed according to the amount of the atypical infested cells by EBV [12, 42].

Grade I is defined as a proliferation with a few infected cells (less than 5%), cellular polymorphism and the absence of necrosis.

Grade II is characterized by sparse infected cells (between 5 to 20%), cellular polymorphism and foci of necrosis

Grade III (considered as a high grade B cell lymphoma) is characterized by the presence of nests of infected cells by EBV, cellular monomorphism and extensive foci of necrosis

c. Immunohistochemistry

The few tumor cells of B phenotype express CD20 and express rarely CD79 and CD 30. CD15 antibody is never positive. Immunohistochemical study enables to identify LMP1 and EBNA 2 (EBV nuclear antigen 2) in B lymphomatous cells attesting of an EBV infection. Diagnosing a restriction of expression of kappa and lambda light chains is usually impossible in grade 1 lesions. T reactive lymphocytes express CD3, CD4 and rarely CD8 antigens [12].

d. Molecular biology / Genetic abnormalities

The association of the techniques of molecular pathology (Southern Blot, PCR, hybridation in situ) and immunohistochemical techniques enables to show an EBV infection and to assess a clonal rearrangement of immunoglobulin. These techniques are insufficient in cases with a few tumor cells or diffuse necrosis [42].

8.6.4. Other B Primary Lung Lymphomas

In less than 10% of the cases, B primary lung lymphomas don't meet the diagnostic criteria of MALT non Hodgkin lymphoma. These cases may correspond to a lymphocytic lymphoma, follicular lymphoma or mantle cell lymphoma. Mantle cell lymphoma shares the same radiologic findings than MALT lymphoma [1]. Primary plasmocytomas are extremely rare with only 40 cases reported in the literature [1]. Lung intravascular lymphoma is exceptional with only 7 cases reported in the literature. Microscopically, the lesion is characterized by a thickening of the interstitium and an atypical proliferation of lymphoid cells in the vessels [1].

8.6.5. Primary Pulmonary T Lymphomas

T lymphomas are very rare. Microscopic features consist in a pleomorphic proliferation with median to large cells infiltrating the inter.alveolar septa. The infiltration of the vascular wall is frequent. Immunohisotchemical study enables to confirm the T lymphoid nature of the proliferation (CD3+, CD20.). These tumors are similar to the extra.lymph node T lymphomas that are usually derived

from activated cytotoxic T lymphocytes. These lymphomas have a poor prognosis like the peripheral T lymphomas [1].

9. Tumor Associations

9.1. Synchronous Association of Adenocarcinoma and Pulmonary MALT Lymphoma

The association adenocarcinoma.MALT lymphoma has been described in the stomach where the helicobacter pylorus (HP) was incriminated in its pathogenesis. A few cases have been reported in the lung (48). Two pathogenic hypotheses have been reported. The first one implicated HP like in the stomach but because of the absence of the identification of HP in the lung, this hypothesis seems to be inappropriate. The second theory supports a genetic abnormality because of the identification of trisomia 3 in both MALT lymphoma and non small cell lung carcinoma.

9.2. Association to Other MALT Lymphomas

In 25 to 35% of the cases, MALT pulmonary lung lymphoma can be associated at presentation or in recurrent forms with extra.lymph node and extra.thoracic lymphomas [1]. This fact highlights the particular tropism of lymphomatous cells to lymphoid mucosal tissue. In its study about 70 cases, *Cordier* described an association of MALT PLL to extra.thoracic localizations in 6 patients [43].

9.3. Association to Other Neoplasia

An association between PLL to other neoplasms has been reported by some authors. Kurtin reported an association with a myeloma in one case, a urothelial carcinoma in 3 cases, a melanoma in 2 cases and a Hodgkin lymphoma in 1 case [44].

10. Differential Diagnoses

10.1. Differential Diagnoses According To the Radiologic Findings

10.1.1. MALT Lymphoma and High Grade B Cell Lymphoma

Radiologic findings of MALT lymphoma and large B cell lymphoma may mimic:

a. Mediastinal primary non Hodgkin lymphomas

These lymphomas may appear in chest.x.ray in the form of a polycyclic medastino.pulmonary mass, large, with regular mediastinal limit and an ill.defined external limit associated to an interstitial fibrosis. Hilar lymph nodes and inter.tracheo.bronchial lymph nodes may be observed. A pleural, pericardial, parietal infiltration is frequent [46]. CT.scan may be helpful in showing the mediastinal or pulmonary origin of the mass. The presence of a mass which is mainly pulmonary represents an important diagnostic element of PLL [1].

b. Pulmonary metastases of non Hodgkin lymphomas

Pulmonary metastases of non Hodgkin lymphomas are more frequent than primary localizations and are observed in 25% of the cases [36, 38]. In patients with a past medical history of lymphoma who present secondary pulmonary localizations, the diagnosis is easy and pulmonary localization represents a poor prognostic factor. Other cases may be challenging when the pulmonary localization is identified incidentally in patients without a particular past medical history [36, 38].

c. Primary pulmonary carcinomas and lung metastases

Primary pulmonary carcinomas can present as a peripheral nodule with a normal endoscopy. Lung metastases may have all radiologic aspects observed in PLL [1, 36, 38].

d. Tuberculosis

The tuberculosis is an endemic disease in our country and the diagnosis must be evoked facing any radiologic features. Radiographic findings consist in opacities or cavities of the upper lobes. Otherwise, the opacities may be disseminated in pseudotumoral tuberculosis. A round isolated opacity evokes a tuberculoma [1, 36, 38]. The negativity of the intra.dermo.reaction, the negativity of Koch's bacillus in the sputum and the inefficiency of the treatment are the clue of the diagnosis. Pulmonary calcifications are frequently observed in tuberculosis. They have never been reported in PLL.

e. Sarcoidosis

Sarcoidosis may be evoked especially in cases of hilar or mediatinal lymph nodes. The association of PLL and sarcoidosis has been reported [1,38, 46].

10.1.2. LG

The radiologic findings of LG consist in multiple excavated nodules. Facing these radiologic findings, many diagnoses may be suspected including metastases, tuberculosis, pulmonary infarct, Wegener granulomatosis, rheumatoid polyarthritis, infectious pneumonia, multiple hamartochondromas, amyloidosis and pneumoconiosis

10.2. Differential Diagnoses Based on Microscopic Features

10.2.1. MALT Lymphomas

The diagnosis of MALT lymphoma may be difficult in small biopsies. In these cases, this proliferation may mimic other small cell lymphomas (follicular lymphoma, mantle cell lymphoma and lymphocytic lymphoma) and lympho.proliferative disorders such as diffuse lymphoid hyperplasia, interstitial lymphoid pneumonia or a follicular bronchitis. Immunohistochemical studies are helpful in differentiating PLL and lymhpoproliferative disorders when showing the polyclonal character [1].

a. Lymphoid interstitial pneumonia (LIP)

LIP has been initially described by Carrington and Liebow in 1969. It is a pulmonary lymphoproliferative disease. Its etiopathogenesis and relation with PLL remain debated [47]. Some cases of lymphomas have been

reported following LIP. This fact made some authors suppose a pre.neoplasic potential of this lesion. In fact, LIP has been reported in association to dysimmune disease, to HIV and EBV viruses. According to the immunohistochemical techniques and molecular studies, we consider that a few cases of LIP may transform into lymphomas. It is more likely that the cases of transformation of LIP reported in the literature consist in a transformation of MALT lymphoma that wasn't diagnosed. LIP is characterized by a polymorphous lymphoid infiltrate, interstitial, dense and rarely nodular made of small mature lymphocytes, plasmocytes and histiocytes. A thickening of the alveolar septa, a pneumocytic hyperplasia and a macrophagic alveolitis are reported. Many lymphoid follicles with clear germinal centers have also been reported. These follicles are situated in the alveolar septa or in contact with bronchovascular axes. Lymphoid cells are of B and T phenotypes. T cells are observed in the interstitium and B cells in lymphoid follicles. The lesions may cause an architectural disorganization with honeycomb features. Epithelioid granulomas and amyloid deposits may be observed. Differentiating LIP from a MALT lymphoma may be challenging. In lymphomas, the cellular infiltrate is more dense and monomorphous. Pulmonary architecture is destroyed with the presence of lympho.epithelial lesions and an infiltration of the lymphoid follicles. Immunohisotchemical and molecular techniques are helpful in assessing the diagnosis [1, 49].

b. Follicular bronchitis(FB)

This entity is rarer than LIP. It is mainly observed in a special context such as Gougerot.Sjögren syndrome, rheumatoid poyarthritis or HIV infection. According to Bienenstock, it results from an antigenic stimulation of the BALT inducing a polyclonal lymphoid hyperplasia [50]. Microscopically it is characterized by numerous lymphoid follicles in the peribronchial tissue or within the bronchioles and pulmonary arterioles, inducing an airway compression. The infiltrate may extend to the alveolar interstitium without infiltrating the alveolar septa like in LIP. The bronchial epithelium is infiltrated by the lymphocytes without being destroyed. Intra.luminal exudate may be observed in 50% of the cases or rarely in foci of organized pneumonia. Microscopic features of FB and LIP may be inter.mixed and differentiating these entities may be challenging in such cases [1, 49].

c. Nodular lymphoid hyperplasia (NLH)

The existence of this benign entity has been debated. In 1963, Salzstein described pseudolymphomas as nodular lymphoid proliferations with numerous germinal centers [5]. In 1980, many cases diagnosed previously as non Hodgkin lymphoma appeared to be MALT lymphomas making the existence of this entity doubtful. Kardin and Mark redefined this entity in 1983 [51]. In 1999, the WHO and the International Association for the Study of Lung Cancer recognized it and the terminology of nodular lymphoid hyperplasia replaced the term 'pseudolymphoma' [52]. This lesion consists in well limited nodules measuring about 2,5 cm, white.grey, soft, unique or multiple. Microscopically, this lesion consists in a lymphoid tissue with numerous germinal centers with preservation of the mantle cell zone and an important sinusal histiocytosis. Russell bodies may be seen but without lympho.epithelial lesions, amyloid deposits and Dutcher bodies. Center.cell follicle cells express CD20, inter.follicular cells express CD3 [1].

d. Intra.pulmonary lymph nodes

They are rare, incidental and usually observed in smokers. These lesions are always peripheral, inferior to 2 cm, well limited and with preserved architecture. Moreover, they are generally anthracosic and may be associated to silicotic lesions [49].

e.Other microscopic lesions

Other microscopic entities may be also discussed because of their radioclinical presentation and the presence of a lymphoid component.

• Extrinsic allergic alveolitis can mimic a lymphoma in cases of a diffuse lymphoid and plasmocytic infitrate. The T phenotype of this infiltrate, the presence of an associated bronchiolitis and the presence of eosinophils help to diagnose this lesion [1].

• Inflammatory myofibroblastic tumors may mimic lymphoma in case of absence of infiltrated germ cell center but the absence of lymphoepithelial lesions and the presence of a diffuse fibrosis and the presence of numerous polyclonal plasmocytes are diagnostic keys of these tumors [1].

10.2.2. High Grade B cell Non Hodgkin Lymphomas

These tumors cause less diagnostic concern than MALT lymphomas. In small specimen, these tumors may mimic small cell carcinoma, melanoma or a sarcoma because of the artifact. Sometimes, the cytologic polymorphism of the lymphoid proliferation may make the differentiation between a non Hodgkin lymphoma of high grade and a transformation of MALT lymphoma difficult [1, 5].

10.2.3. LG

Differential diagnoses include Wegener granulomatosis and sarcoidosis with necrosis, benign lymphocytic and granulomatous angeitis [1].

a. Extra.lymph node nasal type T/NK lymphoma

LG has been confused with this lymphoma. Then, it has been proved that LG is a B proliferation with numerous T cells, EBV positive. This lymphoma is aggressive characterized by a diffuse lymphomatous proliferation with angiotropism and agiodestruction.

Vascular fibrinoid foci and necrosis may be seen. Tumor cells are small, median to large with numerous figures of mitoses. Lymphoid cells are mixed to lymphocytes, histiocytes and eosinophils. Tumor cells express CD 2, CD 56 and CD3. Occasionally, they may express CD 7 or CD 30 or EBV antibodies [1].

b. High grade B cell lymphoma with many lymphocytes

This lymphoma mimics mainly Grade II LG. it is characterized by numerous lymphocytes and histiocytes

and a few tumor cells representing less than 10%. There is no angiotropism. Tumor cells express CD 20 antibody and reactive lymphocytes are of T phenotype [1, 16].

c. Wegener granulomatosis

LG has been initially confused with WG which is characterized by its pulmonary and renal tropism. The presence of neutrophils cytoplasm antibodies is observed in 80% of the cases. Microscopically, WG is characterized by a vascular attempt with the presence of a palissading histiocytic granuloma with numerous giant cells and the presence of microabscesses. Large atypical cells are never observed [1, 16].

d. Necrotic sarcoidosis

This entity is very rare. It is characterized by lung excavated opacities. In the absence of mediastinal opacities, transthoracic lung biopsy is performed and microscopic examination shows parenchymal necrosis with typical epithelial and giganto.cell granulomas without atypical lymphoid cells [1, 16].

11. Extension and Stadification

In order to retain the diagnosis of PLL, other localizations must be assessed in order to retain the primary origin of the neoplasm. The extension of the disease must be assessed in order to validate the treatment modalities and to appreciate the response of the tumor.

12. Treatment

Because of the rarity of PLL, their management remains non consensual [1]. Treatment modalities include surgery, radiotherapy and chemotherapy. The efficacy of the different treatment modalities can't be compared because of the absence of comparative studies. New therapeutic modalities using monoclonal antibodies are studied [1]. Therapeutic abstention has been discussed in some low grade non Hodgkin lymphomas because of their slow evolution and indolence [1, 42].

12.1. Therapeutic Modalities

12.1.1. Surgical Resection

It is the mainstay treatment in localized forms according to *Cadranel*, *Ferraro*, *Graham* and *Eynden* [1, 36]. The resection should be complete. Usually surgical resection is followed or not by a chemotherapy with or without radiotherapy. Surgical resection consists in tumorectomy, segmentectomy, lobectomy or a pneumonectomy. Some authors advocate a penumonectomy in all cases because of the high rate of recurrences that are estimated to more than 50% [6, 7, 17, 33].

12.1.2. Radiation Therapy

It is rarely used in association to surgical resection or to the chemotherapy. The doses are limited to 15.20 grays because of the adjacent pulmonary parenchyma. The complications of radiation therapy are multiple including cutaneous toxicity, pulmonary fibrosis, dysphagia and hematologic troubles [1, 42].

12.1.3. Chemotherapy

It plays a key role in the treatment of PLL

a. The monotherapy

The products used in monotherapy are Endoxan and Chlorambucil.

b. Polychemotherapy

The objective of associating many drugs is to achieve a complete response and remission. The different protocols used are similar to those used in lymph node lymphomas.

The 2 main protocols include CVP protocol associating Cyclophosphamide, Vincristine and Prednisone and CHOP protocol associating Cyclophosphamide, hydroxydaunorbicin, Vincristine and Prednisone. These first.line generation protocols are the most used in PLL because of the majority of low grade lymphomas [1]. Nowaday, Rituximab has been added in maintenance treatment. It is a monoclonal antibody against CD20 which is expressed by all lymphomatous B cells [34].

12.2. Indications and Results

The indications are based on the age, the general state, the tumoral mass stage, the existence of an extra.thoracic localization and the histologic grade [1, 42].

12.2.1. Low Grade Non Hodgkin Lymphoma

The treatment of these tumors remains debated. Some authors advocate the surveillance but the majority of the authors recommend surgical resection or chemotherapy or an association of both. Today no publications have demonstrated the efficacy of the surgical resection or the chemotherapy or the association of both in the treatment of these tumors [1, 34, 42].

a. Localized forms

In these forms, surgical resection represents a mainstay treatment. Complete surgical resection enables 90% of survival. Adjuvant chemotherapy has been proposed by some authors in order to reduce recurrences and disseminations and especially the transformation of these lymphomas into high grade lymphomas. In elderly patients, a palliative treatment seems to be sufficient [1, 21, 51].

b. Diffuse forms

The treatment is based on chemotherapy. Some authors have proposed pneumonectomy in multiple forms of PLL of low grade that are localized in one lung but this attitude seems to be too aggressive in comparison to the indolence" of these tumors [1, 21, 33]. Zinzani et al, support the use of fludarabine and mitoxantrone.containing regimens as first.line therapy in the treatment of diffuse forms (53).

12.2.2. High Grade Non Hodgkin Lymphoma

The treatment is based on chemotherapy. It is used initially in disseminated forms or in association to surgical resection in localized forms [1, 21, 33, 42].

12.2.3. Lymphomatoid Granulomatosis

Therapeutic treatment modalities are non consensual. The most employed treatment is corticosteroids used alone or in association with chemotherapy. In both studies of *Fauci* and *Lipford*, a complete and prolonged remission was observed in respectively 54% and 50% of the patients treated by prednisone in association to cyclophosphamide [52, 54]. Other authors showed a high survival rate using polychemotherapy in grade III tumors [30]. In grade I and II tumors, Rituximab and interferon 2b seem to be encouraging [1]. Localized forms have been treated successfully using surgical resection and/or radiotherapy. Radiotherapy has also been reported in diffuse forms and/ or extra.thoracic forms particularly those with cerebral localizations [1].

13. Evolution

The comparison of the results of the different studies is difficult because of the few numbers of cases reported and the heterogeneity of therapeutic modalities [1, 7].

14. Prognostic Factors

The rarity of PLL and the heterogeneity of therapeutic modalities make the analysis of prognostic factors difficult.

14.1. Histologic Factors

14.1.1. Histologic Grades

Histologic grade is the most relevant prognostic factor reported by *Kennedy* and many other authors [1, 44]. In low grade lymphomas, the evolution is generally favorable with a 5.year survival superior to 80% of the cases and a median survival of 10 years. It has also reported that the survival of those patients was similar to healthy patients of the same age [1, 44, 51]. The 5.year survival of high grade lymphomas ranges between 0 to 60% of the cases with a median survival varying from 8 to 10 years. The evolution of these lymphomas is fast characterized by the multiplicity of recurrences [1, 22, 32, 44].

The prognosis of LG is generally poor with a median survival of 4 years. Death occurs in 38 to 80% of the cases [1].

14.1.2. Histologic Criteria

The number of atypical cells, vascular infiltration and necrosis have been reported as prognostic factors. The presence of germinal centers or the degree of agressivity toward the epithelium are non consensual and debated factors [1, 34]. *Kurtin* reported that the presence of amyloid deposits was a bad prognostic factor and that the lympho.epithelial lesions represent a good prognostic factor [44].

14.2. Age/ Sexe

An age superior to 60 years is considered as a poor prognostic factor. The risk of death is 4.5 ti superiorin patients aged more than 60 years [1, 21, 33].

14. 3. Clinical Factors

The presence of symptoms at presentation has a non consensual value. The association to an auto.immune disease is a poor prognostic factor with a risk ratio of 1.88 according to the study of *Kurtin* [34]. In LG, some factors have been considered as poor prognostic factors such as the existence of a neurologic lesion or a hepatosplenomegaly, the presence of leucopenia, a persistent fever or an anergy [1, 36, 33].

14.4. Clinical Stage

The regional lymph node infiltration doesn't seem to engage the prognosis. No significant relation has been established between the survival and the attempt of another mucosa. Medullary infiltration seems to be a poor prognostic factor [1, 36, 33]. In their retrospective studies, *Ferraro* and *Graham* haven't noticed a significant difference in survival rates between the different stages. A 5.year survival of 63% has been reported in IE stage toward 79% in IIE stages (p=0.8) [36, 33].

14.5. Biologic Factors

In lymph node lymphomas, levels of LDH and β2 microglobulin are correlated with the tumoral mass that is life.threatening. These markers have been rarely mentioned in PLL. *Kim* notes an increased level of LDH and β2 microglobulins in high grade lymphomas in comparison with low grade lymphomas suggesting a prognostic value of these markers.

Otherwise, the presence of a monoclonal gammapathy is correlated to a severe prognosis and a follow up of these markers is suitable in order to detect an early recurrence or dissemination [1, 21].

14.6. Therapeutic Factors

The prognostic value of the different therapeutic modalities is unknown because of the lack of standardization. *Eynden* reported a better 5.year survival in patients with complete resection in comparison to those with incomplete resection with respective rates of 87.5% and 25% (p=0.08) [48]. In the other hand, *Ferraro* reported in his study that the completeness of the resection has no prognostic value [33]. In both studies, the survival rates don't differ according to the association to chemotherapy.

15. Conclusion

Primary lung lymphomas are rare tumours, which are challenging in their diagnosis and management. Microscopic examination is mandatory to assess an accurate diagnosis but it is becoming more and more difficult facing the smaller size of the specimen obtained.

Molecular pathology is playing a key-role and may influence and guide the management and the treatment of these tumours by offering new molecular targets in the future.

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