Pulmonary mucosa-associated lymphoid tissue lymphoma revisited

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Pulmonary MALT Lymphoma Revisited

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Abstract

This general review sought to clarify the pathophysiological, diagnostic, prognostic, and therapeutic features of pulmonary mucosa-associated lymphoid tissue (MALT) lymphoma.

MALT lymphoma is the most common pulmonary B-cell lymphoma, which usually occurs in the context of acquired MALT. The disease is slow-growing with an asymptomatic chronic alveolar opacity visible on radiography. Diagnosis requires tissues samples that should be retrieved with minimally-invasive techniques, such as bronchoscopy or CT-guided biopsies. Pathophysiological includes cytogenetic abnormalities and auto-immune diseases, whereas an association with a chronic pulmonary infection is still suspected but not yet demonstrated. Disease prognosis is typically excellent and the current available treatments are discussed in this review, including decision not to treat, surgery, and single- or double-agent chemotherapy.

Keywords: primary pulmonary lymphoma (PPL), mucosa-associated lymphoid tissue (MALT), chronic alveolar opacity

Introduction

Our last review pertaining to mucosa-associated lymphoid tissue (MALT) lymphoma was published over 10 years ago [1]. We thus deemed it appropriate to provide an update in view of the recent advances that have since been made on this topic, thereby covering disease pathophysiology, diagnostic approaches, and novel treatments. B-cell lymphoma may occur in the lungs as secondary localization originating from extra-pulmonary lymphomas. T-cell lymphomas, however, are uncommon. Primary pulmonary lymphoma (PPL) is defined as a clonal lymphoid proliferation affecting parenchyma and/or bronchi of one or both lungs, with no detectable extra-pulmonary involvement at diagnosis or during the subsequent 3 months [2, 3]. PPL presents clinically in several different ways, each associated with a distinct B-cell lymphoma histological subtype. The most common PPL types are, in order of decreasing frequency [2, 4]: (1) extranodal marginal zone lymphoma (MZL) of MALT lymphoma, (2) diffuse large B-cell lymphoma (DLBCL), and (3) lymphomatoid granulomatosis (LG).

This general review sought to focus on and clarify the pathophysiological, diagnostic, prognostic, and therapeutic features of pulmonary MALT lymphoma.

Terminology

MALT lymphoma is the most common type of indolent B-cell PPL [5] (Table I), originating from post-germinal centre memory B-cells. They belong to the group of marginal zone B-cell lymphomas (MZLs) which also includes nodal and splenic MZL. However, these 3 MZL subtypes present very distinct clinical, morphological and molecular features [6-10]. MALT lymphomas represent 8% of adults diagnosed cases of non-Hodgkin lymphoma (NHLs) [11], making them the fourth most common histological subtype after DLBCL, follicular lymphoma, and chronic lymphocytic leukemia/small lymphocytic lymphoma [5].

From MALT to MALT lymphoma

MALT lymphomas rarely occur at sites where MALT is physiologically abundant, the Peyer's patches of the terminal ileum, most frequently found rather at sites usually devoid of MALT, such as the stomach, salivary glands, lungs, and thyroid.

Marginal zone (MZ) and bronchial mucosa-associated lymphoid tissue

The histological features of the marginal zone (MZ) of lymphoid follicles was first described in the spleen [12], later recognized in other sites, such as the Peyer's patches and in lymph nodes. Functionally, MZ B-lymphocytes are memory B-cells, and are involved in T-cell-dependent or -independent immune responses. MALT is a lymphoid tissue specialized in defending the mucosa [2], first described in the gastrointestinal tract (GALT) in animal models, then later in the ileum in humans. MALT is composed of four compartments: (1) organized mucosal lymphoid tissue, that consists of reactive lymphoid follicles which forms Peyer's patches when concentrated in the terminal ileum; (2) the lamina propria; (3) intraepithelial lymphocytes; (4) the mesenteric lymph nodes (Figure 1) [2].

Peyer's patches are mucosal non-encapsulated aggregates of lymphoid tissue, the structure of which is similar to that of nodal lymphoid follicles. The MZ surrounds the mantle zone of the follicle and extends toward the mucosal surface. It is composed of centrocyte-like cells, which resemble monocytoid cells and express pan B antigens, surface IgM, and surface IgA1, whereas being negative for surface IgD, CD5, and CD10. This differentiates them from naive B cells, which do express surface IgD. MZ B cells have mutated *Ig variable* region genes and the majority is post-germinal center memory B-cells. The B-cells found in MALT retain the ability to return to the tissues in which they underwent antigen stimulation, probably by means of surface integrin expression. MZ B-cells can also form clusters of intraepithelial B-cells. The lamina propria contains IgA-secreting plasma cells, macrophages, and B- and T-lymphocytes. The intraepithelial lymphocytes predominantly found in the jejunum consist of

CD8 T cells that express the human mucosal lymphocyte-1 antigen (HML-1, CD103). The basic structure of mesenteric lymph nodes is the same as that of peripheral lymph nodes, with a prominent MZ. Memory B-cells from post-germinal centers circulate in the peripheral blood and include cells from the MZ of the spleen, lymph nodes, and MALT.

Bronchus-associated lymphoid tissue (BALT) was first described in fetal and neonatal lungs affected by pulmonary infections of undetermined nature [2]. BALT can also be found in follicular bronchiolitis and be associated with various autoimmune disorders, such as Sjögren's syndrome, yet is not found in normal lungs. The stomach is the most commonly-affected organ in terms of MALT lymphoma, and several features of stomach MALT lymphoma can be extrapolated to MALT lymphoma in other locations like the lungs.

MALT chronic antigen stimulation

Lymphomas of the MZ are generally associated with chronic antigen stimulation, regardless of whether the antigens are auto-antigens or of microbial origin (Figure 2) [12]. This is an unusual form of lymphoproliferation, in which the infectious agent does not infect or directly transform the lymphoid cells, unlike lymphomas associated with Epstein-Barr virus (EBV), human herpesvirus 8 (HHV8), or human T-cell leukemia virus 1 (HTLV1) [13]. In MZ lymphomas, the infectious agent increases the risk of lymphomatous transformation by chronically stimulating B-lymphocyte proliferation. In cases of chronic antigen stimulation, such as *helicobacter pylori* (*H. pylori*) infection, MALT develops in the stomach and can later undergo lymphomatous transformation starting with the B-lymphocytes in the MZ. In the original observation of gastric MALT lymphoma, the malignant B-cell clone process initially requires the presence of the *H. pylori* antigen in order to proliferate, *H. pylori* being detected in almost 90% of gastric biopsies from patients with gastric MALT lymphoma [14, 15], and its eradication leads to complete and prolonged disease remission in 60-80% of early-stage gastric MALT lymphoma cases. *H. pylori* eradication has also been reported to be effective in

localized gastric DLBCL [12, 14, 16]. However some recent studies show an increasing rate of *H. pylori* -negative patients of up to 30-50% of gastric MALT lymphoma [17]. The reason for this remains unclear; the liberal use of antibiotic in patient with suspected *H. pylori* infection or symptoms might be a potential explanation for a shift in MALT lymphoma characteristics in the near future.

Other infectious agents have been suggested as possible causes of MALT lymphoma at other sites [12, 18, 19]. A causal relationship has been suggested between *Campylobacter jejuni* infection and small intestine MALT lymphoma, formerly known as alpha-chain disease or Mediterranean lymphoma, as well as between hepatitis C virus infection and some cases of splenic MZ lymphoma. Several studies have also found associations, though no proven causal relationship, between *Borrelia burgdorferi* (the agent that causes Lyme disease) infection and skin MALT lymphoma, and between *Chlamydophila psittaci* and ocular adnexal MALT lymphoma.

A causative antigen associated with MALT lymphoma in the lungs has not yet been identified. One study used polymerase chain reaction (PCR) in order to detect deoxyribonucleic acid (DNA) traces of *Chlamydophila pneumoniae*, *Chlamydia trachomatis*, *Chlamydophila psittacci* or *Mycoplasma pneumoniae* in tissues from patients with pulmonary MALT lymphoma (n=69). The results were compared to control specimens of other pulmonary lymphoproliferative disorders (n=30) and non-lymphoproliferative disorders (n=44) [20]. In this study, chlamydiaceae DNA was detected more frequently in MALT tissue than in samples taken from patients with non-lymphoproliferative disorders, although the difference was not statistically significant. Mycoplasma DNA was not detected. In addition, a recent multicentric European study using a 16S ribosomal ribonucleic acid (RNA)-based approach found DNA from *Achromobacter xylosoxidans* in 57/124 pulmonary MALT lymphomas *vs.* 15/82 controls (p=0.004)[21]. Further studies are now required to prove the

causal relationship between this pathogen and pulmonary MALT lymphoma. Using a non-*a priori* approach, our team assiduously pursues its research in this field using modern microbiology techniques. Powerful tools have, in fact, been developed for both DNA and RNA sequencing [22], enabling the analysis of all DNA and RNA present in a given sample, which could provide some evidence of a specific pathogen's presence be associated with pulmonary MALT lymphoma [23].

Chronic antigen stimulation may also be of autoimmune origin (Figure 2). MALT lymphomas in the salivary and thyroid glands have been more commonly observed in patients with auto-immune disease, Sjögren's syndrome or Hashimoto's thyroiditis, respectively. A meta-analysis involving 29,423 patients [24] confirmed that those with Sjögren's syndrome or systemic lupus erythematosus exhibited increased risk of MZ lymphoma. Primary or secondary Sjögren's syndrome was reported to be associated with a 6.5-fold increased risk of any type of lymphoma, a 1000-fold increased risk of salivary gland MALT lymphoma, and a 5-fold increased risk of lymphoma at other extranodal sites. Systemic lupus erythematosus was associated with a 2.7-fold increased risk of any type of lymphoma, and a 12.9-fold increased risk of extranodal lymphoma. Disorders involving chronic antigen stimulation, such as systemic lupus erythematosus, multiple sclerosis, Hashimoto's thyroiditis, and, in particular, Sjögren's syndrome, are all recognized risk factors for developing pulmonary MALT lymphoma [24].

Due to environmental risk factors, bakers and oil workers display an increased risk of ocular adnexal and cutaneous MALT lymphoma lymphomas, respectively [25]. However this risk has not yet been evidenced in pulmonary MALT lymphomas.

Cytogenetic abnormalities

The cytogenetic abnormalities that characterize and promote MALT lymphomas have been known for several years (Table II, Figure 2). Both the frequency and type of cytogenetic

abnormality vary depending on the lymphoma's site, and may also be related to the patient's origin. As opposed to other forms of lymphoma, MALT lymphomas are not characterized by a diagnostic genetic aberration, with the exception being to some extent t(11;18)(q21;q21) (API2-MALT1) discussed below, but rather display a variety of genetic features. Cytogenetic abnormalities are most frequently found in the lungs, and translocations are the most common abnormality type, with t(11;18)(q21;q21) being the most common translocation found and specific to MALT lymphomas [26]. This translocation is detected in 42% of pulmonary cases, 22% of gastric cases, and 15% of intestinal cases, though absent in most cases of thyroid, salivary gland, and liver MALT lymphoma [27, 28]. In gastric MALT lymphoma, the t(11;18)(q21;q21) translocation has been associated with lymph node dissemination and resistance to *H. pylori*-targeting antibiotics. As a consequence of this, the *API2* gene (apoptosis inhibitor 2), located on chromosome 11, fuses with the *MALT1* gene (MALT lymphoma-associated translocation), located on chromosome 18, resulting in the production of a chimeric protein: AP12-MALT1. Other translocations include the t(1;14)(p22;q32)/IGH-BCL10, t(14;18)(q32;q21) (IGH-MALT1), two rarer translocations reported in the stomach, lung and skin for the t(1;14) and in the liver, lung and ocular adnexa for the t(14;18) [27]. In each case, the translocation results in transcriptional dysregulation of the modified gene, and overexpression of BCL10 and MALT1, respectively in tumors cells. Another translocation, t(3;14)(p14.1;q32)(*FOXP1-IGH*), has recently been described, but is not specific of MALT lymphomas since it has also been reported in diffuse large B-cell lymphomas. Its presence excludes t(11;18)(q21;q21). FOXP1 protein is also overexpressed in MALT lymphomas with trisomy 3, suggesting that increased gene copy number may be another mechanism of deregulated gene expression.

All the translocations listed above, with the exception of t(3;14)(p14.1;q32), result in the constitutive activation of the NF-κB signaling pathway. The above-mentioned translocations

can be detected detected either by interphase fluorescent *in situ* hybridization (FISH) in formalin-fixed paraffin-embedded (FFPE) tissue sections or alternatively by reverse-transcriptase PCR assays (RT-PCR) in frozen tumor samples [24][26]. Other cytogenetic abnormalities associated with MALT lymphoma are trisomy 3 and 18 [26]. Aneuploidy is rarely associated with t(11;18).

Finally, MALT lymphoma could develop as a result of both cytogenetic abnormalities and antigenic stimulation. Illustrating this point, a mouse model simulating bcl10 or API2-MALT overexpression demonstrated the development of marginal zone hyperplasia without lymphoma. On the other hand, the mice undergoing API2-MALT1 overexpression developed lymphoma following antigenic stimulation with Freund adjuvant [29-31].

Epidemiology, clinical tests, and imaging

PPLs are rare clinical entities, representing only 0.5-1% of lung neoplasia cases (Figure 3). MALT lymphomas represent over 80% of PPL cases, constituting the most common type of pulmonary lymphoma [32-34]. PPL onset usually occurs at around 50-60 years of age, very occasionally affecting those under 30 years old [1]. Smoking rates (≈35%) were not found to be no higher among people that develop PPL than in the general population [34], and women were affected just as often as men. The presence of an immune system disorder was identified to be a predisposing factor for developing a MALT lymphoma, with a recent study reporting that 16% of patients presented an autoimmune disease at the time of diagnosis [34].

In nearly half of MALT lymphoma cases the patients are asymptomatic at diagnosis, and investigations are initiated solely due to an abnormal chest X-ray. If symptoms are present, they are mostly nonspecific, commonly including cough, minimal dyspnea, and chest pain, with hemoptysis also sometimes reported. Crepitant rales are detected by pulmonary auscultation in less than 20% of cases. While general symptoms like fever and weight loss are

observed in less than a quarter of MALT lymphoma patients, these are particularly associated with aggressive disease forms [1].

On radiological examination, MALT lymphomas typically manifest as a chronic alveolar localized opacity, less than 5cm in diameter, and associated with air bronchogram in nearly 50% of cases [35-39]. Computed tomography (CT) (Figure 4), which is more sensitive than standard X-ray, has demonstrated that the majority of MALT lesions are bilateral (60-70% of cases), multiple (70-77% of cases) [40, 41], and contain a clear patch within each lesion, corresponding to the intact bronchial lumen. MALT lymphomas are often diagnosed based on the presence of distended bronchi within lesions [41], and in less than 10% of cases, there are diffuse reticulonodular opacities in both lungs, atelectasis or pleural effusion [35-37]. Hilar or mediastinal lymphadenopathy may also be found on CT scan [35]. The mean time between the initial abnormal clinical or radiological findings and diagnosis is 9 months, though this may vary widely from 15 days up to 8 years [34-38].

On the clinical level, the challenge is to correctly diagnose MALT lymphoma based on radiological findings of chronic diffuse or localized alveolar opacities, which can correspond to several different etiologies (Table III).

Diagnostic approach

In cases where patients present with pulmonary lesions and when a MALT lymphoma is suspected, several approaches may be required to obtain sufficient information for a correct diagnosis, in order to exclude other inflammatory conditions and malignancies as well as accurately classify the exact lymphoma subtype. Tissue biopsy is the gold standard for diagnosis. FFPE biopsy samples are used for histological assessment and immunohistochemistry, while frozen samples are employed for molecular genetic analysis (PCR for immunoglobulin gene rearrangements). Biopsy samples can also provide cells for

cytological examination and flow cytometry. The goal of the diagnostic approach is to use minimally-invasive techniques, such as bronchoscopy and CT-guided needle biopsy, in order to limit the number of invasive procedures, such as thoracotomy with surgical biopsies.

Contribution of bronchoscopy with biopsies and bronchioloalveolar lavage

While the macroscopic findings on bronchoscopy are usually normal [35], abnormalities like inflammatory mucosa and bronchial stenosis may be observed [35]. Polypoid endobronchial lesions are very rare and usually appoint towards a small-cell non-Hodgkin lymphoma. Bronchial and transbronchial biopsies are more fruitful when carried out on endobronchial lesions or guided by the topography of abnormalities mapped by CT scanning [35]. The sensitivity of bronchial and transbronchial biopsies in detecting MALT lymphoma was reported to be 31 and 88%, respectively (Figure 5) [34].

Bronchioloalveolar lavage (BAL) performed during bronchoscopy may also aid in diagnosing chronic alveolar opacities. This technique can indicate the absence of tumor epithelial cells that are found in other malignancies, *e.g.*, lepidic adenocarcinoma (formerly termed bronchioloalveolar carcinoma), or the presence of pathogens pointing towards a chronic infection. The presence of lymphocytic alveolitis can also be indicative of PPL [42], though this lymphocytosis often presents a T-cell phenotype and does not appear to be specific to PPL, unless the B-lymphocyte level is greater than 10% [35, 42, 43]. Lymphocytes obtained by BAL may also include monocytoid, centrocyte-like or plasmacytoid cells. The diagnostic value of B-lymphocyte alveolitis is at its most significant, if the clonality can be demonstrated by illustrating the clonal rearrangement of immunoglobulin genes using either molecular biology techniques or light-chain restriction by flow cytometry [44-48]. Nevertheless, a negative result does not exclude a MALT lymphoma diagnosis. In a recent study, 84% of patients with MALT lymphoma (n=35) exhibited over 15% of lymphocytic alveolitis. B-lymphocytes accounted for more than 10% of the alveolar lymphocytes in cases where

phenotyping was available, and the B-cell clone was identified in 71% of cases [49]. Moreover, the translocation t(11 :18)(q21 ;q21), specific to MALT lymphomas, can be evidenced in BAL [50]. This data confirms that BAL could represent a powerful diagnostic tool that is currently underemployed in clinical practice.

If no specific lesion is identified by bronchoscopy, CT-guided aspiration and biopsy must be considered, particularly appropriate for peripheral nodules or masses. The sensitivity of this test has been reported to be 80% (Figure 5) [34]. Diagnostic surgery may then be performed as a last resort. This invasive approach requires significant effort, expense, and post-biopsy recovery time for the patient, yet does offer the advantage of providing larger biopsy samples than less-invasive procedures. Lymphomas can be morphologically and immunophenotypically complex, sometimes associated with reactive elements like non-neoplastic reacting T cells, granulomas, amyloid or fibrosis, rendering any diagnosis difficult using just small biopsy samples. When a localized lesion is present, a surgical approach provides the opportunity for radical treatment to be performed at the same time as the biopsy procedure (see below: Treatment section).

Pathological diagnostic criteria

The diagnosis of MALT lymphoma is established based on histological analysis of tumor tissue. The typical macroscopic characteristics of MALT lymphoma are a whitish mass, which is poorly delimited and soft, not dissimilar in texture to the cut surface of a lymph node affected by the lymphoma. Rare cases of focally-cystic MALT lymphoma have previously been observed.

The histological features of MALT lymphoma are the presence of lymphoid infiltrate expanding the marginal zone of reactive lymphoid follicles composed of small cells with variable cytologic appearance including small round lymphocytes, centrocyte-like cells or

monocytoid cells. Scattered centroblasts are present. Plasma cell differenciation is often seen in the lung. The tumor cells infiltrate the bronchiolar or the alveolar epithelium resulting in lymphoepithelial lesions. Follicular colonization by the tumor cells may be observed [33, 36, 51-53]. Cohesive sheets of large B-cells must suggest the diagnosis of DLBCL associated with MALT lymphoma.

Plasma cells may be numerous and may or may not show light chain restriction. Tumor cells infiltrates may also be seen along the bronchovascular bundles and interlobular septa in the masses' periphery, such as the alveolar and bronchiolar walls [54]. The density of MALT lymphoma infiltration often produces a widening of the alveolar walls, and collapses the residual alveolar lumens. The airways are often left intact, which correlates with air bronchograms seen on CT scan (Figure 6). More unusual forms of MALT lesions may include amyloid deposits or granulomatous reaction, vascular invasion [53-57] or fibrosis of varying degrees [54], though these are not key diagnostic features.

Contribution of immunohistochemistry

Immunohistochemistry analysis of FFPE tissue sections is mandatory to confirm the diagnosis of MALT lymphoma and to exclude reactive follicular hyperplasia or secondary localization to the lung of a nodal B-cell lymphoma. Tumor cells express CD20 and CD79a B-cell antigens and expand along bronchovascular bundles and interlobular septa (Figure 7) [33, 36, 38, 39, 51-54, 58]. They are CD5 negative which allows excluding the diagnosis of mantle cell lymphoma or chronic lymphocytic leukemia [46]. Residual lymphoid follicles may be highlighted with the staining of CD21+ CD23+ residual follicular dendritic cells [35, 45, 47]. Small reactive T-lymphocytes (CD3) can also be detected within the parietal alveolar infiltrate and around the peribronchiolar nodules [52, 54]. Plasma cell differentiation is further explored with immunostaining with anti-kappa and anti-lambda antibodies, and is very useful

to distinguish MALT lymphoma with monotypic plasma cells from a reactive plasma cell infiltrate. Morphology and immunohistochemistry allow ruling out the lung localization of mantle cell, follicular, lymphoplasmocytic or lymphocytic lymphomas [52, 54]. The proliferative index is usually low (Ki-67<10%).

Contribution of molecular biology

Current molecular biological techniques consists of PCR-based methods of frozen or FFPE tissue samples (sometimes with prior microdissection) to determine B-cell clonality. This analysis is very useful for cases where the morphological and immunohistochemical features are not sufficient to establish the diagnosis of MALT lymphoma. Chromosomal translocations are detected either by RT-PCR or by interphase FISH on FFPE tissue sections using break apart probes for the *MALT1* gene

FISH techniques can also detect extra copies of chromosomes 3, 8, and 18 that are common in MALT lymphomas. Alternatively to immunohistochemistry with anti-kappa and anti-lambda antibodies, chromogenic in situ hybridization with kappa and lambda probes may also be used to determine if the tumoral plasma cell component shows light chain restriction (clonal).

However molecular biology is not sufficient for the diagnosis of MALT lymphoma even in presence of a specific translocation. Moreover specific translocations are not actually treated by a targeted therapy.

Differential diagnosis

The primary challenge in terms of histology, particularly when using a small specimen, is to distinguish MALT lymphoma from (1) diffuse lymphoid hyperplasia and lymphocytic interstitial pneumonia (LIP); (2) follicular bronchiolitis and chronic aspecific inflammatory reaction, or (3) other low grade B-cell lymphomas as previously discussed and chronic non-

specific inflammatory reaction [53, 60]. While lymphoepithelial lesions may be observed in reactive conditions, detecting an intraepithelial lymphocytic infiltrate with a dual CD20/CD43-positive phenotype is nonetheless a strong indicator of MALT lymphoma [53]. Molecular based methods for B-cell clonality and interphase FISH are useful tools to distinguish reactive conditions from lymphoma. Lastly, a unique nodular presentation may correspond to plasma cell granuloma, inflammatory myofibroblastic tumor, or IgG4 syndrome.

Prognosis and treatment

Pretherapeutic staging

Lymph node lymphoma with secondary dissemination to the lungs can be ruled out using CT scan with contrast medium injection of the chest, abdomen, and pelvis, with contrast injection (Table IV). Bone marrow biopsy is not essential but may show MALT lymphoma dissemination in 13-30% cases (Figure 3) [7, 34, 61-63]. Similarly, concomitant disease in other mucosa-associated lymphoid sites is present in 25-35% of cases [62-64] (Figure 3), being more frequently observed in nondigestive MALT lymphomas. In a recent study of 63 MALT lymphoma cases, approximately 50% exhibited extrapulmonary involvement, 33% stomach involvement, and 14% bone marrow involvement [34]. Other mucosal sites must also be assessed only if symptomatic patients, including the eyes, ears, nose, and throat, in addition to magnetic resonance imaging (MRI) or ultrasound of the salivary and lacrimal glands, if in doubt, and gastroscopy and colonoscopy. Some cases may require evaluating the small-bowel transit.

Positron emission tomography using 18-fluorodeoxyglucose (PET-FDG) has yet to be investigated in detail. Its sensitivity and specificity can vary depending on the organ under consideration. PET-FDG assessment of the stomach appears to be associated with high rates of false-negatives, achieving a sensitivity of between 50 and 89% [65]. When assessing

pulmonary disease it produces better results, with a sensitivity of between 80 and 100% [66, 67]. PET-FDG cannot enable assessment of bone marrow involvement [34], though can detect plasmacytic differentiation with higher sensitivity [68].

The only laboratory tests that are useful in pretreatment screening are lactate dehydrogenase (LDH) levels, serum electrophoresis, and immunoelectrophoresis. Monoclonal gammapathy, which is present in 8 out of 10 IgM-type cases, is also found in 20-60% of MALT lymphoma cases. It is detected more frequently if plasmacytic differentiation is revealed [35, 37-39] and in extrapulmonary disease cases [34]. Finally, increased β2 microglobulin level appears to be an independent factor associated with poor prognosis [62].

Prognostic factors

The prognosis for patients with MALT lymphomas is good, with overall 5-year survival rates surpassing 80% and a median survival of over 10 years [33-39, 51, 56, 62-64, 69]. MALT lymphoma patients actually benefit from longer overall survival than patients with nodal or spleen MZ lymphoma [7]. However, the survival of patients with MALT lymphoma has not been demonstrated to be equivalent to that of the general population [32, 56]. The median survival of patients exhibiting MALT lymphoma of the digestive tract does not differ from that of other sites, yet progression-free survival seems to be shorter for diseases at other sites, particularly the lungs [61]. A long period of monitoring is required in these cases, as almost 50% of patients experience disease recurrence, either in the same location or outside the thoracic region [35, 39, 51, 56, 58], after >2 years following surgical resection.

The prognostic factors for MALT lymphomas have not yet been clearly demonstrated. None of the factors like gender, delay to diagnosis, symptom presence, whether the lesions were bilateral or not, extra-pulmonary involvement or medullar location offered prognostic power [34]. In a multivariate analysis including all disease sites, elevated ß2 microglobulin levels

[62], and Stage IV classification according to the Ann Arbor system [70] were found to influence prognosis. In a study of 63 patients with pulmonary MALT lymphoma, age and performance status were poor prognostic factors for overall survival [34]. A further retrospective study involving 48 MALT lymphoma patients failed to identify any prognostic factors at all [71]. In a retrospective cohort of lymphoma associated with Sjögren syndrome, active Sjögren syndrome was associated with worse prognosis. However, this cohort included both MALT lymphoma and DLBCL cases [72]. Very recently Thieblemont and al. had proposed a simple and effective prognosis factor including only age>70, Ann Arbor stage>2 and elevated LDH [73]. In a cohort of 393 patients, this 3 factors, when added, discriminated 3 risk groups with different 5-year progression free survival (78%, 63% and 29%; $p < 0.001$), and 5-year overall survival (99%, 92% and 74%, $p < 0.001$).

The transformation of MALT lymphoma to DLBCL has been suggested by the fact that the two histological subtypes could be observed on sequential biopsies in one single patient, with similar rearrangements of the *IGH* genes and accumulation of genetic abnormalities [27, 33, 37, 39, 52, 54, 74]. Nevertheless, given the t(11:18) presence, a more aggressive treatment strategy could be justified [75].

Main therapeutic options

The most recent recommendations have been centered on more frequent gastric MALT lymphoma [76, 77]. No microorganism has been identified that plays an equivalent role to *H. pylori* in gastric lymphoma. We are thus unable to use effective antibiotic treatment for pulmonary MALT lymphoma. However, a partial response has recently been reported in a patient with pulmonary MALT lymphoma, undergoing four courses of 14 days of clarithromycin (2g/d) without any pathogen evidenced [78].

Current treatments include surgery, chemotherapy, immunotherapy and radiotherapy. It is not possible to assess the relative effectiveness of these treatments, as comparative groups do not exist, and even non-treatment could be considered [79]. Nevertheless, surgical resection or radiotherapy may be considered if the lesion is localized [35, 37, 80]. Radiotherapy may then offer the benefit of less morbidity [81, 82].

The use of chemotherapy alone is permitted in cases of bilateral or extra-pulmonary disease, or in cases of disease recurrence or progression. Multiple-agent chemotherapy treatment, such as CHOP, is not thought to be superior to single-agent chemotherapy treatment using either chloraminophen or fludarabin [34, 35]. Furthermore, cyclophosphamide- or anthracycline-based chemotherapy in comparison to chloraminophen were poor prognostic factors for progression-free survival in one study [34]. Anti-CD20 monoclonal antibodies (rituximab) are effective, producing a 70% response rate in MALT lymphoma irrespective of the disease site, yet they are associated with high disease recurrence rates (36%) [83].

A prospective Phase III study involved 231 patients not suitable for local therapy, initiating them on a course of rituximab or rituximab-chloraminophen [84]. The primary objective was achieved, with significantly better 5-year event-free survival rates observed in the double-therapy group compared to the monotherapy (68% *vs.* 50%, p=0.02). Double-therapy increased the complete response rate (78% *vs.* 65%). The 5-year progression-free survival rate was increased in the double-therapy group, although not significantly [84]. The 5-year survival was not improved (89% rate). Grade 3-4 neutropenia was more common in the double-therapy group, whereas infection and toxic-death rates were equivalent in both. Rituximab alone was also evaluated in a third arm that was secondarly opened, the results of which being expected. In a retrospective cohort of gastric MALT lymphoma, the remission rate was 100% at 6 weeks when applying double-therapy, *versus* 45% with rituximab alone [75]. In the same cohort, the complete response rate after 104 weeks of chloraminophen alone

was 78% (20/27) *vs.* 39% in patients with and without the t(11:18), respectively [85]. However, there is no data available on pulmonary MALT lymphoma cases, despite the common presence of t(11:18) in this setting. Alternative therapies that have proven antitumoral effects are currently available, such as purine analogues (fludarabine; cladribine), pentostatin, NFκB inhibitor (bortezomib) or multiple-agent chemotherapy with chloraminophen/mitoxantrone/prednisone or bendamustine/rituximab [77, 86, 87]. However, the respective value of each treatment is difficult to estimate, particularly considering their side-effects [88]. Lenalidomide or bortezomib have also been evaluated, in second-line therapy [89-93].

Finally, local therapy should be considered when feasible. Medical therapy must take into consideration age, symptoms, dissemination, and performance status, and a watch-and-wait attitude could potentially be the best solution. First line therapy actually mostly used is rituximab-chloraminophen therapy. However, one should consider the cost and the risk of hematological complications, giving chloraminophen alone as an option.

Conclusion

Significant progress has been made in identifying the oncogenic mechanisms involved in the development of pulmonary MALT lymphoma. No infectious agent has so far been isolated as the cause for pulmonary MALT lymphomas, which may play an equivalent role to *H. pylori* in the development of gastric MALT lymphomas. The diagnosis of clonal lymphoproliferative disease has also benefited from using immunohistochemistry and molecular biological techniques. The techniques' potential contribution should be more widely evaluated, in particular using bronchoscopic biopsy with small specimens, in order to avoid traumatic thoracotomy procedures that are at times performed purely for diagnostic purposes.

In the absence of randomized trials specifically focused on pulmonary MALT lymphoma, the same treatment is currently offered for all MALT lymphoma types, regardless of the localization. When there is other localization or respiratory contra-indications, surgery or radiotherapy should be considered. Otherwise chloraminophen-rituximab should be envisaged on a case-by-case basis, and in some instances, simply monitoring the patient may be the most appropriate approach.

Table I: Primary pulmonary lymphoma according to the World Health Organization classification of tumors of hematopoeitic and lymphoid tissues

MATURE B CELL NEOPLASMS
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue/MALT lymphoma
Chronic lymphocytic leukemia / small lymphocytic lymphoma
Lymphoplasmacytic lymphoma / Waldenström macroglobulinemia
Primary pulmonary diffuse large B-cell lymphoma
Primary pulmonary plasmacytoma
Lymphomatoid granulomatosis
MATURE T-CELL AND NK-CELL NEOPLASMS
Peripheral T-cell lymphoma
Anaplastic large cell lymphoma
NK/T cell lymphoma
HODGKIN LYMPHOMA
POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS

Table II. **Main cytogenetic abnormalities involved in marginal zone lymphoma [15]**

Cytogenetic abnormality	Site (frequency)
t(11;18)(q21;q21) API2-MALT1	Lung (30-50%)
	Intestine (≈40%)
	Stomach (5≈30%)
	Ocular adnexa (0-5%)
t(14;18)(q32;q21) IgH-MALT1	Ocular adnexa, skin, salivary glands, liver (frequent)
	Lung (10%)
	Stomach (rare)
t(1;14)(p22;q32) BCL10-IgH	Stomach (5%)
	Lung (rare)
t(3;14)(p14.1;q32) FOXP1-IgH	All sites (10%)
	Thyroid (50%)
	Ocular adnexa (20%)
	Skin (10%)
Trisomy 3, 12, 18	Intestine
	Salivary glands
	Ocular adnexa

Table III. Main etiologies to be considered in cases of chronic single or multiple alveolar opacities

Frequent causes
Bacterial or viral pneumonia, slow to resolve
Organizing pneumonia
Tuberculosis
Pulmonary infarction
Less frequent causes
Lepidic adenocarcinoma
Pseudo-alveolar sarcoidosis
Lymphoma
Bacterial pneumonia involving slow-growing organisms (nocardiosis, actinomycosis)

Table IV Recommended procedures for initial staging of patients with disseminated MALT lymphoma according to ESMO consensus [76]

Mandatory	Full blood count Blood cytology Blood flow cytometry Serology for HCV, HBV and HIV CT scan BM aspirate and biopsy
Recommended	Reticulocytes GD endoscopy + ENT evaluation
Optional	Splenectomy Lymph node biopsy Autoimmune screening FISH and cytogenetics Clonality

BM Bone marrow, GD gastro-duodenal, ENT Ear-nose throat

Legends of Figures

Figure 1. The four compartments of MALT: (1) organized mucosal lymphoid tissue, consisting of Peyer's patches when concentrated in the terminal ileum; (2) the lamina propria; (3) the intraepithelial lymphocytes; (4) the mesenteric lymph nodes.

Normal small intestine pathogen/antigen filtration

Initiation of the immune response. Production of memory and effector B and T cells. Recirculation and domiciliation within other mucosa Lycke N, Nature Reviews. Immunology 2012; Isaacson PG, Nature Reviews. Cancer 2004

Figure 2. Pathophysiology of pulmonary MALT lymphoma. Development of MALT has been demonstrated to be related to chronic infection in the gut but not yet in the lung, and could be related to chronic auto-antigens stimulation (i. e. Sjögren Syndrome). Almost 50% of pulmonary MALT lymphoma show cytogenetic abnormalities and become independent from antigen stimulation if any.

Figure 3. Respective percentages of lung neoplasia. Primary pulmonary lymphomas (PPL) are rare; with MALT lymphomas the most common type of PPL.

Figure 4. Representative CT-scans with different pattern all confirmed to be pulmonary MALT lymphoma.

Figure 5. The diagnosis strategy adopted in a retrospective series of 63 patients with pulmonary opacity. First step: 61 bronchial and trans-bronchial biopsies during bronchoscopy;

second step: computed tomography (CT)-guided percutaneous transparietal biopsies. In the absence of previous diagnosis, the last step was open lung biopsy [34].

Figure 6. Representative section of a CT-scan, lung macroscopic and microscopic exams obtained from a patient with pulmonary MALT lymphoma. (A) The CT scan shows alveolar localized opacity with distended bronchi within lesions. (B) Macroscopic exam shows a whitish mass that revealed to be MALT lymphoma in microscopic exam with representative section of (C) respect of bronchial wall and (D) bronchial distention due to alveolar collapse.

Figure 7 Pulmonary MALT lymphoma. Panel A: proliferation in peribronchovascular interstitium (arrow head: septa; arrow: vascular lumen). Panel B: lymphoepithelial lesion, with bronchiolar epithelium masked or partially destroyed by the lymphoid infiltrate. Residual epithelial cells shown using anti-cytokeratin 10 antibody

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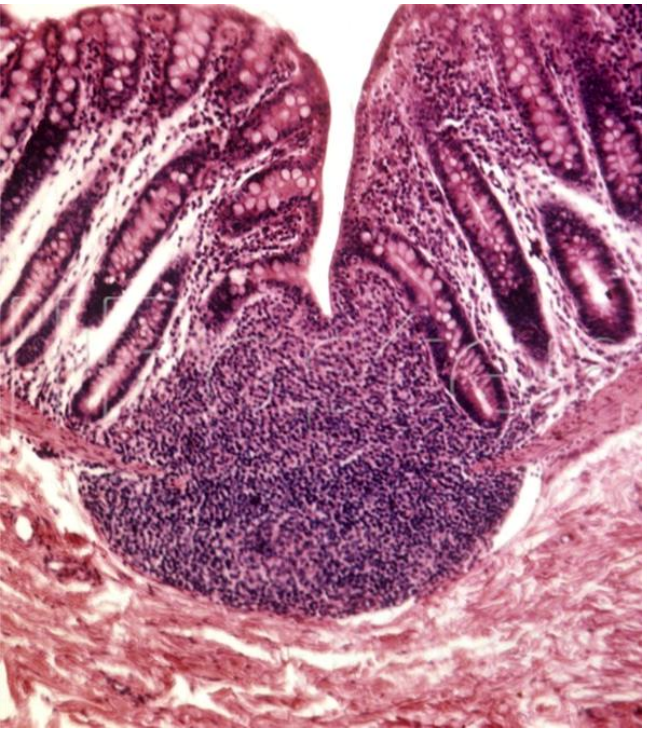
Figure 1



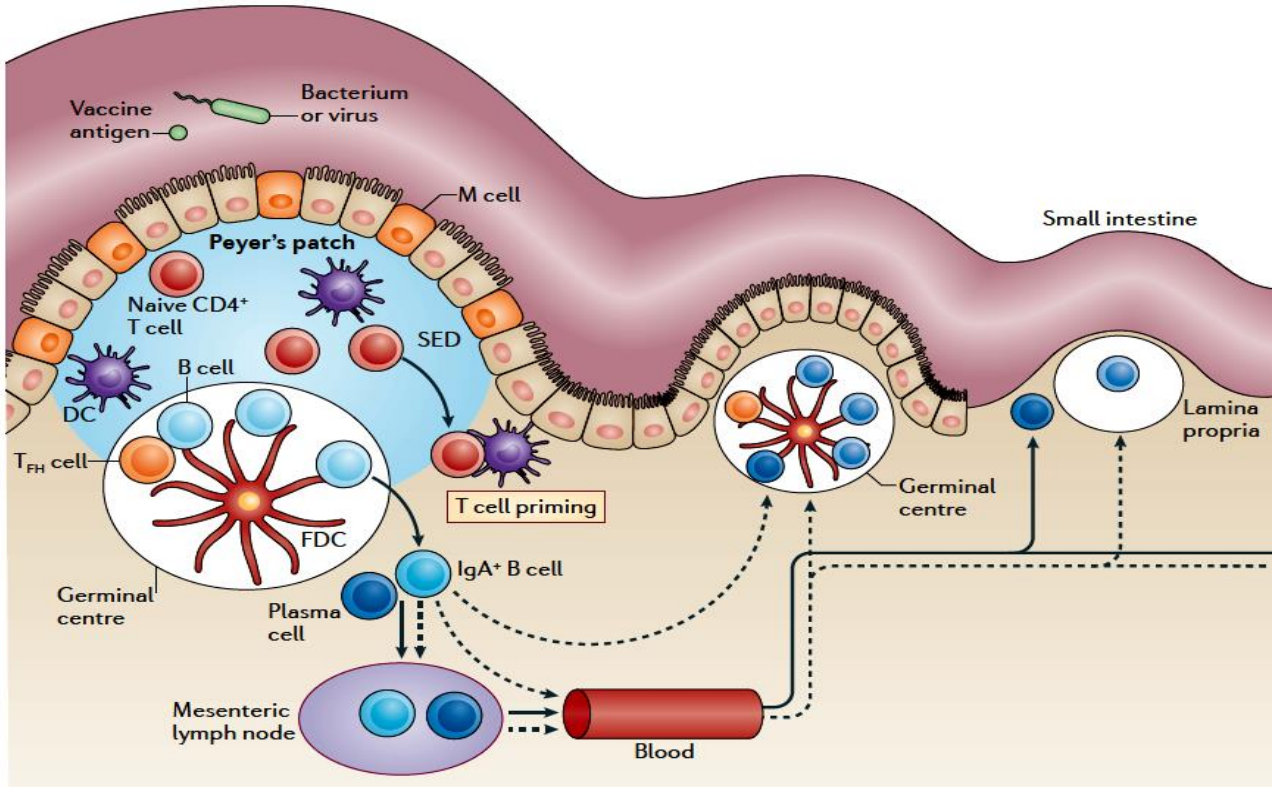

Vaccine antigen
Bacterium or virus
M cell
Small intestine
Peyer's patch
Naive CD4+ T cell
SED
B cell
DC
TFH cell
T cell priming
Lamina propria
Germinal centre
FDC
IgA+ B cell
Germinal centre
Plasma cell
Mesenteric lymph node
Blood

Figure 2

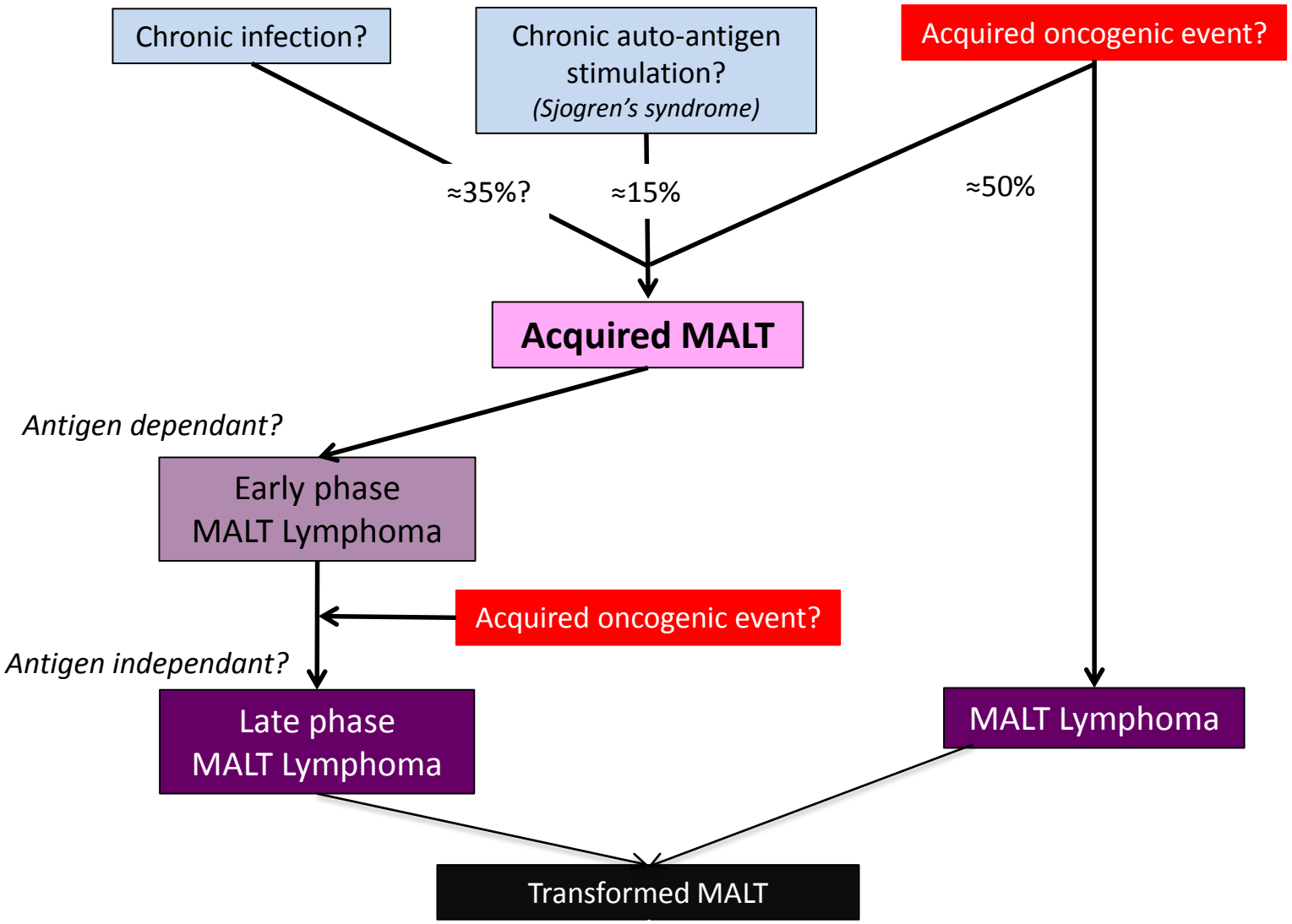

Chronic infection?
Chronic auto-antigen stimulation?
(Sjogren's syndrome)
Acquired oncogenic event?
≈35%?
≈15%
≈50%
Acquired MALT
Antigen dependant?
Early phase MALT Lymphoma
Acquired oncogenic event?
Antigen independant?
Late phase MALT Lymphoma
MALT Lymphoma
Transformed MALT

Figure 3

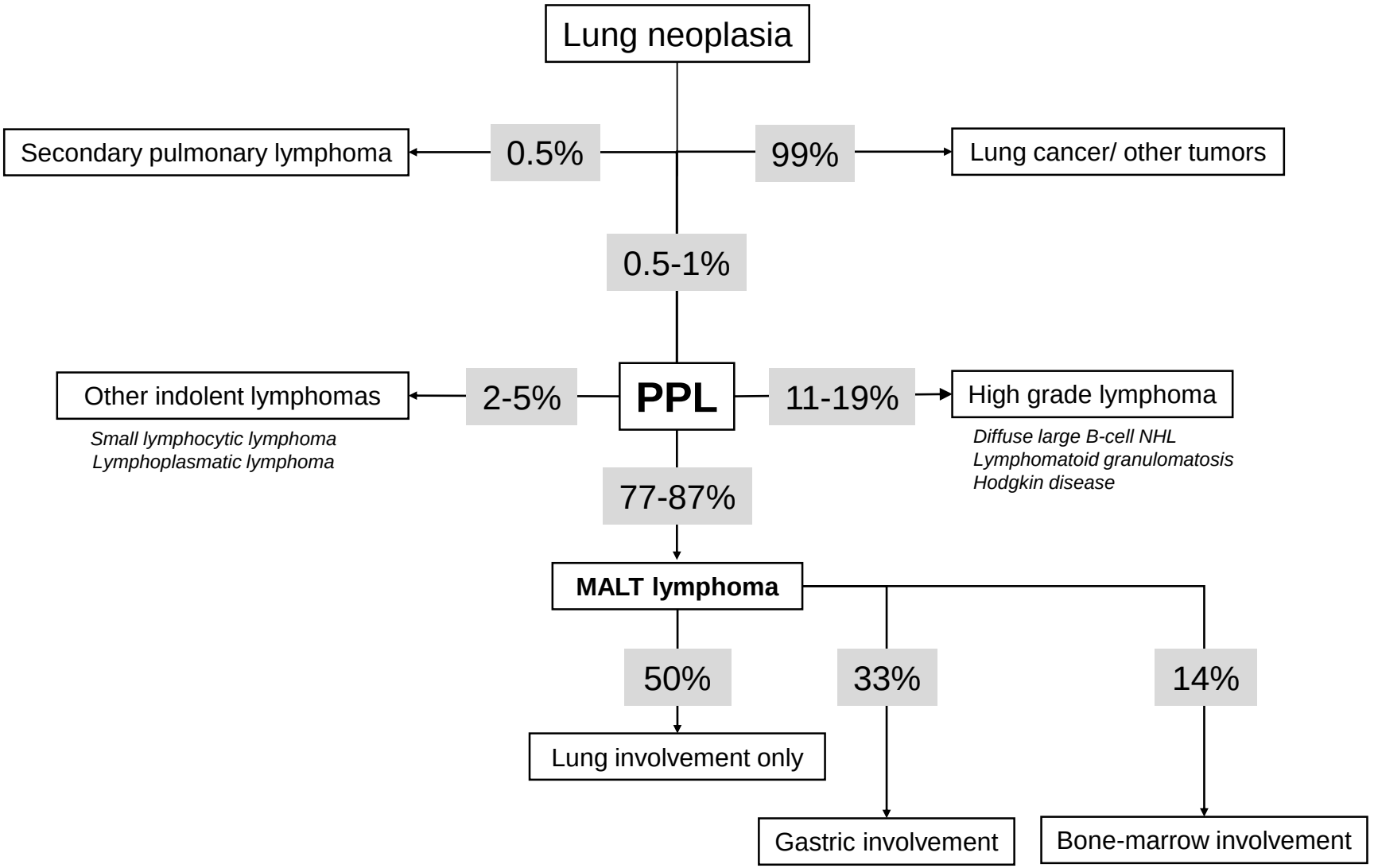

Lung neoplasia
Secondary pulmonary lymphoma
0.5%
99%
Lung cancer/ other tumors
0.5-1%
Other indolent lymphomas
2-5%
PPL
11-19%
High grade lymphoma
Small lymphocytic lymphoma
Lymphoplasmatic lymphoma
Diffuse large B-cell NHL
Lymphomatoid granulomatosis
Hodgkin disease
77-87%
MALT lymphoma
50%
33%
14%
Lung involvement only
Gastric involvement
Bone-marrow involvement

Figure 4

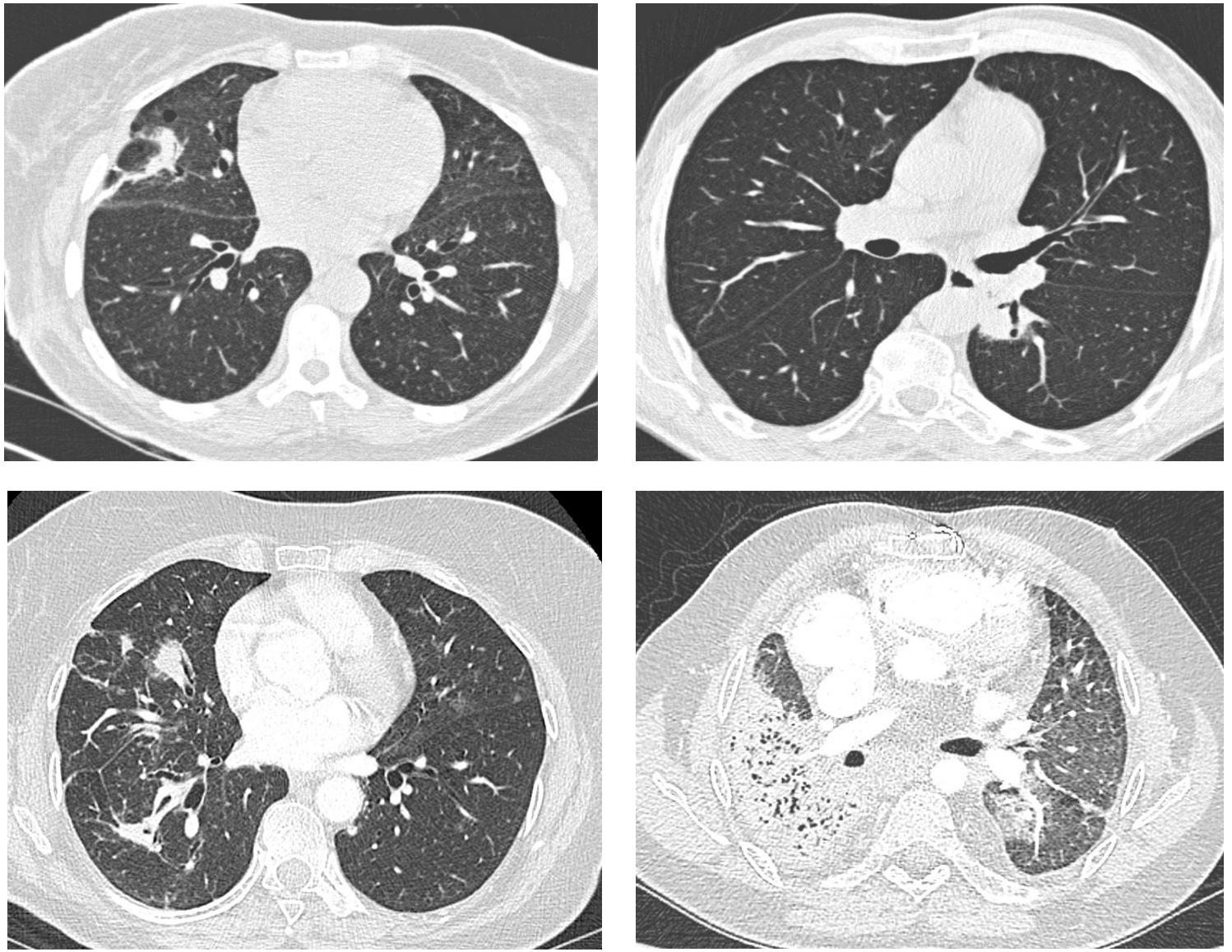


Figure 5

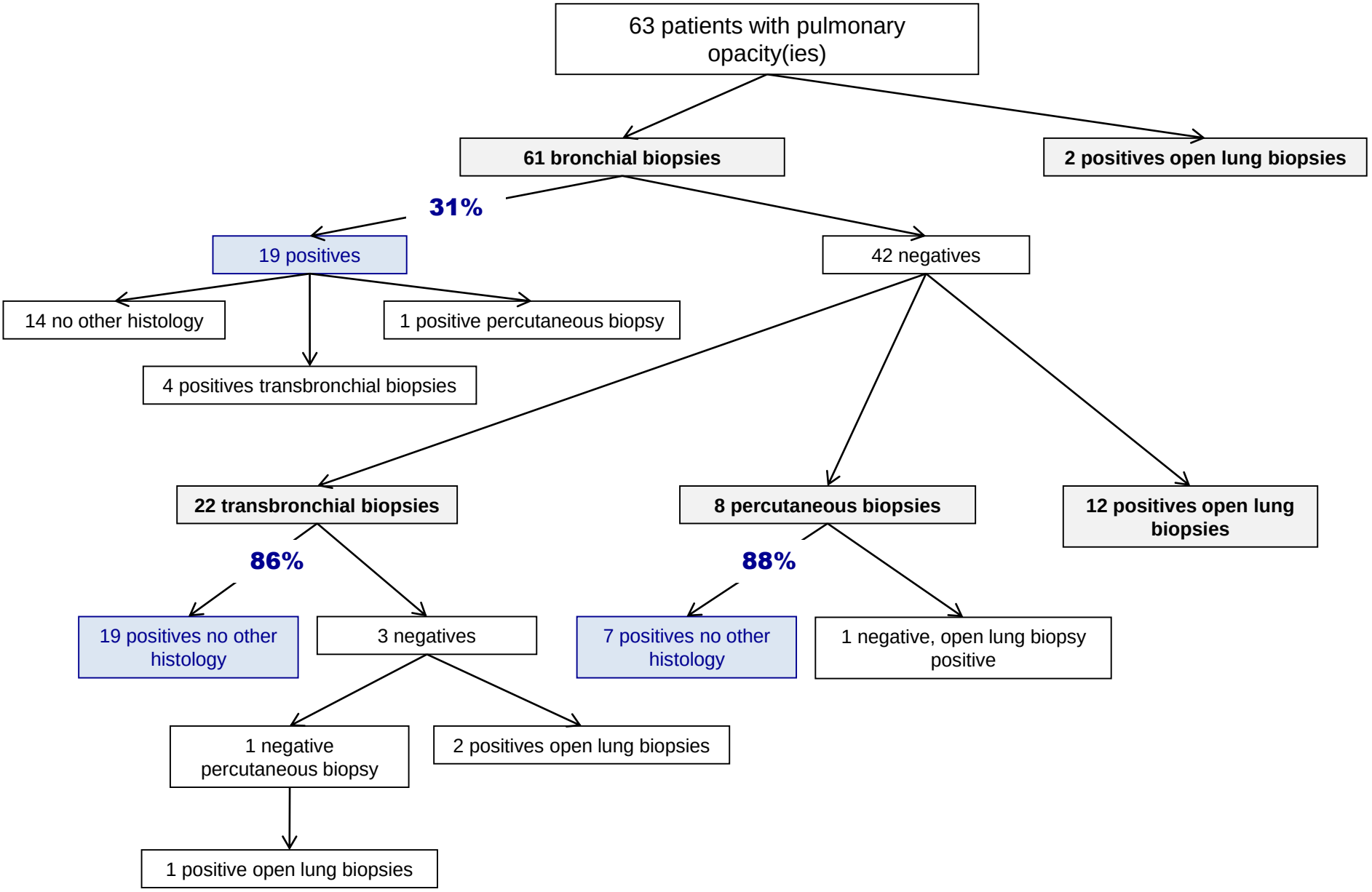

63 patients with pulmonary opacity(ies)
61 bronchial biopsies
2 positives open lung biopsies
31%
19 positives
42 negatives
14 no other histology
1 positive percutaneous biopsy
4 positives transbronchial biopsies
22 transbronchial biopsies
8 percutaneous biopsies
12 positives open lung biopsies
86%
88%
19 positives no other histology
3 negatives
7 positives no other histology
1 negative, open lung biopsy positive
1 negative percutaneous biopsy
2 positives open lung biopsies
1 positive open lung biopsies

Figure 6

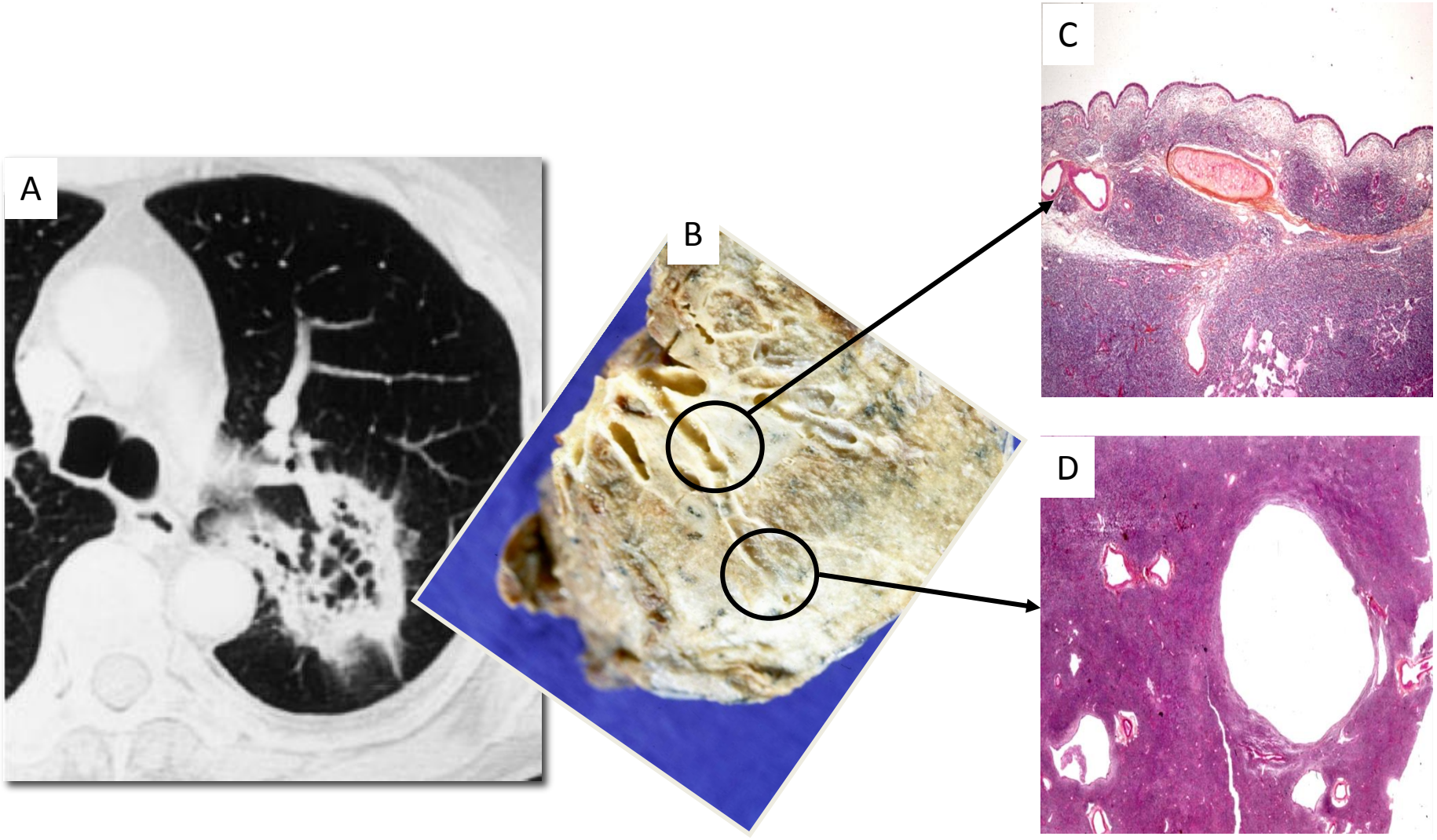


Figure 7

Histology