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Primary Pulmonary B-cell Lymphoma

Katalin Kelemen*, Lisa M. Rimsza, Fiona E. Craig

Mayo Clinic Arizona, Division of Hematopathology, Department of Laboratory Medicine and Pathology, Phoenix, Arizona

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Introduction

Primary pulmonary B-cell lymphoma is rare, representing less than 1% of all non-Hodgkin lymphoma, and 3-4% of all extranodal non-Hodgkin lymphoma,[1] and may involve the lung parenchyma, pleura, or mediastinum. Spread of systemic lymphoma to these sites is much more frequent, and is important to recognize because it is associated with an unfavorable prognosis.[2–5] Some subtypes of systemic B-cell lymphoma have a high prevalence of extranodal disease, including EBV-positive diffuse large B-cell lymphoma (DLBCL), post-transplant lymphoproliferative disorders (PTLD), and other iatrogenic immunodeficiency-associated lymphomas.[6] Although intravascular large B-cell lymphoma is often found in the lung at autopsy, the diagnosis is rarely established at this site.[7,8] Therefore, in order to distinguish primary pulmonary lymphoma from lung involvement by systemic lymphoma, a diagnosis requires absence of extra-pulmonary disease at presentation and over the course of the subsequent three months. [9]

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is the most frequent subtype of primary pulmonary B-cell lymphoma, with only rare reports of other subtypes of low-grade lymphoma, and approximately 10% primary pulmonary DLBCL.[9] Primary B-cell lymphoma involving the pleural cavity is rare and includes DLBCL associated with chronic inflammation, such as pyothorax-associated lymphoma (PAL), and primary effusion lymphoma. Large B-cell lymphoma presenting in the mediastinum represents approximately 5% of all non-Hodgkin lymphoma, with slightly more frequent DLBCL, NOS (non-thymic) than primary mediastinal (thymic) large B-cell lymphoma (PMBL), but this difference may reflect difficulty in establishing a confident diagnosis of PMBL.[10] In this article we will discuss the normal lymphoid tissue of the lung and pleura, the benign entities nodular lymphoid hyperplasia (NLH) and lymphocytic interstitial pneumonia (LIP) that can be challenging to distinguish from lymphoma, MALT lymphoma, DLBCL, NOS, DLBCL associated with chronic inflammation, and PMBL. Primary effusion lymphoma is discussed in another article in this series. Other lymphoproliferative disorders of the lung and mimickers of lymphoma, including lymphomatoid granulomatosis (LYG), IgG4 related disease, Castleman disease, Epstein-Barr virus positive mucocutaneous ulcer, graft versus host disease, and PTLD are also discussed elsewhere in this series.

Lymphoid tissue in the lung and pleura

The lung is rich in lymphoid elements and lymphatics. The lymphoid elements are arranged in two separate systems: the bronchus-associated lymphoid tissue (BALT), which represents the mucosa-associated lymphoid tissue of the lung, and the system of intra-parenchymal lymph nodes.

BALT is a system of nodular aggregates of lymphoid tissue at distal bronchial and bronchiolar division points composed of poorly formed primary follicles, mantle and marginal zones, and interfollicular regions. [11] BALT is the first responder to airway-derived antigenic and infectious stimuli. After an exposure to an inhaled antigen, BALT undergoes reactive changes of secondary follicle formation, polarization, development of conspicuous mantle zones, and expansion of the interfollicular region. Another component of BALT is the specialized airway “lymphoepithelium” overlying the lymphoid elements. The lymphoepithelium is a uniquely adapted pseudostratified mucosal layer of epithelial cells which lack cilia, and have decreased number of goblet

* Corresponding author: Dr. Katalin Kelemen, Mayo Clinic Arizona, 5777 East Mayo Boulevard, Phoenix, Arizona 85054.
E-mail address: Kelemen.Katalin@Mayo.edu (K. Kelemen).

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cells. Cells of the lymphoepithelium have the ability to selectively phagocytose and pinocytose and they are critical for antigen presentation of airway-born antigens.

The second lymphoid system of the lung is composed of intraparenchymal lymph nodes and lymphatic channels. The lung is equipped with an abundant delicate system of lymphatics that serve to drain fluid away from the airspaces toward hilar and mediastinal lymph nodes, and ultimately, into the thoracic duct. Within the lung, the lymphatics are distributed within and around bronchovascular bundles, within the interlobular septa, and in the pleura. Lymphoid proliferations, both reactive and neoplastic, commonly demonstrate a classic lymphangitic pattern of distribution within the lung.

Nodular lymphoid hyperplasia (NLH)

Nodular lymphoid hyperplasia is an unusual benign process in the lung that is important to distinguish from low grade B-cell lymphoma (in particular MALT lymphoma). This entity was described in 1963 by Saltzstein as “pseudolymphoma” composed of “an infiltrate of mature lymphocytes and other inflammatory cells, true germinal centers, and lymph nodes free of lymphoma”. [12] Over a number of years it became clear that many cases that were originally thought represent pseudolymphoma on morphologic grounds, were actually low-grade B-cell lymphoma. [13] This was confirmed with the introduction of immunohistochemistry, cytogenetic and molecular techniques to establish clonality[14], and therefore the diagnosis of NLH has become less frequent. A diagnosis of NLH today requires strict histopathologic, immunophenotypic, and genotypic criteria to ensure distinction from B-cell lymphoma, including preservation of normal immunoarchiatecture, absence of immunophenotypic aberrancy of the lymphocytes, and lack of evidence of clonality either by immunoglobulin gene rearrangement molecular study or by a cytogenetic method (fluorescence in situ hybridization (FISH) or karyotype). Using these criteria, a small series of 14 NLH presented by Abbondanzo et al. demonstrated a broad age range (19 to 80 years), with an average age of 60 years at presentation and a female predominance of 4:3.[14] Most patients were asymptomatic at presentation. Two thirds had a solitary pulmonary lesion without hilar or mediastinal lymphadenopathy. Computed tomography (CT) imaging revealed a discrete solitary mass or less commonly coalescence of multiple nodules with focal lymphangitic expansion adjacent to the mass. Surgical excision was curative and there were no recurrences. On gross examination, NLH most commonly measures 2-4 cm (average 2.1 cm) in greatest dimension, though occasionally may be up to 6 cm. The classic NLH is a sharply demarcated, non-encapsulated mass. The edge of the lesion can exhibit minimal extension along alveolar septa. Histologically, the mass is composed of lymphoid follicles with reactive germinal centers showing polarization and tingible body macrophages. Figure 1. The follicles are surrounded by discrete mantle zones. Interfollicular zones may contain sheets of plasma cells and lymphocytes. Immunohistochemical and molecular studies are in line with a polyclonal, reactive proliferation, as demonstrated by polytypic plasma cells, and lack of immunophenotypic aberrancies of the B lymphocytes (CD5 CD10, CD43, and cyclin D1 negative). Bcl-2 is negative in germinal centers, being restricted to mantle zones and T-cells. Amyloid deposits and colonization of germinal centers by marginal zone cells are absent, and would strongly support a diagnosis of MALT lymphoma. Although the presence of polytypic plasma cells would support a reactive process, light chain restriction can be difficult to demonstrate in MALT lymphoma because of admixed reactive plasma cells.

Lymphocytic interstitial pneumonia (LIP)

Lymphocytic interstitial pneumonia is another benign lymphoid proliferation in the lung that may be considered in the differential diagnosis of MALT lymphoma. This entity was described by Liebow and Carrington as a form of idiopathic interstitial pneumonia.[15] With the application of immunohistochemistry, some of the cases originally classified as LIP have been reclassified as MALT lymphomas. Furthermore, it became clear that the majority of the cases are associated with an underlying systemic disorder, such as a collagen vascular disease (e.g., Sjogren syndrome, rheumatoid arthritis, systemic lupus erythematosus), a congenital or acquired immunodeficiency state (common variable immunodeficiency, allogeneic bone marrow transplantation, human immunodeficiency virus infection), a viral or bacterial infection (Epstein Barr virus, Legionella, Mycoplasma, Chlamydia pneumoniae), a drug reaction, or pulmonary alveolar proteinosis.[16,17] As a result, the number of true idiopathic LIP cases is thought to be very few.

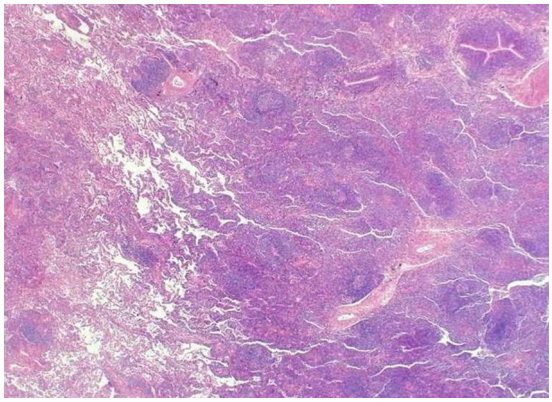

Figure 1. Nodular lymphoid hyperplasia. H&E stained section shows a sharply demarcated, non-encapsulated mass with minimal extension along alveolar septa along the edge of the nodule (100x). There are frequent reactive lymphoid follicles surrounded by discrete mantle zones, with germinal centers showing polarization and tingible body macrophages. Interfollicular zones may contain sheets of plasma cells and lymphocytes. Immunohistochemical and molecular studies are in line with a polyclonal, reactive proliferation.

Clinically, LIP affects a wide range of ages from infants to sixth decade. The patient usually presents with dry cough, dyspnea, fatigue and bibasilar crackles on auscultation.[18] The chest radiograph shows bilateral, fine reticular or reticulonodular opacities, predominantly in the lower lungs.[16] In contrast to NLH, the microscopical pattern of LIP is a diffuse interstitial infiltrate of small lymphocytes, immunoblasts, plasma cells, and histiocytes that expands the interlobular and alveolar septa. Occasional epithelioid and giant cell histiocytes may be present. Generally, lymphocytes are more numerous than plasma cells, though in some cases plasma cells may predominate. In a typical case the parenchyma is uniformly infiltrated. The interstitial small lymphocytes are predominantly CD3+ T-cells and the B-cells represent isolated foci of follicles along bronchi. Plasma cells demonstrate polytypic expression of kappa and lambda light chains. The differential diagnosis of LIP includes a variety of infections, other patterns of idiopathic interstitial pneumonias, and pulmonary involvement by a low grade B-cell lymphoma, such as MALT lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), and mantle cell lymphoma. It is important that in LIP the flow cytometric and immunohistochemical analysis demonstrates the predominance of T-cells, whereas, in low-grade B-cell lymphomas there is a predominance of small B-cells. In LIP, B-cells are polyclonal and show no immunophenotypic aberrancies, while clonality of the B-cells and /or that of plasma cells can be demonstrated in B-cell lymphoma by flow cytometry or B-cell immunoglobulin gene rearrangement testing. The diagnosis of LIP should prompt a careful clinical assessment of associated conditions, as the treatment should be directed to the underlying systemic disease. In true idiopathic cases the first line of treatment represents corticosteroids, with cyclophosphamide and chlorambucil reserved for second line of therapy. [16]

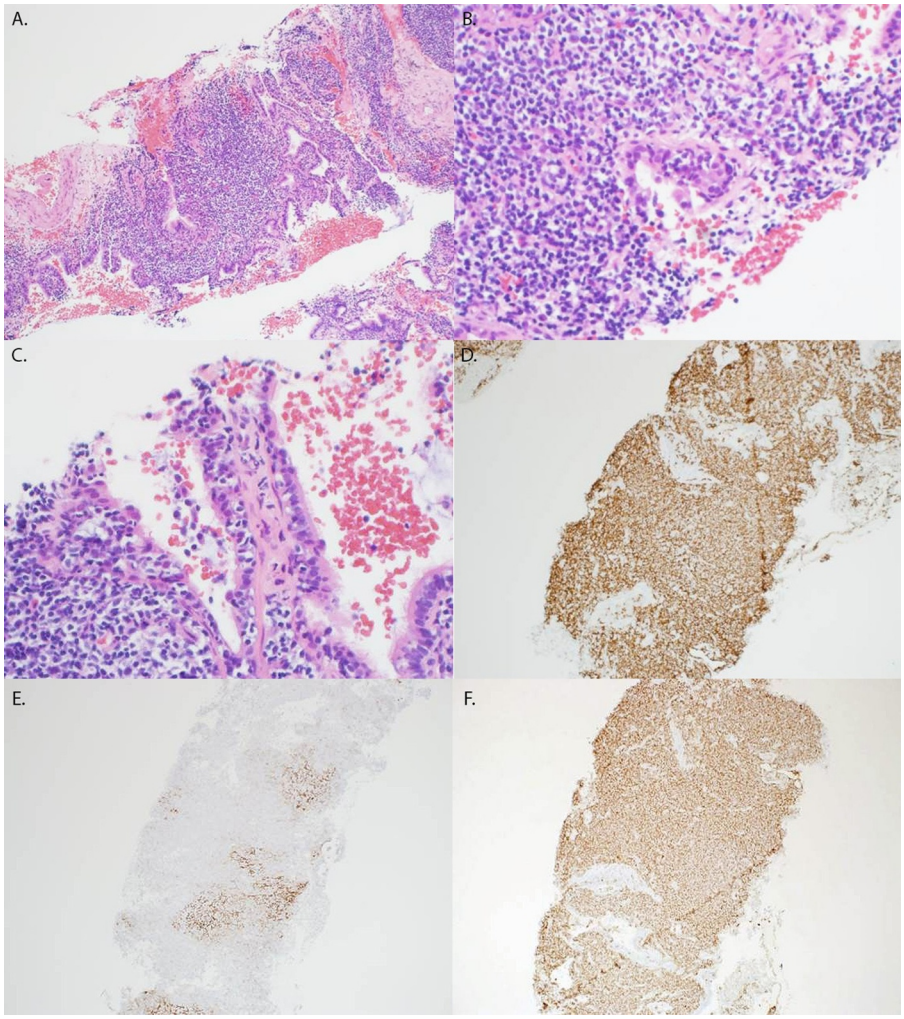

Figure 2. Marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) in the lung: morphologic and immunophenotypic features. (A) and (B) A dense nodular and diffuse infiltrate of small lymphocytes effacing the underlying lung parenchyma. A small bronchiolus shows lymphoid infiltration of the epithelium (A H&E stain, 100x; B H&E stain, 200x). C. Lymphoepithelial lesions (H&E, 200x). (D) The lymphocytic infiltrate is composed of CD20 positive B-cells (CD20 immunostain, 100x). (E) CD21 immunostain demonstrates follicular dendritic cell meshworks in the background of the B-cell infiltrate (CD21 immunostain, 100x). (F) The B-cell lymphoma aberrantly expresses CD43 (CD43 immunostain, 100x).

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

MALT lymphoma is the most common type of primary pulmonary lymphoma accounting for up to 90% of cases.[19–23] Since primary malignant lymphoma of the lung is rare, large case series are lacking in the literature, and some earlier reports are difficult to interpret due to a suboptimal distinction between true lymphoma and psedolymphoma. Pulmonary MALT lymphoma constitutes 15% of all MALT lymphoma,[24] and shares many features of MALT lymphoma at other sites, such as the gastrointestinal tract, thyroid, salivary glands, ocular structures. The current World Health Organization classification of Tumors of Haematopoietic and Lymphoid Tissues (WHO classification) defines MALT lymphoma as an extranodal lymphoma composed of morphologically heterogenous small B-cells including marginal zone cells, monocytoid cells, small lymphocytes, scattered large immunoblasts and centroblasts, and variable numbers of plasma cells.[25] Neoplastic cells reside in the marginal zone of reactive follicles and extend into the interfollicular region. On occasion, lymphoma cells may colonize germinal center. In mucosal sites, lymphoma cells typically infiltrate the epithelium forming lymphoepithelial lesions.

MALT lymphoma is closely linked to chronic inflammatory disorders that result in the accumulation of extranodal lymphoid tissue. The chronic inflammatory environment may be the result of an infection [10], smoking, [26] autoimmunity, most notably Sjogren syndrome [27] or unknown stimuli. Unlike MALT lymphoma in other organs that are associated with chronic infections, such as Helicobacter pylori in the stomach[28], Chlamydia psittaci in ocular MALT lymphoma[29], Borrelia burgdorferi in the skin[30], Campylobacter jejuni in immunoproliferative small intestinal disease[31], and hepatitis C in the liver[32], pulmonary MALT lymphoma does not have an identified infectious agent. Similar to MALT lymphoma of the thyroid gland, the pulmonary type has a strong association with autoimmune disorders, such as Sjogren's syndrome, rheumatoid arthritis, primary biliary cirrhosis, and others. [27,33]

Understanding of the cytogenetic and molecular changes that contribute to MALT lymphoma continues to evolve. Up to 50% of MALT lymphomas carry one of four chromosomal translocations: t(11;18)(q21;q21), t(1;14)(p22;q32), t(14;18)(q32;q21), and t(3;14)(p14.1;q32) resulting in the production of a chimeric protein (BIRC3-MALT1) and in transcriptional deregulation of BCL10, MALT1, and FOXP1, respectively. [34,35] Trisomy of chromosome 3 and 18 are nonspecific but are frequent findings in MALT lymphoma. In the lung, the most common cytogenetic abnormality is the t(11;18)(q21;q21) (30-50%), followed by trisomy 3 (20%), t(14;18)(q32;q21) (6-10%), then trisomy 18, and t(1;14)(p22;q32) (2%).[36] [37] Though not specific to MALT lymphoma, abnormalities of TNFAIP3 on chromosome 6q23, which may include deletions, mutations, and promoter methylation, occur in 15-30% of cases[38]. *MYD88 L265P* mutations have been reported in 6-9% of MALT lymphoma, based on studies performed on a spectrum of gastrointestinal, ocular, lung, head-and-neck, and skin MALT lymphomas. The specific prevalence of the mutation in MALT lymphoma of the lung is not yet known.[39, 40]

Clinically, patients with MALT lymphoma usually present in the 6th and 7th decades of life, with a median age of 67 years. The disease is

more common in females. One third of patients have a previously diagnosed autoimmune disorder. The majority of patients are asymptomatic, while approximately 30% may present with cough or dyspnea. Chest pain and hemoptysis are rare. Up to a third to a fourth of patients have a serum monoclonal IgM spike, and less frequently, IgG and IgA class monoclonal gammopathies have also been described. [13, 15,19, 41,42] IgD is usually negative. The light chain type of the serum monoclonal protein always matches the light chain type expressed by the neoplastic cells. Other laboratory studies are unrevealing. A defining feature of primary pulmonary lymphoma on radiographic studies is evidence of a pulmonary lymphoid infiltrate with the absence of hilar and mediastinal adenopathy. Chest radiographic and computed tomography (CT) imaging findings of pulmonary MALT lymphomas represent single or multiple nodules in one lung in the majority of cases. In 25% of cases, both lungs contain tumor nodules.[41,43] Ill-defined infiltrates containing air bronchograms are also frequently observed.

Microscopic examination of pulmonary MALT lymphoma shows disruption of the lung architecture by lymphoid infiltrates, see Figure 2. On a low-power review, infiltration pattern may vary from discrete nodular lesions, to a lymphatic-type distribution along the pleura, interlobular septae, and around bronchovascular bundles, or a combination of interstitial nodular collections of lymphocytes with bronchovascular infiltrates.[13,19–22,42, 44,45] The cells within the lymphoid infiltrates are heterogeneous, composed of small centrocyte-like lymphocytes, monocytoid lymphocytes exhibiting more abundant pale eosinophilic cytoplasm, and variable numbers of plasma cells. Plasma cells may contain immunoglobulin inclusions, forming intracytoplasmic Russell bodies and intranuclear Dutcher bodies. Although monoclonal plasma cells are commonly identified, there are often admixed reactive polytypic plasma cells. Scattered large immunoblasts and centroblasts are usually found in the infiltrate, but sheets of large lymphoid cells should not be present, and should raise suspicion of transformation to DLBCL. Lymphoepithelial lesions are usually present, characterized by infiltration and sometimes disruption of the ciliated bronchiolar epithelium, or a more cuboidal-appearing altered epithelium, by clusters of lymphoid cells. The lymphoepithelial lesions by themselves are not diagnostic of lymphoma because they are a feature of hyperplastic BALT. Broad sheets of prominent centrocyte-like lymphocytes that efface the underlying pulmonary architecture are an important morphologic feature that separates lymphoma from a reactive condition. Scattered large centroblastic cells are common, but should be in a minority and are usually singly dispersed. Reactive germinal centers are commonly present within the lymphoma. [13,21–23,42] Follicular colonization is often present and results in abnormal germinal centers that are devoid of tingible body macrophages, and may contain a monotonous infiltrate of small lymphoid cells or many plasma cells. In cases with monotypic plasma cell differentiation, follicular colonization can be visualized by a monotypic plasma cell population within the germinal centers. Figure 3. Although not specific, other histologic features that may be found in MALT lymphoma of the lung include vascular invasion without necrosis, [22,42] fibrosis.[23,42] ill-formed non-necrotizing granulomas[21,23,42], massive crystal storing histiocytosis,[46-48] nodular or interstitial amyloid deposition,[21,42, 49,50] and multinucleated giant cells.[17] Figure 3.

The classical immunophenotype of MALT lymphoma is positive for B-cell markers CD20, CD19, CD22, and CD79a, positive for Bcl-2, and negative for CD5, CD10, CD23, and cyclin D1[25]. Since the CD5 negative, CD10 negative immunophenotype overlaps with normal B-cells, additional immunophenotypic abnormalities, when present, are important to help to distinguish a MALT lymphoma from a reactive lymphoid infiltrate. Aberrant marker expression may include CD43, CD5, or rarely, Bcl-6 or CD10 on the B-cell lymphoma[25]. However, only about 50% of MALT lymphomas exhibit a distinct immunophenotypic aberrancy of the B-cells. Therefore, demonstrating light chain restriction of the plasma cells and/or the B lymphocytes may be essential to support the diagnosis of lymphoma. Molecular studies can also be used to demonstrate immunoglobulin heavy chain and light chain rearrangement, but may be confounded by a prominent polyclonal background.

The differential diagnosis of MALT lymphoma includes NLH and other types of small B-cell lymphomas, such as chronic lymphocytic leukemia /small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma, low-grade follicular lymphoma and lymphoplasmacytic lymphoma (LPL). The typical immunophenotypic features of these lymphomas help to differentiate them from MALT (expression of CD10 and Bcl-6 in follicular lymphoma, CD5 and LEF1 in CLL/SLL, CD5 combined with Cyclin D1 and SOX11 in mantle cell lymphoma). LPL is uncommon in the lung, and though the morphologic and immunophenotypic features may overlap with MALT lymphoma, additional systemic findings, such as involvement of extra-pulmonary lymph nodes and the bone marrow would be helpful to differentiate these two entities. Although presence of *MYD88* mutation is not specific for LPL, absence can help to exclude that possibility. In addition, cytogenetic findings by FISH could also help to identify a follicular lymphoma, or a mantle cell lymphoma, as opposed to a MALT lymphoma. Recently, immunoglobulin superfamily receptor translocation-associated protein 1 (IRTA) and myeloid nuclear differentiation antigen (MNDA) have been identified as useful markers in MALT lymphoma.[51,52] IRTA1 expression, evaluated by immunohistochemistry or in situ hybridization, is frequent in MALT lymphoma and rare in other small B-cell neoplasms.[51,52] MNDA is expressed in many MALT lymphoma, and a moderate number of other types of small B-cell lymphoma, but is rare in follicular lymphoma.[52]

The estimated lymphoma-specific survival rates at 1, 3, 5, and 10 years for patients with pulmonary MALT lymphoma were 95.0%, 87.4%, 84.5%, and 71.7%, respectively in one major study.[33] Pulmonary MALT-lymphoma can transform to DLBCL, and is recognized by the presence of confluent sheets or large aggregates of large B-cells. In one study, 18% of low-grade MALT lymphoma had a concurrent large B-cell lymphoma at diagnosis, which was clonally related to the low-grade component as demonstrated by concordant light chain restriction.[33] The recognition of large cell transformation of MALT-lymphoma is important so that the patients can receive appropriate treatment. When anthracycline-containing chemotherapy regimens are administered, patients with a frank DLBCL can have the same survival as those with low grade MALT lymphoma only.[33]

Diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS)

Primary pulmonary DLBCL represents 10% of primary pulmonary B-cell lymphoma, and includes equal proportions of large cell transformation of MALT lymphoma and de-novo disease.[9] Although mostly a disease of adults over 60 years old (30-80 years at presentation),[53] pediatric primary pulmonary lymphoma has been described and is associated with a high incidence of underlying immunodeficiency.[54] Patients with primary pulmonary DLBCL usually present with non-specific symptoms, such as cough, dyspnea or pectoral pain, with or without constitutional symptoms[53] and have diverse radiologic findings, which are frequently bilateral, and include consolidation, nodules, a reticular / interstitial infiltrate or ground-glass appearance, with or without mediastinal lymphadenopathy.[53,1] Primary pulmonary or mediastinal DLBCL, have morphologic, immunophenotypic, and molecular features indistinguishable from systemic / nodal DLBCL- NOS[2]: centroblastic or immunoblastic appearance, expression of pan-B-cell antigens, such as CD20 and Pax-5, germinal center (CD10, BCL6, LM02 expression) or non-germinal center cell of origin by immunohistochemistry (lacking GC markers, expressing MUM1), and absence of EBV and HHV8. Therefore, the clinical history and distribution of disease are essential for a definitive diagnosis of primary pulmonary DLBCL-NOS. LYG is another important differential diagnostic consideration for primary pulmonary DLBCL. However, LYG can usually be distinguished from primary pulmonary DLBCL by the presence of EBV-positive large B-cells, and often by the associated polymorphic inflammatory

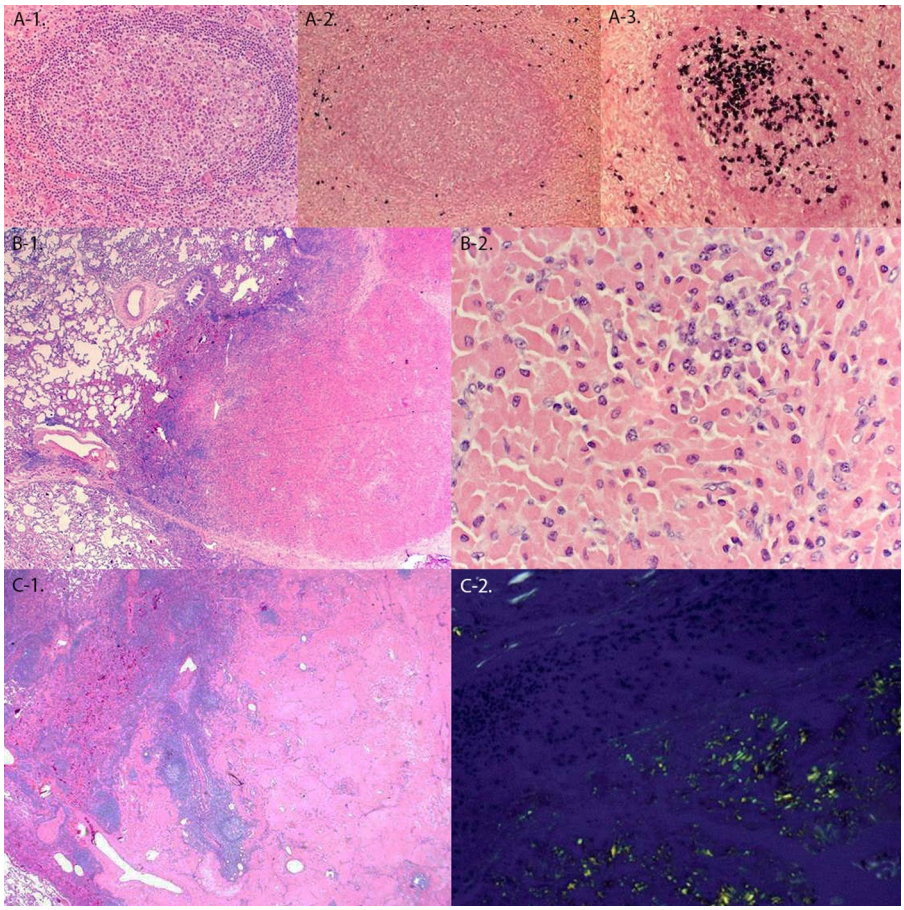

Figure 3. Marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma): additional morphologic findings. (A) Follicular colonization. The germinal center is effaced by collections of plasma cells and lacks tingible body macrophages (A-1, H&E stain). The plasma cells are monotypic kappa positive by kappa and lambda light chain in situ hybridization (A-2 lambda, A-3 kappa light chain RNA probes). **(B) Crystal-storing histiocytosis**. A well-circumscribed mass composed of sheets of large histiocytes with abundant pink cytoplasm, surrounded by a rim of lymphocytes and plasma cells (B-1 and 2). The plasma cells were kappa light chain monotypic by in situ hybridization (not shown). **(C) Amyloid deposition**. A well demarcated mass of pink hyaline-like material embedded in a background of lymphoplasmacytic infiltrate with several lymphoid follicles (C-1, H&E staini). A Congo red stain shows apple green birefringence (C-2).

background, including an abundance of admixed reactive T-cells, and vascular infiltration with associated necrosis.[6] LYG will be discussed in more detail in another article in this series.

Diffuse large B-cell lymphoma associated with chronic inflammation

DLBCL involving the pleura is rare (0.3-1% of extranodal lymphoma). A subset of primary pleural DLBCL is human herpes virus-8 (HHV-8) positive, and classified in the WHO classification as primary effusion lymphoma (PEL), which will be discussed in another article in this series. Of the HHV-8-negative cases, a subset could be considered HHV-8 negative PEL,[55] and are mostly EBV-negative. Of interest, some HHV-8-negative PEL have an immunophenotype similar to HHV-8-positive PEL, lacking expression of B-cell antigens such as CD20, and CD20 expression has been identified as a favorable prognostic factor, along with age.[55] Earlier literature describes primary pleural lymphoma that is EBV-positive and associated with prior chronic inflammation.

Pyothorax-associated lymphoma (PAL) is the prototypical example of DLBCL associated with chronic inflammation, usually developing more than 20 years after artificial pneumothorax for pulmonary tuberculosis or tuberculous pleuritis. This therapeutic approach to tuberculosis was popular in Japan in the 1930s, peaked in incidence in 1951, and is no longer in use.[56] Occasional cases of PAL not associated

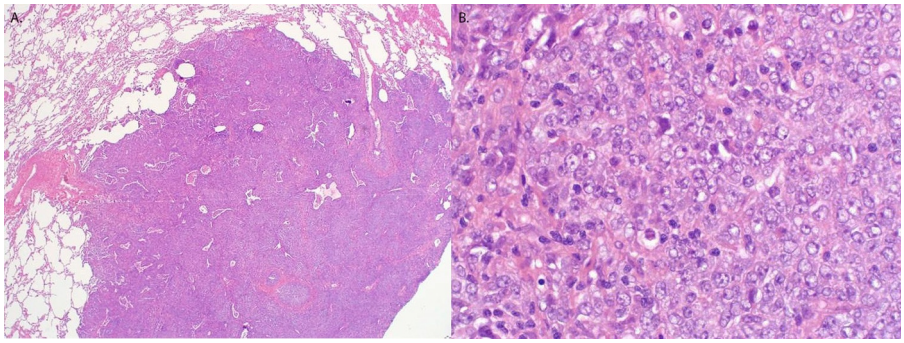

Figure 4. Diffuse large B-cell lymphoma. (A) Infiltrate of abnormal lymphoid cells in the lung parenchyma (H&E, 20x). (B) On higher magnification, the infiltrate is composed of large centroblastic cells with vesicular chromatin (H&E, 50x).

with tuberculosis have been described.[56] It has been proposed that PAL arises in the setting of local chronic immune stimulation and possibly local immunodeficiency.[56] PAL usually presents with chest pain, and a pleural effusion with one or more associated mass lesions, but without involvement of the pulmonary parenchyma. Biopsy demonstrates fibrosis and an infiltrate of large abnormal lymphoid cells, with scant associated non-neoplastic small lymphoid cells and plasma cells.[57] Most PAL are composed of large cells with an immunoblastic appearance and a CD20-positive, CD30-negative B-cell immunophenotype. PAL may show plasmacytoid features, with expression of CD138 and cytoplasmic immunoglobulin, and usually has a CD10-negative, MUM1-positive post germinal center immunophenotype.[6] Aberrant T-cell antigen expression has been described in PAL, and along with lack of B-cell antigen expression in some cases may lead to uncertainty about lineage.[57,58] EBV is identified in approximately 70% PAL, usually with a latency III pattern.[6] Although the morphologic appearance and immunophenotype of PAL may resemble primary effusion lymphoma (PEL), PAL is HHV8 negative and is not associated with a systemic immunodeficiency disorder. *TP53* mutations, *MYC* gene amplification and a complex karyotype are frequent in PAL.[56,59] Some patients reach a durable remission with therapy, but co-morbidities are frequent, and PAL often has an aggressive behavior. Fibrin-associated EBV-positive DLBCL has been separated from DLBCL of chronic inflammation in some sites, such as heart, endovascular graft thrombi, and pseudocysts, because of a more indolent clinical course,[5,6,60] but this distinction has not been made in the lung and pleural cavity.

Primary mediastinal large B-cell lymphoma (PMBL)

Primary mediastinal B cell lymphoma (PMBL) is covered in this chapter on pulmonary B cell lymphoma because of its origin in the anterior mediastinum with penchant for local invasion and therefor frequent invasion of the lung and pleura. PMBL was initially reported in 1986 with the key clinical features outlined, including location in the anterior mediastinum, local invasion, relatively young patient age at diagnosis, more common in female patients (1 of only 2 lymphomas, along with nodular sclerosis Hodgkin with a female predominance), and relatively good clinical outcome.[61,62] The authors proposed that the cell of origin of PMBL may be a thymic B cell. Dissemination outside the thorax includes kidneys, adrenals, ovaries, liver, brain, skin, and the gastrointestinal tract. Initially, there was resistance to the general concept that cases within the morphologic spectrum of DLBCL should be further classified based on tissue of origin. Thus, PMBL remained a subtype of DLBCL in the Revised European and American Lymphoma Classification in 1994.[63] However, PMBL was established as a distinct entity by the publication of the WHO Classification of Tumors of the Haematopoietic System in 2003, and continued as its own disease type in the 2008 and 2016 editions. Since then, additional studies such as those detailed in the following paragraphs further established PMBL as a disease entity distinct from DLBCL. Importantly, recent clinical trial data suggest that a more dose-intense treatment regimen than that usually administered for DLBCL may benefit patients with PMBL.[64] These sorts of dose intense regimens that omit radiation treatment may be particularly important in young females to reduce the long-term risk of breast cancer and cardiovascular disease.[65] However, a precise diagnosis on which to base informative clinical trials can be difficult because PMBL traditionally relies on a combined radiologic/clinical/histologic diagnosis, each with its own pitfalls. In particular, the histologic features PMBL can exhibit morphologic and immunophenotypic profiles that overlap with other types of lymphoma. In addition, the radiologic features are not always reliable since histologically similar-appearing DLBCL can occur in the mediastinum and conversely PMBL-like tumors can be found at other anatomic locations in both adults and children.[66-68] Thus, it is becoming ever more critical to recognize PMBL cases so that appropriate clinical trials can be conducted and correct therapy can be administered

Histologically, key characteristics of PMBL typically include a diffuse pattern of invasion, large cells with centroblastic or sometimes multilobulated nuclei, conspicuous nucleoli, moderate to abundant amounts of clear cytoplasm, and fine compartmentalizing sclerosis with few to moderate numbers of background inflammatory cells. Immunohistochemical stains can be used to identify remnants of thymic epithelial cells (See Figure 5). Immunohistochemically, there are no specific features. PMBL expresses mature B cell markers and, intermittently, germinal center markers (CD10, BCL6); however, often lacks surface immunoglobulin. Activation markers CD23 and CD30 are also frequently observed although of variable frequency and intensity. MAL, TRAF and REL are other suggested IHC markers. However, at present, there is no generally agreed upon IHC approach.[69-71] Of note, CD30 has recently become an important target of therapy with use of the anti-CD30 antibody brentuximab vedotin.[72]

Active study of PMBL has increased understanding of this entity, and provided possible diagnostic strategies and therapeutic approaches. By cytogenetics, amplifications of 2p16 (including the genes *C-REL* and *BCL11A*, implicating the nuclear factor-kappa B pathway), and 9p24.1 (including the genes programmed death ligand 1 and 2 genes *PDL1, PDL2*) implicating immune-escape; as well as Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathways are key mechanisms in PMBL lymphomagenesis (see additional discussion below). [73-75]

Previously, detailed evaluations of the cellular pathways perturbed in PMBL were published almost simultaneously by two research groups using gene expression profiling of snap frozen tissue biopsies.[76,77] Both papers emphasized the differences between PMBL and usual DLBCL confirming that PMBL should be considered a separate disease entity. Intriguingly, both papers also described patterns of gene expression in PMBL that overlapped with classical Hodgkin lymphoma (cHL) particularly with regard to over-expression of genes related to the JAK-STAT pathway. The degree to which non-Hodgkin B cell lymphomas and cHL are difficult to separate is reflected in the 2008 WHO classification with the appearance of the diagnostic category termed “B Cell Lymphoma, Unclassifiable, with Features Intermediate Between DLBCL and cHL” also known as Grey Zone Lymphomas (GZL). This terminology is used for cases with the morphologic appearance of DLBCL with immunophenotypic features of cHL or cases with the morphologic appearance of cHL but the immunophenotype of DLBCL. While GZL is typically used to describe cases with features intermediate between DLBCL and cHL, PMBL is also usually part of the differential diagnosis. Simplistically, while DLBCL demonstrates the complete immunophenotype of a mature B cell including CD45(+), CD20(+), surface immunoglobulin(+), Oct2/Bob1(+); PMBL expresses mature B cell markers but lacks surface immunoglobulin; while cHL lacks both mature B cell markers and surface immunoglobulin. GZL falls into an intermediate immunophenotypic category. One unifying marker of all these diseases is the pan-B cell antigen Pax5.

In PMBL, advanced techniques have described, in addition to gains/amplifications at 2p15 and 9p24.1, frequent translocations of the master transactivator of the major histocompatibility complex II gene (*MHC2TA* or *CIITA*). These *CIITA* translocations have ubiquitous partners and can be detected in 38% of PMBL cases. Inactivation of *CIITA* results in under expression of MHC II, and together with alterations in PDL1/PDL2, result in immune evasion. These findings are supported by previous GEP studies showing that indeed, there are fewer tumor infiltrating T cells in large B cell lymphoma without MHC II expression and that PMBL cases without MHC II expression had a worse outcome.[78-80] A recent comprehensive paper evaluating structural

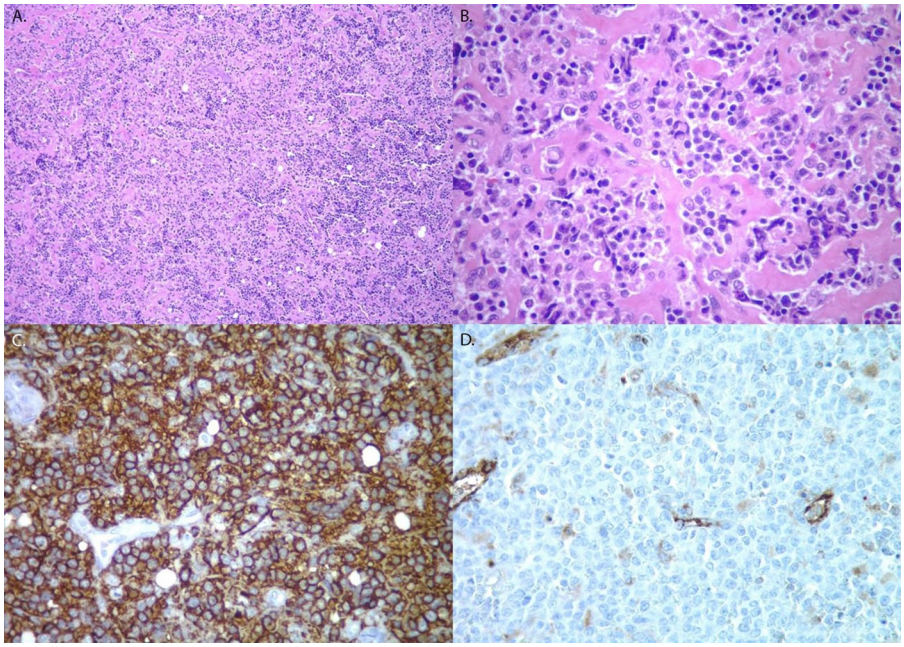

Figure 5. Primary mediastinal large B-cell lymphoma. (A) From medium power, a diffuse, somewhat pauci-cellular infiltrate is present (-H&E stain, 200x); (B) a higher power magnification demonstrates fine, compartmentalizing sclerosis with round and also multilobated large lymphoid cells (H&E stain, 400x); (C) CD20 is strongly expressed (CD20 immunostain, 400x); (D) HLA-DR, an MHC Class II antigen presenting molecule is negative indicating tumor immune evasion (HLD-DR immuno stain, 400x).

abnormalities and mutations in PMBL further underscores the immune-evasion strategy of PMBL.[81,82] In this study, the authors confirmed the previous observations regarding structural aberrations and mutations involving *CIITA*; as well as copy number alterations and rearrangements of the *PDL1* (CD274) and *PDL2* (CD273) genes at 9p24.1 responsible for T cell mediated immune responses. Furthermore, mutations in the interferon regulatory factor (IRF) genes including a mutational hotspot in *IRF4* itself and its downstream target genes, involved in B cell immune response, were detected in 52% of cases. Altogether, this multi-pronged genetic approach on the part of PMBL, affecting antigen presentation, as well as responses from T cells, B cells, natural killer cells and macrophages creates an immune privileged phenotype for PMBL. Sequencing studies demonstrated that the JAK-STAT and NF-kappaB signaling pathway genes, including suppressor of cytokine signaling 1 (*SOCS1*), appear to be most frequently altered. Intriguingly, and harkening back to prior gene expression studies, the driver gene mutation profile in PMBL was more similar to Hodgkin lymphoma than to DLBCL.

As the biology of PMBL has become clearer, and treatment has diverged from usual DLBCL, it has become ever more important to accurately diagnose these cases. In 2018, a quantitative digital gene expression method for use in formalin-fixed, paraffin-embedded tissues was described with excellent accuracy and reproducibility between laboratories.[83] This assay, known as the “Lymph3Cx”, uses digital gene expression profiling to measure the expression levels of 58 genes. This assay demonstrated 100% reproducibility between biological replicates (different sections from the same tissue block) and between laboratories. In conjunction with morphology and immunophenotype, reliable molecular diagnostic tools such as the Lymph3Cx, *CIITA* translocations by FISH, and gene mutation profiles, will be important to accurately classify PMBL cases in order to generate informative clinical trial results to improve patient care.

Declaration of Competing Interest

LM Rimsza is an inventor on a patented gene expression profiling assay described in this article.

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