Lymphomas and lymphoproliferative diseases of the lung

Aliyah R Sohani

Judith A Ferry

Abstract

Primary pulmonary lymphoma is a rare disease and the majority of cases represent extranodal marginal zone lymphoma, followed by diffuse large B-cell lymphoma. Other lymphomas that commonly involve the lung include lymphomatoid granulomatosis, a neoplasm of large EBV-positive B cells that are typically outnumbered by non-neoplastic T cells, and classical Hodgkin's lymphoma, which usually reflects systemic dissemination or direct mediastinal extension. The differential diagnosis of marginal zone lymphoma includes secondary involvement by other systemic low-grade B-cell lymphomas and chronic reactive conditions, such as nodular lymphoid hyperplasia, while the other entities elicit a differential diagnosis that includes various high-grade lymphoid neoplasms. A specific diagnosis can usually be achieved on the basis of histological evaluation and immunophenotyping, although molecular genetic studies may be required in certain situations. Such a multiparameter approach may be warranted to accurately diagnose these entities due to differing clinical implications in terms of prognosis and treatment.

Keywords differential diagnosis; diffuse large B-cell lymphoma; Hodgkin's lymphoma; lung; lymphomatoid granulomatosis; MALT lymphoma

Introduction

Primary pulmonary lymphoma is rare, accounting for 0.3% of primary lung neoplasms, 3–4% of extranodal lymphomas and <0.5% of all lymphomas. It is defined as lymphoma presenting with one or more pulmonary lesions, without clinical, radiologic or pathologic evidence of lymphoma elsewhere in the past, at present, or for 3 months following presentation.[1] Patients typically present with respiratory symptoms, including cough, dyspnoea, chest pain, haemoptysis and wheezing, while constitutional symptoms are less frequently seen. Asymptomatic clinical presentations occur in up to 40% of patients and are more commonly seen with low-grade lymphoma. Accurate diagnosis typically requires surgical procedures, such as video-assisted thoracoscopic surgery (VATS), wedge biopsy or segmentectomy. In contrast to primary lung lymphoma, secondary pulmonary involvement by lymphoma is relatively common, with lung involvement developing at some point in the disease course in 38% of Hodgkin's lymphoma and 24% of non-Hodgkin's lymphoma.[2] In these circumstances, pulmonary involvement may reflect direct extension of tumour involving the hilum or mediastinum or may be due to distant metastasis arising from haematogenous spread. In this review, we will provide an overview of the most common types of lymphoma that involve the lung, with a focus on a multiparameter approach to diagnosis, and discuss challenging issues in their diagnosis and differential diagnosis, including distinction from non-neoplastic entities.

Aliyah R Sohani *MD James Homer Wright Pathology Laboratories of the Massachusetts General Hospital and Department of Pathology, Harvard Medical School, Boston, MA, USA. Conflicts of interest: none.*

Judith A Ferry *MD James Homer Wright Pathology Laboratories of the Massachusetts General Hospital and Department of Pathology, Harvard Medical School, Boston, MA, USA. Conflicts of interest: none.*

Extranodal marginal zone lymphoma (MALT lymphoma)

Clinical and pathological features

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is a low-grade B-cell lymphoma that accounts for more than 70% of primary pulmonary lymphoma. Patients are typically adults with a median age of presentation in the 6th or 7th decade and a slight female predominance. A monoclonal serum paraprotein has been reported in up to 43% of patients at the time of presentation. A history of cigarette smoking or underlying immunologic abnormality, such as autoimmune disease or prior or ongoing infection, is common. Associated autoimmune diseases include Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis and common variable immunodeficiency. MALT lymphoma has also been in reported in the setting of viral infection, including human immunodeficiency virus (HIV) and hepatitis C virus. The cell of origin, a marginal zone B-cell of bronchus-associated lymphoid tissue, is thought to undergo clonal transformation in the setting of chronic antigenic stimulation. On imaging, MALT lymphoma may present as solitary or multiple lesions in a unilateral or bilateral distribution. These lesions may take the form of nodules, masses or infiltrates resembling focal areas of parenchymal consolidation.[1]

Histologically, MALT lymphoma is composed of small monomorphous lymphocytes with oval to slightly irregular nuclei, inconspicuous nucleoli and scant to moderately abundant clear or pale eosinophilic cytoplasm (termed "marginal zone cells") with admixed plasmacytoid lymphocytes and plasma cells (Figure 1a).[3] The latter may be conspicuous in cases with plasmacytic differentiation, which may also manifest itself by the presence of intranuclear immunoglobulin pseudoinclusions (Dutcher bodies). Large cells may be present, but are typically rare and scattered. The lymphoma cells demonstrate a nodular or diffuse sheet-like growth pattern in the centre of the lesion, with an interstitial pattern of infiltration at the periphery resulting in widening of the alveolar septae with the occasional formation of small nodules away from the main lesion (Figure 1b). Invasion of blood vessels and of bronchi with erosion of bronchial cartilage may be seen, and plaque-like growth may be present when the lymphoma involves the overlying pleura. As with MALT lymphomas at other extranodal sites, lymphoepithelial lesions may be present; these are relatively frequent in pulmonary MALT lymphoma and may involve bronchiolar or bronchial epithelium, or occasionally mucous glands. Colonization of pre-existing reactive follicles may be evident on routine sections or with the aid of immunohistochemical stains for germinal centre or follicular dendritic cell antigens (Figure 1c).

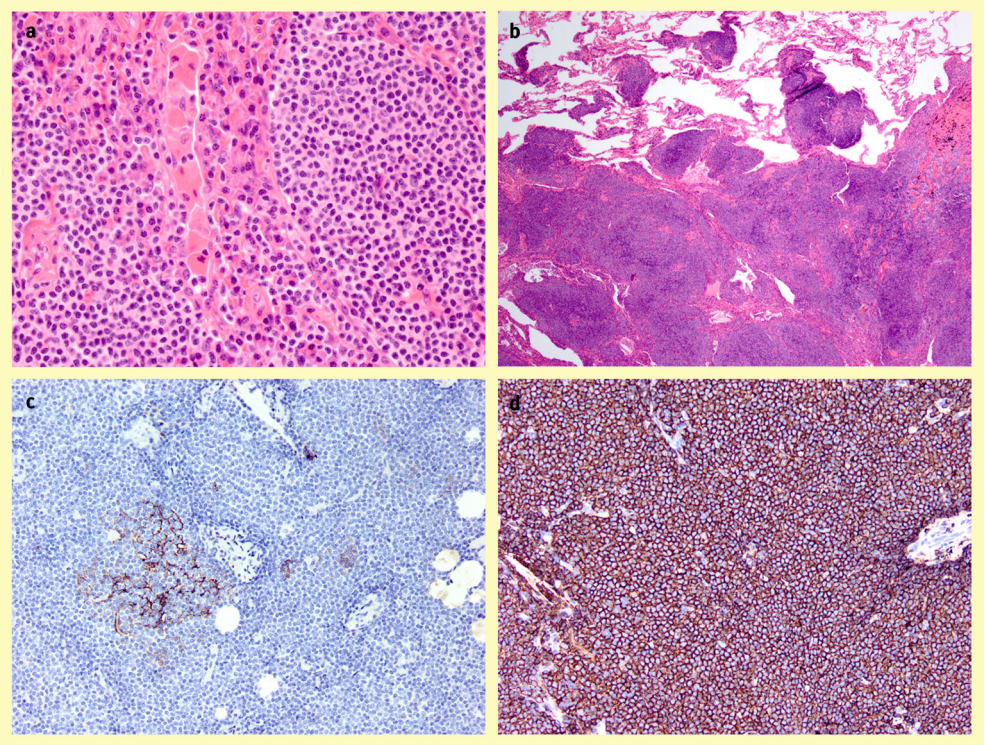

Figure 1 Extranodal marginal zone lymphoma (MALT lymphoma). The lymphoma is composed of sheets of monomorphous small lymphoid cells with irregular nuclei, inconspicuous nucleoli and moderately abundant pale pink cytoplasm. Admixed plasmacytoid lymphocytes and plasma cells are present in the centre of the image, consistent with plasmacytic differentiation (**a**). On low-power magnification, the lesion exhibits an interstitial pattern of infiltration at the periphery resulting in widening of the alveolar septae with the formation of small satellite nodules (**b**). A CD23 stain shows disruption of follicular dendritic cell aggregates (**c**), consistent with colonization of pre-existing reactive follicles by the lymphoma cells, which are overwhelmingly positive for CD20 (**d**).

Upon immunophenotyping, the lymphoma cells demonstrate positivity for pan-B-cell antigens such as CD20 and PAX5, which show diffuse, predominant staining in comparison to T-cell antigens (CD2, CD3 and CD5) (Figure 1d). CD43, normally expressed by mature T cells, is aberrantly expressed by a subset of MALT lymphomas and, when detected, can be helpful in supporting the diagnosis. Clonal immunoglobulin light chain restriction can be demonstrated by immunohistochemistry or *in situ* hybridization on tissue sections in cases with plasmacytic differentiation; in these cases, the light chain class will be the same as that of the serum M-component, if present. The lymphoma cells are typically negative for CD5, CD10, CD23 and cyclin D1. In cases lacking plasmacytic differentiation in which the associated plasma cells are polytypic, clonality may be confirmed by flow cytometry or by polymerase chain reaction (PCR) for *IGH@* gene rearrangement studies; the latter may be necessary in cases lacking fresh tissue for flow cytometric analysis. Clonality may also be demonstrated by the detection of chromosomal rearrangement involving *MALT1* by fluorescence *in situ* hybridization (FISH). The *API2-MALT1* fusion reflects a balanced translocation between *API2* on chromosome 11q21 and *MALT1* on chromosome 18q21 and may be detected in up to 40% of pulmonary MALT lymphomas, typically in cases not associated with underlying autoimmune disease.[4] Other less common translocations that may be seen in pulmonary MALT lymphomas include t(14;18)(q32;q21)/*IGH-MALT1* and t(1;14)(p22;q32)/*IGH-BCL10*.[5]

Special issues in the diagnosis of pulmonary MALT lymphoma relate to large cell transformation and amyloid deposition. Areas of transformation to diffuse large B-cell lymphoma (DLBCL) may be identified in 10–18% of cases. This is reflected by sheet-like growth of large, atypical lymphoid cells with nuclear size equivalent to or exceeding that of histiocyte nuclei (Figure 2).

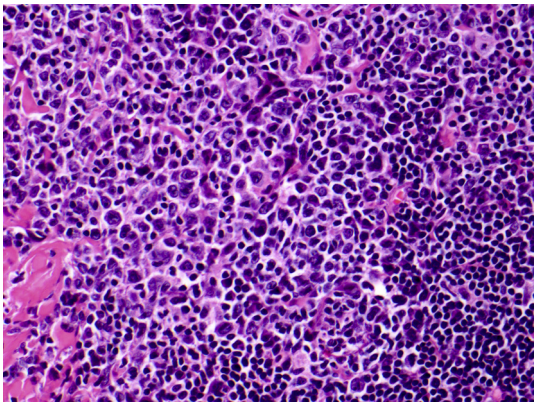

Figure 2 MALT lymphoma with area of transformation to diffuse large B-cell lymphoma. The lower right portion of the image contains an infiltrate of small lymphocytes and scattered plasma cells characteristic of MALT lymphoma, while the upper left portion of the image shows a diffuse proliferation of large pleomorphic cells with irregular nuclei and prominent nucleoli, consistent with transformation to a higher-grade process that is best characterized as diffuse large B-cell lymphoma.