Marginal Zone Lymphomas

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DEFINITION AND CLASSIFICATION OF MARGINAL ZONE LYMPHOMAS

In the World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues the group of marginal zone lymphomas (MZL) comprises three different entities, namely the extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (currently named ''MALT lymphoma'' and previously defined as ''low grade B-cell lymphoma of MALT type''), the nodal marginal zone B-cell lymphoma (previously known as ''monocytoid lymphoma''), and the splenic marginal zone B-cell lymphoma (with or without circulating villous lymphocytes).[1]

The term MZL means that extranodal MZL, nodal MZL, and splenic MZL are believed to derive from B cells normally present in the marginal zone, which is the outer part of the mantle zone of B-cell follicles. Most of the marginal zone B cells are naïve B cells, with a restricted immunoglobulin repertoire. Postgerminal center memory B cells are also present in the marginal zone, as well as plasma cells, macrophages, T cells, and granulocytes.

While splenic and nodal MZL are quite rare, each comprising approximately 2% of lymphomas, the extranodal MZL of MALT type is not uncommon; in a survey of more than 1,400 non-Hodgkin's lymphomas from nine institutions in the United States, Canada, the United Kingdom, Switzerland, France, Germany, South Africa, and Hong Kong, this entity represented approximately 8% of the total number of cases, including both the most common gastrointestinal and the less usual nongastrointestinal localizations.[2] This article addresses each of these entitites.

EXTRANODAL MARGINAL ZONE LYMPHOMA OF MALT (MALT LYMPHOMA)

General Description of Histologic Features and Etiopathogenesis

Primary gastric MALT lymphoma is the most common and best-studied MALT lymphoma, but the histologic features of extranodal B-cell MZL (MALT lymphomas)

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are largely similar, regardless of the site of origin.[3,4] The most striking feature of MALT lymphoma is the presence of a variable number of lymphoepithelial lesions defined by evident invasion and partial destruction of mucosal glands by the tumor cells. The morphology of MALT lymphoma cells is heterogeneous. Marginal-zone cells are the predominant component and are small to medium-sized cells with irregularly shaped nuclei (centrocyte-like cells). Other cell types comprise monocytoid cells and small B-lymphocytes. A variable degree of plasma cell differentiation is often present. Any of these cytologic aspects can predominate, or they can coexist within the same case. The B-cells of MALT lymphoma show the immunophenotype of the normal marginal zone B cells present in spleen, Peyer's patches, and in lymph nodes. Therefore, the tumor B-cells express surface immunoglobulins and pan-B antigens (CD19, CD20, and CD79a), express the marginal zone-associated antigens CD35 and CD21, and lack CD5, CD10, CD23, and cyclin D1 expression. A number of non-neoplastic, reactive T cells is often present. Scattered transformed large blast cells are also usually found. Their prognostic significance is not fully understood, but only when solid or sheet-like proliferations of large cells are present should the lymphoma be considered to have transformed. The resulting tumor cannot reliably be distinguished from other diffuse large B-cell lymphomas. Therefore, current recommendation is that such cases are defined as diffuse large B-cell lymphoma, avoiding the term ''high-grade'' MALT lymphomas.[3]

Certain histologic features appear to indicate that the MALT lymphoma B cells might be or have been involved in an immune response: the presence of tumor lymphocytes in the germinal centers of non-neoplastic follicles (follicular colonization), the presence of scattered transformed blasts, the often prominent plasma cell differentiation, and the often rich T-cell non-neoplastic component. MALT lymphoma usually arises in mucosal sites where lymphocytes are not normally present and where a MALT is acquired in response to either chronic infectious conditions or autoimmune processes: *Helicobacter pylori* gastritis, Hashimoto's thyroiditis, Sjögren syndrome.[5] Sequence analysis of the immunoglobulin genes expressed by the MALT lymphoma B cells shows a pattern of somatic hypermutation and intraclonal variation, suggesting that the tumor cell has undergone antigen selection in germinal centers and they continue to be at least partially driven by direct antigen stimulation.[6] In the context of this continual antigenic stimulation, abnormal B cell clones acquiring successive genetic abnormalities can progressively replace the normal B cell population of the inflammatory tissue, giving rise to the lymphoma. The acquisition of MALT is induced by a series of agents that are likely different in each organs.

H. pylori was identified by epidemiologic studies in the early 1990s as likely being involved in gastric MALT lymphomas pathogenesis, and this recognition was supported by the repeated demonstration of tumor regressions in 60% to 100% of patients with early-stage *H. pylori*-positive gastric MALT lymphoma treated with anti-*helicobacter* antibiotic therapy.[7–16] Hence, this tumor became a popular model of the pathogenetic link between chronic inflammation and lymphoma development.[5,17] Recognition of the driving sources of the antigenic stimulation in different tissues may therefore have important therapeutic implications. Indeed, other bacterial infections had later been found to be possibly implicated in the pathogenesis of marginal zone lymphomas arising in the skin (*Borrelia burgdorferi*),[18] in the ocular adnexa (*Chlamyophila psittaci*),[19] and in the small intestine (*Campylobacter jejuni*).[20]

Wide geographic variations have been reported in the prevalence of gastric MALT lymphoma, likely related to variations of the *H. pylori* incidence in the examined populations.[21] Indeed, *H. pylori* infection can be found in 70% to 90% of patients with primary MALT lymphoma of the stomach.[22,23]