Review article
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The histopathology and immunohistology of gastric MALT lymphoma

KEYWORDS: Stomach Neoplasms; Lymphoma, Mucosa-Associated; Lymphoid Tissue; Immunohistchemistry; Lymphoma, B-Cell

ABSTRACT
MALT lymphoma mostly occurs in adults with a median age of 61 years and slight female preponderance. At an early stage, tumor is confined to the gastric mucosa and its growth depends critically on H. pylori mediated immunological stimulation and regression after H. pylori eradication. The neoplastic cells infiltrate between pre-existing lymphoid follicles, initially localized outside the follicular mantle zone. As the lesion progresses, the neoplastic cells colonize and eventually overrun the lymphoid follicles resulting in a vague nodular knot. Lymphoepithelial lesions, typical for MALT lymphoma, are defined as infiltration of the glandular epithelium by clusters of neoplastic lymphoid cells with associated destruction of gland architecture. The tumor cells of MALT lymphoma are: CD20+, CD5-, CD23-, CD45+- (weak); immunostaining for cytokeratin highlights lymphoepithelial lesions. MALT lymphomas run an indolent course and are slow to disseminate. The tumors are sensitive to radiation therapy, and local treatment may be followed by prolonged disease-free intervals.

DEFINITION

Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is an extranodal lymphoma comprising morphologically heterogeneous small B-cell including marginal zone (centrocyte-like) cells, cells resembling monocytoid cells, small lymphocytes, and scattered immunoblast and centroblast-like cells (1). There is plasma cell differentiation in a proportion of the cases. The infiltrate is in the marginal zone of reactive B-cell follicles and extends into the interfollicular region. The neoplastic cells typically infiltrate the epithelium, forming lymphoepithelial lesions (2).

EPIDEMIOLOGY

Approximately 40% of all non-Hodgkin lymphomas arise at extranodal sites, with the gastrointestinal (GI) tract as the most common extranodal site, accounting for about 4%-14% of all non-Hodgkin lymphomas in Western countries (2,3). Within the GI tract, the stomach is the most frequent site of involvement constituting up to 10% of all gastric malignancies; its incidence appears to be increasing but this may be due to the recognition of the neoplastic nature of lesions previously termed "pseudolymphoma" (4). Most cases occur in adults with a median age of 61years and slight preponderance in women (male: female ratio 1:1.2) (5, 6).

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PRECURSOR LESIONS/CONDITIONS

In many cases of MALT lymphoma, there is a history of chronic inflammatory, often autoimmune disorders that result in accumulation of extranodal lymphoid tissue. Examples include *Helicobacter pylori* associated chronic gastritis, Sjögren syndrome of Hashimoto thyroiditis. At an early stage, the tumor is confined to the gastric mucosa and its growth depends critically on *H. pylori* mediated immunological stimulation and regresses after *H. pylori* eradication (7,8). Infection with *H. pylori* is one of the most frequent infections worldwide. Prevalence varies between 40% and over 90%, depending on the country and social status. It has been recognized that certain antigens associated with H. pylori infection may play a crucial role for the development of chronic gastritis, duodenal and gastric cancer, or MALT lymphomas respectively (9).

ETIOLOGY

Helicobacter pylori infection

Initial studies of low-grade MALT lymphoma suggested that the tumor was associated with *H. pylori* in 92%-94% of cases; subsequent studies have suggested an association in 62%-77%. *H. pylori* infection is seen less frequently in high-grade lymphomas with a low-grade component (52%-71%) and in pure high-grade lymphomas (25%-38%) (11). The organism has been shown to be present in 90% of cases limited to the mucosa and submucosa, falling to 76% when deep submucosa is involved, and is present in only 48% of cases with extension beyond the submucosa (11). It has been shown that the infection by *H. pylori* precedes the development of lymphoma, both by sequential serological studies and by retrospective studies of archival gastric biopsy material.

Both immunological and genetic factors are implicated in the genesis of gastric MALT lymphoma and may be synergistic in their effects. The host immune response to *H. pylori* induces and sustains an actively proliferating B-cell population, which is constantly subject to genototoxic insult by activation of neutrophils (7). During the course of this chronic inflammatory disease, genome may be unstable and genetic abnormalities such as trisomy three may develop in B cells and consequently lead to a "partially" transformed B-cell clone in rare cases. In the presence of growth help from *H. pylori* specific T cells, this abnormal B-cell clone may undergo clonal expansion and gradually form a MALT lymphoma (7).

Lymphomas may arise or involve the stomach in patients with both congenital and acquired immunodeficiency. In general, the incidence, clinical features and the histology of the lesions are indistinguishable from those that develop outside the stomach. Up to 23% of GI tract non-Hodgkin lymphomas arising in HIV infected patients occur in the stomach and the vast majority of these are large B-cell or Burkitt/Burkitt-like lymphomas (12) although occasional low-grade MALT lymphomas are described (13).

MORPHOLOGY

Endoscopy

Some cases show enlarged gastric folds, gastritis, superficial erosions or ulceration. In these cases the surrounding normal appearing gastric mucosa may harbor lymphoma, and accurate mapping of the lesion requires multiple biopsies from all sites including those appearing macroscopically normal. Endoscopic examination shows sometimes very minor changes such as

hyperemia. High-grade lymphoma is usually associated with more florid lesions, ulcer and masses. It is often impossible to distinguish lymphoma from carcinoma endoscopically.

Histopathology

The organization of the lymphoma mimics that of normal MALT and cellular morphology, and immunophenotype is essentially that of the marginal zone B cell. The neoplastic cells infiltrate between pre-existing lymphoid follicles, initially localized outside the follicular mantle zone in a marginal zone pattern. As the lesion progresses, the neoplastic cells erode, clonize, and eventually overrun the lymphoid follicles resulting in a vague nodularity to an otherwise diffuse lymphomatous infiltrate (14). The morphology of the neoplastic cells can be variable even within a single case. Characteristically, the cell is of intermediate size with pale cytoplasm and an irregular nucleus. The resemblance of these cells to the centrocyte of the follicle center has led to the term centrocyte-like (CCL) cell being applied to the neoplastic component of MALT lymphomas. In some cases, the CCL cell may be more reminiscent of a mature small B lymphocyte while in other cases, the cell may have a monocytoid appearance with abundant, pale cytoplasm and a well-defined cell border. Plasma cell differentiation is typical and may be very prominent. Dutcher bodies may be identified. The CCL cells infiltrate and destroy aÐacent gastric glands to form lymphoepithelial lesions. Lymphoepithelial lesions typical for MALT lymphoma are defined as infiltration of the glandular epithelium by clusters of neoplastic lymphoid cells with associated destruction of gland architecture and morphological changes within the epithelial cells, including increased eosinophilia (14).

In some cases it will not be possible to make a definite distinction. Between reactive infiltrates and lymphoma and in these cases a diagnosis of "atypical lymphoid infiltrate of uncertain nature" is appropriate (14).

IMMUNOHISTOCHEMISTRY

Tumor cells of MALT lymphoma are: CD20+, CD5-, CD10-, CD23-, CD43+/- (weak). There is no specific marker for MALT lymphoma at present (14). The demonstration of immunoglobulin light chain restriction is important in the differential diagnosis with benign lymphoid infiltrates. In the differential diagnosis with other small B-cell lymphomas, absence of the characteristic markers for those neoplasms is important: lack of CD5 is useful in distinction from mantle cell lymphoma, and CD10 in the differential diagnosis with follicular lymphoma. Immunostaining for cytokeratin highlights lymphoepithelial lesions.

The emergence of clusters of large transformed "blastic" B-cells reflects transformation to high-grade lymphoma. As long as a low-grade component remains, this tumor may be termed high-grade MALT lymphoma, but during further progression, all traces of pre-existing low-grade lymphoma are lost, making it impossible to distinguish the lesion from a diffuse large B-cell lymphoma of unspecified type.

PROGNOSIS AND PREDICTIVE FACTORS

MALT lymphomas run an indolent natural course and are slow to disseminate; recurrences may involve other extranodal sites. The tumors are sensitive to radiation therapy, and local treatment may be followed by prolonged disease-free intervals. Involvement of multiple extranodal sites and even bone marrow involvement do not to appear to confer a worse prognosis. Protracted remission may be induced in H. pylori - associated gastric MALT lymphoma by antibiotic therapy for H. pylori. Cases with the t(11;18) (q21;q21) appear to be resistant to H. pylori eradication therapy. Transformation to diffuse large B-cell lymphoma may occur (14).

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