Gastric MALT Lymphoma and Helicobacter pylori

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Primary gastric low-grade B-cell lymphomas are neoplastic mimics of mucosa associated lymphoid tissue (MALT) as exemplified by Peyer’s patches in the terminal ileum. Architectural and immunophenotypic properties of the neoplastic cells suggest that they originate from MALT-derived marginal zone B-cells. Paradoxically, the normal human stomach is devoid of organized MALT within which a lymphoma can develop. Lymphoid tissue is acquired in the stomach in response to antigenic stimulation, predominantly associated with Helicobacter pylori infection. Studies of patients with low-grade MALT lymphoma have confirmed a high incidence of H. pylori infection and suggest that the infection pre-dates neoplastic transformation. Certain morphological features of MALT lymphomas suggest that the tumor cells remain responsive to antigen drive. Given the close association between gastric MALT lymphoma and H. pylori, it is possible that this organism provides such a drive. In vitro studies have shown that the tumor cells proliferate in a T-cell-dependent way to the presence of H. pylori. Several studies have now demonstrated that eradication of the organism in patients with low-grade gastric MALT lymphoma can result in regression of the tumor. In cases with a high-grade component, the associated low-grade part may regress, but most high-grade gastric MALT lymphomas are unresponsive to this conservative therapy.

INTRODUCTION

In 1983, Isaacson and Wright [1] recognized a group of low-grade B-cell lymphomas of the gastrointestinal tract that were clinicopathologically distinct from other low-grade B-cell lymphomas of nodal type. These lymphomas were noted to be composed of a diffuse infiltrate of small lymphoid cells with an irregular nuclear outline and moderately abundant pale eosinophilic cytoplasm (Figure 1). This led to application of the term centrocyte-like (CCL) cells for these tumor cells. The neoplastic cells were observed to infiltrate the overlying epithelium with destruction of the gland architecture to form so-called lymphoepithelial lesions (Figure 2). Isaacson and Wright noted that these features resembled those seen in mucosa associated lymphoid tissue (MALT) (Figure 3) and concluded that these tumors arose from within MALT [1]. The pattern of infiltration together with the cytology and immunophenotype of the CCL cell suggest that these lymphomas arise specifically from the marginal zone B-cell population of MALT [2].

Non-neoplastic lymphoid follicles are an integral component of MALT lymphoma. Even in those cases where follicles appear to be absent, immunostaining reveals numerous aggregates of follicular dendritic cells that represent follicles that have been overrun by tumor [3]. The CCL cells interact with the reactive follicles in a complex way, known as follicular colonization, which can be divided into three types [4]. In the first type, the reactive follicles are replaced by CCL cells. In the second type, the follicle centers are selectively replaced by CCL cells while the mantle zone remains intact. The intrafollicular CCL

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Abbreviations: CCL, centrocyte-like; MALT, mucosa-associated-lymphoid tissue."
Figure 1. Gastric low-grade B-cell lymphoma of mucosa-associated-lymphoid tissue (MALT) showing a diffuse infiltrate of centrocyte-like (CCL) cells around reactive lymphoid follicles extending into the epithelium (hematoxylin and eosin).

Figure 2. Centrocyte-like (CCL) cells surround gastric glands infiltrating and destroying some to form characteristic lymphoepithelial lesions (hematoxylin and eosin).
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Figure 3. Normal human Peyer's patch showing reactive germinal center surrounded by a mantle zone and an expanded marginal zone extending to the dome epithelium (hematoxylin and eosin).

Figure 4. Low-grade lymphoma of mucosa associated lymphoid tissue showing typical centrocyte-like (CCL) cells and evidence of plasma cell differentiation (hematoxylin and eosin).
population may appear larger and more "active" or may undergo blast transformation. In the third type, the intrafollicular CCL cells show plasma cell transformation.

The property of follicular colonization displayed by MALT lymphoma mimics the reaction of normal marginal zone B-cells to antigen exposure [5]. Certain other features of MALT lymphoma, including the presence of scattered transformed cells and the finding of subepithelial plasma cell differentiation of tumor cells (Figure 4), suggest that there may be continued antigen drive to tumor proliferation.

**ACQUIRED MALT AND HELICOBACTER PYLORI**

The great paradox of lymphomas of MALT type is the finding that these tumors arise at sites normally devoid of organized lymphoid tissue. Moreover, the site at which the greatest quantity of normally occurring MALT is seen, Peyer's patches in the terminal ileum, is an uncommon site for the development of MALT lymphoma. Without the presence of organized lymphoid tissue within the stomach, primary gastric lymphoma cannot occur. Organized lymphoid tissue of MALT type must, therefore, be acquired before gastric MALT lymphoma can develop.

It has recently been shown that acquired gastric MALT is a feature of the chronic gastritis associated with *Helicobacter pylori* infection (Figure 5). Lymphoid follicles are seen in 27 to 100 percent of patients with *Helicobacter*-associated gastritis compared to 0 to 10 percent of uninfected controls [6-10]. The incidence of the finding of lymphoid follicles is dependent on the number of gastric biopsies examined and probably approaches 100 percent if sufficient tissue is sampled [10]. Wotherspoon et al. showed that the features of this organized lymphoid tissue recapitulated the architecture of MALT with infiltration of the gastric epithelium to form a lymphoepithelium characteristic of this lymphoid tissue [8].
LOW-GRADE GASTRIC MALT LYMPHOMA

The morphological features of gastric MALT lymphoma are similar to those seen elsewhere [11]. A diffuse infiltrate of CCL cells surround pre-existing germinal centers and infiltrate the glandular epithelium to form lymphoepithelial lesions. Follicular colonization of any of the three types can be seen although type 1 is the most frequent. The criteria for the diagnosis of MALT lymphoma include the presence of atypical CCL cells and the presence of lymphoepithelial lesions [12]. There is usually subepithelial plasma cell differentiation, and, in some cases, this can be very prominent. Dutcher bodies are not an invariable finding but when present are suggestive of lymphoma [12]. Immunoglobulin light chain restriction confirming the presence of a neoplastic clone can be demonstrated on resection specimens after optimal fixation, but staining on biopsy material frequently proves unrewarding. In all cases, there is rearrangement of the immunoglobulin genes demonstrating the neoplastic nature of the disease [13]. Involvement of oncogenes commonly associated with other low-grade B-cell lymphomas of nodal type, such as bcl-1 and bcl-2, are not found [14]. In those cases in which successful cytogenetic studies have been undertaken, clonal aberrations can be detected, and recent studies suggest that trisomy of chromosome 3 is important in low-grade MALT lymphomas irrespective of the site of origin [15].

Although special techniques and, in particular, the use of the polymerase chain reaction for the detection of immunoglobulin heavy chain rearrangements, have been employed, the gold standard for the diagnosis of low-grade MALT lymphoma remains histological examination using the strict criteria alluded to above [16].

Recent studies of partial gastrectomy specimens have demonstrated that MALT lymphoma may spread within the gastric mucosa to produce multiple small lesions away from the main tumor mass [17]. These lesions or micro lymphomas consist of microscopic infiltrates of CCL cells in the marginal zone region surrounding isolated lymphoid follicles of the pre-existing follicular gastritis. The neoplastic nature of these foci can be demonstrated by the finding of immunoglobulin light chain restriction. Although intra-mucosal spread is seen, extra-gastric dissemination and bone marrow involvement is very rare and usually occurs only late in the course of the disease.

LOW-GRADE MALT LYMPHOMA AND HELICOBACTER PYLORI

Following the recognition that colonization of the gastric mucosa by H. pylori results in the acquisition of MALT type lymphoid tissue, two histological studies addressed the incidence of infection with this organism in patients with low-grade gastric MALT lymphoma [8, 18]. Helicobacter organisms were found either in the resection specimen or the diagnostic biopsy in 92 to 98 percent of stomachs harboring MALT lymphoma. A retrospective serological based study demonstrated a similarly high incidence of H. pylori infection in patients with gastric MALT lymphoma that was not present in patients who developed nodal lymphoma [19]. This study also confirmed that the infection predated the development of lymphoma. Genta et al. demonstrated that the predominantly antral/pyloric distribution of gastric MALT lymphoma reflects the distribution of reactive MALT acquired in response to H. pylori infection [20]. The evidence, therefore, suggests that H. pylori is the major stimulus for the acquisition of gastric MALT within which lymphoma may subsequently develop in a proportion of individuals.

Given this close association between gastric MALT lymphoma and H. pylori, it is possible that the organism provides an antigenic drive necessary for the growth of these tumors. In vitro studies have shown this to be the case. Tumor cells extracted from gastric resection specimens containing MALT lymphoma proliferated and synthesized tumor immunoglobulin when co-cultured with heat-killed whole preparations of H. pylori [21].
This proliferative response was only generated by a single _H. pylori_ strain, which was case specific. The tumor cell proliferation was not the direct result of an interaction between antigen and neoplastic B-cell but was only seen in the presence of tumor infiltrating T-cells [21, 22]. In a single case in which splenectomy had been performed, the host spleen-derived T-cells failed to induce tumor cell proliferation when co-cultured with the stimulating _H. pylori_ strain [22]. These findings, together with earlier studies that demonstrated that the tumor cell immunoglobulin in cases of gastric MALT lymphoma was not directed against _H. pylori_ antigens but rather against a variety of auto-antigens [23], demonstrates that the proliferative drive in MALT lymphoma is dependent upon _H. pylori_-specific T-cells and their products rather than the bacteria themselves.

From these studies it is apparent that _H. pylori_ infection is an essential first step in the progression to gastric MALT lymphoma resulting in the acquisition of organized reactive lymphoid tissue, from within which, in a small proportion of individuals, a neoplastic clone can arise. The oncogenic stimuli and genetic changes in the progression from reactive MALT to lymphoma remain obscure, but it is apparent that in the early stages following neoplastic transformation, when the growth of the tumor is dysregulated, there is still some immunologically-derived proliferative drive to the tumor cells. This stimulus to tumor cell proliferation remains the same antigen-derived stimulus that resulted in the initial acquisition of the lymphoid tissue, namely _H. pylori_.

**ERADICATION OF HELICOBACTER PYLORI AND MALT LYMPHOMA REGRESSION**

The observation of _H. pylori_-dependent growth in _in vitro_ studies of gastric MALT lymphoma led Wotherspoon and co-workers to study the effect of _H. pylori_ eradication on patients with gastric low-grade MALT lymphoma [24]. Of six cases studied, five showed regression of the lymphoma on repeated endoscopic gastric biopsy assessed by conventional histology and molecular techniques [24]. In each case, the lymphoma had been treated with a standard anti- _Helicobacter_ regime consisting of a combination of antibiotics and acid-lowering drugs (proton pump inhibitor or H₂-antagonist), and the patients were subjected to repeat endoscopies performed by the same endoscopist, who was confident of biopsying the same region of the stomach that had contained tumor at the diagnostic procedure. In this study, the authors were able to review biopsies from four of six patients up to 38 months before the diagnostic samples. In each case, the histological features were largely unchanged prior to the introduction of anti- Helicobacter therapy, confirming that the regression was indeed related to the eradication of the organism and demonstrating the ability of the endoscopist to biopsy the site of the tumor on each occasion.

Bayerdorffer et al. [25] studied a further 33 patients with clinical stage EI, gastric MALT lymphoma. Regression was seen in 27 of 33 patients, which was complete in 23 cases (70 percent). Of the six cases in their study that failed to respond, four cases were subsequently found to be stage EII, and five of six cases had high-grade lymphoma diagnosed at gastric resection (four B-cell and one T-cell). In one case, the lymphoma had previously been treated with chemotherapy, and the exact tumor stage was uncertain. Other series and single case-reports have confirmed the finding of tumor regression in response to _H. pylori_ eradication in early MALT lymphoma [16, 26-30]. A single case-report has demonstrated the regression of a significant tumor mass following eradication of the organism [26]. Reinfection after initial eradication-induced regression might result in multifocal relapse of aggressive tumor [31]. High-grade gastric MALT lymphoma does not respond to _H. pylori_ eradication [25, 32], and high-grade nature of lesions with a low-grade component might be unmasked following regression of the low-grade component in response to _H. pylori_ eradication [25].
CONCLUSIONS

Low-grade B-cell lymphoma of MALT is an indolent neoplasm that disseminates late in the course of the disease. It is of necessity predated by the acquisition of organized reactive gastric lymphoid tissue, which has the architecture of reactive MALT and is found almost exclusively in relation to infection of the gastric mucosa by \textit{H. pylori}. Lymphoma develops from within this acquired MALT following as yet undetermined genetic events, but at an early stage, the neoplastic cells retain a T-cell dependent proliferative response to the presence of the organism. At that stage, eradication of the organism results in tumor regression in a substantial number of patients. Although it is unknown whether this regression can be induced in tumors of a more advanced stage, the presence of multifocal low-grade deposits of lymphoma in the surrounding mucosa suggests that anti-\textit{Helicobacter} therapy should be an integral part of all therapies for low-grade gastric MALT lymphoma.

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