Gastric Mucosa-Associated Lymphoid Tissue Lymphoma: Review of the Literature and a Case Report

MİDENİN MALT LENFOMASI: LİTERATÜRÜN GÖZDEN GEÇİRİLMESİ VE BİR OLGU SUNUMU

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Summary

Extranodal B-cell lymphomas of mucosa-associated lymphoid tissue (MALT) type are so called because they have the features of MALT (Peyer's patches) rather than those of lymph nodes. MALT lymphomas arise in a wide variety of extranodal sites most, but by no means all, of which are mucosal or epithelial. In Gulhane Military Medicine Academy we treated a helicobacter pylori negative gastric MALT lymphoma with chemotherapy and radiotherapy in the year 2000. The patient is still in remission. We discussed the results in the light of the literature.

Key Words: Mucosa-associated lymphoid tissue, Lymphoma, Gastric

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Özet

Ekstranodal B hücreli MALT lenfomaların bu şekilde adlandırılmasının nedeni lenf nodundan çok Peyer plaklarının özelliklerini göstermeleridir. Pek çok ekstranodal bölgeden kaynaklansalar da mutlaka epiteliyal veya mukozal kökenlidirler. Gülhane Askeri Tıp Akademisinde 2000 yılında helikobakter pilori izole edilemeyen bir hasta kemoterapi ve radyoterapi ile tedavi edilmiş olup halen remisyondadır. Sonuçlar literatürün ışığında tartışılmıştır.

Anahtar Kelimeler: Mukoza kaynaklı lenfoid doku, Lenfoma, Mide

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The suggestion that the histology and clinical behavior of certain gastrointestinal lymphomas were related to mucosa-associated lymphoid tissue (MALT) rather than nodal lymphoid tissue was first made in 1983 (1). Subtle histological differences were noted between primary gastrointestinal and comparable nodal B-cell lymphomas in that the structure and cytology of the former resembled those of MALT (Peyer's patches) rather than lymph nodes. These observations were later extended to include a number of other extranodal B-cell lymphomas including those of the salivary gland, lung, and thyroid (2). The clinical observations that these lymphomas shared common properties, including a tendency to remain localized, were thought to be in keeping with the specific circulation pathways and homing properties of MALT, from which they arose. MALT lymphomas, now classified in the WHO classification as "extranodal marginal zone lymphomas of MALT-type" (3) arise in numerous extranodal sites and account for 7.2% of non-Hodgkin's lymphomas (4). Gastric MALT lymphoma is by far the most common and because of this and its accessibility has been the most, extensively studied and is, therefore, the paradigm for the group as a whole.

Like other sites where MALT lymphomas occur, the gastric mucosa is normally devoid of lymphoid tissue, After infection with Helicobacter pylori, lymphoid tissue of MALT-type accumulates in the gastric mucosa (5,6) Gastric MALT lymphomas arise from this "acquired MALT," and accordingly, H pylori can be found in most cases (6). There are, however, cases where some other, as yet unknown, stimulus is responsible for the accumulation of gastric MALT.

Gastric MALT lymphoma typically occurs in patients over 40 years of age but can occur at any age. The sex incidence is equal. The presenting symptoms are usually those of nonspecific dyspepsia and more suggestive of gastritis or peptic ulcer rather than a neoplastic lesion. Likewise, endoscopy more often shows inflamed, sometimes eroded mucosa than a tumor mass. In this manuscript we reported the treatment result of a gastric MALT lymphoma patient.

Case

22-year old male was registered in our institution in November 2000. His gastroscopy revealed only antral gastritis, but biopsy specimen was reported as MALT lymphoma (Figure 1). H. pylori could not be isolated. He was staged as stage II-E according to Ann Arbor staging system, and given 6 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy

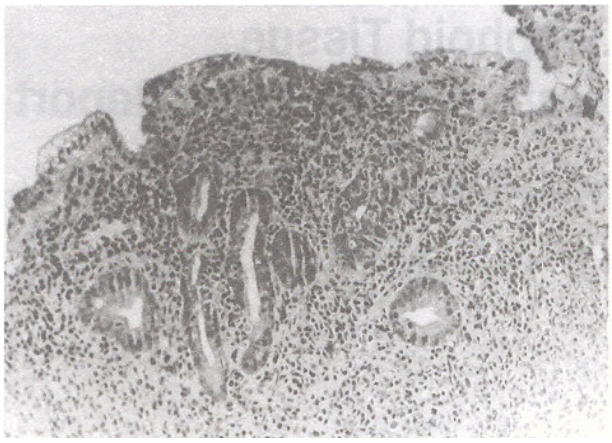

Figure 1. Atypical lymphocytes diffusely found in lamina propria of the stomach mucosa are infiltrating mucosal glands and forming lymphoepithelial lesion (HEx200).

and 40 Gy of external radiotherapy consecutively. Radiotherapy was applied to stomach and paraaortic lymphatic drainage regions, by parallel opposed antero/posterior fields with 6 MV X-rays. Only grade 1 nausea was observed due to radiotherapy. The patient is still alive and in free of the disease.

Discussion

Most MALT lymphomas of the stomach arise in the antrum and macroscopically are characterized by an ill-defined, thickened, inflamed, and ulcerated mucosa. The histological features (7) comprise a lymphomatous infiltrate in the marginal zone around reactive non-neoplastic follicles. The infiltrate extends into the gastric mucosa and invades individual gastric glands to form characteristic lymphoepithelial lesions. Although the term centrocyte-like (small cleaved cell-like) is most commonly used to describe the cells of low grade MALT lymphoma, their cytological characteristics are more variable and they may more closely resemble small lymphocytes or show the features of so-called monocytoid B cells. Scattered transformed blasts are usually present and plasma cell differentiation, characteristically maximal beneath the surface epithelium, is present in one third of cases. The lymphoma cells may specifically colonize reactive follicles and this may lead to an appearance closely resembling follicular lymphoma (8). MALT lymphoma may undergo transformation to diffuse large B-cell lymphoma (DLBCL) (9). Residual foci of MALT lymphoma, when present, should be reported but the term "high-grade MALT lymphoma" should not be used for such cases.

The B cells of MALT lymphoma express surface and, to a lesser extent, cytoplasmic immunoglobulin (usually IgM) and show light chain restriction. The cells express mature B-cell antigens including CD20, CD79a, CD21, and CD35. They are CD5 and CD10 negative. This phenotype is homologous, with that of marginal zone B cells that are now acknowledged as the normal cell counterpart (10).

Most gastric MALT lymphomas are at clinical stage 1E at the time of diagnosis (11) but approximately 20% have spread to the gastric lymph nodes or beyond. The more common distal sites include the small intestine (12), spleen (13) and bone marrow (11). In both lymph nodes and spleen the lymphomatous infiltrate tends to concentrate in the marginal zone. The histological appearance in lymph nodes is identical to that of nodal marginal zone lymphoma (monocytoid B-cell lymphoma).

In comparison with nodal low grade B-cell lymphoma, such as follicular lymphoma, which, at the time of diagnosis is characteristically at an advanced stage, MALT lymphoma is usually at stage IE or IIE when diagnosed and is slow to disseminate. The 10-year survival approximates 90% but is slightly poorer (80%) in cases with a higher proportion of transformed cells (14, 15).

There are several lines of evidence that implicate H. pylori in the pathogenesis of gastric MALT lymphoma. These include the fact that normal gastric mucosa is devoid of organized lymphoid tissue which, however, accumulates as a consequence of H. pylori infections and the observation that the organism can be detected in most cases (6). The epidemiological study of Parsonnet et al (16) which showed that there was a significantly higher frequency of preceding H. pylori infection in patients with gastric lymphoma compared with matched controls with nongastric lymphoma, added further support to this association. The evidence became even more compelling after in vitro studies (17), which showed that the cells of low-grade gastric MALT lymphoma respond to H. pylori antigens via a T-cell mediated mechanism. The clinical significance of these findings was first shown by Wotherspoon et al (18) who described regression of gastric MALT lymphoma in patients after eradication of H. pylori using appropriate antibiotics. Subsequent studies have shown that eradication of H. pylori may result in striking regression of the lymphoma in approximately 75% of the cases (19-21). Clinically, it would be extremely useful to be able to identify those cases of gastric MALT lymphoma that do not respond to eradication of *H. pylori*, but in a study in which endoscopic ultrasound was used it was have suggested that if the tumor has invaded beyond the submucosa, it will not respond (22).

In survey of the literature we identified four published studies (summarized in Table 1) reporting treatment outcome specificially for stage I and II patients with low grade MALT lymphoma of the stomach followed for over 30 months (23-27). Pinotti et al. (23) treated 86 patients with local treatment alone, combined treatment, chemotherapy alone, and antibiotics alone. 26 of these

Table 1 Results of tratment in MALT lymphoma of the stomach

Study	Number of patients	Stage	Median follow-up	Treatment	Relaps free rate (%)	5-year overall survival (%)
Blazquez (26)		I	54 months	Ct±Rt, Gast+Rt	100	-
Fung (27)	15	I	88 months	Gast and/ or Rt±Ct	93	93
Cogliatti (24)	71	I and II	55 months	Gast±Ct±Rt	I----84 II---67	I---95 II--82
Pinotti (23)	26	I and II	34 months	Gast and/ or Rt±Ct	Systemic---43 Local ---100	82
Ruskone (25)	28	I and II	48 months	Gast and/ or Rt± Ct	Local+systemic 93 Local 93	93

Gast: Gastrectomy Ct: Chemotherapy Rt: Radiotherapy

patients was undergone local treatment (gastrectomy or radiotherapy). Local control rate for these 26 patients was 100%. In patients treated only with antibiotics local control rate was 67% (23). Cogliatti et al. studied pathologic specimens and prognosis of 145 patients all of whom had gastrectomy (24). 71 of these patients had MALT lymphoma. Patients at stage I E had a significantly better survival probability than those at stage II E in this study ($p<0.0001$). Five-year overall survival for stage I patients was 95% and 82% for stage II patients (24). Ruskone et al. (25) reported the treatment results of 91 patients with primary digestive tract lymphoma. 28 of these patients had gastric MALT lymphoma. They observed better results for Stage I patients and for patients under 65 year of age (25). Blazquez et al (25) treated 16 patients of whom six had stage I disease, and reported 100 % survival rate for all stages with combined modality therapy. Fung et al. (27) reported treatment results of 21 patients of whom 16 had stage I disease. They found the outcomes of patients (n=13) who had only radiotherapy comparable to those who had combined modality treatment (27).

Patients in these studies were treated with various combinations of gastrectomy, radiation therapy, and chemotherapy. The relaps free rates ranged from 44% to 100%, whereas overall survival rates ranged from 82% to 91% at 5 years. Hammel et al reported a 45% event free survival rate in stage I-IV patients treated with single agent chemotherapy (28). Fischbach et al. (29) reported results of 266 patients. 61 of these patients who were H.pylori negative and/or stage II disease, 28 were watched after surgery. 33 of them were treated with additional 40 Gy external beam radiotherapy. Observation group had bad survival rate especially if they had tumor residues after surgery (29).

These results (23-28) suggest that chemotherapy alone is associated with significant failure rate and may not be an optimal treatment for localized gastric MALT lymphoma. Results in the literature show that, when gastrectomy and/ or radiation therapy are part of initial treatment for stage I and II patients, the probability of remaining relapse free survival is 79-100% (24-26).

Nonetheless, there is substantial evidence to suggest that radiation therapy may be the optimal primary treatment for most cases of gastric MALT lymphoma when antibiotics have failed or are inappropriate. Gastrectomy may be indicated for certain emergency situations, such as perforation or intractable life-threatening hemorrhage.

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