

REVIEW

Primary Gastric Lymphoma

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The pathogenesis of gastric MALT lymphoma starts with accumulation of MALT following infection of the stomach by *H. pylori*. Rarely this lymphoid infiltrate contains cells with a growth advantage possibly due to a genetic change (trisomy 3?). The result is a monoclonal lymphoproliferative lesion which is responsive to *H. pylori* driven T-cell help. Because its growth is dependent

on the presence of local antigen, gastric MALT lymphoma remains localized for long periods and it is during this phase that the lymphoma can be treated by eradication of *H. pylori*. Further genetic changes, as yet uncharacterized may lead to escape from T-cell dependency and ultimately high grade transformation. (Pathology Oncology Research Vol 2, No1-2, 5-10, 1996)

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Introduction

Primary extranodal lymphomas account for between 25 and 40 percent of non-Hodgkin's lymphomas.^{1,2} Extranodal lymphomas can arise from extranodal lymphoid organs such as the spleen, from non-lymphoid organs that contain a substantial amount of native lymphoid tissue, such as the gastrointestinal tract, or from organs such as the brain in which there is normally no lymphoid tissue. The gastrointestinal tract is the commonest site of primary extranodal lymphoma and most arise in the stomach. Studies of gastric lymphomas have suggested that their clinicopathologic features are more closely related to the structure and function of mucosa associated lymphoid tissue (MALT) than of peripheral lymph nodes.^{3,4,5}

Mucosa associated lymphoid tissue (MALT)

In contrast to peripheral lymph nodes, which are adapted to deal with antigens carried to the node in afferent lymphatics, MALT appears to have evolved to protect mucosal tissue which is directly in contact with antigens in the external environment. MALT has been most thoroughly characterized in the gastrointestinal tract where it comprises four lymphoid compartments.

The first, and most relevant to lymphoma, are the Peyer's patches. The other compartments are the lamina propria, the intraepithelial lymphocytes and the mesenteric lymph nodes.

Peyer's patches

The histology of Peyer's patches differs from that of lymph nodes in several important respects. Unlike lymph nodes Peyer's patches are unencapsulated and lack afferent lymphatics. The B-cell component is dominant and consists of a central follicle which is surrounded by a prominent marginal zone. This is surmounted by the dome epithelium which contains intraepithelial B-cells; these should be distinguished from the intraepithelial T-cells which are present in the rest of the intestinal epithelium (*Fig. 1*).

Functional properties of MALT

Animal experiments have shown a pattern of circulation of plasma cell precursors derived from activated organized MALT.^{6,7,8} Antigens from the gut lumen enter Peyer's patches directly by a transport mechanism involving specialised "M" cells.⁹ Following antigen stimulation, MALT B-cells leave the mucosa via efferent lymphatics, traverse mesenteric lymph nodes and enter the circulation via the thoracic duct. These B-cells then "home" back to the gut where they comprise the lamina propria plasma cells. The homing mechanism is thought

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Figure 1. Normal Peyer's patches comprising reactive B-cell follicles surrounded by a broad marginal zone. Clusters of B-cells are present in the dome epithelium.

to be mediated through a receptor ligand-system on high endothelial venules in the T-cell areas of Peyer's patches.^{10,11} This "homing" mechanism could have significant bearing on the behaviour of B-cell lymphomas derived from MALT.

Gastric MALT Lymphoma

In 1983, Isaacson and Wright³ noted that, just as low grade nodal lymphomas recapitulated the features of peripheral lymph nodes, certain low grade gastrointestinal lymphomas, including gastric lymphoma, recapitulated the features of MALT as exemplified by Peyer's patches. The MALT lymphoma concept, as it came to be known,¹² grew to include a number of low grade extranodal B-cell lymphomas which shared similar clinicopathological properties but, because of its frequency and accessibility, gastric lymphoma has remained the paradigm for the group as a whole.

Clinical presentation

Low grade gastric lymphoma occurs predominantly in individuals over 50 but an increasing number of cases are being reported in younger patients. The symptoms are usually those of non-specific dyspepsia and endoscopy usually shows nonspecific gastritis and/or a peptic ulcer. Extra-abdominal dissemination is unusual.

Pathology

Gastric lymphoma usually causes a flat infiltrative lesion sometimes associated with one or more ulcers. The histological features of low grade gastric MALT lymphoma closely simulate those of the Peyer's patch.^{4,5} (Fig.2) The lymphoma infiltrates around reactive follicles in the region corresponding to the Peyer's patch marginal zone, spreading diffusely into the surrounding mucosa. The tumour cells closely resemble follicle centre centrocytes. A central feature of low grade MALT lymphomas is the presence of lymphoepithelial lesions formed by invasion of individual crypts by aggregates of these centrocyte-like cells. Certain additional histological features suggest that the cells of low grade gastric MALT lymphoma may be participating in an immune response. These include the presence of scattered transformed blasts, plasma cell differentiation, which is maximal beneath the surface epithelium, and follicular colonization.¹³

Molecular genetics

Genotypic investigations of MALT lymphoma using the Southern blotting technique have confirmed the presence of both clonal heavy and light chain Ig gene rearrangements.¹⁴ Low grade MALT lymphomas do not show rearrangement of the *bcl-2* or *PRAD-1* gene which characterize follicular and mantle cell lymphoma respectively¹⁵ but

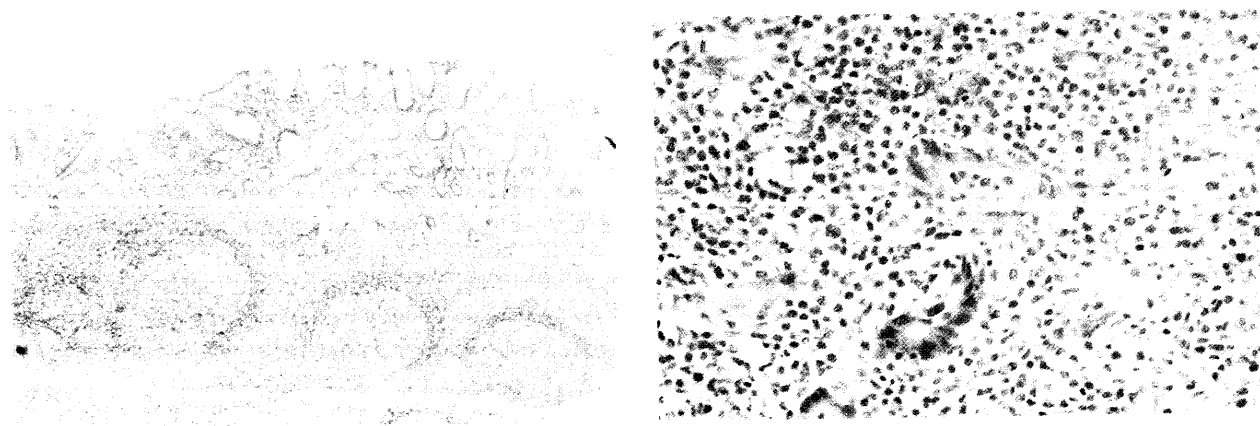


Figure 2. (A) Low magnification of a low grade B-cell gastric MALT lymphoma. The tumour infiltrates around reactive B-cell follicles. (B) Higher magnification of lymphomatous infiltrate showing lymphoepithelial lesions.

60% show trisomy 3.¹⁶ Other clonal genetic abnormalities described in MALT lymphoma include t(1;14) and t(11;18).¹⁷

Clinical behaviour

The behaviour of low grade MALT lymphoma differs strikingly from comparable lymphomas arising in peripheral lymph nodes. Low grade nodal B-cell lymphomas are usually already widely disseminated, with bone marrow involvement, when first diagnosed; treatment is at first effective but most patients die within 7-10 years, often following high grade transformation of the lymphoma. By contrast, low grade MALT lymphomas are seldom disseminated at the time of diagnosis, rarely involve the bone marrow and prolonged survival following therapy is usual. In the series of Cogliatti *et al*,¹⁸ the survival was 91 % at 5 years and 75% at 10 years. This contrasts with a 20% survival at 6 years for immunocytoma (lymphoplasma-cytic lymphoma) of peripheral lymph nodes.¹⁹

High grade gastric lymphoma

High grade primary gastrointestinal lymphoma is more common than the low grade lesion. Foci of high grade lymphoma may be seen in low grade MALT lymphoma showing that transformation from one to the other can occur.²⁰ In some cases there are sheets of transformed blasts within the predominantly low grade infiltrate while others are characterized by a predominance of high grade lymphoma with only small residual low grade foci which can be difficult to find. Those cases in which a low grade component cannot be detected must be presumed to be primary high grade lymphomas *de novo*. Whether this latter group should be categorized as MALT lymphoma is debatable. Since the histological and cytological features of primary and secondary high grade lymphoma are identical and there is no significant difference in their clinical behaviour,¹⁸ it would seem that there is nothing to be gained by classifying such cases as a separate group.

Clinical behaviour

Some reports suggest that this high grade gastric lymphoma behave more favourably than equivalent nodal disease,²¹ but others²² have shown that a higher grade results in less favourable behaviour. Cogliatti *et al*¹⁸ found that the 5 year survival of high grade gastric lymphoma, while better than that of comparable nodal lymphomas, was significantly worse than that of low grade gastric disease (75 vs 91 %). There was no difference between the survival of those high grade gastric lymphomas with or without a low grade MALT component, which is further evidence that both share the same lineage.

The favourable clinical behaviour of gastric MALT lymphoma

Because of their favourable behaviour, it was common to apply the term "pseudolymphoma" to lymphoproliferative lesions of the stomach with the features now described as characteristic of low grade MALT lymphoma. These lesions were not thought to represent true malignancy and to some extent this view still prevails. The favourable behaviour of MALT lymphomas could also be due to the homing properties of gut derived B-cells. A final possibility is that the growth of low grade gastric MALT lymphomas is influenced by a local antigen.

Malignant properties of low grade gastric MALT lymphoma

Malignant tumours are monoclonal, should show a clonal genetic abnormality, be invasive and be capable of metastasis. Low grade MALT lymphomas are monoclonal¹⁴ and cytogenetic studies have shown a number of clonal abnormalities of which trisomy 3 is the commonest.¹⁷ Using interphase cytogenetics, Wotherspoon *et al* have shown that trisomy 3 is present in 60% of low grade MALT lymphomas arising in the stomach and other extranodal sites.¹⁶ Low grade gastric MALT lymphomas invade the gastric mucosa causing ulceration and may invade deep into, or even through the muscularis. Finally, gastric MALT lymphomas often involve the regional lymph nodes and distant spread to sites such as the bone marrow, although rarely present at the time of diagnosis, is well documented.²³ Thus all four hallmarks of malignancy are manifested by low grade gastric MALT lymphomas.

Lymphocyte homing in low grade gastric MALT lymphoma

It has been proposed that endothelial vascular addressins expressed in particular anatomic sites mediate the extravasation of lymphocytes expressing site specific homing receptors and there is evidence that human plasma cell precursors originating from either systemic or mucosal immunisation differ in their expression of homing receptors.^{10,11} However, there is no evidence to suggest that such a system could mediate the movement of lymphocytes to a specific site within the gastrointestinal tract and experiments in animals show that "homing" of plasma cell precursors derived from the intestine occurs along the length of the intestine.^{7,8}

Antigenic drive and low grade gastric MALT lymphoma

If the growth of gastric MALT lymphoma was influenced by a local antigen, it could explain the prolonged period of localized growth since, although neoplastic

lymphocytes almost certainly spread to distant sites, they would fail to grow there in the absence of the antigen. There are several lines of evidence that suggest that this is the case. Some of the histological features of low grade gastric MALT lymphoma, including the presence of blasts, plasma cell differentiation and follicular colonization, are consistent with the tumour being subject to antigenic drive. In one case of gastric lymphoma which appeared clinically to be confined to the stomach and small intestine²⁴ tumour cells were identified in the splenic marginal zone although there was no evidence of proliferation in this population. Finally, it has been known for many years that in patients with early stages of immunoproliferative small intestinal disease (IPSID), a specific form of MALT lymphoma, sterilization of the small intestine with antibiotics may lead to regression of the lymphoma.²⁵ If antigenic drive is important for the growth of low grade gastric lymphoma then, taking IPSID as an example, the antigen is likely to be an infectious organism. The only organism known to occur with any frequency in the stomach is *Helicobacter pylori*.

Helicobacter pylori and gastric lymphoma

Helicobacter pylori, was first identified as a gastric pathogen in 1982.²⁶ Subsequently, the importance of *H. pylori* in the pathogenesis of a variety of gastric diseases including chronic gastritis, peptic ulcer disease and gastric carcinoma has been shown.

The fact that the stomach is the commonest site of MALT lymphoma is paradoxical since the normal stomach, unlike the intestine, lacks organized lymphoid tissue. However, *H. pylori* infection of the stomach leads to accumulation of lymphoid tissue in the gastric mucosa within which B-cell follicles and a lymphoepithelium are charac-

teristically present.^{27,28,29} The presence of this MALT in the gastric mucosa is almost pathognomic of *H. pylori* infection.²⁷ There are several lines of evidence that suggest that gastric lymphoma arises from this acquired MALT. The first is that *H. pylori* can be demonstrated in the gastric mucosa of over 90% of cases of gastric MALT lymphoma²⁸ which is well over the prevalence in most populations. Secondly, in at least one geographic area, the Veneto region of Italy, where there is a remarkably high incidence of primary gastric lymphoma, there is an accompanying high prevalence of *H. pylori* infection.³⁰ Finally, a case control study has shown an association between previous *H. pylori* infection and the development of primary gastric lymphoma.³¹ More direct evidence confirming the importance of *H. pylori* in the pathogenesis of gastric lymphoma has been obtained from in vitro studies³² and clinical evaluation of the effect of eradicating the organism in cases of low grade gastric lymphoma.³³

Response of cells of low grade gastric MALT lymphoma to H. pylori

Cells teased from specimens of low grade primary B cell gastric lymphoma cultured under standard conditions usually die within 5 days. However, in 3 cases the addition of heat killed whole cell preparations of *H. pylori* (a different strain in each case) resulted in clustering and proliferation of tumour cells.³² This was associated with expression of IL-2 receptors and release of tumour cell derived Ig and IL-2 into the culture medium. Control cells derived from other low grade lymphomas did not respond to any strains of *H. pylori*. Removal of T-cells from cell suspensions of gastric lymphomas before initiating the cultures abolished all activation induced by the *H. pylori*. These and other experiments showed that *H. pylori* stimulated intratumoural

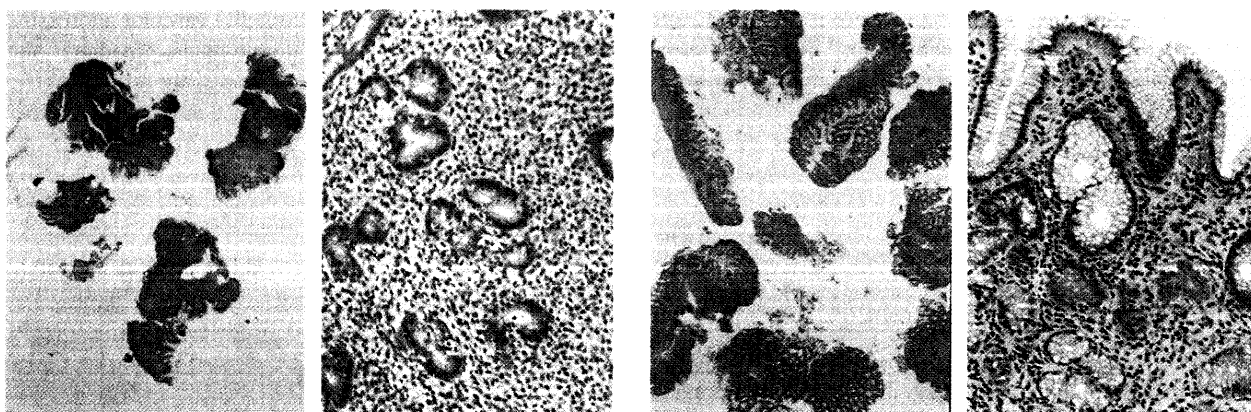


Figure 3. (A) Multiple gastric biopsies from a case of low grade gastric MALT lymphoma and *Helicobacter pylori* infection. All biopsies were infiltrated by lymphoma. Detail of infiltrate with lymphoepithelial lesions is seen in right hand panel. (B) Repeat gastric biopsies 7 months after eradication of *H. pylori*. The lymphoid infiltrate has almost completely disappeared apart from small clusters of lymphocytes shown in right hand panel.

T-cells which in turn provide help for tumour cell proliferation.³⁴ The tumour B-cells themselves were not directly stimulated by *H. pylori*.³⁵ In 1 case it was possible to show that splenic T-cells from the same patient did not respond to the stimulating strain of *H. pylori* demonstrating that the *H. pylori* responsive T-cell population was local. This provides an explanation for the observation that gastric MALT lymphomas remain localised to the primary site since the lymphomas are dependent on activated *H. pylori* specific T-cells, which, while present in *H. pylori* gastritis, are unlikely to be present outside the stomach.

Although the specificity for strains of *H. pylori* appears to reside in the tumour infiltrating T-cell population in the cases studied, the progenitor B cell of the malignant clone must have some property which results in its uncontrolled proliferation in the presence of T-cell help. This may be either a genetic alteration resulting in growth advantage or an abnormal biological property of the cell such as the ability to recognise autoantigen or both.

Regression of low grade gastric MALT lymphomas following eradication of H. pylori

In the light of the evidence that the growth of low grade gastric MALT lymphoma is influenced by antigen, and the more substantial experimental evidence summarized above, an attempt was made to evaluate the effect of eradicating *H. pylori* in six clinical cases of gastric MALT lymphoma with *H. pylori* infection.³³ (Fig.3,4) In five of the six, molecular analysis using the polymerase chain reaction (PCR) had confirmed a monoclonal B-cell population in the lesion. In all patients the lymphoma had not given rise to an identifiable tumour mass and was, thus, thought to represent early disease. Following the diagnostic biopsy the patients received appropriate antibiotics for eradication of *H. pylori*. Repeat post-treatment biopsies were performed at regular intervals and each biopsy evaluated for the histological changes of lymphoma, the presence of *H. pylori* and for any molecular evidence of a monoclonal B-cell population. In all 6 patients, *H. pylori* were successfully eradicated and complete remission of the lymphoma was achieved as judged on endoscopic, histologic and molecular grounds. Studies on further cases⁴¹ have shown similar results except that in some cases molecular evidence of the presence of monoclonal tumour cells has persisted in the absence of any histological evidence of disease.^{36,37}

Several independent groups have now confirmed that eradication of *H. pylori* may induce remission in cases of low grade B-cell lymphoma of the stomach.^{38,39,40,41}

As work progresses, a number of important questions are emerging. Among these are the optimum interval after which the effects of antibiotic treatment should be judged, the significance of persistent "monoclonality", the response of more deeply invasive lymphomas to *H. pylori*

eradication and the likely duration of remissions induced by antibiotics. The possibility of relapse of infection leading to lymphoma recurrence also has to be considered. Clearly, cases of gastric MALT lymphoma that have disseminated beyond the stomach are unlikely to respond to antibiotics and a way of testing the sensitivity of the tumour would be desirable.

Conclusions

The pathogenesis of gastric MALT lymphoma starts with accumulation of MALT following infection of the stomach by *H. pylori*. Rarely this lymphoid infiltrate contains cells with a growth advantage possibly due to a genetic change (trisomy 3?). The result is a monoclonal lymphoproliferative lesion which is responsive to *H. pylori* driven T-cell help. Because its growth is dependent on the presence of local antigen, gastric MALT lymphoma remains localized for long periods and it is during this phase that the lymphoma can be treated by eradication of *H. pylori*. Further genetic changes, as yet uncharacterized may lead to escape from T-cell dependency and ultimately high grade transformation.

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