Helicobacter pylori infection and gastric lymphoma

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Gastric lymphoma of mucosa associated lymphoid tissue (MALT) has characteristic clinicopathological features that are different from nodal-type B cell lymphomas. Before a lymphoma can arise within the stomach, MALT has to be acquired as part of a response to an immunological stimulus. In most instances, gastric MALT is acquired in response to infection by Helicobacter pylori. There are several features of MALT lymphoma, such as plasma cell differentiation and follicular colonisation, that suggest that these lymphomas, although demonstrated on the basis of clonality studies to be neoplastic, retain some immunological drive. In vitro studies have shown that co-culturing cells derived from low grade MALT lymphomas with H. pylori results in tumour cell proliferation in a T cell dependant manner. Clinical studies have taken this discovery further and shown that patients with early low grade gastric MALT lymphoma treated with anti-Helicobacter therapy can show regression of their tumours. It is now generally accepted that eradication of H. pylori is a central component of the management of MALT lymphoma.

Primary gastric lymphoma comprises about 3–6% of all gastric malignancies. Almost all are B cell non-Hodgkin’s lymphomas most commonly of high grade. Gastric T cell lymphomas and Hodgkin’s disease are extremely rare. In 1983, Isaacson and Wright recognised that the low grade B cell lymphomas that arose within the stomach had clinicopathological features that were distinct from other recognised low grade B cell lymphomas. They suggested that these lymphomas arose specifically within dedicated extra nodal lymphoid tissue known as mucosa associated lymphoid (MALT).

In the normal individual, MALT is found constitutively in the intestine with the highest concentration in the terminal ileum in the form of Peyer’s patches. These are non-encapsulated localised and organised collections of lymphoid tissue consisting of a central follicle (with germinal centre and follicular mantle) surrounded by a further zone of B cells – the marginal zone – whose cells extend into the overlying dome.
epithelium to form a lymphoepithelium. Plasma cells are seen within the surrounding lamina propria and in the subepithelial region. A T cell compartment is seen at the lateral borders and around the base of the follicle. Within the dome epithelium, there are specially adapted epithelial cells (M cells) that are thought to absorb, transport, process and present luminally derive antigens to the underlying lymphoid tissue.

The paradox about the suggestion that primary gastric lymphoma arises within MALT is that there is no organised lymphoid tissue of that type in the gastric mucosa of the normal individual. Hence, the first step on the pathway to the development of gastric lymphoma is the acquisition of organised lymphoid tissue of MALT-type within which subsequent genetic events may occur that result in the development of lymphoma.

**Acquired gastric MALT**

As the gastric environment is generally hostile to infective organisms and the mucosa is protected from diffusible antigen, there are only a limited number of stimuli that result in the acquisition of gastric MALT. The most frequent event associated with the finding of organised lymphoid tissue in the gastric mucosa is infection with *Helicobacter pylori*. In the most comprehensive study by Genta et al, lymphoid follicles were found in all patients with *H. pylori* infection but were absent in normal controls. Wotherspoon et al demonstrated that the lymphoid tissue seen in *H. pylori* infected stomachs had all the morphological features of MALT. Although *H. pylori* is genetically diverse, the accumulation of lymphoid tissue appears to be a universal response unrelated to bacterial strain.

*H. pylori* is not the only stimulus to the acquisition of gastric MALT which can also be seen in relation to infection by *H. helimannii* (personal observations) and has been reported in patients with coeliac disease.

**Gastric MALT lymphoma**

*Clinical features*

The age range for gastric MALT lymphoma is wide, but the majority of patients are over the age of 50 years at presentation. The sex distribution is approximately equal. The majority of patients present with non-specific dyspeptic symptoms, nausea or vomiting while weight loss or the presence of an epigastric mass is rare. The endoscopic picture can be very variable with some patients having minimal changes with mild
Gastric lymphoma

Gastritis while others will have thickened gastric folds, erosions or ulceration. Mass lesions are relatively rare. Although any region of the stomach may be involved, the majority arise within the antrum or distal body. Gastric MALT lymphomas, in common with MALT lymphomas of other sites, are indolent tumours and dissemination beyond the stomach and local draining lymph nodes is rare, although spread to other extra nodal sites is recognised. Bone marrow dissemination is rare.

**Histopathology**

The organisation of MALT lymphomas mimics that of Peyer’s patches. Neoplastic cells infiltrate around pre-existing lymphoid follicles initially occupying the marginal zone but eventually becoming diffuse. The cells themselves have a variable appearance but in the commonest form are small to medium sized with pale cytoplasm and irregular nuclei. These features resemble the appearance of the follicle centre centrocyte and has led to the term ‘centrocyte-like’ (CCL) cell being applied to the neoplastic cells of MALT lymphoma. Plasma cell differentiation and scattered blast cells are a constant feature. The CCL cells have a characteristic interaction with the glandular epithelium in a mimic of the interaction between the marginal zone B cells and the dome epithelium of the Peyer’s patches. In MALT lymphoma, the neoplastic lymphocytes infiltrate and destroy the glands to form so-called lymphoepithelial lesions which are an invariable finding in the lymphomas. High grade transformation occurs in MALT lymphoma and can be inferred in such cases, either by the presence of a low grade component within the tumour, or by the recognition of MALT-like features such as lymphoepithelial lesions.

The reactive follicles are integral to MALT lymphomas. In some cases, their presence is not obvious but is suggested by a vague nodularity to the infiltrate. In these cases, immunocytochemical staining for follicular dendritic cells reveals a distorted network confirming the presence of lymphoid follicles that have been infiltrated and overrun by the CCL cells. In other cases, there may be specific colonisation of the follicle centres by the neoplastic cells with maintenance of the normal mantle. Plasma cell differentiation may be seen in the intra follicular CCL cell population.

Immunophenotypically, the CCL cells express pan-B cell markers but do not express CD5 or CD10. They express surface, and to a lesser extent cytoplasmic, immunoglobulin (usually IgM or IgA and rarely IgG) which is light chain restricted. Genotypically, all cases show clonal re-arrangement of the immunoglobulin genes. Trisomy 3 has been found as a characteristic association with MALT lymphomas and genetic abnormalities including t(11;18) and t(1;14) have also been reported.
**Gastric MALT lymphoma and H. pylori**

The close association between gastric MALT lymphoma and *H. pylori* is beyond doubt and is seen in 72–98% of low grade cases\(^5\)\(^,\)\(^,\)\(^17\)\(^,\)\(^,\)\(^18\). *H. pylori* is less commonly found in high grade gastric lymphomas being seen in up to 71% of cases with a concomitant low grade component\(^18\), but only in 38–51% of high grade tumours with no specific MALT features\(^18\)\(^,\)\(^,\)\(^19\). *H. pylori* infection is only seen in approximately 51% of individuals with secondary involvement of the stomach by lymphomas of nodal-type\(^18\). In a retrospective serologically based study, Parsonnet *et al*\(^20\) demonstrated that infection by *H. pylori* predated the development of the lymphoma by many years and was associated with an odds ratio for the development of lymphoma of 6.3.

There are several morphological features of MALT lymphomas that suggest the presence of a residual immunologically based proliferative drive. These include the presence of plasma cell differentiation in the tumour cell population and the presence of follicular colonisation. Migration to the follicle centre has been shown to be a property of marginal zone B cells under antigenic stimulation\(^21\)\(^,\)\(^22\) and it is from this B cell population that MALT lymphomas are thought to arise so the presence of this feature is compelling evidence for such an immunological influence on the tumour cell behaviour. *In vitro* studies have shown that tumour cells derived from partial gastrectomy specimens containing low grade gastric MALT lymphoma show increased proliferation when co-cultured with heat-killed whole preparations of *H. pylori*\(^23\). This proliferative drive is strain specific for each of the cases examined and is not seen in MALT lymphomas from other sites, nor is it seen in high grade lesions. Further experiments have shown that this proliferative response is dependant upon the presence in the culture system of tumour infiltrating T cells and is not seen when these cells are substituted with splenic T cells from the same individual\(^24\). Additionally, it has been shown that this is a contact-dependant phenomenon and is not seen when the T cell population is absent but T cell derived diffusible substances are present in the form of supernatants from other proliferative cultures.

**Regression of gastric lymphoma with eradication of H. pylori**

Recognition of the importance of *H. pylori* to the proliferation of gastric MALT lymphoma led Wotherspoon and co-workers to observe the effect of eradication of the organism on a small series of early lymphomas\(^25\). They found tumour regression in 5/6 cases treated by *H. pylori* eradication alone. Subsequent studies have supported the suggestion that
eradication of *H. pylori* can induce tumour regression in the absence of any other therapy (Table 1). Although this has mostly been investigated in cases of ‘early’ gastric MALT lymphoma, at least one case with a large gastric mass has shown prolonged remission with *H. pylori* eradication\(^{26}\). Regression of the lymphoma may be seen in some cases before complete eradication of the organism (personal observation). In general, high grade lesions would not be expected to respond to *H. pylori* eradication alone\(^{27,28}\), although some responses in high grade lesions have been reported\(^{29}\) and any low grade component within a high grade lymphoma may show remission with *H. pylori* eradication\(^{30}\). Relapse of lymphoma has been reported in some cases and this may or may not be associated with recrudescence/re-infection events\(^{31-34}\).

Recently, cases of extra-gastric MALT lymphoma arising within the duodenum\(^{35,36}\) and the salivary gland\(^{37}\) have been reported to show regression following treatment with anti-*H. pylori* therapy. The reason for these findings remains obscure.

Although gastric MALT lymphoma responds well to conventional therapeutic options – including surgery, radiotherapy and chemotherapy, either alone or in combination – it is still recommended that *H. pylori* eradication is achieved in all cases and many workers would now accept and anti-*H. pylori* therapy should be considered as the first option in cases of early low grade gastric B cell lymphoma of MALT.
References


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