Gastric MALT lymphoma and *Helicobacter pylori*

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Introduction

Primary gastric non-Hodgkin's lymphoma comprises 3-6% of all gastric malignant tumours but the incidence is thought to be increasing.[1,2] The majority of these are high grade B cell lymphomas but a significant proportion are low grade tumours. In 1983 Isaacson & Wright[3] recognised that the clinicopathological features of these lymphomas were distinct from those of nodal-type B cell lymphomas and suggested that they arose from within specialised extranodal lymphoid tissue termed "mucosa associated lymphoid tissue" (MALT). In the normal human MALT is found almost exclusively in the intestine and is most prominent in the terminal ileum in the form of Peyer's patches. This MALT has specifically adapted and evolved to protect the freely permeable membrane of the gastrointestinal tract. A Peyer's patch is non-encapsulated, localised and organised nodular area of lymphoid tissue the most prominent component of which is the lymphoid follicle with a reactive germinal centre surrounded by a mantle zone of small B lymphoid cells. Outside this there is a zone of slightly larger B cells with pale cytoplasm comprising the marginal zone and which extends to the overlying epithelium with marginal zone B cells infiltrating this epithelium to form a "lymphoepithelium". Plasma cells are present in the lamina propria and are most

prominent in the subepithelial region. A T cell zone lies laterally and below the follicle. Within the dome epithelium there are specially adapted epithelial cells (M cells) that are thought to absorb, transport, process and present luminally derived antigens to the underlying lymphoid tissue.[4] Antigens taken up by the M cells are transported to the Peyer's patches where antigen specific B cells are stimulated to undergo switching from IgM to IgA producing B cells. Following stimulation the B cells leave the mucosa and enter the circulation. These home back to the mucosa and are seen in the lamina propria as plasma cells.[5-7]

Gastric lymphoid tissue and *Helicobacter pylori*

The paradox of primary gastric lymphoma is that the normal gastric mucosa is devoid of lymphoid tissue. In order for lymphoma to develop within the stomach wall some organised lymphoid tissue must first be acquired. It is within this acquired lymphoid tissue that a series of molecular events may subsequently take place leading to the development of a primary gastric lymphoma. The stomach is a hostile environment for infective organisms due to the low luminal pH and the mucosa is non-absorptive, lacks M cells and is protected from diffusible antigen by the thick viscous mucous layer and the gastric acid. The stimuli that result in the acquisition of organised lymphoid tissue in the gastric mucosa are therefore limited. Several studies have shown that infection with *Helicobacter pylori* (*H. pylori*) is associated with accumulation of organised lymphoid tissue while non-infected individuals rarely have such tissue in their gastric mucosa.[8-15] In the most comprehensive study in which numerous gastric biopsies were taken from multiple regions of the stomach Genta et al[12] demonstrated that lymphoid follicles could always be found in *H. pylori* infected individuals while no follicles were found in normal healthy controls. Wotherspoon et al[10] showed that this acquired lymphoid tissue had the morphological features of MALT including the presence of a lymphoepithelium. Reactive gastric MALT is not exclusively found in cases with *H. pylori* infection but can also be seen in individuals infected by the related organism *Helicobacter heilmannii* and has been reported in uninfected individuals with coeliac disease.[16]

Histology of gastric MALT lymphoma

The histological appearances of low grade MALT lymphoma mimics the arrangement of Peyer's patches.[17] The neoplastic cells infiltrate around reactive lymphoid follicles initially occupying the marginal zone but eventually expanding to form a diffuse infiltrate. The tumour cells are small to medium sized with moderately abundant cytoplasm. In general the nuclei are small and irregular with indis-

tinct nucleoli and the similarity of these cells to the centrocyte of the follicle centre led to their designation "centrocyte-like" (CCL). Variation in morphology can occur even within a single case with the CCL cells adopting a mature lymphocyte-like appearance with rounder nucleus and scanty cytoplasm or a monocytoid form with abundant pale cytoplasm and well demarcated cell borders. Transformed blastic cells are scattered within the infiltrate and plasma cell differentiation within the neoplastic population is invariably seen. This latter feature is most prominent in the subepithelial region but may be so pronounced and widespread as to raise the differential diagnosis of extra-medullary plasmacytoma.

The CCL cells interact with the surrounding epithelium mimicking the infiltration of the dome epithelium by marginal zone B cells in Peyer's patches. In gastric MALT lymphomas the neoplastic CCL cells infiltrate the epithelium usually in the neck region of the glands but occasionally that of the luminal surface. This is associated with destruction of the glandular architecture and morphological changes in the epithelial cells.[18] The resulting structure - the lymphoepithelial lesion (LEL) - is characteristic of lymphomas of MALT-type.

The reactive lymphoid follicles are an important and ubiquitous component of MALT lymphomas.[19] Their presence may be obvious or only apparent due to a faint nodularity to the tumour infiltrate and the demonstration of an underlying residual follicular dendritic cell network. The neoplastic CCL cells show selective colonisation of these reactive follicle centres to a variable degree. In some cases the follicles are overwhelmed leading to the vague nodularity described above while in other cases the follicle centres are replaced by CCL cells while the surrounding mantle zone remains intact. In these cases the intrafollicular component may appear larger than the diffuse infiltrate while in other cases they may show marked plasma cell differentiation.

High grade transformation may occur in MALT lymphoma. Although the majority of gastric lymphomas are high grade with no specific features in some cases an origin from a pre-existing low grade MALT lymphoma can be inferred. In some cases there is a small persistent low grade component which, if present, is usually seen at the edge of the high grade tumour.[20] In other cases the presence of LEL's formed between the high grade lymphoma cells and the glandular epithelium suggests an origin from MALT.[21] Histologically the cells of the high grade MALT lymphomas are large with abundant cytoplasm, vesicular nuclei and prominent nucleoli and generally resemble centroblasts but more immunoblastic or plasmablastic morphologic may be encountered.

When there is dissemination of low grade MALT lymphoma to draining lymph nodes the CCL cells initially adopt a marginal zone pattern of infiltration which eventually expands to efface the entire nodal architecture. The distinction be-

tween early involvement of mesenteric lymph nodes, which have a prominent marginal zone, may be problematic.

The cell of origin of MALT lymphoma

The immunophenotypic and genotypic distinction between MALT lymphomas and those nodal -types of lymphoma that arise from the cells of the lymphoid follicle centre or mantle suggests that the CCL cell is derived from a separate B cell population. The architectural arrangement around lymphoid follicles with a marginal zone pattern, the cellular morphology and the immunophenotype all point to the origin of MALT lymphomas from the marginal zone B cell population. This suggestion would also help to explain the follicular colonisation alluded to above which would be the neoplastic equivalent to the normal physiological/immunological response of marginal zone B cells which have been shown to migrate into follicle centres when exposed to antigen.[22,23]

Gastric MALT lymphoma and *Helicobacter pylori*

The close association between low grade gastric MALT lymphoma and *H. pylori* is beyond doubt and is seen in 72-98% of cases.[10,24,25] In a retrospective serologically based study Parsonnet et al were able to demonstrate that the infection predated the development of the tumour with an odds ratio for lymphoma development of 6.3.[26] The role of *H. pylori* infection in gastric lymphomagenesis revolves around the acquisition of MALT from within which the tumour can develop. However there are certain morphological features of low grade MALT lymphoma which suggest persistent immunological drive to the lymphoma cells by antigen. These features include the presence of scattered transformed blastic cells, subepithelial plasma cell differentiation and follicular colonisation. These appearances and the apparent intimate association between *H. pylori* and gastric MALT lymphoma led to in-vitro studies looking at role of *H. pylori* in the proliferation of the lymphoma cells. Tumour cells derived from gastric resection specimens containing low grade gastric MALT lymphomas were shown to proliferate and synthetise tumour immunoglobulin when co-cultured with heat-killed whole preparations of *H. pylori*.[27,28] Each case examined responded to a separate strain of the organism and a similar proliferative drive was not seen in non-gastric MALT lymphoma nor in lymphomas of nodal-type. Subsequent experiments have demonstrated that this is not a direct effect but is mediated by tumour infiltrating T cells and was contact dependant.[29]

Eradication of *Helicobacter pylori* and regression of gastric MALT lymphoma

At about the same time as the in-vitro studies of MALT lymphoma and *H. pylori* were progressing an in-vivo study by Wotherspoon et al[30] demonstrated regression of gastric MALT lymphoma in patients treated with eradication of the organism alone. Initial studies have supported the contention that eradication of *H. pylori* is sufficient to induce remission in cases of early low grade MALT lymphoma (Table 1).[13,30-43] In one of the largest follow-up studies published to date Zucca et al have reported complete remission in 55% of 217 patients treated by *Helicobacter* eradication alone with partial remission in a further 15%.[44] Thiede and co-workers have been able to demonstrate complete remission in 81% of the 84 patients enrolled in their multicentre trial with partial remission in a further 8%[45] and Savio et al found a rapid and persistent histological remission in 73% of patients in their study of 76 patients with a delayed response in a further 6 patients.[46] The question of durability of the remissions is becoming clearer with Isaacson et al reporting the 6 year follow-up of their original 6 patients.[47] In all cases the remission has persisted although there had been two instances when

Table 1. Initial studies of regression of low grade gastric MALT following successful eradication of *H. pylori.*

	Year	Cases eradicated	Total regression of lymphoma	Partial regression of lymphoma
Wotherspoon et al	1993	6	5	
Stolte et al	1993	13	12	
Wotherspoon et al	1994	8	7	
Weber et al	1994	1	1	
Bayerdorffer et al	1995	27	23	4
Montalban et al	1995	5	4	
Cammerota et al	1995	1	1	
Dragosics	1995	10	6	
Fischbach	1995	10	8	
Roggero et al	1995	25	15	
Blecker et al	1995	1	1	
Stolte et al	1996	84	67	6
Sackman et al	1996	17	10	4
Fischbach et al	1996	14	14	
Savio et al	1996	12	11	
Montalban et al	1996	8	7	
Zucca et al	1996	47	33	

histological relapse had become apparent in biopsy specimens. In each case the relapse was undetectable in subsequent biopsy specimens.

While histological regression may be observed rapidly after initial *Helicobacter* eradication, molecular studies may detect residual lymphoma populations for many months after apparent remission. In one study this was observed in 19 of 39 patients (49%) in whom this investigation was possible.[45] The significance of the persistence of this residual disease is unknown, but this study that patients in whom histological relapse subsequently occurred were within this group.[45]

Failure to respond to *Helicobacter* eradication may be due to cryptic high grade lesions.[34] However Sackmann et al studied the relationship between remission rates and depth of invasion of the gastric wall as measured by endoscopic ultrasound.[39] In their study 12 of 14 patients with lymphoma confined to the mucosa and superficial submucosa achieved remission compared to none of the 10 patients with deeper infiltration of the gastric wall.

In general high grade MALT lymphoma is not responsive to anti-*H. pylori* therapy[43] but a low grade component may regress with this treatment. Relapse of the lymphoma has been reported in some cases and this may or may not be associated with recrudescence/reinfection by *H. pylori*.[38]

Conclusion

Low grade MALT lymphoma is a clinicopathologically distinct B cell lymphoma which is thought to arise from within the marginal zone B cell population of acquired organised extranodal lymphoid tissue. In vitro studies have shown that the proliferation of tumour cells in low grade MALT lymphoma is driven by the presence of the organism in a way that is T cell dependant. Studies in early gastric MALT lymphomas have demonstrated tumour regression in response to *H. pylori* eradication.[13,30-47] Most observers would now recommend eradication of *H. pylori* in all cases of gastric MALT lymphoma although the role of this therapeutic option in more advanced stage low grade disease is debatable and it is likely to be ineffective in the high grade areas of transformed cases. Although there is debate about the most effective therapy for gastric MALT lymphoma eradication of *H. pylori* is now established as an essential component of the management of these tumours and in some early cases may itself be sufficient to induce regression of the lymphoma.

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