A Critical Review of the Effect of *Helicobacter pylori* Eradication on Gastric MALT Lymphoma

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Low-grade B-cell lymphomas of mucosa-associated lymphoid tissue (MALT) are thought to arise within organized lymphoid tissue in the gastric mucosa that is most frequently acquired in response to *Helicobacter pylori* infection. This close association between the organism and the lymphoma is further reflected by the demonstration that the proliferation of the lymphoma cells can be driven by the presence of *H. pylori* organisms through a complex path of cellular interactions involving specific T cells. From these observations it was suggested that removal of one of the proliferative drives to the neoplastic cells in the form of eradication of the organism might induce a remission in the tumor. Several large multicenter studies are now underway to consider this question, and interim reports suggest that long-term remissions can be induced in low-grade MALT lymphomas in 70% to 80% of cases. The lymphomas that are most likely to respond to *H. pylori* eradication are those that are located superficially within the gastric mucosa. It has been suggested that certain genetic abnormalities, such as t(11;18) and the Bcl-10 mutation, may be associated with lack of response to this therapy. Recurrences of low-grade lymphoma are encountered in patients treated by *H. pylori* eradication, but these appear to be infrequent and may be self-limiting and spontaneously regress without further therapy.

Introduction

The great paradox concerning primary gastric lymphoma, in common with primary lymphomas at many extra-nodal sites, is the absence of organized lymphoid tissue within the organ in the normal individual. If no lymphoid tissue is present, then no lymphoma can arise at that site. This paradox is solved by the recognition that lymphoid tissue can be acquired in association with certain stimuli. Indeed, this acquired lymphoid tissue used to be so frequently encountered in the stomach that at one time lymphoid follicles were thought to be a normal finding in the gastric mucosa—a proposal that we now recognize as incorrect.

In the majority of patients, the acquisition of organized gastric lymphoid tissue is associated with local infection by *Helicobacter pylori* [1]. The stomach is a hostile environment, and few organisms are able to withstand the low pH and thrive within this organ. This probably explains the very close association between the acquisition of the lymphoid tissue and this particular organism that is almost unique in its ability to thrive under these hostile conditions. As *H. pylori* is associated closely with the acquisition of the lymphoid tissue from which a lymphoma would have to arise, it is probably unsurprising that the low-grade lymphoma that most frequently arises within this lymphoid tissue, B-cell lymphoma of mucosa-associated lymphoid tissue (MALT), is also associated with this organism. The recognition that there was an in vitro relationship between the neoplastic cell proliferation in this lymphoma and the presence of the organism (albeit an indirect proliferative drive involving specific tumor-related T cells) provoked initial studies of the effect of its eradication on tumor development [2,3]. Early studies suggested that successful eradication of *H. pylori* could result in regression of low-grade gastric MALT lymphomas [4,5].

The finding of tumor regression associated with eradication of an infective organism has proved controversial. Initially some observers questioned whether these lesions could be considered to be lymphomas because tumors "by definition" could not respond to normal regulators of cell turnover (proliferation/apoptosis) or differentiation [6]. This does not acknowledge the possibility that they were using a definition of a tumor that is inconsistent with the realities of current knowledge in tumor behavior and strategies for the management of solid organ malignancies such as those arising in the prostate and breast.

Recent studies have confirmed that eradication of *H. pylori* gives real regression in real lymphomas of MALT type arising within the stomach [7]. This ultra-conservative therapy has the potential to give the patient a remission with conservation of gastric integrity and function in the absence of any real risk of side effects associated with the

treatment. The regression induced in this way is not seen in all cases of gastric MALT lymphoma. The current challenges revolve around the prediction of which patients will benefit from this approach, when a patient can be identified as a non-responder and be directed to more conventional anti-lymphoma therapies, and what is the prognosis for those patients in whom the tumor regresses with respect to the risk of relapse.

Terminology in Gastric Lymphoma and the Relationship Between Low-grade and High-grade Lesions

The recognition that the vast majority of "low-grade" lymphomas arising within the gastrointestinal tract are MALT lymphomas is now widely accepted. The stomach may be involved by primary nodal-type "low-grade" B-cell lymphomas such as follicular lymphoma or mantle cell lymphoma as part of widespread dissemination, but these are very infrequently found as primary gastric lesions. There is more controversy concerning the terminology and derivation of the histologically high-grade, large B-cell lymphomas. Although some investigators include all large B-cell lymphomas arising within the gastric mucosa as high-grade MALT lymphoma, others restrict this term for use with large B-cell lymphomas that are specifically associated with either a pre-existing diagnosis of typical MALT lymphoma or in cases where a concurrent low-grade area can be identified. Controversy remains over the terminology of lesions in which there are increased numbers or small clusters of blasts—a group identified by De Jong *et al.* [8] as being associated with a poorer prognosis than standard low-grade MALT lymphoma. Also, some authors include those lymphomas composed of cells that resemble blastic monocytoid/marginal B cells, or cases in which the large cells form lymphoepithelial lesions, in the group of high-grade MALT lymphoma. This situation is further confused by the guidelines published for the new World Health Organization (WHO) classification of lymphoma, which suggest that the term "high-grade MALT lymphoma" should not be used and should be supplanted by the term "diffuse large B-cell lymphoma plus or minus areas of marginal zone/MALT lymphoma" [9].

In addition to the controversies surrounding the terminology used to designate these lymphomas, there is also some debate as to the origin of the large-cell lymphomas and their relationship to the low-grade components. Initial studies have suggested that there is clonal identity between the two components in all cases [10,11], but this proposal has recently been questioned by a study that found a distinct clonal origin of the two components in a single case [12]. This situation would be comparable with the findings in Richter's transformation of B chronic lymphocytic leukemia, where some cases show clonal relationship between the original leukemia and the transformed, large-cell area, whereas others show the high-grade area to be a de novo large B-cell lymphoma.

Association Between *H. pylori* and Gastric MALT Lymphoma

Initial studies suggested that low-grade gastric MALT lymphoma was associated with *H. pylori* infection in excess of 90% of cases [13,14]. Subsequent studies suggested that this association was less common, being found in approximately 62% to 77% of cases [15,16,17,18•,19]. Although this may be a reflection of geographic differences, there may be a more fundamental explanation. A recent study by Eck *et al.* [20] suggests that, although *H. pylori* could be detected in only 77% of the low-grade MALT lymphomas in their study, when histologic examination of biopsy material was performed, *H. pylori*-specific IgG serum antibodies could be detected in 95% of patients. These authors suggest that the discrepancy may result from loss of the organism during the progression of the tumor associated with disruption of the gastric micro-environment. This supports the findings of a study by Nakamura *et al.* [18•], which had previously suggested that *H. pylori* organisms were detected in gastric MALT lymphoma in decreasing frequency with increasing depth of tumor invasion. This suggests either that the organism has been lost in the course of the development of the tumor or that *H. pylori*-negative lymphomas present with more advanced disease (possibly being more locally invasive) than do their *H. pylori*-positive counterparts. Whereas depth of tumor invasion may be the most important factor, no study to date has examined the relationship between lateral tumor extent within the mucosa—which may cause significant loss of antral glandular epithelium upon which the organism most frequently resides—with the non-serologic detection of the organism.

The question of whether there are organism-related factors that predict a higher risk for development of MALT lymphoma remains controversial. Logic would predict that, as all *H. pylori* infections are associated with an inflammatory response that in the vast majority of cases includes lymphoid follicle formation, all *H. pylori* organisms would have the same potential for lymphomagenesis. Several studies have found no association between MALT lymphoma and CagA or VacA positive strains, although this is not clear cut [21–23]. A recent study has suggested that the majority of patients with MALT lymphoma harbored *H. pylori* strains containing a 19-kD protein that was an FldA homologue [24]. This appeared to be the result of a nucleotide G insertion at position 481 of the fldA gene within the bacterium. However, in a poster presentation at the recent meeting of the European Association for Haematopathology (EAHP), London, 2000, Liu *et al.* from Isaacson's group reported on their examination of 28 MALT lymphomas, 20 cases of *H. pylori*–associated gastritis, and 24 clinical strains of the organism, in which they found this insertion in all cases. They suggested that this was a wild-type gene rather than a pleomorphism. At present there appear to be no specific organism-related factors that are associated with a higher risk for the development of gastric lymphoma.

H. pylori Eradication and Regression of Gastric Lymphoma

Initial studies suggesting that gastric MALT lymphoma can be successfully treated by eradication of *H. pylori* infection alone have now been widely accepted. Zucca *et al.* [25] recently reported complete remission in 55% of 217 patients treated by *H. pylori* eradication alone with partial remission in a further 15%. Thiede *et al.* [26•] have demonstrated complete remission in 81% of the 84 patients enrolled in their multicenter trial with partial remission in a further 8%. Savio *et al.* [27•] found a rapid and persistent histologic remission in 73% of their study population of 76 patients with a delayed response in a further six patients. The durability of these remissions is now being addressed as the follow-up period for these patients increases. Isaacson *et al.* [28•] recently presented the 6-year follow-up data on their original six patients. In all cases, the remission has persisted, although there had been two instances when histologic relapses were apparent in the biopsy specimens. In each of these cases, the relapse became undetectable in the subsequent examinations without further therapy, and each patient remains apparently disease free 4 years after the relapse episode. This finding of self-limiting microscopic relapse has also been observed by Savio *et al.* [27•]

Whereas histologic regression may be observed rapidly after initial *H. pylori* 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%) [26•]. The significance of the persistence of this residual disease is unknown, but this study showed that several of the patients in whom histologic relapse occurred were in this group [26•].

High-grade lymphomas would be expected to be unresponsive to *H. pylori* eradication alone. In the studies that have included cases that have shown failure to respond to this therapy, the failure has frequently been ascribed to the presence of high-grade transformation in many of these cases [5]. However, very occasional cases in which high-grade lymphoma has responded to *H. pylori* eradication alone have been reported [29].

Prediction of Lymphoma Regression with *H. pylori* Eradication

Whereas the most optimistic studies have suggested a response rate of up to 80% for low-grade MALT lymphomas treated with *H. pylori* eradication [26•], a significant number of cases will fail to respond to this therapy. In some instances, this failure may be associated with cryptic high-grade lymphoma that becomes apparent following surgical resection of the unresponsive lesion [5]. The identification of lesions that are less likely to respond to anti–*H. pylori* therapy would allow early intervention with more conventional therapy in these instances, whereas those patients in whom a response would be expected but may be delayed can be observed for a longer time before further therapies are considered. Several investigators have addressed this issue. Sackmann *et al.* [30•] studied the relationship between remission rates and depth of invasion of the gastric wall measured by endoscopic ultrasound. In this study, 12 of 14 patients with lymphoma confined to the mucosa or submucosa achieved complete remission, compared with none of the 10 patients with more advanced disease.

Initial studies have suggested that molecular markers may also be useful in the prediction of response to *H. pylori* eradication. Bcl-10 is an apoptotic regulatory molecule that was initially identified through its involvement in the t(1;14)(p22;q32) translocation [31], which was identified in a minority of cases of MALT lymphoma [32,33]. Whereas this translocation is a rare finding in these lymphomas, the tumors that show this abnormality have a rare ability to grow in unstimulated in vitro culture with prolonged survival. This contrasts with other MALT lymphoma cell cultures. Studies of the mutation of the bcl-10 gene in MALT lymphomas treated with *H. pylori* eradication showed that the mutation was not present in the 22 patients who had responded to this therapy, but the mutation was present in 3 of 11 patients in whom there was no response [34]. This study, together with the in vitro observations, suggests that lymphomas with this mutation may have become *H. pylori*-independent and that treatment by eradication alone may be insufficient.

The translocation t(11;18) has been reported to be a frequent finding in MALT lymphomas [35,36,37•]. This translocation has been found as the sole abnormality in many lymphomas of this type and has not been observed in combination with other cytogenetic abnormalities or in high-grade lesions, raising the possibility that this translocation, although lymphomagenic in its own right, may confer stability on the genome, preventing acquisition of further genetic aberrations and therefore decreasing the likelihood of transformation. Nevertheless, it has recently been suggested that lymphomas with the t(11;18) translocation present with more advanced-stage lymphoma and that cases that show response to *H. pylori* eradication are very rarely associated with this translocation [38].

Conclusions

It is now well accepted that many low-grade gastric MALT lymphomas will respond to anti-*H. pylori* therapy alone. This ultra-conservative and cheap therapy appears to give durable remissions with conservation of gastric function and minimal side effects. Relapses may occur within the stomach and may show spontaneous remission without further therapy. At present there are several areas that remain uncertain and controversial and these require further study. The length of time in which a patient without complete remission can be observed following *H. pylori* eradication before other therapies should be considered

remains conjectural. There is no universally accepted regime for the follow-up of patients in whom remissions have been induced, and no guidelines exist for the frequency of endoscopy in these patients. Evidence so far suggests that relapse may occur at any time, so that lifelong follow-up in these patients seems essential, but the intensity of this watchful policy is yet to be determined.

Prediction of cases likely or, perhaps more importantly, those unlikely to show significant response to *H. pylori* eradication remains an important area for study. Early, superficial lesions are more likely to respond than are deeper lesions. This makes accurate staging of the lesion essential, and for this purpose endoscopic ultrasound has proven to be the most valuable tool. Reporting of the depth of invasion of the gastric wall appears paramount, with the distinction between mucosal/superficial submucosal and deeper lesions being the most important predictor of response so far identified. It is possible in the future that simple molecular tests might have the capability to identify lesions with different potential to respond to *H. pylori* eradication, but at present this does not appear to be the case.

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