Helicobacter pylori and Less Common Gastric Diseases

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Abstract

Helicobacter pylori (H. pylori) is associated with a wide spectrum of gastroduodenal diseases. Strong evidence has shown that H. pylori is implicated in the development of gastritis, gastric and duodenal ulcers, MALT lymphoma and gastric cancer. The result of multiple clinical trials had also found out that eradication of H. pylori results in cure of gastric and duodenal ulcers. The improvement of gastric inflammation after therapy is well documented and a substantial proportion of MALT lymphoma can be well treated by H. pylori eradication regimen. Progress has been made to widen the spectrum of gastric diseases associated with H. pylori infection. In recent years there were reports relating this microorganism with the less common gastric diseases. The long term complication of peptic ulcer disease, gastric outlet obstruction was found to be related to H. pylori infection in a substantial number of cases and eradication treatment can dilate the stenosis. As high as 90% of Menetrier's disease had been found to be related to H. pylori infection. Possible elimination of gastric hyperplastic polyps by H. pylori eradication therapy had been reported. The possible role of H. pylori in lymphocytic gastritis and granulomatous gastritis had been well investigated. Revolutionalized concept to treat these diseases by antimicrobial therapy had been substantiated by the successful experience of various authors. However, large series of prospective randomized clinical trials are still lacking in these fields. (J Intern Med Taiwan 2002;13:1-9)

Key Words: Helicobacter pylori, Gastric outlet obstruction, Menetrier's disease, Gastric hyperplastic polyps, Lymphocytic gastritis, Granulomatous gastritis.

Introduction

Since Warren and Marshall disclosed Helicobacter pylori (H. pylori) in gastric mucosa of gastritis patients in 1983, multiple studies have shown that H. pylori is associated with the development of gastritis, gastric and duodenal ulcers, MALT lymphoma and even gastric adenocarcinoma. There had been strong evidence relating H. pylori infection with chronic gastritis, gastric ulcer, and duodenal ulcer. Effective eradication therapy of H. pylori infection had resulted in over 90% of cure rate of gastric and duodenal ulcers. In addition, a substantial number of cases of MALT lymphoma, especially low grade lymphoma, had been well treated with this antibacterial therapeutic regimen. Evidence from pathological and epidemiological studies has also identified the relationship between chronic H. pylori infection and the subsequent development of gastric cancer. This had led the working group of the WHO International Agency for Research on Cancer to place H. pylori in the list of group 1 carcinogen in humans in 1994. Greater awareness of spectrum of diseases associated with H. pylori had prompted more investigational studies. In recent years there were also reports relating this microorganism with the less common gastric diseases. This category included gastric outlet obstruction, hypertrophic gastropathy, gastric polyps, lymphocytic gastritis, granulomatous gastritis and miscellaneous rarer gastric diseases.
Helicobacter pylori and Gastric Outlet Obstruction

Benign gastric outlet obstruction (GOO) may be a long term complication of chronic peptic ulcer disease, or in the minority of cases, a result of nonsteroidal anti-inflammatory drug-related disease. The incidence of GOO is estimated to be 2-8% of peptic ulcer disease. In the past, patients of GOO with clinical symptoms were first treated medically by acid suppression therapy. Aggressive intervention such as surgical operation or balloon dilatation would be undertaken if the initial treatment option failed, or in severe intractable condition such as long standing fibrotic stenosis.

In recent years, clinical reports regarding H. pylori eradication therapy in these patients had been interesting and fascinating. Accumulating evidence suggests that H. pylori infection was related to a substantial proportion of peptic ulcer induced GOO, and antibacterial therapy was efficient to relieve the symptoms and ultimately dilate the stenosis. The authors suggested that oral eradication therapy should be attempted before operational procedure.

There was evidence showing that even long standing fibrotic stricture appears to dilate after H. pylori eradication. W. de Boer in 1995 reported two cases of pin-point pyloric stenotic patients with successful treatment by oral eradication regimen. Both cases had been treated previously with acid suppression therapy without effective outcome, but the pyloric stenosis disappeared rather "unexpectedly" after H. pylori eradication therapy. In this report, the author emphasized the preference for quadruple therapy regimen for optimal treatment, and stated that the regimen works even in non-empty stomach, presumably by their topical effect, which was in agreement with Kimura's work. The therapeutic success of W. de Boer was supported by clinical report of Italian authors, who successfully treated stenotic cases with one week triple therapy. The Australian group had followed up patients of stenosis for 4 to 8 years, and had concluded that these patients, some with near pin-point stricture, responded well to quadruple therapy. They stated that tight stricturing and presumably associated fibrosis could be reversible.

It seems that the associated luminal edema resolves early after H. pylori eradication, with improvement of gastric emptying and symptoms, whereas the scarred lesion requires more time to soften. The explanation held by these authors is "that the long standing fibrotic stricture appears to dilate presumably due to the incessant pump action akin to a built-in dilator, which progressively stretches the softening fibrosis — provided the underlying H. pylori-driven inflammation is removed".

There were also different opinions presented by other authors. A Tursi and his coworkers pointed out that H. pylori eradication is not necessarily effective in older stenosis. Rinaldi and Zullo emphasized the importance of the width of pyloric opening in predicting successful therapy. Gibson DM recently reviewed a cohort of 24 patients underwent surgery, and found that only 8 (33%) were H. pylori positive.

In conclusion, based on the successful experience of many authors, H. pylori eradication therapy might be considered as a first-line treatment for GOO, if H. pylori infection is documented, and quadruple therapy appears to be the optimal treatment regimen. Dilatation or surgery should be reserved for patients who do not improve after antibacterial treatment. Finally it remained to be reminded that long term prospective comparative trial is still lacking in this field.

Helicobacter pylori and Hypertrophic Gastropathy

Hypertrophic gastropathy comprises entities of diseases associated with thickened gastric folds. The most common form of these diseases is hypertrophic gastritis which is histologically characterized by hypertrophy of glandular and foveolar layers associated with severe H. pylori infection. It is believed that the majority of cases is simply a rugal hyperplasia condition secondary to H. pylori infection. Normally no severe clinical condition is found associated to this form of gastritis, but in the long run, as in other chronic H. pylori related gastritis, it may proceed to atrophic gastritis and intestinal metaplasia, which subsequently may be predisposed to increased frequency of cancer transformation.

Another well known disease in this category is Menetrier's disease. The histological features of this disease is characterized by foveolar hyperplasia, atrophy of glands and increased mucosal
It is a rare disease often regarded as of unknown etiology, and clinically manifested as protein-losing gastropathy and hypoproteinemia\textsuperscript{27}. Increased incidence of gastric cancer association as high as 13\% had been reported\textsuperscript{28}. There was some evidence that the altered expression of transforming growth factor-alpha might play a role in its etiology\textsuperscript{29,30}. Recently \textit{H. pylori} has been implicated as a pathogenic factor in the cause of this disease\textsuperscript{31}. In 1992, the Dutch Menetrier's study group has reported a low prevalent rate of \textit{H. pylori} infection in adult Menetrier's disease\textsuperscript{32}. More recently, Stolte and Bayerdorffer et al in 1995 had retrospectively investigated 138 patients with hypertrophic gastropathy, and found that this disease was associated with \textit{H. pylori} infection in more than 90\% of cases\textsuperscript{33}. In view of this finding, the study group treated a case of Menetrier's disease associated with protein losing gastropathy, with documented \textit{H. pylori} infection. This case was treated previously with cimetidine for more than 3 years, with little benefit. A 14-day course of dual therapy with amoxicillin and omeprazole led to \textit{H. pylori} eradication and normalization of the giant folds in a 4-week period, and increased serum protein concentration to normal range in 6-week period\textsuperscript{34}. Several other reports had also shown that effective \textit{H. pylori} eradication therapy resulted in remission of protein-losing hypertrophic gastropathy\textsuperscript{35-37}. Some authors have proposed that \textit{H. pylori} might act as a local antigen to sensitize the gastric mucosa, which leads to an abnormal response ultimately resulting in hypertrophic gastropathy\textsuperscript{38}. It has been shown that gastric mucosa infected with \textit{H. pylori} is in a state of hyperproliferation, evidenced from expression of PCNA\textsuperscript{39}. Animal study of infected transgenic mice has shown sustained anti-\textit{Helicobacter felis} serum antibody response, with subsequent development of adenomatous and cystic hyperplasia of the surface foveolar epithelium\textsuperscript{40}. \textit{H. pylori} had been implicated in cases of hypertrophic gastropathy in both adults and children\textsuperscript{35,41}. Yamada M. in 1997 had reported a 3-year-old boy with severe protein-losing gastropathy\textsuperscript{35}. Abdominal scintigraphy using IV 99m Tc-labelled albumin showed massive protein excretion from the stomach. A 2 week antibacterial treatment was prescribed and this resulted in rapid improvement of protein loss with subsequent improvement of hypoproteinemia and edema in 4 weeks time.

Taking account of the fact that protein-losing gastropathy with intractable hypoproteinemia is sometimes a life-threatening condition, this report

Table 1 Clinical Features of Patients with Hyperplastic Gastric Polyps Treated by \textit{Hp} Eradication Therapy Reported in English Literature

<table>
<thead>
<tr>
<th>Reference</th>
<th>Case number</th>
<th>Description of lesions</th>
<th>Associated clinical features</th>
<th>Treatment</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veerman et al.</td>
<td>2</td>
<td>multiple polyps</td>
<td>mild chronic gastritis</td>
<td>amoxicillin+ bismuth x 2w</td>
<td>disappearance and recurrence of polyps(1y, 2y)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>size not stated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 polyps</td>
<td>diffuse gastritis</td>
<td></td>
<td></td>
<td>disappearance</td>
</tr>
<tr>
<td></td>
<td>2mm, 7 mm</td>
<td>healed GU</td>
<td></td>
<td></td>
<td>of symptoms (no follow-up endoscopy)</td>
</tr>
<tr>
<td>Mocek et al.</td>
<td>1</td>
<td>multiple polyps</td>
<td>post gastrectomy status 5 y with</td>
<td>bismuth+ tetracycline+ metronidazole</td>
<td>disappearance of polyps (less than 1 y)</td>
</tr>
<tr>
<td></td>
<td>size not stated</td>
<td></td>
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should encourage a prompt treatment option aiming at eradication of *H. pylori* in cases of protein-losing gastropathy with severe hypoproteinemia.

In conclusion, the data presented suggest that *H. pylori* is a pathogenic factor in substantial cases with hypertrophic gastropathy. It seems rational to treat *H. pylori*-associated hypertrophic gastropathy with antibacterial eradication regimen.

### Gastric Hyperplastic Polyps and Helicobacter pylori Treatment

The etiology of gastric hyperplastic polyps had been obscured. The polyps often appear as a late consequence of chronic gastritis. Usually small polyps less than 1 cm in size have little predisposition to malignant change, but large polyps greater than 2 cm may present clinical risk of bleeding, obstruction and malignant transformation (1.5-3% incidence). Therefore, larger polyps are often removed endoscopically or surgically to avoid later complications.

In recent years, reports regarding *H. pylori* infection with hyperplastic polyps, and disappearance of polyps after eradication treatment has been interesting and encouraging (Table 1). In 1990 Veereman et al has reported that in cases with persistent presence of *H. pylori*, along with chronic gastritis and hyperplastic polyps for more than three years, successful *H. pylori* eradication treatment had resulted in disappearance of hyperplastic polyps. In 1994 Mocek et al reported multiple recurrences of hyperplastic gastric polyps in 6-year period, despite sessions of treatment by acid suppression therapy and surgery. These polyps ultimately subsided after *H. pylori* eradication. In 1997 Ohkusa et al had reported elimination of multiple hyperplastic gastric polyps 1 year after *H. pylori* eradication therapy. In 1998 the same Japanese group conducted a randomized controlled study of 35 patients with *H. pylori* infection and hyperplastic polyps. Successful clearance of *H. pylori* with omeperazole-based triple therapy regimen resulted in 80% disappearance of polyps, which was associated with regression of gastritis and lowering of both

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Mean no. of polyps</th>
<th>Mean size (mm)</th>
<th>Presence of chronic gastritis</th>
<th>Treatment</th>
<th>Disappearance of polyps</th>
<th>Mean time of disappearance (m)</th>
<th>Changes in gastrin level</th>
<th>Changes in pepsinogen I/II ratio</th>
<th>Changes in Hp Ab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suzuki et al.</td>
<td>1</td>
<td>15 polyps</td>
<td>8-26 mm</td>
<td>Mostly presence of DU, GU</td>
<td>lanzoprazole + amoxicillin x 2w</td>
<td>disappearance of polyps (1 y)</td>
<td>↓ gastrin level</td>
<td>↑ pepsinogen I/II ratio</td>
<td></td>
<td>↓ Hp Ab</td>
</tr>
<tr>
<td>Ohkusa et al.</td>
<td>12</td>
<td>Mean no. 4½</td>
<td>Mean size 9.3 mm</td>
<td>Mostly presence of DU, GU</td>
<td>PPI+ + amoxicillin + clarithromycin / ecabet sodium</td>
<td>disappearance of polyps, average 7.1 m.</td>
<td>↓ gastrin level</td>
<td></td>
<td>↓ Hp Ab</td>
<td></td>
</tr>
<tr>
<td>Koay et al. (Taiwan)</td>
<td>1</td>
<td>8 polyps</td>
<td>Largest size 18 mm</td>
<td>Post-gastrectomy status</td>
<td>amoxicillin + omeprazole + clarithromycin x 2w</td>
<td>disappearance of smaller polyps, 3 m. and large polyps 9 m.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GU = gastric ulcer; y = year; Hp Ab = *Helicobacter pylori* antibody; DU = duodenal ulcer; w = week; m = month; ↓ = decreased; ↑ = increased
serum gastrin level and IgG titer. The authors proposed that H. pylori promotes inflammation and contributes to the reactive hyperplasia of the gastric mucosa which leads to the formation of hyperplastic polyps, and they recommended that eradication therapy should be attempted before endoscopic removal of the polyps.

The issue of large polyps management is important due to their tendency to induce complications and malignant transformation. In the previously mentioned articles, no information had been provided specifically regarding the larger polyps. In our own experience, we had reported a case of multiple hyperplastic gastric polyps of variably sized, associated with H. pylori infection. The largest polyp was measured to be 18 mm in size. We prescribed a 2-week therapeutic regimen with omeperazole, amoxicillin and clarithromycin, and follow up endoscopy after 3 months and 9 months. We found successful eradication of H. pylori was accompanied by dramatic disappearance of most of the polyps and partial resolution of the large polyp in a 3-month period. Complete elimination of polyps with normal appearance of gastric mucosa was noted in 9-month period. Now the patient had been followed up in our outpatient clinic for 3 years, without clinical evidence of polyps recurrence and H. pylori reactivation. We therefore concluded that multiple hyperplastic polyps may be treated by H. pylori eradication therapy, if there is a well documented H. pylori infection, before attempting endoscopic or surgical resection. Eradication therapy for large gastric polyps may be tried, but it is too early to draw conclusion for large polyp, as the experience is limited till now.

The pathogenesis of the H. pylori-induced mucosal hyperplasia and hyperplastic polyp is being elucidated. In 1993 Correa had proposed that H. pylori induced a chronic inflammatory response that leads to an increased rate of mucosal proliferation. Subsequent studies by other authors have shown increased proliferative indices, proliferating cell nuclear antigen (PCNA) staining, 5-bromo-2'-deoxy-uridine (BrdU) incorporation in patients with H. pylori infection. In 1992, Saito et al proposed that H. pylori infection induces increased inflammatory cell infiltration of gastric mucosa, and results in reactive epithelial cell proliferation and hyperplastic polyp formation. In 1998 Ohkusa et al had investigated patients of gastric hyperplastic polyps with H. pylori infections. Successful clearance of H. pylori caused subsidence of polyps which correlated well with decreased number of inflammatory cell infiltration of gastric mucosa. These evidences clearly indicated a close relation between H. pylori infection, inflammatory cell infiltration and hyperlastic polyp.

Further investigation of its pathophysiology was done by several authors. Experiment performed on mice had shown that host immune response notably the adaptive immune response, specifically T-cells, is an important mediator contributing to the gastric epithelial hyperproliferation seen after H. pylori infection. Clinical studies on interleukin-1β and hepatocyte growth factor had shown that increased production of these factors after H. pylori infection may stimulate epithelial cell proliferation and foveolar hyperplasia.

The Role of Helicobacter pylori in Lymphocytic Gastritis

Lymphocytic gastritis (LG) was first described by Haot et al in 1988. It is a rare disease which involves an increase in intraepithelial lymphocytes in the surface and foveolar epithelium of gastric mucosa. Endoscopically LG may present a picture of multiple chronic raised erosions or giant folds gastritis, mostly located over corpus. Its etiopathogenesis has been linked to celiac disease and H. pylori infection. The exact relationship between H. pylori and LG is still unclear. There were several case reports of LG association with H. pylori infection. Some authors had suggested that LG represents an abnormal response of gastric mucosa to a local antigen, which may be the pathogen, H. pylori in many cases. Dixon et al had reported a 41% positive rate of H. pylori infection in biopsied specimen of LG, and 82% positive rate when tested serologically. Wu et al had investigated 103 patients with LG and identified a distinct etiology in 84 patients (82%). This included 39 with celiac disease, 30 with H. pylori infection, 4 with varioliform gastritis and 11 with other entities of diseases. Niemela et al had followed up cases of LG associated with H. pylori infection for 10 years. The authors observed that LG was associated with increase in the grades of corpus gastritis, neutrophilic granulocytes and intestinal metaplasia during the 10 year interval.
LG was also found to be more prevalent in patients with gastric adenocarcinoma (12.3%) and primary gastric lymphoma (13.7%) than in unselected patients undergoing endoscopy (0.83%, 2.5%) 59.

Healing of LG by pharmacologically eradicating *H. pylori* has been reported 60, 61, 62. Hayat et al had treated 11 patients of LG associated with *H. pylori* infection, with a one week course of omeperazole, clarithromycin and metronidazole. Two months after treatment, they found a significant reduction of gastric intra-epithelial lymphocyte counts, improvement of corpus inflammation, and all patients turned *H. pylori* negative histologically 61. More recently, Mullel et al had treated 61 patients of LG with documented *H. pylori* infection (29 by histology, 32 by serology), with a control group of 37 patients of LG without *H. pylori* association. They found much improvement of gastritis parameters including normalization of intra-epithelial lymphocyte counts in both the treatment groups in 93.1% and 84.3% of cases 62. This study supports the notion that most cases of LG might be a consequence of *H. pylori* infection.

**The Controversial Role of Helicobacter pylori in Granulomatous Gastritis**

Granulomatous gastritis has long been considered as part of a local or systemic disease. The frequency of its association with other local or systemic diseases varies widely, and the more commonly related entities are Crohn's disease, sarcoidosis and infection 63. In 1963 Fahimi et al reported 3 cases of granulomatous gastritis without evidence of associated local or systemic disease, and proposed that idiopathic granulomatous gastritis (IGG) could be regarded as a distinct clinicopathologic condition 63. The concept of IGG had later gained acceptance by clinicians and pathologists 64. The possible role of *H. pylori* infection in garnulomatous gastritis was proposed early by Dhillon in 1989, who reported 3 cases of granulomatous gastritis associated with "Campylobacter-like organisms" 65. Ectors et al in 1993 had found that in a series of 71 patients with granulomatous gastritis, a pattern of chronic gastritis with atrophy was noted in 95% of patients and *H. pylori* was detected in 92% of the biopsies 66. On the contrary, Shapiro et al (1996) had retrospectively reviewed 42 cases with granulomatous gastritis, and concluded that granulomatous gastritis per se was not associated with *H. pylori*. In this series, performed in a Crohn's disease referral center, the majority of cases belongs to Crohn's diseases (55%) and sarcoidosis. However, as stated by the author, in cases of IGG, a statistically significant association with *H. pylori* infection was found 67.

**Conclusion**

The spectrum of *H. pylori*-related gastroduodenal diseases is still expanding. New and accumulating experience of *H. pylori*-relating disease entities is still being studied and reported. There were recent reports of a rare case of *H. pylori*-induced gastric lymphonodular hyperplasia with gastric outlet obstruction, which improved after *H. pylori* treatment 68, and a case of metaplastic duodenal polyp with complete resolution after *H. pylori* eradication therapy 69. The possible causal role of *H. pylori* in the development of gastric polyposis and double pylorus 70 had been reported and is still under investigation. There is also evidence that lymphoid hyperplasia and nodular gastritis appear to be more frequent in children, and usually regress well after *H. pylori* eradication 41. At present, it may be concluded that there were evidences of *H. pylori* association with gastric outlet obstruction, Menetrier's disease, gastric hyperplastic polyps, granulomatous gastritis and lymphocytic gastritis. However, long term prospective clinical studies are still lacking in these fields. In addition, further research concerning the host factors, subtypes of *H. pylori*, molecular basis for pathogenic interaction and animal models for pathogenic elucidation are required to explain the different clinical outcomes of *H. pylori* infection.

**References**


幽門螺旋桿菌與罕見胃疾病

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摘 要

幽門螺旋桿菌（Helicobacter pylori, H. pylori）已被証實與許多胃腸疾病有關，包括慢性胃炎、胃及十二指腸潰瘍，胃黏膜相關淋巴瘤（MALT lymphoma）以及胃癌。許多臨床研究顯示根除治療幽門螺旋桿菌（H. pylori eradication therapy），可使消化性潰瘍癒合，促使慢性胃炎改善。部份胃黏膜相關淋巴瘤（MALT lymphoma）亦可經由 H. pylori eradication therapy 治愈。近年已有文獻報告 H. pylori 與一些較罕見的胃腸疾病有關係。學者發現部份因長期消化性潰瘍導致的 gastric outlet obstruction 與 H. pylori infection 有關，根除治療 H. pylori 可改善 pyloric stenosis 及其引發的阻塞症狀。其他醫學研究亦發現 90% 的 Menetrier's disease 與 H. pylori infection 有關，單一或多發性的 gastric hyperplastic polyps 可經由 H. pylori eradication therapy 後消失，另外 lymphocytic gastritis 及 granulomatous gastritis 與 H. pylori infection 之關係亦有不少研究文獻。上述研究的發表已引發一些比較革命性的疾病思考觀念及治療方法，但是值得提醒的是較大規模的前瞻性臨床研究仍然相當匱乏。