

Review Article

The Other Side of *Helicobacter Pylori* Infection-Protein-Losing Gastropathy

Ikuo MURATA

Division of Pharmacotherapeutics, Department of Clinical Pharmacy, Nagasaki University Graduate School of Biomedical Sciences

Helicobacter pylori (*H. pylori*) is now regarded as a pathogen for various disease of the gastrointestinal tract. Recent reports indicated that it rarely causes protein loss from the stomach leading to hypoproteinemia, a condition termed as protein-losing gastropathy (PLG). Several conditions are recognized in protein-losing gastropathy caused by *H. pylori*. Hypertrophic gastropathy with protein-loss, traditionally called Menetrier's disease, is one of manifestations of this condition. This condition may be subdivided in two categories; hypertrophic gastropathy with minimal inflammation and hypertrophic gastritis with giant folds. The latter includes a histological entity termed hypertrophic lymphocytic gastritis. Varioliform gastritis that has characteristic endoscopic features is another entity of the condition showing PLG, which also often shows histological features of lymphocytic gastritis. To our knowledge, lymphocytic gastritis is a rarely seen in Japanese patients. Previously, these conditions were treated with various drugs such as a somatostatin analogue, H2 receptor antagonist, and proton pump inhibitor, resulting in incomplete responses. Recently, a significant number of reports have documented usefulness of eradication therapy for *H. pylori*. As more than 90 % of patients with gastropathy or gastritis accompanying PLG are positive for *H. pylori*, treatment of its infection in these patients with PLG is recommended.

ACTA MEDICA NAGASAKIENSIA 47 : 1-7, 2002

Key Words: *Helicobacter pylori*, protein-losing gastropathy, Menetrier's disease, varioliform gastritis

Address Correspondence: Ikuo Murata, M.D.

Division of Pharmacotherapeutics, Department of Clinical Pharmacy, Nagasaki University Graduate School of Biomedical Sciences, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan

TEL&FAX: +81-95-848-4259

E-mail: imurata@net.nagasaki-u.ac.jp

Introduction

Helicobacter pylori (*H. pylori*) is a common bacterium infecting about half the world's population (1). Prevalence of *H. pylori* varies by geographical location, ethnic background, socioeconomic conditions, and age. In Japan, the prevalence of the infection exceeds 50 % of aged population. This gram-negative microorganism colonizes the human epithelial layer in the stomach and induces a state of chronic inflammation that does not resolve the underlying infection and often leads to gastric or duodenal ulcers, or more rarely to gastric neoplasms including carcinoma and lymphoma (2, 3) (Fig. 1). Infection with *H. pylori* has been established as a risk factor for gastric adenocarcinoma in the middle of 1990s(4). At present, the concept of sequential progression of the gastric lesions from chronic gastritis, atrophic gastritis with intestinal metaplasia to formation of carcinoma in *H. pylori* infection is widely accepted. This sequence has been also shown in an animal model with long-term *H. pylori* infection (5). *H. pylori* strains with the *cag* pathogenicity island (PAI) induce particularly intense inflammatory responses of the gastric epithelium (6,7). This inflammation is a hypothesized mechanism by which *H. pylori* infection leads to atrophic gastritis and gastric carcinoma (8, 9).

A recent Japanese large population study showed

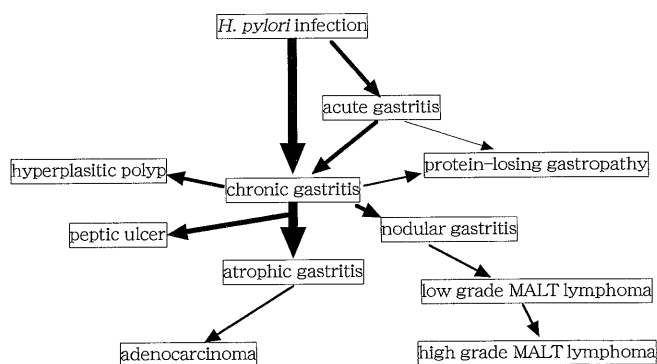


Figure 1. Progression of the gastric lesions in *Helicobacter pylori* infection.

that atrophic gastritis and intestinal metaplasia were strongly associated with *H. pylori* and not with aging (10). In their report, atrophic gastritis was shown to increase from 9.4% in those less than 20 years of age to > 70% in those aged 60 or older and to be strongly associated with *H. pylori* infection. The overall prevalence of atrophic gastritis in *H. pylori* infection was 82.9% compared with 9.8% among uninfected. Intestinal metaplasia was present in 43.1% of *H. pylori* positive persons compared with 6.2% among the uninfected. The data indicates that atrophic gastritis in *H. pylori* positive Japanese was very high in the younger generation as well as in the aged one.

Surprisingly, most people infected with *H. pylori* are asymptomatic, which suggests that additional factors are necessary for the development of *H. pylori*-associated diseases. These factors may affect the outcome of *H. pylori* infection, including the host response and the extent and severity of gastric inflammation. For example, the amount of parietal cells may influence acid secretion in *H. pylori* infection. Furthermore, gastric cancer can be caused not only by *H. pylori* infection, but also by a combination of various factors such as food and the environment. Gastric cancer is epidemiologically linked with diets high in salt and low in fresh fruit. Salt, a diet lacking antioxidant vitamins, and cigarette smoking strongly predispose to both peptic ulcer and gastric cancer.

Gastroduodenal ulcers and gastric cancer are common and serious diseases but occur in only a minority of people with this infection. On the other hand, *H. pylori* infection is known to cause various diseases in the alimentary tract and extraintestinal organs. Greater awareness of the spectrum of diseases other than peptic ulcer and carcinoma associated with *H. pylori* may well lead to their increased recognition of these diseases. In the stomach, lymphoproliferative disorders, Menetrier's disease, and hyperplastic polyps are reported as rare complications of *H. pylori* infection. The association has been proposed based on epidemiology or outcome of medical intervention such as *H. pylori* eradication. This article will briefly summarize our current understanding of *H. pylori*-related protein loss from the stomach.

***H. pylori*-associated protein-losing gastropathy**

Protein-losing gastroenteropathy (PLE) is a rare condition characterized by gastrointestinal protein loss leading to hypoproteinemia. Several mechanisms have been proposed for the plasma protein loss across the gastrointestinal mucosa. The plasma protein loss may

occur through (1) inflamed or ulcerated mucosa as occasionally seen in inflammatory bowel diseases, (2) disordered mucosal cell structures as seen in celiac disease, (3) the intercellular space of the mucosal epithelium in the presence of increased lymphatic or venous pressures as seen in inflammatory or neoplastic involvement of lymphatic system, and (4) rupture of dilated lymphatic vessels in the mucosa as seen in intestinal lymphangiectasia.

Plasma protein loss through the gastric mucosa is termed as protein-losing gastropathy (PLG), which occurs in combination with several conditions such as inflammation, neoplasia and polyposis of the stomach. Recently, several conditions with PLG have been shown to be associated with infective factors such as *H. pylori* and cytomegalovirus (11,12). PLG behaves somewhat differently from the general group of PLE, marked by excellent responses to elimination of *H. pylori*, antisecretory therapy, and surgical resection. There are several conditions of PLG caused by *H. pylori*. Based on our experiences and literature, endoscopic features of *H. pylori*-associated PLG can be roughly divided in following two categories;

- 1) Menetrier's disease (hypertrophic gastropathy)
- 2) Erosive gastritis or varioliform gastritis

1) Menetrier's disease (hypertrophic gastropathy)

Menetrier's disease is a well-known but rare condition that was first reported by Menetrier in 1888 (13). It is characterized by remarkable hypertrophy of the gastric mucosa accompanied by hypoproteinemia due to protein loss from the gastric mucosa (Fig. 2, 3). Associated features include hypochlorhydria, normal or slightly elevated fasting serum gastrin, and increased risk for gastric carcinoma. Recently, it has been reported to be associated with *H. pylori* infection, and there are reports describing the improvement of Menetrier's disease after eradication therapy for *H. pylori* infection (14-19).

There has been controversy in recognition of Menetrier's disease. First described by Menetrier (13), the disease is a poorly delineated syndrome characterized by gastric rugal hypertrophy. Because it is an ill-defined condition, the diagnosis is mainly based on the basis of clinical and histological criteria (13, 20, 21). The most accepted criteria include giant folds especially in the fundus and body, hypoalbuminemia due to PLG, and histological features of foveolar hyperplasia, gland atrophy, and marked increase in mucosal thickness (22). However, Wolfsen et al. (23) indicated that there are two distinct entities in



Figure 2. Hypertrophic gastric folds in a patient with Menetrier's disease.

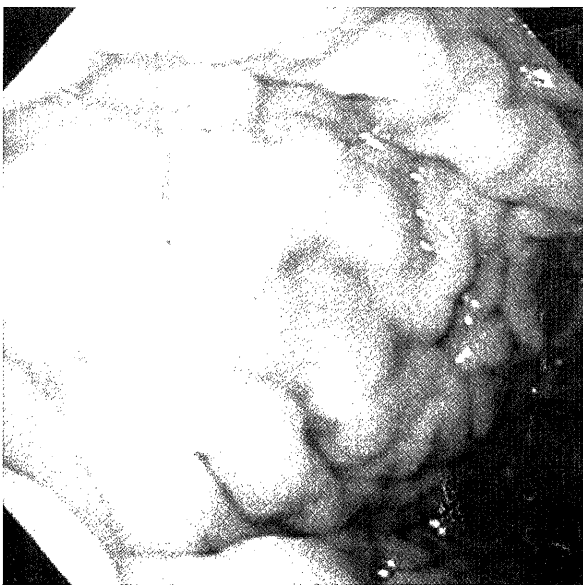


Figure 3. Endoscopic view of the corpus showing prominent folds in Menetrier's disease.

conditions showing features of Menetrier's disease. They analyzed and reviewed 23 patients previously diagnosed with Menetrier's disease and found that the patients actually represent at least two diseases: Hypertrophic lymphocytic gastritis (HLG) in 13 patients and Massive foveolar hyperplasia and minimal inflammation (MFH) in 10 patients. Clinical features and frequency of *H. pylori* were similar in these two groups. Patients with HLG, which is a recently described histological entity characterized by increased lymphocytes in the superficial gastric epithelium and foveolae (24), had severe inflammation with numerous intraepithelial lymphocytes and mild foveolar hyperplasia. Alternatively, patients with MFH had greater foveolar hyperplasia, significantly thicker mucosa, and greater mucosal edema, and less inflammatory cell infiltration. Therefore, they concluded that patients with MFH represent a form of hypertrophic gastropathy and should be designated as having Menetrier's disease, whereas patients with HLG should be considered part of the spectrum of lymphocytic gastritis. Groisman *et al.* (15) also reported that there are two distinct histopathological features regarded as separate entities in patients with giant gastric folds accompanying by a protein-losing state; hypertrophic lymphocytic gastritis (HLG) and classical Menetrier's disease. Most recent reports, however, have used the term "Menetrier's disease" without discussing this distinction, probably because the original description of this disease (13) was ill defined. I support the concept that there are two separate entities, namely gastritis and gastropathy, in conditions showing hypertrophy of the gastric mucosa accompanied by PLG.

The differential diagnosis of (classical) Menetrier's disease includes other forms of hypertrophic gastropathy such as Zollinger-Ellison syndrome, hypertrophic hypersecretory gastropathy, lymphocytic gastritis, or an infiltrating neoplasm. Very high serum gastrin levels should raise the possibility of Zollinger-Ellison syndrome, which may also produce gastric mucosal hypertrophy with foveolar hyperplasia. Lymphocytic gastritis includes a subgroup of patients with giant gastric folds or varioliform gastritis and a protein-losing state, a condition termed HLG and its diagnosis depends on histology of biopsy specimen (24).

The frequencies of clinical manifestations in Menetrier's disease are follows; epigastric pain (65%), asthenia (60%), anorexia (45%), weight loss (45%), edema (37.5%), vomiting (37.5%), hypoalbuminemia of < 35 g/l (81%), and an abnormal enteric protein loss (85%) (18). We experienced several patients with Menetrier's disease, most of whom had gastrointestinal symptoms.

Exceptionally, one case with no symptoms was found by general health check-up. This patient seemed to be healthy, except for showing hypertrophic gastropathy and hypoproteinemia.

2) Erosive gastritis and varioliform gastritis

Erosive gastritis is a common disease that is caused by many etiologic factors such as drugs and *H. pylori*. Varioliform gastritis has a distinct gross appearance that is multiple aphthous erosions with surrounded by a ring elevation of the mucosa (25-29), and is easily recognized by endoscopy and barium meal study. Several reports have shown the close relationship between varioliform gastritis and a histological entity of lymphocytic gastritis (30-32). Rarely, *H. pylori*-related erosive gastritis and varioliform gastritis can be associated with PLG when the lesions are severe enough to cause significant protein loss. We recently experienced two rare cases with erosive gastritis leading to PLG and hypoproteinemia caused by *H. pylori* infection. One showed typical endoscopic features of varioliform gastritis in the body and antrum of the stomach (Fig. 4) (29), and another showed varioliform gastritis in the body and diffuse erosions in the antrum (Fig. 5) (33). The former patient had no significant gastrointestinal symptoms, while the latter complained severe epigastralgia and anorexia leading to weight loss. Endoscopy showed multiple erosions with abundant mucous or exudates secretion from gastric mucosa, and colonization of the gastric mucosa with *H. pylori* was confirmed in both cases. Histology of biopsies from both patients revealed intraepithelial lymphocyte

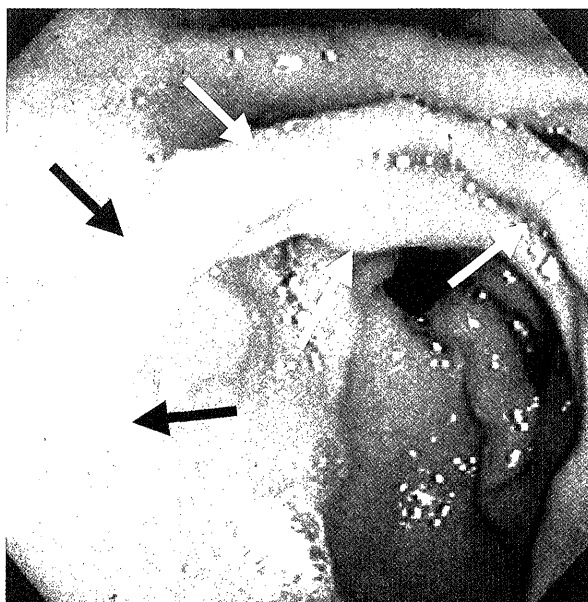


Figure 4. Endoscopic view of varioliform gastritis showing multiple aphthous erosions (arrows) in the antrum.

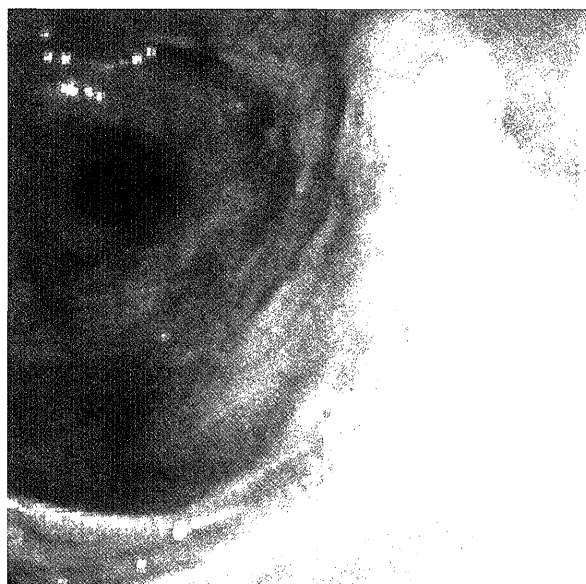


Figure 5. Endoscopic view of the antrum with extensive erosive gastritis with protein-losing gastropathy. This patient had multiple erosions resembling varioliform gastritis in the corpus.

phocyte infiltration, but their histological findings did not fulfill the criteria for lymphocytic gastritis proposed by Haot *et al.* (24) that more than 30 % of epithelial cells are infiltrated with intraepithelial lymphocytes. I consider that the incidence of lymphocytic gastritis fulfilling this histological criterion may be extremely low in Japan. This discrepancy between Japan and Western countries in the recognition of this disease needs to be elucidated in the future.

Mechanism of protein loss from the stomach

The mechanism of gastric protein loss is multifactorial and includes loss through abnormal mucosa and superficial ulceration, a paracellular route via an abnormality of tight junctions, and a transcellular route (34, 35). Careful endoscopic observation may disclose abundant mucus secretion from erosions and ulcers of the stomach. Mucosal electron microscopy (EM) changes of vacuolization and tight junction abnormalities have recently been described in *H. pylori*-associated gastritis (36, 37). Badov *et al.* (38) also reported that EM of biopsies from the stomach showed degenerate epithelial cells with simplification of the tight junctions and separation of the adjacent cells, with markedly abnormal granular vesicles abundant in the cytoplasm, and suggested that these latter changes were abnormally dilated Golgi apparatus and rough endoplasmic reticulum. Thus, the EM

observation suggests that protein loss occurs via intercellular junction disruption and altered mucus properties, as well as surface ulceration.

Diagnosis of protein loss from the stomach

The diagnosis of PLE should be considered in all patients with hypoproteinemia and edema without other known causes. Several techniques have been developed for the detection of protein loss into the gastrointestinal tract. The diagnosis has been established by plasma alpha 1-antitrypsin (alpha 1-AT) clearance or nuclear studies. Alpha 1-AT is a serum enzyme with same molecular weight as albumin, and is resistant to proteolysis by intestinal enzymes and not degraded in the intestine. The alpha 1-AT clearance test

is a reliable and less expensive method for evaluating gastrointestinal protein loss. However, this test often provides false negative results in case of protein leakage into the stomach, because alpha 1-AT is denatured in the acidic gastric lumen (29, 39). In this occasion, administration of acid suppressants such as histamine H2 receptor antagonist (H2RA) or proton pump inhibitor (PPI) may help to establish the correct alpha 1-AT clearance (33, 40, 41).

Nuclear studies are simple and useful methods to demonstrate the gastrointestinal protein loss. These involved the use of intravenous administration of radiolabeled macromolecules such as ^{125}I -labeled serum albumin, $^{51}\text{CrCl}_3$, ^{51}Cr -labeled albumin, and ^{111}In indium chloride (In-Cl). Among several radioactive isotopes, we employed scanning with ^{111}In -Cl, which combines with serum transferrin when administered intravenously or in vitro (42-44). As leakage of plasma protein occurs, ^{111}In -Cl leaks with transferrin into the gastrointestinal tract. This technique can clearly demonstrate gastrointestinal protein loss without collecting feces (Fig. 6). Although nuclear studies have some disadvantages such as high cost and need for radioactive materials, they are simple and reliable tests for diagnosis of PLG.

Treatment of protein-losing gastropathy associated with *H. pylori* infection

The treatment of PLG should focus principally on the treatment of the underlying disease after it has been identified. Therapeutic choices, therefore, must involve clinical acumen, empiricism, and understanding of the pathophysiology of the underlying disease process of each individual patient. The etiology of Menetrier's disease is not fully understood. Various etiologic factors were proposed including increased epidermal growth factors (EGF) in saliva (45, 46), immunological abnormalities including antibodies to gastric parietal cells (47), and finally infection with CMV in children (12) and *H. pylori* in adults (14-16). A retrospective analysis found that the disease was associated with *H. pylori* in more than 90% of patients (16). It is reasonable, therefore, that primary therapy should be oriented for *H. pylori* infection. A plenty number of recent reports indicated that eradication of *H. pylori* with antibiotics and anti-ulcer drugs successfully improved PLG, being associated with resolution of gastric lesions such as Menetrier's disease and varioliform gastritis (15, 16, 33). This evidence strongly supports that *H. pylori* is an important etiologic factor for PLG.

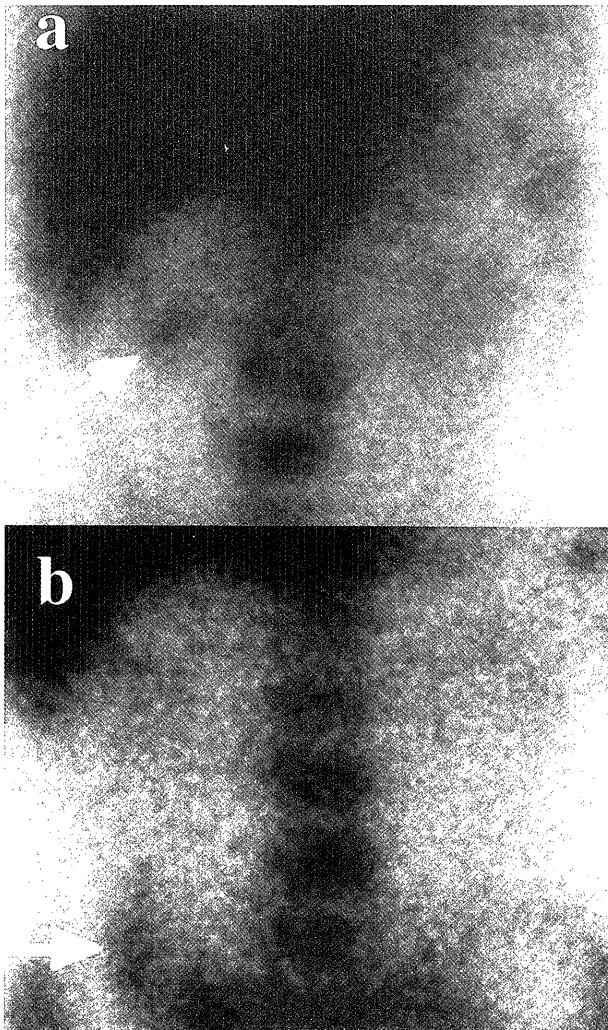


Figure 6. Abdominal scintigraphic scan showing radioactivity in the duodenum (a; 5 hrs. after intravenous administration of ^{111}In indium chloride) and colon (b; 24 hrs after administration), indicating gastrointestinal protein loss.

Before era of *H. pylori*, various treatments were tried for PLG including H2RA, PPI and octreotide, a long-acting somatostatin analogue (46). However, only a few reports documented that H2RAs, cimetidine and ranitidine, were effective in the treatment of PLG. Kristensen and Nilsson (48) suggested that the cimetidine might decrease abnormal mucus secretion in a 37-year-old patient with Menetrier's disease, leading to resolution of PLG. Krag *et al.* (49) reported a case with Menetrier's disease that was successfully treated by cimetidine, and suggested based on EM findings that cimetidine decreases a paracellular protein secretion by 'tightening' the tight junctions of the gastric epithelium. However, the precise mechanism by which H2Rs improve protein loss remains unclear.

PPI also has been tried in the treatment of PLG. We reported a case with varioliform gastritis accompanying PLG who was successfully treated by omeprazole alone (29). Ladas *et al.* (50) reported that excellent clinical remission of Menetrier's disease and the associated PLG was obtained with long-term omeprazole maintenance treatment. The mechanism for resolution of these conditions by PPI is unclear, but the following mechanisms are suggested; (1) PPI improves ulcers and erosions where plasma protein leaks, (2) it may reduce mucus secretion from gastric mucosa, and (3) it may induce *H. pylori* suppression. Nevertheless, efficacy of H2RA and PPI in the treatment of PLG is unstable and not established because there are a significant number of reports denying their usefulness in single use (51, 52). Most of recent reports indicated that eradication therapy of *H. pylori* with antibiotics and PPI or H2RA is beneficial in the treatment of *H. pylori*-associated PLG (15-19, 50, 51). As stated previously, administration of H2RA or PPI alone may induce clinical remission of PLG, although in rare occasion. The reason for the difference in response to various treatments is unknown, but probably the severity of the immune response against *H. pylori* is different in each case.

H. pylori is recognized to be a serious pathogen, but there is still controversy as to who should be treated. As in the guidelines, the eradication of *H. pylori* is strongly recommended in all patients with peptic ulcer and in those with low-grade gastric mucosa-associated lymphoid tissue lymphoma. It may be also recommended in patients following gastric cancer resection. Although relationship between non-ulcer dyspepsia and *H. pylori* infection is still controversial, it may be worth to try the eradication therapy in infected patients with functional dyspepsia, as it leads to long-term symptom improvement in a subset of patients (53). Lymphocytic gastritis and giant-fold

gastropathy (Menetrier's disease) may also respond well to treatment (54). Therefore, treatment of *H. pylori* infection in these patients with PLG is recommended before other, more invasive treatment modalities including surgical resection.

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