〈Regular Article〉

The role of Kyoto classification in the diagnosis of *Helicobacter pylori* infection and histologic gastritis among young subjects in Japan

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ABSTRACT **BACKGROUND AND AIM**: *Helicobacter pylori (H. pylori)* infection induces inflammation of the gastric mucosa and leads to erosions, gastro-duodenal mucosa atrophy, and intestinal metaplasia. The Kyoto classification diagnoses *H. pylori* infection via endoscopic findings. We aimed to clarify the role of the Kyoto classification in diagnosing *H. pylori* infection and histologic gastritis in young Japanese individuals.

METHODS: From1031 consecutive subjects aged ≤29 years who underwent esophago-gastroduodenal endoscopy at our two hospitals from 2010 to 2017, 220 were selected for participation in the present study. Endoscopic biopsy specimens from the antrum and corpus were used to investigate *H. pylori* infection and histology. Endoscopic and histological interpretations were based on the Kyoto classification and updated Sydney System. *H. pylori* infection was confirmed by histology and Giemsa or Gimenez staining.

RESULTS: Endoscopic findings were normal in 103 cases. Atrophy was found in 56 cases; diffuse redness, in 45 cases; nodularity, in 38 cases; and mucosal swelling, in 34 cases. The infection rate was 30.9% (68/220). In total, 67 subjects with *H. pylori*-positive endoscopic findings and confirmed as *H. pylori*-positive had histologic gastritis of the antrum and corpus. In contrast, of 153 subjects with *H. pylori*-negative endoscopic findings only 1 was subsequently confirmed to be *H. pylori* positive. Among the 67 subjects with *H. pylori*-positive endoscopic findings, 23 (34.3%) presented with histological atrophic gastritis of the corpus and 6 (9.0%) with intestinal metaplasia.

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CONCLUSIONS: Our findings show that *H. pylori* infection is strongly associated with endoscopic and histologic gastritis in young subjects and both *H. pylori* infection and histologic gastritis can be evaluated endoscopically based on the Kyoto classification. Furthermore, prompt *H. pylori* eradication may prevent gastric cancer development given the high prevalence of atrophic gastritis and intestinal metaplasia in young Japanese individuals.

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Key words：*Helicobacter pylori*, Kyoto classification; Gastritis, Young subjects

INTRODUCTION

Since 1983, when Warren and Marshall[1)] provided the first description of *Helicobacter pylori (H. pylori)* , strong evidence has accumulated that *H. pylori* infection plays an important role in the pathogenesis of chronic gastritis, peptic ulcers, and gastric cancer[2-4)]. H. pylori infection can lead to development of histologic gastritis and results in multiple endoscopic findings that include redness, erosions, atrophy, enlarged fold, and nodularity[3, 5, 6)].

A standardized classification of gastritis was proposed by a working group at the World Congress of Gastroenterology in Sydney in 1990 (Sydney System)[7)], and this classification has been adopted as the updated Sydney System[8)]. Thus, endoscopic and histologic gastritis has been classified in recent years as per the updated Sydney System. Since February 2013, all *H. pylori*-positive subjects have been cured under the national health insurance in Japan, however esophago-gastroduodenal endoscopy is required before treatment to exclude possible related diseases e.g. gastric cancer, peptic ulcers, and reflux esophagitis. In addition, the test for *H. pylori* infection is indicated only for patients suspected to be *H. pylori*-positive by endoscopy. Therefore, it is important to evaluate *H. pylori* infection by endoscopy. We have recently established the Kyoto classification of gastritis to diagnose *H. pylori* infection based on endoscopy in the Japanese population[9)]. Most reported studies on *H. pylori* infection and gastritis have focused on middle aged and elderly populations, as diseases such as gastric cancer, peptic ulcer, and atrophic gastritis are common in those age groups. Earlier testing and treatment for *H. pylori* infection are required to prevent development of gastrointestinal diseases, including gastric cancer[10, 11)]; however, little is known about endoscopic and histological findings in young subjects.

The aim of this study was to evaluate endoscopic and histological findings based on the Kyoto classification among young subjects in Japan.

SUBJECTS AND METHODS

Patients

In total, 1,031 consecutive outpatients under the age of 29 years old who underwent esophago-gastroduodenal endoscopy at two hospitals (General Medical Center and Kawasaki Medical Hospital) from 2010 to 2017 were eligible for inclusion in this study. From those, we selected 220 subjects in whom complete retrospective observation of the whole stomach was conducted to evaluate endoscopic findings as per the Kyoto classification and at least two biopsy specimens (one from the greater curvature of the antrum and one from the greater curvature of the corpus) were obtained to evaluate status of *H. pylori* infection and histologic gastritis. The reasons for endoscopy included precise examination of gastrointestinal symptoms (n = 187, 85.0%), health-care check (n = 6, 2.7%) and others (n = 27, 12.3%). The main gastrointestinal symptoms were epigastralgia (n = 80, 36.4%), abdominal pain in other areas (n = 27, 12.3%), vomiting/nausea (n = 21, 9.5%),

upper abdominal discomfort (n = 16, 7.3%), and heartburn (n = 9, 4.1%). Exclusion criteria included use of certain medications, including nonsteroidal anti-inflammatory drugs (NSAIDs), antacids, H_2-receptor antagonists, proton pump inhibitors, and antibiotics in the month preceding endoscopy, a history of gastric surgery, pregnancy, a history of systemic diseases such as collagen disease, inflammatory bowel disease and eosinophilic gastroenteritis, and a history of treatment to cure *H. pylori*.

The study was approved by the ethics committee of our university (Approval number: 2965) and the study was conducted according to the principles of the Declaration of Helsinki with the study participants' understanding and consent.

Endoscopic findings

Endoscopy was performed for all patients in the absence of any pre-medication and after an overnight fast. Endoscopic findings were evaluated by three endoscopists (M.S, T.K, and K.H) who were blinded to the subjects' symptoms, laboratory data, histological reports of biopsy specimens and *H. pylori* infection status as per the classification criteria of the Kyoto classification (Table 1, Fig. 1)[9]. Any disagreement was resolved by joint discussion to reach consensus. The degree of endoscopic atrophic change of the corpus was classified into six grades (from C1 (none) to O3 (extremely severe) as per the Kimura-Takemoto classification[12].

Assessment of histological gastritis and H. pylori infection

Gastric biopsy specimens were obtained during endoscopy and histologically assessed for all patients. At least two biopsy specimens were obtained during endoscopy from each patient. One specimen was obtained from the greater curvature of the antrum and another specimen was obtained from the greater curvature of the mid-corpus. Specimens were fixed in 10% buffered formalin, embedded in paraffin, sliced into 4-μm sections, and stained with hematoxylin and eosin (H&E) for histologic examination and Giemsa stain or Gimenez staining for *H. pylori* identification (Fig. 2). All Giemsa- and Gimenez-stained and H&E-stained biopsy specimens were reviewed by trained pathologists (YM and TA) who were blinded to the subjects' data. Histologic interpretation was based on the updated Sydney System. Inflammation of gastric mucosa was defined as presence of inflammatory infiltrates comprising neutrophils, lymphocytes, and plasma cells. Mucosal atrophy was defined as loss of glandular tissue. Inflammation, mucosal atrophy, and intestinal metaplasia were classified based on their degree of severity into four categories: none, mild, moderate, and severe.

H. pylori infection status was determined by Giemsa or Gimenez staining along with presence of histological inflammation. Moderate or higher degree of inflammation was regarded as significant infiltration of *H. pylori* infection. Subjects were determined to be uninfected if both investigations (*H. pylori* by Giemsa or Gimenez staining and histological inflammation over moderate) were negative.

RESULTS

The subjects in this study included 95 males and 125 females, with a mean age of 21.7 years (range: 13-29 years) for males and 22.8 years (range: 10-29 years) for females.

Endoscopic diagnosis of 220 subjects showed 103 (46.8%) were normal, 67 (30.5%) had gastritis, 19 (8.6%) had duodenal ulcer, and 4 (1.8%) had gastric ulcer.

Based on the Kyoto classification, atrophy was found in 56 (25.4%), diffuse redness in 45(20.5%), nodularity in 38 (17.3%), mucosal swelling in 34 (15.5%), red streak in 20 (9.1%), fundic gland polyp in 18 (8.2%), raised erosion in 10 (4.5%), hematin in

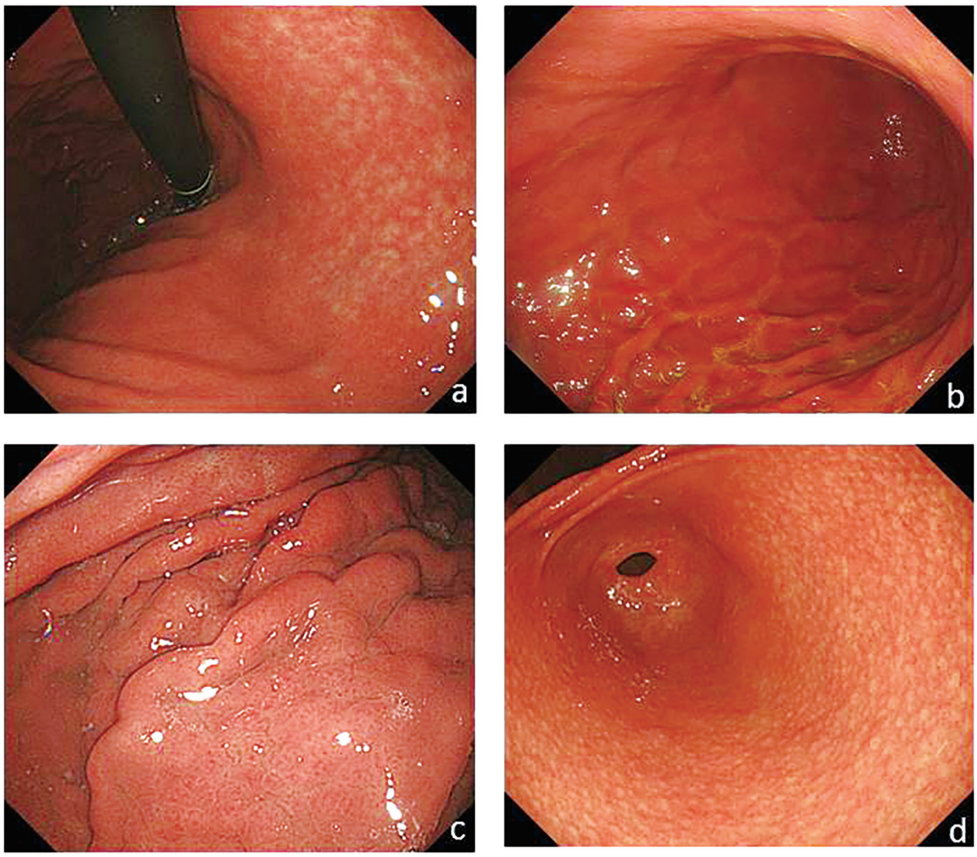

Fig. 1. Typical endoscopic findings of *H. pylori*-positive subjects.
(a) Atrophy: Atrophy is recognized as a region discolored to a diffuse white tone, and the atrophy boundary exhibits C3.
(b) Diffuse redness: Diffuse redness is observed over the entire field of view of greater curvature of the corpus with uniform redness and continuous expansion.
(c) Mucosal swelling: Mucosal swelling is seen as soft and thick irregularities.
(d) Nodularity: Nodularity is observed as uniform small granular elevation, shaped like cobblestones and highly concentrated in the antrum.

Table 1. Endoscopic findings of 220 cases (number of findings includes duplicate cases with multiple findings in one case) in *H. pylori* positive and negative young subjects

***H. pylori*-positive endoscopic findings (N = 67)**	
Atrophic gastritis (more than C2)	N = 56
Diffuse redness	N = 45
Nodularity	N = 38
Mucosal swelling	N = 34
Enlarged fold, tortuous fold	N = 5
Xanthoma	N = 1
***H. pylori*-negative endoscopic findings (N=153)**	
Normal	N = 103
Red streak	N = 20
Fundic gland polyp	N = 18
Raised erosion	N = 10
Hematin	N = 9
Depressive erosion	N = 3

9 (4.1%), enlarged fold in 5 (2.3%), and depressive erosion in 3 (1.4%); the remaining subjects were normal. Among the *H. pylori*-positive subjects the main endoscopic findings were atrophy 56 (83.6%), diffuse redness 45 (67.2%), nodularity 38 (56.7%), mucosal swelling 34 (50.7%), and enlarged fold 5 (7.5%); one case had normal endoscopic findings. Among the *H. pylori*-negative subjects, 103 (67.3%) had normal findings, 20 (13.1%) had red streak, 18 (11.7%) had fundic gland polyp, 10 (6.5%) had raised erosion, 9 (5.9%) had hematin, and 3 (2.0%) depressive erosion (Table 1). According to the Kyoto

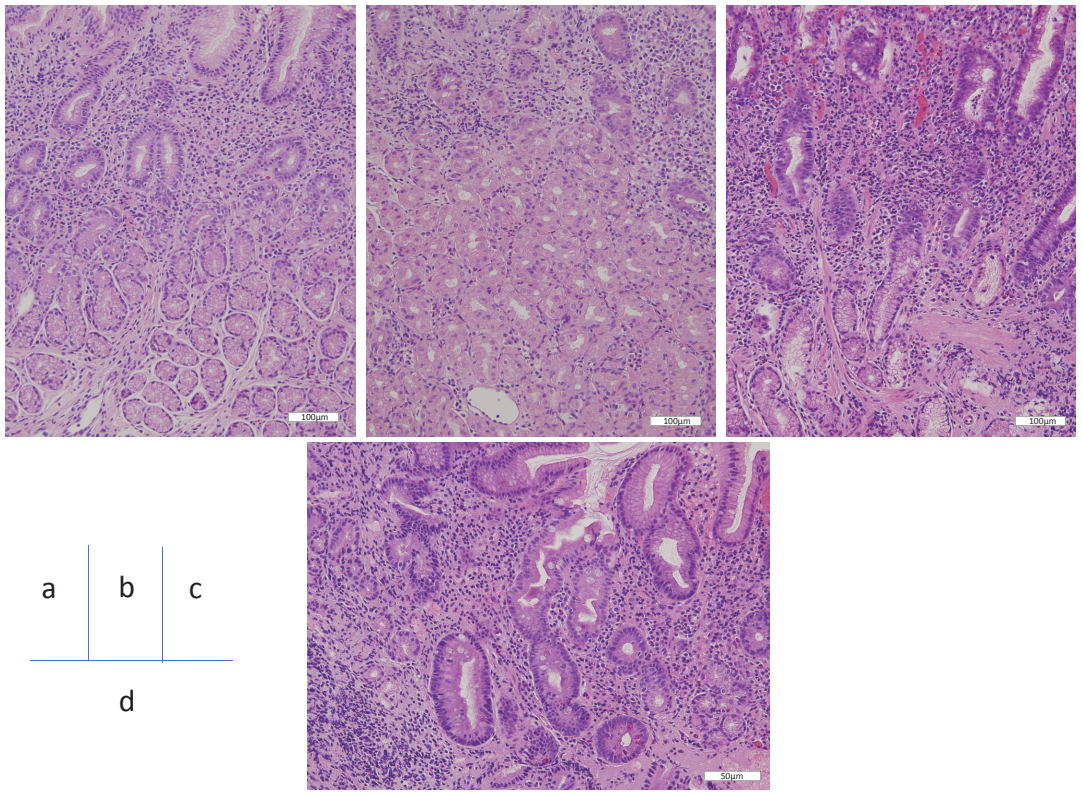

Fig. 2. Histologic findings of *H. pylori* positive subjects.
(a)Moderate inflammation of the antrum: Pyloric gland mucosa that exhibits moderate neutrophil infiltration and lymphoid cell infiltration. (Original magnification X200)
(b)Moderate inflammation of the corpus: Fundic gland mucosa that exhibits moderate neutrophil infiltration and lymphoid cell infiltration. (Original magnification X200)
(c)Atrophy of the corpus: Advanced chronic inflammatory cell infiltration can be seen, fundic gland has decreased due to atrophy. (Original magnification X200)
(d) Intestinal metaplasia of the antrum: Pyloric gland mucosa that exhibits intestinal metaplasia. (Original magnification X200)

classification, endoscopic findings are classified into two categories, *H. pylori*-positive or *H. pylori*-negative. All subjects with 67 *H. pylori*-positive endoscopic findings as per the Kyoto classification, were histologically confirmed to have *H. pylori* infection. In contrast, among the 153 subjects with *H. pylori*-negative endoscopic findings, *H. pylori* infection was subsequently confirmed in 1 subject. In total, 68 of 220 subjects (32 females; mean age 22.7 years) were diagnosed as being *H. pylori*-positive and 152 of subjects (93 females; mean age 22.1 years) as being *H. pylori*-negative by histological examination using Giemsa or Gimenez staining. Therefore, the endoscopic findings using the Kyoto classification had 98.5% sensitivity and 100% specificity for *H. pylori* infection (Table 2).

Table 2. Sensitivity and specificity of the diagnosis for *H. pylori* infection as per Kyoto classification in young subjects

		H. pylori infection via biopsy specimens		
		positive	negative	Total
H. pylori infection via the Kyoto classification	positive	67	0	67
	negative	1	152	153
Total		68	152	220

Sensitivity 67/68 = 98.5%
Specificity 152/152 = 100%
Positive predictive value 67/67 = 100%
Negative predictive value 152/153 = 99.3%
Accuracy 219/220 = 99.5%

Among the subjects with *H. pylori*-positive endoscopic findings as per the Kyoto classification,

Table 3. Histologic findings of the antrum and corpus in *H. pylori* positive and negative young subjects.

Histologic findings in *H. pylori*-positive endoscopic findings

		Antrum			Corpus		
Feature		I	A	IM	I	A	IM
Grade	none	0	21	62	2	44	65
	mild	3	39	3	14	19	2
	moderate	38	4	2	37	2	0
	severe	26	3	0	14	2	0
Total		67	67	67	67	67	67

Histologic findings in *H. pylori*-negative endoscopic findings

		Antrum			Corpus		
Feature		I	A	IM	I	A	IM
Grade	none	143	152	152	149	152	153
	mild	10	1	0	3	1	0
	moderate	0	0	0	0	0	0
	severe	0	0	1	1	0	0
Total		153	153	153	153	153	153

I: Inflammation
A: Atrophy
IM: Intestinal metaplasia

the histological findings of the antrum revealed mononuclear cell infiltration in all cases; 3 (4.5%) mild, 38 (56.7%) moderate, 26 (38.8%) severe, mucosal atrophy in 68.7%: 39 (58.2%) mild, 4 (6.0%) moderate, 3 (4.5%) severe and intestinal metaplasia in 5 (7.5%): 3 mild, 2 moderate. Histological gastritis of the corpus revealed mononuclear cell infiltration in 97% cases; 14 (20.9%) mild, 37 (55.2%), moderate, 14 (20.9%) severe, mucosal atrophy in 34.3%: 19 (28.4%) mild, 2 (3.0%) moderate, 2 (3.0%) severe, and intestinal metaplasia was noted in 2 subjects (3.0%) (Table 3). Among these cases, one patient presented with histologic intestinal metaplasia in both the antrum and the corpus. Among the subjects with *H. pylori*-negative endoscopic findings as per the Kyoto classification, the histological findings of the antrum revealed mild mononuclear cell infiltration in 10 (6.5%), mild atrophy in one (0.7%), and mild intestinal metaplasia in one (0.7%) cases. In the corpus, mononuclear cell infiltration was found in 2.6% of cases: 3 (1.9%), mild; 1 (0.7%), severe; and 1 (0.7%), mild atrophy. No intestinal metaplasia was noted (Table 3).

In addition to the histologic examination, *H. pylori* infection diagnostic tests were also administered to 35 of 220 cases; 15 received the rapid urease tests, 15 the urease breath test, and 10 the serum anti-*H. pylori* IgG antibody test. The results of these diagnostic tests matched the histological diagnoses.

DISCUSSION

Our study has two key messages. First, the Kyoto classification is a useful method to diagnose *H. pylori* infection and histologic gastritis based on endoscopic findings among young Japanese subjects. Second, there is a high prevalence of atrophic gastritis in *H. pylor*i-positive young Japanese patients. Therefore, early diagnosis and prompt curative therapy for *H. pylori* infection are required to prevent development of gastric cancer in our population.

The updated Sydney system[8] is useful to diagnose and classify gastritis, however, this classification system was not established to diagnose *H. pylori* infection and to evaluate the effect of *H. pylori* treatment and associated risk of gastric cancer based on endoscopic findings. In addition, there are

several problems in the updated Sydney system. Several endoscopic findings such as exudative, redness, and edema are difficult to diagnose objectively based on endoscopic observations. In addition, nodularity is included as an endoscopic finding but the diagnosis of nodular gastritis is not included in the classification of gastritis. Nodular gastritis is important as it represents a high risk of gastric cancer in our population[13]. Recently we developed the Kyoto classification of gastritis based on endoscopic characteristics of *H. pylori* infection-associated gastritis that allows grading of endoscopically visible risk factors for development of gastric cancer[9]. This classification system divides the endoscopic findings into three groups: *H. pylori*-negative (no gastritis), current *H. pylori* infection (active gastritis), and previously infected with *H. pylori* (inactive gastritis). This including scoring five parameters of gastritis (atrophy, intestinal metaplasia, enlarged folds, nodularity, and diffuse redness. Pathological reporting systems, such as the Sydney system[7], the Houston-updated version[8], and the operative link on gastritis assessment (OLGA) system[14], are widely used to evaluate gastritis severity and the risk of gastric cancer[15]. Although pathological evaluation of biopsy specimens may be useful in identification of patients at risk for gastric cancer, biopsy has associated risk of gastrointestinal bleeding, especially in patients taking antiplatelet drugs and anticoagulants, and is also an expensive procedure. In addition, pathological findings are limited to the information provided by the biopsy specimen and do not provide information about the whole stomach.

This study is the first report demonstrating that the Kyoto classification of gastritis is useful to evaluate *H. pylori* infection and histologic gastritis in young subjects. Previously multiple studies have demonstrated that characteristic endoscopic findings such as atrophy of the corpus, intestinal metaplasia, enlarged folds, nodularity, and diffuse redness are closely related to *H. pylori* infection[3, 5, 6]; however, these reports have focused on the elderly population. The prevalence of those endoscopic findings, especially atrophic change and intestinal metaplasia increases with advancing age[16–18]. Therefore, it is easier to diagnose *H. pylori* infection and the presence of histologic gastritis by endoscopic findings in older subjects. In addition, earlier curative treatment for *H. pylori* may be more effective prevention of gastric cancer[19], and therefore is important for the young Japanese population.

The first recognizable characteristic of endoscopic findings was atrophy of the corpus; 56 of 68 (82.4%) *H. pylori*-positive subjects showed atrophy of the corpus and 4 showed severe atrophic gastritis. In addition, histological study biopsy specimens showed atrophic gastritis of the corpus and intestinal metaplasia in 35.3% (24/68) and 8.8% (6/68) of *H. pylori*-positive subjects, respectively. Intestinal metaplasia and atrophic gastritis are closely related to development of gastric cancer[20, 21]. Atrophic gastritis may progress to moderate or severe atrophic gastritis with advancing age. In a 10-year prospective follow-up study that induced annual endoscopy, Sakaki et al.[22] reported that the cumulative progression rate of atrophic patterns was 6% after 2 years, 22% after 4 years, 34% after 6 years, and 43% after 10 years in *H. pylori*-positive patients. Our previous study[3] showed that accurate endoscopic assessment of gastritis as per the updated Sydney System in conjunction with gastric fold findings and endoscopic assessment of atrophic gastritis are important indicators of *H. pylori* infection in the Japanese population. We also showed that the prevalence of atrophic gastritis increased and gastric acid secretion decreased with age in *H. pylori*-positive patients and that atrophic gastritis is extremely rare, regardless of age, in *H. pylori*-negative subjects[23].

The second recognizable characteristic of

endoscopic findings in *H. pylori*-positive young patients was nodularity. Nodular gastritis is an antral gastritis characterized endoscopically by an unusual small-granulated pattern, and the main histological feature is hyperplasia of lymphoid follicles with intense inflammatory cell infiltration in the propria lamina of the stomach[24]. Nodular gastritis is often referred to as antral nodularity according to the updated Sydney System. Previous studies have shown that nodular gastritis is strongly associated with *H. pylori* infection in both children[25] and adults[26]. Our recent study indicates that nodular gastritis may be associated with gastric cancer of the corpus and may be a significant risk factor for diffuse-type gastric cancer[13].

Surprisingly, the high prevalence of atrophic change of the corpus evaluated by endoscopy (83.6%, 4 cases with severe atrophic gastritis) was noted in subjects with *H. pylori*-positive endoscopic findings. No atrophic change as evaluated by endoscopy was found in subjects with *H. pylori*-negative findings. In addition, based on histological assessments of biopsy specimens, our study showed that both inflammation and atrophy of the corpus were frequently found in subjects with *H. pylori*-positive endoscopic findings (more than moderate inflammation 76.1% and atrophy 34.3%). Among subjects less than 29 years old in this study, intestinal metaplasia was detected in 6 (9.0%) subjects with *H. pylori*-positive endoscopic findings. Histological corpus gastritis might progress to atrophy of the corpus with advancing age. Asaka et al.[17] performed a 21 multi-center study in Japan and showed that atrophic gastritis was very high in *H. pylori*-positive young patients (38.5% in those less than 20 years, 58.5% in those 21-30 years). Our previous cross-sectional study also indicated that atrophic gastritis and decrease in gastric acid advances with age[23].Therefore, atrophic gastritis is strongly associated with *H. pylori* infection and age. Before the discovery of *H. pylori*, atrophic gastritis and intestinal metaplasia were linked to gastric cancer, especially intestinal-type cancer[27]. Recently, *H. pylori* has been recognized as a risk factor for gastric cancer[4, 21]. We previously showed that *H. pylori* infection is strongly associated with gastric cancer and atrophic gastritis and that it might contribute to the pathogenesis of gastric cancer in young patients[28]. Wong et al. [29] showed that the eradication of *H. pylori* significantly decreased development of gastric cancer in *H. pylori* carriers without precancerous lesions. Recent multiple studies also indicate that the *H. pylori* curative therapy decreases development of gastric cancer and improves atrophic gastritis[10, 11]. In this study, 49 of 68 cases (72.1%) of *H. pylori*-positive patients received eradication treatment, of which 38 were successfully treated, 1 failed treatment, and 10 were lost to follow-up. In 2017, gastric cancer was the second most common malignancy in male and the fourth most common malignancy in female populations, with 45,226 (29,745 males and 15,481 females) gastric cancer related deaths[30]. The incidence of gastric cancer increases with age. Thus, *H. pylori* should be cured as early as possible to prevent progression of atrophic gastritis.

In general, gastric cancer is more common in males than in females, however no difference is found in young subjects[28]. Previous studies indicate that atrophic gastritis and intestinal metaplasia are more common in males compared to females[16, 31]. We investigated the endoscopic and histologic findings between sexes in this study, and no significant difference was observed between male and female young subjects.

There were several limitations to this study. First, this was a retrospective study. Second, disagreement of interpretation between a trained endoscopist and our three evaluators was found in several cases and a consensus needed to be reached by the three evaluators. One *H. pylori*-positive patient was diagnosed as having normal endoscopic findings

by retrospective evaluation; however, the trained endoscopist diagnosed this patient as a case of mild atrophic gastritis of the corpus. Third, biopsy specimens were obtained from two defined areas (the greater curvature of the antrum and corpus), and therefore the evaluation of histologic gastritis in this study may not be a comprehensive assessment of the whole stomach. Both inflammation and atrophy are diffuse changes and can be diagnosed by spot biopsy; however, intestinal metaplasia is a patchy change of gastric mucosa and multiple biopsy specimens or dye staining method are required for a reliable diagnosis. Finally, the diagnosis for *H. pylori* infection was performed by histologic examination using Giemsa or Gimenez staining. The sensitivity of this method for diagnosis of *H. pylori* infection is only 88%[32].

In conclusion, our present study demonstrates that the Kyoto classification is useful to diagnose both *H. pylori* infection and histologic gastritis based on endoscopic findings, and that prompt curative therapy for *H. pylori* is required to prevent development of gastric cancer especially considering the high prevalence of atrophic gastritis in *H. pylori*-positive young subjects in Japan.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

AUTHORS' CONTRIBUTION

M.S., T.K. and K.H.: subjects' enrollment, data acquisition, design of the study, data interpretation and manuscript drafting; Y.M. and T.A.: histopathology examination of the biopsy samples and critical review of the scientific data; J.N., N.M. and T.M.: subjects' enrollment, data-acquisition and statistical analysis; A.S. and H.K.: subjects' enrollment, data interpretation and manuscript drafting. All the authors critically revised the manuscript, read and approved its final version.

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