〈Regular Article〉

Clinicopathological features of advanced gastric cancer discovered after *Helicobacter pylori* eradication

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ABSTRACT　*Helicobacter pylori* infection is closely associated with gastric cancer, and its eradication is expected to prevent gastric cancer. However, gastric cancer is often detected discovered after eradication therapy for *H. pylori* infection. We aimed to investigate the endoscopic and clinical features of advanced gastric cancer after *H. pylori* eradication.

We retrospectively investigated tumor location, macroscopic and histological type, endoscopic gastric mucosal atrophy (using the Kimura-Takemoto classification), and the interval between eradication and detection of gastric cancer.

Nine patients (five males; mean age, 65.3 years [range, 44-79 years]), histologically diagnosed with advanced gastric cancer after successful *H. pylori* eradication between April 2003 and December 2018, were enrolled in this study.

In all cases, the cancer was located in the middle-to-upper portion of the stomach. With respect to macroscopic type, six cases were ulcerative, two were scirrhous, and one was polypoid. Histologically, all cancers were poorly or moderately differentiated adenocarcinomas. Endoscopic mucosal atrophy was mild in two cases, moderate in two cases, and severe in five cases. Two cases of scirrhous tumors developed from mild mucosal atrophy. Moreover, the tumor was detected within 36 months after *H. pylori* eradication in six patients (maximum: 120 months, mean: 38.7 months).

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Our data demonstrated that post-eradicated advanced gastric cancers were located in the middle-to-upper portion of the stomach and were mainly ulcerative, poorly or moderately differentiated adenocarcinoma. More than half of the patients exhibited severe mucosal atrophy. Notably, advanced gastric cancer of the scirrhous type may develop from mild mucosal atrophy.

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Key words：*Helicobacter pylori*, Gastric cancer, Disease eradication, Atrophy, Clinical pathology

INTRODUCTION

The association between *Helicobacter pylori (H. pylori)* infection and development of gastric cancer (GC) is well established, as ascertained by epidemiologic studies[1-3], experimental carcinogenesis in Mongolian gerbils[4, 5], the findings of a prospective observational study[6], and the prevention of GC by eradication therapy[7-14]. Uemura *et al.*[6] reported that GC developed in 36 (2.9%) of 1246 *H. pylori*-infected patients, but in none of the 280 uninfected patients, over a mean follow-up period of 7.8 years. In large randomized controlled trials (8, 9) and in recent meta-analyses and systematic reviews[10-14], the incidence of primary and metachronous GC significantly decreased following *H. pylori* eradication compared with patients not undergoing eradication.

On the other hand, GC may occur after successful eradication of *H. pylori*. In our previous prospective study[15], GC was detected after successful eradication therapy in 20 (17 male, male:female ratio = 5.7:1) of 1787 patients (1.1%), and the risk of GC was determined as 2.2% at nine years after *H. pylori* eradication (0.24% per year). Additionally, our study[15], along with others[16-18], revealed that such metachronous GCs were primarily of the early, non-cardiac, intestinal type with ulceration, and mostly occurred in patients that had exhibited baseline severe atrophic gastritis of the corpus. Therefore, regular endoscopic surveillance is necessary even after successful eradication of *H. pylori*. Additionally, in our previous study[15], only 1 advanced GC (poorly differentiated adenocarcinoma) was detected 3 years after *H. pylori* eradication. To our knowledge, few cases of advanced GC have been discovered after *H. pylori* eradication. Although advanced GC affects a patient's prognosis, the features of this particular class of advanced tumors is unclear. The aim of our study was to investigate retrospectively the endoscopic and clinicopathological features of advanced GC discovered after *H. pylori* eradication.

SUBJECTS AND METHODS

Patients

This study was conducted in two hospitals from April 2003 through December 2018. We enrolled nine patients (five men, mean age 65.3 years [range 44-79 years, median 66.0 years]) in whom GC had not been detected before *H. pylori* eradication, but in whom advanced GC had been histologically diagnosed after successful *H. pylori* eradication. GC after *H. pylori* eradication was defined as a gastric neoplasm identified approximately one year after eradication was confirmed to be successful.

Seven patients (four males) attended one hospital, and two (one male) attended the other. All patients received eradication therapy for *H. pylor*i from 2000 through 2017. The ^{13}C-urea breath test (UBiT, Otsuka Corporation, Tokyo, Japan) was performed for each patient to determine *H. pylori* status (confirmation of eradication) at least two months after completion of therapy. Moreover, when GC was suspected, each patient underwent esophagogastroduodenal examination and biopsy for the diagnosis of GC and a ^{13}C-urea breath test

for *H. pylori* infection.

The study protocol was approved by our institution's Ethics Committee (approval number: 3404 and 3404-1) and has been performed in accordance with the ethical standards laid down in the Declaration of Helsinki (as revised in Brazil 2013).

The contents of this study are presented on the hospital website, where patients may opt out at any time.

Endoscopy

In line with our standard procedure, target biopsy was performed when gastric cancer was suspected by endoscopy. An Olympus (GIF-H240, GIF-H260, or GIF-HQ290; Olympus Corporation, Tokyo, Japan) or FUJIFILM (EG-530N or EG-L580NW7; Fujifilm Holdings Corporation, Tokyo, Japan) videoscope was used throughout the study. Biopsy specimens were obtained from lesions suspected to be GC or another major gastric disease, such as gastric ulcer, and assessed histologically. Mucosal atrophy was evaluated during endoscopy using the Kimura-Takemoto classification system[19]. This system is used to divide gastric mucosal atrophy into six grades (C-I, C-II, C-III, O-I, O-II, and O-III) based on endoscopic findings of the extent of the atrophic border. C-I and C-II are defined as mild atrophy, C-III and O-I are defined as moderate atrophy, and O-II and O-III are defined as severe atrophy.

Diagnosis of gastric cancer

For the purposes of this study, GC was defined as malignant epithelial tumor cells with glandular differentiation, and an evident invasion of neoplastic epithelium into the lamina propria of the mucosa or beyond. Early GC was defined as invasion of neoplastic epithelium limited to the lamina propria of the mucosa, or the submucosa, and advanced GC was defined as invasion beyond the submucosa.

Location, macroscopic and histological type, depth, and stage of tumors were defined according to the Japanese Classification of Gastric Carcinoma, 15th edition[20]. Location was classified as either U (upper: fundus-upper corpus), M (middle: angulus-mid corpus), or L (lower: antrum and pylorus). In addition, the position on the gastric wall was classified as either anterior, posterior, lesser curvature, or greater curvature. Tumor size was expressed as the maximum diameter of the resected specimen. Macroscopic type was classified as either type 1 (polypoid), type 2 (localized ulcerative), type 3 (infiltrating ulcerative), or type 4 (diffusely infiltrating). The degree of tumor differentiation (histological type) was classified as well-differentiated tubular adenocarcinoma (tub1), papillary adenocarcinoma (pap), moderately differentiated tubular adenocarcinoma (tub2), poorly differentiated adenocarcinoma (por), or others, such as signet-ring cell carcinoma (sig). When a tumor consisted of more than one histological type, all were described regardless of the grade of malignancy. Depth of advanced tumor invasion was classified as muscularis propria (MP), subserosal (SS), serosal exposure (SE), or serosal invasion (SI). Tumor stage was classified, according to tumor depth, metastasis, and lymph node metastasis, as one of the following: stage I (A, B), II (A, B), III (A, B, C), or IV. The interval of survival was defined as days from the date of diagnosis of advanced gastric cancer to December 2019.

Diagnosis of H. pylori infection and eradication therapy

H. pylori infection was diagnosed if positive results were obtained in one or more of the following *H. pylor*i tests: a ^{13}C-urea breath test, a serum anti-*H. pylori* antibody test (E-plate, Eiken Chemical Co., Ltd., Tokyo, Japan) (cut-off value: 10 U/mL), a rapid urease test (Helicocheck, Otsuka Corporation, Tokyo, Japan) and/or a histological

test (Giemsa staining). All patients were informed of their infection status, and those with an active *H. pylori* infection received eradication therapy for one week if they consented to undergo the treatment. First-line *H. pylori* eradication treatment consisted of lansoprazole (30 mg) or vonoprazan (20 mg) with amoxicillin (750 mg) and clarithromycin (200 or 400 mg), each taken twice daily for 1 week. Where first-line eradication treatment failed, participants were provided an opportunity to undergo a second-line regimen. Second-line eradication treatment consisted of lansoprazole (30 mg) or vonoprazan (20 mg) with amoxicillin (750 mg) and metronidazole (250 mg), each taken twice daily for 1 week.

Outcome measures

We retrospectively reviewed the abovementioned clinicopathological findings of all nine patients, as well as the interval since eradication and the last endoscopy, patient age and sex, presence of distant metastasis, and survival outcome.

Statistical analyses

All statistical analyses in this study were performed using JMP software version 13.2 (SAS Institute Japan Ltd., Tokyo, Japan).

RESULTS

Clinicopathological features of advanced GC after H. pylori eradication

Table 1 indicates demographics and clinicopathological characteristics of advanced GC among patients who underwent eradication treatment. All tumors were located in the middle to upper portions of the stomach, four were located in the anterior gastric wall, three were located in the greater curvature, and two were located in the lesser curvature. With respect to macroscopic type, six cases were ulcerative (type 2 [n = 5], type 3 [n = 1]), two were scirrhous (type 4), and one was polypoid (type 1). The histological types were poorly or moderately differentiated adenocarcinoma in all patients.

Eight patients survived, and one died three months after the operation (case 1). The mean interval of survival for the eight patients was 5.75 years (range, 1-12 years; standard error of the mean, 1.77 years).

Table 1. Patient demographics and clinicopathological features of advanced gastric cancer after *H. pylori* eradication

Case	Age	Sex	Location	Size (mm)	Macroscopic type	Histologic type	Depth	LN metastasis	Distant metastasis	Stage	Survival outcome (interval)
1	64	M	M (anterior)	40	2	por	SE	N2	CY, Liver	IV	Death
2	70	M	M (anterior)	25	2	por > tub2	MP	N0	None	IB	Alive (12 yrs)
3	73	M	M (anterior)	35	2	tub2 > por	SS	N0	None	IIA	Alive (12 yrs)
4	79	F	U (lesser curvature)	30	3	tub2 > por	SS	N2	None	IIIA	Alive (9 yrs)
5	66	M	M (greater curvature)	25	1	tub2	MP	N0	None	IB	Alive (8 yrs)
6	67	F	M-U (lesser curvature)	140	4	por	SE	N1	None	IIIC	Alive (2 yrs)
7	44	F	U (greater curvature)	50	2	por > sig	SS	N0	None	IIA	Alive (1 yr)
8	60	M	U (anterior)	20	2	tub2	SS	N2	None	IIIA	Alive (1 yr)
9	65	F	U (greater curvature)	40	4	por > sig	SE	N3	CY	IV	Alive (1 yr)

Clinicopathological findings are provided according the Japanese Classification of Gastric Carcinoma (15th edition)[20]

Table 2. Interval and characteristics of advanced gastric cancer after *H. pylori* eradication

Case	Endoscopic diagnosis before eradication	Year of eradication	Year of gastric cancer diagnosis	Eradication-diagnosis interval (months)	Penultimate endoscopy-diagnosis interval (months)	Endoscopic mucosal atrophy
1	gastric ulcer	2000	2003	36	36	O-I
2	gastric ulcer	2005	2007	24	24	O-III
3	gastric ulcer	2005	2007	24	24	O-II
4	atrophic gastritis	2000	2010	120	84	O-II
5	atrophic gastritis	2009	2011	24	24	O-II
6	atrophic gastritis	2013	2017	48	48	C-II
7	nodular gastritis	2017	2018	12	12	C-III
8	atrophic gastritis	2017	2018	12	12	O-II
9	atrophic gastritis	2014	2018	48	36	C-II

Endoscopic mucosal atrophy was classified according to the Kimura-Takemoto classification system[19] .

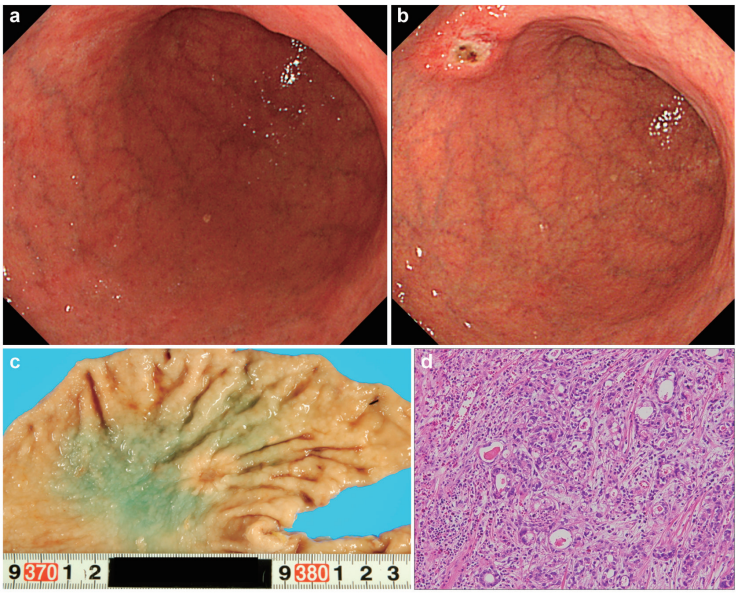

Fig. 1. Case of advanced gastric cancer detected two years after *H. pylori* eradication
(a) Gastric cancer was not detected at the start of *H. pylori* eradication. (b) Two years after eradication, gastric cancer was detected in the anterior of the angulus with severe mucosal atrophy. (c) Macroscopic photo of the resected specimen revealed that it was a localized ulcerative tumor (type 2). (d) Pathological findings revealed that it was a combination of poorly and moderately differentiated adenocarcinoma (hematoxylin-eosin, 10x40)

The interval and characteristics of advanced GC after H. pylori eradication

Table 2 summarizes the interval and characteristics of post-eradication advanced GC. The tumor was detected within 36 months after eradication in six the patients (66.7%), and after more than 36 months in the remaining three patients (33.3%) (maximum interval: 120 months, mean interval: 38.7 months [standard error of the mean: 11.0 months]). In addition, two cases (cases 7 and 8) were detected one year after eradication treatment. In the remaining seven cases, the intervals between the penultimate endoscopic examination and diagnosis of GC were 2 years or more (for these seven cases, the maximum interval was 84 months, the mean interval was 39.4 months, and the standard error of the mean was 8.2 months).

The endoscopic mucosal atrophy grade was mild

in two cases, moderate in two cases, and severe in five cases. To be noted, the two cases (cases 6 and 9) of scirrhous-type tumors developed from mild atrophy of the corpus. The endoscopic diagnosis before eradication treatment was gastric ulcer in three cases, atrophic gastritis in five cases, and nodular gastritis in one case. None of the cases had a history of duodenal ulcer.

A representative case is demonstrated in Fig. 1 (case 2). This 70-year-old male had a gastric ulcer for five years before eradication therapy. No tumor was evident at the start of *H. pylori* eradication (Fig. 1a). Two years after successful *H. pylori* eradication, an irregular, localized ulcerative tumor was detected in the anterior of the lower corpus (Fig. 1b). The degree of endoscopic mucosal atrophy was severe (O-III) and the atrophy was accompanied by xanthoma. The gastric tumor was resected via distal gastrectomy (Fig. 1c) and pathological findings revealed a combination of poorly differentiated adenocarcinoma and moderately differentiated tubular adenocarcinoma (Fig. 1d).

DISCUSSION

In the present study, we investigated nine cases of advanced GC discovered after *H. pylori* eradication. We revealed that all tumors were located in the middle to upper portion of the stomach, the majority (6/9) were ulcerative, all were poorly or moderately differentiated adenocarcinomas, and more than half (5/9) exhibited severe mucosal atrophy. Notably, scirrhous type GC occurred in cases with only mild mucosal atrophy. Unfortunately, we did not determine the frequency of advanced tumors among GCs identified after *H. pylori* eradication in this study.

Previous studies demonstrated that gastric mucosal atrophy[15, 21–26], intestinal metaplasia[15, 22–25], and map-like redness[25, 26] are potential risk factors for development of GC after *H. pylori* eradication. Take *et al.*[21] demonstrated that the grade of gastric endoscopic mucosal atrophy was closely related to the development of post-eradication GC. Specifically, during a mean follow-up time of 3.9 years, GC developed in 9 of 953 patients cured of infection and in 4 of 178 who had persistent infection (P = .04). Shichijo *et al.*[22] indicated that patients with histologic intestinal metaplasia or severe endoscopic atrophy were at a higher risk for GC development after eradication treatment, compared with patients without intestinal metaplasia or those with no/mild mucosal atrophy. On the other hand, in a recent long-term follow-up study (mean follow-up of 7.1 years), Take *et al.*[24] indicated that, in the second decade after eradication treatment, patients with mild-to-moderate baseline gastric atrophy were more likely to develop diffuse-type GC than intestinal-type GC. In our study, two cases (case 6 and 9) with scirrhous tumors also developed from mild atrophy of the corpus. Regular endoscopic surveillance (once a year) should therefore be continued after eradication of *H. pylori*, irrespective of the severity of gastric atrophy.

In our study, one patient succumbed three months after gastrectomy (case 1). In this case, liver metastasis was observed at the time of discovery of the GC, and the cancer was stage IV. To reduce fatalities due to GC after *H. pylori* eradication, the disease must be detected before it becomes advanced. Therefore, annual, detailed endoscopy is required for patients who have undergone eradication therapy. However, in our study, annual endoscopic examinations were not performed in seven cases, and GC was discovered after an interval of at least 2 years after the penultimate examination. Reasons for irregular post-eradication endoscopies may be that patients are poorly informed or that a patient is refused examination.

Most gastric cancer cases after eradication were detected in early stages, but in the current analysis, we focused on advanced cases. In our study, the primary locations of GC were the anterior wall of

the angulus and the greater curvature of the corpus. Endoscopic observation is likely to be tangential to the anterior and posterior wall of the angulus. Moreover, the gastric wall may be insufficiently stretched due to poor insufflation in the greater curvature of the corpus, which may cause the lesion to be missed. Therefore, careful detailed endoscopic observation is needed for these areas. Second, recent reports[27, 28] have demonstrated that eradication of *H. pylori* increased the risk of developing of intestinal-type GC with submucosal invasion despite annual follow-up endoscopy. Finally, Menon and Trudgill[29] revealed that 4.3 % - 9.5 % of upper gastrointestinal cancers are missed in endoscopic screenings performed in the year before diagnosis. In our study, two cases (case 7 and 8) were diagnosed one year after eradication; it is possible that these cases already had GC at the time of eradication, but that endoscopic examination yielded false negative results at the time.

There were several limitations to this study. First, the number of patients was too small for generalization. In future, we will consider expanding the study to multiple medical centers in Japan and possibly to other Asian countries. Second, it was retrospective in nature. Third, the periods of follow-up were relatively short. We will also consider performing a similar study with a longer follow-up period after *H. pylori* eradication in future studies. Fourth, it is difficult to distinguish between previously missed lesions and new lesions. In the near future, we would like to prospectively evaluate the characteristics of advanced GC after *H. pylori* eradication in a large, multicenter study.

In conclusion, our data suggests that nine advanced GCs after *H. pylori* eradication are mainly located in the middle to upper portion of the stomach, are predominantly ulcerative, and classified as poorly or moderately differentiated adenocarcinoma with severe mucosal atrophy. We also demonstrated that scirrhous-type advanced GC may develop from mild mucosal atrophy.

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