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Research Article

Helicobacter pylori Uninfected early Gastric Signet-Ring Cell Carcinoma: Endoscopic Images and Therapy

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Abstract

Objective: *Helicobacter pylori* (*HP*)- uninfectedearly gastric signet- ring cell carcinoma (*HP*-un-EGS) cases, *HP* unrelated cancers are rare. In this study, 46HP-un-EGSs were evaluated by Endoscopy and treated by ESD (Endoscopoic Mucosal Dissection). We here report the characteristics findings of *HP*-un-EGS that we experienced.

Patients and Methods: 43cases46 lesion with *HP*-un-EGSs were evaluated and resected by ESDat our hospital between Apr. 2003 and Apr. 2015. Negativity of *HP* infection was diagnosed by six tests: serological tests for IgG antibody and the pepsinogen method, the urea breath test, histologyof ESD-resected specimens, endoscopic findings of regular arrangement of collecting venules (RAC), and no history of eradication therapy.

Results: 46 lesions were signet- ring cell carcinoma by histology. They composed of 21 males and 22 females and cancers were located at the gastric body in 24 lesions (62%) and antrum in 15(38%). The average size was 8.2 mm. In terms of invasion depth, all cases had cancer confined to the mucosal layer and all tumors were curatively resected by ESD. There was no adverse event by ESD. As endoscopic characteristics, there were 24 lesions IIc (90%) and 22 lesions IIb (10%) lesions macroscopically, while faded color were observed in 44lesions (95%). 22(21%) lesions appear Irregular vascular pattern using Magnified Endoscopy-Narrow Band Imaging (ME-NBI). 31(79%). 22 lesions with irregular vascular pattern showed signet- ring cell carcinoma on the mid to surface mucosa. **Conclusions** As the characteristics of *HP*-un-EGSs of faded colors were observed predominantly and curatively treated by ESD. Their cancer cells were located only proliferative zone and upper side of the mucosa. *HP*-un-EGSs are rare; all the cases were cure by ESD. It is important to notice faded color lesion to find early stage of signet-ring cell carcinomas in *HP* uninfected stomach.

Keywords:

Helicobacter pyroli uninfected; Early gastric cancer; Signet-ring cell carcinoma; Endoscopic submucosal dissection

Introduction

A number of studies have demonstrated the relationship between *Helicobacter pylori* (*HP*) infection and occurrence of

gastric cancer, such as possible prevention of secondary cancer after eradication [1-3]. On the other hand, it has been reported that HP-uninfected cancer accounts for 1 - 3% of all gastric cancers and it is known that such cancer is rarely observed [4-9]. However, HP-uninfected gastric cancer is hard to define and *HP* infection can be overlooked in cases with a past history of HP eradication and poor inflammatory findings.

HP-uninfected gastric cancer cases have been sporadically reported, the definition is unclear. In this study, the characteristics of *HP*-uninfected gastric cancer were clarified by employing the strict criteria for negative infection with *HP*. We here report the characteristics of *HP*-un-EGSs we experienced.

Patients and Methods

The characteristics of43 cases46lesions with *HP*-un-EGSs treated by ESD between Apr. 2005 and Apr.2015at our hospital were investigated. The criteria for negative infection with *HP* are shown in Table 1: (1) negative for HP IgG antibody; (2) negative by the pepsinogen method; (3) negative by the urea breath test; (4) positive regular arrangement of collecting venules (RAC) at the lower body of the stomach [10]. (5) no infiltration of inflammatory cells in resected samples; and (6) no history of eradication therapy. Gastric cancer cases that satisfied all criteria were considered to be negative for HP infection and those that failed to meet at least one criterion were excluded. There were 39 lesions with gastric cancer that met all criteria and they were all undifferentiated-type cancers. We used Magnified endoscopy with Narrow Band Imaging (ME-NBI) by Olympus corp (Tokyo). Moreover, all cases met the expanded criteria for ESD [11]

Serum anti-*HP* titer <3 IU/l
Negative by the pepsinogen method
Negative by the urea breath test
Microscopic observation: absence of *HP* and histological gastritis
Endoscopic observation: absence of atrophic change, presence of RAC
No history of *HP* eradicationtherapy

Table 1: Definition of *HP*-uninfected cancer.

Techniques of ESD and clinical courses after hospitalization

In all cases, biopsy samples were taken from the areas around the lesion that were presumed to be negative for cancer and absence of cancer cells was confirmed around main lesions. Patients were admitted to the hospital for one week and treated by ESD on day 1 of hospitalization. IT knife 2 (Olympus Co.) and electrosurgical generator VIO (ERBE) were employed for ESD. The settings for marking, peripheral incisions, and dissection were used. APC was used with a coagulation mode for marking. A needle knife was used for precutting. Hyaluronic acid was injected into the sub mucosal layer and the lesion was incised and dissected with the IT knife 2. After ESD, the ulcer bed was treated for hemostasis with a pair of hemostatic forceps or hemostatic clips. After no bleeding was confirmed endoscopic ally on the next day, a fluid meal was started and meals were changed to more solid ones gradually from the next day until discharge one week later.

Results

- There were 21 males (54%) and 22 females (46%) with the average age of 50.0 years.
- Table 2. Macroscopic morphology by endoscopic observations revealed 24IIc (90%) and 22IIb cases (10%). Faded color and redness were observed in 44(95%) and two cases (5%), respectively. Gastric cancer was located at the body in 24 and antrum in 22 cases. Representative endoscopic images in nine cases are shown in Figure 1. The average size was 8.2 mm and endoscopic characters were faded color.
- Adverse events after ESD and pathological results (Table 3)

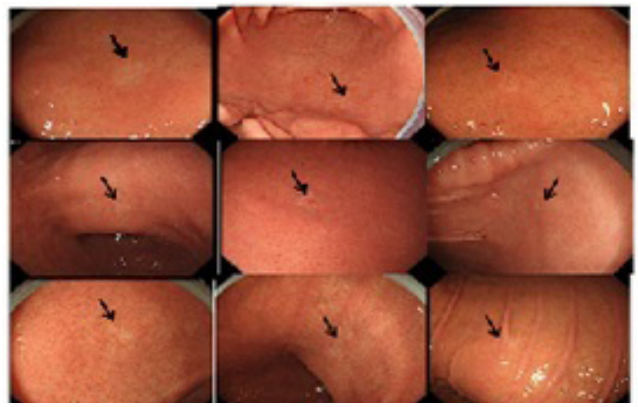

Figure 1: Characteristic endoscopic images of *HP*-uninfected early gastric signet-ring cell carcinoma observed faded color typically.

Macroscopic appearance (IIc:IIb)	24:22 (52%: 48%)
Color: (faded color: redness)	44:2 (96%: 4%)
Location: (U:M:L)	0:24:22(0%: 52%: 48%)

Table 2: Endoscopic observation (*HP*-uninfectedearly gastric signet-ring cell carcinoma).

Bleeding	0/46 (0%)
Perforation	0/46 (0%)
Curative resection	46/46(100%)
Invasion Depth (M:SM)	46:0 (100%: 0%)
Histological Type(sig:por)	46:0
Pathological curative	46/46(100%)

Table 3: ESD results (*HP*-uninfected undifferenitated-type early gastric cancer).

No case had postoperative bleeding or perforation. Pathology revealed signet-ring cell carcinoma in 46cases (97%). Invasion depth was the mucosal layer (mucosal cancer/M cancer) and all tumors were curatively resected with negative horizontal and vertical margins and negative vascular infiltration.

According to Magnified Endoscopy-Narrow Band Imaging (ME-NBI), we could divided into 2 groups.

One group has irregular vascular pattern in the lesion. The other one has only stuructual change, there was not vascular pattern. 22 lesions revealed vascular pattern, other lesions revealed structural pattern (Figure2).

About pathological findings in detail, Signet-ring cell carcinoma was located in mid mucosa as proliferative zone (PZ) and mid mucosa to upper mucosa. (Figure3)

There are relation ME-NBI findings and pathological findings. Signet-ring cell carcinoma was located at mid-to surface mucosal revealed vasucular pattern using ME-NBI (Figure 4).

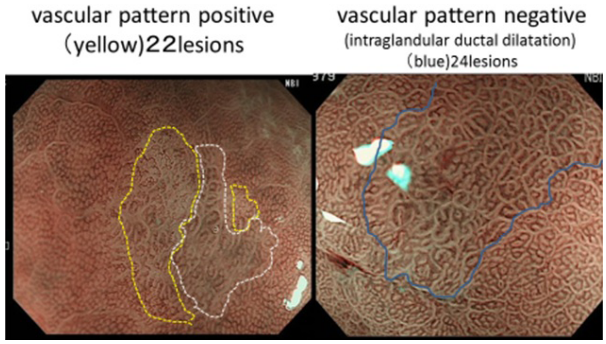

Figure 2: Mgnnified Endoscopy withNarrow Band Imaging(ME-NBI) of *HP*-un-EGSs

Divided into vasculat patttern positive and negative. 24 lesions have vasucular pattern. 22 lesions have no vasuculra pattern.

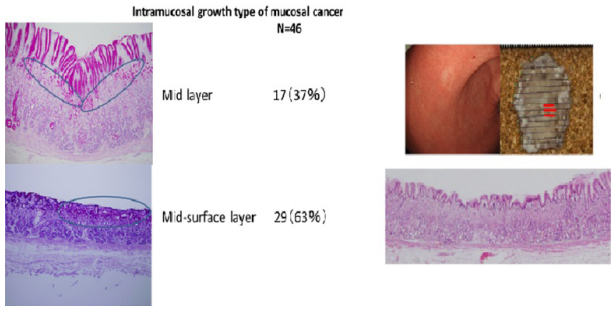

Figure 3: Hitological pattern of the signet-ring cell carcinoma.

Signet-ring cell carcinoma of 17 lesionswere located only mid mucosa.

29 lesions were located mid to surfase mucosa in histology.

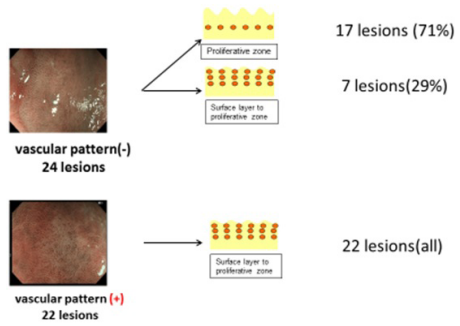

Figure 4: Relationship between ME-NBI findings and signet-ring cellcarcinoma location in the mucosa.
Signet-ring cell carcinomas were located mid to surafese mucosa in histology were revealed vascular pattern with ME-NBI. 71% cases of carcinomas were located only mid mucosa revealedvascular pattern negative.

Case presentation

Case 1(Figure 5)

A 41-years-old woman, there was a faded color area at the lesser curvature of the lower gastric body. The lesion showed a IIc shape macroscopically 3 mm in size and slightly depression using indigocarminesprayed(Figures 5a, 5b, 5c). Biopsy revealed signet-ring cell carcinoma and ESD was carried out. Macroscopic appearance by resected specimen and histological mapping (de). Mucosal cancer was observed at the indicated site in the figure5f. Signet-ring cell carcinoma expanded predominantly at the proliferative zone of the mucosa and it was curatively resected (Figure 5).

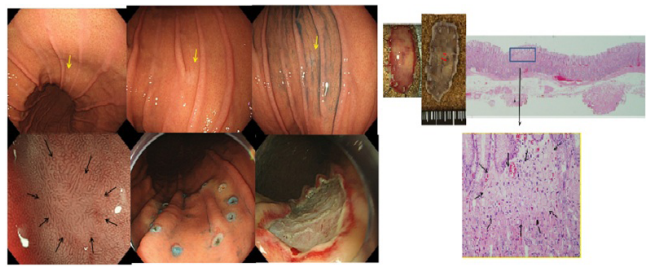

Figure 5: An endoscopic image Faded color lesion was located on the lower body of the Stomach. Slightly depression with indigocarminesprayed (Figure 5). ME-NBI findings revealed non vascular pattern. (d) Marked by Argon Plasma Coaglatoraround the lesion (e) and ulcer after resected(f). And resected specimen (g) and Cancer mapping on the specimen (h). a) Ahistopathological specimen. Signet-ring cell carcinoma was located in intramucosal and only mid mucosa (j).

Discussion

It has been reported that there is a close relationship between occurrence of gastric cancer and *HP* infection and secondary cancer can be prevented by *HP* eradication.[1] In addition, a highly toxic cagA-positive strain among various *HP* strains is closely associated with occurrence of gastric cancer [12,13]. *HP*-uninfected gastric cancer was diagnosed as undifferentiated-type cancer in all cases in this study. *HP*-associated gastric cancer derives from the sequence of chronic gastritis to intestinal metaplasia to well-differentiated adenocarcinoma, [13,14] whereas *HP*-uninfected gastric cancer is not related with this pathway. Moreover, it has been reported that *HP*-uninfected gastric cancer is markedly rare and it accounts for 0.6-3% of all gastric cancers [4-9]. In these reports, definition of *HP* negativity was various and the basis for negative infection with *HP* ranged from histological findings alone to a combination of several variables.

Kakinoki et al. [4] diagnosed negative infection with *HP* based on histological background and reported that *HP*-negative gastric cancer was observed in 3.11% with a predominance of undifferentiated-type cancer and all cases had the gastric-type mucin phenotype. In our institute, about 300 cases with early gastric cancer are treated by ESD every year, which indicated that *HP*-negative cancer was observed in about 2.6%. Since all 24 cases in this study had undifferentiated-type gastric cancer, they were categorized into those with expanded indications of ESD.

Undifferentiated type early gastric cancer, even mucosal cancer, exhibits lymph node metastasis in 1.5-3% [11]. Moreover, it has been reported that determination of the resection area of undifferentiated-type cancer is difficult because of expansion at the proliferative zone. Therefore, such cancer is categorized into the lesion with expanded indications of ESD. We previously reported cases with undifferentiated-type gastric cancer treated by ESD, [12] and prognosis by ESD was excellent in cases with invasion depth M, 20 mm or less in length and UL(-) [13].

There was a report that no gastric cancer occurred in *HP*-negative (negative for IgG antibody and the pepsinogen method) cases, [15] and it was suggested that upper gastrointestinal endoscopy was necessary only every five years[16]. As the characteristics of the *HP*-uninfected stomach, RAC[10] at the gastric bodyand existence of fundic polyps [17] have been suggested. The cases in this study had RAC on the background mucosa and some cases showed gastric fundic polyps. All cases showed characteristic endoscopic images of gastric cancer with faded colors. The results were related with undifferentiated-type cancer by histology. Gastric cancer is rarely detected in the *HP*-uninfected stomach compared with *HP*-positive cases. Furthermore, it was reported recently thatfundic-type gastric cancer existed and occurred in the *HP*-negative stomach. [20] Recently *HP*-uninfected gastric cancer has been sporadically reported. However, the definition was various and diagnosis was made pathologically, serologically, or by a combination of various tests. At present, it is unreliable to diagnose negative infection with *HP* by only one test. The strictest criteria were employed only in the reference [5]. The definition of negative infection with *HP* was determined by five tests such as serology, histology, and the CLO test [5]. There was no significant difference in gender, histological types, and location between *HP*-negative and *HP*-positive cases, whereas advanced cancer was more often observed in *HP*-negative cases [21,22]. The criteria we employed in this study for determination of negative infection with *HP* were strict and therefore the characteristics of *HP*-uninfected gastric cancer were thought to be reliable.

We already reported that NBI findings and pathological findings of undifferentiated adenocarcinoma [23.24]. On *HP*-uninfected cases, there is a similar relation between NBI findings and cancer location in the mucosa. We could not seen vascular pattern without mid- to surface infiltration in the mucosa.

It is expected that cases with the *HP*-uninfected stomach will increase in Japan [25]. It is also predicted that undifferentiated-type cancer with faded colors at the gastric body and antrum and gastric fundic-type cancer occurring in the gastric fundic gland area of the gastric body reported in the literature are the characteristics of gastric cancer occurring in the *HP*-uninfected stomach. As the *HP* infection rate drops, occurrence of gastric cancer will decrease but gastric cancer with some special features may occur continuously. Therefore, it is important to carry out endoscopic examinations with the characteristics of faded colors of undifferentiated-type cancer in mind.

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