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SHORT COMMUNICATION

Comparative analysis of upper gastrointestinal endoscopy, double-contrast upper gastrointestinal barium X-ray radiography, and the titer of serum anti-*Helicobacter pylori* IgG focusing on the diagnosis of atrophic gastritis

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Abstract
Background Upper gastrointestinal endoscopy (UGI-ES) and double-contrast upper gastrointestinal barium X-ray radiography (UGI-XR) are two major image-based methods to diagnose atrophic gastritis, which is mostly induced by *Helicobacter pylori* infection. However, there have been few studies directly comparing them.
Methods Atrophic gastritis was evaluated using the data of 962 healthy subjects who underwent UGI-ES and UGI-XR within 1 year.
Results and conclusion Based on UGI-ES and UGI-XR, 602 subjects did not have atrophic gastritis and 254 subjects did have it. Considering UGI-ES-based atrophic gastritis as the standard, sensitivity and specificity of UGI-XR-based atrophic gastritis were 92.0 % (254/276) and 92.8 % (602/649), respectively. The seven-grade Kimura–Takemoto classification of UGI-ES-based atrophic gastritis showed a strong and significant association with the four-grade UGI-XR-based atrophic gastritis. Sensitivity and specificity of serum anti-*Helicobacter pylori* IgG to detect UGI-ES/UGI-XR-based atrophic gastritis were 89.4 % (227/254) and 99.8 % (601/602), indicating that atrophic gastritis can be overlooked according to serum anti-*Helicobacter pylori* IgG alone.

Keywords Atrophic gastritis · *Helicobacter pylori* · Upper gastrointestinal endoscopy (UGI-ES) · Double-

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contrast upper gastrointestinal barium X-ray radiography (UGI-XR) · Kimura–Takemoto classification

Abbreviations

UGI-ES	Upper gastrointestinal endoscopy
UGI-XR	Double-contrast upper gastrointestinal barium X-ray radiography

Introduction

Various countermeasures for gastric cancer have been developed and used in East Asia, where the incidence of gastric cancer is quite high [1]. These measures can be broadly classified into two groups: those that aim to detect gastric cancer itself (cancer screening), and those that aim to evaluate the premalignant condition of gastric mucosa (risk stratification) [2]. Double-contrast upper gastrointestinal barium X-ray radiography (UGI-XR) [3–5] and upper gastrointestinal endoscopy (UGI-ES) [6–8] are the typical measures belonging to the former group, whereas serum markers including anti-*Helicobacter pylori (H. pylori)* IgG, pepsinogens, gastrin-17, methylation status of several genes, etc. [9–14] are representative measures affiliated with the latter group.

Nowadays, there is a growing tendency to make another new use of UGI-XR and UGI-ES for gastric cancer: namely, UGI-XR as well as UGI-ES are expected not only to detect gastric cancer but also to evaluate atrophic gastritis [2]. Atrophic gastritis is a well-established premalignant condition of gastric mucosa mostly induced by chronic infection of *H. pylori* [15, 16]. Although UGI-ES and UGI-XR are the two major "no-histological image-based" methods that can evaluate mucosal atrophy of stomach [2, 17–20], very few reports have directly compared their diagnostic accuracy for atrophic gastritis.

Based on the foregoing backgrounds, we have two aims in the present study. The main aim is a direct comparison between UGI-ES and UGI-XR in terms of their accuracy to detect atrophic gastritis. The second aim is to evaluate an association between serum anti-*H. pylori* IgG titer and "atrophic gastritis" diagnosed by UGI-ES and UGI-XR. In addition, we wish to supply our large-scale raw data from 962 generally healthy subjects that include diagnoses by UGI-ES and UGI-XR, titers of serum anti-*H. pylori* IgG, values of serum pepsinogens, etc. We believe our results and data will be useful concerning future screening and risk stratification of gastric cancer.

Methods

Study subjects

The study subjects were 962 generally healthy subjects who underwent UGI-XR in 2010 and also underwent UGI-ES within 1 year at our institute for a medical checkup. They agreed to participate in our study, were not users of gastric acid suppressants, and had no history of gastrectomy and eradication for *H. pylori*.

The seven-grade Kimura–Takemoto classification of UGI-ES-based atrophic gastritis and the four-grade UGI-XR-based atrophic gastritis

According to the Kimura–Takemoto classification [18, 19], atrophic changes of the gastric mucosa diagnosed by UGI-ES were classified into no atrophic change (C0), three closed types of atrophic gastritis (C1, C2, C3), and three open types of atrophic gastritis (O1, O2, O3) based on the endoscopic atrophic border (a boundary between the pyloric and fundic gland areas, and also a boundary between non-atrophic and atrophic gastric mucosae recognized endoscopically by discriminating differences in color and height of the gastric mucosa [21, 22]).

By referring to several previous reports [23–25], we have recently established the four-grade classification of UGI-XR-based atrophic gastritis judging from the irregular shapes of areae gastricae and their expansion (normal, mild, moderate, and severe) [2]. These two categorizations of image-based atrophic gastritis and double/triple check of the images are minutely described in Fig. 1 and supplementary methods.

Serum anti-*H. pylori* IgG, serum pepsinogen I and II, and other factors

Serum anti-*H. pylori* IgG and pepsinogens were measured using commercial kits (E-plate; EIKEN, Tokyo, Japan) [26–30]. According to the manufacturer's instructions, a titer of anti-*H. pylori* IgG $\geq$10 U/ml was considered as positive for *H. pylori* infection. The ratios of serum pepsinogen I and II were classified into ">3", ">2", and $\leq$3", and "$\leq$2" [28, 31]. Other factors used in our analyses are minutely described in the supplementary methods.

Statistics

We used SAS 9.1.3 for statistical analyses. To compare the four-grade UGI-XR-based and the seven-grade UGI-ES-

a The seven-grade Kimura-Takemoto classification of UGI-ES-based atrophic gastritis

Type	Characteristics of the seven types of atrophic gastritis based on the endoscopically recognized atrophic border.
C0	No atrophic change is observed in the entire stomach.
C1	Atrophic border lies in the antrum: consequently, atrophic change is observed in the antrum, but not in the angle, body, and fornix.
C2	The atrophic border lies on the lower half of the lesser curvature in the gastric body.
C3	The atrophic border lies on the upper half of the lesser curvature in the gastric body.
O1	The atrophic border lies on both the lesser curvature and the anterior wall.
O2	The atrophic border lies on the anterior wall only.
O3	The atrophic border lies between the anterior wall and the greater curvature: consequently, most widely spread atrophic mucosa is observed in the stomach.

b The four-grade types of UGI-XR-based atrophic gastritis

Type	Characteristics of the four types of UGI-XR-based atrophic gastritis judged from the irregular shapes of areae gastricae and their expansion.
A	Normal gastric mucosa. Areae gastricae cannot be detected or can be recognized as small, round, and regular shapes in all the mucosal surface of stomach. Such no atrophic gastric mucosa covers the entire stomach.
B	Mild atrophic gastritis. Enlarged areae gastricae with slight angularity and irregularity (mild mucosal atrophy) are observed in the antrum but not in the body.
C	Moderate atrophic gastritis. Obviously enlarged areae gastricae with considerable angularity and irregularity (moderate mucosal atrophy) extend from the antrum to body and/or fornix.
D	Severe atrophic gastritis. Very small or absent areae gastricae accompanied with irregularly rugged mucosal surface (severe mucosal atrophy) extend diffusely in the entire stomach.

Fig. 1 Detailed features of the seven-grade Kimura–Takemoto classification of upper gastrointestinal endoscopy (UGI-ES)-based atrophic gastritis and the four-grade types of double-contrast upper gastrointestinal barium X-ray radiography (UGI-XR)-based atrophic gastritis

based atrophic gastritis, the polychoric correlation coefficient was calculated.

Results

UGI-XR-based atrophic gastritis shows a strong and significant association with UGI-ES-based atrophic gastritis

The characteristics of the present study subjects are shown in Table 1 and Fig. 2. Of the 962 generally healthy subjects, 602 subjects (62.6 %) were diagnosed to be free from atrophic gastritis by both UGI-ES (C0) and UGI-XR (normal), whereas 254 subjects (26.4 %) were diagnosed to have atrophic gastritis by both UGI-ES (C2-O3) and UGI-XR (mild, moderate, or severe).

When UGI-ES-based atrophic gastritis was considered to be the standard, the sensitivity and specificity of UGI-XR-based atrophic gastritis were 92.0 % (254/276) and 92.8 % (602/649), respectively (Fig. 2). A high polychoric correlation coefficient value ($r = 0.9069$) demonstrated that there is a strong and significant association between the seven-grade UGI-ES-based atrophic gastritis (Kimura–Takemoto classification) and the four-grade categories of UGI-XR-based atrophic gastritis.

The titer of serum anti-*H. pylori* IgG cannot reliably detect atrophic gastritis that is diagnosed by UGI-ES and UGI-XR

We next evaluated the association between the serum titer of anti-*H. pylori* IgG and atrophic gastritis diagnosed by UGI-ES and UGI-XR. Distributions of the serum anti-*H. pylori* IgG titers in the 602 subjects without atrophic gastritis and the 254 subjects with atrophic gastritis are shown in Fig. 3a, b. Values of pepsinogen I, pepsinogen II, and pepsinogen I/II ratio are also shown in Figures S1 and S2.

We next examined whether the positive titer of serum anti-*H. pylori* IgG could predict atrophic gastritis diagnosed by UGI-ES and UGI-XR, because atrophic gastritis is predominantly induced by chronic infection of *H. pylori* [17, 22]. On the basis of UGI-ES/UGI-XR-based diagnoses, the sensitivity and specificity to detect atrophic gastritis with the positive titer of anti-*H. pylori* IgG were 89.4 % (227/254) and 99.8 % (601/602), respectively (Fig. 3c). Our results also revealed that the positive and negative predictive values were 99.6 % (227/228) and 95.7 % (602/628), respectively (Fig. 3c).

Discussion

Presently, detection of chronic *H. pylori* infection is thought to be important for predicting the risk of gastric cancer [32–35]. For endoscopic observation, atrophic gastritis is established as the most typical and frequent appearance of gastric mucosa with *H. pylori* infection [22, 35, 36]. Therefore, a strong association between "UGI-ES-based" and "UGI-XR-based" diagnoses suggests that detection of UGI-XR-based atrophic gastritis can lead to evaluation of chronic *H. pylori* infection. In the case of the positive titer for serum anti-*H. pylori* IgG, mucosal atrophy was observed with 99.6 % accuracy (Fig. 3c): this indicates that chronic *H. pylori* infection can be diagnosed almost completely by UGI-XR. In contrast, in the case of negative titer for serum anti-*H. pylori* IgG, as many as 4.3 % had atrophic gastritis (Fig. 3c): this indicates that other factors may have some critical role in the development of UGI-ES/UGI-XR-based atrophic gastritis, or that serum anti-*H. pylori* IgG titer is insufficient to diagnose *H. pylori* infection. In either case, our results reveal that UGI-ES/UGI-XR-based atrophic gastritis can be overlooked

Table 1 Characteristics of the total 962 study subjects, 602 subjects without atrophic gastritis, and 254 subjects with atrophic gastritis based on UGI-ES and UGI-XR

Factor	Total 962 study subjects	The 602 subjects without atrophic gastritis based on UGI-ES and UGI-XR	The 254 subjects with atrophic gastritis based on UGI-ES and UGI-XR
Age (years)	48.4 ± 8.7	46.7 ± 8.3	52.1 ± 8.0
Range	21–79	21–79	34–78
Sex			
Male	547 (56.9 %)	338 (56.1 %)	152 (59.8 %)
Female	415 (43.1 %)	264 (43.9 %)	102 (40.2 %)
Body mass index	22.7 ± 3.2	22.7 ± 3.3	22.9 ± 3.2
Anti-*Helicobacter pylori* IgG (U/ml)	15.7 ± 30.5	0.9 ± 1.1	48.9 ± 38.2
<3	654 (68.0 %)	590 (98.0 %)	10 (3.9 %)
<10 and ≥3	40 (4.2 %)	11 (1.8 %)	17 (6.7 %)
≥10	268 (27.8 %)	1 (0.2 %)	227 (89.4 %)
Pepsinogen I/II ratio	5.49 ± 1.97	6.41 ± 1.29	3.25 ± 1.63
>3	823 (85.6 %)	602 (100 %)	120 (47.2 %)
≤3 and >2	85 (8.8 %)	0 (0.0 %)	83 (32.7 %)
≤2	54 (5.6 %)	0 (0.0 %)	51 (20.1 %)
Pepsinogen I (ng/ml)	53.4 ± 31.0	49.2 ± 30.4	61.3 ± 31.3
>70	140 (14.6 %)	44 (7.3 %)	74 (29.1 %)
≤70 and >50	304 (31.6 %)	191 (31.7 %)	83 (32.7 %)
≤50 and >30	431 (44.8 %)	312 (51.8 %)	70 (27.6 %)
≤30	87 (9.0 %)	55 (9.2 %)	27 (10.6 %)
Pepsinogen II (ng/ml)	11.8 ± 9.4	7.9 ± 5.3	20.9 ± 10.7
>30	38 (4.0 %)	1 (0.2 %)	33 (13.0 %)
≤30	924 (96.0 %)	601 (99.8 %)	221 (87.0 %)

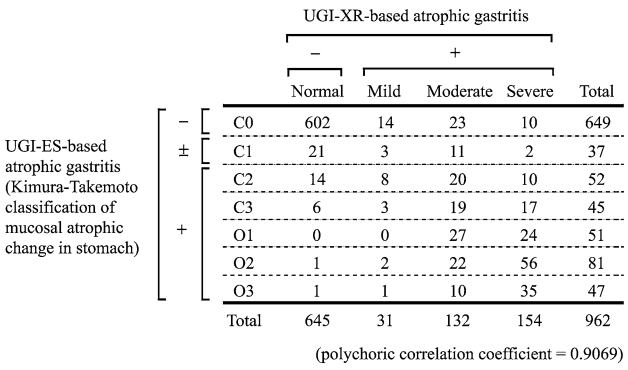
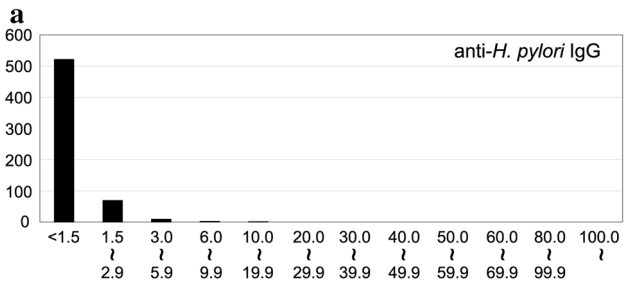


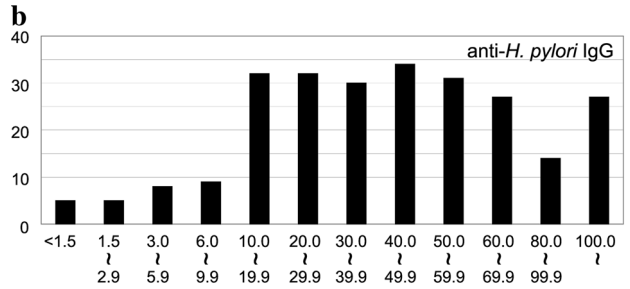
Fig. 2 Comparison between UGI-ES-based atrophic gastritis and UGI-XR-based atrophic gastritis using the data of 962 generally healthy subjects

when the serum titer of anti-*H. pylori* IgG alone is used as an indicator.

Internationally standard risk stratification methods for gastric cancer are still histological evaluation of random biopsy specimens such as OLGA [37, 38], OLIGM [39], etc. In contrast, endoscopic diagnosis of premalignant atrophic gastritis is widely conducted in Japan [35]. The Kimura–Takemoto classification of atrophic gastritis by UGI-ES is the most widely used method, which has been validated by several reports showing the reliable association between endoscopic findings and histological appearances [18, 19, 22, 40]. In this study, we showed a significantly strong association between UGI-ES-based atrophic gastritis and UGI-XR-based atrophic gastritis (Fig. 2). Taking all these into consideration, UGI-XR-based atrophic gastritis should reflect the premalignant histological condition of gastric mucosa, which is mostly induced by *H. pylori* infection. Based on these results, we are now planning to evaluate the clinical meaning of UGI-XR-based atrophic gastritis from the aspect of predicting future gastric cancer development.

In Table S1, we provide all the data of our 962 study subjects, which include the Kimura–Takemoto classification of UGI-ES-based atrophic gastritis, the four-grade types of UGI-XR-based atrophic gastritis, serum titers of anti-*H. pylori* IgG, age, gender, body mass index, smoking history, alcohol use, serum pepsinogens, the ABCD risk classification of gastric cancer [9], the three-grade types of UGI-XR-based enlarged folds [24, 25], etc. Extracted data





c

	The presence of atrophic gastritis based on UGI-ES and UGI-XR	The absence of atrophic gastritis based on UGI-ES and UGI-XR	Total
Anti-*H. pylori*-IgG≧10	227 (89.4%)	1 (0.2%)	228 (3.3%)
10>anti-*H. pylori*-IgG	27 (10.6%)	601 (99.8%)	628 (96.7%)
Total	254 (100%)	602 (100%)	856 (100%)

Sensitivity: 89.4 % Specificity: 99.8 %
Positive predictive value: 99.6% Negative predictive value: 95.7%

Fig. 3 Distribution of the serum anti-*Helicobacter pylori* IgG titers in the 602 subjects without atrophic gastritis (**a, c**) and that in the 254 subjects with atrophic gastritis (**b**, **c**), based on UGI-ES and UGI-XR

of the 602 subjects without UGI-ES/UGI-XR-based atrophic gastritis and those of the 254 subjects with UGI-ES/UGI-XR-based atrophic gastritis are also provided in Tables S2 and S3. We believe these data will be helpful for future research concerning the screening and risk stratification of gastric cancer.

Conclusion

The four-grade categories of UGI-XR-based atrophic gastritis showed a strong and significant association with the seven-grade Kimura–Takemoto classification of UGI-ES-based atrophic gastritis. UGI-ES/UGI-XR-based atrophic gastritis can sometimes be overlooked when the serum titer of anti-*H. pylori* IgG alone is used as an indicator.

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Compliance with ethical standards

Conflict of interest None of the authors have conflicts of interest to declare.

Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study.

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