

[ORIGINAL ARTICLE]

Clinicopathological Features and the Prevalence of Oxyntic Gland Neoplasm: A Single-center Retrospective Study

Hikari Asahara¹, Toshitatsu Takao², Yumiko Asahara³, Masakyo Asahara³, Douglas Motomura⁴, Hiroya Sakaguchi², Tetsuya Yoshizaki², Nobuaki Ikezawa², Madoka Takao², Yoshinori Morita², Takashi Toyonaga², Masato Komatsu⁵, Ryoji Kushima⁶ and Yuzo Kodama²

Abstract:

Objective We explored the clinicopathological characteristics and disease frequency of oxyntic gland neoplasms (OGNs).

Methods We retrospectively evaluated the data of patients pathologically diagnosed with OGN at an internal medicine clinic.

Patients A total of 13,240 upper gastrointestinal endoscopies were performed on 7,488 patients between December 1, 2017, and March 31, 2021.

Results We identified 27 patients with 30 histopathologically confirmed OGNs, yielding a disease frequency of 0.36% (27/7,488). Furthermore, multiple simultaneous lesions were found in 3 of 27 patients (11%). One (3.3%) of the 30 lesions was present in the antrum, whereas the remaining lesions occurred in the body of the stomach. Nine (33%) of the 27 patients had no history of *Helicobacter pylori* infection, whereas the remaining 18 (67%) were either currently or had been previously infected. Nevertheless, 27/30 lesions (90%) still occurred in non-atrophied regions. After endoscopic treatment, a histopathological examination of the resected specimens revealed submucosal infiltration in 8 (44%) of the 18 lesions; however, none of the lesions showed submucosal desmoplasia. For all patients with submucosal involvement, only observation was performed. There were no recurrent lesions found on follow-up.

Conclusion The period prevalence of OGN was 0.36%, which is much higher than previously reported. The discovery of a small submucosal appearing lesion with a faded yellow or white color and dilated microvasculature, especially in a non-atrophic area of the stomach, should raise suspicion for an OGN, which can be endoscopically managed.

Key words: oxyntic gland neoplasm, Gastric adenocarcinoma of fundic-gland type, oxyntic gland adenoma

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Background

Differentiated gastric adenocarcinoma was once thought to have a stereotypical development cascade, from chronic gastritis (often *Helicobacter pylori*-related), progressing to

atrophy, intestinal metaplasia, and then carcinoma. Thus, the vast majority of differentiated gastric adenocarcinoma cases have an intestinal phenotype and are subsequently named “intestinal-type gastric carcinoma”. However, recent advances in histochemical and immunohistological techniques have revealed that some gastric neoplasms retain a gastric

¹Department of Gastroenterology, Kobe Red Cross Hospital, Japan, ²Department of Gastroenterology, Kobe University Graduate School of Medicine, Japan, ³Asahara Clinic, Japan, ⁴Division of Gastroenterology, Department of Medicine, University of British Columbia, Canada, ⁵Division of Diagnostic Pathology, Kobe University Graduate School of Medicine, Japan and ⁶Department of Pathology, Shiga University of Medical Science Hospital, Japan

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Correspondence to Toshitatsu Takao, t.takao1234@gmail.com

Table 1. Patient Characteristics.

	n=27	%
Age (yr)		
Mean	67	-
Median	69 [45-84]	-
Sex		
Male	15	56
Female	12	44
H. pylori		
Naïve	9	33
Currently infected	4	15
previously infected	14	52
Atrophic gastritis		
No	9	33
Yes	18	67
Antacid		
None	17	63
PPI	9	33
Other	1	3.7
Multiple lesions		
No	24	89
Yes	3	11

phenotype without associated metaplasia. This group includes the foveolar, pyloric, and fundic gland types, and is collectively termed “gastric-type gastric adenocarcinoma”.

In 2007, Tsukamoto et al. reported the first case of a gastric adenocarcinoma with chief cell differentiation (1). In 2010, Ueyama et al. collected similar cases and proposed the term “gastric adenocarcinoma of the fundic gland type” (GA-FG; chief cell-predominant type) as a new entity of gastric adenocarcinoma (2). Subsequently, several cases of gastric-type gastric adenocarcinoma began to be described in case reports and series (3-6). Aatur et al. recommended the name “oxyntic gland polyp/adenoma” in lieu of “gastric adenocarcinoma with chief cell differentiation” owing to its benign behavior (3). The 2017 Japanese Classification of Gastric Carcinoma (15th edition) categorized GA-FG as a special type of gastric cancer that includes not only tumors invading the submucosa but also intramucosal neoplasms (7). The 2019 World Health Organization (WHO) Classification of Gastric Carcinoma (5th edition) stated that neoplasms retained within the mucosa are defined as oxyntic gland adenomas (OGAs), whereas lesions demonstrating submucosal invasion are referred to as GA-FG (3, 8). In 2020, Ushiku et al. reported 26 cases of oxyntic gland neo-

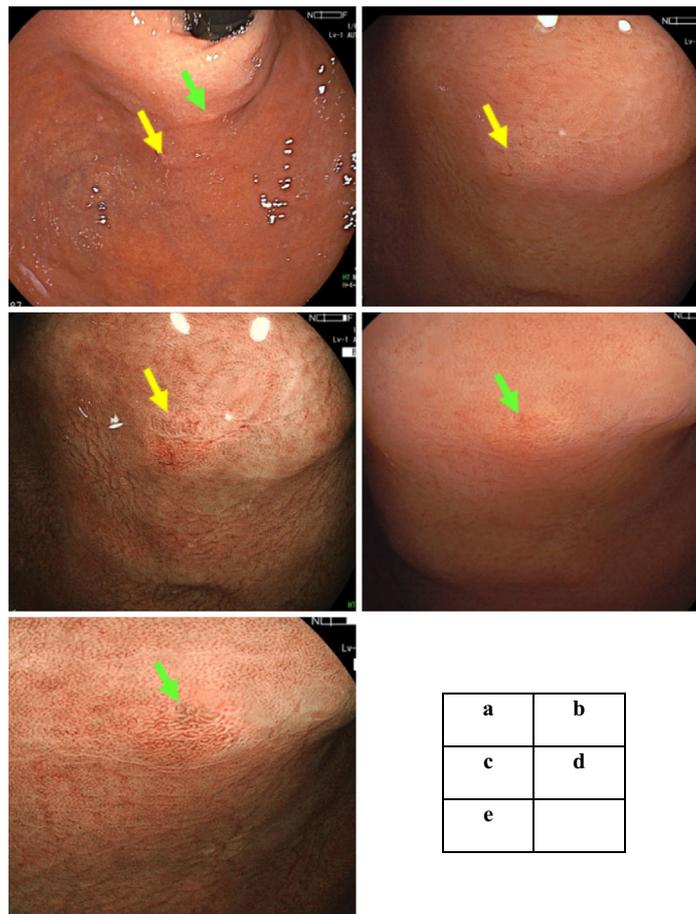


Figure 1. Endoscopic findings of multiple lesions of OGN. (a) Conventional endoscopic image. Pale, elevated lesions were observed on the posterior wall of the fundus (yellow and green arrows). (b) Conventional endoscopic image (yellow arrow). (c) Narrow-band imaging with slight magnification (yellow arrow). (d) Conventional endoscopic image (green arrow). (e) Narrow-band imaging with slight magnification (green arrow).

Table 2. Lesion characteristics.

	n=30	%
Location		
Upper	26	87
Middle	3	10
Lower	1	3
Cross sectional location		
Greater curvature	15	50
Lesser curvature	3	10
Anterior wall	6	20
Posterior wall	6	20
Macroscopic size (mm)		
Mean	3.7	-
Median	3 [2-8]	-
Macroscopic type		
Elevated	16	53
Flat	13	43
Depressed	1	3.3
Color of lesion		
Normal	5	17
Yellow	12	40
Faded	12	40
Red	1	3
Distribution of lesion		
Atrophic area	3	10
Non-atrophic area	27	90

plasms (OGNs) including OGA and GA-FG (9). In addition, Ueyama et al. proposed the classification “gastric epithelial neoplasm of fundic gland mucosa lineage”, which included OGA and GA-FG but also added GA-FGM, as a new classification in 2021 (10). However, to simplify the varied terminology found in the literature, we have elected to use the term OGN in this paper.

The typical endoscopic finding of OGN is a flat, elevated lesion with a submucosal appearance, commonly located in the upper-to-middle third of the stomach. The lesion is often whitish in color and can contain dilated vessels with branching architecture (5, 11). The stomach itself is usually non-atrophic, and the rates of *H. pylori* infection in patients with OGN are relatively low. In terms of immunohistochemistry, this type of lesion is positive for pepsinogen-I (a chief cell marker), H^+/K^+ -ATPase (a parietal cell marker), and MUC6 (a mucous neck cell marker), which are all features of a gastric-type tumors (12-14). As mentioned above, the clinical features of OGNs are still being elucidated, and the classification is still developing (7-12). The majority of previous reports were limited to individual case reports or multicenter series accumulated at tertiary referral centers. This has led to uncertainty concerning the real-world frequency of OGNs (8), as previous reports have described the prevalence at less than 1/10,000 (<0.01%). Furthermore, the relationship with *H. pylori* infection, association with oral proton pump inhibitor (PPI) use, frequency of submucosal invasion, and rate of lymph node metastasis have not yet been clarified (8, 11, 12, 14-21).

The present study examined consecutive cases of OGN in a real-world outpatient cohort and clarified the prevalence and clinicopathological features of these lesions.

Methods

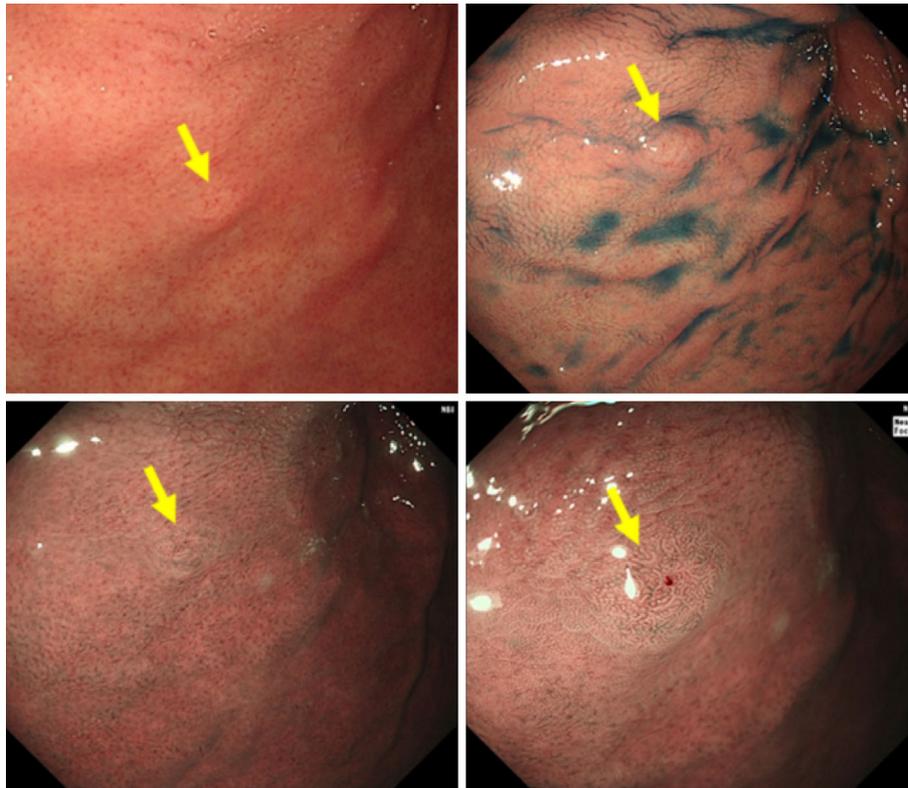
Between December 1, 2017, and March 31, 2021, patient records at a high-volume outpatient internal medicine and endoscopy clinic (Asahara Clinic, Akashi, Japan) were reviewed retrospectively. Patients with a diagnosis of OGN via upper gastrointestinal endoscopy were included in the cohort. Screening tests were performed using high-definition endoscopy with the GIF-HQ290 or GIF-H290Z (Olympus, Tokyo, Japan). Conscious sedation was administered in all cases, and carbon dioxide gas was used for insufflation. All screening tests were performed after thoroughly cleaning the stomach using the waterjet function (OFR-2; Olympus). All endoscopists had a clinical experience of over 10 years.

All biopsy specimens taken in this study were re-evaluated by a gastrointestinal pathologist with expertise in OGNs (co-author RK). The diagnosis of OGN was confirmed based on the nuclear and cellular atypia of highly differentiated columnar cells mimicking the fundic gland cells, as well as immunostaining results, such as findings of MUC5AC, MUC6 pepsinogen-I, and H^+/K^+ -ATPase. In Japan, OGNs are regarded as low-grade cancers, and all patients diagnosed with these lesions were offered endoscopic treatment. Patients amenable to treatment were referred to Kobe University Hospital (Kobe, Japan). After resection, a specialized pathological evaluation was performed in the Department of Diagnostic Pathology of Kobe University Graduate School of Medicine. The period prevalence of OGN was defined as the number of patients with detected OGNs divided by the total number of patients undergoing upper gastrointestinal endoscopy over the study period. The presence of atrophy was noted when areas of faded gastric mucosa and vascular transparency were examined under white-light endoscopy. The extent of atrophy was classified according to the Kimura and Takemoto classification (22). The presence or absence of *H. pylori* infection at the time of lesion detection was evaluated using the endoscopic findings of the background gastric mucosa according to the Kyoto classification (23). Along with the results of their most recent urea breath test, patients' *H. pylori* infection status was classified as naive, current, or previous (24).

Endoscopic management varied depending on the lesion size and location. Endoscopic mucosal resection using a cap-fitted endoscope (EMRC) was performed for cases in which the attending endoscopist deemed margin-negative *en bloc* resection (complete R0 resection) feasible with this technique (25). In cases where *en bloc* resection via EMRC was expected to be difficult, endoscopic submucosal dissection (ESD) was performed instead (26).

Ethics approval

This retrospective study was conducted in accordance



a	b
c	d

Figure 2. Endoscopic findings of oxyntic gland neoplasm (OGN) without *H. pylori* infection in the non-atrophic region. (a) Conventional endoscopic image. A pale, subepithelial tumor-like elevated lesion was observed in the posterior wall of the fundus. A regular arrangement of collecting venules in the surrounding mucosa was observed. Dilated vessels were seen in the elevated lesion. (b) Image after indigo carmine dye spraying. (c) Narrow-band imaging without magnification. (d) Narrow-band imaging with slight magnification. Mildly dilated crypt opening and slightly enlarged glands were noted.

with the ethical principles embodied in the Declaration of Helsinki (Fortaleza revision) and in compliance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan.

In addition, this study was approved by the Institutional Review Board (IRB) of the Public Health Research Foundation (approval number: 21G0002). The requirement for the acquisition of informed consent from patients was waived because the analysis used anonymous clinical data. We applied the opt-out method to obtain consent using a paper-based notification. The notification was also approved by the IRB. The authors have no conflicts of interest to declare.

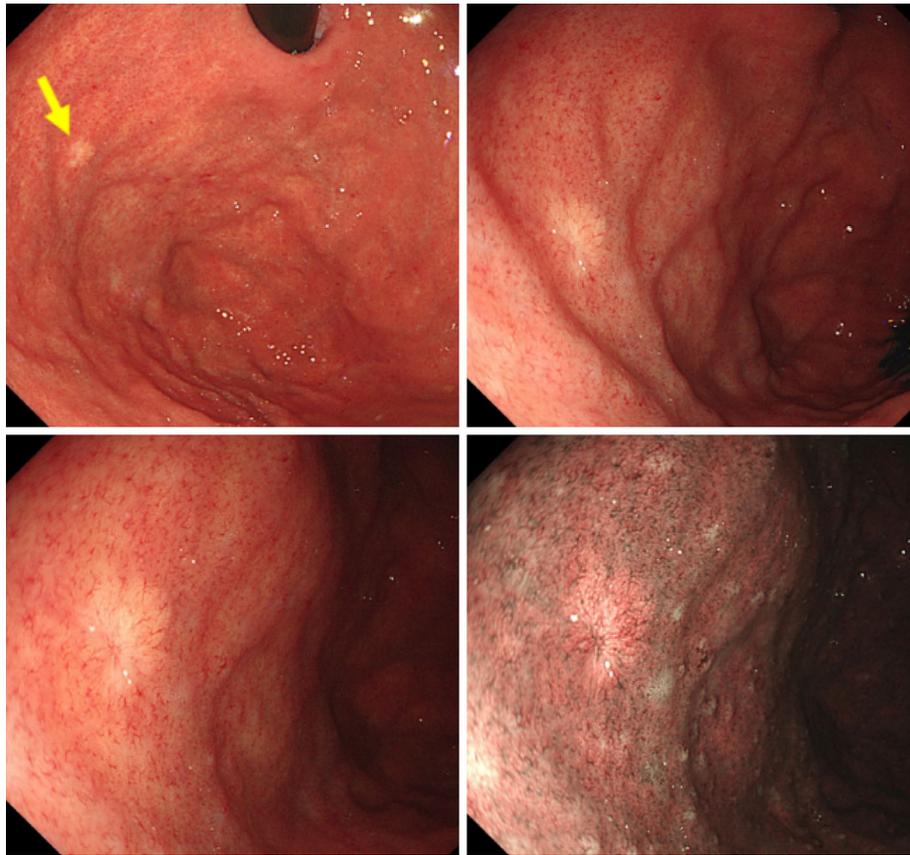
Results

Between December 1, 2017, and March 31, 2021, a total of 13,240 upper gastrointestinal endoscopies were performed on 7,488 patients. In this cohort, 30 lesions in 27 patients were pathologically diagnosed as OGN. Thus, the disease

frequency of OGN was determined to be 0.36% (27/7,488) per patient. The lesion discovery rate per examination administered was 0.23% (30/13,240). The number of gastric cancers other than OGN detected during the same period was 132 lesions in 122 patients.

Table 1: summarizes the clinical characteristics of the patients diagnosed with OGNs. There were 15 men and 12 women, with an age range of 45-84 (median: 69) years old. In terms of the *H. pylori* infection status, 9 of the patients were naïve, 4 were currently infected, and 14 had been previously infected. Ten (37%) of the 27 patients were using proton pump inhibitors (PPIs; n=9) and H2 blockers (n=1) at the time of lesion discovery. The median duration of use was 646 (35-5,381) days. Three (33%) of the 9 patients who had taken PPIs had fundic gland polyps at the time of endoscopy. Three (11%) of the 27 patients had multiple OGNs simultaneously (Fig. 1).

Table 2: shows the lesion characteristics. The lesions were located in the upper/middle/lower third of the stomach



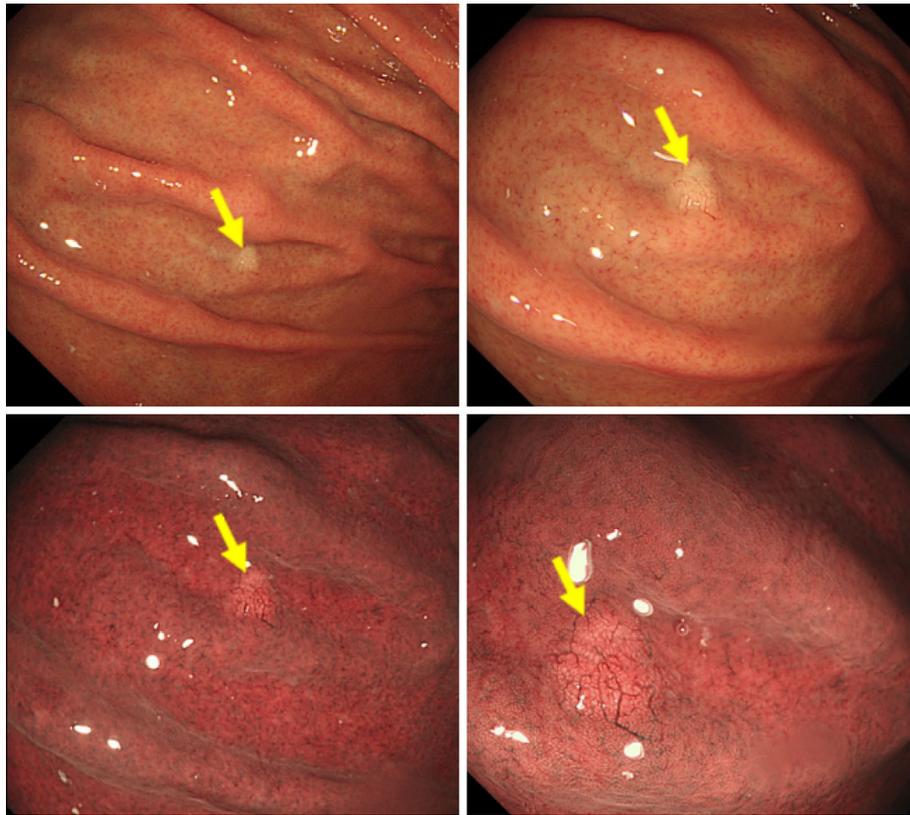
a	b
c	d

Figure 3. Endoscopic findings of OGN with current *H. pylori* infection in the atrophic region. (a) Conventional endoscopic image. The surrounding mucosa was atrophic. A whitish, subepithelial tumor-like elevated lesion was observed at the posterior wall of the fundus. Constriction after a biopsy was seen in the lesion. (b) Dilated vessels were observed on the elevated lesion, extending from the periphery towards the center of the tumor. (c) Conventional endoscopic image with slight magnification. (d) Narrow-band imaging with slight magnification.

in 26/3/1 case, respectively. The color of the mucosa was normal/yellow/faded/red in 5/12/12/1 case, respectively. The surface mucosal findings included a pale-yellow tone with dilated microvessels coursing towards the center from the edge of the tumor and slight dilation of the glandular ducts (Fig. 2-4). One lesion was located in the antrum (Fig. 5). Pigmentation was observed in only one lesion. Twenty-six of 30 lesions were histopathologically diagnosed as OGN via a biopsy. In two lesions, the diagnosis was made optically due to the tiny size of the lesion preventing sampling. The final two lesions were discovered incidentally in patients undergoing endoscopic resection. Because they displayed the typical optical features and were in proximity to the target lesions, a high probability of synchronous OGN was considered. These lesions were therefore resected endo-

scopically without a biopsy.

Table 3: shows the treatment and pathological characteristics of the 18 resected lesions. The median pathological size (width) of the 18 lesions was 3.5 mm (2-8 mm). Ten lesions (54%) were intramucosal, whereas 8 (44%) showed submucosal infiltration (Fig. 6). The median size of the tumors with submucosal infiltration was 5 mm (range: 2-8 mm), and the depth from the lower end of the muscularis mucosae to the advanced tumor region was 40 to 950 μ m. None of the eight lesions with submucosal infiltration showed desmoplasia in the submucosa around the tumor (Fig. 7). No lymphovascular invasion was observed in any lesions with submucosal infiltration. The median Ki-67 index of the endoscopically resected specimens was 1% (range: 1%-8%). All patients with submucosal infiltration were managed conserva-



a	b
c	d

Figure 4. Endoscopic findings of OGN with previous *H. pylori* infection in the non-atrophic region. (a) Conventional endoscopic image. A small, whitish lesion was seen at the greater curvature of the upper third of the stomach. (b) The surrounding mucosa was not atrophic. A whitish, subepithelial tumor-like elevated lesion was observed. More dilated microvessels were noted at the periphery of the lesion. (c) Narrow-band imaging without magnification. (d) Narrow-band imaging with slight magnification. Slightly dilated crypt opening was observed on the lesion. Dilated microvessels at the periphery were easily recognized under narrow-band imaging magnification.

tively without additional surgical resection, and none developed metastasis during the follow-up period, which ranged from 61 to 436 (median: 100) days.

Discussion

This is the first study to report the prevalence of OGN. The period prevalence based on the consecutive patients undergoing upper gastrointestinal endoscopy was 0.36% (27/7,488). In addition, our results showed that 11% (3/27) of the patients had multiple OGNs simultaneously. We believe that if OGNs are recognized by more endoscopists and pathologists, the detection rates will increase, and more accurate disease frequencies will be clarified.

Period prevalence

According to the WHO Classification of Gastric Carci-

noma (5th edition), the exact prevalence of OGNs is unknown (8). A previous report described a frequency of < 0.01% (27) as calculated in a cohort of 30,182 individuals who underwent yearly checkup endoscopies during the study period. However, this figure was limited by the inclusion of a considerable number of patients undergoing multiple procedures. Our prevalence rate is presented per person rather than per procedure, resulting in a more accurate disease frequency. In addition, our rate of 0.36% was considerably higher than previously reported, likely due to advances in knowledge concerning these lesions and increased experience with the typical features and optical diagnoses.

Endoscopic findings

The typical endoscopic presentation of OGN is a yellowish, gently rising, elevated lesion characterized by the dilation of microvessels on the surface (19). The manifesta-



a	b
c	d

Figure 5. Endoscopic findings of OGN found in the antrum. (a) Conventional endoscopic image. A pale, flat lesion was observed in the posterior wall of the gastric antrum. (b) Image after indigo carmine dye spraying. (c) Narrow-band imaging without magnification. (d) Narrow-band imaging with slight magnification. Dilated microvessels at the periphery of the lesion and slightly enlarged glands were recognized, which raised suspicion for an OGN.

tions of these characteristics may vary based on the size of the OGN, with these features gaining prominence as the lesion grows. However, at smaller sizes, we found the lesions to be flat, with colors ranging from a dull, pale yellow to normal tones, and microvasculature that runs from the periphery towards the center of the tumor (Fig. 2-5). Furthermore, during observation with narrow-band imaging and magnification, a mildly dilated crypt opening and slightly enlarged glands appear to support the presence of an OGN, especially in smaller lesions (Fig. 4). Xanthomas are examples of lesions that are endoscopically similar to OGNs in terms of color. However, their surface is finely granular, and they do not show dilation of microvessels. Conversely, although dilated microvessels are also observed on the surface of neuroendocrine tumors, these lesions are more hemispherical and often occur in a background of autoimmune gastritis, unlike OGN. Therefore, when a xanthoma-like lesion or a neuroendocrine tumor-like lesion is detected in the stomach without atrophy, the possibility of OGN should be

considered while conducting a careful optical examination.

***H. pylori* infection and PPI use**

Initially, OGNs were reported to be found only in patients uninfected by *H. pylori*; however, later reports revealed that they were also present in those who had been previously infected (27, 28).

Of the 27 patients in whom we found lesions, 18 (with 20 lesions) had a history of *H. pylori* infection and atrophic gastritis (Table 1). However, 17 of the 20 lesions were found in the non-atrophic areas. Similar to the reports by Chiba et al. and Tohda et al., the results of our research suggest that OGNs are tumors that are easily detected in endoscopic, non-atrophic regions, regardless of the history of *H. pylori* infection (27, 28).

It has also been reported that the histology of some OGN cases is similar to that of a fundic gland polyp (FGP) (4, 10). Since FGPs may occur with long-term PPI use, it has been suggested that there may be a relationship

Table 3. Pathological Characteristics of the Treated Lesions.

	n=18	%
En bloc resection rate		
ESD	6/6	100
EMRC	11/12	92
Complications		
Perforation	0	0
Postoperative bleeding	0	0
Pathological tumor size (mm)		
Mean	3.9	-
Median	3.5 [2-8]	-
Depth		
M	10	56
SM	8	44
Horizontal margin		
Positive	0	0
Negative	17	94
Unclear	1	6
Vertical margin		
Positive	0	0
Negative	17	94
Unclear	1	6
Vascular Invasion		
Yes	0	0
No	18	100
Lymphatic invasion		
Yes	0	0
No	18	100
MUC5AC		
Positive	2	11
Negative	16	89
MUC6		
Positive	17	94
Negative	1	6
Pepsinogen		
Positive	15	83
Negative	3	17
H ⁺ /K ⁺ -ATPase		
Positive	13	72
Negative	5	28
Ki-67 (%)		
Mean	2.2	-
Median	1 [1-8]	-

between the development of OGN and oral administration of PPI (19, 29). Chan et al. reported that, in a 12-case series, 7 patients had received acid suppressive therapy (6 with PPIs and 1 with H₂ blockers) (29). In our study, 37% (10/27) of patients were taking antacids (9 with PPIs and 1 with H₂ blockers) (median duration of administration: 646 [35-5,381] days) (Table 1). However, of these nine patients, only three had concomitant FGP, which calls into question the role of FGP in the pathogenesis of OGN.

Pathological findings

A pathological study showed that 10 lesions were con-

finied to the mucosa, whereas the remaining 8 (44%, 8/18) had infiltrated the submucosa. In this study, we did not find any atypia in the foveolar epithelium suggesting GA-FGM. In our cohort, the median size of intramucosal tumors was 3.9 mm, and the median size of the 8 submucosal infiltrating lesions was 5 (2-8) mm. Chiba et al. reported that 80% of 10 lesions in 9 patients who underwent ESD exhibited submucosal infiltration (median tumor diameter: 7 mm, width: 2-20 mm) (26). Thus, OGNs appear to be unique tumors that frequently infiltrate the submucosa, despite their very small size.

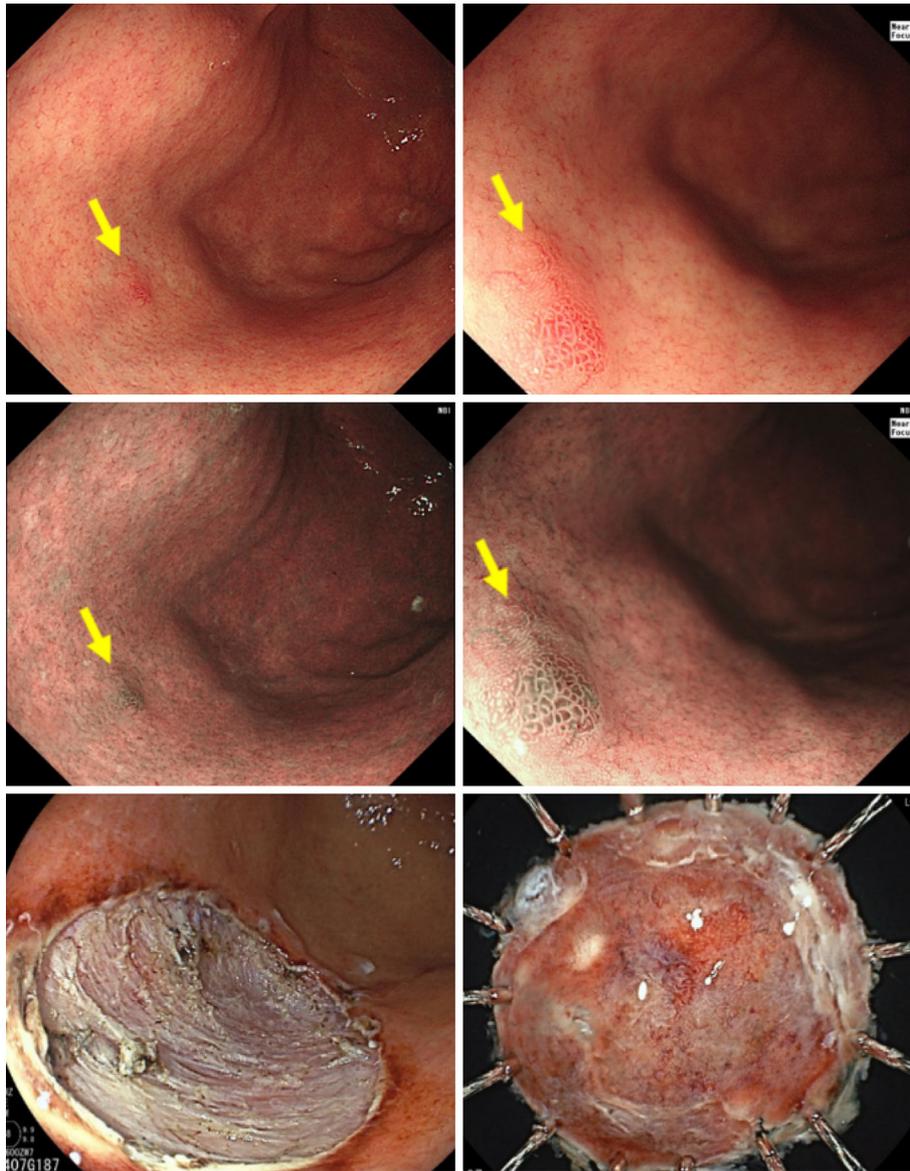
There is an ongoing discussion as to the relationship between OGA and GA-FG. In the WHO classification (Page 83, oxyntic adenoma section), the description states that “a morphological continuum” exists from OGA to GA-FG (8). In addition, Ueyama et al. proposed that OGA, GA-FG, and GA-FGM be regarded as gastric epithelial neoplasms of a fundic-gland mucosa lineage (10). They suggested that OGA and GA-FG were low-grade epithelial neoplasms and that OGA should be regarded as an intramucosal phase of GA-FG.

Furthermore, whether or not the submucosal extension of GA-FG is true invasion remains controversial. In the present study, no desmoplastic reaction at the advanced part of the tumor was observed in any of the eight cases with submucosal infiltration (Fig. 7). The Ki-67 labelling indexes were very low (median value: 1, width: 1-8) in all endoscopically resected OGNs (Table 3). This held true even in lesions with submucosal involvement. These findings may support the hypothesis that GA-FG shows prolapse-type infiltration of tumors (3, 9) rather than typical submucosal invasion. This may explain the lack of high-risk histologic features or metastatic disease in both our cohort and the available literature. Considering these findings, GA-FG without stromal reaction may be considered a prolapse-type change in OGA into the submucosa.

Treatment outcomes

Of the 27 patients (with 30 OGN) discovered in the outpatient setting, 17 (with 20 lesions) underwent endoscopic treatment at Kobe University Hospital. The remaining 10 patients selected conservative management; this cohort included patients whose lesions were too small to be certain of the presence of a residual lesion after a biopsy and those with a significantly advanced age. Of the 20 lesions managed endoscopically, 13 were treated by EMRC and 7 ESD. The en-bloc resection rates were high in both techniques (92% and 100% for EMRC and ESD, respectively) (Table 3). Given the simplicity and efficacy of EMRC, this may be the method of choice for treating these small lesions and avoiding the technical difficulty and time requirements of submucosal dissection. In two lesions there was no evidence of a residual tumor on the final histology, so we concluded that they had been completely resected at the time of the biopsy, given their small size.

In the present study, all of the OGNs with submucosal in-



a	b
c	d
e	f

Figure 6. An OGN resected by endoscopic submucosal dissection. (a) Conventional endoscopic image. A slightly elevated lesion was observed on the posterior wall of the fundus. The anal side in the lesion was reddish, and the glands were slightly enlarged. In addition, there seemed to be regenerative or post-inflammatory tissue from previous erosions. (b) Conventional endoscopic image with slight magnification. (c) Narrow-band imaging without magnification. (d) Narrow-band imaging with slight magnification. (e) Ulcer bed after the lesion was endoscopically resected en bloc. (f) The resected specimen.

filtration were endoscopically suspected to be intramucosal lesions prior to resection. We believe it is difficult to optically diagnose submucosal infiltration. OGNs frequently infiltrate the submucosa at a very small size. This may lend merit to the strategy of offering endoscopic resection to any

detected OGN, regardless of diameter. However, given the indolent nature of these lesions, there is also interest in conservative management (2, 14). In our present study, the eight patients with submucosal infiltration all elected to receive continued observation without additional surgical interven-

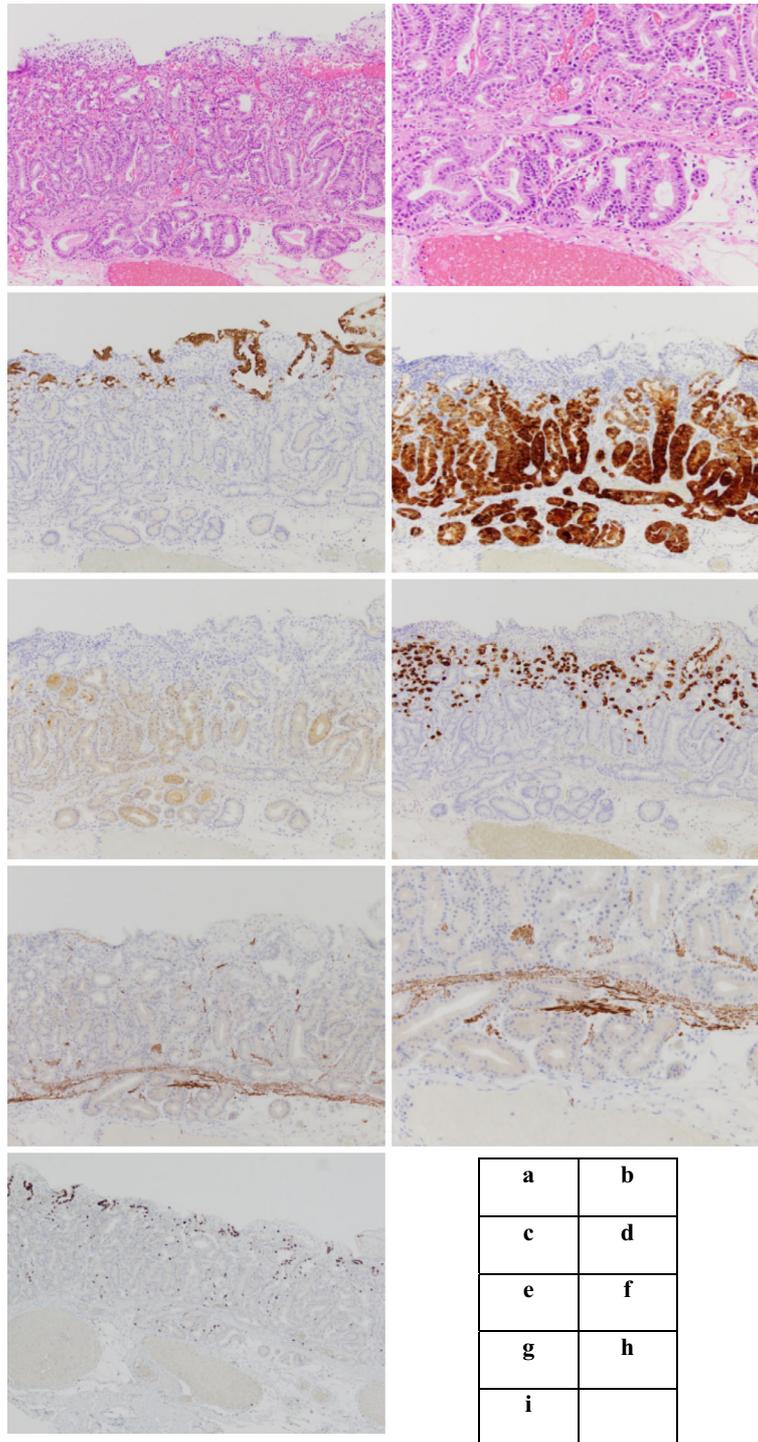


Figure 7. Histopathological findings of the OGN shown in Figure 6. (a) Hematoxylin and Eosin (H&E) staining (low-power field). The superficial layer was covered with non-neoplastic mucosa. Tumor glands proliferated mainly in the middle and deep layers of the mucosa. (b) H&E staining (high-power field). There were tumor glands below the muscularis mucosa. The advanced part of the tumor appeared to have slipped through the muscularis mucosa and infiltrated the submucosa. No desmoplastic reaction was observed at the advanced part of the tumor. (c) MUC5AC was positive only in non-neoplastic foveolar epithelial cells on the surface layer. (d) MUC6 was diffusely positive in the tumor. (e) Pepsinogen-I was also diffusely positive in the tumor in the middle and deep layers. (f) H⁺/K⁺-ATPase was positive in the vicinity of the glandular neck. (g) Desmin staining (low-power field) clearly showed where the muscularis mucosa was. (h) Desmin staining (high-power field) showed that the tumor had infiltrated the submucosa without destroying the muscularis mucosa. (i) The Ki-67 index was slightly positive in the tumor. The adjacent regenerative epithelium and inflammatory cells also seemed to have a positive Ki-67 index on the surface mucosa after erosion healing.

tion. Thus far, there has been no evidence of recurrence, although the long-term outcomes will need confirmation. The optimal management strategy for OGN is thus still under consideration.

Finally, we propose that OGA and GA-FG be collectively referred to as OGN. The primary reason for this is that the two entities appear to have significant clinical overlap. Second, distinguishing between OGA and GA-FG is often impossible endoscopically or with a biopsy specimen. Finally, the WHO classification and Japanese gastric cancer classification use the term “GA-FG” in different ways, which may add additional confusion to already complicated nomenclature.

Limitations

Several limitations associated with the present study warrant mention. First, this was a single-center retrospective study. The population was only 7,488 people, which may not be completely representative of the complete Japanese populace and may limit generalizability in certain cases. However, the average age of the patients in this study was only 67 years old. We therefore do not suspect the prevalence rate was falsely elevated due to a significantly elderly cohort. Second, our follow-up period may have been too limited to make definitive comments on recurrence rates and lymph node metastases. We are continuing to actively follow the patients in the cohort to further investigate these questions. Future multicenter studies including a larger database of cases will help document these seemingly rare occurrences. Third, this study was unable to fully investigate the relationship between oral PPI use and the development of OGNs. While we were able to confirm oral PPI use in patients diagnosed with OGNs, this must be compared to the usage rate in all patients who underwent endoscopy in the clinic. As the association between OGNs and PPI use has been a controversial topic, larger-scale prospective studies will be necessary to answer these questions.

Conclusion

Our study revealed the period prevalence of OGN to be 0.36%, which is much higher than previously reported in the literature. These lesions are frequently endoscopically managed with high success rates. Further investigation into the natural history, risk factors, and post-treatment prognosis is required.

The authors state that they have no Conflict of Interest (COI).

Statements

Author contributions

HA and TT collected the data, performed assessments, and wrote the manuscript. TT revised the manuscript as a corresponding author. YA, MA, DM, HS, TY, NI, MT, YM, TT, MK, RK, and YK revised the manuscript as co-authors. All authors read and approved the final manuscript.

Data availability

The datasets analyzed in this study are available from the corresponding author on reasonable request.

References

1. Tsukamoto T, Yokoi T, Maruta S, et al. Gastric adenocarcinoma with chief cell differentiation. *Pathol Int* **57**: 517-522, 2007.
2. Ueyama H, Yao T, Nakashima Y, et al. Gastric adenocarcinoma of fundic gland type (chief cell predominant type): proposal for a new entity of gastric adenocarcinoma. *Am J Surg Pathol* **34**: 609-619, 2010.
3. Singhi AD, Lazenby AJ, Montgomery EA. Gastric adenocarcinoma with chief cell differentiation: a proposal for reclassification as oxyntic gland polyp/adenoma. *Am J Surg Pathol* **36**: 1030-1035, 2012.
4. Park ES, Kim YE, Park CK, Yao T, Kushima R, Kim KM. Gastric adenocarcinoma of fundic gland type: report of three cases. *Korean J Pathol* **46**: 287-291, 2012.
5. Ueyama H, Matsumoto K, Nagahara A, Hayashi T, Yao T, Watanabe S. Gastric adenocarcinoma of the fundic gland type (chief cell predominant type). *Endoscopy* **46**: 153-157, 2014.
6. Miyazawa M, Matsuda M, Yano M, et al. Gastric adenocarcinoma of fundic gland type: Five cases treated with endoscopic resection. *World J Gastroenterol* **21**: 8208-8214, 2015.
7. Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma. 15th ed. Kanehara, Tokyo, 2017 (in Japanese).
8. Yao T, Vieth M; Oxyntic Gland Adenoma. Digestive System Tumours. In: WHO Classification of Tumours Editorial Board. World Health Organization Classification of Tumours. 5th ed. International Agency for Research on Cancer, World Health Organization, 2019: 83-84.
9. Ushiku T, Kunita A, Kuroda R, et al. Oxyntic gland neoplasm of the stomach; expanding the spectrum and proposal of terminology. *Mod Pathol* **33**: 206-216, 2020.
10. Ueyama H, Yao T, Akazawa Y, et al. Gastric epithelial neoplasm of fundic-gland mucosa lineage: proposal for a new classification in association with gastric adenocarcinoma of fundic-gland type. *J Gastroenterol* **56**: 814-828, 2021.
11. Ueyama H, Yao T, Matsumoto K, et al. Establishment of endoscopic diagnosis for gastric adenocarcinoma of fundic gland type (chief cell predominant type) using magnifying endoscopy with narrow-band imaging. *Stomach Intest* **50**: 1533-1547, 2015.
12. Ishibashi F, Fukushima K, Ito T, Kobayashi K, Tanaka R, Onizuka R. Influence of Helicobacter pylori Infection on Endoscopic Findings of Gastric Adenocarcinoma of the Fundic Gland Type. *J Gastric Cancer* **19**: 225-233, 2019.
13. Chen O, Shao ZY, Qiu X, Zhang GP. Multiple gastric adenocarcinoma of fundic gland type: A case report. *World J Clin Cases* **7**: 2871-2878, 2019.
14. Kino H, Nakano M, Kanamori A, et al. Gastric Adenocarcinoma of the Fundic Gland Type after Endoscopic Therapy for Metachronous Gastric Cancer. *Intern Med* **57**: 795-800, 2018.
15. Iwamuro M, Kusumoto C, Nakagawa M, et al. Endoscopic resection is a suitable initial treatment strategy for oxyntic gland adenoma or gastric adenocarcinoma of the fundic gland type. *Sci Rep* **11**: 7375, 2021.
16. Sato Y, Fujino T, Kasagawa A, et al. Twelve-year natural history of a gastric adenocarcinoma of fundic gland type. *Clin J Gastroenterol* **9**: 345-351, 2016.
17. Ueo T, Yonemasu H, Ishida T. Gastric adenocarcinoma of fundic gland type with unusual behavior. *Dig Endosc* **26**: 293-294, 2014.
18. Takahashi K, Ueno N, Sasaki T, et al. Long-term Observation of Gastric Adenocarcinoma of Fundic Gland Mucosa Type before and after Helicobacter pylori Eradication: a Case Report. *J Gastric*

- Cancer **21**: 103-109, 2021.
19. Benedict MA, Lauwers GY, Jain D. Gastric Adenocarcinoma of the Fundic Gland Type: Update and Literature Review. *Am. J. Clin. Pathol* **149**: 461-473, 2018.
 20. Okumura Y, Takamatsu M, Ohashi M, et al. Gastric Adenocarcinoma of Fundic Gland Type with Aggressive Transformation and Lymph Node Metastasis: a Case Report. *J. Gastric Cancer* **18**: 409-416, 2018.
 21. Yoshitake K, Kumashiro Y, Watanabe T, et al. Laparoscopic Gastrectomy for Gastric Adenocarcinoma of the Fundic Gland Type - Report of a Case. *Gan To Kagaku Ryoho* **43**: 1875-1877, 2016 (in Japanese).
 22. Kimura K, Takemoto T. An endoscopic recognition of the atrophic border and its significance in chronic gastritis. *Endoscopy* **1**: 87-97, 1969.
 23. Kamada T, Haruma K, Inoue K, et al. [Helicobacter pylori infection and endoscopic gastritis -Kyoto classification of gastritis]. *Nihon Shokakibyō Gakkai Zasshi* **112**: 982-993, 2015 (in Japanese).
 24. Haruma K, Kato M, Inoue K, et al. *Kyoto Classification of Gastritis*. 1st ed. Tokyo Japan: Nihon Medical Center, Tokyo, Japan, 2017.
 25. Inoue H, Kawano T, Tani M, et al. Endoscopic mucosal resection using a cap: techniques for use and preventing perforation. *Can J Gastroenterol* **13**: 477-480, 1999.
 26. Ono H. Endoscopic submucosal dissection for early gastric cancer. *Chin J Dig Dis* **6**: 119-121, 2005.
 27. Tohda G, Osawa T, Asada Y, et al. Gastric adenocarcinoma of fundic gland type: endoscopic and clinicopathological features. *World J Gastrointest Endosc* **8**: 244-251, 2016.
 28. Chiba T, Kato K, Masuda T, et al. Clinicopathological features of gastric adenocarcinoma of the fundic gland (chief cell predominant type) by retrospective and prospective analyses of endoscopic findings. *Dig Endosc* **28**: 722-730, 2016.
 29. Chan K, Brown IS, Kyle T, et al. Chief cell-predominant gastric polyps: a series of 12 cases with literature review. *Histopathology* **68**: 825-833, 2016.

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