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Clinicopathological features and incidence rate of oxyntic gland neoplasm: A single center retrospective study

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Article

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Abstract

In this retrospective study, we aimed to examine oxyntic gland neoplasms (OGNs) identified in patients visiting an internal medicine clinic over a 40-month follow-up period. Additionally, we wished to clarify the clinicopathological characteristics and frequency of occurrence of these lesions. From December 1, 2017 to March 31, 2021, we performed 13,240 upper gastrointestinal endoscopies on 7488 patients. Of these, we identified 27 patients with 30 histopathologically confirmed OGNs, yielding a disease frequency of 0.36% (27/7488). Further, in three of 27 patients (11%), multiple simultaneous lesions had occurred. One of the 30 lesions (3.3%) was present in the antrum. Nine of the 9 patients (33%) had no history of *Helicobacter pylori* infection, and remaining 18 (67%) were either currently or previously infected. However, 27/30 lesions (90%) occurred in non-atrophied regions. After endoscopic treatment, submucosal infiltration was observed in eight (47%) of the 17 lesions that underwent histopathological evaluations, which showed no submucosal desmoplasia in all eight cases. Additional resection was not performed while patient progress has been monitored. No cases of recurrence have been reported. In conclusion, we found that the frequency of oxyntic gland neoplasms was much higher than previously reported.

Background

Oxyntic gland neoplasm is a tumor that develops from cervical mucous cells and differentiates into two types of fundic gland cells (chief cells and parietal cells). In 2007, Tsukamoto et al. discovered a case of a well-differentiated adenocarcinoma of remnant cardia that had differentiated into the fundic glands, and reported the case of gastric adenocarcinoma with chief cell differentiation [1]. Ueyama et al. collected similar cases and proposed treatment under the name of gastric adenocarcinoma of fundic gland type (chief cell predominant type) in 2010 [2]. Subsequently, the first few cases of oxyntic gland neoplasms began to be reported as case reports and case series [3–6]. The Japanese Classification of Gastric Carcinoma, 15th Edition (2017) classified them as a special type of gastric cancer [7]. The 2019 WHO Classification of Gastric Carcinoma (Fifth edition) stated that among OGNs, lesions retained within the mucosa are deemed as oxyntic gland adenomas, whereas lesions demonstrating submucosal invasion are referred to as gastric adenocarcinomas of fundic-gland type (GA-FGs) [3, 8]. Reports of OGNs indicate that the *Helicobacter pylori* (*H. pylori*) infection rates of patients with this type of neoplasm are relatively low. Other characteristics include the primary occurrence in the non-atrophied areas of the upper stomach, where the color is pale yellow, with vascular dilation on the surface. In addition, as OGNs proliferate toward the bottom of the gland, the tumor surface is often covered with normal mucosa [9], and its morphology is also described as submucosal tumor-like [10]. In terms of immunostaining, this type of gastric tumor is positive for the chief-cell marker pepsinogen-I, parietal cell marker H+/K+-ATPase, and cervical mucous gland marker MUC6, and that it presents with the features of a gastric-type tumor [11–13]. However, most reports of the disease are small reports; the frequency of the disease, its relationship with oral proton pump inhibitor (PPI) use, the details of endoscopic images, the frequency of submucosal invasive cancer, and the rate of lymph node metastasis have not yet been

clarified. [8, 13–19]. The purpose of this study was to collect and examine cases of oxyntic gland neoplasm, and to clarify the clinicopathological features thereof, including disease frequency.

Results

A total of 13,240 upper gastrointestinal endoscopies were performed on 7488 patients. Of these, 27 patients with 30 lesions were newly pathologically diagnosed with OGNs between December 2017 and March 2021 (Figure 1). Thus, the disease frequency of OGNs was determined to be 0.36% (27/7488) per patient. The lesion discovery rate per examination administered was 0.23% (30/13240).

Table 1 summarizes the clinical characteristics of the patient in our cohort. Oral antacid use (proton pump inhibitors [PPI] and H2 blockers) was reported in 37% (10/27) of the patients at lesion discovery: PPI (n = 9) and H2-blocker (n = 1). The median duration of use was 646 days (35–5381 days). Of 9 patients who were taking PPI, three had fundic gland polyps simultaneously, while six did not. Regarding the trigger for the discovery, six of the above 30 lesions first underwent upper esophagogastroduodenoscopy (EGD), which revealed the oxyntic gland neoplasm for the first time. In patients who underwent follow-up EGDs, 22 lesions were detected. The remaining two cases were found as separate lesions during endoscopic treatment.

Table 2 summarizes the lesion characteristics. The endoscopic findings of the lesion were as follows. The color of the mucosa was normal/ yellow/ fading tone / red in 5, 12, 12 and 1 cases, respectively. The surface mucosal findings included a pale-yellow tone with dilated microvessels towards the center from the edge of the tumor, and slight dilation of the glandular duct (Figure 1). Pigmentation was observed in only one lesion (Figure 1 **(case 15)**). The biopsies of 26 lesions from the total of 30 were histopathologically diagnosed as OGNs. In two cases, endoscopic evaluation was necessary for diagnosing the lesions as OGNs, because of their small size making these specimens ineligible for biopsy to avoid loss of the tumor Endoscopic treatment was performed instead. In two other lesions, during endoscopic treatment, yellow masses were observed adjacent to the lesions under treatment, which were considered as OGNs with a high probability, and therefore endoscopically resected them without biopsy.

Table 3 summarizes the treatment and pathological characteristics of the lesions. The median pathological size (width) of the 17 lesions was 4 mm (2–8). The pathological depth of these 17 lesions was mucosal/sub-mucosal (M/SM) = (9/8). The median diameter of the pathological tumor with submucosal infiltration was 5 mm (2–8), and the distance from the lower end of the muscularis mucosae to the advanced tumor region was 40 to 950 μm. None of the 8 cases showed desmoplasia in the submucosa (Figure 2).

The *en bloc* resection rate of the 17 resected lesions was 100%, and the margin-negative *en bloc* resection rate was 100% (5/5) for ESD and 92% (11/12) for EMRC. There were no complications such as perforation or postoperative bleeding.

All patients with submucosal invasion were followed up without additional surgical resection.

Thirteen lesions in 13 patients diagnosed with OGNs had been previously imaged during endoscopy, but were not recognized as lesions by the endoscopists performing the procedure at the time. In addition, biopsies had already been collected from lesions at the time of the past EGD in four patients and four lesions, however, pathological diagnoses at that time were all Group 1.

Discussion

This was the first study to report the disease prevalence rate per patient among those undergoing endoscopy, which has great significance. We discovered 30 oxyntic gland neoplastic lesions in 27 patients over a 40-month period between December 2017 and March 2021 at the Asahara Clinic (a single facility). The rate of identification of these lesions per number of patients undergoing upper gastrointestinal endoscopy was 0.36% (27/7488). Second, our results showed that OGNs metastasized to adjoining areas in 11% of patients (3/27). While OGNs are characterized with early submucosal infiltration. In this study, despite locating the lesions being found while they were quite small with a median pathological size (width) of 5 mm (2–8), submucosal infiltration occurred in 47% (8 /17) of the lesions.

According to WHO Classification of Gastric Carcinoma (Fifth edition), the exact frequency of OGNs is unknown [8]. The previous report listed as a reference have reported a value of < 0.01% on the frequency of OGNs [24]. This 0.01% figure was calculated as the proportion of 30,182 individuals who underwent yearly check-up endoscopies during a period of 3 years and 11 months. However, this rate was not an accurate prevalence because some individuals underwent multiple screenings during the study period. We estimated the incidence of OGNs as 0.36% (27/7488) for the entire cohort of 7488 patients. Screening by experienced endoscopist with a high-definition endoscope might lead to more frequent detection of OGNs.

Thirteen lesions in 13 patients diagnosed with OGNs had been previously imaged during endoscopy. From this, we concluded that diagnosis of oxyntic gland neoplasm was difficult if an endoscopist and a pathologist performing the diagnosis were not familiar with both the endoscopic and histological images of the oxyntic gland neoplasm. Should endoscopists and pathologists become aware of OGNs, their identification/incidence rates would improve.

OGNs have been reported as slow-growing tumors [2] At the same time, cases of lymph node metastasis and OGNs with advanced cancer have also been reported [13, 14]. We should carefully examine each case such that these rare lesions are not missed during gastric screening.

It has been reported that the endoscopic image of the oxyntic gland neoplasm is a yellowish, gently rising elevated lesion characterized by dilation of microvessels on the surface [16]. The manifestations of these characteristics may vary based on the size of the oxyntic gland neoplasm. As the lesion grows, the above findings manifest. However, at the microlesion stage, its characteristics are as follows: the lesion is flat, its color ranges from a dull, pale yellow to normal color tones, and the microvasculature runs from the periphery of the tumor towards the center. Furthermore, we believe that during observation with narrow

band imaging (NBI) and magnification, a slightly dilated, circular crypt opening supports the presence of an oxyntic gland neoplasm (Figure 1).

Xanthomas are examples of lesions that are endoscopically similar to OGNs. Xanthomas are pale yellow in color, similar to OGNs. However, their surface is finely granular, and they do not involve dilation of microvessels, which distinguishes them from the endoscopic image of OGNs. Dilated images of microvessels are also observed on the surface of neuroendocrine tumors. However, neuroendocrine tumors are more hemispherical than oxyntic gland neoplasm and, unlike oxyntic gland neoplasm, often occur in a background of autoimmune gastritis.

When we recognize xanthoma-like lesions or neuroendocrine tumors in the stomach without atrophy, we should carefully examine them after considering oxyntic gland neoplasm in the differential diagnosis.

It has been reported that the histology of some oxyntic gland neoplasm cases was similar to that of a fundic gland polyp (FGP) [4]. Since edema-like FGP may occur with long-term PPI use, it has been pointed out that there may be a relationship between the development of oxyntic gland neoplasm and oral administration of PPI [16, 26]. Chan et al. reported that in a 12-case series, seven patients received acid suppressive therapy (six PPI and one H2 blocker) [26]. In our study, 37% (10/27) of patients were taking antacids (nine PPI and one H2 blocker) (median duration of administration 646 days (35-5381 days)) (**Table 1**). However, of the 9 patients who took antacids, FGP was found with oxyntic gland neoplasm in only three patients, and it was not clear whether FGP was related to the pathogenesis of OGNs.

Initially, OGNs were reported to be found only in stomachs uninfected by *H. pylori*, but later reports revealed that they were also discovered in stomachs that had already been infected with *H. pylori* [24, 25]. Of the 27 patients in whom we found lesions, 18 patients with 20 lesions had a history of *H. pylori* infection and atrophic gastritis (**Table 1**). Of the 20 lesions, 17 lesions were found in the non-atrophic region. Similar to the reports by Chiba et al. and Tohda et al., our research results suggest that the oxyntic gland neoplasm is a tumor that is easily detected in endoscopic non-atrophic regions, with or without a history of *H. pylori* infection. [24, 25].

For the two lesions without any cancer-specific histopathological findings after endoscopy, we concluded that they were completely resected at the time of biopsy because of their small size. Of the 19 lesions that underwent endoscopic treatment, 9 had remnant tumors in the mucosa; the remaining eight lesions had infiltrated the submucosa. The median pathological tumor size (width) of the eight submucosal infiltrating lesions was as small as 5 mm (2–8); this confirms that OGNs infiltrate the submucosa while still quite small. Chiba et al. reported that of the 10 lesions in nine patients who underwent ESD (median tumor diameter: 7 mm, width 2 to 20 mm), 80% of the lesions were SM infiltrated [25]. In this study, no desmoplastic reaction was observed at the advanced part of the tumor in all eight cases with submucosal infiltration (Figure 2). Therefore, we ascertained SM infiltration as a tumor prolapse. In WHO classification (on page 83, oxyntic adenoma part), the description says that “a morphological continuum exists from OGA to GA-FG. However, there is ongoing discussion as to whether OGA should be regarded

as an intramucosal component of GA-FG". Considering our results, GA-FG without stromal reaction could be regarded as the prolapse-type changes of OGA into the submucosa.

In this study, all the oxyntic gland neoplasm with SM infiltration were endoscopically diagnosed as intramucosal cancer, preoperatively. We believe it is difficult to endoscopically diagnose SM infiltration of OGNs before endoscopic treatment. OGNs infiltrate SM frequently at a very early stage and should be resected endoscopically as soon as they are discovered. Alternatively, since previous reports have reported that the malignant potential is low, it is necessary to wait for future case accumulation to determine whether follow-up is a good practice [2, 13]. In this study, eight patients with pathological diagnosis of SM infiltration were followed up without additional surgical resection in all patients. No recurrence was observed in all patients. However, in five of the eight cases, the period from the endoscopic treatment date to the final CT examination date was less than 1 year, and we believe that careful follow-up is required in the future.

Limitations

This study had several limitations. First, this was a single-center retrospective study, which may have led to selection bias that can be eliminated in future studies with a larger sample size. Such efforts will enable the evaluation of more generalizable disease prevalence rates. Nevertheless, no previous figures on the prevalence of OGNs per patient have been presented until now.

There is a need to identify if it is acceptable to follow-up patients with oxyntic gland neoplasm, considering its association with a high rate of submucosal invasion, without endoscopy. Further, research needs to be conducted on whether lymph node metastasis is extremely rare even if submucosal invasion occurs. Longer-term observations would adequately provide answers to these questions. Third, this study did not fully investigate the relationship between oral PPI use and the development of oxyntic gland neoplasms. We were able to confirm the use of oral PPIs in patients diagnosed with oxyntic gland neoplasms; however, we could not confirm the history of PPI use in all patients who underwent endoscopy elsewhere and, thus, could not compare the data. As the association between oxyntic gland neoplasm and PPI use has been a topic of controversy, more data collection is necessary.

In future studies, larger data from multiple institutions will help examine the rate of lymph node metastasis caused by the depth of oxyntic gland neoplasms that could be useful to establish appropriate treatment strategies.

Methods

We retrospectively evaluated the data of patients diagnosed by upper gastrointestinal endoscopy and biopsy, or post-endoscopic pathological evaluation as oxyntic gland neoplasms at Asahara clinic and examined their clinicopathological features. The study period was from December 2017, when the first case of oxyntic gland neoplasm was discovered the clinic, to March 2021. At this clinic, screening tests in

all cases were performed using a high-definition endoscope, such as the GIF-HQ290 (Olympus, Tokyo, Japan), or the GIF-H290Z (Olympus, Tokyo, Japan). All screening tests were observed after thoroughly cleaning the stomach using the waterjet function (OFR-2, Olympus, Tokyo, Japan). All the endoscopists had over 10 years' clinical experience.

All specimens used in this study were re-evaluated by a gastrointestinal pathologist, whose expertise included oxyntic gland neoplasm, to confirm that they were indeed cases of oxyntic gland neoplasms. In Japan, oxyntic gland neoplasms are considered low-grade cancer, and all patients diagnosed with these neoplasms were proposed for endoscopic treatment. All patients who requested endoscopic treatment were referred to Kobe University Hospital. After endoscopic treatment, a specialized pathological evaluation was performed by the Department of Diagnostic Pathology of Kobe University Graduate School of Medicine.

The lesion frequency of oxyntic gland neoplasms in our clinic was defined as the ratio of the number of patients with oxyntic gland neoplasms found at Asahara Clinic divided by the number of patients who underwent upper gastrointestinal endoscopy at the same clinic. With respect to the presence and/or spread of atrophic gastritis, area with faded gastric mucosa or with vascular transparency when observed under white light in routine endoscopic examination were defined as atrophic regions. The spread of atrophy was classified according to Kimura & Takemoto [19]. The presence or absence of *H. pylori* infection at the time of the lesion detection was evaluated by endoscopic findings of the background gastric mucosa according to the Kyoto classification [20]. Together with the results of their most recent urea breath test, patients' infection status was classified as naive, current, or previous [21]. In terms of endoscopic treatment, the endoscopic mucosal resection using a cap-fitted panendoscope (EMRC) method was performed in cases where the attending endoscopist judged that EMRC method could be used for margin-negative *en bloc* resection (complete R0 resection) based on the size and localization of the lesion [22]. Cases in which the attending endoscopist determined that the margin-negative *en bloc* resection was difficult by the EMRC method were treated by the endoscopic submucosal dissection (ESD) method [23]. On top of that, we reviewed the past endoscopic images in patients who had a history of EGD at our hospital before the discovery of the lesion.

Ethics Approval

This retrospective study was conducted in accordance with the ethical principles of the Declaration of Helsinki (Fortaleza revision) and in compliance with the ethical guidelines for medical and health research involving human subjects in Japan.

This study was approved by the institutional review board of Public Health Research Foundation (approval number: 21G0002). The requirement of informed consent to conduct the study was waived because the analysis used anonymous clinical data. We applied Opt-out method to obtain consent on this study by using the poster. The poster was also approved by the institutional review board. The authors have no conflicts of interest to declare.

Conclusion

We revealed that the disease frequency of oxyntic gland neoplasms was determined to be 0.36%. The frequency of oxyntic gland neoplasms was found to be much higher than previously reported.

Declarations

Author contributions

HA and TT gathered the data, performed assessments, and wrote the manuscript.

TT revised the manuscript as a corresponding author. YA, MA, TY, NI, MT, YM, TT, RK and YK revised the manuscript. 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.

Competing interests

The authors declare that they have no conflicts of interest.

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Tables

Tables 1 to 3 are available in the Supplementary Files section

Figures

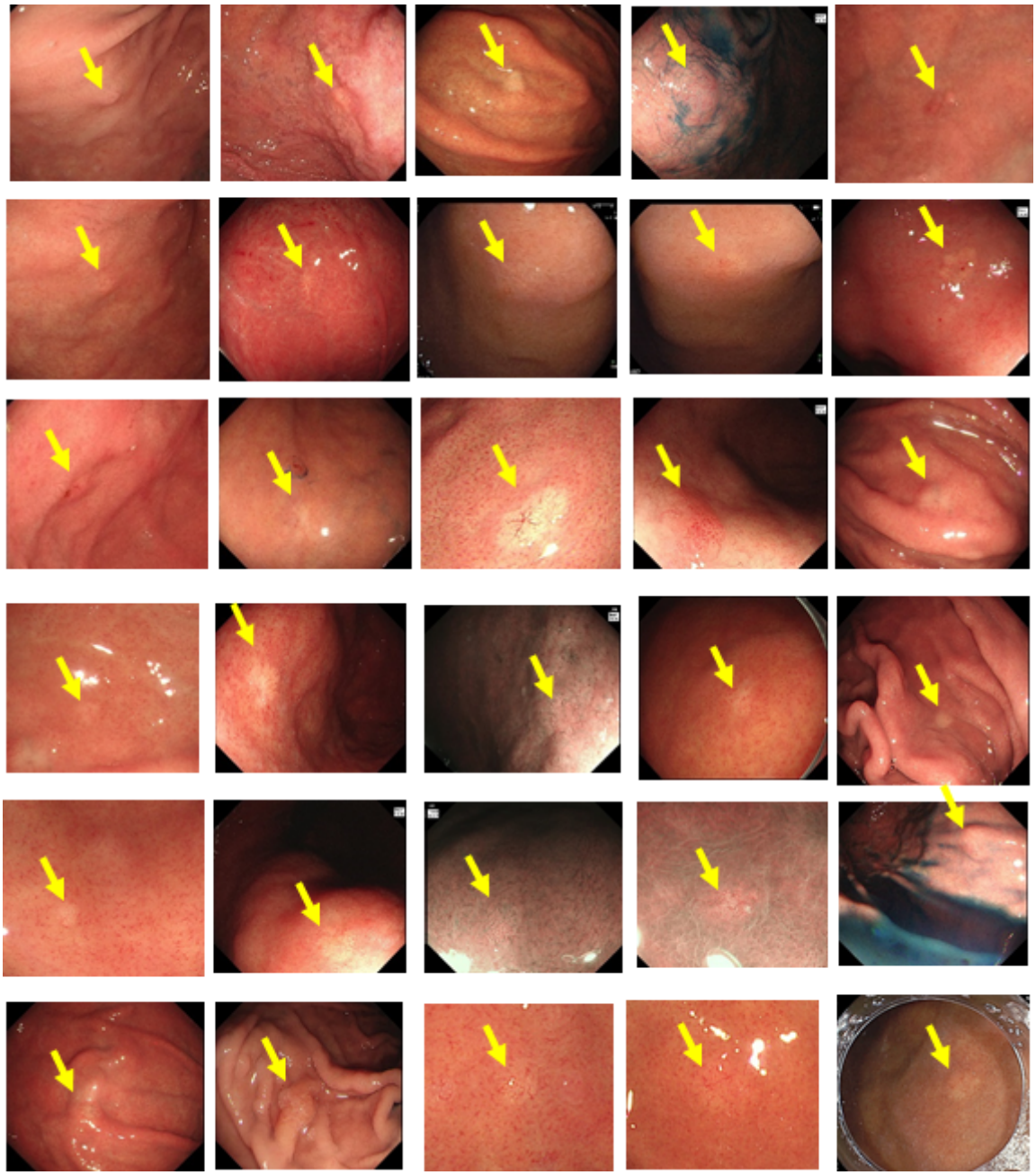

Figure 1

Endoscopic images of all the lesions

Numbers denote case numbers. Cases 8 and 9, 12 and 13, and 17 and 18 are multiple lesions from one patient. The lesions are indicated by yellow arrows.

Case 1	Case 2	Case 3	Case 4	Case 5
Case 6	Case 7	Case 8	Case 9	Case 10
Case 11	Case 12	Case 13	Case 14	Case 15
Case 16	Case 17	Case 18	Case 19	Case 20
Case 21	Case 22	Case 23	Case 24	Case 25

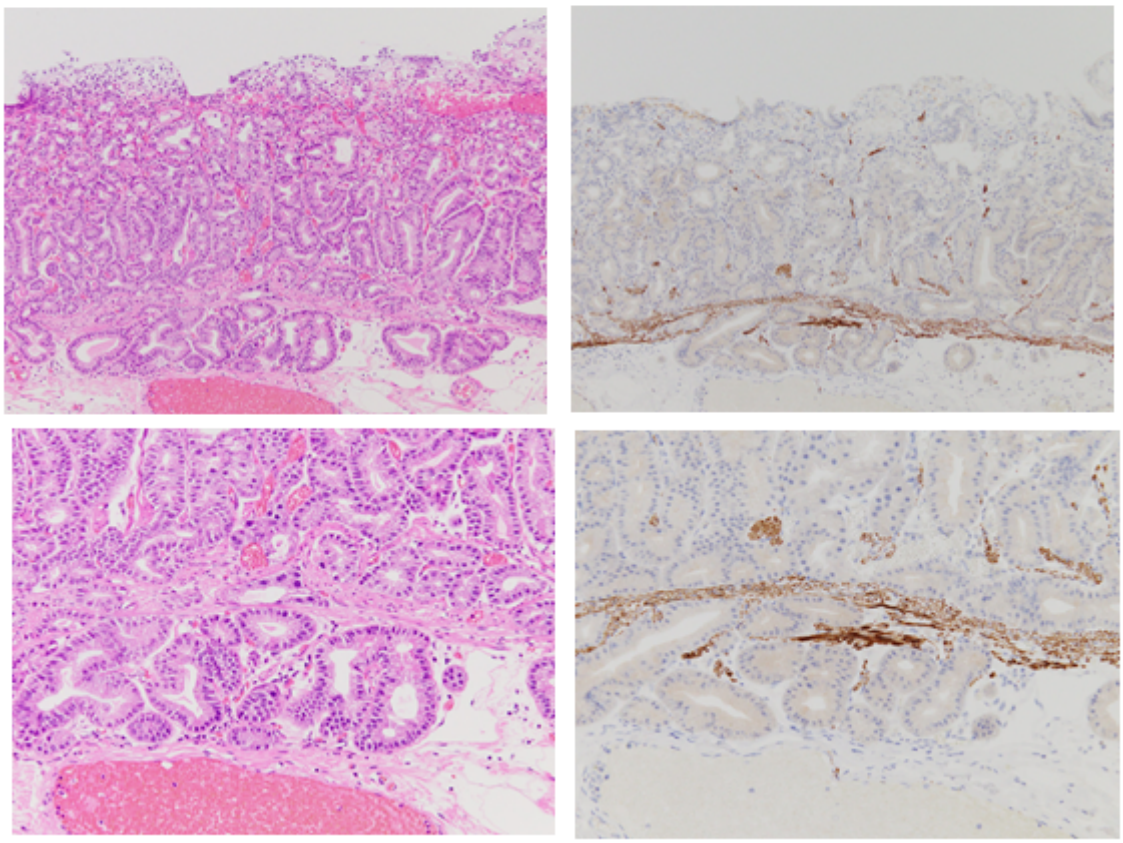

Figure 2

Example of submucosal infiltration of oxyntic gland neoplasm (**Figure 1**, case 14)

Figure 2a: Hematoxylin and eosin (H.E.) staining. Low magnification view shows the advanced part of the tumor in the submucosal layer.

Figure 2b: Desmin staining of the region described in Figure 2a.

Figure 2c: H.E. staining. Moderate magnification view shows absence of desmoplasia in the submucosa.

Figure 2d: Desmin staining of the region described in Figure 2c.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table13202203121.xlsx