

## Magnified Endoscopic Features of Duodenal Follicular Lymphoma and Other Whitish Lesions

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The sensitivity and specificity of magnified endoscopic features for differentiating follicular lymphoma from other diseases with duodenal whitish lesions have never been investigated. Here we compared the magnified endoscopic features of duodenal follicular lymphoma with those of other whitish lesions. We retrospectively reviewed the cases of patients with follicular lymphoma (n = 9), lymphangiectasia (n = 7), adenoma (n = 10), duodenitis (n = 4), erosion (n = 1), lymphangioma (n = 1), and hyperplastic polyp (n = 1). The magnified features of the nine follicular lymphomas included enlarged villi (n = 8), dilated microvessels (n = 5), and opaque white spots of various sizes (n = 9). The lymphangiectasias showed enlarged villi, dilated microvessels, and white spots, but the sizes of the white spots were relatively homogeneous and their margin was clear. Observation of the adenoma and duodenitis revealed only whitish villi. Although the lymphangioma was indistinguishable from the follicular lymphomas by magnified features, it was easily diagnosed based on the macroscopic morphology. In conclusion, magnified endoscopic features, in combination with macroscopic features, are useful for differentiating follicular lymphomas from other duodenal diseases presenting whitish lesions.

**Key words:** duodenal neoplasm, follicular lymphoma, gastrointestinal lymphoma, magnifying endoscopy

The gastrointestinal tract can be affected by follicular lymphomas as a primary site or due to secondary extranodal involvement from a nodal origin. It is well known that of all of the gastrointestinal tract sites, the duodenum is the most frequently affected by follicular lymphomas [1-4]. Duodenal involvement of a follicular lymphoma is an uncommon disease entity, although the number of patients newly diagnosed with this disease is increasing. For example, a report from

Europe stated that duodenal follicular lymphoma had been diagnosed at the rate of once per 3,000 to 7,000 gastroduodenoscopies [5]. Despite its infrequency, duodenal follicular lymphoma is now widely noted among endoscopists and hematologists, because it seems to have some clinical features that are distinct from those of follicular lymphomas of nodal origin. The results of several studies suggest that follicular lymphoma arising in the duodenum is a remarkably indolent variant [4-8]. In this context, the prompt

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and appropriate diagnosis of duodenal lesions of follicular lymphomas by endoscopic examination is essential.

Small whitish granular lesions involving the duodenal second portion constitute the distinctive endoscopic findings of intestinal follicular lymphoma. Recent advances in magnifying endoscopy have also provided more detailed features: opaque whitish spots, enlarged villi, and a dilated vascular pattern within the villi have been reported by several authors as characteristic images of intestinal follicular lymphoma [9–15]. Although it can be speculated that these microstructures would be useful in terms of the differential diagnosis of follicular lymphoma from other diseases, no study has been conducted to investigate their diagnostic impact, to our knowledge. In the present study, to reveal the microstructures that are specific to each pathologic entity, we comparatively analyzed the magnified endoscopic features of duodenal follicular lymphomas and other diseases featuring whitish lesions in the duodenum.

### Patients and Methods

We enrolled patients with duodenal whitish lesions who underwent magnifying endoscopy and biopsy for whitish lesions at Okayama University Hospital or Onomichi Municipal Hospital between January 2008 and January 2013. Diagnoses were made histologically based on morphologic and, if necessary, immunophenotypic analyses of endoscopically biopsied specimens. The diagnosis of follicular lymphoma was made according to the World Health Organization (WHO) classifications [1, 16]. Histopathological grading was also determined according to the WHO criteria [1].

A total of 33 patients were enrolled in this study. The pathological diagnosis of the duodenal whitish lesions included follicular lymphoma ( $n=9$ ), lymphangiectasia ( $n=7$ ), adenoma ( $n=10$ ), duodenitis ( $n=4$ ), erosion ( $n=1$ ), lymphangioma ( $n=1$ ), and hyperplastic polyp ( $n=1$ ). The magnified endoscopic features of these lesions were retrospectively reviewed by board-certified endoscopists (authors M.I. and H.O.).

This retrospective study was approved by the institutional ethical review board of the Okayama University Graduate School of Medicine, Dentistry

and Pharmaceutical Sciences (no. 745).

### Results

The histopathological grade of the duodenal follicular lymphoma lesions was grade 1 in all 9 of the patients whose pathological diagnosis was follicular lymphoma. The patients with follicular lymphoma lesions included primary intestinal follicular lymphoma cases (clinical stage I in the Lugano system,  $n=7$ ) and systemic follicular lymphoma with duodenal involvement (clinical stage IV in the Lugano system,  $n=2$ ). The magnified features of the duodenal lesions of these follicular lymphoma cases included whitish villi ( $n=9$ , 100%), enlarged villi ( $n=8$ , 89%), elongated microvessels ( $n=5$ , 56%), and opaque white spots of various sizes ( $n=9$ , 100%) (Fig. 1). These white spots were flat in 5 cases (56%) and granular in 4 cases (44%).

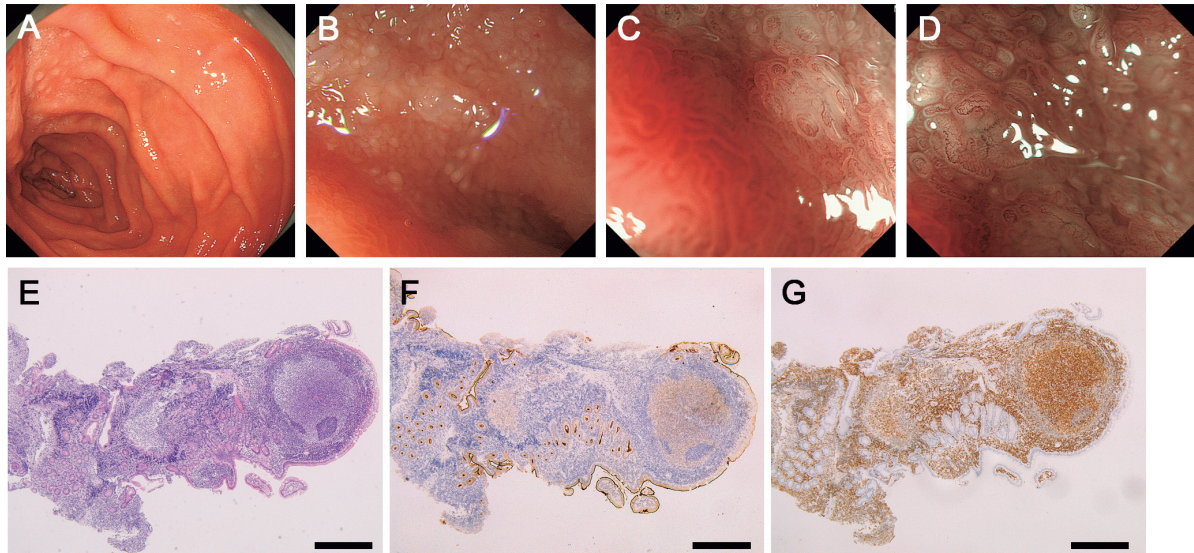
Representative endoscopic images and histological images of other diseases are illustrated in Fig. 2–4. One case of lymphangioma also presented with enlarged villi, elongated microvessels, and flat opaque white spots (Fig. 3D–F). However, this case was macroscopically diagnosed as lymphangioma based on the morphology of the submucosal tumor. The magnified features of the 7 cases of lymphangiectasia included enlarged villi ( $n=7$ , 100%), dilated microvessels ( $n=7$ , 100%), and white spots ( $n=7$ , 100%). The white spots of the lymphangiectasias were of relatively homogeneous size, and their margin was clear (Fig. 3A–C).

In contrast, only whitish villi were observed by magnifying endoscopy in the cases of adenoma ( $n=10$ , 100%; Fig. 2A–C), duodenitis ( $n=4$ , 100%; Fig. 4A–F), and hyperplastic polyp (Fig. 2D–F). Enlarged villi, dilated microvessels, and white spots were not observed in the adenoma, duodenitis, or hyperplastic polyps. Duodenal erosion showed the disappearance of the villous structure and infiltration of inflammatory cells (Fig. 4G–I).

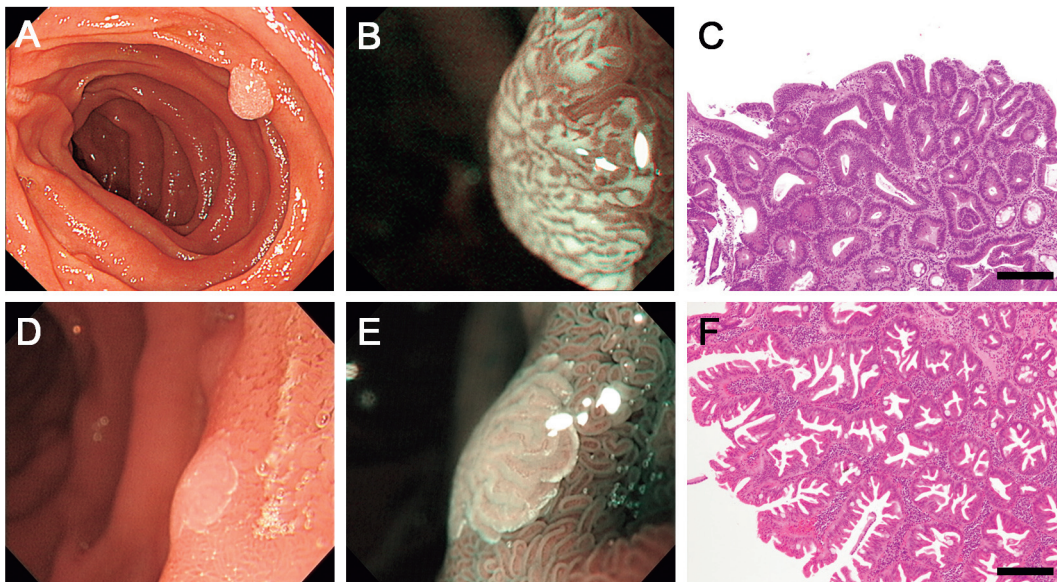
The magnified endoscopic features of each disease are summarized in Table 1.

### Discussion

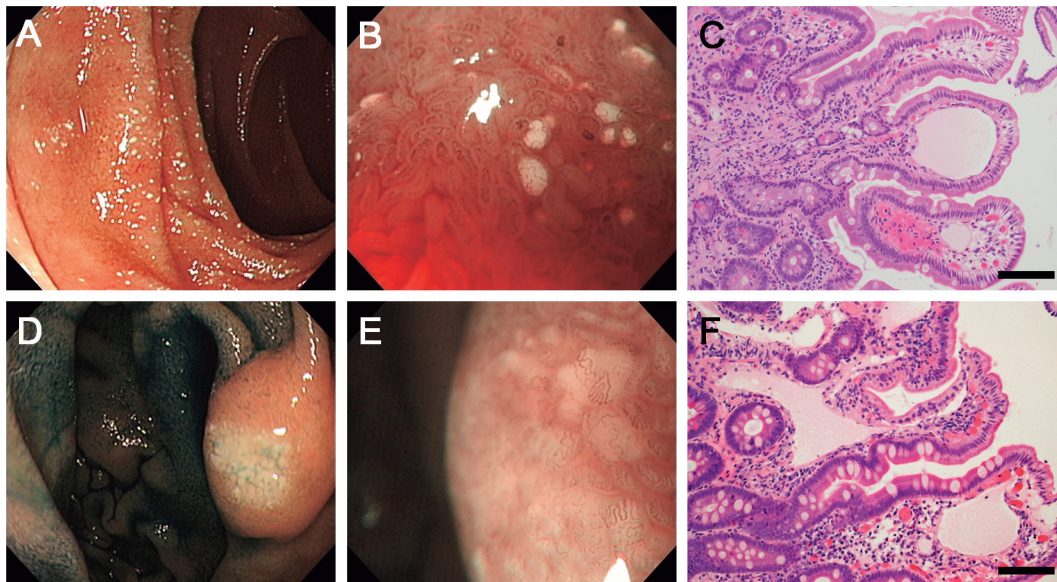
The reported features of duodenal follicular lymphomas in endoscopic magnifying observations include



**Fig. 1** A patient with a duodenal follicular lymphoma that presented with relatively tiny lesions (67-year-old male, Lugano stage I). **A**, Esophagogastroduodenoscopy revealed whitish granules around the ampulla of Vater; **B**, Magnified view showed tiny white depositions and enlarged whitish villi; **C**, Narrow-band imaging emphasized opaque white spots with slight elevation, elongated microvessels; and **D**, enlarged villi; **E**, Pathologically, lymphoma cells infiltrated the duodenal villi, which formed lymphoid follicles (hematoxylin and eosin staining); **F**, Lymphoma cells were positive for CD10 and **G**, CD20. Scale bars = 500  $\mu$ m (E-G).



**Fig. 2** Patients with duodenal adenoma (A-C, a 57-year-old female) and hyperplastic polyp (D-F, a 61-year-old male). **A**, A duodenal adenoma was observed as a solitary whitish polyp; **B**, Magnified view with narrow-band imaging showed whitish villi; **C**, Atypical epithelial cells forming hyperplastic glandular structures were identified pathologically; **D**, The hyperplastic polyp was presented as a whitish lesion with slight elevation; **E**, A magnified view with narrow-band imaging emphasized whitish mucosa; **F**, In the biopsied specimen, hypertrophic glands without epithelial atypia were seen. Scale bars = 200  $\mu$ m (C, F).



**Fig. 3** Patients with lymphangiectasia (A-C, a 76-year-old male) and lymphangioma (D-F, a 65-year-old male). **A**, The typical endoscopic findings of lymphangiectasia were white dots; **B**, A magnified view with narrow-band imaging revealed whitish depositions with round and clear margins. Some of the duodenal villi were enlarged. Elongated microvessels were also seen; **C**, Dilated lymphatic structures were confirmed pathologically; **D**, Lymphangioma appeared as a soft submucosal tumor with white spots. The details of this case were reported previously (17); **E**, The elongated microvessels were more clearly visualized by narrow-band imaging; **F**, Multiple dilated lymphatic structures were detected in the biopsy specimen. Scale bars = 200 $\mu$ m (C, F).

**Table 1** Summary of the magnified endoscopic features of the duodenal whitish lesions

	n	Whitish villi	White spots of various sizes with unclear margin	White spots of homogenous sizes with clear margin	Enlarged villi	Elongated microvessels	Loss of villous structure
Follicular lymphoma	9	9 (100%)	9 <sup>a</sup> (100%)	—	8 (89%)	5 (56%)	—
Lymphangiectasia	7	7 (100%)	—	7 (100%)	7 (100%)	7 (100%)	—
Adenoma	10	10 (100%)	—	—	—	—	—
Duodenitis	4	4 (100%)	—	—	—	—	—
Erosion	1	—	—	—	—	—	1 (100%)
Lymphangioma	1	1 (100%)	1 <sup>b</sup> (100%)	—	1 (100%)	1 (100%)	—
Hyperplastic polyp	1	1 (100%)	—	—	—	—	—

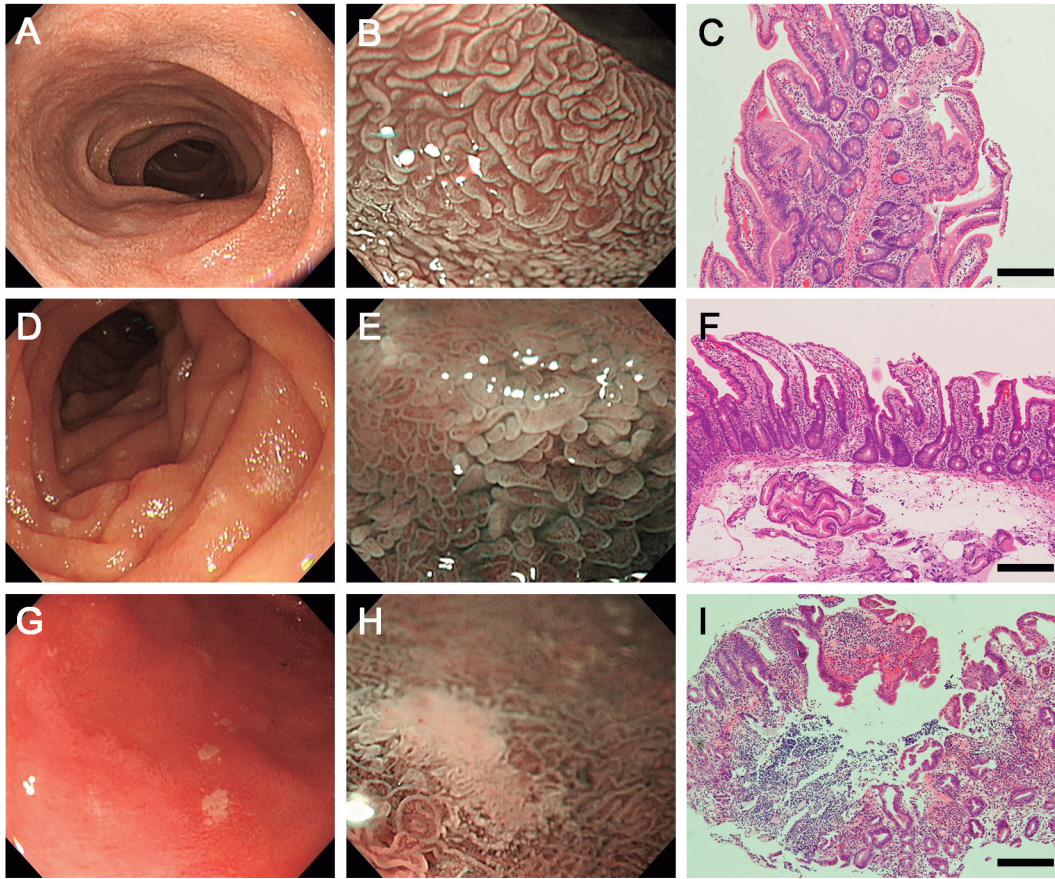
<sup>a</sup>Elevated (n = 5, 56%) or flat (n = 4, 44%) white spots. <sup>b</sup>Flat white spots.

opaque whitish spots, enlarged villi, and a dilated vascular pattern within the villi. The results of our present study further revealed that (i) whitish villi can frequently be seen in both follicular lymphomas and other whitish lesions, (ii) enlarged villi and elongated microvessels can be observed in lymphangiectasias and lymphangiomas as well as follicular lymphomas, and (iii) the white spots that we observed in the follicular lymphomas and lymphangiomas were of various sizes with unclear margins, whereas the white spots of the

lymphangiectasias were of homogenous sizes with clear margins.

Taken together, our findings led us to consider that a combination of magnified features such as white spots of various sizes with unclear margins, enlarged villi, and elongated microvessels is probably useful for the differentiation of follicular lymphomas from other whitish lesions, except for lymphangiomas.

Because these features were also identified in lymphangiomas, a distinction between follicular lymphangiomas

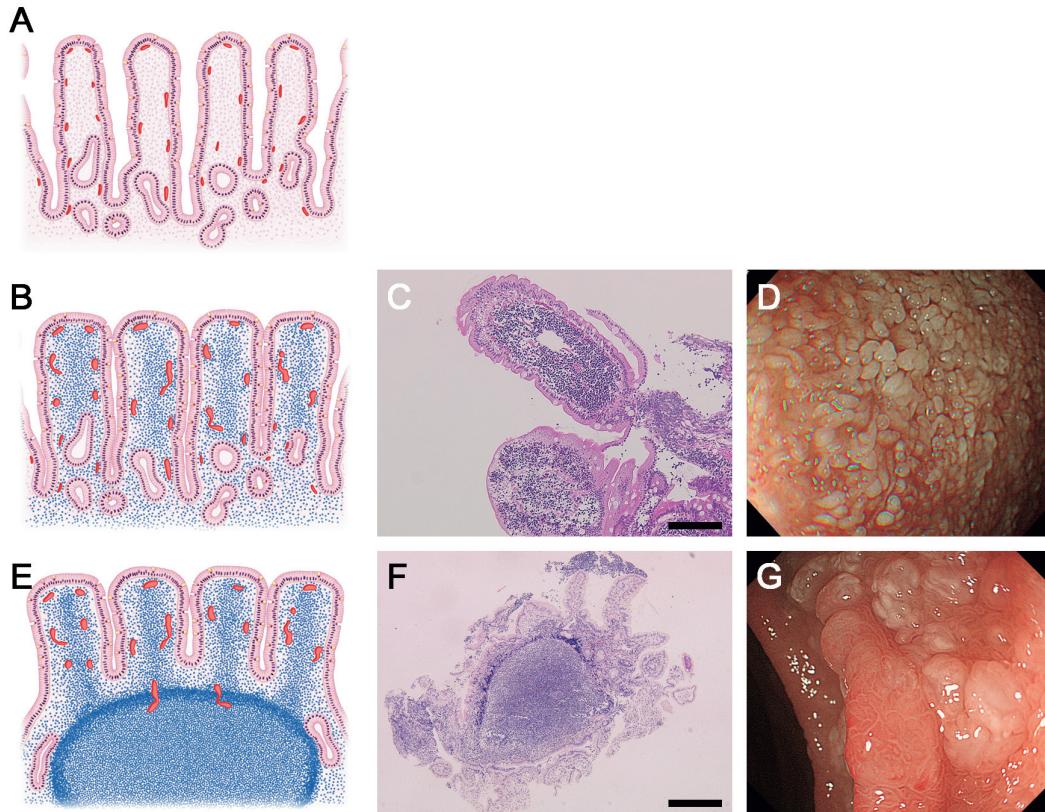


**Fig. 4** Patients with duodenitis (A–C, a 50-year-old male, D–F, a 65-year-old female) and erosion (G–I, a 75-year-old male). **A**, The color of the duodenal mucosa was diffusely whitish; **B**, A magnified view with narrow-band imaging showed whitish duodenal villi; **C**, An infiltration of inflammatory cells was observed pathologically; **D**, In another case with duodenitis, multiple patchy whitish areas were seen; **E**, A magnified view showed whitish duodenal villi as well; **F**, In this case, the biopsied specimen contained submucosal edema, in addition to the inflammatory cell infiltration; **G**, The duodenal erosion also appeared as patchy whitish areas; **H**, Magnifying endoscopy revealed the loss of villous structure; **I**, Disappearance of the villous structure and infiltration of inflammatory cells were pathologically confirmed. Scale bars = 200 $\mu$ m (C, F, I).

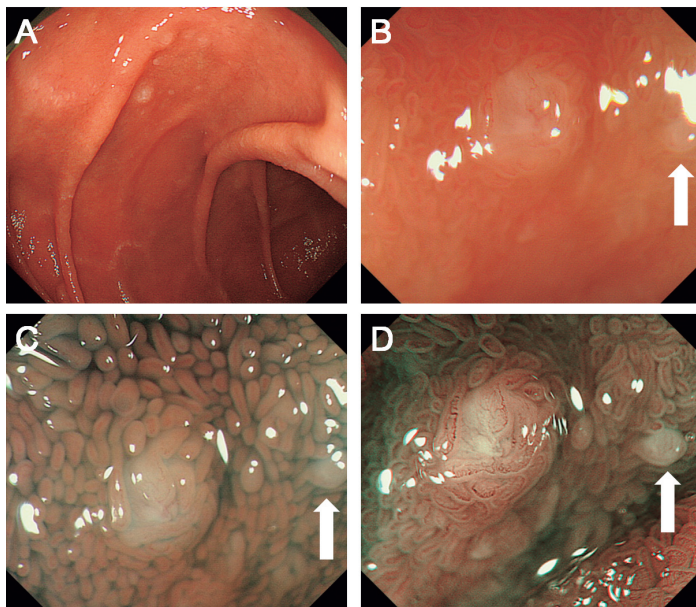
phoma and lymphangioma by endoscopic magnifying observation may be impossible. However, we speculate that the differential diagnosis of lymphangioma and follicular lymphoma will not turn into a clinical issue, because lymphangiomas are easily diagnosed based on the macroscopic morphology. Duodenal lymphangiomas generally appear as submucosal tumors, as also found in the present study [17]. Consequently, we consider that a combination of macroscopic appearance and magnified observation of microstructures will enable the exact endoscopic diagnosis of follicular lymphomas.

We speculate that such characteristic endoscopic features of duodenal follicular lymphomas reflect the

underlying pathological structure. Typical pathologic features of duodenal follicular lymphoma include neoplastic cells infiltrating the villi and lymphoid follicles (Fig. 5). Enlarged whitish villi may result from the deposition of lymphoid cells in the villi. Infiltrating neoplastic cells may also disturb the perfusion of microvessels in the villi and result in the dilatation of vessels [16]. Opaque white spots appear to be formed by lymphoid follicles deposited within the mucosa or submucosa. We believe that a better understanding among endoscopists of the pathology and the microstructures will improve the detection rate and eventually enable prompt diagnoses of duodenal follicular lymphomas.



**Fig. 5** Schematic diagram of pathologic features of duodenal follicular lymphoma. **A**, Normal mucosa; **B**, In duodenal follicular lymphoma, lymphoma cells infiltrate the duodenal villi and cause the enlargement of the villi. Infiltrating neoplastic cells may also disturb the perfusion of microvessels in the villi and result in the dilatation of vessels; **C**, Pathological image; **D**, Enlarged whitish villi; **E**, Lymphoid follicles formed by lymphoma cells are also a typical feature of follicular lymphoma; **F**, Pathological image of lymphoid follicle; **G**, Lymphoid follicles are seen as opaque white depositions. Scale bars = 200  $\mu$ m (C, F).



**Fig. 6** Endoscopic images of a primary duodenal follicular lymphoma. **A**, Esophagogastroduodenoscopy showed several tiny whitish lesions in the second portion of the duodenum, but the lesions were less noticeable; **B**, Endoscopic magnified observation revealed enlarged villi (arrow), in addition to opaque whitish spots; **C**, Endoscopic magnified observation after indigo carmine dye spraying; **D**, A magnified view with narrow-band imaging showed the opaque whitish spots and enlarged villi (arrow) more clearly. These microstructures facilitated the diagnosis of follicular lymphoma. Scale bars = 50  $\mu$ m (C) and 200  $\mu$ m (F).

Multiple dilated lymphatic structures within the villi are discriminative pathological findings of lymphangiectasia and lymphangioma. In these disease entities, duodenal villi are dilated and the microvessels are stretched due to the retention of chyle in the lymphatic structures [17]. Retained chyle is observed as a white deposition in the duodenal mucosa. In the present study, the magnifying endoscopy of the seven lymphangiectasias detected enlarged villi, elongated microvessels, and white spots with clear margins. The size of the white spots was relatively homogeneous. Therefore, we consider that lymphangiectasia can be endoscopically distinguished from follicular lymphomas by the homogeneous size and clear margin of the white spots. In contrast, although the single lymphangioma showed irregularly shaped white spots with unclear margins (which resembled magnified features of follicular lymphoma), it could be macroscopically distinguished from the follicular lymphoma lesions based on the submucosal tumor appearance.

Duodenitis is pathologically characterized by the infiltration of inflammatory cells. In our study, the biopsied specimens obtained from 2 of the 4 cases with duodenitis also had edema in the mucosal layer ( $n = 1$ ) or submucosal layer ( $n = 1$ ). We speculate that infiltrated inflammatory cells, in addition to the mucosal/submucosal edema, are responsible for the whitish villi observed by endoscopy. In the duodenal erosion, we observed endoscopically and pathologically that the villous structure had vanished. Infiltrated inflammatory cells in the erosion might be recognized as a whitish area by endoscopy. A proliferation of atypical epithelial cells forming hypertrophic glandular structures is pathologically seen in duodenal adenomas. In the hyperplastic polyp examined in the present study, we observed hyperplasia of the duodenal gland with intact epithelial cells. Such hyperplasia of the glandular structure or a cellular arrangement of higher density than that of the normal structure might result in whitish mucosa. The precise mechanism producing the whitish mucosa in adenomas and hyperplastic polyps remains to be revealed.

We found that the magnified observation of microstructures is useful to detect and differentiate intestinal follicular lymphoma from other whitish lesions, particularly in cases presenting tiny lesions or atypical macroscopic features. Fig. 6 is endoscopic images of a 59-year-old woman diagnosed with primary duodenal

follicular lymphoma. Esophagogastroduodenoscopy showed several whitish lesions in the second portion of the duodenum, but the lesions were less noticeable because of their unobtrusive appearance (Fig. 6A). Endoscopic magnified observation revealed enlarged villi (Fig. 6B–D, arrows), in addition to opaque whitish spots. Thus, these microstructures facilitated the endoscopic diagnosis of follicular lymphoma.

Our endoscopic magnified observation of another patient with duodenal follicular lymphoma revealed confluent whitish granules in the duodenum, distinct from the nodules or polyps that are typical findings of intestinal follicular lymphoma [15]. In this case, magnifying endoscopy with narrow-band imaging was also helpful for a prompt diagnosis, revealing whitish enlarged villi in an elongated and coiled vascular pattern. Consequently, we believe that magnified observation is a valuable technique for the prompt endoscopic diagnosis of intestinal follicular lymphoma.

There are several limitations associated with this study. First, the sample size was small; a total of 33 patients, including nine with follicular lymphoma and 24 cases with other diseases. Such a small sample size resulted from the nature of the study design. We enrolled pathologically diagnosed cases, although biopsy is generally not done for non-neoplastic diseases (*e.g.*, lymphangiectasia, lymphangioma, duodenitis and erosion); biopsies are performed only for suspected neoplastic diseases (*e.g.*, adenoma and follicular lymphoma). The relatively low prevalence of follicular lymphoma and adenoma is another reason for the small sample size. A larger sample size that would enable the statistical comparison of each microscopic feature between diseases is desirable. Second, because this was a retrospective study, it is not known how the magnified observation facilitated the endoscopic diagnoses. We believe that prospective multicenter studies will reveal whether the examination of magnified endoscopic features will be effective for differentiating follicular lymphoma from other whitish lesions.

In conclusion, magnifying endoscopy provides characteristic findings of duodenal follicular lymphoma. Although the majority of duodenal follicular lymphomas present with typical endoscopic features of whitish granular lesions, several cases have reportedly shown different morphologies [15, 18]. In such cases, we believe magnified endoscopic features, in combination with macroscopic features, are useful for

differentiating follicular lymphoma from other whitish lesions. Moreover, magnified endoscopic features may be helpful for the detection of small follicular lymphoma lesions, which would enable prompt diagnoses at earlier stages.

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