

Case Report

## Detection of Minute Duodenal Follicular Lymphoma Lesions Using Magnifying Endoscopy

Masaya Iwamuro<sup>a,b\*</sup>, Eisei Kondo<sup>a</sup>, Fumio Otsuka<sup>a</sup>, Katsuyoshi Takata<sup>c</sup>,  
Tadashi Yoshino<sup>c</sup>, Yoshiro Kawahara<sup>d</sup>, and Hiroyuki Okada<sup>b,d</sup>

Departments of <sup>a</sup>General Medicine, <sup>b</sup>Gastroenterology and Hepatology, <sup>c</sup>Pathology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, <sup>d</sup>Department of Endoscopy, Okayama University Hospital, Okayama 700-8558, Japan

Esophagogastroduodenoscopy revealed small duodenal lesions in a 56-year-old Japanese man and a 92-year-old Japanese woman with stage IV follicular lymphoma. Magnifying endoscopy examination revealed tiny white deposits in the second duodenal portion of the former patient and slightly enlarged duodenal villi in the latter. In both cases, biopsy revealed infiltration of follicular lymphoma cells and incipient formation of neoplastic follicles. Here, we discuss the usefulness of magnifying endoscopy and narrow-band imaging for the detection of small duodenal lesions in follicular lymphoma cases.

**Key words:** intestinal follicular lymphoma, duodenal neoplasms, gastrointestinal endoscope, narrow-band imaging

Endoscopic images of intestinal follicular lymphoma typically portray small whitish granular lesions in the second duodenal portion [1–3]. Developments in magnifying endoscopy technology have enabled the visualization of more detailed features such as opaque whitish spots and enlarged whitish villi as the distinctive endoscopic findings of intestinal follicular lymphoma [4–9]. These magnified endoscopic features appear to be useful for the recognition of subtle follicular lymphoma lesions.

We recently experienced 2 cases of stage IV follicular lymphoma of nodal origin involving the duodenum. Duodenal involvement presented as tiny whitish lesions in both cases that were initially considered insignificant changes unrelated to the lymphoma due to their subtle appearance. However, magnifying observation revealed small whitish deposits in one case and

slightly enlarged whitish villi in the other. Narrow-band imaging enabled easier recognition of these lesions. Biopsy examinations of the lesions in both patients showed follicular lymphoma cell infiltration. To our knowledge, the endoscopic images shown herein present the smallest duodenal lesions reported to date. These cases underscore the importance of narrow-band imaging and magnifying observation for the detection of minute duodenal lesions in systemic follicular lymphoma patients.

### Case Report

**Case 1.** A 56-year-old Japanese man with stage IV follicular lymphoma was referred to our hospital for further investigation and treatment. Computed tomography (CT) scanning revealed swelling of the parotid, submandibular, and mediastinal lymph nodes. Positron

emission tomography (PET) scanning showed tracer uptake in the spleen and iliac bone as well as in the swollen lymph nodes. There were no abnormalities in the gastrointestinal tract on CT or PET scans, and the patient had no gastrointestinal symptoms. The patient was diagnosed with grade 2 follicular lymphoma upon examination of a biopsied submandibular lymph node [1]. Esophagogastroduodenoscopy performed using conventional white-light observation revealed that the mucosa of the second duodenal portion was intact (Fig. 1A), whereas narrow-band imaging showed a tiny white spot (Fig. 1B). Magnifying observation further revealed the spot as a whitish deposit with a slight elevation (Fig. 1C). A thorough investigation of the duodenum revealed another tiny whitish nodule with a dilated microvessel (Fig. 2). Formation of a neoplastic follicle and grade 1 follicular lymphoma cell infiltra-

tion was confirmed by biopsy examinations of the tiny whitish deposit (Fig. 3A–E) and the nodule, whereas a biopsy sample from the intact duodenal mucosa contained no lymphoma cells (Fig. 3F).

**Case 2.** A 92-year-old Japanese woman was diagnosed with grade 1 follicular lymphoma upon an examination of a biopsied inguinal lymph node. CT scanning showed swelling of the submandibular, para-aortic, and inguinal lymph nodes. Tracer uptake in multiple bones and swollen lymph nodes were seen on PET scanning. The gastrointestinal tract was intact on CT and PET scanning. Involvement of the bone marrow was also confirmed. Thus, the patient was diagnosed with stage IV follicular lymphoma. Screening esophagogastroduodenoscopy showed tiny whitish patches in the mucosa of the duodenal periampullary region. Magnifying observation revealed whitish areas com-

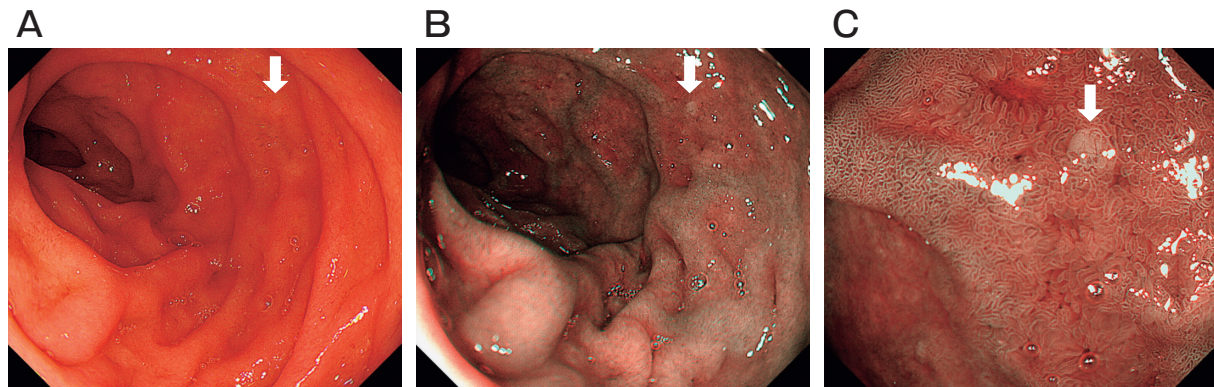


Fig. 1 Esophagogastroduodenoscopy images of Case 1. Although the duodenal mucosa seemed to be intact by conventional white light observation (A), narrow-band imaging made it easier to visualize a tiny white spot (B) (arrows). A whitish deposit with slight elevation was visible on magnifying observation (C).

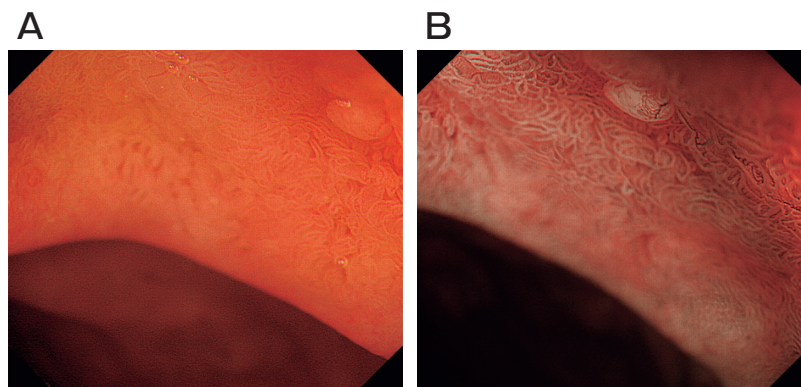
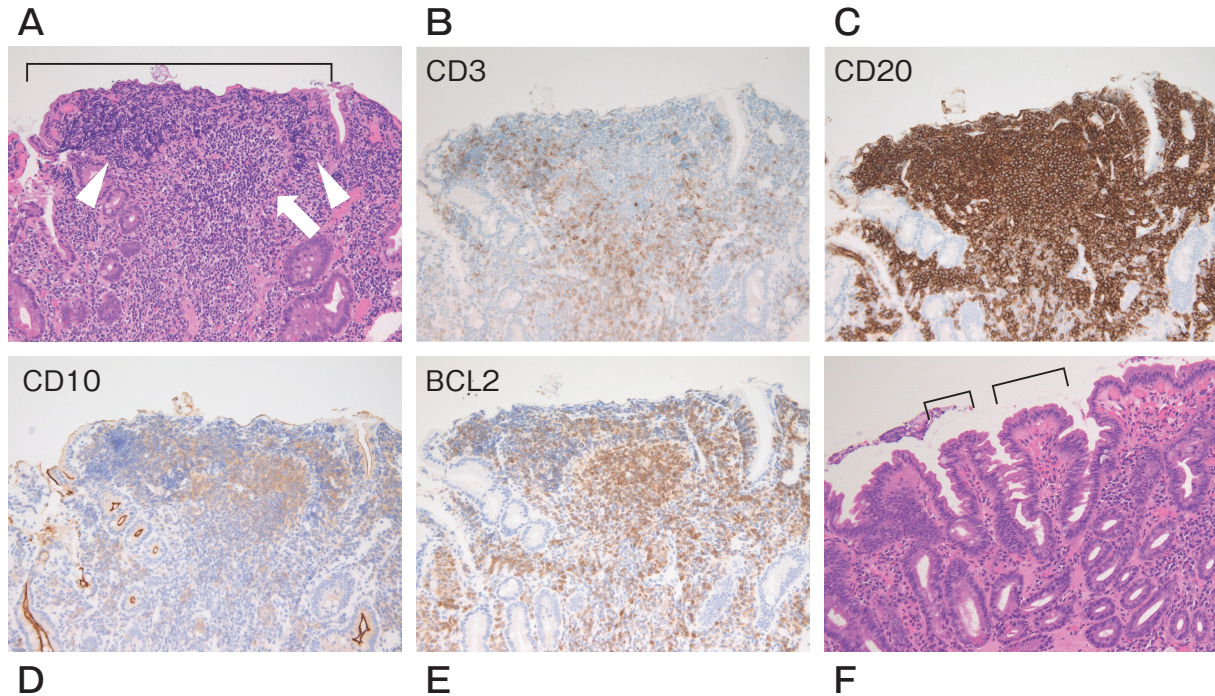
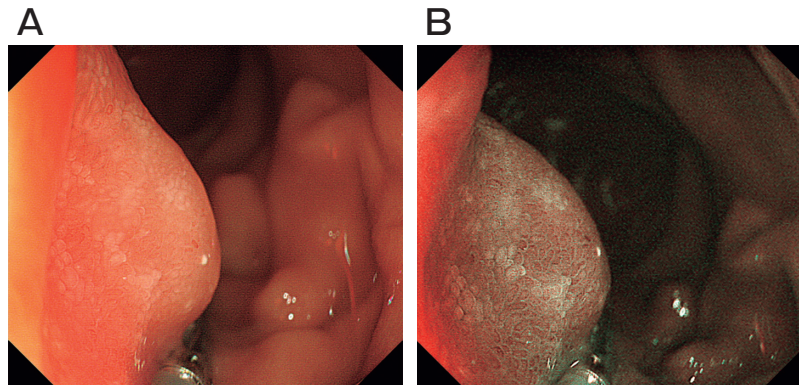


Fig. 2 Esophagogastroduodenoscopy images of Case 1. A tiny whitish nodule was detected in addition to the tiny white spot shown in Fig. 1. A, white-light observation; B, narrow-band imaging observation.





**Fig. 3** Histological images of biopsy samples taken from the tiny white spot shown in Fig. 1. Diffuse infiltration of follicular lymphoma cells (arrowheads) and neoplastic follicle formation (arrow) were seen (A, hematoxylin and eosin staining). Lymphoma cells were negative for CD3 (B) but positive for CD20 (C), CD10 (D), and BCL2 (E). In contrast, biopsy specimen taken from the “endoscopically intact” duodenal mucosa contained no lymphoma cells (F). Note that lymphoma cell infiltration resulted in a nodular structure (A, square bracket) after destroying the normal architecture of the duodenal villi (F, square brackets).

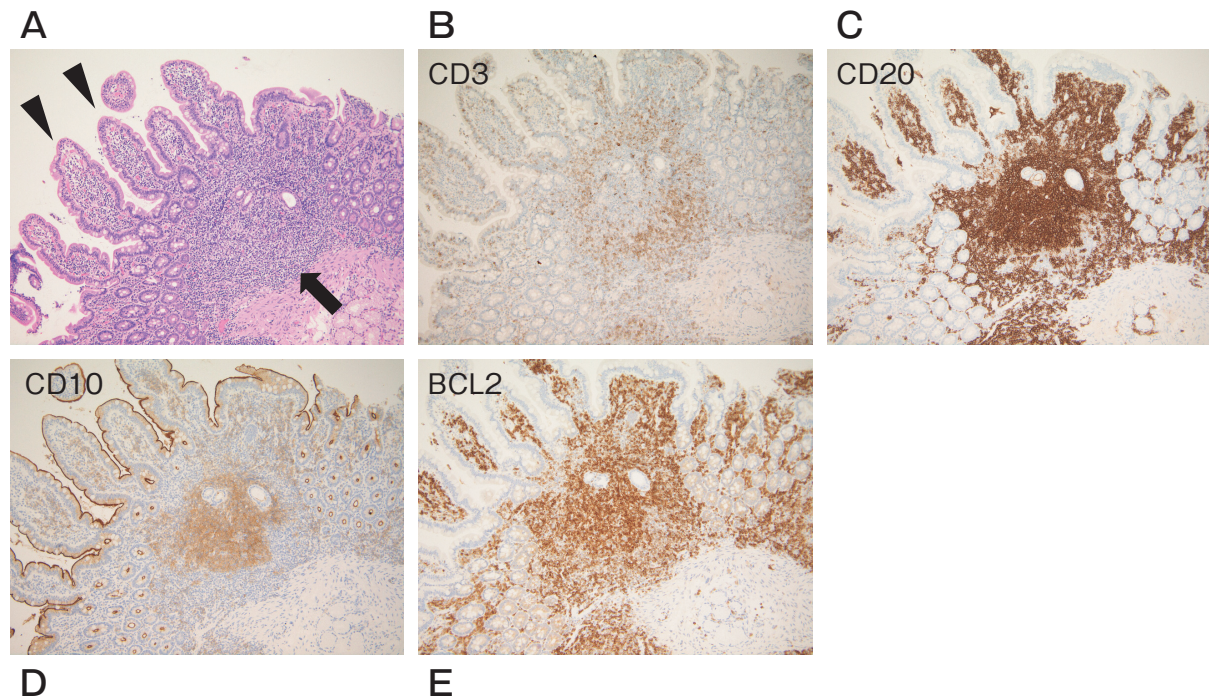


**Fig. 4** Esophagogastroduodenoscopy images of Case 2. Magnifying endoscopic observation showed slightly enlarged whitish villi (A). Narrow-band imaging more clearly emphasizes the mucosal color change to whitish (B). Examination of the biopsy sample revealed follicular lymphoma cell infiltration.

posed of slightly enlarged whitish villi (Fig. 4A). Narrow-band imaging enabled easier identification of enlarged whitish villi and also showed whitish mucosal change (Fig. 4B). Biopsy examination of this area showed grade 1 follicular lymphoma cell infiltration in the duodenal villi (Fig. 5).

### Discussion

An increase in the incidence of follicular lymphoma in the duodenum was reported by Yoshino *et al.* in 2000 [2]. Since then, there have been major advances in our understanding of primary intestinal follicular



**Fig. 5** Histological images of biopsy samples taken from the whitish villi shown in Fig. 4. Most of the follicular lymphoma cells were observed as diffuse infiltration of the duodenal villi (arrowheads), whereas formation of a small neoplastic follicle (arrow) was also found (A, hematoxylin and eosin staining). Lymphoma cells were negative for CD3 (B) but positive for CD20 (C), CD10 (D), and BCL2 (E). Note that the architecture of the duodenal villi was preserved, despite the diffuse infiltration of the follicular lymphoma cells (A, arrowheads).

lymphoma (3, 10–13). Consequently, this disease was officially listed in the WHO classification system as a rare variant of follicular lymphoma [1]. Endoscopic images of primary intestinal follicular lymphomas commonly show small whitish polypoid nodules in the duodenum [10, 11, 14, 15]. On the other hand, endoscopic features of duodenal follicular lymphomas of nodal origin have rarely been reported. Nakamura *et al.* summarized 27 cases of follicular lymphoma with intestinal involvement including patients in stage I (n = 19), stage II (n = 2), and stage IV (n = 6) [16]. Endoscopically, the intestinal lesions presented as polypoid lesions in all patients. Norimura *et al.* reported a case of stage IV follicular lymphoma with duodenal involvement [9]. They noted small whitish granules in the duodenum. In our recent study, which included cases of primary intestinal follicular lymphoma (n = 7) and systemic follicular lymphoma with duodenal involvement (n = 2), we investigated the magnifying endoscopy features of duodenal follicular lymphoma lesions [4]. The duodenal lesions were macroscopically observed as whitish granules in all

cases. Thus, although there may be differences between the biological behavior and pathogenesis of nodal-origin cases and primary intestinal cases of follicular lymphoma [3, 10, 12, 13], the duodenal lesions in these pathologies show similar endoscopic features.

As described above, magnifying endoscopy findings such as opaque whitish spots and enlarged whitish villi are the distinctive features of intestinal lesions of follicular lymphoma [4–9]. It can be speculated that such characteristic endoscopic features reflect the underlying histological structure (Table 1) [4]. Primary duodenal follicular lymphomas histologically present with neoplastic cells infiltrating the villi and forming lymphoid follicles [1, 2]. Enlarged whitish villi appear to be caused by an infiltration of neoplastic cells in the villi. Opaque white spots may be formed by lymphoid follicles deposited within the mucosa or submucosa. Deposited lymphoma cells may also disturb the microvessel perfusion in the villi and lead to vessel dilatation [17]. Multiple opaque white spots and enlarged whitish villi may thus constitute a typical macroscopic structure known as “whitish granules.”



**Table 1** Typical endoscopic features and possible underlying histological features of follicular lymphoma lesions in the duodenum

Typical macroscopic feature	Magnifying endoscopy features *	Underlying histological features possibly corresponding to magnifying endoscopy images
Whitish granules	<ol style="list-style-type: none"> <li>1. opaque white spots of various sizes</li> <li>2. enlarged whitish villi</li> <li>3. dilated microvessels</li> </ol>	<ol style="list-style-type: none"> <li>1. lymphoid follicles deposited within the mucosa or submucosa</li> <li>2. infiltration of neoplastic cells in the villi</li> <li>3. disturbed perfusion of the microvessels in the villi by lymphoma cell deposition</li> </ol>

\*These features were more easily and clearly identified by narrow-band imaging

Since the endoscopic images shown in this report are subtle and diminutive, their morphologies differ from the representative features of duodenal follicular lymphoma lesions. However, it was noteworthy that the histological findings of the 2 cases are consistent with the typical pathomorphology of primary duodenal follicular lymphoma. As shown in Fig. 3A, biopsy specimens from the tiny white spot of Case 1 contained a diffuse infiltration of follicular lymphoma cells within the duodenal mucosal layer (Fig. 3A, arrowheads). Neoplastic follicle formation was also confirmed (Fig. 3A, arrow). As a result of the lymphoma cell infiltration, the villous structure was partially lost (Fig. 3A, square bracket). Such a morphological alteration appears to result in tiny whitish spots or nodules within the duodenal mucosa. The biopsy specimen from Case 2 also had diffuse infiltration of neoplastic cells in the duodenal villi (Fig. 5A, arrowheads) and small follicle formation (Fig. 5A, arrow). However, in contrast to the pathomorphology of Case 1, the biopsy in Case 2 demonstrated a preserved villous architecture. We speculate that the slightly enlarged whitish villi in the latter resulted from an infiltration of lymphoma cells in the villi. Thus, we believe that the duodenal lesions presented in this report are 2 different types of incipient lesions of intestinal involvement of follicular lymphoma.

Whitish lesions in the duodenum can be part of the diagnoses of many different conditions, including duodenitis, adenoma, lymphangiectasia, and lymphangioma, in addition to follicular lymphoma. In the previous study we compared the magnifying endoscopy features of cases with follicular lymphomas (n = 9), lymphangiectasia (n = 7), adenomas (n = 10), duodenitis (n = 4), erosion (n = 1), lymphangiomas (n = 1), and hyperplastic polyps (n = 1) (4). Enlarged villi (8/9, 88.9%), dilated microvessels (5/9, 55.6%),

and opaque white spots of various sizes (9/9, 100%) were detected in follicular lymphoma cases, whereas none of these magnifying endoscopy features were observed in cases with adenomas, duodenitis, erosion, or hyperplastic polyps. Adenomas, duodenitis, and hyperplastic polyps showed only whitish villi, and erosion presented as a loss of villous structure. Observations of cases with lymphangiectasia revealed enlarged villi, dilated microvessels, and white spots. However, unlike the case in follicular lymphoma, these white spots were homogeneous in size and had clear margins. Although the lymphangioma was indistinguishable from follicular lymphoma based on magnified features, it was easily diagnosed based on macroscopic morphology. Therefore, these microstructures are useful in distinguishing follicular lymphoma from other whitish lesions in the duodenum [4].

This report includes 2 important implications regarding the detection of duodenal follicular lymphoma lesions. First, narrow-band imaging may facilitate easy detection of the small lesions. In Case 1, tiny spots and deposits were not easily identified on normal white light observation (Figs. 1A, 2A), whereas narrow-band imaging provided a clear contrast of the white spots/nodules and brownish intact mucosa (Figs. 1B, 1C, 2B). In case 2, narrow-band imaging enabled easier identification of enlarged whitish villi, since surface contours of individual villi were emphasized. Second, a detailed endoscopic observation likely enables sampling of tissues containing lymphoma cells. For example, in Case 1, the biopsy from the “endoscopically intact” duodenal mucosa contained no lymphoma cells (Fig. 3F), while both biopsy specimens from the tiny whitish spot and nodule had enough neoplastic cells for us to confirm the follicular lymphoma involvement.

In summary, we report endoscopic findings of 2

cases of duodenal involvement of follicular lymphoma. Although both cases presented with minute duodenal lesions, narrow-band imaging and magnifying observation were useful for the diagnosis. Since both cases already involved systemic follicular lymphomas of nodal origin, detection of the duodenal lesions did not alter the treatment strategies. However, we believe that the detailed endoscopic images shown herein will enable prompt diagnoses at earlier stages of follicular lymphoma involvement in the duodenum in other cases.

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