Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.3995-19
Intern Med 59: 1395-1399, 2020
http://internmed.jp

【 CASE REPORT 】

Primary Colorectal Follicular Lymphoma Observed by Magnifying Endoscopy, with a Five-year Follow-up

Masaki Katsurahara[1], Yuhei Umeda[2], Takashi Sakuno[2], Jyunya Tsuboi[2], Reiko Yamada[2], Misaki Nakamura[2], Yasuhiko Hamada[1], Hiroyuki Inoue[2], Kyosuke Tanaka[1], Noriyuki Horiki[1] and Yoshiyuki Takei[2]

Abstract:
Colorectal involvement is very rare in cases of follicular lymphoma. Colonoscopy of a 69-year-old man revealed an aggregation of multiple whitish nodules in the sigmoid colon. Magnifying endoscopy with narrow-band imaging demonstrated a coiled and elongated microvascular pattern on the surface and crystal violet staining showed a type I pit pattern. A biopsy showed follicular lymphoma (Grade 1), and no other involvement of lymphoma was detected. Following a diagnosis of primary colorectal follicular lymphoma stage I (Lugano classification), the patient was monitored by watch-and-wait therapy. We documented the endoscopic images of colorectal follicular lymphoma in the present case.

Key words: colorectal follicular lymphoma, endoscopic image, watch-and-wait therapy

(Intern Med 59: 1395-1399, 2020)
(DOI: 10.2169/internalmedicine.3995-19)

Introduction

Despite being a common nodal lymphoma, follicular lymphoma (FL) is rare in the gastrointestinal (GI) tract. The most common location of gastrointestinal follicular lymphoma (GI-FL) is the duodenal second portion, followed by the jejunum, and involvement of the colon is extremely rare (1). Consequently, the endoscopic appearance and progression of primary colorectal FL have not been clarified in detail.

Case Report

A 69-year-old man with no noteworthy medical history had been found to have a flat elevated lesion in the sigmoid colon by colonoscopy in another hospital, five years previously (Fig. 1). The lesion was biopsied and diagnosed as lymphoid hyperplasia. Although the patient had been advised to undergo colonoscopy annually, he did not return to the hospital. After an interval of five years, colonoscopy was performed at the other hospital, following a positive fecal occult blood test. Colonoscopy again revealed a flat, elevated lesion in the sigmoid colon; this had increased in size and a biopsy specimen was suspicious of follicular lymphoma. The patient was referred to our hospital for a detailed examination. His blood pressure was 135/67 mmHg, his body temperature was 36.6℃, and his heart rate was 67 beats per minute. There was no abdominal tenderness, and bowel sounds were normoactive. The peripheral lymph nodes, liver and spleen were not palpable. A blood test revealed a white blood cell count of 5,300/μL (normal range: 3,300-8,600), a hemoglobin level of 14.1 g/dL (13.7-16.8) and a platelet count of 215,000/μL (158,000-348,000). Lactate dehydrogenase (LDH) measured 139 U/L (124-222), and interleukin-2 receptor was 349 U/mL (122-496). All other test findings were normal.

Colonoscopy revealed an aggregation of multiple whitish

[1]Department of Endoscopic Medicine, Mie University Graduate School of Medicine, Japan and [2]Department of Gastroenterology and Hepatology, Mie University Graduate School of Medicine, Japan
Received: September 30, 2019; Accepted: January 23, 2020; Advance Publication by J-STAGE: March 12, 2020
Correspondence to Dr. Masaki Katsurahara, mkatura@clin.medic.mie-u.ac.jp

nodules in the sigmoid colon, occupying approximately one quarter of the circumference of the lumen (Fig. 2). Magnifying endoscopy with narrow-band imaging (ME-NBI) showed a coiled and elongated microvascular pattern on the surface (Fig. 3), and crystal violet staining demonstrated a regular arrangement of round pits (type I pit pattern), suggesting a submucosal tumor (Fig. 4). The biopsy specimen comprised follicular structures consisting of proliferations of small-sized abnormal lymphocytes and immunohistochemical staining revealed that these abnormal cells were positive for CD10, CD20 and Bcl-2 but negative for CD3 (Fig. 5), consistent with a diagnosis of FL (Grade 1). Subsequently, although upper endoscopy and video capsule endoscopy were performed, no other involvement of lymphoma was detected. Whole-body CT showed no apparent mass or lymphadenopathy, and fluorine-18 fluorodeoxyglucose (^{18}F-FDG)-positron emission tomography with computed tomography, performed for staging of the lymphoma, revealed no ^{18}F-FDG uptake. A bone marrow examination revealed normocellular marrow. Based on these findings, the patient was diagnosed with primary colorectal FL, clinical stage I according to the Lugano classification, and was monitored closely by watch-and-wait therapy.

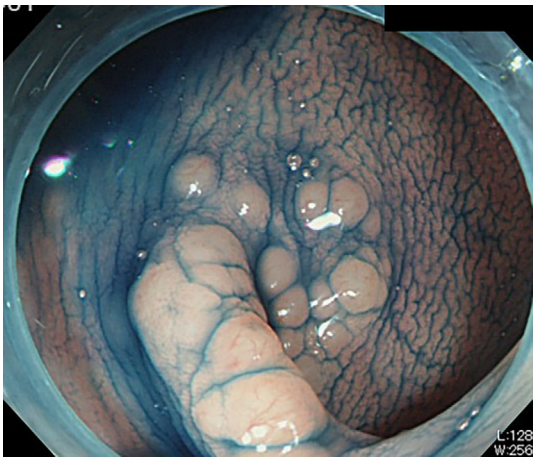

Figure 1. Colonoscopy from another hospital five years earlier, showing a flat elevated lesion.

Discussion

FL is characterized by germinal center B cells with a follicle shape, containing centrocytes and centroblasts (2). The t (14; 18) (q32; 21) translocation is a characteristic chromosomal abnormality of FL with high diagnostic value and the long-term survival of B cells, attributable to the overexpression of anti-apoptotic Bcl-2, has been implicated in the pathogenesis of FL.

FL is one of the most common subtypes of indolent non-

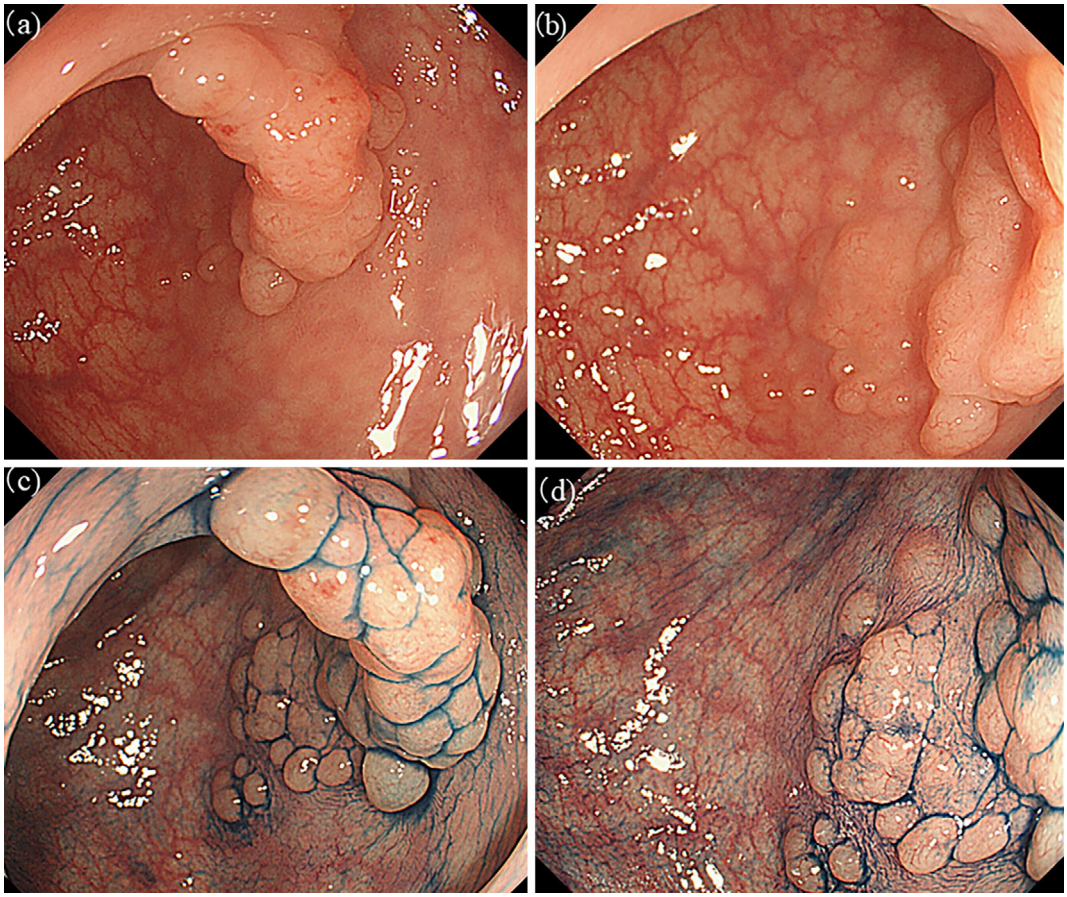

Figure 2. (a, b) Colonoscopy showing multiple whitish nodules. (c, d) Colonoscopy after indigo carmine spraying.

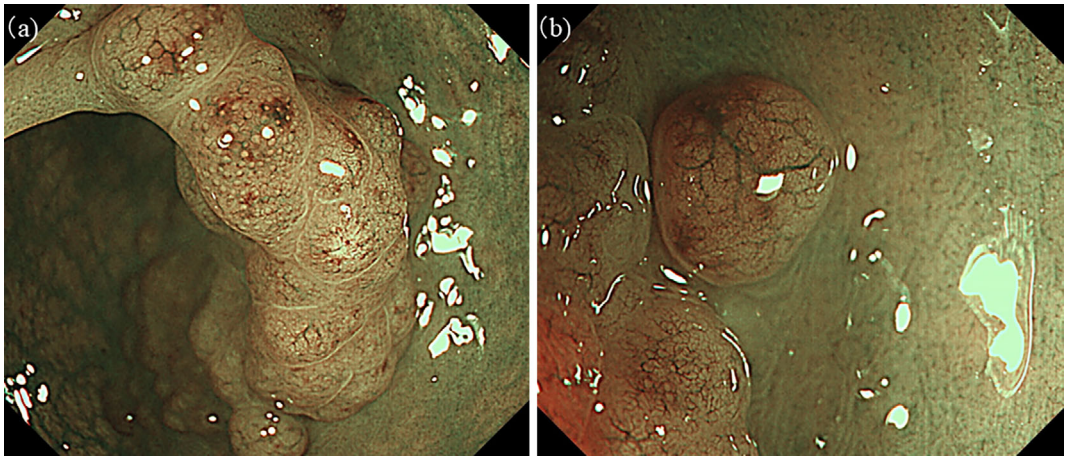

Figure 3. **(a, b) NBI showing a coiled and elongated microvascular pattern.**

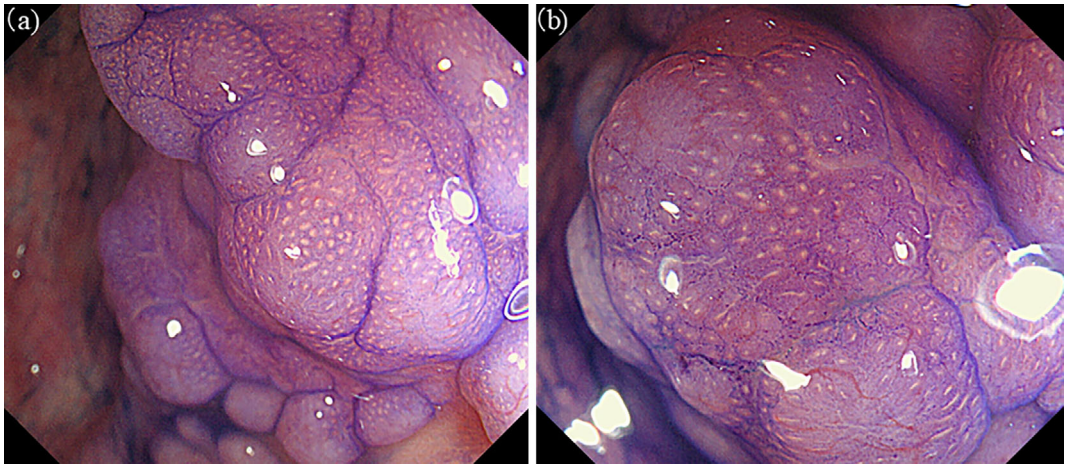

Figure 4. **(a, b) Crystal violet staining showing a type I pit pattern.**

Hodgkin's lymphoma and arises in the lymph nodes as well as the spleen, liver and bone marrow. Approximately 40% of all FL cases are of extranodal origin (1), with the GI tract being the site most frequently involved in extranodal FL. Gastrointestinal FL (GI-FL) accounts for only 1-3% of GI lymphomas (1) and has been regarded as a relatively rare disease. Balloon-assisted enteroscopy and video capsule endoscopy, which were established recently, enable surveillance of the entire GI tract, including the small intestine. The site involved most frequently in GI-FL is the duodenal second portion, followed by the jejunum and ileum (1). In contrast, colorectal involvement is less common in cases of FL. In a large series of GI-FL, LeBrun et al. reported that only 3 of 31 patients with GI-FL had a tumor originating in the colon (3), and Takata et al. reported that, among 125 patients with GI-FL, colorectal FL occurred in only 5 (1).

Multiple whitish nodules are considered to be the typical endoscopic appearance of duodenal FL (4, 5), but the endoscopic features of colorectal FL have been reported rarely in the literature. Iwamuro et al. divided the endoscopic features of 12 colorectal FL cases, including stages I, II_1 and IV (Lugano classification), into 3 subtypes as follows: papular type (4 cases), polypoid type (4 cases) and flat elevated type (4 cases) (6). Interestingly, all 12 cases had raised lesions, and no ulcerations or erosions were seen. In other case reports, endoscopic images of primary colorectal FL, limited to stage I or II_1 (Lugano classification), have been published (n=8 cases). The median age was 65.8 (range: 56-75) years old, and the male-to-female ratio was 4:4. According to the Lugano classification, the ratio of clinical stages I:II_1 was 6:2 and the endoscopic appearances of papular, polypoid and flat elevated type were observed in 4, 2 and 2 cases, respectively (7-14), and all of which showed raised lesions (Table). Nakamura et al. reported that the endoscopic features of intestinal lymphoma may be classified as polypoid, ulcerative, multiple lymphomatous polyposis (MLP), diffuse, and mixed type (15). The most common type of intestinal lymphoma is the ulcerative type but the case reports of colorectal FL mentioned above described raised lesions. Morphologically, the raised type may be characteristic of colorectal FL, although it is difficult to distinguish FL from other lymphomas by conventional endoscopy.

Only two case reports have described primary colorectal FL with magnifying endoscopy (9, 13). Several authors re-

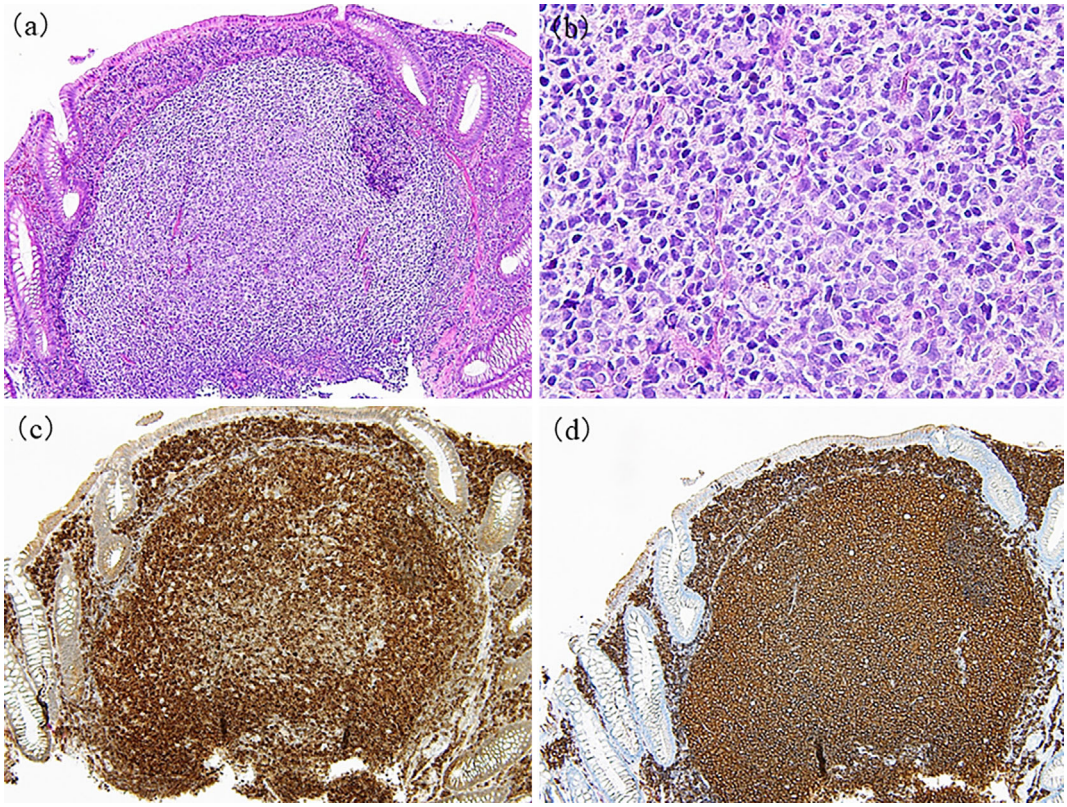

Figure 5. **(a) A low-powered microscopic view of the biopsy specimen (×100). (b) A high-powered microscopic view of the biopsy specimen with proliferation of small-sized, abnormal lymphocytes (Hematoxylin and Eosin staining) (×400). (c) Bcl-2 (×100). (d) CD20 (×100).**

Table. **Eight Cases of Primary Colorectal Follicular Lymphoma.**

Case	Reference	Age	Sex	Stage	Endoscopic appearance
1	7)	74	F	I	polypoid
2	8)	60	F	I	flat elevated
3	9)	69	F	I	papular (MLP)
4	10)	68	M	II_1	polypoid
5	11)	75	M	I	papular
6	12)	62	M	I	papular(multiple)
7	13)	56	F	I	flat elevated
8	14)	62	M	II_1	papular (multiple)

MLP: multiple lymphomatous polyposis

ported that the representative ME-NBI features of duodenal FL were opaque, whitish spots and enlarged villi with a dilated vascular pattern within the villi (5, 16, 17). These findings reflect the pathological features of infiltrated follicular lymphoma cells within the villi and the development of lymphoid follicles (5). Norimura et al. reported that the ME-NBI features of colorectal FL, similar to duodenal FL, were a coiled and elongated microvascular pattern on the surface and white, opaque spots under the microvessels (9). Kuroha et al. reported that ME-NBI is a useful diagnostic tool for distinguishing lymphoid hyperplasia from FL (13). Fujiya et al. reported that the detection of decreased numbers of vascular networks (DVNs) and irregular vessels on the surface by NBI in the terminal ileum or colon were useful for distinguishing intestinal lymphoma from lymphoid hyperplasia with high diagnostic accuracy (18). DVNs and irregular vessels corresponded to a coiled and elongated microvascular pattern in our case, and the shape and density of vessels were considered the most important findings for diagnosing intestinal lymphoma.

Duodenal FL is a slow-growing tumor with low-grade malignancy. Schmatz et al. reported that, among 63 patients with duodenal FL defined as stage I, only 2 of 24 untreated patients developed nodal disease, and the remaining 61 had no extra-intestinal disease or transformation to aggressive B-cell lymphoma over a median of more than 6 years (19). The authors concluded that an aggressive therapeutic approach should not be used to treat duodenal FL. Tari et al. reported that, in a prospective study of 29 patients with intestinal FL, there were no significant differences in the

progression-free survival (PFS) between the watch-and-wait therapy group and the rituximab-combined chemotherapy group, and the overall survival (OS) was 100% in both groups (20). The authors concluded that watch-and-wait therapy is desirable as a treatment for asymptomatic intestinal FL. However, for primary colorectal FL, there is no consensus concerning the optimal treatment strategy, as the progression of the disease is uncertain. In the present case, comparing the endoscopic findings of five years ago with the current findings, the colorectal FL had increased in size but there were no significant morphological changes and no invasion of the lymph nodes. Therefore, we considered watch-and-wait therapy appropriate for monitoring the progression of colorectal FL.

We encountered a rare case of colorectal FL and report the outcomes, including endoscopic images of colorectal FL, which have rarely been described. Colorectal FL should be considered as a differential diagnosis in patients with a raised lesion on colonoscopy. ME-NBI and crystal violet staining were helpful supplementary studies for the accurate diagnosis of colorectal FL. To our knowledge, this is the first report of colorectal FL where it was possible to compare the current endoscopic findings with those obtained five years earlier. This case report highlights the endoscopic images and progression of primary colorectal FL, which is regarded as a rare colonic malignancy.

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

References

1. Takata K, Okada H, Ohmiya N, et al. Primary gastrointestinal follicular lymphoma involving the duodenal second portion is a distinct entity: a multicenter, retrospective analysis in Japan. Cancer Sci **102**: 1532-1536, 2011.
2. Kahl BS, Yang DT. Follicular lymphoma: evolving therapeutic strategies. Blood **127**: 2055-2063, 2016.
3. LeBrun DP, Kamal OW, Cleary ML, Dorfman RF, Warnke RA. Follicular lymphomas of the gastrointestinal tract: pathologic features in 31cases and bcl-2 oncogenic protein expression. Am J Pathol **140**: 1327-1335, 1992.
4. Yoshino T, Miyake K, Ichimura K, et al. Increased incidence of follicular lymphoma in the duodenum. Am J Surg Pathol **24**: 688-693, 2000.
5. Iwamuro M, Kondou E, Takata K, Yoshino T, Okada H. Diagnosis of follicular lymphoma of the gastrointestinal tract: a better initial diagnostic workup. World J Gastroenterol **22**: 1674-1683, 2016.
6. Iwamuro M, Okada H, Takata K, et al. Colorectal manifestation of follicular lymphoma. Intern Med **55**: 1-8, 2016.
7. Ferreira A, Goncalves R, Rolanda C. A different kind of colon polyp. Gastroenterology **143**: 1440, 1693-1694, 2012.
8. Esaki M, Matsumoto T, Nakamura S, et al. Capsule endoscopy findings in intestinal follicular lymphoma. Endoscopy **39**(Suppl 1): E86-E87, 2007.
9. Norimura D, Isomoto H. Colorectal involvement of follicular lymphoma-findings with narrow band imaging and magnifying endoscopy. Endoscopy **45**(Suppl 2): UCTNE: 296-E297, 2013.
10. Hiraide T, Shoji T, Higashi Y, Matsuda I, Terada T. Extranodal multiple polypoid follicular lymphoma of the sigmoid colon. Gastrointest Endosc **73**: 182-184, 2011.
11. Eso Y, Nishikawa Y, Takai A. Follicular lymphoma of the caecum resected endoscopically. Arab J Gastroenterol **17**: 143-144, 2016.
12. Saito M, Miyashita K, Miura Y, et al. Coexistence of primary colorectal follicular lymphoma and multiple myeloma: a case report. Int J Gen Med **11**: 363-367, 2018.
13. Kuroha M, Endo K, Sato Y, et al. Magnifying endoscopy findings in follicular lymphoma of the rectum using narrow band imaging. Endoscopy **43**(Suppl 2): E346-E347, 2011.
14. Jin S, Lee HS, Jeong JY, Jo WY. Primary colonic follicular lymphoma presenting as four diminutive sessile polyps found incidentally during colonoscopy. Clin Endosc **51**: 388-392, 2018.
15. Nakamura S, Matsumoto T, Iida M. Endoscopic diagnosis of intestinal malignant lymphoma. Gastroenterol Endosc **51**: 3-9, 2009 (in Japanese, Abstract in English).
16. Inoue N, Isomoto H, Shirakuwa S, Mizuta Y. Magnifying endoscopic observation of primary follicular lymphoma of the duodenum by using the narrow-band imaging system. Gastrointest Endosc **69**: 158-159, 2009.
17. Iwamuro M, Okada H, Takata K, et al. Magnified endoscopic features of duodenal follicular lymphoma and other whitish lesions. Acta Med Okayama **69**: 37-44, 2015.
18. Fujiya M, Kashima S, Ikuta K, et al. Decreased numbers of vascular networks and irregular vessels on narrow-band imaging are useful findings for distinguishing intestinal lymphoma from lymphoid hyperplasia. Gastrointest Endosc **80**: 1064-1071, 2014.
19. Schmatz AI, Streubel B, Kretschmer-Chott E, et al. Primary follicular lymphoma of the duodenum is a distinct mucosal/submucosal variant of follicular lymphoma: a retrospective study of 63 cases. J Clin Oncol **29**: 1445-1451, 2011.
20. Tari A, Kitadai Y, Mouri R, et al. Watch-and-wait policy versus rituximab-combined chemotherapy in Japanese patients with intestinal follicular lymphoma. J Gastroenterol Hepatol **33**: 1461-1468, 2018.