

Primary Intestinal Follicular Lymphoma Diagnosed by Double Balloon Endoscopy: Endoscopic Features and Treatment Outcomes

Kinichi Hotta^{[a],[c],*}; Toshimi Mitsuishi^[b]; Yoshinori Miyata^[a]; Akihisa Tomori^[b]

^[a]M.D., Department of Gastroenterology, Saku Central Hospital, Nagano, Japan.

^[b]M.D., Department of Internal Medicine, Saku Central Hospital, Nagano, Japan.

^[c]M.D., Division of Endoscopy, Shizuoka Cancer Center, Shizuoka, Japan.

* Corresponding author.

Received 7 February 2015; accepted 22 July 2015
Published online 26 August 2015

Abstract

Objective: Little is known about the endoscopic features and clinical significance of small bowel (SB) lesions in primary intestinal follicular lymphoma (IFL). This study aimed to describe, based on a case series, detailed endoscopic features of SB lesions in IFLs and the relationship between clinical and histological stages.

Methods: This retrospective study included 14 patients (8 females, median age, 61.5 years) newly diagnosed with IFL of SB. All patients underwent double balloon endoscopy (DBE), with both anterograde and retrograde approaches.

Results: The distribution of IFLs in the GI tract were stomach 7%(1/14), duodenal bulb 7% (1/14), second part of the duodenum 93% (13/14), third part of the duodenum 86% (12/14), jejunum 93% (13/14), and ileum 43% (6/14). No colorectal lesions were detected. Multiple granules were the most frequently detected lesion, and were found in all patients. Nodule/mass lesions were detected in 5 patients. Nodule/mass lesions and ileal lesions were highly associated with the Lugano international classification. Eleven of 14 patients received chemotherapy plus Rituximab. Ten of 11 patients achieved complete response (CR). One patient achieved partial response (PR), but later exhibited disease progression. Four patients experienced grade 3 or 4 neutropenia, but all recovered without permanent side effects. One patient that achieved CR exhibited progressive disease after 54 months. All patients survived for a median of 35 months.

Conclusions: DBE was necessary for the precise diagnosis of IFL involving the SB. Endoscopic features included a nodule/mass and ileal lesions, which were related to the clinical stage.

Keywords: follicular lymphoma, gastrointestinal tract, small bowel, double balloon endoscopy, rituximab

Hotta, K., Mitsuishi, T., Miyata, Y., & Tomori, A. (2015). Primary Intestinal Follicular Lymphoma Diagnosed by Double Balloon Endoscopy: Endoscopic Features and Treatment Outcomes. *Canadian Social Science*, 2(2), 1-7. Available from: <http://www.cscanada.net/index.php/css/article/view/5234>
DOI: <http://dx.doi.org/10.3968/5234>

INTRODUCTION

Follicular lymphoma (FL) is the second most frequent lymphoma in western countries. It comprises approximately 20% of all non-Hodgkin lymphomas (NHLs)^[1]. Primary intestinal follicular lymphoma (IFL) is a relatively rare entity among NHLs of the gastrointestinal tract. IFLs account for 3.6%-5.9% of all GastrointestinalNHLs^[2-3].

Most patients with IFLs were asymptomatic or had vague GI symptoms and were diagnosed during a esophago-gastricduodenoscopy (EGD) screening^[4]. Recently, screening EGDs were widespread in Japan for the detection of early esophago-gastric cancers; thus, asymptomatic IFLs were occasionally detected by chance. Indeed, reports of IFLs in Japan have increased in the past few years^[5-7].

Little is known about the natural history and prognosis of IFLs. Therefore, a standard therapeutic strategy for IFLs has not been established. In current practice, physicians typically choose treatment regimens that refer to nodal FLs. Before the general use of small intestinal endoscopies, surgical resection or radiotherapy were indicated for localized duodenal FLs^[4]. Currently, small

intestinal endoscopies include the wireless capsule endoscopy (WCE) and the double-balloon endoscopy (DBE).

Some IFL studies have demonstrated with DBE that involvement in the jejunum and ileum occurred frequently^[5-7]; thus, localized treatments for IFLs should be reconsidered. However, there is little knowledge about the detailed endoscopic features and clinical significance of IFLs. The aim of this study was to describe, based on a case series, the detailed endoscopic features of small bowel (SB) lesions of IFLs with DBE, and to determine the relationship between the clinical and histological stages. Additionally, we evaluated the therapeutic choices, responses, and mid-term prognoses of this case series.

PATIENTS AND METHODS

Patients

A total of 14 patients (8 females, median age, 61.5 years)

were newly diagnosed with FLs of the SB between October 2005 and June 2009. All patients underwent DBE, with both antegrade and retrograde approaches. All DBEs were performed by a single experienced endoscopist (KH), who used a double balloon endoscope (EN-450P5/T5, Fujifilm Co., Saitama, Japan). The diagnosis, endoscopic features, and treatments were retrospectively investigated. The diagnoses were grouped as either asymptomatic or symptomatic (e.g. abdominal pain) evaluations. Moreover, previous histories of EGD were investigated in the endoscopic database.

Endoscopic Features of FLs

Endoscopic features of FLs were categorized as either multiple granules or a nodule/mass. Multiple granules were whitish in color and irregular in size, when located in the duodenum (Figure 1a) and the jejunum (Figure 1b); in contrast, they mimicked large-sized lymphoid follicles, when located in the ileum (Figure 1c). Nodules/masses were defined as lesions that protruded more than 1 cm from the intestinal wall (Figure 1d).

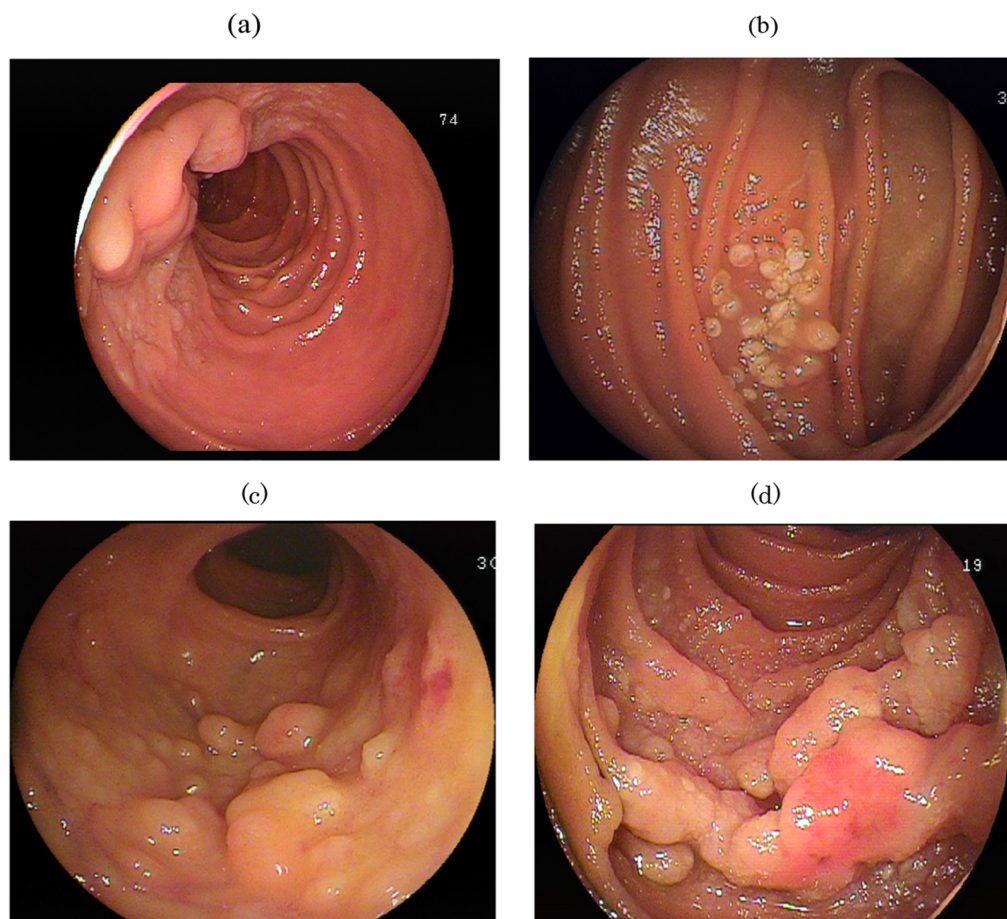


Figure 1
Endoscopic Features of Primary Intestinal Follicular Lymphomas. (a) Whitish Multiple Granules Around the Papilla Vater, (b) Whitish Multiple Granules in the Jejunum, (c) Multiple Granules That Look Like Lymphoid Follicles in the Ileum, (d) A Nodule/Mass Lesion in the Jejunum

Pathological Evaluation

Endoscopic biopsies were taken from all lesions suspected to be FLs to perform a definite diagnosis. Biopsy specimens showed that the proliferation of atypical lymphocytes had formed lymphoid follicles (Figure 2a). This proliferation was clearly evident in the high power

field view (Figure 2b). Pathologically, diagnosis of FL was indicated when atypical lymphocytes were diffusely positive for CD20, bcl-2, and CD10 (Figure 2c), and negative for CD3, CD5, and cyclin D1. The histological grading of FLs was based on the criteria of Mann and Berard^[8].

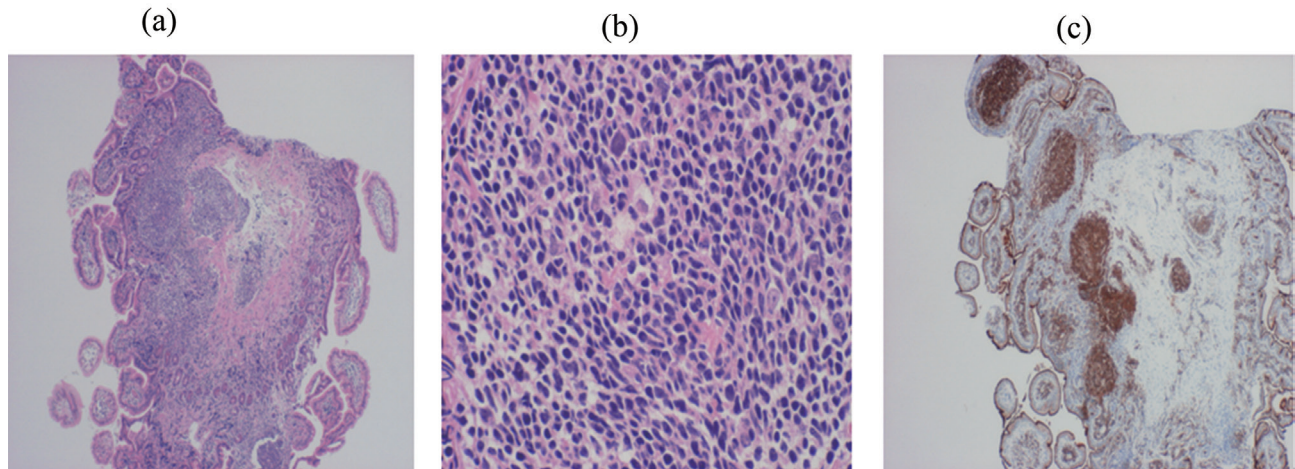


Figure 2
Pathological Findings of Primary Intestinal Follicular Lymphomas. (a) Low Power View Shows Multiple Follicles In The Jejunum (H&E, ×40), (b) High Power View Shows a Diffuse Proliferation of Atypical Lymphocytes of Small to Medium Sizes (H&E, ×400), (c) Low Power View Shows Lymphocytes Were Diffusely Positive for CD10 (CD10, ×40)

Staging

In the staging process, we included a physical examination, laboratory data, chest and abdominal computed tomography (CT), total colonoscopy, bone marrow examination, and/or 18F-fluorodeoxyglucose positron emission tomography (¹⁸F-FDG-PET). The Lugano international classification^[9] was used to identify the clinical stage and to analyze the association between clinical and endoscopic findings.

TREATMENT AND RESPONSE

There was no standard therapy with strong evidence. Therefore, our strategy was based on inform and patient's selection. In the localized stage (I and II₁), we informed patients of multiple treatment choices, including watch and wait, rituximab monotherapy, and chemotherapy with rituximab. In advanced stages (II₂–IV), we recommended chemotherapy with rituximab, on principle. Regimens of chemotherapy were selected according to the patient's general condition. Cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab (R-CHOP) were the primary regimen^[10-11]. However, for older patients or patients with cardiovascular complications, doxorubicin was replaced with pirarubicin (R-THP-COP). In principle,

6 to 8 cycles of chemotherapy were performed for each patient. Adverse effects that corresponded to grades 3–4 in the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, were evaluated throughout the chemotherapy course. Response to treatment was assessed by EGD, CT, and DBE, when necessary, every 6-12 months. Responses were evaluated based on a Response Evaluation Criteria in Solid Tumors (RECIST) criteria, which included a complete response (CR), a partial response (PR), progressive disease (PD), and stable disease (SD)^[12].

Follow-up examinations after treatments and during watchful waiting were annual assessment using EGD, CT and DBE.

RESULTS

Eleven patients were asymptomatic and IFL was detected by screening with an EGD; the other 3 patients presented with mild abdominal pain (Table 1). Ten of the 14 patients received an EGD before the diagnosis of FL. The median interval between disease initiation and detection was 12 months (range: 7-25 months). Based on a retrospective review of endoscopic pictures from previous EGDs, we could point out lesions due to FL in 9 out of 10 patients (Table 1).

Table 1
Clinical Features and Treatments of Intestinal Follicular Lymphomas

Case	Age	Sex	Presentation	Previous EGD	Treatment regimen (course)	Adverse effects (G3-4)	Response	Follow-up period
1	55	F	Asymptomatic	25M(FL+)	R(8)-CHOP(6)	—	CR	62(S)
2	60	M	Symptomatic	No	R(8)-CHOP(6)	—	CR→PD	60(S)
3	69	M	Asymptomatic	12M(FL+)	R(8)-CHOP(6)	—	PR→PD	57(S)
4	58	F	Asymptomatic	12M(FL+)	R(8)-CHOP(6)	—	CR	53(S)
5	74	M	Asymptomatic	12M(FL+)	Watchful waiting	—	SD	43(S)
6	52	M	Symptomatic	No	R(6)-CHOP(6)	—	CR	41(S)
7	54	F	Asymptomatic	7M(FL+)	R(8)-CHOP(6)	—	CR	35(S)
8	66	M	Asymptomatic	13M(FL+)	R(6)-THP-COP(6)	Neutropenia G3	CR	30(S)
9	62	F	Asymptomatic	13M(FL+)	Rituximab monotherapy(6)	—	CR	27(S)
10	70	F	Asymptomatic	12M(FL+)	R(7)-THP-COP(6)	Neutropenia G4	CR	29(S)
11	61	F	Asymptomatic	19M (FL-)	R(6)-CHOP(6)	Neutropenia G4	CR	25(S)
12	81	F	Symptomatic	No	R(6)-THP-COP(6)	Neutropenia G4	CR	22(S)
13	80	F	Asymptomatic	12M(FL+)	Watchful waiting	—	PD	20(S)
14	47	M	Asymptomatic	No	R(6)-THP-COP(6)	—	CR	19(S)

Note. FL: follicular lymphoma, R-CHOP: Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone, R-THP-COP: Rituximab, Pirarubicin, Cyclophosphamide, Vincristine, and Prednisone, CR: complete response, PR: partial response, PD: progressive disease, SD: stable disease, S: survival

Endoscopic Features

The endoscopic features are summarized in Table 2. The FL involved different parts of the GI tract, including stomach 7% (1/14), duodenal bulbs 7% (1/14), second part of the duodenum 93% (13/14), third part of the duodenum 86% (12/14), jejunum 93% (13/14), and ileum 43% (6/14). No colorectal lesions were detected. The most frequent finding was multiple granules, which was detected in all patients. Nodule/mass lesions were detected in 5 patients. Erosion of the stomach was detected in only one patient with gastric involvement.

A nodule/mass lesion and ileal lesions were highly associated with the Lugano international classification. Therefore, these findings were useful for estimating the Lugano international stage II₁ or above. For instance, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of a nodule/mass were 83.3%, 100%, 100%, and 88.9%, respectively, and for ileal lesions, they were 83.3%, 87.5%, 83.3% and 87.5%, respectively (Table 3). Meanwhile, no association was found between the histological grade and endoscopic features.

Table 2
Endoscopic Features of Primary Intestinal Follicular Lymphomas

Case	Site	Stomach	Duodenum			Jejunum	Ileum	Stage	Grade
			Bulbus	2 nd part	3 rd part				
1		—	—	MG, nodule/mass	Nodule/mass	MG, nodule/mass	MG	II ₂	2
2		—	—	MG	MG	MG	—	I	1
3		—	MG	MG	MG	MG	MG	IV	1
4		—	—	MG	MG	MG	—	I	1
5		—	—	MG	MG	MG	—	I	1
6		—	—	—	MG	MG	—	I	1
7		—	—	MG	MG	MG	MG	I	1
8		—	—	MG	MG	MG, nodule/mass	—	II ₁	1
9		—	—	MG	—	—	—	I	1
10		Erosion	—	MG	MG	MG	MG, nodule/mass	IV	2
11		—	—	MG	—	MG	—	I	1
12		—	—	MG	MG	MG, nodule/mass	MG	II ₂	1
13		—	—	MG	MG	MG	—	I	1
14		—	—	MG	MG, nodule/mass	MG, nodule/mass	MG, nodule/mass	II ₁	1
		1(7%)	1(7%)	13(93%)	12(86%)	13(93%)	6(43%)		

Note. MG: multiple granules

Table 3
Estimating Lugano International Stage II₁ or Above From Endoscopic Findings

Endoscopic findings	Sensitivity	Specificity	PPV	NPV
Nodule/mass	83.3%(5/6)	100%(8/8)	100%(5/5)	88.9%(8/9)
Ileal lesion	83.3%(5/6)	87.5%(7/8)	83.3%(5/6)	87.5%(7/8)

Note. PPV: positive predictive value, NPV: negative predictive value

Treatments and Responses

The treatments and responses are summarized in Table 1. Eleven of 14 patients received chemotherapy that included rituximab (R-CHOP or R-THP-COP). Ten of 11 patients achieved CR, and one patient achieved PR, but progressed later. Grade 3 or 4 neutropenia appeared in 4 patients, but all patients recovered without permanent side effects. One patient that achieved CR exhibited disease progression after 54 months, but he had survived with the disease at the 60-month follow-up. All patients that received chemotherapy survived to a median follow-up period of 35 months. One patient's condition progressed, but the others were stable with disease-free status. Two patients chose watch and wait; one of these maintained SD, but the other exhibited PD. Both patients that chose watchful waiting survived with the disease to a median follow-up period of 31 months. One patient received rituximab monotherapy and achieved CR. He survived and exhibited a disease-free state at 27 months. Collectively, all patients survived to the follow-up periods.

DISCUSSION

In this case series, most patients with IFLs were asymptomatic and were diagnosed based on the chance detection of duodenal lesions in an EGD screening. In a previous review on IFL, the authors described 150 previously reported cases, where 43% were asymptomatic and 9% presented vague GI symptoms^[4]. In that review, abdominal pain, intestinal obstruction, and intestinal bleeding were present in 29, 8, and 6 %, respectively^[4].

In our series, IFLs were frequently overlooked. Our investigation of previous endoscopic pictures showed that 90% of patients that underwent previous EGDs had presented duodenal FL lesions that had been overlooked. Based on our results, to prevent overlooking IFLs, it is most important to check for multiple whitish granules in the second part of the duodenum. For the early diagnosis of IFLs, we found that two factors were important; first, careful observation must be performed with sufficient air infiltration of the duodenum; second, it is important to distinguish FLs from benign lymphoid follicles and other lesions with whitish villi.

In the present study, we demonstrated high involvement of the jejunum (93%) and ileum (43%). Most of these lesions were distributed multifocally. The

frequencies we found were higher than those reported before the general use of small bowel endoscopy^[13-15]. Recently, a few case series of IFL that had been diagnosed by DBE demonstrated a similar lesion distribution^[5-7]. Those reports showed that the frequency of involvement was higher in the jejunum than in the ileum. Colonic involvement was never observed in our case series. This finding was consistent with those of other recent case series from Japan^[5-7, 16]. Moreover, we observed one case with gastric involvement, which is considered very rare among small bowel lesions. In our endoscopic findings, the most frequent was multiple granules of various sizes. This is distinct from the characteristics of benign lymphoid follicles. The granules were whitish in color in the duodenum and jejunum. Granules in the duodenum tended to gather to the Papilla Vater^[17]. On the other hand, the granules in ileum were the same color as the surroundings, and looked like uneven lymphoid follicles. In some cases, a nodule or mass formation was found with multiple granules, and these were accompanied by erosive or ulcerative changes. The findings also showed massive increases in lymphoma cells in local areas.

In the present study, we found new knowledge for an association between endoscopic features and the clinical stage. Nodule/mass lesions and ileal lesions were both useful factors for estimating Lugano international stage II₁ or above. On the other hand, it was difficult to estimate the histological grade from endoscopic findings. The histological grade of IFLs is important information for designing an adequate treatment strategy. Grade 3 treatment should be similar to that for a diffuse large B cell lymphoma. However, grade 3 IFLs were observed at low frequency^[4]. There was no grade 3 case in our case series. DBE offers the advantage of providing an opportunity for taking a biopsy specimen and diagnosing the histological grade. However, due to the low frequency of grade 3 IFLs, a WCE can be used in place of a DBE. The WCE is also considered to be effective for evaluation after treatment^[18].

The natural history and long-term prognosis of IFLs have not been demonstrated. In a case series with relatively small numbers of patients with or without treatment, the relapse-free median survival time was 31 to 45 months (13,15), similar to that of nodal FLs. On the other hand, an analysis of previously reported IFL cases showed a better prognosis than that for nodal FLs^[16]. The median relapse-free survival after achieving CR was 98

months in 96 patients with IFL^[4]. There have been no randomized controlled trials (RCTs) for testing treatments for IFLs. Therefore, the standard therapeutic strategy for IFLs has not been established. Currently, the therapies for IFL are based on the regimens for nodal FL, which include chemotherapy, monoclonal antibody therapy, radiotherapy, surgery, or combination therapies^[19]. Recently, it was acknowledged that IFL tended to involve the small bowel; therefore, the localized therapies, like radiotherapy and surgery appear to be unsuitable for treating IFLs. Based on a few recent case series, including this study, rituximab plus chemotherapy demonstrated a more favorable complete response rate for IFL than for nodal FL (7). This suggested that a complete cure of IFL might be expected, except in the case of stage IV disease. In our limited data, R-CHOP achieved the highest complete response rate. Recently, watch & wait is considered a practical strategy for low-tumor-burden FL^[20-21]. However, strong evidence was lacking for watch & wait for IFLs. Therefore, many type treatments were conducted in practice^[20]. Rituximab monotherapy is hopeful for low toxic and good tumor response^[20-21]. It will be important to conduct an RCT of IFLs. However, that represents a challenge, due to the rarity of the disease and the necessity of long follow-up periods (> 10 years). The limitation of this study was that it was a retrospective small case series and short follow-up period.

CONCLUSION

DBE was found to be necessary for a precise diagnosis of GI-FLs that involved the small intestine. Endoscopic features, including a nodule/mass and an ileal lesion were possibly associated with the clinical stage.

REFERENCES

- [1] Armitage, J. O., & Weisenburger, D. D. (1998). New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. *J. Clin Oncol*, *16*, 2780-95.
- [2] Nakamura, S., Matsumoto, T., & Takeshita, M. et al. (2000). A clinicopathologic study of primary small intestine lymphoma: Prognostic significance of mucosa-associated lymphoid tissue-derived lymphoma. *Cancer*, *88*, 286-94.
- [3] Yoshino, T., Miyake, K., & Ichimura, K, et al. (2000). Increased incidence of follicular lymphoma in the duodenum. *Am J Surg Pathol*, *24*, 688-93.
- [4] Yamamoto, S., Nakase, H., & Yamashita, K. et al. (2010). Gastrointestinal follicular lymphoma: Review of the literature. *J Gastroenterol*, *45*, 370-88.
- [5] Nakamura, S., Matsumoto, T., & Umeno, J., et al. (2007). Endoscopic features of intestinal follicular lymphoma: The value of double-balloon enteroscopy. *Endoscopy*, *39* (Suppl1), E26-7.
- [6] Higuchi, K., Komatsu, K., & Wakamatsu, H., et al. (2007). Small intestinal follicular lymphoma with multiple tumor formations diagnosed by double-balloon enteroscopy. *Intern Med*, *46*, 705-9.
- [7] Akamatsu, T., Kaneko, Y., & Ota, H., et al. (2010). Usefulness of double balloon enteroscopy and video capsule endoscopy for the diagnosis and management of primary follicular lymphoma of the gastrointestinal tract in its early stages. *Dig Endosc*, *22*, 33-8.
- [8] Mann, R. B., & Berard, C. W. (1983). Criteria for the cytologic subclassification of follicular lymphomas: A proposed alternative method. *Hematol Oncol*, *1*, 187-92.
- [9] Rohatiner, A, d'Amore, F., & Coiffier, B., et al. (1994). Report on a workshop convened to discuss the pathological and staging classifications of gastrointestinal tract lymphoma. *Ann Oncol*, *5*, 397-400.
- [10] Czuczman, M. S., Weaver, R., & Alkuzweny, B., et al. (2004). Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin's lymphoma treated with rituximab plus CHOP chemotherapy: 9-year follow-up. *J Clin Onco*, *22*, 4711-6.
- [11] Hiddemann, W., Kneba, M., & Dreyling, M., et al. (2005). Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: Results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood*, *106*, 3725-32.
- [12] Therasse, P., Arbuck, S. G., Eisenhauer, E. A., et al. (2000). New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*, *92*, 205-16.
- [13] Damaj, G., Verkarre, V., & Delmer, A., et al. (2003). Primary follicular lymphoma of the gastrointestinal tract: a study of 25 cases and a literature review. *Ann Oncol*, *14*, 623-9.
- [14] Huang, W. T., Hsu, Y. H., & Yang, S. F., et al. (2008). Primary gastrointestinal follicular lymphoma: A clinicopathologic study of 13 cases from Taiwan. *J Clin Gastroenterol*, *42*, 997-1002.
- [15] Shia, J, Teruya-Feldstein, J., & Pan, D., et al. (2003). Primary follicular lymphoma of the gastrointestinal tract: a clinical and pathologic study of 26 cases. *Am J Surg Pathol*, *26*, 216-24.
- [16] Tari, A., Asaoku, H., & Kunihiro, M., et al. (2011). Clinical features of gastrointestinal follicular lymphoma: comparison with nodal follicular lymphoma and gastrointestinal MALT lymphoma. *Digestion*, *83*, 191-7.
- [17] Nadal, E., Martinez, A., & Jimenez, M., et al. (2002). Primary follicular lymphoma arising in the ampulla of Vater. *Ann Hematol*, *81*, 228-31.

- [18] Sapoznikov, B., Morgenstern, S., & Raanani, P., et al. (2007). Follicular lymphoma with extensive gastrointestinal tract involvement: Follow-up by capsule endoscopy. *Dig Dis Sci*, 52, 1031-5.
- [19] Takata, K., Okada, H., & Ohmiya, N., et al. (2011). Primary gastrointestinal follicular lymphoma involving the duodenal second portion is a distinct entity: A multicenter, retrospective analysis in Japan. *Cancer Sci* 102,1532-6.
- [20] Schmatz, A. I., Streubel, B., & Kretschmer-Chott, E., et al. (2011). Primary follicular lymphoma of the duodenum is a distinct mucosal/submucosal variant of follicular lymphoma: A retrospective study of 63 cases. *J Clin Oncol*, 29,1445-51.
- [21] Kahl, B. (2012). *Is there a role for "watch and wait" in follicular lymphoma in the rituximab era* (pp.433-8)? Hematology Am Soc Hematol Educ Program.