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Case Report

Primary Duodenal Follicular Lymphoma Treated With Rituximab Monotherapy and Followed-up for 15 Years

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A 41-year-old woman was diagnosed with duodenal follicular lymphoma. She had no other lesions and was assigned to a "watch and wait" policy. Swelling of the inguinal lymph nodes appeared 45 months later, and rituximab monotherapy resulted in complete remission. However, follicular lymphoma recurred in the stomach, rectum and mesenteric and external iliac lymph nodes 81 months after the therapy. The patient received rituximab monotherapy again and has remained in complete remission in the fifteenth year after the initial diagnosis. This case suggests the usefulness of rituximab monotherapy in the long-term management of intestinal follicular lymphoma.

Key words: follicular lymphoma, duodenum, rituximab

Follicular lymphoma is defined as a neoplasm of transformed follicle center B cells [1]. Although most follicular lymphoma cases present with nodal involvements, primary follicular lymphoma lesions can arise in the gastrointestinal tract [2–7]. The number of patients newly diagnosed with primary gastrointestinal follicular lymphoma has been increasing in recent years, as increasing numbers of endoscopists and gastroenterologists become familiar with this entity. As a result, primary gastrointestinal follicular lymphoma was listed in the latest version of the World Health Organization (WHO) classification of lymphoid tissues as a distinct variant of systemic follicular lymphoma [6]. However, the standard therapy for primary gastrointestinal follicular lymphoma remains to be determined. Moreover, only a few reports are available regarding the long-term prognosis of this disease, particularly that beyond 10 years.

Here we describe a patient with primary duodenal follicular lymphoma who was treated with single-agent rituximab and followed-up for 15 years. It is noteworthy that the disease relapse occurred not in the duodenum, but in the stomach and rectum. This case underscores the importance of surveillance of not only the duodenum but the entire intestinal tract during the follow-up of primary duodenal follicular lymphoma cases.

Case Report

A 41-year-old woman underwent esophagogastroduodenoscopy for screening as a routine medical checkup. Multiple white nodules were detected in the

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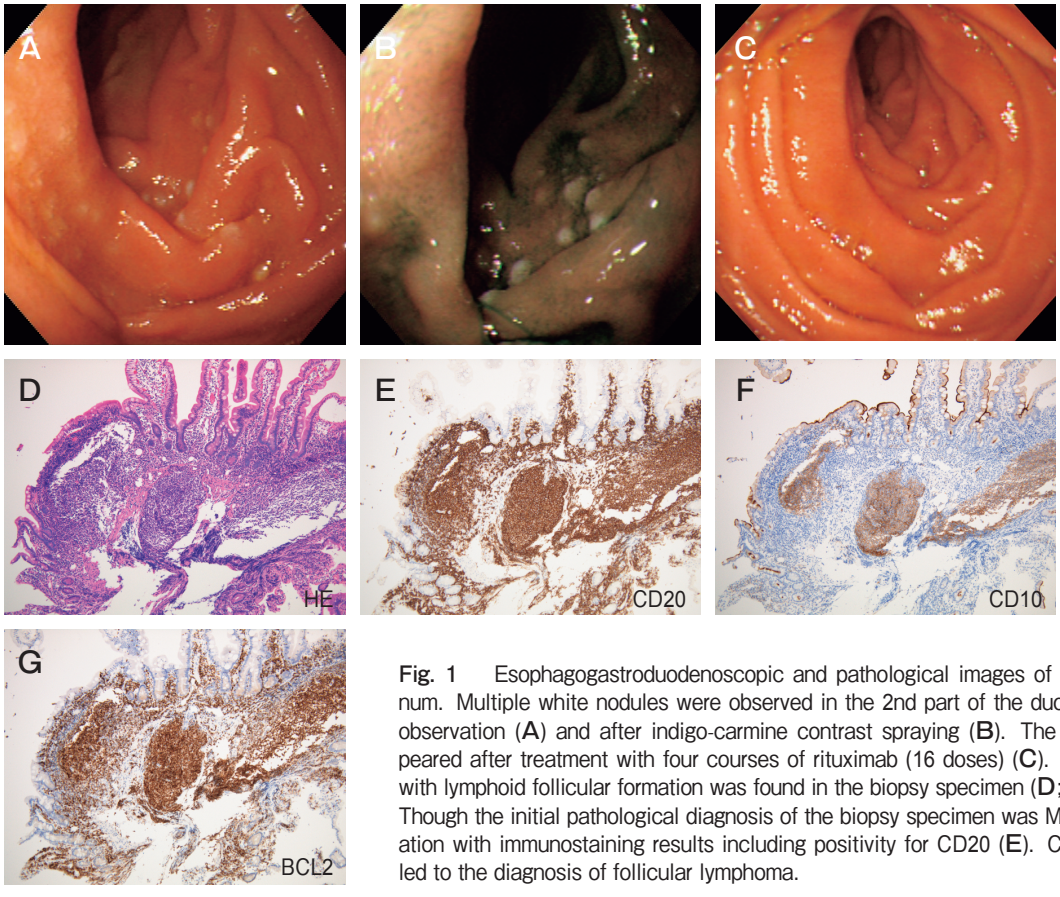

Fig. 1 Esophagogastroduodenoscopic and pathological images of the lesion in the duodenum. Multiple white nodules were observed in the 2nd part of the duodenum under white-light observation (**A**) and after indigo-carmine contrast spraying (**B**). The duodenal lesions disappeared after treatment with four courses of rituximab (16 doses) (**C**). Infiltration of tumor cells with lymphoid follicular formation was found in the biopsy specimen (**D**; hematoxylin and eosin). Though the initial pathological diagnosis of the biopsy specimen was MALT lymphoma, reevaluation with immunostaining results including positivity for CD20 (**E**). CD10 (**F**), and BCL2 (**G**) led to the diagnosis of follicular lymphoma.

2nd part of the duodenum (Fig. 1A, B). Though the initial pathological diagnosis of the biopsy specimen was extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), reevaluation with immunostaining results including positivity for CD20, CD10, and BCL2 led to the diagnosis of follicular lymphoma [8] (Fig. 1D–G). The pathological grade was 1, according to the WHO classification [6]. The patient had no history of gastrointestinal or lymphoproliferative diseases. Physical examination revealed no abnormalities, and there was no evidence of hepatosplenomegaly or peripheral lymphadenopathy. Colonoscopy and computed tomography (CT) scanning of the neck, chest, abdomen and pelvis revealed no lymphoma lesions in other parts of the body. The duodenal lesions were also too small to detect by CT scanning. Bone marrow aspirate and biopsy were negative for lymphoma infiltration. The patient had no symptoms, and thus she was assigned to a "watch and wait" policy. However, suspicious swelling of the inguinal lymph nodes appeared 45 months later. Progression of follicular lymphoma was confirmed by pathological evaluation of biopsied samples of the lymph node. Treatment with 4 courses of rituximab (375 mg/m^2 intravenous infusion once weekly for 4 weeks/course, every 6 months) resulted in the disappearance of the duodenal and inguinal lesions.

The patient remained in complete remission until an esophagogastroduodenoscopy performed 81 months after the start of rituximab monotherapy detected a 10-mm reddish, flat lesion in the gastric fundus (Fig. 2), despite the fact that the duodenal lesions showed no signs of recurrence (Fig. 1C). Additionally, colonoscopy showed small-protruded lesions in the rectum, and biopsy specimens from both the gastric and rectal lesions confirmed the involvement of follicular lymphoma (Fig. 3). Positron emission tomography scanning demonstrated swelling of the mesenteric and right external iliac lymph nodes and

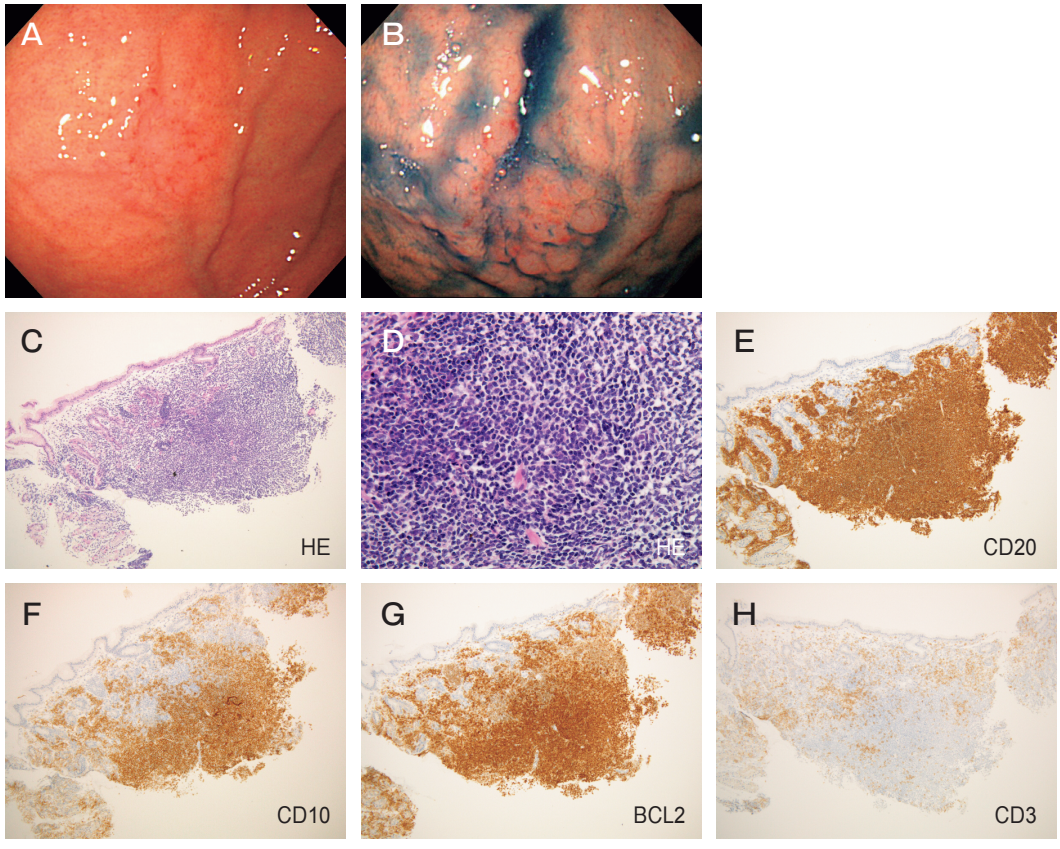

Fig. 2 Esophagogastroduodenoscopic and pathological images of the stomach lesions. A 10-mm-size reddish, flat lesion was detected in the gastric fundus under white-light observation (**A**) and after indigo-carmine contrast spraying (**B**). The biopsy specimen confirmed the diagnosis of follicular lymphoma (**C**, **D**; hematoxylin and eosin, **C**, **D**). Immunohistochemical studies of the biopsy specimen showed that lymphoma cells were positive for CD20 (**E**), CD10 (**F**), and BCL2 (**G**) and negative for CD3 (**H**).

tracer uptake of fluorodeoxyglucose within these lesions (Fig. 4). These involvements were considered to be relapsed follicular lymphoma lesions rather than de novo lymphoma lesions, although clonality testing was not done. Rituximab monotherapy was restarted, and the disappearance of the stomach lesion was confirmed by esophagogastroduodenoscopy 5 months after the initiation of therapy (Fig. 5A, B). The patient received another four courses of rituximab monotherapy. The rectal lesion disappeared 14 months after the initiation of rituximab therapy, and the treatment was completed 2 years after induction (Fig. 5C). No recurrence of follicular lymphoma has been detected for 4 years since the completion of the second course of rituximab monotherapy. The patient appears to be in complete remission in the fifteenth year since being diagnosed with duodenal follicular lymphoma.

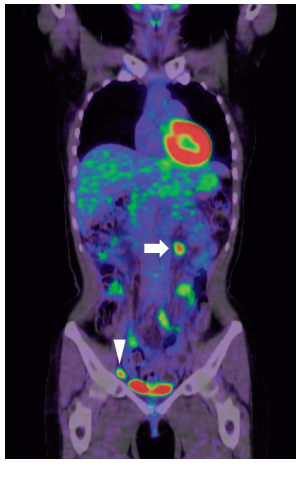

Fig. 4 Positron emission tomography scanning images. Swelling of the mesenteric (arrow) and right external iliac lymph nodes (arrowhead) and tracer uptake of fluorodeoxyglucose within these lesions were observed.

Discussion

The duodenum is one of the most frequently

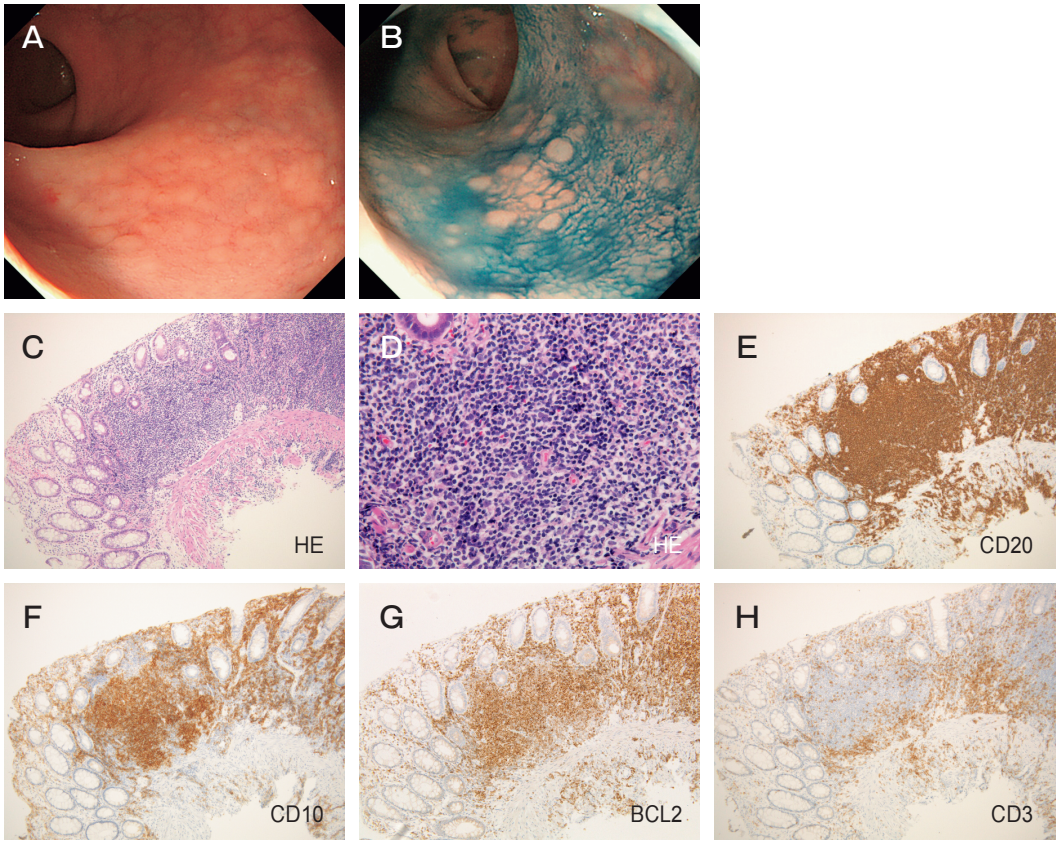

Fig. 3 Colonoscopic and pathological images of the rectal lesions. Small, protruding lesions were shown in the rectum under white-light observation (**A**) and after indigo-carmine contrast spraying (**B**). The biopsy specimen revealed that the lesion was follicular lymphoma (**C**, **D**; hematoxylin and eosin, **C**, **D**). Immunohistochemical studies showed that the lymphoma cells were positive for CD20 (**E**), CD10 (**F**), and BCL2 (**G**) and negative for CD3 (**H**).

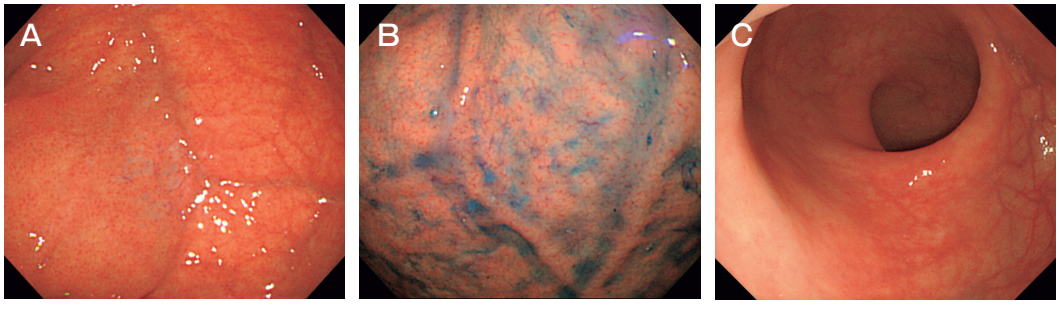

Fig. 5 Esophagogastroduodenoscopic and colonoscopic images. After treatment with rituximab every 6 months, the gastric (**A**, **B**) and the rectal lesions (**C**) disappeared.

affected sites in cases with primary intestinal follicular lymphoma [2]. The typical endoscopic presentation of duodenal follicular lymphoma is well known to be multiple tiny whitish granules, as presented in our case [7, 9–10]. Historically, the first case of gastrointestinal follicular lymphoma was reported in 1997 [11]. Subsequently, Yoshino and coworkers summarized their cases in 2000 and indicated increased incidence of this disease arising in the duodenum [2]. Therefore, it has only been possible to shed light on the features of primary intestinal follicular lymphoma in the last decade.

Generally, follicular lymphoma of nodal origin is characterized by slow-growing lymphadenopathy [6, 12]. Thus, because of its indolent nature, nodal follicular lymphoma patients with limited stage show favorable overall survival; 10-year overall survival rates after radiation therapy range from 60 to 80%, and the median survival is approximately 19 years [12-13]. We assume that primary follicular lymphomas arising in the gastrointestinal tract have prognoses similar to or even better than those of limited-stage nodal follicular lymphomas, particularly in cases with duodenal involvement [7, 15]. In this context, analysis of the prognosis over a long term of 10 years or more is considered to be crucial. However, the long-term clinical course has rarely been reported due to the historical background of this disease entity as described above. For example, although case series of gastrointestinal follicular lymphomas have recently been reported by several institutions [9, 15-16] as well as by us [7], few studies include cases followed up for more than 10 years [17].

Besides the detailed depiction of the 15-year clinical course, our present case has 2 important implications regarding the management of primary intestinal follicular lymphomas. First, single-agent rituximab caused the lymphoma lesions to regress. In cases of nodal-origin follicular lymphomas, there are many reports on the efficacy of rituximab monotherapy. Colombat *et al.* [18] noted that 80% of untreated follicular lymphoma patients with a low tumor burden responded, and that 48% of the patients analyzed achieved complete molecular remission after four infusions of rituximab at 1-week intervals. In terms of long-term prognosis, 40/46 nodal cases treated with rituximab monotherapy were followed-up for 84 months [18]. The median progression-free survival was 23.5 months, and the overall survival rate was 91.7%. Though 5/46 patients died due to progression (n=1), myelodysplasia (n=1), diffuse large B-cell lymphoma (n=1) and solid tumors (n=2), the majority of patients with a low tumor burden were progression-free as a result of rituximab monotherapy. Schmatz *et al.* reported that, in gastrointestinal follicular lymphoma cases, rituximab monotherapy resulted in complete regression (n=4) and stable disease (n=1) without progression or relapse during the median follow-up of 36 months (29-118 months) [9]. Although a retrospective case series or prospective observational study should be conducted to examine the usefulness of rituximab monotherapy for gastrointestinal follicular lymphomas cases, these previous results indicate that rituximab monotherapy may be a therapeutic option for intestinal cases as well as nodal cases. Additionally, our case suggests that single-agent rituximab might be useful for treating relapse lesions in the intestinal tract.

In the present patient, rituximab was administered over an extended period of time for a total of 16 doses (intravenous infusion once weekly for 4 weeks/course, every 6 months) as the first-line treatment. The same treatment regimen was applied when the lymphoma lesions relapsed, because the progression-free survival had been long (over 6 years) after the initial treatment. This regimen was reported by Hainsworth *et al.* in 2002 as the first-line therapy for indolent non-Hodgkin's lymphomas [19]. In their report, the 36 patients with follicular lymphoma or small lymphocytic lymphoma who were treated showed high overall response (73%) and complete response (37%) rates. The usefulness of maintenance administration of rituximab for 2 years has also been reported in a phase 3, randomized controlled trial for patients with high-tumor-burden follicular lymphoma [20]. The trial study demonstrated that, although the overall survival was not different, progression-free survival was superior in patients treated with a 2-year administration of rituximab after immunochemotherapy compared with immunochemotherapy alone. Though there has been no report showing an advantage of rituximab administration for such an extended period of time (a total of 16 doses) over the usual regimen (a total of 4 doses) in follicular lymphoma patients with a low tumor burden, the present case shows the potential benefit of this protocol.

The second important implication is that the disease relapse was observed not in the duodenum where the lymphoma primarily had arisen, but in the stomach and rectum. To our knowledge, no report has described such a recurrence in distant gastrointestinal parts. Soubeyran *et al.* studied the natural clinical course of 26 cases with stage I nodal follicular lymphoma who underwent complete resection as an initial therapy [21-22]. Of these 26 patients, exactly half (13; 50%) had relapsed during a median follow-up of 6.3 years; the relapse site was local in 6 cases and distant from the resected lesion in 7. Consequently,

we consider that gastrointestinal follicular lymphoma patients should be followed up with esophagogastroduodenoscopy, colonoscopy and CT scanning, preferably in combination with enteroscopy, to detect the progression or relapse of lymphoma.

In summary, our present case with primary duodenal follicular lymphoma received rituximab monotherapy and was in complete remission in the 15th year after the initial presentation, despite a relapse in the stomach and rectum. This case indicates that rituximab monotherapy can result in long-term disease control in gastrointestinal follicular lymphoma patients. Moreover, periodic surveillance with gastroduodenoscopy and colonoscopy may be required during the follow-up period.

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