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Duodenal-type follicular lymphoma more than 10 years after treatment intervention: A retrospective single-center analysis

Saito M *et al.* D-FL after treatment intervention

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Abstract

BACKGROUND

Duodenal-type follicular lymphoma (D-FL) has been recognized as a rare entity that accounts for approximately 4% of primary gastrointestinal lymphomas. D-FL follows an indolent clinical course compared with common nodal FL and is generally considered to have a better prognosis. Therefore, the “watch and wait” approach is frequently adopted as the treatment method. Alternatively, there is an option to actively intervene in D-FL. However, the long-term outcomes of such cases are poorly understood.

AIM

To clarify the clinical outcomes after long-term follow-up in cases of D-FL with treatment intervention.

METHODS

We retrospectively analyzed patients who met the following criteria: the lesion was confirmed by endoscopy, the diagnosis of D-FL was confirmed histopathologically, and the patient was followed-up for more than 10 years after the intervention at our center.

RESULTS

We identified five cases of D-FL. Two patients showed a small amount of bone marrow involvement (Stage IV). Rituximab was used as a treatment for remission in all five patients. It was also used in combination with chemotherapy in 2 Stage IV patients as well as for maintenance treatment. Radiation therapy was performed in 2 cases, which was followed by complete remission (CR). Eventually, all 5 patients achieved CR and survived for more than 10 years. However, 3 patients experienced recurrence. One patient achieved a second CR by retreatment, and in another case, the lesion showed spontaneous disappearance. The remaining patient had systemic widespread recurrence 13 years after the first CR. Biopsy results suggested that the FL lesions were transformed into diffuse large B-cell lymphoma. The patient died four years later despite receiving various chemotherapies.

CONCLUSION

In this study, the treatment for patients of D-FL in Stage IV was successful. In the future, criteria for how to treat “advanced” D-FL should be established based on more additional cases. This study of patients with D-FL indicates that whole-body follow-up examinations should continue for a long time due to a fatal recurrence 13 years after reaching CR.

Key Words: Duodenal-type follicular lymphoma; Treatment; Long-term follow-up; Radiation; Rituximab; Chemotherapy

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Core Tip: Since duodenal-type follicular lymphoma (D-FL) progresses more indolently than common nodal FL, the “watch and wait” approach is frequently used without

intervention. To elucidate the clinical assessments of long-term follow-up in cases of D-FL with treatment intervention, we retrospectively examined 5 D-FL patients more than 10 years after treatment at our center. All 5 patients eventually achieved complete remission and survived for a long time. However, 3 patients experienced recurrence, and 1 patient died of the primary disease 21 years after first onset. In the future, it will be necessary to establish criteria for how to treat Stage IV “advanced” D-FL.

INTRODUCTION

Duodenal-type follicular lymphoma (D-FL) is an entity that was newly classified as a variant of FL in the 2017 World Health Organization classification^[1]. Most D-FLs are asymptomatic and are often incidentally found by esophagogastroduodenoscopy (EGD). Many large-scale clinical analyses of D-FL have been conducted in Japan^[2,3], where endoscopic screening for gastric cancer is frequently performed. This is because the incidence of gastric cancer is higher in Japan than in Western countries due to genetic and dietary factors^[4]. The most common endoscopic findings are “white granular or multiple nodular, polypoid lesions” in the descending portion of the duodenum^[5]. In addition, 85% of D-FL cases have been shown to have jejunal or ileal lesions, which were detected by capsule or double-balloon enteroscopy^[6].

D-FL follows an indolent progression compared with common nodal FL and has a generally better prognosis. Gene expression profiling of D-FL has yielded results similar to those obtained for mucosa-associated lymphoid tissue (MALT) lymphoma^[7,8]. Sufficient consensus has not yet been reached as to whether therapeutic treatment should be administered to patients with D-FL, and the “watch and wait” strategy is currently frequently performed^[9,10]. Long-term observations after intervention for D-FL have not been reported, and the long-term outcome of therapeutic treatment is not well understood. To clarify the clinical outcomes after long-term follow-up in cases of D-FL with treatment, we analyzed patients with D-FL who were followed-up for more than 10 years after intervention at our center.

MATERIALS AND METHODS

Study design

This was a retrospective, observational study at our center.

Patients

We included D-FL patients who were diagnosed endoscopically and histopathologically and followed clinically for more than 10 years after starting treatment intervention at our center between January 1998 and December 2009.

FL was predominantly diagnosed by a pathological diagnosis, although the detection of IgH-BCL2 by fluorescence in situ hybridization (FISH) was also respected to the same extent. In addition to EGD, patients were examined by colonoscopy, contrast computed tomography (CT), positron emission tomography (PET)-CT, bone marrow aspiration/biopsy, and, wherever possible, enteroscopy of the distal small intestine. Patients with a predominant systemic spread of nodal lesions were excluded. However, not all patients with swelling of the lymph nodes were excluded, as mentioned below in the “Results” section. Characteristics of the patients were assessed by performance status (PS), histological grading, and follicular lymphoma international prognostic index (FLIPI). Staging followed the Lugano classification for gastrointestinal lymphoma.

Treatment

This study was carried out as part of standard care in daily clinical practice under Japanese health insurance, and no treatments specific to this study were performed. Because bendamustine had not been approved by health insurance in Japan by 2010, we did not use it at the time of initial onset for applicable patients. Since 2008, for patients with newly developed nodal FL that progressed to Ann Arbor Stage III or higher, our center has provided maintenance treatment with rituximab bimonthly after reaching complete remission (CR).

RESULTS

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Five patients were included in this study. Of these patients, 4 were referred by Hokkaido University Hospital (Cases 1-4), including 1 recurrent patient (Case 1), and we were requested to continuously follow these patients. Table 1 shows the clinical features of these patients. Three patients were males in their 40 s, and two patients were females in their 60s. None of the 5 patients had subjective symptoms, and the trigger for the diagnosis was discovered incidentally by EGD. In all patients, PS was 0, and the histopathological grade was 1. Enteroscopy of the small bowel was performed in 3 patients, and distal intestinal lesions were observed in 2 patients (Figure 1A and B). Two patients showed a small amount of bone marrow involvement and were evaluated as Stage IV. Based on the FLIPI, 4 patients were low risk, and 1 patient was intermediate risk.

In all 5 patients, therapeutic intervention was performed with the goal of remission, and the treatment details and outcomes are shown in Table 2. Two patients were treated because of an advanced stage (Stage IV), and the other 2 patients requested treatment.

Rituximab was used as a treatment for remission in all five patients. In 2 patients, it was used as a single agent, and in 2 Stage IV patients it was used in combination with chemotherapy. Additionally, it was used for maintenance treatment. Radiation therapy was performed in 2 cases, followed by CR. Eventually, all 5 patients achieved CR and survived for more than 10 years. However, 3 patients experienced recurrence not only within 10 years. One patient achieved a second CR by retreatment, and for another patient, the lymphoma lesion disappeared spontaneously. The remaining patient had systemic widespread recurrence 13 years after the first CR. Later, the biopsy results suggested that the FL lesions had transformed into diffuse large B-cell lymphoma (DLBCL). The patient died four years later despite receiving various anticancer drugs.

Treatment summary of five cases

Case 1: Rituximab monotherapy (375 mg/m² × 4 times) resulted in a first CR at Hokkaido University Hospital. However, one year and three months later, D-FL

recurred not only locally in the duodenum but also in the cervical lymph nodes (Lugano Stage IV). Six cycles of R-THP-COP chemotherapy (a regimen in which doxorubicin in CHOP was changed to pirarubicin, which is less cardiotoxic; rituximab 375 mg/m² + cyclophosphamide 750 mg/m², pirarubicin 50 mg/m², and vincristine 1.4 mg/m², all on day 1, and prednisone 60 mg/body on days 1-5, every 3 wk) were administered, and this patient achieved a second CR.

Case 2: In addition to the duodenum, FL lesions spread to the jejunum and a slight extent to the bone marrow. *IgH-BCL2* was detected in barely 1% of the nucleated cells by FISH. The lesion was in Stage IV and presented an intermediate risk in FLIPI. The patient's first CR, including bone marrow findings (*IgH-BCL2*, 0.0%), was reached after administration of 3 cycles of R-CVP (rituximab + cyclophosphamide 750 mg/m² and vincristine 1.4 mg/m², all on day 1, and prednisone 60 mg/body on days 1-5 every 3 wk) and 5 cycles of R-F (rituximab + oral fludarabine 40 mg/m² on days 1-5 every 4 wk). Maintenance treatment with rituximab monotherapy was performed; however, one year and seven months later, PET-CT indicated lesions of the intestinal tract and nearby mesenteric lymph nodes in the ileocecal region (Figure 1C). Although no abnormalities were found in the duodenum or jejunum by endoscopy, multiple lymphomatous polyposis-like lesions were found in the ascending colon to the cecum (Figure 1D) and the rectum. *IgH-BCL2* positivity was found in 78.0% of the cells in biopsy tissue by FISH, suggesting recurrence (Lugano Stage III). After follow-up with no treatment, the lesion disappeared spontaneously approximately 1 year later (Figure 1E).

Case 3: FL lesions were observed not only in the duodenum (Figure 1F) but also in the mesenteric small lymph nodes (Figure 1G, diagnosed by biopsy) and bone marrow. *IgH-BCL2* positivity was observed in 5.8% of the nucleated cells by FISH (Stage IV). The distal small intestine was not searched by enteroscopy, and it cannot be ruled out completely that an extraduodenal primary lesion was present. The first CR was

achieved after 8 cycles of R-CHOP (rituximab + ⁴ cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1.4 mg/m², all on Day 1, and prednisone 60 mg/m² on days 1-5 every 3 wk), and maintenance treatment with rituximab was administered. The patient has not relapsed and still maintains the first CR.

Case 4: Double-balloon enteroscopy revealed no abnormal lesions in the distal small intestine. Radiation therapy (30 Gy) was performed, and rituximab (375 mg/m²) was administered twice during this treatment. This treatment strategy resulted in CR. The patient's D-FL did not recur without additional treatment.

Case 5: A ¹⁰ 42-year-old male was incidentally found to have an FL lesion ¹⁰ in the descending portion of the duodenum by EGD screening at our hospital, and he was pathologically diagnosed with D-FL (Figure 2A-C). Although small bowel enteroscopy had not been performed, the tumor indicated Lugano Stage I. Thus, we continued the 'watch and wait' approach for a year. However, the patient and his family requested treatment. He underwent chemotherapy with CHOP × 2 cycles, followed by oral therapy with etoposide (50 mg) for 2 mo. The extent of the duodenal lesion was slightly decreased (minimal response), and the patient was followed-up without treatment. Rituximab, which had at that time just been approved for use in Japan, was then administered as a single agent (once weekly, 4 times), and the lesion regressed steadily (partial response). Seven months later, radiation (40 Gy) was administered, and the patient's first CR was finally achieved 3 years after the intervention. Treatment-free follow-up continued nearly 13 years after achieving the first CR, and then the patient noted swelling in his neck. Despite having a lymph node biopsy, a pathological diagnosis could not be made. ¹ PET-CT showed clear ¹ uptake in the lungs and lymph nodes throughout the whole body. The maximum standardized uptake value (SUVmax) ranged from 3 to 15, which is consistent with the recurrence of FL (Stage IV) (Figure 3A-C). The duodenal lesion had maintained CR. After R-CHOP × 1 (stable disease), the patient underwent six cycles of the B-R regimen (rituximab + bendamustine 90 mg/m²

days 1-2, every 4 wk) and achieved metabolic CR according to PET-CT. He then received maintenance treatment with rituximab every 2-3 mo, however, the lesions of the lung and pelvic lymph nodes recurred. After 3 cycles of chemotherapy with R-BAC (rituximab + bendamustine 70 mg/m² days 1-2, cytarabine 800 mg/m² days 1-3, every 4 wk), the lung lesions disappeared, however, the nodal lesions in the pelvic cavity had progressed on PET-CT (Figure 3D). He was then treated with 2 cycles of CHOEP (cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m² all day 1, etoposide 100 mg/body days 1-3, and prednisone 60 mg/m² days 1-5, every 3 wk) and with various other drugs, including obinutuzumab, however, he remained non-CR. Biopsy of the pelvic lesion showed that the tumor cells were CD20-negative (Figure 2D and E). However, they were positive for BCL2 (Figure 2F), and B-cell clonality was demonstrated by the polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP) method (Figure 2G). The pathological diagnosis was DLBCL transformed from FL. The patient died approximately 4 years after recurrence and 21 years from the first onset.

DISCUSSION

D-FL is a unique subtype of FL that is classified in the WHO 2017 classification of FLs^[1]. It is usually localized to the intestinal tract and does not spread to the lymph nodes^[11]. Two clinical studies conducted by Takata et al and Schmatz et al reported that of a total of 162 patients with D-FL, no patients had a Lugano stage higher than Stage II^[6,11]. Epidemiologically, D-FL has been recognized as a rare entity that accounts for approximately 4% of primary gastrointestinal lymphomas^[9]. Bende et al identified the expression of surface IgA, which is not found in nodal FL, in the mucosal immune system as a feature of D-FL cells in the intestinal mucosa and the expression of $\alpha 4\beta 7$ integrin, which is thought to mediate "mucosal homing"^[12]. In addition, the gene expression profile of D-FL has been shown to be similar to that of MALT lymphoma^[8]. D-FL is almost asymptomatic and has an indolent clinical course, suggesting that it is biologically more similar to MALT lymphoma than to nodal FL^[7]. Therefore, follow-up

with a “watch and wait” approach without immediate intervention after diagnosis is frequently applied in cases of D-FL^[9,10]. In Case 2, FL lesions recurred in the ileocecal region and the rectum but spontaneously regressed. It was previously reported that D-FL disappeared spontaneously in 3%-30% of patients^[6,11]; as a result, it may have been possible to address this patient even if “watch and wait” was initiated.

Radiation is a representative treatment for D-FL, and there are several reports on its effectiveness^[11,13,14]. However, Takata *et al*^[6] reported that 46 of 54 patients (85%) with D-FL in the descending portion of the duodenum also had lesions in the distal small intestine, primarily the jejunum; thus, it is necessary to reliably determine the extent of the lesion. In Case 4, enteroscopy was performed, and the lesion did not extend to the distal small intestine. Because the lesion was localized to the duodenum, local irradiation was considered to be the most reasonable treatment.

Anticancer drug treatments for D-FL are based on the administration of rituximab ± chemotherapy, such as R-CHOP/R-CVP and B-R. D-FL is a low-grade malignancy and rarely requires chemotherapy, except in cases that exhibit histological transformation^[11,15]. ¹In indolent non-Hodgkin B-cell lymphoma, it has been reported that B-R was significantly better in progression-free survival than R-CHOP^[16], and there is also a case report of D-FL for which B-R was effective^[17]. However, as mentioned above, bendamustine was not yet available in Japan until 2010. In this case series, two patients had Lugano Stage IV disease (Case 2 and Case 3), and therapeutic intervention was performed using R-CHOP/R-CVP (change to fludarabine during the treatment course in Case 2). CR was reached in both cases, and maintenance treatment with rituximab monotherapy was performed. Rituximab monotherapy is effective for patients with high tumor-burden nodal FL^[18] and has also been used as a treatment at our center. The efficacy and safety of chemotherapy in Stage IV “advanced” D-FL cases without histological transformation and the importance of subsequent rituximab maintenance therapy should be investigated in a large number of cases in the future.

In Case 5, this patient was treated with a long nontreatment interval and reached his first CR over 3 years after the intervention. Considering this result, it might have been

possible to achieve CR earlier by radiation-centered treatment from the beginning, as in Case 4. Unfortunately, the patient relapsed nearly 13 years after reaching his first CR. Although he was treated with various anticancer drugs, he died of the primary disease approximately 4 years after recurrence. The PET-CT findings at the time of recurrence were consistent with FL. Lesions showing SUVmax 15 (> 13.55 , mean value of FL-grade 3b/DLBCL^[19]) were also detected, suggesting that they contained partial DLBCL component. Therefore, we clinically speculated that the initial D-FL in this patient underwent clonal evolution to become the final DLBCL. The incidence of histological transformation of D-FL into DLBCL was found to be 3.8%^[20] in 5 retrospective studies^[2,14,15,21,22] and 1 prospective study^[3]. This incidence is lower than the incidence of nodal FL, which has an incidence of histological transformation of 10.7% over 5 years at a rate of 2% per year^[23]. This transformation incidence is close to that of gastric MALT lymphoma, which is almost 3%^[24]. In past cases, D-FL patients with histological transformation to DLBCL did not receive systemic chemotherapy at the time of onset but instead underwent the “watch and wait” approach^[15,25-27]. Even in that situation, since the lymphoma was in remission due to R-CHOP chemotherapy, D-FL did not require aggressive treatment in the absence of histological transformation. Thus, the “watch and wait” follow-up approach was approved. However, in recent years, several patients with D-FL with histological transformation refractory to R-CHOP chemotherapy have been reported^[20,28]. The reason why our patient became refractory was likely histological transformation in addition to a change of the immunophenotype of the tumor to CD20-negative^[29]. Furthermore, the therapeutic response to the anticancer drugs was not good at the first onset. Fatal histological transformation occurred even after a long period of more than 17 years from the first onset; thus, patients with D-FL require lifelong follow-up.

CONCLUSION

In this study, five patients with D-FL who received treatment intervention regardless of clinical stage were evaluated with respect to the therapeutic effects. The treatment of

three Stage IV cases was successful, and in the future, criteria for how to treat “advanced” D-FL should be established based on more additional cases. This study indicates that it is necessary to continue to follow-up with whole body examinations while paying careful attention to the possibility of recurrence in D-FL because fatal recurrence can occur even 13 years after a patient achieves CR.

ARTICLE HIGHLIGHTS

Research background

Duodenal-type follicular lymphoma (D-FL) has been recognized as a rare primary gastrointestinal lymphoma. Because D-FL follows an indolent clinical course compared to nodal FL, the “watch and wait” approach is currently the general follow-up policy.

Research motivation

There is still insufficient consensus regarding the appropriate treatment of D-FL, and an option to actively treat D-FL is available. The long-term outcomes following the active treatment of D-FL are poorly understood.

Research objectives

² This study aimed to clarify the clinical outcomes through ² long-term follow-up in cases of D-FL with treatment intervention.

Research methods

We retrospectively examined five D-FL patients who underwent therapeutic intervention at our center from January 1998 to December 2009 and followed the clinical course of these patients for more than 10 years.

Research results

As a result of therapeutic intervention, all 5 cases reached complete remission (CR) and survived for more than 10 years. However, 3 of these cases experienced recurrence. One

patient achieved a second CR after retreatment, and in the other case, the lesion spontaneously disappeared. The remaining patient experienced widespread systemic recurrence 13 years after the first CR. This patient died four years later despite treatment with various anticancer chemotherapies.

Research conclusions

Five patients with D-FL who received treatment intervention regardless of clinical stage were evaluated with respect to the therapeutic effects of the treatment. Because fatal recurrence was found to occur even 13 years after the first CR, it is necessary to continue whole-body follow-up examinations for individuals diagnosed with D-FL.

Research perspectives

Only 5 cases were examined in this study. By including more D-FL patients and evaluating their treatment, criteria for how to treat Stage IV “advanced” cases can be explored.

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Figure Legends

Figure 1 Videography findings of cases 1-3. A and B: Endoscopic findings of case 1, lesions at (A) the descending portion of the duodenum and (B) the jejunum; C-E: Positron emission tomography findings of case 2; the arrow indicates a mesenteric nodal lesion in the ileocecal region (C); colonoscopy findings showed multiple lymphomatous polyposis-like lesions in the ascending colon (D); one year later, the lesion spontaneously disappeared (E); F and G: Esophagogastroduodenoscopy findings

of case 3; lymphoma lesions were revealed in the descending portion of the duodenum (F); abdominal computed tomography findings. Mesenteric lymph nodes were swollen (arrowhead) (G).

Figure 2 Pathological findings of case 5. The upper row shows the histology at the time of onset; the lower row shows images obtained 21 years later and at the final stage of treatment; A and B: HE staining; C and D: CD20 staining; E and F: BCL-2 staining; G: ⁶ The polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP) method, the arrow indicates bands that represent B-cell clones.

²³ **Figure 3 Positron emission tomography-computed tomography imaging of case 5.** Arrows point to lymphoma lesions at recurrence; A: Longitudinal image; B: Chest; C: Pelvic cavity; D: After treatment with various anticancer drugs, the nodal lesions in the pelvic cavity progressed further.

Table 1 Clinical features of five patients

| Case | Age | Sex | Trigger to be found | PS | Grade | Distal lesion | intestinal | Extra-duodenal lesion | Initial stage | FLIPI |
|------|-----|-----|---------------------|----|-------|---------------|------------|----------------------------|---------------|-------|
| 1 | 65 | F | Screening EGD | 0 | 1 | Jejunum | (-) | | I | Low |
| 2 | 63 | F | Follow-up for GERD | 0 | 1 | Jejunum | | Bone marrow | IV | Int |
| 3 | 40 | M | Screening EGD | 0 | 1 | Not tested | | Bone marrow, mesenteric LN | IV | Low |
| 4 | 42 | M | Screening EGD | 0 | 1 | (-) | (-) | | I | Low |
| 5 | 42 | M | Screening EGD | 0 | 1 | Not tested | (-) | | I | Low |

PS: Performance status; FLIPI: Follicular lymphoma international prognostic index; EGD: Esophagogastrroduodenoscopy; GERD: Gastroesophageal reflux disease; LN: Lymph nodes

Table 2 Treatment and outcome of five patients

| Case | Treatment motive | Initial Treatment | Effect | Rituximab maintenance | Relapse lesion / re-Stage (From the end of treatment) | 2nd Treatment | Outcome (From the 1st onset) |
|------|---|--------------------|--------|-----------------------|--|----------------------|---|
| 1 | (previously followed doctor's judgment) | RTX | 1st CR | (-) | Duodenum + cervical LN/ Stage IV (1 year and 3 months) | R-THP•COP | 2nd CR (18 years <) |
| 2 | In Stage IV | R-CVP+R-F | 1st CR | (+) | Colon + mesenteric LN/ Stage III (1 year and 7 months) | watch | 2nd CR (12 years <) |
| 3 | In Stage IV | R-CHOP | 1st CR | (+) | (-) | — | 1st CR (13 years <) |
| 4 | patient's request | Radiation + RTX | 1st CR | (-) | (-) | — | 1st CR (16 years <) |
| 5 | patient's request | CHOP/RTX/Radiation | 1st CR | (-) | Lung + systemic LN/ Stage IV (13 years) | B-R/R-BAC/CHOEP/ONTZ | Death due to primary disease (21 years) |

RTX: Rituximab; R-CVP: Rituximab + cyclophosphamide, vincristine, and prednisone; R-F: Rituximab + oral fludarabine; CHOP: Cyclophosphamide, doxorubicin, vincristine, and prednisone; THP•COP: Cyclophosphamide, pirarubicin, vincristine, and prednisone; B-R: Rituximab + bendamustine; BAC: Bendamustine and cytarabine; CHOEP: Cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone; ONTZ: Obinutuzumab.

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