Diagnosis of the jejunoileal lymphoma by double-balloon endoscopy

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Abstract

AIM: To investigate the feasibility of double-balloon endoscopy (DBE) to detect jejunoileal lymphoma, compared with fluorodeoxyglucose positron emission tomography (FDG-PET).

METHODS: Between March 2004 and January 2011, we histologically confirmed involvement of malignant lymphoma of the jejunoileum in 31 patients by DBE and biopsy. In 20 patients of them, we performed with FDG-PET. We retrospectively reviewed the records of these 20 patients. Their median age was 64 years (range 50-81). In the 20 patients, the pathological diagnosis of underlying non-Hodgkin’s lymphoma (NHL) comprised follicular lymphoma (FL, \(n = 2\)), enteropathy associated T cell lymphoma (ETL, \(n = 1\)) and anaplastic large cell lymphoma (ALCL, \(n = 1\)).

RESULTS: Ten cases showed accumulation by FDG-PET (50%). FDG-PET was positive in 3 of 12 FL cases (25%) while in 7 of 8 non-FL cases (88%, \(P < 0.05\)). Intestinal FL showed a significantly lower rate of positive FDG-PET, in comparison with other types of lymphoma. Cases with endoscopically elevated lesions (\(n = 10\)) showed positive FDG-PET in 2 (20%), but those with other type NHL did in 8 of 10 (80%, \(P < 0.05\)). When the cases having elevated type was compared with those not having elevated type lesion, the number of cases that showed accumulation of FDG was significantly smaller in the former than in the latter.

CONCLUSION: In a significant proportion, small intestinal involvement cannot be pointed out by FDG-PET. Especially, FL is difficult to evaluate by FDG-PET but essentially requires DBE.

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Key words: Double-balloon endoscopy; Non-Hodgkin’s lymphoma; Jejunoileum; Fluorodeoxyglucose positron emission tomography; Follicular lymphoma

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INTRODUCTION

The clinical stage of non-Hodgkin’s lymphoma (NHL) is usually determined by imaging modalities such as com-
MATERIALS AND METHODS

Patients
Between March 2004 and January 2011, we histologically confirmed involvement of malignant lymphoma of the jejunoileum in 31 patients by DBE and biopsy. In 20 patients of them, we performed with FDG-PET. We retrospectively reviewed the records of these 20 patients. Their median age was 64 years (range 50-81 years). Their demographic and clinical characteristics are summarized in Table 1. In the 20 patients, the pathological diagnosis of underlying NHL comprised follicular lymphoma (FL, n = 12), diffuse B cell lymphoma (DLBCL, n = 4), mantle cell lymphoma (MCL, n = 2), enteropathy associated T cell lymphoma (ETL, n = 1) and anaplastic large cell lymphoma (ALCL, n = 1) (Table 2).

Eligibility criteria for DBE in lymphoma patients
Eligibility criteria for DBE in lymphoma patients were: (1) lymphoma infiltration of the stomach, duodenum or colon proven by gastrointestinal endoscopy or colonoscopy which are routine evaluation of lymphoma patients in our institution; (2) intraabdominal lesion suspected from CT or gallium-scintigraphy/FDG-PET imaging; or (3) any gastrointestinal symptoms such as a bloated sensation in the abdomen, abdominal pain, diarrhea, constipation, protein-losing syndrome or hematochezia. Exclusion criterion was poor performance status of grade 3 or 4 assessed by Eastern Cooperative Oncology Group classification[7]. We conducted DBE from both oral and anal routes in principle. However, in the patients who did not give consent to this dual approach mainly due to the examination burden, we selected only one-sided insertion according to the information of preceding gastrointestinal endoscopy and colonoscopy.

Locations and multiplicity of lymphoma lesions confirmed by DBE
We observed jejunum and ileum in 11 cases by the combination of both oral and anal approach, only jejunum in 4 cases by oral approach, and only ileum in 5 cases by anal approach. Six, five and nine patients had lesions in the jejunum, ileum, and in both, respectively. We observed multiple lesions in 16 cases, solitary lesion in 2 cases, and diffuse lesion in 2 cases.

DBE
DBE was carried out in the Endoscopy Unit of Gifu University Hospital using a Fujinon system (EN450-T5/W, Fujinon Corporation, Saitama, Japan). The whole procedure is similar to that described in detail elsewhere[8-10]. In brief, the system comprises an endoscope and a flexible overtube that are both provided with soft latex balloons connected through a built-in air route to a controlled pump system. Patients ingested 2 L of a polyethylene glycol-based solution on the day before the examination. The small intestine was examined endoscopically using a combination of anterograde (oral) and retrograde (anal) DBEs. We obtained biopsy specimens of all lesions detected during the procedure.

Statistical analysis
Pretreatment characteristics were compared between FDG-PET-positive and -negative patients by the Fisher’s exact test or Student’s t-test. P values of < 0.05 indicated significance.
In the 10 cases that showed accumulation of FDG, 4 tumors were classified as ulcerative type (Figure 1), 2 as MLP type, 1 as elevated type (Figure 2), 1 as diffuse-infiltrating type, 1 as diffuse infiltration+ulcerative and 1 as elevated + MLP type. In other 10 cases that did not show accumulation of FDG, 4 tumors were classified as elevated type (Figure 3), 1 as ulcerative type, 1 as MLP type, and 4 as elevated + MLP type. When the cases having elevated type was compared with those not having elevated type lesion, the number of cases that showed accumulation of FDG was significantly smaller in the former than in the latter (P < 0.05) (Table 2).

**Other parameters**
Clinical stage, abdominal symptom, B symptom, other gastrointestinal tract lesions, performance status (PS), lactate dehydrogenase (LDH), hemoglobin (Hb) or soluble interleukin-2 receptor (sIL-2R) did not produce significant difference in the accumulation of FDG (Table 2).

**Adverse events of DBE**
We had no complications associated with DBE in all twenty cases.

**DISCUSSION**
NHL frequently involves the gastrointestinal tract and forms multiple tumors. Since the small intestine is a preferential site of such involvement and could be complicated with perforation following chemotherapy, it is important to diagnose NHL invasion into the small intestine in advance. For this aim, DBE is invasive while FDG-PET is not. Thus, FDG-PET is now a routine measure for staging and follow-up of patients with malignant lymphoma, since it has been proven as useful to clinically evaluate these patients. In our study, however, FDG-PET could not detect small intestinal involvement in 10 (50%) of the 20 patients with confirmed small intestinal involvement. Therefore, we emphasize that DBE is essential for the diagnosis of such involvement of lymphoma and for the subsequent management of the patients. Less invasive capsule endoscopy can image the 10 cases, histopathological classification was FL in 3 cases, DLBCL in 3, MCL in 2, ETL in 1 and ALC in 1. In the cases which did not show FDG accumulation, histopathological classification was FL in 9 cases and DLBCL in 1. Thus, intestinal FL showed a significantly lower rate of positive FDG-PET, in comparison with other types of lymphoma (P < 0.05) (Table 2).

### Table 2 Characteristics of fluorodeoxyglucose positron emission tomography-positive or -negative patients

|                  | FDG-PET | P value |
|------------------|---------|---------|
|                  | All cases | Positive | Negative |
| Histology        |          |         |         |
| FL               | 20       | 10      | 10      |
| DLBCL            | 4        | 3       | 1       |
| MCL              | 2        | 2       | 0       |
| ETL              | 1        | 1       | 0       |
| ALC              | 1        | 1       | 0       |
| FL               | 12       | 3       | 9 < 0.05 |
| Others           | 8        | 7       | 1       |
| Endoscopic findings |      |         |         |
| Elevated         | 5        | 1       | 4       |
| Ulcerative       | 5        | 4       | 1       |
| MLP              | 3        | 2       | 1       |
| Diffuse infiltration | 1    | 1       | 0       |
| Diffuse infiltration + ulcerative | 1 | 1 | 0 |
| Elevated + MLP   | 5        | 1       | 4       |
| Including elevated | 10    | 2       | 8       < 0.05 |
| Not including elevated | 10   | 8       | 2       |
| Clinical Stage   |          |         |         |
| I                | 1        | 1       | 1       |
| II               | 5        | 3       | 2       |
| III              | 3        | 1       | 2       |
| IV               | 9        | 5       | 5       |
| I / II           | 6        | 4       | 3       |
| III / IV         | 12       | 6       | 7       |
| Abdominal symptom|          |         |         |
| Present          | 6        | 5       | 1       |
| Absent           | 14       | 5       | 9       |
| B symptom        |          |         |         |
| Present          | 10       | 5       | 5       |
| Absent           | 10       | 5       | 5       |
| Other gastrointestinal tract lesions | |
| Absent           | 10       | 6       | 4       |
| Present          | 10       | 4       | 6       |
| Esophagus        | 2        | 2       | 0       |
| Stomach          | 6        | 4       | 2       |
| Duodenum         | 12       | 5       | 7       |
| Colon            | 2        | 2       | 0       |
| PS               |          |         |         |
| 0                | 18       | 9       | 9       |
| 1                | 2        | 1       | 1       |
| Hemoglobin (g/dL) |          |         |         |
| Median           | 13.7     | 13.1    | 14.1    |
| (range)          | (7.8-17.1) | (7.8-16.3) | (12.1-17.1) |
| Lactate dehydrogenase (IU/L) | | |
| Median           | 196      | 197     | 187     |
| (range)          | (108-1195) | (108-342) | (126-1195) |
| Soluble interleukin-2 receptor (U/mL) | |
| Median           | 1350     | 2302    | 802     |
| (range)          | (363-7410) | (371-6880) | (363-7410) |

1By Fisher’s exact test. FDG-PET: Fluorodeoxyglucose positron emission tomography; DLBCL: Diffuse large B-cell lymphoma; FL: Follicular lymphoma; MCL: Mantle cell lymphoma; ETL: Enteropathy associated T-cell lymphoma; ALC: Anaplastic large cell lymphoma; MLP: Multiple lymphomatous polyposis; PS: Performance status; NS: Not significant.

### RESULTS

#### Histopathological classification
Ten of 20 cases with malignant lymphoma confirmed by DBE showed accumulation by FDG-PET (50%). In these 10 cases, histopathological classification was FL in 3 cases, DLBCL in 3, MCL in 2, ETL in 1 and ALC in 1. In the cases which did not show FDG accumulation, histopathological classification was FL in 9 cases and DLBCL in 1. Thus, intestinal FL showed a significantly lower rate of positive FDG-PET, in comparison with other types of lymphoma (P < 0.05) (Table 2).
tions of 18F-FDG in the primary lesions, giving a low diagnostic sensitivity of 12.5%. In our study, the proportion of patients with positive FDG-PET was significantly lower in FL cases when compared to other types of lymphoma (Table 2). On the other hand, it is reported that FDG-PET detected disease on at least one site in 98% of FL patients [5] supporting its usefulness for staging of patients with FL [24]. However, in another report of duodenal FL, 18F-FDG accumulated in the mesenteric lymph nodes but not in the primary duodenal site [25]. Hoffmann et al [26] also reported that FDG-PET is not useful for clinical assessment of primary duodenal FL. Higuchi et al [27] further reported that increased uptake of 18F-FDG was not observed in the confirmed jejunoileal FL lesions in their 6 patients. We also experienced FL case that 18F-FDG accumulated in the intraabdominal lymph nodes, whereas there was no obvious uptake in the jejunoileal site (Figure 3). We thus think that FDG-PET is not useful for clinical assessment of jejunoileum FL and DBE is essential to diagnose the gastrointestinal involvement of FL. Thus, as reported by Tanaka et al [28], intestinal FL seems to have distinct clinicopathological characteristics from other intestinal lymphoma.

The morphological features of small intestinal involvement were basically the same as those in the stomach or duodenum [11-14]. We identified a variety of morphologies, such as ulcerative, MLP, diffuse infiltration, entire gastrointestinal tract and thus might also be useful to detect small intestinal involvement of lymphoma [16,17]. However, application of this method is limited, because biopsy specimens cannot be obtained. Although invasive, DBE is the sole endoscopic approach that enables biopsy of small intestine.

The good diagnostic ability of FDG-PET for extranodal lymphoma lesions has been demonstrated with sensitivity of 67%-100% [18-22]. Our sensitivity of FDG-PET was lower than previous reports, probably because the number of FL cases was large. Yamamoto et al [23] reported that in 14 of 16 FL cases of the small intestine, there were no obvious accumula-
and elevated types. The most typical finding in FL was multiple whitish small nodules. Nakamura et al. showed that endoscopic findings of primary intestinal FL by DBE were varied, including mass formation, swelling of folds, and stenosis of intestine. In our analysis, multiple whitish small nodules, mass formation and swelling of folds were included in elevated type.

In the cases including elevated type, accumulation of FDG appeared in significantly fewer cases than in those without elevated type (Table 2). For the reason, we suppose that majority of FL patients showed elevated type of small intestinal involvement.

Although we had no complications associated with DBE in all twenty cases, it is reported that 40 adverse events were experienced in 2362 DBE procedure (1.7%) [30], including pancreatitis in 7 patients (0.3%), bleeding in 19 patients (0.8%), perforation in 6 patients (0.3%), and others in 8 (0.3%). However, only regarding diagnostic DBE (1728 patients), the incidence of complication was 0.8% [30]. We think that DBE is a safe and well-tolerated method, but it is necessary to take care about adverse events.

In conclusion, in a significant proportion of lymphoma cases, small intestinal involvement cannot be pointed out by FDG-PET. Especially, the small intestinal FL is difficult to evaluate by FDG-PET but essentially requires DBE.

Figure 3 In other 10 cases that did not show accumulation of fluorodeoxyglucose, 4 tumors were classified as elevated type. A: In a 64-year-old female with follicular lymphoma, we identified abnormally increased fluorodeoxyglucose uptake only in the intraabdominal lymph nodes, but not in the small intestine; B: However, small intestinal involvement was confirmed by double-balloon endoscopy.

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