Follicular Lymphoma of the Duodenum: A Clinicopathologic Analysis of 26 Cases

Kazuhiro Sentani1, Akiko Miyagi Maeshima1, Junko Nomoto2, Dai Maruyama2, Sung-Won Kim2, Takashi Watanabe2, Yukio Kobayashi2, Kensei Tobinai2 and Yoshihiro Matsuno1,3

1Clinical Laboratory, 2Hematology and Stem Cell Transplantation Divisions, National Cancer Center Hospital, Tokyo and 3Department of Surgical Pathology, Hokkaido University Hospital, Sapporo, Japan

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Objective: Follicular lymphomas (FLs) occur commonly in the lymph nodes, and duodenal FL (DFL) is reported to be rare.

Methods: We analysed the clinical, morphological, immunohistochemical and genetic features of 26 cases of DFL. Primary DFLs and systemic FLs that involved the duodenum at any point during the clinical course were included in the analysis.

Results: Typically, primary DFLs (14 cases) were found incidentally at routine medical check-ups, whereas involvement of the duodenum by systemic FLs (12 cases) was found through staging procedures. All cases involved the second portion of the duodenum. Helicobacter pylori infection was common (71%). In all cases, the histologic grade was low (either grade 1 or 2), and CD20, CD10 and Bcl-2 were positive by immunohistochemistry. Immunoglobulin heavy chain gene (IGH) and bcl-2 gene (BCL2) fusion was frequently shown by fluorescence in situ hybridization (FISH) analysis: nine of 12 cases (75%) of primary DFL and 10 of 12 cases (83%) of systemic DFL were positive. Treatment regimens employed were rituximab (R) plus chemotherapy (10), R (6), chemotherapy (3), irradiation (3) and the other three patients were subjected to observation. After a median follow-up duration of 40 months (ranging 11–96 months), 17 patients were alive without disease, seven were alive with disease and one had died of lymphoma.

Conclusions: Primary DFLs resemble systemic and nodal FLs, except that the former has high incidence of early stage and low-grade histology. The duodenum appears to be a frequently involved extranodal site of FL with IGH/BCL2.

Key words: duodenum – follicular lymphoma – immunohistochemistry – FISH

INTRODUCTION

Follicular lymphoma (FL) is a neoplasm of follicular centre B cells and is one of the most common subtypes of non-Hodgkin lymphoma (NHL) in Europe and the USA (1). The most common subtype was reported to be diffuse large B-cell lymphoma (33%), followed by FL (18%) in Japan (2). Most patients with FL present with nodal involvement, and extranodal presentation occurs at the advanced stage. Primary extranodal FL has been reported to occur in the skin (3), salivary gland (4), ocular adnexa (5) and female genital tract (6). The gastrointestinal (GI) tract is the most commonly involved extranodal site of NHL, accounting for ~40% of all extranodal primary NHLs (7). However, FL of the GI tract represents only ~1–3.6% of all GI tract NHLs (8).

Duodenal FL (DFL) is a rare entity, with only a few reported cases (9–11). DFL is reported to be a characteristic clinicopathologic entity due to its localized nature and good prognosis (9,10). Yoshino et al. (9) reported that DFL was present around the Vater’s papilla and showed multiple small-size polyps. Sato et al. (11) reported that DFL had intermediate characteristics of FL and mucosa-associated lymphoid tissue (MALT) lymphoma.

Most cases of nodal FL have a Bcl-2-positive immunophenotype and show immunoglobulin heavy chain gene (IGH) and bcl-2 gene (BCL2) fusion; up to 85% of tumours shows IGH/BCL2 fusion in Europe and the USA (12), whereas 60% does so in Japan (13). However, the situation might differ for cases originating from other sites. For example, FL
of the skin, which is the most common site of extranodal FL, has a Bcl-2-negative immunophenotype and rarely shows IGH/BCL2 fusion (14).

In this study, we examined the clinical, morphological, immunohistochemical and genetic features of 26 cases of DFL at a single institution. We categorized the 26 DFLs for which staging data were available into two groups: 14 primary DFLs and 12 systemic DFLs, and compared them with previously described cases of nodal FL.

PATIENTS AND METHODS

PATIENTS

Twenty-six consecutive cases with a histologic diagnosis of DFL between April 1997 and October 2005 were retrieved from the archival pathology files of the National Cancer Center Hospital, Tokyo, Japan. All of the 26 DFLs were confirmed on the basis of morphologic and immunohistochemical features, and if available, the genetic features of FL. Clinical information was obtained from the medical records. We categorized the 26 DFLs into two groups on the basis of clinical stage: 14 primary DFLs and 12 systemic DFLs. For staging, the Ann Arbor staging system was used. The 26 patients were examined for staging by bone marrow aspiration or biopsy and computed tomography, and optionally, gallium scintigraphy. More recently, positron emission tomography and/or panendoscopy have been advocated as a tool for staging optionally, but were not performed in this series.

HISTOLOGIC EXAMINATION

Biopsy materials were fixed with 10% buffered formalin over-night, then 4 μm-thick sections were made from paraffin blocks and stained with haematoxylin and eosin (HE) for routine diagnosis. Each HE was histologically reviewed by three of the authors (KS, AMM and YM). Following the World Health Organization classification (15), each case was graded based on the number of centroblasts/high-power field (HPF), and patterns of follicular and/or diffuse growth were judged semi-quantitatively. Specifically, FL grade 1 showed 1–5 centroblasts/HPF; grade 2, 6–15 centroblasts/HPF; and grade 3, >15 centroblasts/HPF. The growth patterns were recorded as follicular when >75% of the tumour showed follicularity, follicular and diffuse when 25–75% of the tumour showed follicularity and focally follicular when <25% of the tumour showed follicularity. Helicobacter (H.) pylori infection was assessed by histologic examination using Giemsa staining, serologic testing or rapid urease test and was defined as positive if any of these tests gave a positive result.

IMMUNOHISTOCHEMICAL ANALYSIS

Immunohistochemical analysis was performed using a panel of antibodies. Sections 4 μm thick were cut from each paraffin block, deparaffinized and incubated at 121°C in pH 6.0 citrate buffer for 10 min for antigen retrieval. Antibodies included those against the following antigens: CD3 (PS1, Novocastra, Newcastle-upon-Tyne, UK: Polymer method); CD20 [L26, DAKO, Glostrup, Denmark: labelled streptavidin-biotin method (LSAB)], CD5 (4C7 Novocastra: Polymer method), CD10 (56C6, Novocastra: Polymer method), Bcl-2 (124, DAKO: LSAB) and cyclin D1 (DSC-6, Novocastra: Polymer method). Positive and negative controls were used for each antibody and for each case. CD20 and Bcl-2 were stained using a Biogenex autostainer trimedTM, and CD3, CD5, CD10 and cyclin D1 were stained using a DAKO autostainer plusTM. Immunoreactivity was judged positive if 30% or more of the tumour cells were stained.

RESULTS

The characteristics of the patients are shown in Table 1. The median age was 54 years (range 36–72 years), and there were 13 males and 13 females. The distribution according to the Ann Arbor staging system was stage I, 10 cases (38%); II, four cases (15%); III, one case (4%); IV, 11 cases (42%). Fourteen cases (stage I or II) were classified as primary DFL and 12 cases (stage III or IV) as systemic DFL. Seventy-nine per cent (11 of 14) of primary DFLs were found at routine medical check-ups for gastric cancer screening, and the remaining 21% (three of 14) of patients complained of digestive symptoms. Seventy-five per cent (nine of 12) of patients with systemic DFL complained of lymph node enlargement, weight loss or digestive symptoms, and duodenal involvement was found during the staging procedure at initial presentation. The remaining 25% (three of 12) of systemic DFLs were found at routine medical check-ups. All of the 25 cases for which endoscopic reports were available for review involved the second portion of the duodenum, and in 10 cases (40%), lesions were found in the vicinity of the Vater’s papilla. Fourteen cases had multiple polypoid lesions and 11 cases had a single elevated lesion.

The results of histologic and immunohistochemical analyses are shown in Table 2. The histologic grades of DFLs were as follows: in primary DFL, grade 1, 13 cases (93%); grade 2, one case (7%), in systemic DFL, grade 1, nine cases (75%); grade 2, three cases (25%). Two of the primary DFLs had been diagnosed as MALT lymphoma initially, and
Immunohistochemically, all of the DFLs were positive for CD20, CD10 and Bcl-2, and negative for CD3, CD5 and cyclin D1 (Figure 1). 

Helicobacter pylori infection was frequent in both primary and systemic DFLs: eight of 12 (67%) and seven of nine (78%), respectively. FISH analysis revealed IGH/BCL2 fusion in nine of the 12 cases (75%) of primary DFL and 10 of the 12 cases (83%) of systemic DFL.

Initial therapies for patients with primary DFL included cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) (two cases), rituximab (R) plus CHOP (R-CHOP) (1), irradiation (2), R monotherapy (6) and observation (3). For patients with systemic DFL, initial therapies included R-CHOP (eight cases), cyclophosphamide, vincristine, procarbazine and prednisone (C-MOPP) (1), R-C-MOPP (1) and irradiation (1) (Table 1). Two of the primary DFLs were initially treated by H. pylori eradication because their initial diagnosis was MALT lymphoma, and the clinical response to eradication was no change (NC) in both cases. After a median follow-up duration of 40 months (range 11–96 months), 17 of 25 patients were alive without disease, seven were alive with disease and one had died of lymphoma. The latter patient died due to leukemic change of FL 12 months after the diagnosis of systemic DFL. One of the patients alive with disease experienced transformation to diffuse large B-cell lymphoma in a submandibular lymph node 4 months after the diagnosis of primary DFL. The information on the outcome for one patient was not available.

### DISCUSSION

Primary FL of the GI tract is rare. Misraji et al. (16) reported the first case of primary DFL in 1997. Since then,
several other studies have suggested that DFL may be a characteristic clinicopathologic entity due to its localized nature and good prognosis (9,10). Patients usually present with symptoms related to bowel thickening. In some cases, the symptoms are mild and non-specific; patients often have relatively long-standing symptoms before seeking medical attention. In this series, 79% (11 of 14) of primary DFLs were detected at routine medical check-ups. However, most of the patients with systemic DFL complained of symptoms such as lymph node enlargement and weight loss, and DFL was detected through the staging procedure.

All cases involved the second portion of the duodenum, and in 40% of cases, the lesions were found in the vicinity of the Vater’s papilla. Yoshino et al. (9) speculated that occurrence of primary DFL at this site might be related to bile duct diseases, as suggested by the female predilection of the disease. However, in the present study, both primary and systemic DFL involved the second portion of duodenum, the speculation was not acceptable for systemic DFL.

DFL is reported to have histologic and immunohistochemical features that are similar to those of nodal FL, and not those of cutaneous FL (10). In the present study, all 26 DFLs showed low-grade histology, a predominant follicular growth pattern and immunohistochemical expression of CD20, CD10 and Bcl-2.

FISH, fluorescence in situ hybridization; H. pylori, Helicobacter pylori; ND, not done.

Table 2. Summary of morphologic, immunohistochemical and FISH analyses in 26 cases of duodenal follicular lymphoma

<table>
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<tr>
<th>Case</th>
<th>Grade</th>
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<th>CD20</th>
<th>CD10</th>
<th>Bcl-2</th>
<th>CD3</th>
<th>CD5</th>
<th>Cyclin D1</th>
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FISH, fluorescence in situ hybridization; H. pylori, Helicobacter pylori; ND, not done.

1Categorization as follicular: >75% of lymphoma has follicular pattern; follicular and diffuse: 25–75% follicular pattern.
numbers of cases suggested occurrence of t (14;18)(q32;q21) (9,10). Our FISH analysis indicated a high incidence of IGH/BCL2 fusion, which was detected in nine (75%) of the 12 primary DFLs, and 10 (83%) of the 12 systemic DFLs. DFL is suggested to resemble nodal FL more closely than FL at other extranodal sites. Moreover, in Japan, the frequency of t (14;18) in DFL tends to be higher than that of nodal FL. It is speculated that IGH/BCL2 fusion-positive cells are likely to involve the duodenum. On the other hand, Sato et al. (11) recently reported that most cases of DFL are localized, and appear to have characteristics intermediate between MALT lymphoma and nodal FL according to IGH/BCL2 and VH usage analyses. They detected IGH/BCL2 fusion using the major break point by polymerase chain reaction (PCR) in 27% of DFLs, which was a lower frequency than our result obtained using FISH. The difference might be due to the low sensitivity of PCR using their primer sets, which detect only about half of the translocations.

Patients with DFL underwent chemotherapy, R-containing chemotherapy, irradiation or observation. Although the follow-up period was short, all patients with DFL except one of systemic DFL were alive at the last follow-up, suggesting that DFL is an indolent disease with a favourable outcome, irrespective of whether it is primary or systemic. As R monotherapy was reported to be an effective treatment for a stage I DFL (20), we have a schedule to evaluate the issue in patients with primary DFL in our institute in the future.

In conclusion, we have revealed the characteristics of DFL; primary DFL is found incidentally at medical check-ups, occurs in the second portion of the duodenum in the vicinity of the Vater’s papilla, and appears to have a favourable outcome. It is histologically low grade, and phenotypically and genotypically similar to nodal FL. The characteristics of systemic DFL are similar to those of primary DFL histologically and genotypically. It is found at the time of systemic survey for pre-treatment staging.
Primary DFLs resemble systemic and nodal FLs, except that the former has a high incidence of early stage disease and low-grade histology. Primary and systemic DFLs may constitute a continuous spectrum. The duodenum may be a frequently involved extranodal site of FL with IGH/BCL2.

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Conflict of interest statement
None declared.

References