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Original contribution

Comparison of clinicopathologic characteristics of gastric follicular lymphomas and duodenal follicular lymphomas☆,☆☆

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Summary We compared the incidence, esophagogastroduodenoscopy (EGD) findings, and histopathologic characteristics of gastric and duodenal follicular lymphomas (FL). Of 626 FL cases, primary gastric FL and secondary gastric involvement of FL were observed in 1% and 5% of the cases, respectively, which were lower incidences than duodenal FL (10% and 9%, respectively). Gastric FL usually appeared as submucosal tumors (primary, 71%; secondary, 79%), whereas duodenal FL, as granular lesions (primary, 92%: secondary, 87%). In the granular duodenal lesions, the neoplastic follicles were located sparsely on the muscularis mucosa and could be found between villi, whereas in the stomach, similar lesions were hidden within the lamina propria, and only larger lesions such as submucosal tumors could be detected on the mucosal surface. The differences in the incidences and EGD findings were considered to be associated with structural differences of the lamina propria. Typical FL features: grades 1–2 histology, follicularity, and $CD10^+$ and/or $BCL6^+$ and $BCL2^+$ were usually observed in all primary and secondary gastric and duodenal FL. Gastroduodenal and bone marrow involvement were found in 12% and 33% of the cases, respectively, and there was no significant correlation between them ($P = .095$). Twenty-nine cases (5%) were up-staged by gastroduodenal-positive results. In conclusion, the histopathology of gastric FL was similar to that of duodenal and nodal FL; the differences in the incidence and EGD findings between gastric and duodenal FL were considered to be associated with structural difference of the lamina propria, and EGD was useful as a staging procedure.

1. Introduction

Follicular lymphoma (FL) is the most common low-grade B-cell lymphoma. Primary intestinal FL was described as a variant of FL in the World Health Organization

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Classification of Tumours of Haematopoietic and Lymphoid Tissues published in 2008 [1], and its name was changed to duodenal-type FL in the 2016 revision of the World Health Organization classification of lymphoid neoplasms [2]. The majority of cases of primary FL in the gastrointestinal tract occur in the small intestine, particularly in the second portion of the duodenum, presenting as white granular lesions (multiple small polyps), often as an incidental finding on esophagogastroduodenoscopy (EGD) [3-6]. The morphology, immunophenotypes, and genetic features are similar to those of nodal FLs; specifically, duodenal-type FL usually shows grades 1–2 histology, $CD10^+$ and $BCL2^+$ immunophenotypes, and *IGH/BCL2* fusion [5,7]. Duodenal-type FL has many oncogenic alterations that overlap with in situ FL [8] and extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) [6]; the patient outcomes appear to be excellent, including some patients managed with a watch-and-wait strategy [5,7].

In contrast, FL in the stomach has been rarely reported, and the clinicopathological features of patients with gastric FL have not been analyzed sufficiently. The ratio of gastric FL to duodenal FL was reported as 2:111 [9] and 1:19 [10], and the endoscopic feature of primary gastric FL was non-multiple nodules [9]. Iwamuro et al reported that the ratio of the incidence of secondary involvement of FL in the stomach to duodenum was 1:34 [11]. In our institute, EGD and bone marrow aspiration and/or biopsy are performed as routine staging procedures for FL patients; however, the association between bone marrow involvement and gastroduodenal involvement has not been analyzed previously.

Histopathologically, differential diagnosis between gastric FL and MALT lymphoma is often challenging, and gastric FL can be misdiagnosed as MALT lymphoma. FL resembling MALT lymphoma morphologically and immunophenotypically ($CD10^-$ and/or $BCL6^-$), and FL with lymphoepithelial lesions (LEL) have been reported [12]. LEL in gastric FL lesions were observed in 42% (5/12) of cases [12].

The aim of the present study was to analyze the clinicopathological characteristics of primary gastric FLs and secondary gastric involvement of FLs in comparison with duodenal FLs, and to discuss the reason why the incidence and endoscopic findings differ between gastric and duodenal FLs.

2. Materials and methods

2.1. Patients

The present study included 626 consecutive patients with FL who were diagnosed as having FL and underwent EGD for analyzing the primary gastroduodenal lymphoma or for a staging procedure at the National Cancer Center Hospital, Tokyo, Japan, between 2000 and 2015. Clinical information, including site of the disease, EGD findings, age, sex, stage, level of lactate dehydrogenase, symptoms, treatment, response, and outcomes, were obtained from medical records. The Lugano staging system for gastrointestinal lymphoma [13] was used for staging of primary gastroduodenal FL, and the Ann Arbor staging system was used for staging of FL whose primary sites were not gastroduodenal. The staging procedures included bone marrow aspiration and/or biopsy, EGD, whole-body computed tomography (CT), and optional positron-emission tomography/CT. Response to treatment was defined according to the revised response criteria for malignant lymphoma [14]. The study was approved by the institutional review board of the National Cancer Center.

2.2. EGD findings

Information regarding endoscopic findings and the number of gastric and/or duodenal lesions was collected. Endoscopic findings were classified as granular, fold swelling, submucosal tumor, or ulcerated. Granular lesions were defined as aggregations of multiple small polyps of a few millimeters or less in diameter. Submucosal tumor was defined as large submucosal tumor >5 mm in diameter.

2.3. Histopathologic and immunohistochemical analyses

Materials obtained by biopsy or surgery were fixed in 10% neutral-buffered formalin, embedded in paraffin, cut into 4-μm-thick sections, and stained with hematoxylin and eosin for histological evaluation. All specimens were diagnosed as FL by two hematopathologists (A.M.M. and H.T.) according to the World Health Organization *Classification of Tumours of Haematopoietic and Lymphoid Tissues* published in 2008 [1]. The presence of lymphoepithelial lesions and histologic transformation were also observed.

Immunohistochemical analysis of formalin-fixed, paraffin-embedded tissues was performed using a panel of monoclonal antibodies. Sections 4-μm thick were cut from each paraffin block, deparaffinized, and incubated at 121°C in citrate buffer (pH 6.0) for 10 min for antigen retrieval. Antibodies against the following antigens were used to diagnose FL: CD3 (PS1, 1:25; Novocastra, Newcastle upon Tyne, UK), CD5 (4C7, 1:100; Novocastra), CD10 (56C6, 1:100; Novocastra), CD20 (L26, 1:200; Dako, Glostrup, Denmark), BCL2 (124, 1:100; Dako), BCL6 (PG-B6p, 1:50; Dako), and cyclin D1 (SP4, ready for use; Nichirei, Tokyo, Japan).

2.4. Interphase fluorescence in situ hybridization

Four-μm-thick sections were cut from each paraffin block and used for fluorescence in situ hybridization (FISH) analysis. An LSI IGH Spectrum Green/LSI BCL2 Spectrum Orange Dual Fusion Translocation Probe (Vysis, Downers Grove, IL) was used to detect the t(14;18) translocation that gives rise to *IGH/BCL2* fusion. The fusion gene was identified as previously described [15]. In brief, 50–200 nuclei were scored