Gastric follicular lymphoma: A report of 3 cases and a review of the literature

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Abstract. Follicular lymphoma (FL) occurs primarily in the gastrointestinal tract, with the stomach being one of the rarest sites. According to the literature, <20 cases of primary gastric FL have been reported, with the number of cases with detailed pathological descriptions being even less. The aim of the present study was to compare clinicopathological features of gastric FL with FL at alternative sites. A total of 3 cases of gastric FL were retrieved from among 3,216 cases in the databases of 4 university hospitals in South Korea: Seoul National University (SNU) Hospital, SNU Boramae Hospital, SNU Bundang Hospital (all Seoul, South Korea) and Dongtan Sacred Heart Hospital Hallym University (Dongtan, South Korea), including 2 primary cases and 1 case that was possibly secondary to nodal FL. The 2 primary gastric FL cases were incidentally detected in routine health check-ups. An endoscopy revealed a single polypoid submucosal mass and biopsies failed to confirm the diagnosis due to minimal mucosal involvement. Therefore, a partial gastrectomy was performed. The epicenters of the tumors were submucosal, with focal extension to the muscularis propria. However, 1 case exhibited an isolated FL nodule in the omentum. Histopathological examination revealed FL of grade 1-2 with a follicular pattern and with strong expression of germinall center markers and B-cell lymphoma 2 (BCL2). Rearrangement of BCL2 was not identified using fluorescence in situ hybridization in situ studies in 2 cases. In contrast to these 2 cases, the remaining FL case was confirmed with an endoscopic biopsy. The endoscopy revealed multiple eroded polypoid lesions, and pathology revealed FL of grade 1-2 with a predominantly diffuse pattern, and with immunoglobulin heavy chain IGH/BCL2 translocation. In view of the extensive lymphadenopathy, the last case possibly presented as secondary involvement of nodal FL. It is challenging to diagnose FL in the stomach due to little mucosal involvement, as well as the unfamiliarity of the tumor due to its rarity. However, the results of the present study suggest that primary gastric FL may exhibit unique pathological features, including a predominantly follicular pattern and an absence of BCL2 rearrangement.

Introduction

The stomach is the most frequent site of malignant lymphoma involving the gastrointestinal (GI) tract. Among the subtypes of malignant lymphoma, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) and diffuse large B-cell lymphoma (DLBCL) account for >90% of all cases (1). The incidence of Follicular lymphoma (FL), whether primary or otherwise, has been reported to account for between 0.8 and 3% of gastric lymphomas (2). FL is one of the most common types of non-Hodgkin lymphoma in western countries including United States of America (3) and United Kingdom (4), whereas the incidence in Asian countries including Korea (5), Japan (6) and China (7) is lower than that of western countries. The incidence of FL is typically low in Korea, occupying ~2.9% of malignant lymphoma (8).

Histologic features of FL are characterized by nodular aggregation of two different types of tumor cells, which are small cleaved centrocytes and large centroblasts, and WHO histologic grading system is based on the number of centroblasts per high power field (9). Clinically FL commonly presents as widely spread systemic disease, and prognosis varies according to the extent of the disease and histologic grading at the time of diagnosis (10). In localized early stage...
diseases, watchful waiting or radiotherapy is available due to its slowly progressive nature, while chemotherapy including rituximab is selected in advanced stage diseases with high tumor burdens (11). The origin of tumor cells is germinal center B-cells which are heavily crowded in lymphoid organs, especially lymph nodes (9). Therefore, FL has been recognized as primary nodal lymphoma, and primary extranodal FL has been described in only a few organs including the skin and duodenum (12). The second part of the duodenum is known to be the most frequent site of FL of the GI tract followed by jejunum (10). In the latest revised fourth edition of WHO classification, duodenal FL was described as a distinct variant of FL with typical clinical and immunophenotypical characteristics. However, in majority of cases, FL of the GI tract may present through secondary involvement by widespread nodal FL, therefore, primary gastric FL appears to be rare (9,10,12,13-17). The present study describes 3 cases of gastric FL alongside a comprehensive review of previous cases reported in the literature and compares their features with those of duodenal FL.

Case report

Case selection. A total of 3 cases of gastric FL were retrieved from among the cases in the databases of 4 university hospitals in South Korea (SNU Hospital, SNU Boramae Hospital, SNU Bundang Hospital and Dongtan Sacred Heart Hospital Hallym University). The cases were selected from a total of 3,216 cases of non-Hodgkin's lymphoma of the GI tract, occurring between January 2000 and December 2015 as the only 3 cases of gastric FL. The pathological features were reviewed by 3 experienced hematopathologists. Due to the retrospective nature of the study, ethical approval and patient consent for publication was waived for the present study by the Institutional Review Board of Seoul National University Boramae Hospital (Seoul, South Korea).

Case 1. A 61-year-old man was referred to SNU Boramae Hospital in November, 2015 for the management of a gastric lesion detected during an annual health check-up program at a local clinic. Endoscopic examination revealed a well demarcated, polypoid mass in the anterior wall of the gastric body. Despite three repeat biopsies, the preoperative pathological features were reviewed by 3 experienced hematopathologists. Due to the retrospective nature of the study, ethical approval and patient consent for publication was waived for the present study by the Institutional Review Board of Seoul National University Boramae Hospital (Seoul, South Korea).
every month and remained disease-free at the last follow-up (13 months following diagnosis).

Case 2. A 50-year-old man underwent gastroscopy for routine health check-up in Dongtan Sacred Heart Hospital and presented with a gastric lesion; a single elevated submucosal mass at the fundus, grossly indicative of a GI stromal tumor. As in the first case, no additional abnormalities were identified through systemic examination. The patient underwent a partial gastrectomy following an endoscopic biopsy that failed to provide a pathological diagnosis, which revealed a 1.8x1.6-cm submucosal tumor extending to the muscularis propria. The microscopic features and IHC results were near identical to those in case 1, with the exception of the absence of separate tumor nodule in the omentum. Rearrangement of BCL2 was not detected using the IGH/BCL2 dual fusion probe or BCL2 break-apart probe by FISH (Fig. 2). The colonization of *H. pylori* was not identified in the surrounding gastric mucosa. The patient's final stage was IE2 using the modified Ann Arbor staging system (19,20) and stage I using the Lugano staging system (21). The patient refused any further treatment and remained disease-free for 30 months following the surgery. Subsequently, the patient was lost to follow-up.

Case 3. A 40-year-old man presented with epigastric discomfort for several months. An endoscopy performed on December, 2015 at Seoul National University Hospital (Seoul, Korea) revealed multiple elevated mass-like lesions at the mid-body of the stomach, on the lesser curvature side, and a biopsy confirmed FL of grade 1-2 with a predominantly diffuse pattern. Unlike the 2 aforementioned cases, the subepithelial lamina propria was densely filled with small- to medium-sized lymphoid cells without nodular aggregation. Despite extensive lymphoid infiltration, definite lymphoepithelial lesions were not identified. The tumor cells were positive for CD10, CD20, BCL2 and BCL6, and negative for the presence of *H. pylori* in the surrounding stomach tissue.

Figure 1. Representative features of case 1, primary gastric follicular lymphoma. (A) An endoscopy and (B) the resected specimen revealed a well demarcated polypoid mass in the gastric body. Microscopically, nodular aggregates of small lymphoid cells in the submucosa with little mucosal involvement are characteristic, as demonstrated by hematoxylin and eosin staining at (C) x10 and (D) magnification, x40. (E) Tumor cells were positive for CD10 (magnification, x40). (F) The follicular dendritic cell network was preserved, using anti-CD21 (magnification, x40). The omental nodule revealed similar results following (G) hematoxylin and eosin and (H) anti-CD10 staining (magnification, x40). CD, cluster of differentiation.
for CD3, cyclin D1 and MUM1/IRF4, according to the IHC results. The tumor cells were also positive for IGH/BCL2 translocation, as confirmed by FISH (Fig. 3). In addition to the gastric lesion, multiple large hypermetabolic lymph nodes (≤12.0 cm) were identified in the retroperitoneum, mesentery and abdomen. A bone marrow examination revealed the involvement of FL. The patient’s final stage was IVA using the Ann Arbor staging system (10,18). It was concluded that the gastric lesion was possibly secondary to nodal FL, due to the presence of massive lymphadenopathy. The patient underwent 6 cycles of R-CVP (rituximab 375 mg/m² IV, cyclophosphamide 750 mg/m² IV, vincristine 1.4 mg/m² IV and prednisolone 40 mg/m² PO) every 21 days without surgical intervention, demonstrating partial response on computed tomography (CT) scan. Following R-CVP, he received 9 cycles of rituximab maintenance therapy (750 mg/m² IV every 2 months) and showed complete response. At time of publication, he is planning to undergo 3 more cycles of maintenance chemotherapy (26 months post-diagnosis).

Discussion

FL is a basic nodal-based neoplasm, although several cases of primary extranodal FL have previously been described as specific variants (10,12,13‑15). Involvement of the GI tract by advanced nodal FL may be uncommon, although accurate incidence rates have not been reported (22). Among extranodal FL, primary gastric FL is rare. According to a nationwide survey of malignant lymphoma among Koreans released in 2011 (8), there was no single case of gastric FL in the 1,112 recorded cases of GI lymphoma. To date, <20 cases of primary gastric FL with well documented pathological results have been reported in the literature, although the overall incidence should be slightly higher (Table I) (13,16,23-25). Due to the higher incidence of MALT lymphoma in stomach, and the similar cytologic morphology of tumor cells of MALT lymphoma and FL, primary gastric FL may have been misdiagnosed as MALT lymphoma, especially in small biopsy specimens. Based on a review of previous studies, the majority of gastric FL presented as single- or multiple-polypoid submucosal masses, which could hinder the accurate diagnosis through endoscopic mucosal biopsy. Histologically, the tumor cells were of low grade, consistent with grade 1-2 and exhibited a predominantly follicular pattern, similar to those observed in 2 of the cases described in the present study. In contrast to cases 1 and 2, case 3 was confirmed as FL by endoscopic biopsy due to diffuse tumor cell infiltration in the lamina propria. This diffuse mucosal involvement may be a useful feature to differentiate secondary involvement by nodal FL from primary gastric FL. Takata et al (13,14) suggested that an FDC pattern can help differentiate primary duodenal FL from nodal FL by performing IHC for FDC markers (CD23 or CD43); loss of FDC network in the center, with remnant peripheral FDC exhibiting a ‘hollow pattern’ is identified in duodenal FL, whereas a compact nodular network of FDCs is exhibited in nodal FL. The FDCs are reported to provide a
growth advantage to FL cells by interacting with tumor cells. The hollow pattern may be associated with relatively lower histologic grade and the indolent clinical nature of duodenal FL (15). In contrast, case 1 of the present study exhibited preserved FDC nodules, while case 2 revealed near complete loss of FDCs without peripheral accentuation; these patterns differ from the typical hollow pattern of duodenal FL previously reported (13-15). Case 3 also exhibited an absence of an FDC network, similar to case 2. Therefore, the ‘hollow pattern’ does not appear to be specific to primary gastric FL. Rather, a preserved FDC network may be interpreted as a phenomenon associated with disease progression.

The majority of reported primary gastric FL cases presented with a localized extent of disease. In the present case report, defining the pathological staging of case 1 was difficult due to a concomitant omental tumor nodule without regional lymph node involvement. According to the Tumor-Node-Metastasis staging of the American Joint Committee on Cancer, an omental nodule may be interpreted as a regional lymph node metastasis (N1) or a subserosal invasion (T3) (26). However, there was little evidence of extrafollicular invasion, as observed in the CD10 IHC results in the gastric and omental lesions. Therefore, the omental tumor may be interpreted as multiplicity rather than as a metastatic deposit. Multifocality is one of the well-known characteristics in duodenal FL (27). It was concluded that case 3 of the present study was most likely a secondary involvement of the stomach based on Dawson's criteria of primary GI lymphoma (28), and the final stage was designated stage IV due to bone marrow involvement. Unlike primary gastric FLs, secondary gastric involvement may occur in the advanced stage of nodal FL.

Certain studies have identified the lack of BCL2 translocation in primary cutaneous FL as a distinctive feature that differentiates it from nodal FL, suggesting distinct tumorigenic processes in extranodal sites (29). This conclusion was not supported in GI FL; a number of previous studies have identified BCL2 rearrangement in primary intestinal FL (12,23). However, the incidence of BCL2 translocation in primary gastric FL was decreased compared with that in nodal FL, or even duodenal FL, although the expression of BCL2 protein was consistently observed (2). The 2 primary gastric FL cases described in the present study were negative for BCL2 translocation, whereas the case of secondary involvement of nodal FL exhibited translocation t(14;18). It is possible that the absence of translocation t(14;18) may be a result of the under-recognition of FL disguised as MALT lymphoma. Nevertheless, translocation-negative cases also revealed an overexpression of BCL2 protein, similar to previous studies, suggesting an alternative genetic mechanism rather than an IGH/BCL2 rearrangement (30).

To the best of our knowledge, there has been no proven etiological agent for gastric FL identified to date, although a number of studies presume that local immunity will contribute to the pathogenesis of FL of the GI tract, just as *H. pylori* participates in the development of MALT lymphoma (31). Local
antigen-experienced B-cells are suggested to be the origin of primary FL of the GI tract based on the frequent expression of IgA and the α4β7 mucosal homing receptor in the tumor cells (32). Colonization of *H. pylori* was identified in case 1 and 3 of the present case report, and Hatano et al (17) revealed an ~50% incidence of *H. pylori* in gastric FLs in patients of Japanese origin. Considering that the seropositivity for *H. pylori* is ~54% in patients of Korean origin (33), the causal association of *H. pylori* in gastric FL is not robust enough to be conclusive. However, in case 1 of the present study, follicular gastritis was present in the background mucosa, suggesting the involvement of *H. pylori* in the tumorigenesis of gastric FL. Although antibiotics targeting *H. pylori* in FL failed in a considerable proportion of patients, there were also a limited number of patients that achieved complete remission (34). Nevertheless, there may be a subgroup of gastric FL associated with a local antigen-presenting environment such as *H. pylori* infection, however, further studies are required to elucidate such cases.

Although the vast majority of GI FLs demonstrate a limited disease extent at the time of diagnosis unlike nodal FLs, the prognosis of gastric FLs does not appear to differ from that of nodal FLs considering the relatively indolent behavior of nodal FLs, even in advanced stages reported in previous studies (1,2,10,16,24,25,35). Based on a review of gastric FLs, including 2 cases from the present study, no disease relapses or disease-associated mortalities have been reported (13,16,23-25). Due to this indolent behavior, despite heterogeneous treatment modalities, therapeutic interventions are recommended only in symptomatic or progressive cases (36). In contrast to the majority of nodal FLs that acquire additional genetic alterations leading to widespread disease and high-grade transformation, FL cells of the GI tract tend to reside in the primary site, potentially explaining the indolent nature of the tumor. There are several reports of gastric FLs with a co-existing diffuse large B-cell lymphoma component, yet such patients generally had favorable disease courses (23,37).

The main differential diagnosis of FL in the GI tract includes florid lymphoid hyperplasia, MALT lymphoma, mantle cell lymphoma and secondary involvement of nodal FL. A distinction from reactive lymphoid hyperplasia may be made in the same context as nodal lesions, where monomorphic composition, absence of tangible body macrophages and architectural disruption favor FL. Occasionally, MALT lymphoma or mantle cell lymphoma is dominated by small lymphocytes with a nodular architecture. Tumor cells in MALT lymphoma present a characteristic lymphoepithelial lesion, which is uncommon in the majority of FL cases (2,10,23,27,36). However, there has been one study of gastric FL with a lymphoepithelial lesion resembling MALT lymphoma (24). Furthermore, certain cases of gastric FL with diffuse mucosal involvement lacking BCL2 translocation may easily be misinterpreted as MALT lymphoma, particularly in small biopsy specimens (38). Under these circumstances, IHC results usually provide clear distinctions between these types of tumor cell. Neoplastic cells in MALT lymphoma present with negative BCL6 and CD10 IHC test results. As for mantle cell lymphoma, CD5 and cyclin D1 may assist in forming the correct diagnosis. For determining

| First author, year | Age, years | Sex | Multiplicity | Grade | t(14:18) | *H. pylori* | Stage | Treatment | Outcome, months (Refs.) |
|--------------------|------------|-----|--------------|-------|----------|------------|-------|-----------|------------------------|
| Present case        | 61 M       | No  | 1-2          | No    | Yes      | I          | R-CVP | NED, 8    | (26)                   |
| 50 M               | No         | 1-2 | No           | No    | No       | I          | Surgery only | NED, 30  | (26)                   |
| 40 M               | Yes        | 3a  | Yes          | Yes   | Yes      | IV         | R-CVP | PR, 6     |                        |
| Takata et al, 2013  | 51-81 M (n=4), F (n=4) | Unknown | 1-2 | 3-8 | Unknown | I (n=5), II (n=2), IV (n=1) | Surgery only | Unknown | (9) |
| Tsankov et al, 2002 | 72 F       | No  | 1-2          | Yes   | Unknown  | I          | CHOP  | NED, 13   | (24)                   |
| Huang et al, 2008   | 48 F       | No  | 3ab         | Unknown | Unknown | IIE       | CEOP  | NED, 70   | (23)                   |
| Kanda et al, 2003   | 57 F       | Yes | 1-2          | Yes   | Unknown  | I          | Surgery only | NED, 15 | (16)                   |
| Iwamuro et al, 2013 | 73 M       | No  | 1            | No    | Yes      | IIE       | Surgery and R-CHOP | NED, 30 | (25)                   |
| Misdragi et al, 2001| 67 F       | Yes | 1-2          | No    | No       | I          | Rituximab | MOC, 48 | (27)                   |

*Staged by the Lugano system. *Diffuse large B-cell lymphoma component present. R, rituximab; CVP, cyclophosphamide, vincristine and prednisolone; CEOP, cyclophosphamide, epirubicin, vincristine and prednisolone; CHOP, cyclophosphamide, doxorubicin, oncovin and prednisone; NED, no evidence of disease; PR, partial remission; MOC, mortality from other causes; *H. pylori*, *Helicobacter pylori*. 

Table I. Summarized clinicopathological parameters of cases of gastric follicular lymphoma in the literature.
the secondary involvement of nodal FL, Dawson's criteria for primary GI lymphoma should be applied (1).

In conclusion, primary gastric FL is a rare, under-recognized disease. Although the general prognosis is indolent, similar to that of nodal FL, a lack of BCL2 rearrangement, low-grade histology with a follicular pattern and scarce mucosal involvement may serve as diagnostic indicators for excluding secondary involvement by nodal FL.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Conception and design, JK, YK, JC and SM. Administrative support, JK, YK and JH. Provision of clinical data including patient history, endoscopic findings and images of case 1, JS, SM, JC and JH. Provision and interpretation of histopathologic, immunohistochemical and molecular analysis of case 1, JS, SM, JC and JH. Provision of clinical data including patient history, endoscopic findings and images of case 2, YK, HK, CL and SS. Provision and interpretation of histopathologic, immunohistochemical and molecular analysis of case 2, HK, CL and SS. Provision of clinical data including patient history, endoscopic findings and images of case 3, CL, SS and HK. Provision and interpretation of histopathologic, immunohistochemical and molecular analysis of case 3, CL, SS and HK. Collection and assembly of data, HN and YK. Reviewing the slides for histopathological and immunohistochemical features, HN, YK and JK. Reviewing molecular analysis of cases, JH and HK. Reviewing literature, HN, CL and SS. Manuscript writing and revising, HN and YK. Adding valuable scientific comments in the discussion section, JC, SM, HK and JH. All authors reviewed the manuscript and approved the final article.

Ethics approval and consent to participate

This study has been granted an exemption from requiring ethics approval by the Institutional Review Board of Seoul National University Boramae Hospital. The authors declare that they have no competing interests.

Competing interests

The authors declare that they have no competing interests.

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