Characteristic endoscopic findings of gastrointestinal malignant lymphomas other than mucosa-associated lymphoid tissue lymphoma

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Abstract

Background and study aims: **The gastrointestinal (GI) tract is the most common site of extra-nodal involvement for non-Hodgkin's lymphoma (NHL). The features of GI NHLs remain unclear. The aim of this study was to clarify endoscopic characteristics of GI NHLs.**

Patients and methods: **We retrospectively analyzed the morphological characteristics of 63 GI malignant lymphomas other than mucosa-associated lymphoid tissue lymphoma. Lesions were diagnosed between 2005 and 2020. Macroscopic findings were classified into five subtypes: superficial (S); protruding without ulcer (P); protruding with ulcer (PU); fungating (F); and multiple nodules (MN).**

Results: **Thirty-one lesions in the stomach were classified as S type in 3 cases (9.6%), P type in 6 (19%), PU type in 13 (42%), and F type in 9 (29%). In the stomach, the ulcerated phenotype was more frequent for diffuse large B-cell lymphoma (DLBCL) (89.5%) than for other histological types (41.7%; P = 0.01). In the intestine, 23 tumors were classified as S type in 4 cases (17%), P type in 1 (4%), PU type in 6 (26%), F type in 1 (4%), and MN in 11 (48%). Eleven of the 14 cases (78.6%) of intestinal follicular lymphoma lesions showed MN type. In the colon, eight tumors were classified as S type in 2 cases (25%), P type in 2 (25%), PU type in 1 (13%), and F type in 3 (38%).**

Conclusion: **We have clarified the endoscopic features of GI NHL using macroscopic classifications. The ulcerated phenotype was the most frequent endoscopic finding for DLBCL.** (Acta gastroenterol. belg., **2022,** 85, **477-483**).

Keywords: B cell, endoscopy, non-Hodgkin's lymphoma, T cell.

Introduction

Malignant tumors derived from lymphocytes are known as malignant lymphomas, and those other than Hodgkin's lymphoma are called non-Hodgkin's lymphoma (NHL). The incidence of NHL is 5.1 per 100,000, with a mortality rate of 2.5 per 100,000 world-wide (1). Mortality is declining due to advances in chemotherapy (2). The gastrointestinal (GI) tract is the most common site of extranodal involvement for NHL, accounting for 4–20% of all cases (3,4). The stomach is the most common site for primary and secondary lymphomas, whereas intestinal tract lesions are relatively rare (5).

Gastric lymphomas are mainly represented by mucosa-associated lymphoid tissue (MALT) lymphoma. The treatment method for gastric MALT lymphoma is determined according to the clinical stage and *Helicobacter pylori* infection status (6,7). Eradication of *H. pylori* has been accepted as an initial treatment for gastric MALT lymphoma (8,9). Previously, endoscopic findings have been reported to correlate with response to *H. pylori* eradication and recurrence after complete response in gastric MALT lymphoma (10,11). A tree-like appearance has been reported as a characteristic finding of MALT lymphoma and is useful for selection of the optimal biopsy site (12,13). On the other hand, because of the low number of cases, no consensus has been reached in terms of endoscopic findings to estimate histological subtypes in other types of GI NHL. Furthermore, the optimal macroscopic classifications for GI NHL other than MALT lymphoma have not yet been established.

With advances in endoscopic technology, the incidence of GI malignant lymphoma being diagnosed by endoscopists is increasing. In particular, with the development of capsule endoscopy and double-balloon endoscopy, intestinal lesions of NHL are being detected more frequently (14-18). Although the endoscopic features and clinical outcomes of colorectal MALT lymphoma have been reported, the features of intestinal NHLs other than MALT lymphoma remain unclear (19). Superficial biopsies sometimes yield false-negative results for malignancy, leading to delayed diagnosis. Endoscopists thus need to be able to recognize the endoscopic characteristics of GI NHL.

This study therefore aimed to clarify the endoscopic characteristics for types of GI NHL other than MALT lymphoma.

Methods

This study retrospectively analyzed the morphological characteristics of 63 lesions of GI malignant lymphoma other than MALT lymphoma. Initial endoscopic findings before treatment were analyzed. All GI malignant lym-phoma lesions were diagnosed using biopsy specimens obtained during endoscopy at Nagoya City University Hospital between April 2005 and March 2020. The diagnosis of NHL was based on the World

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Table 1. — **Histological characteristics of gastrointestinal malignant lymphomas**

Site	Total	Diagnosis	Number	
Esophagus	n = 1	Burkitt lymphoma	1	100%
Stomach	n = 31	DLBCL	19	61.3%
		ATLL	3	9.7%
		NK/T cell lymphoma, nasal type	2	6.5%
		Plasmablastic lymphoma	2	6.5%
		Burkitt lymphoma	2	6.5%
		FL	1	3.2%
		EATCL	1	3.2%
		Mantle cell lymphoma	1	3.2%
Intestine	n = 23	FL	14	60.9%
		DLBCL	5	21.7%
		ATLL	1	4.3%
		B lymphoblastic lymphoma	1	4.3%
		Plasmablastic lymphoma	1	4.3%
		Mantle cell lymphoma	1	4.3%
Colon	n = 8	FL	3	37.5%
		Mantle cell lymphoma	2	25.0%
		DLBCL	1	12.5%
		Burkitt lymphoma	1	12.5%
		ATLL	1	12.5%

ATLL, adult T-cell leukemia/lymphoma; DLBCL, diffuse large B-cell lymphoma; EATCL, enteropathy assicuated T-cell lymphoma; FL, follicular lymphoma Intestine includes duodenum, jejunum and ileum.

Health Organization classification (20). By analyzing endoscopic findings, tumors were classified into five subtypes based on macroscopic features: superficial (S); protruding without ulcer (P); protruding with ulcer (PU); fungating (F); and multiple nodules (MN). As a supplementary classification, giant fold was defined for gastric lesions showing a fold width ≥5 mm when the stomach was fully extended by gastroendoscopy (21). Duodenal lesions were included as intestinal lesions. Macroscopic endoscopic classification was assessed by two independent endoscopists. When the lesion showed multiple findings, the most dominant macroscopic finding was used to define the subtype. A video endoscope (Olympus Medical System, Tokyo, Japan) was applied for all endoscopic examinations, and a double-balloon endoscope (FUJIFILM, Tokyo, Japan) was used to determine the macroscopic findings of small intestinal lesions.

This study was approved by the institutional review board and ethics committee of Nagoya City University (approval no. 60-16-0018). The study was performed according to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008). Written informed consent was obtained from all participants.

Statistical analysis

Statistical analysis was carried out using GraphPad Prism for Windows version 9.1.2 (GraphPad, San Diego). The endoscopic features of GI NHL were compared using the χ^2 test.

Values of $p<0.05$ were considered significant.

Results

Endoscopic features of GI NHL

A total of 63 lesions of GI malignant lymphoma were identified, comprising 1 esophageal lesion, 31 gastric lesions, 23 intestinal lesions, and 8 colorectal lesions (Table 1). The pathological diagnosis of the esophageal lesion was Burkitt lymphoma. Gastric lesions comprised diffuse large B-cell lymphoma (DLBCL) in 19 cases, adult T-cell leukemia/lymphoma (ATLL) in 3, Burkitt lymphoma in 2, follicular lymphoma (FL) in 1, nasal-type extranodal NK/T-cell lymphoma in 2, enteropathy-associated T-cell lymphoma in 1, plasmablastic lymphoma in 2 and mantle cell lymphoma in 1. Intestinal lesions comprised FL in 14 cases, DLBCL in 5, and ATLL, B-lymphoblastic lymphoma, plasmablastic lymphoma and mantle cell lymphoma in 1 each. Colorectal lesions comprised FL in 3 cases, DLBCL in 1, Burkitt in 1, ATLL in 1, and mantle cell lymphoma in 2.

Macroscopic types were divided into 5 types by the endoscopic findings. Representative images for the 5 types are shown in Figure 1. Thirty-one lesions in the stomach were classified as S type in 3 (9.6%), P type in 6 (19%), PU type in 13 (42%), and F type in 9 (29%) (Table 2). Next, we classified PU and F as ulcerated phenotypes, and the others as non-ulcerated phenotypes. In the stomach, ulcerated phenotypes were more frequent in DLBCL (89.5%) than in other histological types of lymphoma (41.7%; P = 0.01) (Fig. 2). In addition, giant fold was observed in 3 cases in DLBCL and 1 case in ATLL.

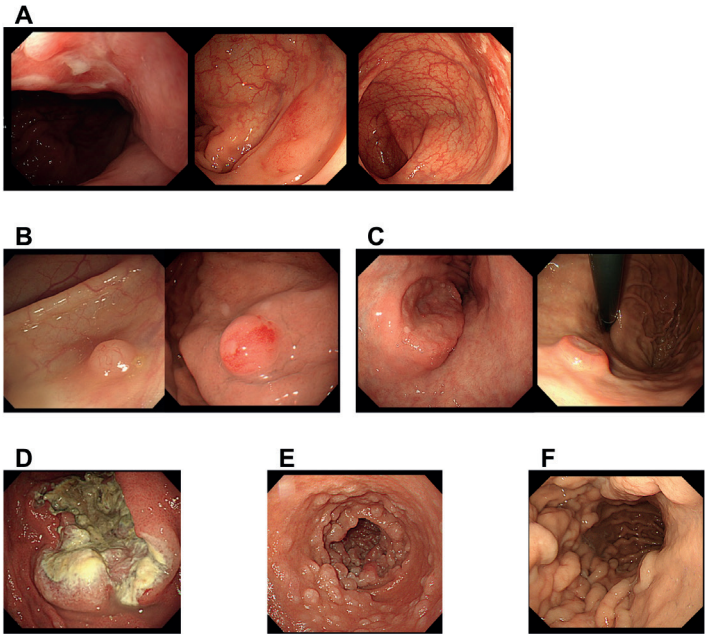

Fig. 1. — Endoscopic classification of gastrointestinal malignant lymphoma.
A) Superficial type. B) Protruding without ulceration type. C) Protruding with ulceration type. D) Fungating type. E) Multiple nodules type. F) Giant fold.

Table 2. — **Macroscopic findings of malignant lymphomas in the stomach**

		Macroscopic classification					
	Total	**S**	**P**	**PU**	**F**	**MN**	**Giant fold**
DLBCL	19	0	2	10	7	0	3
ATLL	3	2	0	1	0	0	1
NK/T cell lymphoma	2	1	0	1	0	0	0
Plasmablastic lymphoma	2	0	1	1	0	0	0
Burkitt lymphoma	2	0	1	0	1	0	0
FL	1	0	1	0	0	0	0
Mantle celllymphoma	1	0	1	0	0	0	0
EATCL	1	0	0	0	1	0	0

ATLL, adult T-cell leukemia/lymphoma; DLBCL, diffuse large B-cell lymphoma; EATCL, enteropathy assicuated T-cell lymphoma; FL, follicular lymphoma; MN, multiple nodules type; P, protruding without ulcer type; PU, protruding with ulcer type; S, superficial type.

In the intestine, the 23 tumors were classified as S type in 4 (17%), P type in 1 (4%), PU type in 6 (26%), F type in 1 (4%), and MN type in 11 (48%) (Table 3). Among the colorectal lesions, the eight tumors were classified as S type in 2 (25%), P type in 2 (25%), PU type in 1 (13%), and F type in 3 (38%). For intestinal FL, 11 of 14 lesions (78.6%) showed MN type (Table 4). On the other hand, only 1 of the 3 lesions (33.3%) was MN type in colon FL. Furthermore, only 1 of 14 lesions (7.1%) showed an ulcerated phenotype in intestinal FL. Conversely, 2 of 3 lesions (66.7%) showed an ulcerated phenotype in colon FL. All DLBCLs in both the intestine and colon showed an ulcerated phenotype. An ulcerated phenotype was thus the dominant macroscopic finding for DLBCL in any site of the GI tract.

A case of gastric DLBCL relapse

A 60-year-old Japanese woman underwent esophagogastroduodenoscopy (EGD) due to severe anemia. EGD revealed a protruding lesion with ulceration on the anterior wall of the lesser curvature at the middle gastric body (Fig. 3A). Biopsy was performed and the lesion was diagnosed as DLBCL. Computed tomography (CT) of the chest demonstrated multiple mediastinal lymph node swellings. Chemotherapy was planned for DLBCL, but chest CT also showed nodular shadows in the right upper lung, diagnosed as lung aspergilloma. Surgical treatment for lung aspergilloma was therefore performed before chemotherapy. During the hospitalization for lung surgery, dexamethasone was used on the day of

Table 3. — **Macroscopic findings of malignant lymphomas in the small intestine**

		Macroscopic classification				
	Total	**S**	**P**	**PU**	**F**	**MN**
FL	14	2	0	1	0	11
DLBCL	5	0	0	4	1	0
ATLL	1	1	0	0	0	0
B lymphoblastic lymphoma	1	1	0	0	0	0
Mantle cell lymphoma	1	0	1	0	0	0
Plasmablastic lymphoma	1	0	0	1	0	0

ATLL, adult T-cell leukemia/lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MN, multiple nodules type; P, protruding without ulcer type; PU, protruding with ulcer type; S, superficial type.

Table 4. — **Macroscopic findings of malignant lymphomas in the colon**

		Macroscopic classification				
	Total	**S**	**P**	**PU**	**F**	**MN**
FL	3	0	1	1	1	0
DLBCL	1	0	0	0	1	0
Burkitt lymphoma	1	0	0	0	1	0
ATLL	1	1	0	0	0	0
Mantle cell lymphoma	2	1	1	0	0	0

ATLL, adult T-cell leukemia/lymphoma; DLBCL, diffuse large B-cell lymphoma; F, fungating type; FL, follicular lymphoma; MN, multiple nodules type; P, protruding without ulcer type; PU, protruding with ulcer type; S, superficial type.

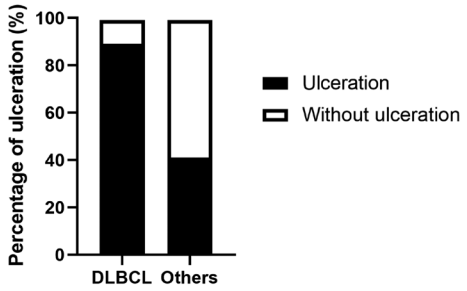

Fig. 2. — Percentages with ulcerated phenotype in gastric malignant lymphoma.
The ulcerated phenotype is more frequent in DLBCL (89.5%) than in other histological lymphomas (41.7%, respectively; p = 0.01). DLBCL, diffuse large B-cell lymphoma.

surgery and the next day, at doses of 30 mg and 100 mg, respectively. At 2 months after surgery, EGD revealed a scar at the lesion site where the tumor had been found on initial endoscopy (Fig. 3B). After 3 months of watchful waiting, EGD was again performed and a PU-type tumor, similar in appearance to that seen at initial endoscopy, was found in the same position in the stomach (Fig. 3C). That tumor was diagnosed as DLBCL by histopathology, and the patient was treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

Discussion

This study clarified the endoscopic features in each type of GI malignant lymphoma other than MALT lymphoma, and also elucidated the relationship between macroscopic classification and pathological diagnosis. We found that the ulcerated type was the most frequent endoscopic finding for DLBCL in both the stomach and intestine. In addition, the multiple nodule type was the dominant macroscopic finding for FL in the small intestine, while FL in the stomach and colon showed various endoscopic findings.

Although the GI tract is the most common site of extranodal NHL involvement, the characteristics of endoscopic findings for GI lymphoma, especially in the intestine, have previously been unclear. One reason is the rarity of GI lymphoma, accounting for only 1-4% of malignancies in the GI tract. In addition, 60-70% of primary GI lymphomas originate from the stomach, so most reported endoscopic findings for GI lymphomas have been related to the analysis of gastric lesions (3, 4, 22,23). For MALT lymphoma, endoscopic and clinical features were reported not only in the stomach, but also in the colorectal region (10,11,13,19). However, the endoscopic findings of GI lymphomas other than MALT lymphoma have not been fully elucidated and optimal classifications based on endoscopic gross morphology have not been established. Previously, some trials to classify macroscopic findings for GI NHL were reported (19,24,25). Those classifications were used for a particular histological type of GI lymphomas and were not applicable for all GI tracts. In this study, we have established endoscopic classification for GI NHL, which is applicable for all GI tracts. We have classified macroscopic findings into 5 subtypes using simple and familiar terms: superficial; protruding without ulcer;

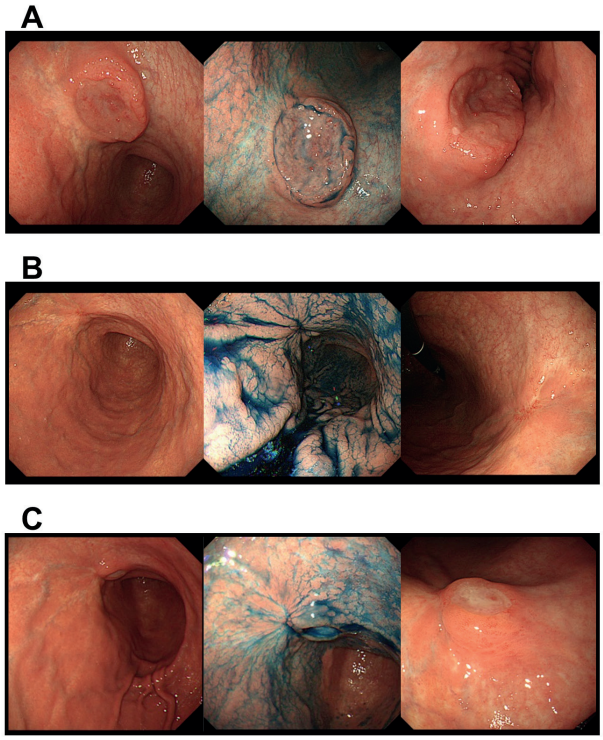

Fig. 3. — A case with relapse of gastric diffuse large B-cell lymphoma.
A) Endoscopic findings at initial diagnosis. A protruding tumor with ulceration is observed on the anterior wall of the lesser curvature of the middle gastric body. B) Three months after initial diagnosis, the tumor has shrunk and turned into a scar. C) After 3 months of watchful waiting, a protruding tumor with ulceration is found at the same position in the stomach, with a similar appearance to that seen at initial endoscopy. The middle panel shows chromoendoscopy with indigo carmine.

protruding with ulcer; fungating; and multiple nodules. This study has shown the correlation between the ulcerated phenotype and DLBCL. Other histological types of GI NHL were extremely rare. Therefore, the accumulation of cases and additional research are necessary to elucidate the macroscopic features of other GI NHL using our endoscopic classification. The lack of optimal endoscopic classification would obstruct communication between clinicians and understanding of the macroscopic features of GI NHL. Our endoscopic classification has advantages in those points. Because our simple classification uses easy terms and is easy to use in daily clinical practice, it would facilitate communication between physicians and improve the endoscopists' understanding of the clinical features of GI NHL.

Giant fold was added as a sub-classification of gastric NHL in this study. Giant fold is also called "giant rugae" and is considered synonymous with rugal hyperplastic gastritis in the Sydney classification (21). Giant fold often presents with swelling and flexion meandering. The groove between folds is narrow, and if flexion meandering becomes stronger, gyrus-like findings are exhibited. Giant fold is found in various diseases, including malignant lymphoma, Menetrier disease, Cronkhite-Canada syndrome, scirrhous gastric cancer, and acute pancreatitis. Although the cause of giant fold depends on the disease, in cases of malignant lymphoma, giant fold and/or thickness of the mucosa was observed as a result of extensive infiltration of lymphoma cells into the submucosa (26). We therefore consider that the finding of giant fold should not be included in the main classification that reflects local morphology, but in a supplementary classification that reflects extensive infiltration of lymphoma cells.

DLBCL can involve the GI tract representing 40-60% of GI NHLs (27,28). However, the literature on endoscopic characteristics of intestinal DLBCL remains scant due to the rarity of these entities. Previous reports have suggested the ulcerated type as the most frequent macroscopic type in intestinal DLBCL (29,30). The present study clarified that ulcerated (PU and F) types are significantly more frequent in both gastric and intestinal DLBCL than in other histological types of NHL. Ulceration could thus represent the main endoscopic characteristic of DLBCL. We have encountered a case of gastric DLBCL relapse (Fig. 3). In the case of DLBCL, the tumor recurred in the same region as the initial diagnosis, and the endoscopic findings showed PU type at the time of recurrence, similar to the initial appearance. Such findings suggest that DLBCL shows ulcerative aspects even in early polypoid lesions.

Knowledge about the relationship between endoscopic features and other histological types of GI tract NHL has remained very limited (5,24,30,31). MN type in the small intestine, especially in the duodenum, is a characteristic feature of FL. However, in the stomach and colon, macroscopic findings of FL show various subtypes. T-cell lymphoma of the GI tract is rare, so obtaining a sufficient size for analysis is difficult. Although the endoscopic features have remained unclear, GI tract lesions of T-cell lymphomas can be classified into five subtypes using our endoscopic classification.

A chromoendoscopy using indigo carmine-dye is useful for clarifying details of surface structure and recognizing the exact extent of the lymphoma lesion, that also helps determine the appropriate biopsy site. Recently, the usefulness of virtual chromoendoscopy, such as narrow-band imaging (NBI), has been reported in gastrointestinal cancers. The vessel plus surface (VS) classification is well known in gastric cancer to distinguish between cancer and non-cancerous lesion. According to the VS classification system, the characteristics of the magnified-NBI findings in gastric cancer are the presence of a demarcation line (DL) and the presence of an irregular microvascular pattern and/or irregular microsurface pattern inside the DL (32,33). In colorectal cancer, the Japan NBI Expert Team (JNET) classification was developed. The JNET classification consists of four categories, types 1, 2A, 2B, and 3 based on the findings of vessels and surface patterns. Types 1, 2A, 2B and 3 correspond to the histopathological

classifications of hyperplastic polyp/sessile-serrated polyp, low-grade intramucosal neoplasia, high-grade intramucosal neoplasia/shallow submucosal invasive cancer, and deep submucosal invasive cancer, respectively (34). Several studies have reported the characteristic magnified-NBI findings in the gastrointestinal MALT lymphoma. Hence, abnormal tree-like blood vessels might be a good indicator of infiltration of gastric MALT lymphoma (11,12). Abnormal branch-like vessels have also been reported in colorectal MALT lymphomas (35). However, in other lymphomas, there are no reports for characteristic findings using virtual chromoendoscopy. Further studies are needed to clarify the relationship between clinicopathological findings of GI NHL and virtual chromoendoscopic features combined with macroscopic findings.

In conclusion, we have demonstrated the endoscopic features of NHL in the GI tract using macroscopic classifications. Superficial biopsy of GI lesions for malignant lymphoma often shows false-negative findings for malignancy, delaying diagnosis and facilitating disease progression. Endoscopists thus need to recognize the relationship between the endoscopic characteristics and histological types of GI tract NHL.

Declaration of interest statement

The authors have no conflicts of interest to declare and received no financial support in association with this study.

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