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Clinical manifestations and endoscopic presentations of gastric lymphoma: a multicenter seven year retrospective survey

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ABSTRACT

Background and aim: To improve the diagnostic rate of gastric lymphoma by analyzing clinical and endoscopic features of patients with gastric lymphoma and suspected gastric lymphoma.

Methods: Clinical and endoscopic records of 35 patients with gastric lymphoma (positive group) and 133 patients with suspected gastric lymphoma but subsequent non-malignant pathology (negative group) were analyzed retrospectively. Data from another 99 gastric lymphoma patients with malignant pathology but nonspecific endoscopy (endoscopy non-suspect group) were analyzed.

Results: Abdominal pain was the predominant symptom reported in both the positive and negative lymphoma groups, representing 60.0 and 52.5%, respectively. No significant differences in age, sex and clinical manifestations in subjects from the two groups were found. In the positive group, 54.3% were ulcerative; 34.3%, infiltrative; 8.5%, polypoid; and 2.9%, granulonodular. In the negative group, 52.6% were infiltrative; 42.1%, ulcerative; 4.5%, granulonodular; and 0.75%, polypoid. The endoscopic results varied between the two groups ($p < 0.05$). In the non-suspect group, 66.7% were ulcerative; 17.2%, infiltrative; 14.1%, polypoid; and 2.0%, granulonodular. With regards to histology, diffuse large B cell lymphoma was the most common subtype. The sensitivity of endoscopy was 60% for detecting malignancy and 21% for gastric lymphoma.

Conclusion: The present study suggests that gastric lymphoma and suspected gastric lymphoma have similar clinical features. Gastric lymphoma presented mainly as macroscopic ulcerative lesions, whereas suspected gastric lymphoma appeared mainly as infiltrative lesions. Although the diagnostic rate of gastric lymphoma was relatively low (21%), it can be identified by endoscopy (60%). To improve diagnosis, repetitive endoscopic biopsies should be performed and novel endoscopic techniques developed in the future.

Key words: Gastric lymphoma. Clinical features. Endoscopy. Pathology. Diagnosis.

INTRODUCTION

Gastric lymphoma is one of the most common types of primary gastrointestinal non-Hodgkin lymphoma (PGI NHL), representing ~50% of all PGI NHL (1-3) and 3-5% of gastric malignancies (4,5). In recent years, the incidence of gastric lymphoma has been increasing worldwide, notably in westernized countries (6,7). A recent study involving a large adult North American population demonstrated an overall increase in the yearly incidence of PGI NHL from 0.13 to 2.10 per 100,000 from 1999 to 2009. Gastric lymphoma also displayed a general increase in incidence during the study period (7).

The clinical manifestations of gastric lymphoma are often vague and indistinguishable from other benign or malignant gastric tumors (8,9). The endoscopic patterns of gastric lymphoma are also varied and non-specific, and may range from simple mucosal changes to a resemblance to adenocarcinoma, thus leading to missed diagnosis or a misdiagnosis (10,11). Doglioni et al. (12) found that the endoscopic study of gastric lymphoma is indicative in only one third of cases. Therefore, the diagnosis of gastric lymphoma remains a challenge, especially in the early stages of the disease, and thus decreases the likelihood of a successful management (12).

Although several recent studies (2,13,14) have addressed the clinical and endoscopic features of gastric lymphoma, limited data are available in order to make an accurate clinical diagnosis of gastric lymphoma by endoscopic or other techniques in suspect cases. Thus, we performed a retrospective multicenter survey to compare the clinical manifestations and endoscopic features of patients with gastric lymphoma and suspected gastric lymphoma in eight hospitals in different cities in the Shandong province in China from June 2008 to December 2015. The aim of the study was to develop improved criteria for the diagnosis of gastric lymphoma.

METHODS

This was a retrospective, multicenter study involving eight hospitals in eight cities in the Shandong province in China. The study

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was approved by the Ethics Committee of the Shandong University Qi-Lu Hospital and followed standard ethical guidelines.

A total of 267 patients were identified between 2008 and 2015, and their relevant clinical, endoscopic and pathologic data were analyzed. Patients with an uncertain diagnosis or < 18 years of age at diagnosis were excluded from the study. Subjects included those with gastric lymphoma diagnosed by endoscopy (endoscopy suspected group, n = 168) and those who had pathologically confirmed gastric lymphoma which was not suspected by endoscopy (endoscopy non-suspected group, n = 99).

For endoscopic assessment, the predominant endoscopic pattern, texture and tumor site of each subject were retrieved and carefully evaluated. The endoscopic pattern was classified as ulcerative (single, multiple, and diffuse), polypoid, granulonodular or infiltrative (distortion, thickening mucosal folds and poor peristalsis) (15) (Fig. 1).

For histological assessment, each biopsy was immunohistochemically stained for CD20 and CD3 and diagnosed by an experienced pathologist according to the 4th edition of the World Health Organization (WHO) criteria (14). Furthermore, additional staining for CD10, CD30, CD43, CD79a, CK19, bcl-2, and Ki-67 (12) were performed in selected cases.

The participating centers and the number of cases for each center were as follows: Qilu Hospital of Shandong University, Jinan city (87 and 58 cases); Linyi People's Hospital, Linyi city (38 and 12 cases); Qingdao Municipal Hospital, Qingdao city (17 and nine cases); Zibo Central People's Hospital, Zibo city (12 and five cases); Jining People's Hospital, Jining city (five and seven cases); Binzhou People's Hospital, Binzhou city (five and two cases); Heze Municipal Hospital, Heze city (three and zero cases); and Liaocheng People's Hospital, Liaocheng city (one and six cases).

Statistical analysis

The Student's t-test was applied for paired observations or the Chi-squared test as appropriate. All statistical analyses were performed using the SPSS statistical software (version 18.0; SPSS Inc., Chicago, IL, USA) with a statistical significance level set at $p < 0.05$.

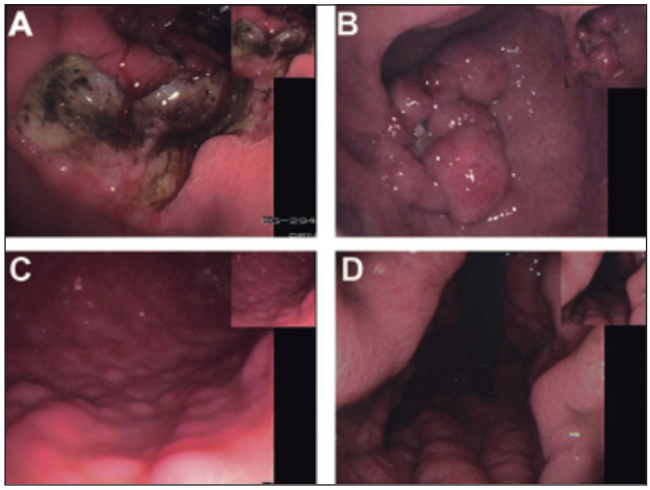

Fig. 1. Endoscopic patterns. A. Ulcerative type. B. Polypoid type. C. Granulonodular type. D. Infiltrative type.

RESULTS

Clinical characteristics

In total, 168 patients had suspected gastric lymphoma by endoscopy, the pathology was conformed in 35 patients (positive subgroup) and 133 patients had a non-confirmed pathology (negative subgroup). The endoscopy suspected group was comprised of 101 males and 67 females and the male to female ratio was 1.51 to 1. The mean age at diagnosis was 52.1 (range, 19 to 80), and 90% of cases were over 40 years of age. The positive subgroup was comprised of 20 males and 15 females with a mean age of 52.5 (range, 23 to 80). The negative subgroup consisted of 81 males and 52 females and the male to female ratio was 1.56 to 1. The average age at diagnosis was 52.0 (range, 19 to 80) (Table 1). There was no significant difference between the age and sex distribution in the two subgroups ($p > 0.05$) (Table 1).

Abdominal pain or discomfort was the predominant symptom in both subgroups, representing 60.0% (15/25) and 52.5% (53/101) of cases, respectively. Dyspepsia or bloating were less frequently reported and were present in 16.0% (4/25) and 17.8% (18/101) of cases, respectively. Weight loss and heartburn had a similar occurrence in both groups, whereas gastrointestinal bleeding was rarely

Table 1. Clinical characteristics of patients in the endoscopy suspected group

Clinical characteristic	*Endoscopy suspected group*		*p value*
	Positive group	*Negative group*	
No.	35	133	
Gender (n, %)			
Male	20	81 (60.9)	0.948
< 40	4 (20.0)	12 (9.0)	
40-49	3 (15.0)	17 (12.8)	
50-59	8 (40.0)	28 (21.1)	
60-69	4 (20.0)	19 (14.3)	
≥ 70	1 (5.0)	5 (3.8)	
Female	15	52 (39.1)	0.839
< 40	3 (20.0)	14 (26.9)	
40-49	4 (26.7)	10 (19.2)	
50-59	2 (13.3)	7 (13.5)	
60-69	2 (13.3)	12 (23.1)	
≥ 70	4 (26.7)	9 (17.3)	
Age (years)			
Mean	52.5	52.0	0.862
Range	23-80	19-80	
Clinical symptoms/signs (n, %)	25	101	0.988
Abdominal pain/discomfort	15 (60.0)	53 (52.5)	
Dyspepsia/bloating	4 (16.0)	18 (17.8)	
Weight loss	3 (12.0)	12 (11.9)	
Heartburn	2 (8.0)	10 (9.9)	
Gastrointestinal bleeding	1 (4.0)	8 (7.9)	

present in both groups. There was no significant difference in the clinical manifestations in the two groups ($p > 0.05$) (Table 1).

Endoscopic presentations

The endoscopic characteristics, including gross endoscopic patterns, texture and predominant involvement sites, of the endoscopy suspected group and the endoscopy non-suspected group are listed in tables 2 and 3.

Endoscopy suspected group

In the positive subgroup, the most common endoscopic pattern was the ulcerative type in 19 (54.3%) cases (single: eleven; multiple: seven; and diffuse: one) infiltrative in 12 (34.3%) cases, polypoid in three (8.5%) cases and granulonodular in one (2.9%) case. In the negative subgroup, the main endoscopic pattern was infiltrative in 52.6% (70/133), ulcerative (single: 32; multiple: 23; and diffuse: one) in 42.1% (56/133), granulonodular in 4.5% (6/133) and polypoid in 0.75% (1/133) of cases.

With regard to the texture of biopsy specimens on endoscopic examination, the main texture was stiff in 15 cases (48.4%), crisp in eight (25.8%) cases, tenacious in four (12.9%) and soft in four (12.9%) cases in the positive subgroup. In the negative subgroup, the main texture was tenacious in 44 (42.7%), crisp in 27 (26.2%), soft in 19 (18.5%) and stiff in the remaining 13 (12.6%) cases. There were significant differences in the endoscopic types and texture of the two subgroups ($p < 0.05$) (Table 3).

The predominant site of lesions was frequently the corpus of the stomach in both subgroups, with 14 (40.0%) cases and 45 (33.9%) cases, respectively. Diffuse involvement was observed in ten (28.6%) and 47 (35.3%) cases, respectively. Antral involvement was noted in nine (25.6%) and 26 (19.5%) cases respectively and lesions in the cardia/fundus were found in two (5.8%) and 15 (11.3%) cases, respectively. The distribution of sites was similar between the two subgroups ($p > 0.05$) (Table 3).

Table 2. Endoscopic features of patients in the endoscopy suspected group

Endoscopic features	*Endoscopy suspected group*		*p value*
	Positive group	*Negative group*	
Endoscopic pattern (n, %)	35	133	0.024
Ulcerative	19 (54.3)	56 (42.1)	
Single	11 (31.4)	32 (24.1)	
Multiple	7 (20.0)	23 (17.3)	
Diffuse	1 (2.9)	1 (0.75)	
Polypoid	3 (8.5)	1 (0.75)	
Granulonodular	1 (2.9)	6 (4.5)	
Infiltrative	12 (34.3)	70 (52.6)	
*Texture**	31	103	0.000
Soft	4 (12.9)	19 (18.5)	
Crisp	8 (25.8)	27 (26.2)	
Tenacious	4 (12.9)\	44 (42.7)	
Stiff	15 (48.4)	13 (12.6)	
Predominant site	35	133	0.484
Solitary site	25 (71.4)	86 (64.7)	
Corpus	14 (40.0)	45 (33.9)	
Antrum	9 (25.6)	26 (19.5)	
Fundus	1 (2.9)	13 (9.8)	
Cardia	1 (2.9)	2 (1.5)	
Multiple sites	10 (28.6)	47 (35.3)	

*The data were unavailable in four cases of the positive group and 30 cases of the negative group.

Table 3. Endoscopic features of patients with gastric lymphoma

Endoscopic features	*Pathology confirmed group (positive group)*	*Endoscopy non-suspected group*	*p value*
Endoscopic pattern (n, %)	35	99	0.161
Ulcerative	19 (54.3)	66 (66.7)	
Single	11 (31.4)	45 (45.5)	
Multiple	7 (20.0)	13 (13.1)	
Diffuse	1 (2.9)	8 (8.1)	
Polypoid	3 (8.5)	14 (14.1)	
Granulonodular	1 (2.9)	2 (2.0)	
Infiltrative	12 (34.3)	17 (17.2)	0.536
*Texture**	31	81	
Soft	4 (12.9)	6 (7.5)	
Crisp	8 (25.8)	29 (35.8)	
Tenacious	4 (12.9)\	14 (17.3)	
Stiff	15 (48.4)	32 (39.4)	
Predominant site	35	99	0.749
Solitary site	25 (71.4)	76 (76.7)	
Corpus	14 (40.0)	38 (38.4)	
Antrum	9 (25.6)	34 (34.3)	
Fundus	1 (2.9)	3 (3.0)	
Cardia	1 (2.9)	1 (1.0)	
Multiple sites	10 (28.6)	23 (23.3)	

*Data were unavailable in four cases of the pathology confirmed group and 17 cases of the endoscopy non-suspected group.

Endoscopy non-suspected group

The features of the endoscopy non-suspected group are detailed in table 3. With regard to the texture of biopsy specimens, the main texture was stiff in 32 (39.4%) cases, crisp in 29 (35.8%) cases, tenacious in 14 (17.3%) cases and soft in six (7.5%) cases. The main endoscopic pattern was ulcerative in 66.7% (66/99) (single: 45; multiple: 13; diffuse: eight), infiltrative in 17.2% (17/99), polypoid in 14.1% (14/99) and granulonodular in 2.0% (2/99) of cases.

The main sites involved were the corpus of the stomach in 38 (38.4%) cases, the antrum in 34 (34.3%), multiple involved sites in 23 (23.3%) and cardia/fundus in four (4.0%) cases. There were no significant differences in the endoscopic features between the endoscopy non-suspected group and pathology confirmed group (positive group) ($p > 0.05$). Importantly, we found that the lesions with irregularly uplifted mucosa and a central ulceration or with multiple superficial ulcerations were often suggestive of gastric lymphoma in both samples.

Histological subtype

The histological subtypes of patients with gastric lymphoma are detailed in table 4. B cell gastric lymphoma comprised 97.1% (34/35) and 97.0% (96/99) of cases in the pathology confirmed subgroup and endoscopy non-suspect group, respectively. Among the B cell lineage, the main histological subtype was diffuse large B cell lymphoma (DLBCL) in both groups (65.8 *vs* 63.6%), followed by mucosal-associated lymphoid tissue (MALT) lymphoma (25.8 *vs* 28.3%) and other type B lymphoma (5.6 *vs* 5.1%). Furthermore, there was no significant difference in the histological subtype of gastric lymphoma patients between the two groups ($p > 0.05$) (Table 4).

Furthermore, the histopathology of the non-gastric lymphoma cases was evaluated in the endoscopy suspected group (Fig. 2). Chronic inflammation (63%) was the most common pathological lesion, followed by poorly differentiated adenocarcinoma (23%), signet-ring cell carcinoma (10%), well-differentiated adenocarcinoma (1%), adenoma (1%) and others (2%).

The diagnostic sensitivity of endoscopy

A total of 35 patients (20.8%, 35/168) in the endoscopy suspected group had a gastric lymphoma that was verified by pathological analysis. Therefore, the diagnostic sensitivity of endoscopy was only 20.8% in the study.

According to the gross morphologic appearance of the lesion, in 59 of 99 patients (60%) it was characterized as malignant in the endoscopy non-suspect group and 32 of 99 patients (32%) were diagnosed with a gastric ulcer (with an unidentified nature). Thus, this method exhibited a sensitivity of 60% for the detection of malignancy.

Table 4. Histological subtype of patients with gastric lymphoma

Histological subtype	*Pathology confirmed group (Positive group)*	*Endoscopy non-suspected group*	*p value*
B lymphoma (n %)	34 (97.1)	96 (97.0)	0.603
DLBCL	23 (65.8)	63 (63.6)	
MALT lymphoma	9 (25.8)	28 (28.3)	
MCL	1 (2.8)	0 (0.0)	
Others	1 (2.8)	5 (5.1)	
T lymphoma (n, %)	1 (2.8)	3 (3.0)	

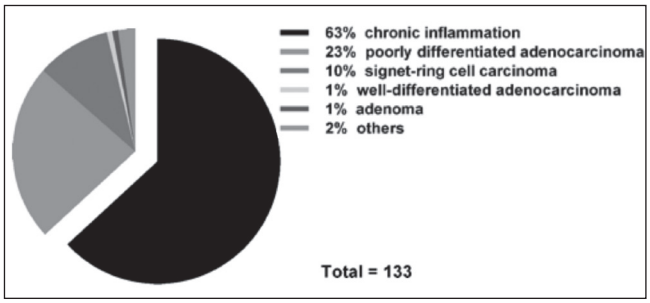

Fig. 2. Histological characteristics of patients in the pathology non-confirmed group (negative group).

DISCUSSION

In this retrospective multicenter study, we compared the endoscopic presentations and clinical manifestations of patients with gastric lymphoma and suspected gastric lymphoma. We found that age, sex distribution and clinical manifestations were similar in both groups. With regard to the macroscopic pattern, subjects with gastric lymphoma had ulcerative lesions in both the pathology confirmed subgroup (positive subgroup) and the endoscopy non-suspected group. On the other hand, in the suspected gastric lymphoma group the main pattern was the infiltrative type in the pathology non-confirmed subgroup (negative subgroup).

The clinical manifestations of patients with gastric lymphoma were often obscure and non-specific. In this study, the most common symptoms were abdominal pain or discomfort (51.2%) and dyspepsia (18.4%) in both the endoscopy suspected group and the endoscopy non-suspected group. These data are consistent with other studies (13,16). In addition, most of the patients were over 40 years of age and were routinely evaluated by endoscopy.

With regard to endoscopic findings, the most common pattern of the gastric lymphoma in the pathology confirmed subgroup (positive group) and endoscopy non-suspected group was the ulcerative type. This is also consistent with several recent studies (13,16,17). Unfortunately, the main macroscopic pattern of suspected gastric lymphoma in the pathology non-suspected subgroup was the infiltrative type (49.4%) and the ulcerative type was less frequent (42.1%). The differences between the macroscopic patterns of the two subgroups may be explained by the high morbidity of gastric carcinoma in China, and thus endoscopy may be performed to identify gastric carcinoma when gastric ulcerative lesions are found. Therefore, it is important to improve the understanding of the use of endoscopic techniques for evaluating gastric lymphoma.

Some studies indicate that large superficial ulcers with long stellate branches or irregular, protrusive lesions with central ulcerations are characteristic of lymphoma (11,14). However, several other types of ulcers such as small or penetrating ulcers may be indistinguishable from benign and carcinomatous ulcers. Furthermore, the infiltrative pattern may also be observed in benign conditions such as Menetrier's disease and in linitis plastica carcinoma (11). In addition, both types of lesions mainly occurred in the middle and distal parts of the stomach, as reported in previous studies (18). Thus the distribution of nonspecific lesions may contribute to misdiagnosis and missed diagnosis. Therefore, it is extremely difficult to obtain a correct diagnosis by endoscopy.

Endoscopy in our study showed a sensitivity of 60% for the detection of malignancy, whereas the endoscopic sensitivity declined to 20.8% for gastric lymphoma. Kelessis et al. (17) reported similar results, with a sensitivity of 61% for malignancy and only 27% for non-Hodgkin's lymphoma. This phenomenon may be caused by the submucosal growth of the lesion, necrotic material taken during biopsy, inadequate amounts of specimen or inadvertent sampling resulting from a crush (17,20).

In order to enhance the sensitivity of endoscopy, repeat biopsies are recommended. Xu et al. (20) found that obtaining repeat biopsies could improve the overall accuracy rate by 40.8%. In addition, endosonography (EUS) played a vital role in identifying gastric lymphoma and other gastric tumors. For example, infiltrative carcinoma tended to show vertical growth in the gastric wall. However, lymphoma tended to show mainly a horizontal extension (21). However, EUS is not a histological technique, and thus should be combined with endoscopic biopsy in order to avoid false negative results.

Confocal laser endomicroscopy, a technique that examines tissue histology *in vivo,* has shown very promising results for diagnosis and differential diagnosis of gastric lymphoma and may be used as an alternative to conventional biopsy (22,23). Moreover, histopathological and immunohistochemical examination is crucial for improving the diagnosis of gastric lymphoma.

With regard to the histopathological subtype of lesions, our results verified the fact that DLBCL was the most common type in patients with gastric lymphoma. The limitation of the study was its retrospective design, which can compromise data integrity and lead bias in the conclusions.

In conclusion, patients with gastric lymphoma and suspected gastric lymphoma in our study had a similar clinical manifestation. Gastric lymphoma mainly presented as macroscopic ulcerative lesions, whereas suspected gastric lymphoma mainly presented as the infiltrative type. Even though the diagnostic rate of gastric lymphoma was relatively low (21%), gastric lymphoma can usually be diagnosed by endoscopy (60%). In order to improve diagnostic sensitivity, endoscopic examinations should be combined with repetitive biopsies, and novel endoscopic techniques should be developed in the future.

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