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Original Article

Role of the Endoscopic Biopsy in the Diagnosis of Primary Gastric Lymphomas: A Retrospective Review of 120 Patients

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ABSTRACT

***Background*:** Gastric lymphomas are heterogeneous disease in terms location, endoscopic patterns, histological subtypes, and treatments offered. We present a retrospective study of clinicopathological profile of primary gastric lymphoma from a single tertiary care center in northern India. The study was done with an aim to evaluate the histological features, patterns of endoscopic findings and role of bone marrow involvement in PGL.

***Methods*:** Consecutive cases of all PGLs within a 14-year period were retrieved. Histological and immunohistochemical features of all cases were evaluated and endoscopic biopsies were compared with resection specimens.

***Results*:** Diffuse large B-cell lymphoma was the commonest PGL subtype accounting for 62.5%. Marrow involvement by lymphoma was not observed in any of the cases. A high diagnostic discordance was observed when biopsy findings were compared with resection specimens. The sensitivity of and specificity of endoscopic biopsy was 92% and 88% respectively for diagnosing lymphoma. Additional histological features (carcinoid, amyloidosis and granuloma) were observed in few cases.

***Conclusion*:** We demonstrated the various endoscopic patterns of gastric involvement in PGL. A high false negative rate for diagnosis of PGL in endoscopic biopsies alone was observed. BM examination as part of initial diagnostic work-up in PGL could be avoided due to rarity of marrow involvement by the disease..

KEYWORDS: Gastric, Primary Lymphoma, Endoscopic Biopsy.

Introduction

Stomach is the commonest site of involvement in extra-nodal non-Hodgkin's lymphoma with incidence ranging between 15 to 20%.[1-3] Nevertheless, primary gastric lymphoma (PGL) is uncommon; accounting only for 2-8% of all tumors of the stomach.[4] The recent reports suggest increase in incidence of primary gastric lymphoma.[5,6]

Most of the gastric lymphomas are of non-Hodgkin type histologically and virtually all gastric lymphomas arise from B-cell. T-cell non-Hodgkin's lymphoma of stomach is extremely rare accounting

for approximately 6% of total cases.[8] PGL is defined according to Dawson's criteria that include (1) absence of peripheral lymphadenopathy at the time of presentation; (2) lack of enlarged mediastinal lymph nodes; (3) normal total and differential white blood cell count; (4) predominance of bowel lesion at the time of laparotomy with only lymph nodes obviously affected in the immediate vicinity; and (5) no lymphomatous involvement of liver and spleen.[9]

Gastric lymphomas are heterogeneous disease in terms of site of involvement, histological subtypes, and treatments offered. Bone marrow (BM) involvement by gastric MALT (mucosa-associated lymphoid tissue) lymphoma has been reported to be around 1-8% cases.[10,11] BM examination is recommended as initial staging work-up according to European Society for Medical Oncology (ESMO)[12] guidelines whereas National Comprehensive Cancer Network (NCCN)[13] guidelines suggest BM examination in selected cases. In the European Gastro-Intestinal Lymphoma Study (EGILS) consensus report (2011)[14], it was suggested that BM examination should only be recommended when tumor regression is not achieved with H. pylori eradication after an adequate time period. The incidence of BM involvement in gastric diffuse large B-cell lymphoma (DLBCL) is not well characterized.

Primary gastric lymphomas have been scarcely reported in India.[15,16] In this study we present a retrospective study of 120 cases of PGL from a single centre in northern India to evaluate the following - 1) diagnostic yield in endoscopic mucosal biopsy for PGL, 2) histological subtypes and associated histological features in patients with PGL, and 3) frequency of BM involvement by PGL.

Materials and Methods

All the gastric biopsies and resected specimens during last 14 years (2001-2014) were retrieved from the hospital records and those with a diagnosis of gastric lymphoma were reviewed. Immunostaining with lymphoma panel (LCA, CK, CD20, CD3, cyclin D1, CD5, CD23, and BCL2) was performed routinely depending on availability of tissue. All the cases were reclassified according to the World Health Organization (WHO) 2016 classification[17] based on morphological and immunophenotypic criteria.

Baseline demographic profile, endoscopic findings and rapid urease test (RUT) results were obtained from case files. Bone marrow aspiration and biopsy slides were evaluated to look for marrow involvement. The endoscopic biopsy finding was compared with resection specimens wherever available.

Results

A total of 7458 gastric specimens (biopsies / resections) were received in a 14-year period. There were 120 (1.6%) cases of primary gastric lymphomas (PGL), 400 (5.4%) cases of gastric carcinoma and 21 (0.3%) cases of primary gastric neuroendocrine tumor diagnosed during this period. There was increasing trend of PGL every year. Thirty-nine of 3006 biopsies (1.3%) were diagnosed from 2001 to 2007 whereas 81 of 4452 biopsies (1.8%) were diagnosed from 2008 to 2014. In 120 cases of gastric specimens diagnosed as lymphoma, 77 cases (64%) had only biopsy, 11 cases had only resection specimen whereas 32 cases had both biopsy and resection specimens.

The age range in 120 cases of gastric lymphoma was 17-87 years (mean 52.5 years, median 51 years). Seventy-seven patients (65%) were more than 50 years of age with a peak incidence in 6th decade. Only one case was diagnosed in a child aged 17 years with histological diagnosis of Burkit lymphoma. There were 90 males and 30 females with M: F ratio of 3:1. The clinical presentation was nonspecific and variable (**table 1**). The anatomic site of lesions is summarized in **table 2**. Endoscopy data was available in 97 cases. The endoscopic appearance was proliferative in 30 cases, ulcerative in 25 (**figure 1A**), ulceroproliferative in 30 cases, diffuse wall thickening in 5 cases and polypoidal in 6 cases. Complications like gastric diverticulum were seen in 3 cases and hiatus hernia was seen in one case.

Histological subtyping

The frequencies of different histological subtypes of PGL are listed in **table 3**. Immunohistochemistry (IHC) was available in 84 patients. Among these 84 cases all cases except one were B cell lymphoma (**figure 1B to 1F**). Diffuse large B-cell lymphoma (DLBCL) was the

commonest PGL subtype accounting for 62.5% followed by maltoma (18.3%). Ten cases (13.3%) of DLBCL had low-grade maltoma component along with high-grade areas. Helicobacter pylori were seen in 22 (18.3%) cases of PGL as documented by biopsy. RUT was conducted in 54 cases of which 23 patients (42.6%) were tested positive and 31 cases (57.4%) were negative. H. pylori were seen on biopsy in 12/65 cases of DLBCL, 5/12 cases of maltoma and in 5/29 cases of lymphoma NOS.

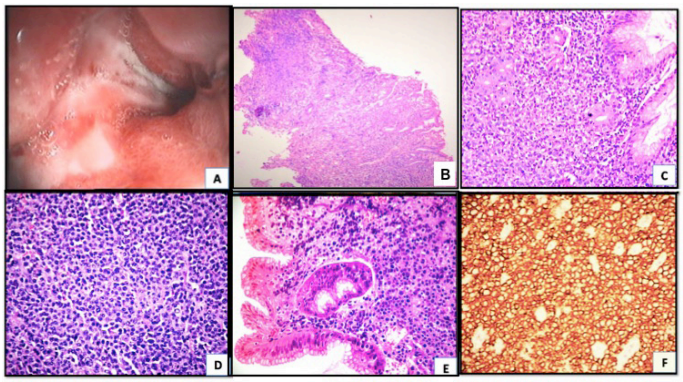

Figure 1 (A): Endoscopic appearance of ulcerative mucosal lesion involving the distal part of stomach. (B): Low power microphotograph showing areas of crush artifact (upper left). (C): Histology of low-grade gastric lymphoma showing diffuse infiltration by small atypical lymphoid cells with crushing artifact. (D): High-grade lymphoma showing abundant mitotic and apoptotic bodies. (E): Prominent lymphoepithelial lesions in a case of lymphoma. (F): Immunohistochemistry showing diffuse membranous positivity for CD20 in tumor cells.

Table 1: Clinical presentation in patients with primary gastric lymphoma.

Symptoms	Number of patients (n=120)
Abdominal Pain	57
Anorexia	42
Weight loss	50
Vomiting	41
GI bleed	24
Dyspepsia	17
Fever	07
Abdominal mass	09
Gastric outlet obstruction	12
Anemia	03
Peritoneal effusion	03
Data not available	06

Bone marrow examination

BM examination (both aspiration and biopsy) was done in 79 cases (including 50 cases of DLBCL). Marrow involvement by lymphoma was not observed in any of the cases.

Resection specimens

A total of 43 resection specimens were received which included 22 cases of distal partial gastrectomy, 1 case of proximal gastrectomy, 5 cases of subtotal (distal) gastrectomy, 12 cases of total gastrectomy and 4 cases of radical gastrectomy. Grossly ulceroproliferative growth

Table 2: Distribution of lesions in the stomach.

Location	Number of cases (n=120)
Antrum	46
Fundus	17
Body	48
Along greater curvature	08
Along lesser curvature	07
Gastroesophageal junction	01
Diffuse involvement of gastric mucosa	05

Table 3: Histological subtypes of primary gastric lymphoma.

Histological typing	N=120
DLBCL	65
Maltoma	12
Maltoma + DLBCL	10
Post-transplant lymphoproliferative disorder	01
Burkitts	01
DLBCL + carcinoid	01
Anaplastic large cell lymphoma	01
NOS	29

was identified in 24 (55.8%) cases, ulcerative in 14 (32.5%) cases and nodular or diffuse thickening in 5 (11.6%) cases with ulceration. Multifocal lesions were identified in 3 of the specimens. Proximal esophageal involvement was seen in one specimen and distal duodenal infiltration was noted in six specimens. Lymph nodes ranging from 0 to 30 (mean 10.2) were dissected in all resected cases of which nodal involvement was seen in 36 (83.7%) cases. Gross infiltration into the liver parenchyma was seen in two cases and one case showed pancreatic as well as splenic involvement.

On microscopic examination of resection specimens, 42 show a diffusely infiltrating growth. No residual tumor was identified in one case (post-chemotherapy). All most all cases showed focal / complete surface ulceration. Lymphoepithelial lesions were identified in 19 (45.2%) cases. In all resected cases tumor was infiltrating the muscularis propria of gastric wall. In 14 patients tumor was confined within the muscularis whereas in 13 cases sub-serosal involvement was also seen and in another 14 cases serosa was also involved. In 20 cases one or more perigastric nodes were involved (with focal / complete effacement of architecture) with perinodal extension of atypical lymphoid cells in three cases.

Correlation of biopsy findings with resection findings

Both biopsy and resection specimens were available in 32 patients. Endoscopic biopsies disclosed malignant lesions in 27 cases (84%) and were diagnostic of lymphoma in 13 (48%). High suspicion of gastric lymphoma was raised in ten cases (**table 4**). In 5 cases biopsy was either inadequate or non-representative or showed extensive crushing artifact making it unsuitable for final diagnosis. We also reviewed the biopsy and resection findings of 63 cases of gastric adenocarcinoma received in 5 years duration, of which two cases were misdiagnosed as lymphoma whereas 61 cases were truly reported as adenocarcinoma on endoscopic biopsy. Thus the sensitivity and specificity of endoscopic biopsy for diagnosing lymphoma in this study was 85% and 97% respectively.

Other miscellaneous findings

Some of the cases showed other associated findings. One resection specimen showed presence of gastric carcinoid distal to the lymphoma lesion. In another specimen, nodular congophilic deposits were identified within the lesion suggesting gastric amyloidosis. Multiple submucosal granulomas were identified in another one case and candidial colonization was observed in one case. Foreign body type giant cell reaction was observed in three cases due to previous biopsy. In another one case multiple granulomas with central caseous necrosis (s/o tuberculosis) were identified in perigastric nodes. Three patients had ascites and were subjected to cytologic fluid analysis. All three patients had lymphomatous infiltration of ascitic fluid.

Discussion

The gastrointestinal tract is the most frequent site of extranodal lymphoma, and the stomach is involved in up to two-thirds of this cases.[18] Although a rare disease, the frequency of PGL is rising in the last decades.[6] Only a few studies on primary gastrointestinal lymphoma have been published from India. In this large retrospective study, 1.6% of the cases were PGL of the 7400 biopsies whereas the incidence of gastric carcinoma was 5.4%.

Nonspecific endoscopy patterns have been described for gastric lymphoma. The endoscopic diagnosis

Table 4: Correlation of histological diagnosis in endoscopic biopsy and resection.

Resection specimen (n=32)	Endoscopic biopsies (n=32)			
Non-Hodgkin lymphoma	Non Hodgkin lymphoma	Poorly differentiated adenocarcinoma	Suspicious for malignancy	Non-representative
	13	4	10	5

of gastric lymphoma at first sight may be difficult, because of the various macroscopic patterns; ranging from benign gastritis to carcinoma.[19] In this study, we analyzed different endoscopic patterns of gastric lymphoma. Although large stellate ulcers are characteristic for NHL, pure proliferative and ulceroproliferative pattern of involvement was seen in more than 50% cases in the present study. Six cases in our series had polypoid mass lesion and five other cases had linitis plastic like diffuse thickening on endoscopy suggestive of carcinoma.

Diffuse large B cell lymphoma (with or without a MALT component) is the most common histological subtype in our series. Sixty percent of cases in the present study were also DLBCL, which is comparable to other Indian large studies[15] and contrasting to western studies.[7] Such high number of cases of DLBCL in Indian population can be explained by late stage of presentation.

A correct histological diagnosis after the first endoscopic biopsy was made in 76% (67/88 biopsies) of the cases which was similar to other studies.[20,21] Lymphoma was misdiagnosed in 4 cases as adenocarcinoma and 5 cases had non-representative biopsy, however a histological suspicion of lymphoma was made in another 10 cases and a repeat biopsy was advised. In a study by Xu *et al*[22] repeat biopsy could diagnose >90% of cases. In the study by Arista-Nasr *et al*[23] a review of the histological sections indicated that the changes, either diagnostic of or compatible with lymphoma, were present in 75% and 18% of the sections, respectively. They also suggested few histological features indicative of gastric lymphoma such as (1) marked increase in density of the lymphoid infiltrate in the gastric mucosa, (2) replacement of gastric glands by lymphoid infiltration, and (3) lymphoepithelial lesions. We obtained a high sensitivity and specificity of endoscopic biopsy for the diagnosis of PGL.

A total of 106 resection specimens (including both NHL and adenocarcinoma) were reviewed in this study. False positive reporting of lymphoma was done in two patients which turned out to be poorly differentiated adenocarcinoma on resection. Therefore a high index of suspicion for lymphoma should be raised on endoscopic biopsies with diffuse pattern of tumor cells and especially if there is crushing artifact on small biopsies. Immunohistochemistry should always be used for confirmation in such type of cases.

Currently BM examination is mandatory for initial staging of gastric lymphomas. A few previous studies on gastric MALT lymphoma showed rare involvement of BM. In a recent study by Park *et al* suggested that BM involvement in gastric MALTOMA is only 1%.[24] This incidence rate is as low as 0.5% in another study.25 None of the cases (including the cases with stage IV disease), in our study had secondary BM involvement. There have been different opinions about the requirement of BM examination in initial staging work-up of gastric MALT lymphoma. According to the European Gastro-Intestinal Lymphoma Study (EGILS) consensus report (2011), BM examination should only be recommended when tumor regression is not achieved with H. pylori eradication after an adequate time period.

The role of H. pylori in the pathogenesis of PGL has been established. Corresponding to this we had nearly half of the cases showing positivity for RUT or presence of H.pylori on histology. DLBCL was the commonest histological subtype (n=65; 62.5%) in our study, followed by low-grade marginal zone lymphoma. This is in accordance to previous studies from India as well as outside India. A low-grade component of MALT lymphoma was seen in 6.76% (n=15) of the DLBCL, which is much lower than 33% reported by Koch et al[26] and higher than 6.7% reported by Arora *et al*.[15]

In a study by Roukos *et al*[21], 28 surgically resected specimens of PGL, 9 cases had limited disease (within submucosa) whereas 19 patients had advanced disease. Forty-three resection specimens in the present study showed surface ulceration as a consistent finding and infiltration of muscularis (corresponding to Paris stage T2) in all cases. Interestingly one case had gastric carcinoid and another had gastric amyloidosis in addition to PGL. Therefore, the rate of advanced disease was higher in the present study. A high rate of diagnostic discordance (65.6%) between endoscopic biopsy and resection specimen (available in 32 cases) could be attributed to multiple factors like a non-representative biopsy, poorly preserved morphology and poorly differentiated carcinoma as mimicker of DLBCL.

However, few limitations were encountered in the study such as the management and follow up data was available for only 40% of cases. Immunohistochemistry was available in 70% of cases which posed difficulty in subcategorizing the cases. None of the patients in present study had BM involvement. Therefore, identifying risk factors for BM involvement could not be studied.

Conclusion

In conclusion, this large retrospective study illustrates the increasing incidence of PGL in current years as compared to gastric carcinoma. A high diagnostic yield of endoscopic biopsy was established in our study in diagnosing PGL. Endoscopic biopsy along with immunohistochemistry could diagnose majority of cases of PGL. Hence gastric resection can be avoided in few selected cases. Moreover, our study showed the BM involvement is extremely rare in PGL, even with advanced disease. Therefore, BM examination as part of initial diagnostic work-up in PGL should be avoided in PGL.

References

1. Schutze W P, Halpern N B. Gastric lymphoma. Surg Gynecol Obstet. 1991;172:33–38.
2. Severson RK, Davis S. Increasing incidence of primary gastric lymphoma. Cancer. 1990 ;66(6):1283-7.
3. Cogliatti S B, Schmid U, Schumacher U. *et al*. Primary B-cell gastric lymphoma: a clinicopathological study of 145 pts. Gastroenterology. 1991;101:1159–70.
4. Speranza V, Lomanto D. Primary gastric lymphoma. In: Holzheimer RG, Mannick JA, editors. Surgical Treatment: Evidence-Based and Problem-Oriented. Munich: Zuckschwerdt; 2001.
5. Severson RK, Davis S. Increasing incidence of primary gastric lymphoma. Cancer. 1990 ;66(6):1283-7.
6. Muller AM, Ihorst G, Mertelsmann R, Engelhardt M. Epidemiology of non-Hodgkin's lymphoma (NHL): Trends, geographic distribution, and etiology. Ann Hematol. 2005;84:1-12.
7. Psyrri A, Papageorgiou S, Economopoulos T. Primary extranodal lymphomas of stomach: clinical presentation, diagnostic pit falls and management. Ann Oncol. 2008;19:1992-99.
8. Nakamura S, Akazawa K, Yao T, Tsuneyoshi M. A clinicopathologic study of 233 cases with special reference to evaluation with the MIB-1 index. Cancer. 1995 15;76(8):1313-24.
9. Dawson I M P, Cornes J S, Morrison B C. Primary malignant lymphoid tumors of the intestinal tract. Br J Surg. 1961;49:80–89.
10. Chung SJ, Kim JS, Kim H, *et al*. Long-term clinical outcome of Helicobacter pylori-negative gastric mucosa-associated lymphoid tissue lymphoma is comparable to that of H. pylori-positive lymphoma. J Clin Gastroenterol. 2009;43:312–7.
11. Cohen SM, Petryk M, Varma M, *et al*. Non-Hodgkin's lymphoma of mucosa-associated lymphoid tissue. The Oncologist. 2006;11:1100–17.
12. Zucca E, Copie-Bergman C, Ricardi U, *et al*. Gastric marginal zone lymphoma of MALT type: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24Suppl 6:vi144-vi148.
13. Zelenetz AD, Gordon LI, Wierda WG, *et al*. Non-Hodgkin's lymphomas, version 2.2014. J Natl Compr Canc Netw. 2014; 12: 916- 46.
14. Ruskoné-Fourmestraux A, Fischbach W, Aleman BM, *et al*. EGILS consensus report. Gastric extranodal marginal zone B-cell lymphoma of MALT. Gut 2011;60:747-58.
15. Arora N, Manipadam MT, Pulimood A, Ramakrishna BS, Chacko A, Kurian SS *et al*. Gastrointestinal lymphomas: Pattern of distribution and histological subtypes: 10 years experience in a tertiary centre in South India. Indian J Pathol Microbiol. 2011;343:712-9.
16. Shirsat HS, Vaiphei K. Primary gastrointestinal lymphomas - A study of 81 Cases from a Tertiary Healthcare Centre. Indian J Cancer. 2014 ;51(3):290-292.
17. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, Jaffe ES. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016 ;127(20):2375-90.
18. Zucca E, Roggero E, Bertoni F, Cavalli F. Primary extranodal non-Hodgkin's lymphomas. Part 1: Gastrointestinal, cutaneous and genitourinary lymphomas. Ann Oncol. 1997; 8:727-737.
19. Zullo A, Hassan C, Cristofari F, Perri F, Morini S. Gastric low grade mucosal-associated lymphoid tissue lymphoma: Helicobacter pylori and beyond. World J Gastrointest Oncol 2010;2:181-6.
20. Taal BG, Boot H, van Heerde P, *et al*. Primary non-Hodgkin lymphoma of the stomach: endoscopic pattern and prognosis in low versus high grade malignancy in

relation to the MALT concept. Gut. 1996;39:556-61.

21. Roukos DH, Hottenrott C, Encke A, Baltogiannis G, Casioumis D. Primary gastric lymphomas: a clinicopathologic study with literature review. Surg Oncol. 1994;3(2):115-25.
22. Xu W, Zhou C, Zhang G, Wang H, Wang L, Guo J. Repeating gastric biopsy for accuracy of gastric lymphoma diagnosis. Gastroenterol Nurs. 2010 ;33(4):313-7.
23. Arista-Nasr J, Jimenez A, Keirns C, Larraza O, Larriva-Sahd J. The role of the endoscopic biopsy in the diagnosis of gastric lymphoma: a morphologic and immunohistochemical reappraisal. Hum Pathol. 1991;22(4):339-48.
24. Park JY, Kim SG, Kim JS, Jung HC. Bone marrow involvement is rare in superficial gastric mucosa-associated lymphoid tissue lymphoma. Dig Liver Dis. 2016;48(1): 81-6.
25. Min BH, Park JY, Kim ER, *et al*. Limited role of bone marrow aspiration and biopsy in the initial staging work-up of gastric mucosa-associated lymphoid tissue lymphoma in Korea. Gut Liver. 2014;8:637–42.
26. Koch P, del Valle F, Berdel WE, Willich NA, Reers B, Hiddemann W, *et al*. Primary gastrointestinal non-Hodgkin's lymphoma: I. Anatomic and histologic distribution, clinical features, and survival data of 371 patients registered in the German Multicenter Study GIT NHL 01/92. J Clin Oncol. 2001;19:3861-73.