Clinicopathological study of primary gastric lymphoma

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ABSTRACT

Objectives: To present a histopathologic and immunohistochemical analysis of primary gastric lymphomas that was reclassified according to the new World Health Organization classification of lymphoid neoplasms.

Methods: We reviewed the morphological and immunohistochemical features of 28 patients with gastric lymphomas, diagnosed in the Department of Pathology at the University Hospital of Tishreen University, Lattakia, Syria, during the period 1994-2003. Specimens were obtained from endoscopic and surgical biopsies. The immunohistochemical study was performed to analyze the immunophenotype of these lymphomas.

Results: Patients were aged 17-71 years. There was a slight predominance of females (male to female ratio, 13:15). Seventeen of the patients had tumors mainly located in the gastric antrum. Histologically, the most common lymphoma was of mucosa-associated lymphoid tissue (MALT) type (20 patients), also with diffuse large B-cell lymphoma (7 patients), and anaplastic large cell lymphoma (one patient).

Conclusion: Our study demonstrates the different patterns of gastric lymphomas in Lattakia, Syria during a 10-year period in 28 Syrian patients, and reveals that the most primary gastric lymphomas are B-cell MALT lymphomas.

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The gastrointestinal tract is the most common site of primary extranodal lymphoma.[1] The lymphomas are almost exclusively of non-Hodgkin's type. Gastrointestinal lymphoma is an uncommon disease in Western countries, accounting for approximately 4-18% of all non-Hodgkin's lymphoma, although there is some evidence that the incidence is rising.[2,3] Considerable geographic variation exists in the incidence of primary gastrointestinal lymphoma, best illustrated by the extraordinarily high incidence in the Middle East. Here, lymphoma is the most common malignancy, and 25% of these lymphomas occur primarily in the gastrointestinal tract. Geographic differences extend also to the site of involvement. In the West, gastric lymphoma is the most common site followed by the small intestine, whereas the reverse is true in the Middle East.[4] Mucosal surfaces along the gastrointestinal tract are usually devoid of lymphatic tissue, except for specific locations, such as Peyer's patches in the ileum. Mucosa-associated lymphoid tissue (MALT) is the lymphatic tissue found in the mucosa, usually acquired after inflammatory reactions or autoimmune processes that trigger the influx of lymphocytes to the site. The presence of MALT can be regarded as an advanced chronic inflammatory process, which is benign by its nature. However, the presence of lymphatic tissue may give rise to lymphoproliferative processes, namely, lymphoma of the non-Hodgkin type. It is believed that ongoing antigenic stimulation is the reason for the transformation from a benign inflammatory process to low-grade lymphoma, and subsequently, to high-grade lymphoma.[5] The new World Health Organization (WHO) classification of gastrointestinal lymphoma is essentially a regrouping of lymphomas listed in the Revised European American Lymphoma (REAL) classification to reflect their occurrence in the gastrointestinal tracts.[6] The B-cell lymphomas account for the majority, and most of these are of MALT type.[7] Other B-cell lymphomas include mantle cell lymphoma (lymphomatoid polyposis), Burkitt's lymphoma, other types corresponding to peripheral lymph node equivalents, and immunodeficiency related lymphomas. Primary gastrointestinal T-cell lymphomas are much less common than B-cell tumors and do not show the same epidemiologic features. In the gastrointestinal tract, they are

divided in to 2 major types: enteropathy associated lymphomas and other types that are not associated with enteropathy. [8]

Methods. Between 1994 and 2003, 28 patients with gastric lymphomas were diagnosed in the Department of Pathology at the University Hospital of Tishreen University in Lattakia, Syria according to the new classification of the WHO of lymphoid neoplasms. This study was approved by the Directorate of Scientific Research at Tishreen University. The patients underwent gastric endoscopy at the Department of Gastroenterology; biopsy samples of multiple sites were taken for histology according to a standardized protocol. Some patients also underwent a surgical resection of the stomach at the Department of Surgery. The clinical features varied, however, primarily included symptoms of epigastric distress (pain, discomfort), weight loss, nausea, and emesis (occasionally bloody). Most patients received a gastroenterology work-up including appropriate radiologic studies. After clinical evaluation, patients underwent a partial gastrectomy for excision of the lesion. Histology of the specimens was assessed according to Isaacson[7] and the new WHO classification of lymphoid neoplasms.[6] Patient with histological diagnosed primary gastric lymphomas at the University Hospital in Lattakia Syria (1994-2003), age >17 and <71 years, absence of superficial lymphadenopathy, a normal white blood count, normal liver, and spleen were in this study. Patient with secondary involvement of the stomach by non-Hodgkin's lymphoma and hepatomegaly/splenomegaly were excluded in this study.

Immunophenotyping studies. The specimen was fixed in 10% buffered formaldehyde. Paraffin sections were prepared and examined using routine hematoxylin and eosin (H&E) stain. Immunohistochemistry was performed on sections retrieved from formalin-fixed paraffin blocks using an avidin-biotin-peroxidase complex method, utilizing the microwave for antigen retrieval. A panel of monoclonal antibodies against LCA/CD45 (Dako), L26/CD20 (Dako), CD3 (Dako), Ber-H2/CD30 (Dako), LeuMI/CD15 (Dako), UCHL-1/CD45RO (Dako), KP1/CD68 (Dako), CD 43/Leu 22 (Dako), Bcl-2 (Dako), E29/EMA (Dako), AEI-AE3 Cytokeratin (Dako), immunoglobulins, and Kappa & Lambda light chains was performed.

Results. ***Clinocopathologic features.*** Patients were aged 17-71 years, (median 48.35 years). The median age of high-grade and low-grade tumors was converging, (50.28 and 49.25 years). There were 15 women and 13 men. Most of the patients had tumors located mainly in the antrum of the stomach (17 patients), location in the body was seen in one patient, and it was multifocal in 10 patients. When the classification suggested by Isaacson[7,9] for gastrointestinal lymphomas was applied, of the 28 patients, 20 were classified as MALT, 7 patients as diffuse large B-cell lymphoma (DLBCL), and one patient as anaplastic large cell lymphoma (ALCL). Macroscopically, 5 of 20 MALT and 2 of 7 DLBCL lymphomas were classified as diffuse ulcerous type (**Figure 1a**), 8 of the MALT, 5 of the DLBCL lymphomas as mass forming (polypoid) type, 7 of MALT and the case of ALCL were classified as hypertrophic type with large, nodular, sometimes giant folds (**Table 1**).

The histologic and immunophenotypic findings were marginal zone B-cell lymphoma of MALT type (20 patients), 71.42% histologically, these lymphomas were characterized by a dense, lymphoid infiltrate within the lamina propria and submucosa that often shows a vaguely nodular architectural pattern (**Figure 1b**). Cytologically, there was diffuse heterogeneous infiltrate of atypical small to medium sized lymphocytes with moderately abundant cytoplasm (monocytoid B-cell) or cleaved nuclei (centrocyte-like), and occasional plasma cells. Lymphoepithelial lesions were noted in most of the cases, whereas lymphoid follicles were very rare. The cells

Table 1 - Clinical and morphological features of primary gastric lymphomas.

Features	MALT	DLBCL	ALCL	Total
Number of cases	20	7	1	**28**
Age range (mean) in years	27-71 (49.25)	25-70 (50.28)	17	
Gender				
Male	10	3	0	
Female	10	4	1	
Location (%)				
Antrum	12 (60)	4 (57)	1	**17**
Body	-	1 (14.3)	-	**1**
Multifocal	8 (40)	2 (28.6)	-	**10**
Macroscopic type (%)				
Ulcerated	5 (25)	2 (28.6)	-	**7**
Polypoid	8 (40)	5 (71.4)	-	**13**
Hypertrophic	7 (35)	-	1	**8**
Depth of infiltration (%)				
Mucosa	3 (15)	1 (14.3)	-	**4**
Submucosa	13 (65)	4 (57)	-	**17**
Muscularis	2 (10)	2 (28.6)	1	**5**
Serosa	2 (10)	-	-	**2**

MALT - mucosa-associated lymphoid tissue, DLBCL - diffuse large B-cell lymphoma, ALCL - anaplastic large cell lymphoma.

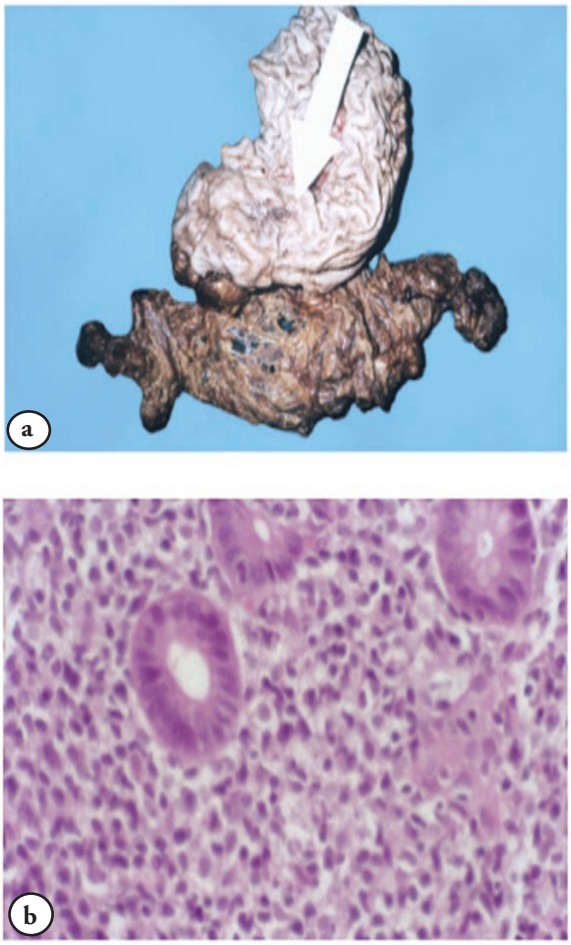

Figure 1 - Histologic and immunophenotypic findings of marginal zone B-cell lymphoma, **a**) hypertrophic type of mucosa-associated lymphoid tissue (MALT) lymphoma grossly, and **b**) morphological features of gastric MALT lymphoma (original magnification x 60).

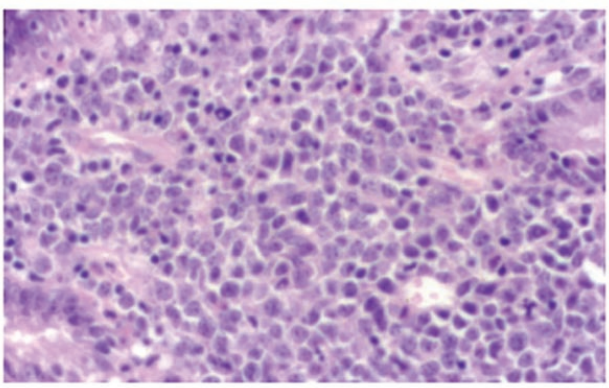

Figure 2 - Morphological features of diffuse large B-cell lymphoma (original magnification x 60).

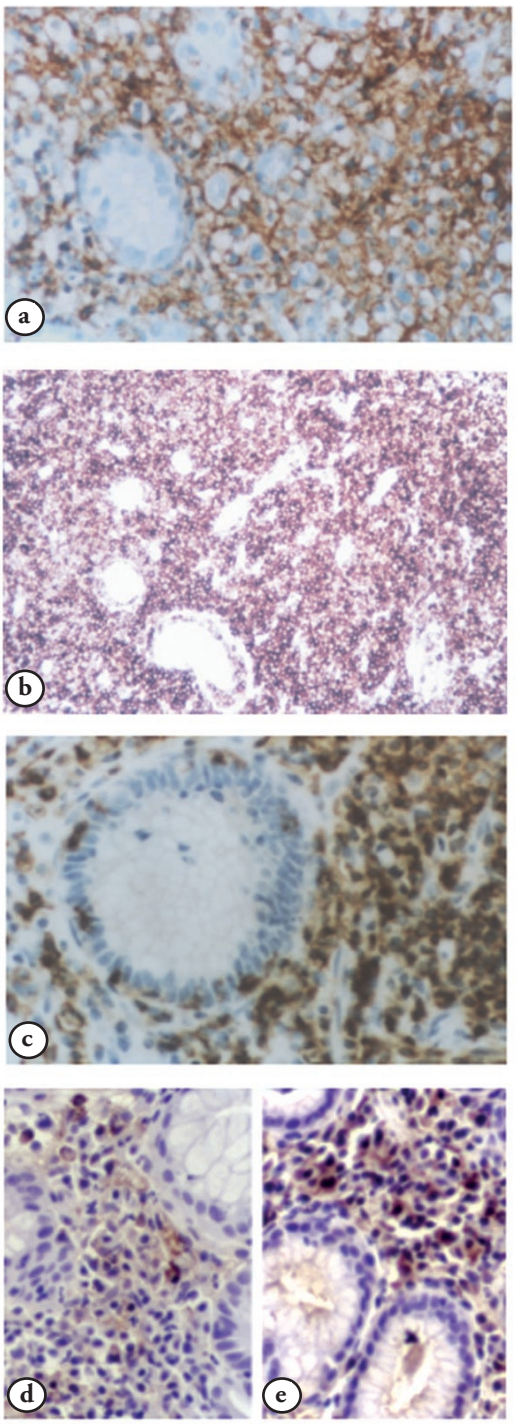

Figure 3 - Immunohistochemical analysis of mucosa-associated lymphoid tissue lymphoma; **a**) CD20 (original magnification x 60), **b**) CD43 (original magnification x 40), **c**) Bcl-2 (original magnification x 60), d) κ light chain, **e**) λ light chain (original magnification x 40).

Table 2 - The immunohistochemistry results in gastric lymphomas.

Antibody	MALT	DLBCL	ALCL
LCA	20/20	7/7	Weekly positive
CD20	20/20	7/7	Weekly positive
CD3	0/20	0/7	0/1
CD15	0/20	0/7	0/1
CD30	0/20	0/7	1/1
Bcl-2	15/20	4/7	0/1
S IgM	17/20	4/7	-
κ Light chain	5/20	1/7	-
λ Light chain	15/20	6/7	-

MALT - mucosa-associated lymphoid tissue, DLBCL - diffuse large B-cell lymphoma, ALCL - anaplastic large cell lymphoma, LCA - leukocyte common antigen, CD - cluster of designation, S Igm - surface membrane of B cells, Bcl-2: Bcl-2 oncoprotein.

of MALT lymphoma express surface immunoglobulin and show light chain restriction (λ more than κ). Also, the neoplastic cells share immunologic features with malignant marginal zone B-cells (sIgM+, CD20+, CD43+, Bcl-2+) (**Figure 3**); DLBCL (7 patients) 25%, these lymphomas were composed of diffuse proliferation of monomorphous large cells with vesicular nuclei, prominent nucleoli and basophilic cytoplasm (centroblasts and immunoblasts) (**Figure 2**). The neoplastic cells occurred in solid sheets between surviving gastric glands. Lymphoepithelial lesions are present in some cases. Immunohistochemically, the neoplastic cells were positive for CD20, sIg, Bcl-2; and negative for CD3 and ALCL (one patient) 4%, the tumor was formed of sheets of pleomorphic cells, with small and large embryo-like multilobated nuclei with prominent nucleoli and abundant cytoplasm. A few binucleate reed-sternberg-like cells were seen, in addition to rare cells with bizarre wreath-like multilobated nuclei. Most of the neoplastic cells, including the giant R-S-like forms, reacted positively for CD30 in a membrane- and dot-like pattern and negatively for CD15 antibodies. They were also positive for CD45. Reaction for T-cell CD45RO and CD3 was negative, while a few tumor cells reacted positively for B-cells CD20 antibodies. **Table 2** shows the immunophenotyping of the 3 histologic types of gastric lymphoma.

Discussion. Malignant lymphomas affect the stomach as a primary tumor or as part of a wider spread disease process. The stomach is the most common site with secondary lymphoma.[10,11] Generally, lymphomas are considered as "primary" in the gastrointestinal tract when the initial symptoms of the disease are in the abdomen indicating a disturbance of gastrointestinal function, or when the bulk of the disease is in the stomach.[12] In 1983, Isaacson and Wright[13] observed that, just as nodal lymphomas recapitulated the histologic features of normal nodal lymphoid tissue, certain low-grade B-cell gastrointestinal lymphomas recapitulated the features of Payer's patches or MALT. The immunophenotype of these lymphomas closely resembles that of marginal zone B-cells in the spleen and Payer's patches. The distinctive nature of this group of lymphomas has found recognition in the real classification of lymphoma,[9] in which they are specifically listed as extranodal marginal zone B-cell lymphomas of the MALT type. Other forms of gastric lymphomas are the non-MALT type, although many may be initially MALT tumors. Rare tumors may be T-cell in origin.[14] Microscopically, low-grade lymphomas may not be easily distinguished from pseudolymphomas, a term used to describe the lymphocytic infiltration of the gastric mucosa, which may occur with chronic gastritis and peptic ulceration. Pseudolymphomas may clinically and endoscopically mimic gastric adenocarcinomas or lymphomas. Pathologists can differentiate between pseudolymphomas and lymphomas based on several histological characteristics, which indicate malignant changes, such as prominent lymphoepithelial lesions (lymphoid infiltration of glands or crypts with partial destruction), Dutcher bodies and moderate cytologic atypia.[15] In cases that cannot be diagnosed with histological differentiation, an immunohistochemical marker studies may facilitate establishing an accurate diagnosis. However, recent studies have indicated that the great majority of pseudolymphomas are in fact, true lymphomas of low-grade malignancy using markers of clonality, and this term preferably has to be abandoned.[16]

Most of the lymphomas in our study were of the MALT type, while reports from Saudi Arabia[17,18] and Jordan[19] have shown a predominance of diffuse large B-cell type. We demonstrate the clinicopathological features and differences between MALT lymphomas and DLBCL. Our data indicate that MALT lymphomas have equal gender preponderance, however, DLBCL appears to have a slight female preponderance (**Table 1**), though the differences did not achieve statistical significance. The mean age of patients with MALT lymphoma was only slightly higher than that of patients with DLBCL. Most of the MALT and DLBCL were of the mass forming type; in our study, 13 (35%) of MALT lymphomas were classified as the hypertrophic type. There is no correlation between macroscopic type and histologic grade. Furthermore, characteristic features of low grade MALT lymphoma; centrocyte-like cells CCL, lymphoid follicles, and lymphoepithelial lesions

LEL, were seen in most of the MALT lymphoma cases, whereas these low components were less prominent in DLBCL. The immunophenotyping reveals λ light chain restriction in the vast majority of cases; this may reflect a specific nature of gastric lymphomas in our region. There were some limitations in this study that may affect the accuracy of the results; this included: First, the small sample size (only 28 cases). Second, follow-up data were not available for some patients. And finally, difficulty to interpret immune stains, particularly in endoscopic specimens, and in the early stage of disease, where gastric lymphoma may resemble chronic gastritis. The concept of primary gastric lymphoma need further studying and clarification, this can be reached by using a large panel of immune stains, applying gene-expression profiling techniques. This will expand our experience and knowledge of the disease.

In conclusion, our study has illustrated several features of gastric lymphomas among 28 Syrian patients. There were no significant clinical differences between MALT lymphomas and DLBCL. Histologically, the MALT lymphoma has prominent monocytoid cells with rare lymphoid follicles and germinal centers. All cases of diffuse large B-cell lymphoma were not associated with a low-grade component.

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