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# Primary gastric lymphoma in Jordan with special emphasis on descriptive epidemiology

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**Abstract**
The aim of this study was to examine the clinicopathological features and epidemiology of primary gastric lymphoma in Jordan as a model for Middle East countries where such data is scarce. From 1991 – 2002, 219 patients with primary gastric malignancy were managed at our hospitals. Among these there were 19 patients with primary gastric lymphoma. Pertinent data for these patients were analyzed. Primary gastric lymphoma constituted 65.5% of all gastrointestinal lymphoma and 8.7% of all gastric malignancies. Male-to-female ratio was 2.8:1. The mean age was 56 years (range 39 – 82). The incidence was 0.6/100 000. The proximal third was the most common localisation. Abdominal pain was the commonest presentation. Low-grade MALT lymphomas, high-grade MALT lymphomas, diffuse large cell B lymphomas and T cell lymphoma were found in 21.1, 26.3, 47.4 and 5.3%, respectively. Nine patients had gastrectomy followed by chemotherapy, 6 patients had palliative resection, 3 patients had chemotherapy only and the remaining patient was treated with Helicobacter pylori eradication. The mean follow-up for all patients was 42.2 months. The 5-year survival rates for stages IE ($n = 5$), IIE ($n = 4$), IIIE ($n = 6$) and IVE ($n = 4$) were 100, 67, 27 and 0%, respectively ($p = 0.0003$). The overall 5 years survival was 48.2%. Primary gastric lymphoma in Jordan shares some epidemiological features with western disease. Jordanian patients are detected and treated after a relatively long delay. Advanced stage at diagnosis correlated with poor outcome. There is a need of an earlier diagnosis and subsequent better care.

**Keywords:** *Diffuse large-cell, epidemiology, gastric, lymphoma, MALT, neoplasm*

## Introduction

Primary gastrointestinal (GI) lymphoma account for 4 – 20% of all non-Hodgkin's lymphomas (NHL) and is the most common extra-nodal site of presentation [1,2]. In the West, the stomach is the predominant site of involvement; while in the Middle East the intestine is the main site [3]. Primary gastric lymphomas (PGL) are relatively uncommon tumors, as they represent only 2 – 8% of all gastric malignancies [4].

In contrast to gastric adenocarcinoma, there is a global increase in the incidence of PGL [5,6]. Most of the detailed studies of PGL have been carried out in developed countries [4 – 11]. Unfortunately, reports from the Middle East are occasional and include only small number of patients [12 – 21]. A strong association between PGL and Helicobacter pylori (H.pylori) infection has been reported [22]. This infection is very common in the Middle East, particularly in Jordan [23]. This, in addition to the fact that there have been no previous detailed reports on PGL from Jordan, prompted one to report experience to gain an insight into what is happening in an area where H.pylori infection is very common. Comparison of this data with neighboring countries and other parts of the world might also highlight some of the risk factors.

## Patients and methods

This study retrospectively reviewed all cases of histologically confirmed PGL managed at Princess Basma Teaching Hospital and Prince Rashed Teaching Hospital, over a 12 year-period (January 1991 – December 2002). These are the only two tertiary centers in Irbid, Northern Jordan, to which all cancer cases are referred. The population of Irbid province as determined in the last census conducted in Jordan in 1994 was 745 774, out of which 385 264 (51.66%) were males. Fifty per cent of the Jordanian population are below the age of 16 years [24].

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Initial data were obtained from the computer database at the Department of Pathology at Jordan University of Science and Technology. This is the only pathology center serving the area. During the study period, histologically confirmed primary gastric malignancy was found in 219 patients, including 189 patients with gastric adenocarcinoma, 19 patients with PGL, 6 patients with gastric stromal tumor and 5 patients with gastric carcinoid. A detailed report regarding the patients with gastric adenocarcinoma was published elsewhere [25]. Only patients with PGL are included in this study. Further information regarding the clinical data, size and location of the tumor were taken from the medical and endoscopy records.

All cases of PGL were morphologically reclassified according to the WHO classification [26]. Immunoperoxidase stains were performed using the streptavidin biotin method using antibodies against leukocyte common antigen, B and T-cells. The diagnosis of mucosa-associated lymphoid tissue (MALT) lymphoma was based on the Isaacson's criteria [27] (i.e. the presence of reactive B-cell follicles, tumor cells consisting of centrocyte-like cells, and lympho-epithelial lesions). Cases with a dense infiltrate composed of centrocyte-like cells, monocytoid B-cells or small lymphocytes with associated lympho-epithelial lesions and germinal centers were classified as low-grade MALT lymphoma. Cases were considered to be high-grade when large sheets of blasts were present; in addition a low-grade component must be present to classify these as high-grade MALT lymphoma.

The study population initially included 30 patients with GI lymphomas. One patient with secondary gastric lymphoma and 10 patients with primary intestinal lymphoma were excluded, leaving 19 patients with PGL. The diagnosis of PGL was only made after obtaining normal peripheral blood count, normal chest and abdomino-pelvic computed tomography (CT) scan and normal bone marrow aspirates with no evidence of liver or splenic involvement. All patients had indirect laryngoscopy to rule out involvement of Waldeyer's ring.

Fifteen patients were initially diagnosed by endoscopic biopsy according to the published histological criteria for the diagnosis of PGL in endoscopic biopsies [28,29]. The remaining 4 patients were diagnosed after surgery.

Tumor staging was made according to the Ann Arbor Staging System as modified by Musshoff [30]. The presence of H.pylori was evaluated on the H&E stained section and confirmed by modified Giemsa stain when necessary.

Follow-up data were obtained during regularly scheduled clinic appointments. Vital status of patients was ascertained from death certificates or from families who were contacted. This enabled one to obtain adequate data about the survival of all patients. All deaths within 30 days of surgery were considered surgical mortality. The incidence rate was calculated and corrected for age in relation to the world population. The survival rate was analyzed for each stage by the Kaplan-Meier method and the survival curves were compared by the log-rank test using the Statistical Package for the Social Sciences Software Program version 11 (SPSS®, Inc., Chicago, IL). Differences were considered statistically significant at $p < 0.05$.

## Results

PGL constituted 8.7% (19/219) of all gastric malignancies in this study. The overall age-adjusted incidence (world population) was 0.6/100 000/year. During the first half of the study only 7 cases were diagnosed, while in the second half of the study period 12 cases were diagnosed. The mean age of the patients at diagnosis was 56 years (SD = 12.86, range 39 – 82) with a male:female ratio of 2.8:1.

Table I shows the distribution of the different histological sub-types according to age and sex. Males predominated in all sub-types. The intragastric locations of the tumors were 3 in the distal third, 3 in the middle third, 8 in the proximal third, and 5 involved the entire stomach.

Presenting features for the patients are summarized in Table II. Acute presentation was seen in 4

Table I. Histopathological distribution of gastric lymphomas according to the age and sex of the patients (%).

| | Age (years) | | Number of patients (%) | | |
|---|---|---|---|---|---|
| Histopathological diagnosis | Mean | Range | Male | Female | Total (%) |
| Low-grade MALT lymphoma | 60.3 | 41 – 82 | 2 | 2 | 4 (21.1) |
| High-grade MALT lymphoma | 52.8 | 39 – 63 | 3 | 2 | 5 (26.3) |
| Diffuse large B-cell lymphoma | 55.2 | 41 – 72 | 8 | 1 | 9 (47.4) |
| T-cell lymphoma | 62 | — | 1 | — | 1 (5.3) |
| Total | 56 | 39 – 82 | 14 (63.7) | 5 (36.3) | 19 (100) |

Table II. Presenting features for the patients with primary gastric lymphoma.

| | Number of patients | % |
|---|---|---|
| Abdominal pain | 15 | 71.6 |
| Weight loss | 10 | 64.7 |
| Dyspepsia | 8 | 48.8 |
| Nausea, vomiting | 8 | 47.8 |
| Abdominal mass | 7 | 30.8 |
| Anorexia | 6 | 28.9 |
| Dysphagia | 2 | 21.9 |
| Gastrointestinal bleeding | 2 | 18.4 |
| Obstruction | 1 | 8.5 |
| Perforation | 1 | 1 |

(21%) patients. The mean delay in diagnosis was 6.5 months (range 2 – 14). In 6 patients this was a result of reluctance in seeking medical advice and/or delay in referring patients for endoscopy. However, in 4 patients the delay was caused by a false negative histological examination of endoscopic biopsies.

Endoscopy was performed for all patients and it showed ulcerative lesions with irregular surrounding walls in 5 patients, protruded tumors in 4 patients, sub-mucosal tumors with intact mucosa in 3 patients and irregular open ulcers in the remaining 7 patients. In 7 patients, repeated endoscopies (range 2 – 5) were performed because the initial biopsies did not reveal the tumors, although the endoscopiest raised the suspicion of malignancy. Still, 4 of them were not diagnosed by endoscopic biopsies.

Endoscopic ultrasonography was not available during the study period. Abdominal CT scan was performed for all patients and it showed a thickened irregular gastric wall in 7 of them. Five patients had stage IE, 4 patients had stage IIE, 6 patients had stage IIIE and 4 patients had stage IVE disease.

H.pylori was found in 100% of low-grade MALT lymphoma compared to 60% of high-grade MALT lymphoma and 22.2% of DLBCL. The 4 patients with low-grade MALT lymphoma were given quadruple eradication therapy (omeprazole, amoxycillin, bismuth and metronidazole). Repeat endoscopy was performed for these patients at 1, 3 and 6 months post-eradication therapy and multiple mapping biopsies were taken at each occasion. Clinical and histological remission was observed in only 1 of them (after a follow-up of 21 months), while the remaining 3 were further treated by surgery.

Gastrectomy with 'curative' intent was performed for 9 patients including the 3 patients who failed to respond to the antibiotics treatment. Palliative resection or bypass was performed for 6 patients. Twelve of the patients who had surgery were given post-operative (CHOP) chemotherapy. Three patients had chemotherapy only; one of them died from massive upper GI bleeding. None of the patients had radiotherapy as part of their treatment. Post-operative morbidity occurred in 33.3% (5/15) of the patients. Surgical mortality occurred in only 1 patient (6.7%).

The mean follow-up was 42.2 months (SD $\pm$ 27; range 1 – 92 months). Survival data analysis included the early post-operative death and the later non-cancer deaths. The 5-year survival rates for stages IE ($n = 5$), IIE ($n = 4$), IIIE ($n = 6$) and IVE ($n = 4$) were 100, 67, 27 and 0%, respectively ($p = 0.0003$) (Figure 1). The overall 5 years survival was 48.2%.

Work-ups to rule out celiac disease, immunoproliferative disorders and HIV infection in the single patient who had T-cell lymphoma were negative.

## Discussion

There are marked geographical differences in the incidence of PGL even in the same region. The age-adjusted incidence of PGL (0.6/100 000/year) is similar to those of developed countries [5,31]. In Western countries and Mexico, PGL represents 2 – 9% of all gastric malignancies [4,32]. PGL constituted 8.7% of all gastric malignancies in northern Jordan, which is similar to the 9% figure from neighboring Iraq [16], but different from the 14 – 22% figures reported from Saudi Arabia [33,34].

In accordance with Western reports [5,6,32], this study revealed that there was a remarkable increase in the frequency of PGL in recent years. This is important because, unlike gastric adenocarcinoma, PGL is a curable disease in most of the cases. Although the increase in diagnosing PGL during the study period is a reflection of a better diagnostic yield after the relatively recent introduction of endoscopic

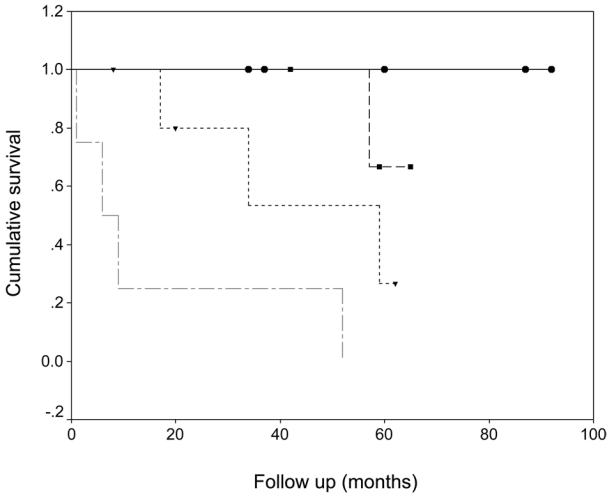


Figure 1. Survival rate of gastric lymphoma patients according to stage using Kaplan-Meier analysis. (●) Stage I; $n = 5$, (■) Stage II; $n = 4$, (▼) Stage III; $n = 6$, (○) Stage IV; $n = 4$.

services throughout the country and the greater use of immunohistochemistry techniques, still the following factors may play a role. First, the abolishing of the pseudolymphoma concept. Reviewing the pathology reports prior to 1991 showed that pseudolymphoma was still in use among pathologists in the area and some of these proved to be a MALT lymphoma after immunohistochemistry studies. Secondly, the rapid change in dietary habits Jordan is witnessing might constitute a risk factor. Vitamin C-rich fresh vegetables and fruits, starch and natural unprocessed wheat products were the major constituents of Jordanian food. However, canned food, hot spices, pickles and animal proteins are now dominating the Jordanian menu. It is known that the environmental risk factors for PGL could be dietary in origin [35]. Thirdly, the already high prevalence of H.pylori in Jordan is increasing and the exposure time is also increasing with the improvement of life expectancy [23].

In accordance with Western reports [6,8], PGL represented 65.5% of all primary GI lymphomas. On the contrary, reports from the neighboring Iraq, Kuwait and Saudi Arabia showed a marked predominance of primary intestinal lymphomas [16–18]. In a previous Jordanian study in 1997, the stomach was also found to be the commonest site of involvement, accounting for 62% of the GI lymphomas [12]. However, in an earlier Jordanian study conducted in 1986, the stomach was the second most frequent extranodal site of NHL after the small intestine, but Mediterranean abdominal lymphoma was less frequent in Jordan than previously thought [13]. The reason for the discrepancy between these findings and reports from other neighboring countries is not clear, but may reflect a combination of variable patient population and a disease definition. The biological significance of these differences remains to be answered. However, it is worth mentioning that, despite that the intestine is the predominant site of GI lymphomas in neighboring countries, the ratio of gastric to intestinal lymphomas is increasing gradually [18]. As alluded to above, this varying pattern in the site of GI lymphomas seems to be environmental in origin [20]. Male predominance, noticed among all histological sub-types in the study group, is consistent with other reports [1].

PGL was reclassified as 'Extranodal marginal zone lymphoma' [26]. Most PGL originates from the MALT. MALT does not occur normally in the gastric mucosa, but lymphoid follicles accumulate at this site in response to H.pylori infection and B cells infiltrate the gastric epithelium to form a lymphoepithelium, constituting MALT [36–38]. MALT lymphomas have peculiar features that distinguish them from other NHL. These include an indolent natural history [38], a tendency to prolonged confinement to the site of origin [39,40], a difficulty in distinguishing early lesions from reactive inflammatory processes [28,29], proliferation of centrocyte-like cells, an association with H.pylori infection [22,41,42] and a response of many cases to treatment by antibiotics [43,44].

A German study showed that 40% of PGL were of low-grade MALT type [8]. In this series, DLBCL was the commonest histological type (47.4%). PGL of MALT type is closely related to H.pylori infection [22,38]. H.pylori infection is very common in Jordan [23] and one was expecting to find most cases to be of MALT type. It was interesting to note that only 4 of the patients had low-grade MALT lymphoma. The low-grade MALT lymphomas run an indolent clinical course [38]. However, it can undergo histological progression to an aggressive high-grade lymphoma or DLBCL [7]. The tumors may lose the histological hallmarks of their MALT origin during this progression [7,45,46]. In this study, PGL generally presented at an advanced clinical stage in contrast to Western series [8]. It is believed that this delayed presentation might partially explain the unexpected low prevalence of MALT lymphomas among the patients. The question to be asked is, is there faster progression from low-grade MALT lymphoma to DLBCL or is it a reflection of underdiagnosis of low-grade MALT lymphoma at the hospitals? It is well known that sometimes there is difficulty in differentiating gastritis from low-grade MALT lymphoma. So there is a possibility that some cases of low-grade MALT lymphoma were diagnosed as H.pylori gastritis and were treated with eradication therapy without noticing the element of the MALT lymphoma in these cases.

Most PGL are of B-cell origin [47], while primary gastric T-cell lymphomas are more common in the Far East [36,48]. One of the patients had a T-cell lymphoma and H.pylori infection. This is consistent with the findings of others, suggesting a causal relationship between T-lymphoma and H.pylori [36,48].

In this study, H.pylori was found in 100% of low-grade MALT lymphoma compared to 60% of high-grade MALT lymphoma and 22% of DLBCL. It has been reported that H.pylori infection was significantly correlated with grade and depth of invasion of MALT lymphoma, since 63% of superficial low-grade MALT were positive for H.pylori compared with 38% of advanced high-grade [49].

Proper management of PGL depends on accurate pathological diagnosis and detailed staging procedures. Endoscopic diagnosis of PGL is difficult because it shows various non-specific gross patterns [15,19]. Even repeated endoscopic biopsies might

fail to establish the diagnosis, partially because early low-grade MALT lymphomas are extremely difficult to be distinguished from gastritis and partially due to sub-mucosal growth or insufficient histological findings on small endoscopic biopsy specimens [50]. Therefore, it is important to perform multiple deep biopsies in every patient with abnormal looking mucosa. Occasionally, it is necessary to perform a diagnostic laparotomy or laparoscopic wedge resection of the stomach [50], in order to obtain definite histological diagnosis, as happened in 4 of these patients.

In addition to histological diagnosis, the technique of PCR-based clonality analysis was found to be useful for the diagnosis of PGL [51,52]. However, this technique may fail to detect monoclonality in up to 30% of cases of overt lymphoma [51–53]. Unfortunately such advanced diagnostic modalities might not be available in most developing countries.

There is considerable controversy regarding the optimal management of patients with PGL. It is still debated whether surgery, chemotherapy or radiotherapy, alone or in combination, is the best mode of treatment [54–60]. Treatment of PGL should be 'patient-tailored' depending on the type, grade and stage of lymphoma [54]. However, surgery still plays an important role in the management of stages IE and IIE, since surgical resection controls the local tumor and prevents the perforation or bleeding, which might occur during chemotherapy, as happened to 1 of the patients [55,56]. However, serious bleeding from chemotherapy alone appears to be less common than previously thought [57,60].

Survival of PGL is much better than adenocarcinoma, partially because of a better response to chemotherapy [59] and partially due to a less aggressive biological behavior of PGL. Brands et al. [10] analyzed the data on 3157 patients with PGL and found that the overall survival rate increased from 37% in 1974 to 87% in 1995. The survival rate for stages I and II is consistent with the rate reported in the Western literature [8,10]. However, this rate was much less for patients with more advanced stages, probably reflecting under-treatment at the institute (Figure 1).

In conclusion, most features of PGL in Jordan (such as incidence, male sex predominance, GI site distribution and tumor localization) were similar to those reported in the West. However, the reduced survival rates and the predominance of DLBCL seem to reflect a delay in presentation of the patients. Open access endoscopy, greater efforts in patient education and improvement of the diagnostic technical skills may be the best chance of detecting PGL early enough so that it is treated successfully.

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