ORIGINAL ARTICLE

# PRIMARY GASTRIC LYMPHOMA

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## ABSTRACT

**Objective:** To evaluate the clinico-pathological status of Primary Gastric Lymphoma (PGL) at presentation in King Fahad Hospital, Madina Munawra, Kingdom of Saudi Arabia (KSA).

**Study Design:** A case series.

**Place and Duration of Study:** Oncology Department of King Fahad Hospital, Madina Munawra, KSA, from 1990 to 1998.

**Patients and Methods:** Case records of 22 patients with a histologically-confirmed diagnosis of PGL were analyzed. Tumors were staged according to the Ann Arbor Classification and divided according to the Rappaport working formulation. According to the treatment modality, different groups were established. Any other histopathological type was excluded from the study. Data were analyzed by frequency calculations. Survival was calculated from the date of surgery.

**Results:** All cases were Non-Hodgkin Lymphoma (NHL). The peak age was in the sixth decades with a slight male preponderance. Most common presenting symptoms were epigastric or upper abdominal pain with or without mass. There were 10 (45%) patients with stage II, and 6 (27%) patients each with stage III and IV diseases. Diffuse large cell lymphoma was found in 12 (55%), poorly differentiated lymphoma in 3 (14%) and diffuse mixed in 7 (32%). Helicobacter pylori infection was found in 2 (9%). Sixteen (73%) patients underwent chemotherapy with some surgical resection, in 5 (23%) surgical procedure was palliative bypass and 11 (50%) had partial gastrectomy. Three (14%) had only chemotherapy after endoscopic biopsy. Two (9%) patients needed urgent surgical intervention. One (5%) patient had total gastrectomy followed by radiotherapy. Eleven (50%) had more than 3 years survival.

**Conclusion:** PGL is usually of NHL type, presenting in the sixth decade, and can be successfully treated with both surgery and chemotherapy when patients presented at stage II. Chemotherapy after sub-total gastrectomy or biopsy was the best treatment option.

**KEY WORDS:** *Gastrointestinal. Helicobacter pylori. Mucosa associated lymphoid tissue. Staging. CHOP chemotherapy. Primary gastric lymphoma.*

## INTRODUCTION

Primary NHL of Gastrointestinal Tract (GIT) is rare but GIT is the most common extra nodal location for the development of NHL. Almost half of these extra nodal presentations occur in GIT, and out of this, are mainly localized in the stomach.[1,2] It represents only a minority (1-7%) of the gastric malignancies.[3] In western countries, gastric involvement in extra nodal NHL is the most common, followed in incidence by the small bowel, the ileocecal area and the colon.[1,4,5] Since the endoscopy became widely available, the diagnosis of gastric NHL is frequently made pre-operatively. In one study, most lymphomas were localized in the stomach and perigastric lymph nodes. The most frequent clinical stage were stage I and II (36% and 33%, respectively).[6] Both gastroenterologists and pathologists must recognize the increase of this neoplasm because unlike gastric adenocarcinoma, gastric lymphoma is a curable disease in a high percentage of cases. The most difficult task in preventing these lymphomas is the recognition of early lesions, which is likely to regress after the removal of the exogenous stimulus. An increased frequency of PGL during the last years has been noted.

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Usually surgery and chemotherapy is the treatment commonly used in gastric lymphoma.[3] However, the literature, advocating gastrectomy as the primary therapy for gastric lymphoma, is abundant. Recent studies investigated the possibility of organ preservation, using chemotherapy and radiation therapy in place of surgery, thus saving patients the potential morbidity of a gastric resection. However, this remains controversial.[7] The prognosis is favorable in gastric lymphoma as contrast to gastric carcinoma but 5 years survival is still disappointing in advanced stages.

The objective of this study was to evaluate the clinico-pathological status of Primary Gastric Lymphoma (PGL) at presentation in King Fahad Hospital, Madina Munawra, Kingdom of Saudi Arabia (KSA).

## PATIENTS AND METHODS

In this retrospective study, charts of 22 patients with diagnosis of PGL, in King Fahad Hospital, Madina Munawra, KSA, over a period of 8 years, from March 1990 to 1998, were reviewed. Any other histopathological type was excluded from this study. Patients' age, gender, symptoms and signs (Table I), endoscopic, radiologic and histopathologic findings, treatment and results were analyzed. Cases were staged according to Ann Arbor staging system. Histological examination was done according to Rappaport classification and working formulation.[8] For diagnostic and staging workup, barium meal, endoscopy, X-rays chest, ultrasound abdomen and pelvis, CT

scan abdomen and pelvis, bone marrow examination and laparotomy/surgery was performed.

Surgical resection was limited in most of the patients to partial gastrectomy. Patients with pathological stage IIE, IIIE and IV received chemotherapy with CHOP combination (Cyclophosphamide 750 mg /m$^2$, Doxorubicin 50 mg/m$^2$, Vincristine 1.4 mg/m$^2$, all on day 1, and Predsnisolon 100 mg orally, day 1 through 5, repeated at 21 days interval. Six to eight courses were given to selected patients. After completion of chemotherapy, patients were restaged, using endoscopic and radiological tools. Survival was calculated from the date of surgery.

## RESULTS

There were 12 males (55%) and 10 female (45%) patients with male to female ratio of 1.2:1. The median age was 53.9 years with an age range of 28-71 years. As shown in Table I, upper abdominal pain, mass and bleeding were the most commonly found first sign of PGL in our cases. Two patients presented with intestinal obstruction.

On barium meal examination (14 cases), predominant finding included masses, filling defects, ulcers and abnormalities of mucosal pattern. A definite radiological diagnosis of gastric lymphoma was made in 10 cases (71%). Upper endoscopy was done in all 22 patients. Endoscopic findings included masses, filling defects, ulcers and abnormalities of mucosal pattern. Polypoidal masses or ulcerative lesions were most common findings. Pre-operative CT scan was done in 18 patients (81.8%) and bone marrow examination in 19 (86.3%) patients. Histological diagnosis was diffuse large cell in 12 patients (54.5%), diffuse mixed cell NHL in 7 (31.8%) and poorly differentiated lymphoma in 3 patients (13.6%). Helicobacter pylori infection was seen in 2 (9%) cases. Laparotomy / surgery were done in 19 patients (86.3%). Surgical findings are shown in Table II, partial gastrectomy was done in 11 (50%) patients (all these received adjuvant chemotherapy), palliative bypass in 7 (31.8%) patients. Out of these 7 patients, 5 patients received chemotherapy postoperatively. Two patients, who underwent only palliative surgery, died postoperatively. Total gastrectomy was done in one (4.5%) patient, who later received radiotherapy; endoscopic biopsy was done in 3 (14%) patients. These 3 cases were later treated with chemotherapy. Primary tumor was <10 cm in size in majority of the patients (14 patients). Perigastric LN involvement was seen in 18 (81.6%) patients. Paraaortic LN was involved in 12 (55%) patients and liver involvement in 6 (27.2%). Bone marrow examination was done in 19 (86.3%) patients and it was negative in all cases. No patients had stage I disease. Ten patients (45.5%) had stage II disease. Six (27.2%) patients had stage III disease. The remaining 6 (27.2%) patients had stage IV disease mainly because of liver involvement.

**Table I**: Frequency distribution of presenting symptoms and signs.

| Presenting symptoms and signs | No. of patient (%) |
|---|---|
| Epigastric or upper abdominal pain | 17 (77%) |
| Nausea and vomiting | 3 (14%) |
| G. I. bleeding (Hematemesis and malena) | 4 (18%) |
| Fever | 2 (9%) |
| Weight loss | 3 (14%) |
| Intestinal obstruction | 2 (9%) |
| Upper abdominal masses | 5 (23%) |
| Diarrhea | 1 (5%) |
| Enlarged palpable liver | 3 (14%) |

**Table II**: Treatment modalities used stage wise and results obtained.

| Treatment | No of patients | Stage | Results |
|---|---|---|---|
| Palliative surgery (bypass) for obstruction | 2 | IIIE-1<br>IV-1 | Died of advanced disease and complications |
| Total gastrectomy and radiation therapy | 1 | IIE | 4 years NED and later lost to follow-up |
| Palliative surgery (bypass) and chemotherapy | 5 | III-3<br>IV-2 | >3 years NED-1<br><2 years and died-4 |
| Partial gastrectomy + chemotherapy | 11 | IIE | >3 years NED-9<br><2 years and died-2 |
| Chemotherapy only | 3 | IV | <1 1/2 years and died-3 |

Treatment and its results as shown in Table II, reveals that 2 (9%) patients were treated with surgery only and both these patients postoperatively developed surgical complications and died. Only one patient (stage II E) was treated with surgery and radiation therapy to the tumor bed. Patient was without any evidence of disease (NED) for 4 years and then was lost to follow-up. Five (23%) patients were treated with palliative bypass surgery (Gastrojejunostomy) and chemotherapy. Only one was more than 3 years NED, all other 4 patients died within 2 years with progressive disease. Eleven (50%) patients were treated with partial gastrectomy and CHOP adjuvant combination chemotherapy with 6-8 courses. Out of that 9 (81.8%) patients had more than 3 years disease- free survival and later were lost to follow up. Two patients developed progressive disease and died within 2 years. Three (11.1%) patients presenting with stage IV disease with liver involvement were diagnosed histopathologically by endoscopic biopsy. These were treated by chemotherapy but all died within one-and-half year with progressive disease. As a whole, 11 (50%) patients had more than 3 years disease-free survival including one patient treated with radiation therapy after surgery.

## DISCUSSION

PGL occurs somewhat more frequently in males than females and reaches its peak incidence during sixth decade of life.[4] Abdominal pain, anorexia, nausea or vomiting are frequently occurring presenting symptoms and are identical to the complaints experienced by patients with gastric adenocarcinoma. An abdominal mass can be palpated in no more than 20% of patients with PGL, while gastric bleeding occur in 10-30% of the affected individuals.[4] In this study abdominal mass was 23% and gastric bleeding was seen in 18% of the cases. Contrast radiographic studies in PGL reveals combination of pattern including a mass filling defect in 71% and ulcerative lesion in 39% of cases. A diffuse infiltrating process with thickened mucosal fold was seen in 20% of cases.[9] Low-grade lymphomas showed superficial spreading lesions, such as mucosal nodularity, shallow ulcer, and minimal fold thickening on upper gastrointestinal radiography, whereas most high-grade lymphomas showed mass-forming

lesions or severe fold thickening. Immuno-histochemistry may be necessary for diagnosis when clear-cut morphological characteristics are lacking.

Prior to initiating treatment of newly diagnosed gastric lymphoma, it is important to rule out the presence of systemic lymphoma. Bone marrow biopsy, chest radiography, and abdominal CT scan are necessary for evaluation and future management.[1,9] Recent advances in computed tomography (CT) technology and three-dimensional (3D) imaging software have sparked renewed interest in using CT to evaluate gastric disease. CT angiography is especially helpful for depicting the gastric vasculature, which may be affected by malignancy. Spiral CT is an effective tool in the pre-operative staging of gastric malignancies.[10] In addition, all patients thought to have PGL should undergo indirect laryngoscopy to rule out involvement of Waldeyer's ring.[9]

The evaluation of nodal extension is important for staging. Regional gastric nodes are difficult to image by CT scan and false negative scan can lead to erroneous pathological down-staging.[4] Endoscopic ultrasonographic imaging is a new technique that can accurately estimate both the depth of invasion and involvement of regional nodes.[11]

The development of endoscopy and improvement in the technique of gastroscopic biopsy have allowed a non-invasive diagnosis of gastric lymphoma to be made with an increasing degree of accuracy.[11,12] Although vast majority of gastric lymphoma are B-cell origin but because of non-availability of immunohistochemistry, it was not possible to be done in our hospital. Histologically, these tumors range from well differentiated (mucosa associated lymphoid tissue, MALT) to high grade large cell lymphoma. Infection with H. pylori appears to increase the risk of gastric lymphoma in general and MALT lymphoma in particular. H. pylori eradication is highly successful in causing lymphoma regression. More advanced low-grade lymphomas or those that do not regress with antibiotic therapy, can be treated with combinations of H. pylori eradication, radiation therapy, and chemotherapy. Nearly 60% of gastric lymphomas are high-grade lesions with or without a low-grade MALT component. These lymphomas can be treated with chemotherapy and radiation therapy according to the extent of disease. Surgery for gastric lymphoma is now often reserved for patients with localized, residual disease after nonsurgical therapy or for rare patients with complications.[13] Spontaneous and complete disappearance of Diffuse Large B-cell Lymphoma (DLBL) of the stomach is extremely rare. However, regression of gastric DLBL after eradication of Helicobacter pylori has recently been reported.

Treatment of H. pylori infection has led to regression of about 75% of gastric MALT lymphoma after antibiotic treatment and it should be considered before surgery, radiation therapy and chemotherapy.[14] H. pylori -negative MALT lymphoma occurs in a small minority of cases in which treatment is based on surgery or chemo-radiotherapy. In our study, 2 patients were H. pylori infection positive and were treated with 3 drug combination therapy but without relief and disease was persistent. This low incidence of H. pylori infection in our cases of lymphoma may be because such cases are treated before by gastroenterology department and only resistant or progressive cases are referred to oncology department. For low-grade MALT lymphomas confined to the stomach, an attempt at eradication of Helicobater pylori is the first choice. If the patient does not have H. pylori, or if eradication is unsuccessful, or if the disease stage is IIE, radiation therapy is the next choice. Chemotherapy is the best option for disease that is stage IIE or higher and for disease that does not respond to antibiotics and radiation. Surgery should be reserved for patients with localized disease who do not respond to other therapies. Recently published experience indicates that chemotherapy plus radiation therapy may be an acceptable alternative to surgery. The entire clinical picture and the patient's preferences must play a role in this difficult management decision. Local radiation therapy should be added in selected cases with residual local disease or bulky tumor.[15] If the tumor is resectable, gastrectomy will provide the most accurate means of diagnosis, staging and locoregional control of the disease.[16]

Subtotal gastrectomy is the procedure of choice. The presence of a malignant lymphoid infiltration at the resection margins does not appear to affect the subsequent outcome if postoperative chemotherapy or radiation therapy is administered.[17] Lymphoid tumor may infiltrate the entire gastric wall with minimal fibrotic reaction, leading to an incidence of spontaneous perforation of 3.4%.[5] Several groups of investigators have reported episodes of hemorrhage and or perforation in 22-38% of patients with unresected PGL following primary treatment with radiation therapy and chemotherapy.[18] Operative mortality rates range from 2.3-25% and are generally higher for palliative procedures which have traditionally been performed not only for symptomatic relief but to remove tumor mass and avoid hemorrhage or perforation.[1,8,9] However, the necessity for debulking to avoid complications has more recently been questioned.[11] In a study of 34 stage IE and IIE gastric lymphoma patients, treated with only radiotherapy and chemotherapy, no patients developed bleeding or perforation.[11]

In some series majority of PGL patients had bulky tumors which were surgically unresectable.[18] High risk of treatment associated bleeding has been noted in patients with locally advanced tumors despite prior surgical resection. Surgical mortality following resection of gastric lymphoma has ranged in the past from 8-18% which is not different from complications if surgery is withheld.[9,12,19] Therefore, the need for a prophylactic surgical resection to prevent hemorrhage or perforation remains uncertain. The indication for such an invasive procedure requires better definition in future.

Princess Margaret Hospital showed 85% survival rate after 10 years in 52 radiated patients with surgically resected stages IE and IIE disease who had <2.5 cm of gross residual lymphoma postoperatively compared with a 12-50% survival in 22 individuals with more bulky residual disease.[20] Although in the present case series only one patient underwent radiation therapy and that too after surgery, that patient had excellent survival.

As there are more chances of systemic rather than isolated recurrence in patients with primary gastric lymphoma, it raises serious reservations about the justification for adjuvant local irradiation.[21] The need for systemic treatment is obvious.

Combination chemotherapy is clearly effective in management of high grade lymphoma and is generally administered following surgical resection and subsequent radiation therapy.

The results of most postoperative chemotherapy trials have been encouraging. For stages IE and IIE, several authors have found excellent 5-year disease-free survival for patients with chemotherapy after surgery.[1,7] In one study, it was suggested that systemic chemotherapy alone may be a reasonable alternative treatment for stage I/II large-cell lymphoma of the stomach. Resection of the primary tumor before systemic chemotherapy does not appear to improve the cure rate of this group of patients. It was further noted that IE-IIE stage patients, who underwent neoadjuvant chemotherapy and surgery survived longer (100%) than those, in whom surgery preceded chemotherapy (66%), whereas IIIE-IVE stage patients, in whom surgery was the first treatment, survived longer (70%) than those, in whom surgery followed chemotherapy (37%).[23] Usually postoperatively, adjuvant chemotherapy comprising cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) is given.[24] Non-surgical treatment may be an optimal therapeutic modality for patients with primary gastrointestinal lymphoma.

Chemotherapy in patients with stages I-II achieves survival results similar to those treated with surgery and with a combination of both. To avoid long-term sequelae after gastric resection, primary CHT is recommended as standard initial treatment in localized gastric lymphoma.[25] In recent years there has been a move away from a surgical approach to primary chemotherapy with or without radiotherapy. Recent data suggest that chemotherapy with the cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) regimen is a highly effective treatment for localized PGL of Diffuse Large B-Cell Histology (DLBCH).[26] CHOP-Bleo (CHOP + Bleomycin) is another alternative.

Although the role of surgery has become an area of controversy in the management of gastric lymphoma but still many investigators advocate surgical resection in gastric lymphoma to debulk, accurately stage and prevent perforation.[27] Some investigators have achieved good results with either combination chemotherapy or combined modality without surgery, particularly for the higher grade lesions.[28] Although a partial or subtotal gastrectomy may be justified in some cases, more extensive surgery such as total gastrectomy should not be routinely performed because of the increased morbidity and curability with alternative therapies.[28,29] Management program at present emphasize organ preservation in this setting.[30] In our cases, although 19 (86%) patients underwent some sort of surgery but except one, all had conservative, subtotal or palliative surgery followed by adjuvant therapy.

CHOP for 6-8 months for patients stages II to IV as primary management, and particularly for those whose surgery is not the treatment of choice, should be used. Those patients who receive chemotherapy as a primary treatment should be observed closely for the initial 7-10 days for signs of hemorrhage or perforation. The addition of local treatment such as radiation or even surgery as consideration following chemotherapy is reasonable but should be subject to the objective assessment in a randomized protocol setting. Until there is a more definitive answer, treatment options should be discussed with patients and therapy tailored to each individual's need and preferences.

Patients with a diagnosis of early stage gastric lymphoma on endoscopic biopsy should initially undergo surgical resection. Surgical therapy provides local control which may not be achieved by chemotherapy and allows better disease assessment than pre-operative staging. Adjuvant chemotherapy should be considered even in early stage disease as most failures with only surgical therapy are extra abdominal. In our study, we found partial gastrectomy (surgery) and chemotherapy as the best treatment option for early stage PGL. Only surgery, as it was done in advanced cases, showed bad prognosis. Surgery with adjuvant radiotherapy showed a very good response. Palliative surgery with chemotherapy also showed discouraging result, although better than that of only surgery, which may be because of extensive disease. Planned surgery with adjuvant or neoadjuvant chemotherapy has good success.

## CONCLUSION

In this study, NHL was found to be the most common type of primary gastric lymphoma. Partial gastrectomy (surgery) and chemotherapy was the best treatment option for early stage PGL. CHOP chemotherapy has provided good success. In all cases, adjuvant treatment with chemotherapy or radiotherapy can provide a survival advantage to only surgical manipulation, which should be offered in all cases. In inoperable cases chemotherapy and radiotherapy can be an alternate.

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