

## **The Profile of Primary Gastrointestinal Lymphoma in Egyptian Patients**

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### **ABSTRACT**

**Introduction:** Forty percent of all non Hodgkin's lymphomas arise at extra-nodal sites with the gastro-intestinal tract as the commonest site. The gastro-intestinal lymphomas are a diverse group of neoplasm which may arise as primary malignancies from within the gastro-intestinal tract or secondary tumors that occur as part of a systemic nodal disease.

**Methods:** A total of 87 cases of primary gastro-intestinal lymphomas were obtained from the Pathology Department at the National Cancer Institute, Cairo University from the years 1998-2000. Twenty four cases were presented as resection specimens with node dissection and the remaining 63 cases were biopsies. Clinical records were reviewed regarding the topographic and demographic data. Histopathologic diagnosis was revised according to the WHO-REAL classification. Immunophenotyping was done to all cases.

**Results:** Primary gastro-intestinal lymphoma constituted 7% of all total gastro-intestinal malignancies and 6.2% of all non-Hodgkin's lymphoma cases. Mean age was 31.4 years, with a range of 3-75 years. The male to female ratio was 1.8. Lymphomas of small intestine contributed (40.2%), stomach was second in frequency (38%), while colorectal was the least common site (21.8%). Regional lymph nodes were involved in 13 (54.2%) cases. Three different histologic subtypes were identified: a) Diffuse large cell lymphoma was the commonest (44.8%), b) Burkitt's lymphoma was the second common (33.4%), and c) Mucosal associated lymphoid tissue (MALT) lymphoma was the least common (21.8%). Large cell lymphoma showed the highest incidence of regional lymph node involvement (64.2%). All cases were positive for CD20 and negative for CD45RO.

**Conclusion:** Primary GI lymphomas are not considered as a common site of extranodal non-Hodgkin's lymphoma. All cases were of the B-cell immunophenotype.

**Key Words:** *Lymphoma - Gastrointestinal - Egyptian.*

### **INTRODUCTION**

Primary gastrointestinal (GI) lymphoma is defined as an extranodal lymphoma arising from the GI tract and its contiguous lymph

nodes without involvement of peripheral lymph nodes, liver, spleen, bone marrow or peripheral blood [5]. Forty percent of all non Hodgkin's lymphomas (NHL) arise at extranodal sites [9], with the GI as the commonest extranodal site constituting 4-8% in the Western countries and up to 25% of cases in the Middle East [35]. The stomach is the most frequent site of involvement in Western countries, while, the small intestine is most frequently affected in the Middle Eastern countries [2].

The clinical presentation and the morphological classification for GI lymphoma differ from that of nodal lymphoma. Primary GI lymphomas are classified according to cell lineage into distinct groups: B-cell lymphomas (66%) which are etiologically related to H.pylori in gastric MALToma, bacterial infections in immunoproliferative small intestinal disease (IPSID) and EBV infection in Burkitt's lymphoma and immunodeficiency lymphomas (post-transplant and AIDS). T-cell lymphomas (34%) may be also related to antigenic stimulation eg. celiac disease (gluten-sensitive enteropathy). True histiocytic lymphoma rarely affects the GI tract and Hodgkin's disease is practically unknown [5] Curative therapy can be offered to a considerable proportion of these patients, but to achieve this goal, the initial diagnostic and therapeutic decisions are of great importance [4].

The aim of this work is to study the profile of primary GI lymphoma in Egyptian patients and to compare it with other populations.

### **MATERIAL AND METHODS**

A total of eighty seven cases of primary GI lymphomas were obtained from the year 1998

to 2000 from the records of the Pathology Department at the National Cancer Institute, Cairo University.

Histopathology was revised according to the new WHO-REAL classification [16]. Clinical records were reviewed to confirm the demographic and topographic data of the tumors and to assure that the GI lymphomas were true primary GI in origin and not secondaries from nodal lymphomas. Out of the 87 cases, 24 were resection specimens while the other 63 cases were biopsies.

Five micron thick sections were cut on L-olylysine coated glass slides. Antigen retrieval was performed using antigen retrieval solution at a dilution of 1:4 with deionized water (Biogenex cat no HK 090-5K). Immunostaining was applied using the labeled streptavidin-biotin-immunoenzyme antigen detection system (Ultra Vision Detection System Anti-polyvalent HRP/DAB ready to use). The monoclonal antibodies CD20 (Dako M0774) for B-cell lineage, CD45RO (Dako N1520) and CD3 (Dako A0452) for T-cell typing were used.

## RESULTS

A total of eighty seven cases of GI lymphomas constituted 7% of the total GI malignancies. The average mean age of GI lymphomas was 31.4 years with a range of 3-75 years. Male to female ratio was 1.8:1. Burkitt's lymphoma showed the youngest mean age of 7.9 years (Table 1). Males predominated in MALT lymphoma and Burkitt's lymphoma with a male to female ratio 1.7:1 and 6.3:1 respectively, while females showed a slight predominance in large cell lymphoma. Lymphomas of the small intestine were present in young age showing the lowest mean age of 17.1 years (Table 2) with the highest frequency of Burkitt's lymphoma at this site (60%) (Fig. 1). The overpronounced male predominance in Burkitt's lymphoma was also reflected in the lymphomas of small intestine (2.9:1).

According to the WHO-REAL new classification, three different subtypes constituted the GI lymphomas in Egyptian patients:

i) Diffuse large cell lymphoma showed the highest incidence being 39 cases (44.8%). It was characterized by sheets of centroblasts and/or immunoblasts invading the glands. The cells had vesicular nuclei and prominent nucleoli.

Nuclear pleomorphism and mitotic activity were also present (Fig. 2).

ii) Burkitt's lymphoma came in the second position with an incidence of 33.4% and a highest frequency in small intestine. Morphologically, Burkitt's lymphoma was formed of diffuse sheets of medium sized cells with scanty cytoplasm and round or oval nuclei containing small nucleoli. Within the sheets there were numerous macrophages giving a "starry sky" appearance. Mitosis and apoptotic bodies were abundant (Fig. 3).

iii) MALT lymphoma was the least common (21.8%), 5 cases were limited to the mucosa and superficial submucosa, whereas, 14 cases showed extensive involvement of the GI wall with involvement of regional lymph nodes in 3 cases (Fig. 4). The histologic picture showed a diffuse infiltrate of small to medium sized irregular nuclei so-called centrocyte-like cells. This infiltrate surrounded reactive-type follicles and invaded the epithelium of the glands and formed lymphoepithelial lesions (Fig. 5). Areas with florid destruction showed isolated residual eosinophilic epithelial cells. Plasma cell infiltration was also observed especially in the superficial part of the mucosa.

The small intestine (40.2%) was the commonest site. Gastric lymphomas were 33 cases (38%), while, lymphomas of colorectum were 19 cases (21.8%). MALT lymphoma constituted 19 cases (21.8%), diffuse large cell lymphoma were 39 (44.8%), while Burkitt's lymphomas were 29 cases (33.4%). The site distribution of each subtype of lymphoma is shown in Table (3). No Burkitt's lymphoma cases were observed in the gastric region which showed the highest incidence of MALT lymphoma.

As regards the regional lymph node status, 13 cases showed involvement of the regional lymph nodes (54.2%), 3 out of 5 cases (60%) of MALT lymphoma showed involved lymph node. In large cell lymphoma, lymph nodes were positive in 9 out of 15 cases (64.2%). On the other hand, Burkitt's lymphoma showed a low (20%) incidence of lymph node involvement (1/4).

All studied cases showed positive reaction to the pan B monoclonal antibody CD20 (Fig. 6), while non of our cases showed positive reaction to either CD45RO or CD3.

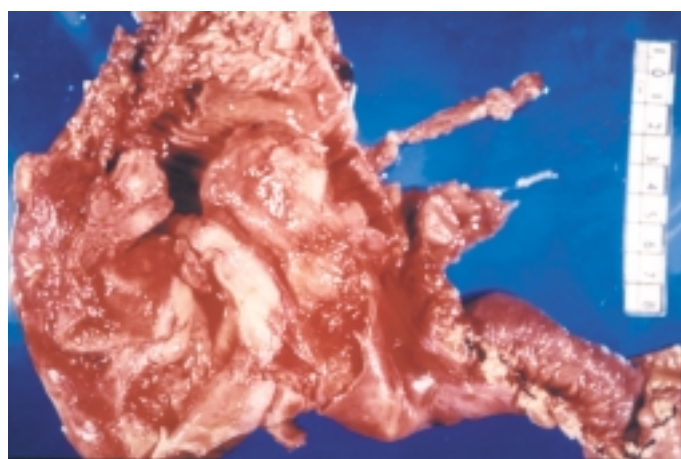


Fig. (1): Gross photograph of burkitt's lymphoma in caecum.

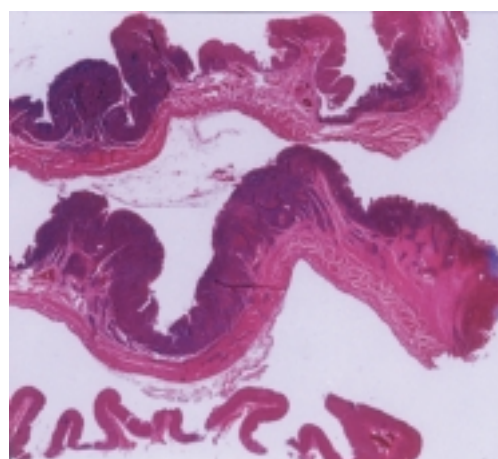


Fig. (4): MALT lymphoma involving mucosa and submucosa (Hx & E x5).

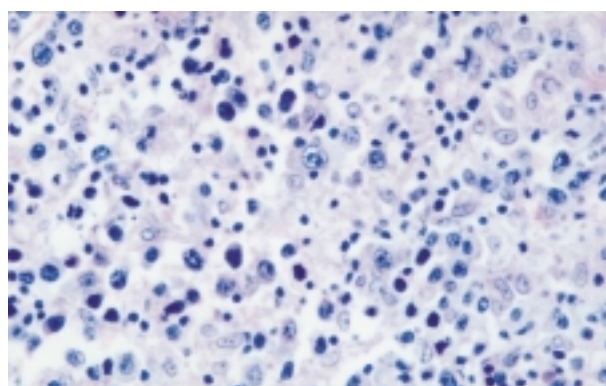


Fig. (2): Diffuse large cell lymphoma with pleomorphism and active mitosis (Hx & E x400).

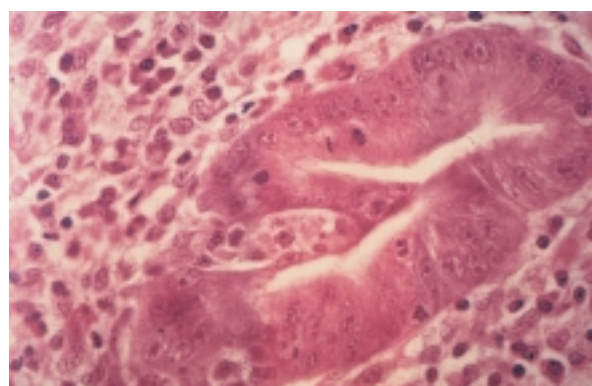


Fig. (5): MALT lymphoma, lymphoepithelial lesion (Hx & E x400).

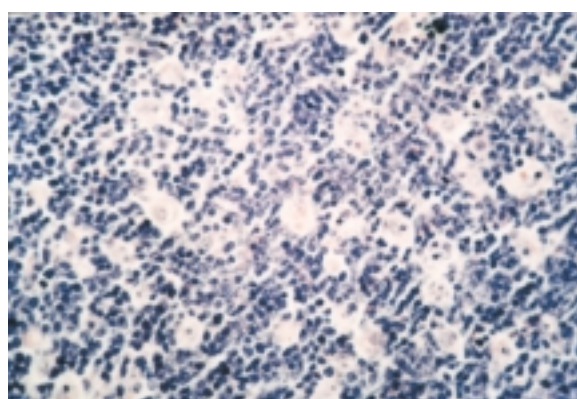


Fig. (3): Burkitt's lymphoma with starry sky pattern (Hx & E x200).

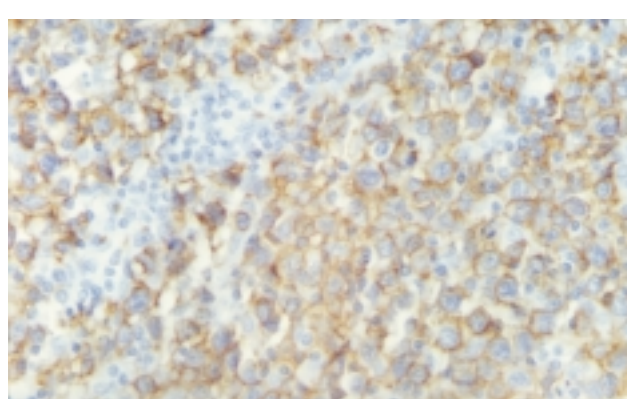


Fig. (6): Diffuse large cell lymphoma with positive membranous staining for CD20 (IP-Mayers Hx counterstain x400).

Table (1): Age and sex distribution in relation to histologic type.

Histologic type	Mean age (range) y	M:F ratio
MALToma	43.3 (22-65)	1.7:1
Diffuse large	43 (4-75)	0.8:1
Burkitt's	7.9 (3-24)	6.3:1

Table (2): Age and sex distribution in relation to topography.

Topography	Mean age (range) y	M:F ratio
Stomach	49 (4-75)	1.3:1
Small intestine	17.1 (3-44)	2.9:1
Colorectm	30.8 (4-65)	1.4:1

Table (3): The frequency and site distribution of 87 cases of GI lymphomas.

Topography / histology	Stomach	Small intestine	Colorectum	Total
MALToma	10 (30.3%)	3 (08.6%)	6 (31.6%)	19 (21.8%)
Diffuse large	23 (69.7%)	11 (31.4%)	5 (26.3%)	39 (44.8%)
Burkitt's	Non (0.0%)	21 (60.0%)	8 (42.1%)	29 (33.4%)
Total	33 (38%)	35 (40.2%)	19 (21.8%)	87 (100%)

## DISCUSSION

The results of the current study showed that primary GI lymphomas constituted 6.2% of the total non-Hodgkin's lymphomas. These results were within the range of other reports who stated that primary GI lymphomas accounted for 3-14% of all lymphoid malignancies [4]. In the last Pathology Registry of the National Cancer Institute, Cairo University [22], GI lymphomas constituted 5.7% of total non-Hodgkin's lymphomas. The recent WHO classification of tumors [35] recorded an incidence of 4-18% in Western countries, while in the Middle East it was up to 25%, this figure probably represents data from other countries in the region.

The primary GI lymphomas were not considered to be common, since, they constituted only 7% of the total GI malignancies. Our data were similar to those who recorded that GI lymphomas were relatively uncommon representing only 1-4% of all GI malignancies [11,12,19,27]. In an earlier in Egypt it was also reported that primary GI lymphomas constituted 10% of total GI malignancy [22].

It was found that lymphomas of the small intestine were the commonest (40.2%). Gastric lymphomas were second in frequency (38%) and colorectal lymphomas were the least common (21.8%) of the GI lymphomas. In Egypt, in a study of cases in the years 1985-1989 it was reported that lymphomas of the stomach were the commonest, then the small intestine followed by the colorectum, 39.2%, 32.4% and 28.4% respectively [22]. The small intestine also showed the highest incidence (32.2%) of GI lymphomas in a report from the Middle East [30]. On the other hand, another study reported that the small bowel showed less frequent involvement than the stomach accounting for about 20% of primary GI lymphomas [8], but they supported our results regarding the large intestine stating a least frequency (15%).

The primary lymphomas of the small intestine in this study, constituted more than half of the cases of small intestinal malignancies (60%), gastric lymphomas constituted 9% of total gastric malignancies, whereas, colorectal lymphomas were more infrequent (3%) of total colorectal malignancies. These figures were almost similar to those reported in the Cancer Pathology Registry [22] regarding colorectal lymphomas (3.1%) and a little higher than those of gastric (15.6%) and small intestinal (70.8%) lymphomas. The low incidence of lymphomas of the large intestine was also stated in other reports accounting for less than 1% of all colonic malignancies [17,34]. The recent WHO classification of tumors [25] also stated that primary colorectal lymphomas accounted for about 0.2% of all neoplasms at this site. Results close to ours were recorded by others who stated that gastric lymphomas constituted 10% of all gastric malignancies and lymphomas of the small intestine ranged from 30 to 50% of total intestinal malignancies [15]. This is mostly related to the fact that epithelial neoplasm at this site is already uncommon.

The classification of GI and other extranodal lymphomas differ from that of nodal lymphoma. The primary GI lymphomas are classified according to cell lineage into distinct groups: the B-cell lymphomas, T-cell lymphomas, true histiocytic (uncommon) and the questionable Hodgkin's disease. The B-cell type (66%) constituted the MALT lymphoma, immunoproliferative small intestinal disease (IPSID), lymphomatous polyposis, large cell lymphoma, Burkitt's lymphoma, follicular lymphoma and plasmacytoma. T-cell lymphomas (34%) are as almost as half as common as B-cell lymphomas and included entropathy associated T-cell lymphoma (EATL), T-cell lymphoma with eosinophilia, peripheral T-cell lymphoma and anaplastic T-cell lymphoma. This reflects the special biology of mucosa associated lymphoid tissue

(MALT) and the specific etiologic mechanisms that operate exclusively in the GI tract [16].

All our cases were of B-cell immunophenotype. This may be due to the rarity of enteropathies predisposing to T-cell GI lymphomas. In Turkey, it was reported that intermediate and high grade lymphomas predominated presenting 75% of GI lymphomas [3]. In Lebanon, one third of the cases of small intestine were diagnosed as IPSID, while, diffuse large cell lymphoma was the dominant type in gastric cases [30]. This high incidence of IPSID may reflect an over-diagnosis of cases or that it was related possibly to an infective etiologic factor which has been controlled. It has been reported that the majority of primary gastric lymphomas are of B-cell lineage [14], whereas, T-cell tumors are very uncommon [24], most of which have been reported from areas of endemic HTLV-1 infection. In these regions, T-cell lymphomas may represent up to 7% of gastric lymphomas [32]. Others related T-cell intestinal lymphomas to coeliac disease and still accounting for a low incidence of 5% of all gastrointestinal lymphomas [6].

The mean age of the cases was 31.4 years with a male to female ratio 1.8:1. Primary GI lymphomas in Turkey showed a mean age of one and a half decade older (45 years) than our patients and little lower male to female ratio of 1.2 [3]. Records of this study were lower than those recorded in other studies which stated a mean range of 50 to 70 years, but a similar male to female ratio of 1.1-2.2:1 [18,26]. Our cases of lymphomas of childhood were mainly of the Burkitt's type with a mean age of 7.9 years and male to female ratio of 6.3:1. These results were similar to those who reported that the pediatric group showed a strong male predominance with a male to female ratio of 5.6-33.1:1 [7,18].

In gastric lymphomas, the mean age of was 49 years with slight male predominance (1.3:1). In the United States, it was recorded that the primary gastric lymphoma is a disease of elderly reaching its peak incidence in the seventh decade with male predominance of 1.2-3.0:1 [13,28]. In Lebanon [30], the average age of gastric lymphoma was 50 years which is equal to our results. Others reported similar results regarding the age but much more male predominance of 3:1 [8]. The WHO classification of tu-

mors stated similar incidence rates in males and females but the age range was wide with the majority of cases over 50 years [35].

Lymphomas of small intestine showed a mean age 17.1 years with male to female ratio 2.9:1, this was related to the higher incidence of Burkitt's lymphoma. The mean age in colorectal lymphoma was 30.8 years with male to female ratio 1.4:1. In multiple Western series it was reported that lymphoma of large intestine showed a peak incidence in the fifth to seventh decade with the sexes being equally affected except in pediatric cases in which males predominated [17,19,29]. This was also reported in the WHO Classification of Tumors which stated no sex predominance and that most cases occurred in older patients [25].

The treatment modality in primary GI lymphomas differ according to the site of disease and histopathologic type, this requires exact and definite diagnosis aided with immunophenotyping. In MALT gastric lymphoma, the standard treatment for patients with early MALT lymphoma and positive for H.pylori is with antibiotics, however, complete disappearance of the disease may take several months [23]. Follow-up endoscopy 3 and 6 months later is mandatory. Patients with complete response should be followed without further treatment. Patients with partial response and remains H.pylori positive should receive a second course of antibiotics before proceeding to more definitive treatment [2]. Patients with persistent disease after antibiotics, local regional irradiation with a low dose (30 Gy) is the treatment of choice, yet, good results have been obtained with total or partial gastrectomy, but, this approach has been associated with long term morbidity [31]. In patients who do not respond to antibiotics, chemotherapy with single-agent chloambucil and local radiotherapy have been shown capable of inducing complete remission in most cases [1].

Burkitt's lymphoma cases should be approached as a medical emergency because of the extremely rapid progression of the disease. Burkitt's lymphoma is one of the first malignancies to be shown to be curable with chemotherapy [36] and the majority of patients should be curable today with aggressive combination chemotherapy regimens. Prophylactic treatment for tumor lysis syndrome is required. Patients with Burkitt's lymphoma have 20-30% life time

risk for CNS involvement. So, CNS prophylaxis is recommended for all patients [20].

As for localized diffuse large B-cell lymphoma, several centers reported excellent results using reduced chemotherapy and involved-field irradiation [10,21]. While regarding diffuse large B-cell lymphoma many studies reported the superiority of an anthracyclin-containing chemotherapy regimen [33]. Owing to the marked diversity in line of treatment of GI lymphomas, this requires a precise and definite histopathologic diagnosis aided by immunophenotyping.

To conclude, primary GI non-Hodgkin's lymphoma is not a common type of extranodal lymphoma or as a malignancy of the GI tract. All cases were of the B-cell immunophenotype. Subtyping of GI lymphomas is essential as the line of treatment differ markedly.

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