GASTROINTESTINAL LYMPHOMA IN THAILAND: A CLINICOPATHOLOGIC ANALYSIS OF 120 CASES AT SIRIRAJ HOSPITAL ACCORDING TO WHO CLASSIFICATION

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Abstract. Clinicopathologic information of gastrointestinal (GI) lymphoma in Southeast Asia is lacking. A retrospective analysis of 120 cases of GI lymphoma in Thailand diagnosed at Siriraj Hospital based on WHO classification was performed. All were non-Hodgkin lymphoma (NHL). The peak age was in the sixth and seventh decades; a slight male preponderance was observed. Sites of involvement included stomach (49.2%), intestine (46.7%), and multiple sites (4.2%). There were 104 cases of primary GI lymphoma (86.7%) and 16 cases of secondary GI lymphoma (13.3%). Presenting GI symptoms were more common in the former; while superficial lymphadenopathy and fever were more common in the latter. Mass lesions were observed in both groups (72.1% *vs* 56.3%). Localized and advanced diseases were found in 68.3% and 31.7% of primary GI lymphomas, respectively. The most common type of lymphoma in both groups was diffuse large B-cell lymphoma. Lymphoepithelial lesions (LEL) were not significantly different between the two groups (58.2% *vs* 42.9%), but *Helicobacter pylori* infection was significantly associated with primary gastric lymphoma ($p<0.0001$). The treatment of choice for localized primary GI lymphoma is controversial. Complete surgical resection may increase the chance of complete remission, but mortality and relapse rates might be higher than those observed with combination chemotherapy alone. GI lymphomas in Thailand are mostly primary B-cell NHL. LEL is not indicative of primary GI lymphoma, but *H. pylori* infection is closely associated with primary gastric lymphoma. A prospective study to determine the treatment of choice for localized GI lymphoma is needed.

INTRODUCTION

Gastrointestinal (GI) lymphoma is one of the most common extranodal lymphoma (Isaacson, 2001). The prevalence of GI lymphoma in Southeast Asia is rarely reported. In Thailand, it constitutes from 4.8% to 8.5% of all non-Hodgkin lymphomas (NHL) (Intragumtornchai *et al*, 1996; Sukpanichnant *et al*, 1998). According to the classification of primary GI lymphomas proposed by Isaacson (2001), marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) or MALT lymphomas are more common than diffuse large cell lymphomas because all the cases of large B-cell lymphomas with the presence of a residual 'low-grade MALT lymphoma' are included in MALT lymphoma as 'high-grade MALT lymphomas'. But this concept has changed with the current WHO classification (2001); the term 'MALT lymphoma' should not be applied to large B-cell lymphomas even if it has arisen in a MALT site (Jaffe *et al*, 2001). We hereby present the results of a retrospective analysis of clinicopathological features of GI lymphoma in Thai adults using the WHO classification.

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MATERIALS AND METHODS

This retrospective clinicopathological study was approved by the Ethics Committee on Research Involving Human Subjects, Faculty of Medicine at Siriraj Hospital, Mahidol University

(No. 42/2001). Consecutive cases of GI lymphoma in Thai adult, aged at least 15 years, diagnosed at the Department of Pathology, Siriraj Hospital from August 1993 to January 2001 (89 months) were collected for analysis. Cases referred from other hospitals and laboratories only for pathologic consultation were not included in this study. All the cases included in this study were reviewed by one author (SS) to give the pathologic diagnosis based on the WHO classification (2001) (Jaffe *et al*, 2001). The phenotype of NHL was determined by paraffin-section immunoperoxidase (PSIP) using antibodies to CD3 (T-cell) and CD20 (B-cell) according to the technique previously described (Sukpanichnant *et al*, 1998). Lymphoepithelial lesions (LEL) were determined according to the WHO classification, as aggregates of 3 or more marginal zone B-cells with distortion or destruction of the epithelium (Jaffe *et al*, 2001). Similar lesions, invaded and destroyed by other types of lymphoma cells were recorded separately. The presence of *Helicobacter pylori* was determined on H&E and Giemsa stained slides, and by PSIP using antibodies to *H. pylori*. Clinical information was retrieved from the pathology request forms at the Department of Pathology and from the clinical records and files of the hematology and gastroenterology units of the Departments of Medicine and Surgery. Clinical data and pathologic findings were analyzed to determine whether the GI lymphoma was primary or secondary.

The distinction between primary and secondary GI lymphomas in the present study was adapted from the definition of primary GI lymphoma by Dawson *et al* (1961) and Isaacson (2001). Primary GI lymphoma was defined as a lymphoma first arising in the GI tract, mostly presenting with GI symptoms. Major pathology focused on the GI tract with little or no pathology in the non-regional lymph nodes, liver, and spleen. Secondary GI lymphoma was defined as lymphomas first arising from outside the GI tract, then later involving the GI tract. The clinical presentation of GI symptoms may occur in secondary GI lymphoma, but the major pathology focused on the lymph nodes and/or non-GI extranodal sites with less pathology in the GI tract.

The clinical staging of primary GI lymphoma was divided into localized and advanced stages. The former included localized involvement of the GI tract, with or without regional lymph node involvement. The latter included involvement beyond the GI tract and regional lymph nodes. The localized stage is comparable to stage EI or EII, whereas the advanced stage is comparable to stage EIII and EIV in the staging system for primary GI lymphoma proposed by Radaszkiewicz *et al* (1992).

For statistical analysis, the chi-square test was used to assess any differences between primary and secondary GI lymphomas with the various clinical features and abnormal laboratory findings. Survival analysis, by the Kaplan-Meier method, was performed. The log rank test was used to assess any differences in survival time between primary and secondary GI lymphomas under various types of treatment.

RESULTS

During the 89-month period, there were 120 cases of GI lymphoma, all of the NHL type, among 1,330 cases of adult NHL. Therefore, GI lymphoma constituted 9% of all adult NHL. There were 69 males and 51 females with GI lymphoma (male to female ratio of 1.4:1). The patient age ranged from 15 to 93 years (mean ± SD, 53.9 ± 16.5 years) with the age peak in the sixth and seventh decades of life. The age, sex, and geographic distribution of GI lymphoma were similar to that of the overall adult NHL, with cases mostly coming from Metropolitan Bangkok, the central and western regions of Thailand (83.5% of all GI lymphoma *vs* 81.4% of all adult NHL).

The sites of involvement included the stomach (59 cases, 49.2%), small intestine and colon (56 cases, 46.7%), and multiple sites (5 cases, 4.2%). Based on the clinical data and pathologic findings, 104 cases were primary GI lymphoma (86.7%) and 16 cases were secondary GI lymphoma (13.3%). Seven cases (43.8%) of secondary GI lymphoma had nodal lymphoma, 5 cases (31.3%) with extranodal lymphoma (4 cases of tonsillar lymphoma and 1 case of thyroid lymphoma), and the other 4 cases (25%) with advanced stages of non-GI lymphoma. The median duration of illness was 3 months before the diag-

nosis of GI lymphoma in 108 cases (range, 2 days to 10 years). The significant differences between primary and secondary GI lymphomas are demonstrated in Table 1, which were GI symptoms ($p<0.0001$), fever ($p<0.05$), and superficial lymphadenopathy ($p<0.0001$). When secondary GI lymphoma presented with any GI symptoms, it was not possible to distinguish it from primary GI lymphoma based on these symptoms alone. Three cases of primary gastric lymphoma did not present first with GI symptoms. One case presented with erythema nodosum and another with chronic iron deficiency anemia; both were found to have asymptomatic gastric lymphoma. The other case was first admitted to investigate obstructive uropathy, but later developed upper GI hemorrhage during admission. The superficial lymphadenopathy found in primary GI lymphoma was small in size and clinically insignificant, which was different from that of secondary GI lymphoma. Based on the mass lesions, 38 of 75 cases (50.7%) of primary GI lymphomas and 1 of 9 cases (11.1%) of secondary GI lymphomas had a first clinical impression of carcinoma of the GI tract. No significant differences in endoscopic findings were observed between primary and secondary GI lymphomas ($p>0.05$); abnormal mucosal appearances, other than ulcer, including large or giant mucosal folds, diffuse nodularity, friable granular mucosa, edematous thickened mucosa, induration, and flat mucosa, could be found in both types of lymphomas.

Table 2 compares the 51 cases of primary gastric lymphoma with the 8 cases of secondary gastric lymphoma. The only significant difference was the predominantly localized stage in primary gastric lymphoma ($p<0.001$). The locations involved by the lymphoma described in 40 cases of primary gastric lymphoma included the antrum (25 cases), body (18 cases), fundus (8 cases), cardia (6 cases), and the whole stomach (4 cases). The locations involved by lymphoma described in the 6 cases of secondary gastric lymphoma included the antrum (2 cases), body (2 cases), and cardia (2 cases). The lower esophagus was involved in 1 case each of primary and secondary gastric lymphomas.

Table 3 compares the 51 cases of primary

Table 1
Comparison of clinical presentations and abnormal physical findings between primary and secondary GI lymphomas at Siriraj Hospital.

Clinical presentation or abnormal physical finding	Primary GI lymphoma No. of cases (%)	Secondary GI lymphoma No. of cases (%)
Presenting with GI symptoms[a]	101/104 (97.1)	4/16 (25.0)
Abdominal pain	66/101 (65.3)	1/4 (25.0)
Palpable abdominal mass	28/101 (27.7)	1/4 (25.0)
Gut obstruction	19/101 (18.8)	0/4 (0)
Upper GI hemorrhage	16/101 (15.8)	1/4 (25.0)
Diarrhea	15/101 (14.9)	1/4 (25.0)
Lower GI hemorrhage	14/101 (13.9)	1/4 (25.0)
Malabsorption syndrome	4/101 (4.0)	0/4 (0)
Presenting with non-GI symptoms[a,b]	3/104 (2.9)	12/16 (75.0)
Weight loss	64/104 (61.5)	8/16 (50.0)
Fever[c]	9/104 (8.7)	5/16 (31.3)
Anemia	30/45 (66.7)	3/5 (60.0)
Mass lesions	75/104 (72.1)	9/16 (56.3)
Intra-abdominal lymphadenopathy	44/104 (42.3)	4/16 (25.0)
Superficial lymphadenopathy[a]	14/104 (13.5)	14/16 (87.5)
Hepatomegaly	22/104 (21.2)	4/16 (25.0)
Splenomegaly	9/104 (8.7)	4/16 (25.0)

[a] $p<0.0001$; [b] See text for detail; [c] $p<0.05$

Table 2
Comparison of the frequency in various clinical findings between primary and secondary gastric lymphomas at Siriraj Hospital.

Clinical findings	Primary gastric lymphoma (51 cases)	Secondary gastric lymphoma (8 cases)
Localized stage[a]	66.7%	0%
Solitary mass	70.6%	75%
Multiple masses	2%	0%
Solitary ulcer	17.6%	25%
Multiple ulcers	17.6%	0%
Abnormal mucosa	13.7%	12.5%
Inoperable mass	19.6%	0%
Obstruction	13.7%	0%
Perforation	5.9%	12.5%

[a]$p<0.001$

Table 3
Comparison of the frequency in various clinical findings between primary and secondary intestinal lymphomas at Siriraj Hospital.

Clinical findings	Primary intestinal lymphoma (51 cases)	Secondary intestinal lymphoma (5 cases)
Localized stage[a]	72.5%	0%
Solitary mass[b]	68.6%	20%
Multiple masses	3.9%	20%
Solitary ulcer	0%	20%
Multiple ulcers	2%	0%
Abnormal mucosa	17.6%	40%
Obstruction	23.5%	0%
Perforation	13.7%	20%
Malabsorption syndrome	7.8%	0%

[a]$p<0.005$, [b]$p<0.05$

intestinal lymphoma with the 5 cases of secondary gastric lymphoma. The significant differences were the predominantly localized stage with primary intestinal lymphoma ($p<0.005$) and the solitary mass associated with primary intestinal lymphoma ($p<0.05$). Intussusception was found as a cause of intestinal obstruction in 5 of 12 cases (41.7%) of primary intestinal lymphoma. Malabsorption syndrome was observed in 4 cases of primary intestinal lymphoma only. The locations involved by lymphoma described in 49 cases of primary intestinal lymphoma included the cecum (14 cases), terminal ileum (12 cases), rectum (8 cases), jejunum, ileum, and ascending colon (6 cases each), appendix (4 cases), the whole small intestine (4 cases), and the whole colon (1 case). The locations involved by lymphoma in 5 cases of secondary intestinal lymphoma included the rectum (2 cases), duodenum (2 cases), jejunum (1 case), and ileocecum (1 case).

The types of lymphoma in both groups according to WHO classification are demonstrated in Table 4. Diffuse large B-cell lymphoma (DLBCL) accounted for 60 of 88 classifiable types (68.2%) of primary GI lymphoma and 8 of 16 classifiable types (50%) of secondary GI lymphoma. MALT lymphoma accounted for 11 of 88 classifiable types (12.5%) of primary GI lymphoma whereas small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL) accounted for 4 of 16 of classifiable types (25%) of secondary GI lymphoma. The unclassifiable lymphoma included 3 cases with the null cell phenotype (failed to stain with either B- or T-cell markers) and the other 13 cases with tissue were not available for immunophenotypic studies. Two of these 16 cases of unclassifiable lymphoma had MALT lymphoma histology and the other 14 cases had large cell morphology. Therefore, overall classifiable GI lymphoma included B-cell NHL (94 cases, 90.4%) and T-cell NHL (10 cases, 9.6%). B-cell phenotype constituted 80 of 88 cases (90.9%) of primary GI lymphoma and 14 of 15 cases (93.3%) of secondary GI lymphoma. During the same period of study, B-cell NHL and T-cell NHL constituted 77.1% and 22.9% of the overall cases of NHL, respectively. A significant difference was observed in the frequency of B-cell NHL between GI lymphoma and overall NHL cases ($p<0.005$).

LEL was found in 46 of 79 cases (58.2%) of primary GI lymphoma in 6 of 14 cases (42.9%) of secondary GI lymphoma; no significant difference was observed between the two groups ($p = 0.44$). Primary GI lymphoma with the presence of LEL included DLBCL (26 cases), MALT lymphoma (10 cases), Burkitt lymphoma (1 case), unclassifiable B-cell NHL (1 case), unspecified

Table 4
Types of lymphoma in primary and secondary GI lymphomas according to the WHO classification (2001).

Type	Primary GI lymphoma (104 cases)			Secondary GI lymphoma (16 cases)		
	Gastric	Intestinal	Multiple sites	Gastric	Intestinal	Multiple sites
B-cell NHL	41	37	2	6	5	3
DLBCL	33	26	1	4	3	1
MALT	6	4	1	-	-	-
FL	1	2	-	1	-	-
BL	-	3	-	-	-	-
MCL	-	2	-	-	-	1
SLL/CLL	-	-	-	1	2	1
UNCL	1	-	-	-	-	-
T-cell NHL	2	6	-	2	-	-
PTCL	2	5	-	1	-	-
ETL	-	1	-	-	-	-
ALCL	-	-	-	1	-	-
Unclassifiable	8	8	-	-	-	-
Total	51	51	2	8	5	3

ALCL: anaplastic large cell lymphoma, BL: Burkitt lymphoma, DLBCL: diffuse large B-cell lymphoma, ETL: enteropathy-type T-cell lymphoma, FL: follicular lymphoma, MALT lymphoma: extranodal marginal zone B-cell lymphoma of MALT, MCL: mantle cell lymphoma, PTCL: unspecified peripheral T-cell lymphoma, SLL/CLL: small lymphocytic lymphoma/chronic lymphocytic leukemia, UNCL: unclassifiable B-cell NHL.

Table 5
Treatment and outcome in primary and secondary GI lymphomas at Siriraj Hospital.

Treatment	Primary GI lymphoma				Secondary GI lymphoma			
	Total	Alive	Dead	Lost[a]	Total	Alive	Dead	Lost[a]
Surgery	22	-	2	20	2	-	-	2
Surgery and adjuvant therapy	31	16	6	9	2	1	-	1
Combination chemotherapy	33	21	3	9	11	4	-	7
No treatment	18	-	3	15	1	-	-	1
Overall	104	37	14	53	16	5	-	11

[a]Lost to follow-up

peripheral T-cell lymphoma (PTCL, 2 cases), enteropathy-type T-cell lymphoma (ETL, 1 case), and unclassifiable lymphoma (5 cases; 2 cases with histology of MALT lymphoma and the other 3 cases with large cell morphology), whereas secondary GI lymphoma, with the presence of LEL, included DLBCL (3 cases), SLL/CLL (2 cases), and anaplastic large cell lymphoma (1 case). Small lymphoid cells invaded the epithelium in all except for 3 cases of DBLCL (2 cases of primary GI lymphoma and 1 case of secondary GI lymphoma) where large lymphoma cells also invaded the epithelium (Fig 1A-G).

Associated *H. pylori* infection was found in 38 of 39 cases (97.4%) of primary gastric lymphoma and 1 of 8 cases (12.5%) of secondary gastric lymphoma by nodal mantle cell lymphoma; a significant difference was observed between the two groups ($p<0.0001$). The types of primary gastric lymphoma with associated *H. pylori* infection included DLBCL (25 cases), MALT lymphoma (7 cases), unclassifiable B-cell

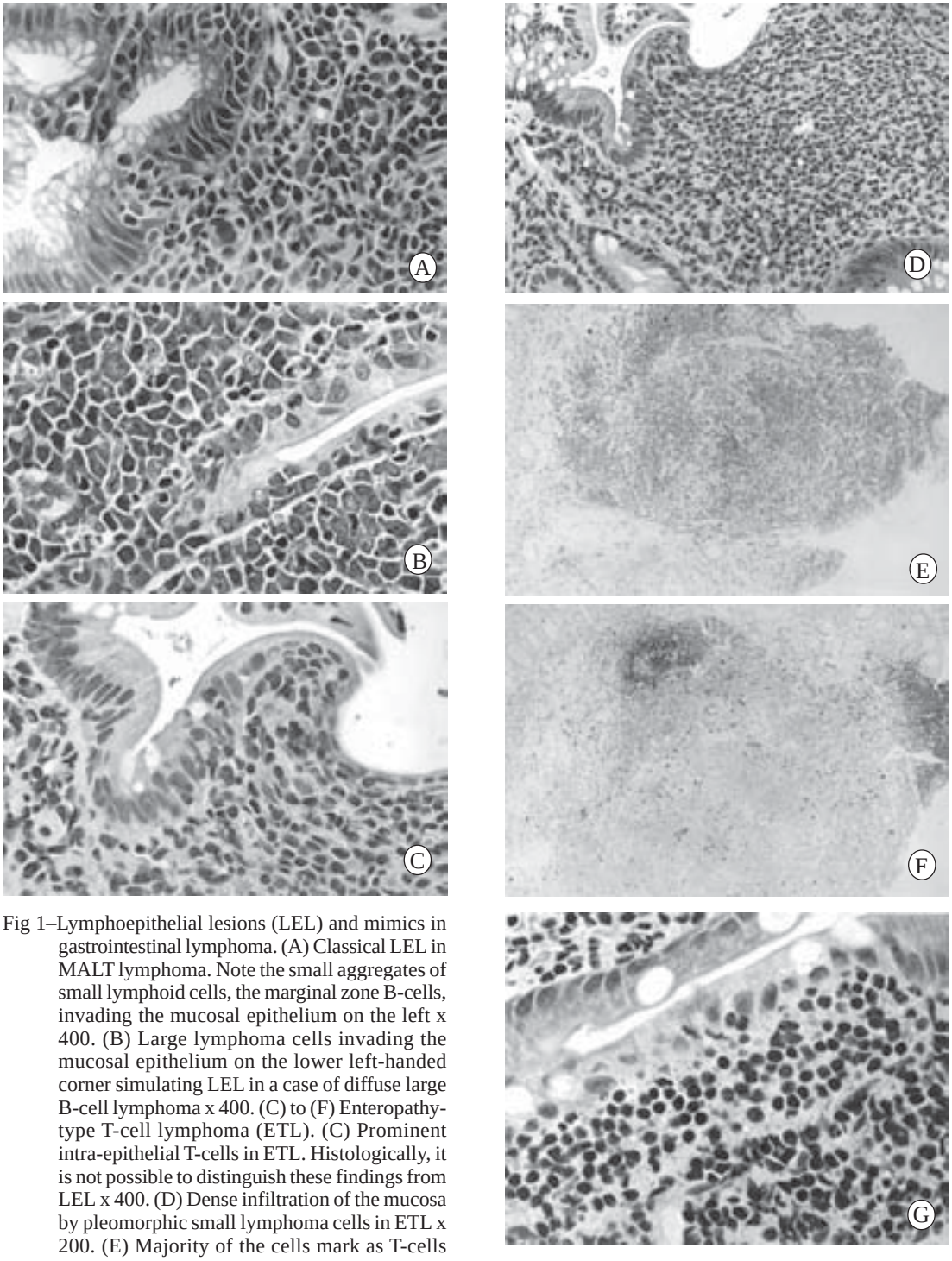

Fig 1–Lymphoepithelial lesions (LEL) and mimics in gastrointestinal lymphoma. (A) Classical LEL in MALT lymphoma. Note the small aggregates of small lymphoid cells, the marginal zone B-cells, invading the mucosal epithelium on the left x 400. (B) Large lymphoma cells invading the mucosal epithelium on the lower left-handed corner simulating LEL in a case of diffuse large B-cell lymphoma x 400. (C) to (F) Enteropathy-type T-cell lymphoma (ETL). (C) Prominent intra-epithelial T-cells in ETL. Histologically, it is not possible to distinguish these findings from LEL x 400. (D) Dense infiltration of the mucosa by pleomorphic small lymphoma cells in ETL x 200. (E) Majority of the cells mark as T-cells (CD3+) x 40. (F) B-cells (CD20+) in a residual lymphoid follicle on the upper left-handed corner and a few B-cell admixed with many CD20- lymphoma cells x 40. (G) Small lymphoma cells invading the epithelium on the upper right-handed corner simulating LEL in a case of secondary GI lymphoma by small lymphocytic lymphoma/chronic lymphocytic leukemia. Note the round nuclei with clumped nuclear chromatin of the small lymphoma cells x 400.

NHL (1 case), PTCL (1 case), and unclassifiable lymphoma (4 cases; 1 case with histology of MALT lymphoma and the other 3 cases with diffuse large cell morphology).

Clinical staging in primary GI lymphoma included localized disease in 71 of 104 cases (68.3%) and advanced disease in 33 of 104 cases (31.7%). Three cases with localized disease later had clinical progression to advanced disease. Clinical staging in secondary GI lymphoma was all advanced at the time of GI involvement. Treatment and clinical outcome in primary and secondary GI lymphomas are summarized in Table 5. Adjuvant therapy after surgery was mainly a combination chemotherapy; only 1 case of secondary GI lymphoma had local irradiation after subtotal gastrectomy, and this was then followed by adjuvant chemotherapy. Varied regimens of combination chemotherapy were used, but the CHOP regimen accounted for 38 of 77 cases (49.4%). Unfortunately, survival analysis could not be performed due to insufficient data. Too many cases were lost to follow-up. Only 44 cases (42.3%) of primary GI lymphoma had available information on survival time after diagnosis. The median survival time was 11 months (range, 1 month to 6 years). The median survival time in 29 cases of localized primary GI lymphoma was 12 months (range, 1 month to 6 years) and in 15 cases of advanced primary GI lymphoma was 9 months (range, 1 month to 2.7 years). In 5 cases (31.3%) of secondary GI lymphoma with available information on survival time after diagnosis of GI involvement by lymphoma, the median of survival time was 12 months (range, 9 months to 4 years).

No significant differences were observed in the clinical outcome of localized primary GI lymphoma between the group treated with surgery and adjuvant chemotherapy (15 cases) and the group treated with combination chemotherapy only (14 cases). Nevertheless, the number of patients who were alive was higher in the latter than that in the former (92.9% *vs* 66.7%, p = 0.17) and the number of patients who had relapse was lower in the latter than that in the former (28.6% *vs* 46.7%, p = 0.53). Among those who were alive, the number of patients who were without disease was higher in the former than that in the latter (60% *vs* 30.8%, p = 0.22).

Relapse was noted in 17 cases (16.3%) of primary GI lymphoma. The median time of relapse after diagnosis was 14 months (range, 3 months to 5 years). Among the 15 cases with known sites of relapse recorded, 13 cases had the same type of lymphoma at the time of relapse, including those relapsed within the GI tract (6 cases), within and outside the GI tract (1 case), and outside the GI tract only (6 cases). The other 2 cases had different types of lymphoma at the time of relapse within the GI tract. One was DLBCL of the rectum that had relapse 2 and 4 years after treatment in the rectosigmoid region with MALT lymphoma, and the other case was MALT lymphoma of the small intestine with malabsorption syndrome which had relapsed a year after diagnosis, as perforation of the ileum involved by DLBCL. Relapse was noted in 3 cases (18.8%) of secondary GI lymphoma – in the lymph node (1 case), tonsil (1 case), and an unspecified site (1 case). The median time of relapse after GI involvement was 5 months (range, 3 months to 4 years).

DISCUSSION

The frequency of GI lymphoma, at this institution, has not changed significantly during the past 5 years: 9% of all NHL in Thai adults in this series *vs* 8.5% of NHL in all age groups in previous series (Sukpanichnant *et al*, 1998). Approximately half of the cases had involvement of the stomach and the other half had involvement of intestine and multiple sites. The antrum, ileocecum, and rectum are the most common sites of lymphoma in the stomach, small and large intestine, respectively. The present series confirms the presenting GI symptoms in most cases of primary GI lymphoma and in 25% of secondary GI lymphoma ($p<0.0001$). It should be emphasized that any GI symptoms can occur in secondary GI lymphoma, even though gut obstruction and malabsorption syndrome were not observed in the present series (only 16 cases of secondary GI lymphoma). Superficial lymphadenopathy and fever are more common in secondary GI lymphoma ($p<0.0001$ and $p<0.05$, respectively). Mass lesions, ulcers in the GI tract, weight loss, anemia,

intra-abdominal lymphadenopathy, and hepatosplenomegaly cannot be used to distinguish between primary and secondary GI lymphomas.

There is no doubt about the usefulness of endoscopy in facilitating the early diagnosis of GI lymphoma (Shutze and Halpern, 1991). Since a solitary mass is the most common finding in primary GI lymphoma, approximately (70% of cases in the present series), endoscopic biopsy should always be performed to distinguish lymphoma from carcinoma or other tumors of the GI tract. Some patients in the present series lost their chance to have a complete cure of their GI lymphoma and were lost to follow-up because of an incorrect clinical impression of inoperable carcinoma, especially when a huge solitary mass was found in the stomach or colon.

The B-cell phenotype is significantly more common in GI lymphoma than in overall NHL during the same period of study (90.4% *vs* 77.1%) ($p<0.005$). The most common type of lymphoma in both primary and secondary GI lymphomas was DLBCL (68.2% and 50%, respectively). These results concur with most previous series (Herrmann *et al*, 1980; Mohri, 1987; Rosen *et al*, 1987; List *et al*, 1988; Maor *et al*, 1990; Cogliatti *et al*, 1991; Shutze and Halpern, 1991; Radaszkiewicz *et al*, 1992; Domizio *et al*, 1993; Shimodaira *et al*, 1994; Nakamura *et al*, 1997; Hsi *et al*, 1998; Ortega *et al*, 1998). MALT lymphoma is the second most common type in primary GI lymphoma (12.5%). Malabsorption syndrome may be required for the diagnosis of ETL to indicate enteropathy, but it can occur in other types of lymphoma, such as 2 cases of MALT lymphoma and 1 case of DLBCL, apart from 1 case of ETL in the present series. Hodgkin lymphoma of the GI tract is extremely rare, none in the present series. One case of an anaplastic variant of DLBCL with monoclonal IgA-lambda was misdiagnosed as Hodgkin lymphoma based on morphology alone by a pathologist from another hospital.

LEL is frequently considered as the most common feature in MALT lymphoma, and is sometimes used as an important feature to indicate MALT lymphoma (Isaacson, 2001; Jaffe *et al*, 2001). The detection of LEL in many types of lymphoma, other than MALT lymphoma of either B-cell and T-cell phenotype, and in secondary GI lymphoma in the present series, raises the question about the specificity of LEL as an evidence of MALT lymphoma and primary GI lymphoma. Furthermore, large lymphoma cells invading the epithelium are observed in 2 cases of primary GI lymphoma and 1 case of secondary GI lymphoma. Large lymphoma cells that invade the epithelium have been reported previously (Bateman and Wright, 1993; Hsi *et al*, 1998). In our viewpoint, the invasion of epithelium by lymphoma cells indicates the nature of malignancy that can be observed in any type of lymphoma. Interestingly, it is not possible to distinguish between LEL and the prominent intraepithelial T-cells described in the standard textbook (Isaacson, 2001) and the ETL case in the present series (Fig 1C-F) without the knowledge of the immunophenotype of the lymphoid cells forming small aggregates within the epithelium.

In contrast to LEL, the presence of *H. pylori* may indicate primary gastric lymphoma, due to the differences in the findings between primary and secondary gastric lymphoma. We strongly recommend complete clinical information and clinical staging to distinguish between primary and secondary GI lymphoma. To avoid difficulty in distinguishing between advanced stages of primary GI lymphoma and secondary GI lymphoma, most studies concentrate on the localized stage of primary GI lymphoma. In the present series, advanced primary GI lymphoma was distinguished from secondary GI lymphoma by criteria adapted from Dawson *et al* (1961) and Isaacson (2001). In the present series, primary GI lymphoma presented as advanced disease in one-third of the cases (31.7%), but it has ranged from 9% to 40.5% in other studies (Herrmann *et al*, 1980; List *et al*, 1988; Radaszkiewicz *et al*, 1992; Hsi *et al*, 1998).

According to List *et al* (1988) the median survival in the resected group was 51 months, whereas in the non-resected group it was only 13 months. The 5-year survival rate of localized primary gastric lymphoma ranges from 55% to 76% (Maor *et al*, 1990; Cogliatti *et al*, 1991; Shutze and Halpern, 1991; Radaszkiewicz *et al*, 1992); whereas localized primary intestinal lymphoma is only 24% in one series (Radaszkiewicz *et al*, 1992). It varies from 25% in T-cell primary in-

testinal lymphoma to 75% in low-grade B-cell primary intestinal lymphoma in another series (Domizio *et al*, 1993). In the present series, there was a problem with a large number of patients being lost to follow-up (51%), which is commonly seen in retrospective studies in developing countries. This precludes any conclusions about clinical outcomes, but it may provide some interesting observations for a prospective studies in the future. For example, the higher number of patients that are alive without disease in the group with localized primary GI lymphoma treated with complete surgical resection and adjuvant chemotherapy compared with in the group treated with combination chemotherapy only.

Several previous retrospective studies of primary GI lymphoma, gastric lymphoma, or intestinal lymphoma show a general agreement on clinical staging as the most important prognostic factor (Herrmann *et al*, 1980; Cogliatti *et al*, 1991; Radaszkiewicz *et al*, 1992; Domizio *et al*, 1993; Hsi *et al*, 1998). Several studies also demonstrate the role of surgery in cases with resectability for a better clinical outcome, including complete remission and relapse-free survival rates (Rosen *et al*, 1987; List *et al*, 1988; Cogliatti *et al*, 1991; Shutze and Halpern, 1991; Radaszkiewicz *et al*, 1992; Hsi *et al*, 1998). A number of studies do not have such a favorable outcome with surgical resection, but show the role of local radiotherapy with or without combination chemotherapy as an option for treatment to conserve the GI tract (Herrmann *et al*, 1980; Maor *et al*, 1990). The role of local radiotherapy, however, is still in question by some investigators (Rosen *et al*, 1987). Regarding pathologic aspect, several studies show the histologic grade as a significant prognostic factor (List *et al*, 1988; Cogliatti *et al*, 1991; Radaszkiewicz *et al*, 1992; Domizio *et al*, 1993) whereas others fail to show a significant association (Rosen *et al*, 1987; Hsi *et al*, 1998). The depth of infiltration is also shown to have prognostic significance (Rosen *et al*, 1987; Radaszkiewicz *et al*, 1992; Shimodaira *et al*, 1994) as well as the tumor size (Shutze and Halpern, 1991).

Relapse in primary GI lymphoma in the present series seems to occur without any influence from the treatment modalities, in particular, complete surgical removal. The median time to relapse is 14 months after diagnosis. It is noteworthy that relapse can occur several years after complete remission; up to 5 years in the present series. In other studies, relapse usually occured in the first 2 years (Maor *et al*, 1990) and the 5-year relapse-free survival rate for localized primary gastric lymphoma ranges from 62% to 74% (Maor *et al*, 1990; Cogliatti *et al*, 1991). Relapse within the GI tract is thought to be due to lymphoma cells spreading to other GI mucosal sites. This postulation included relapse or progression to other non-GI MALT sites (Pelstring *et al*, 1991). We have observed this kind of relapse within or outside the GI tract in several cases in the present series. We have also observed the GI involvement as relapse or progression of nodal or extranodal lymphoma in the present series. The postulation of spread to different MALT sites cannot explain this GI involvement in nodal lymphomas. Most believe the involvement is by chance in advanced nodal lymphoma. Another interesting observation in the present series is the change in lymphoma type at the time of relapse. We observed either less or more aggressive types at the time of relapse. We could demonstrate only the B-cell phenotype in both examples, but the lack of facilities to prove the same clone of lymphoma cells by determination of surface immunoglobulin type or clonal rearrangement of immunoglobulin gene precludes the conclusion of the histologic transformation in lymphoma (Isaacson, 2001; Jaffe *et al*, 2001). It is possible to argue that, in the case of DLBCL at first diagnosis with MALT lymphoma at relapse, these are both DLBCL and MALT lymphomas because LEL was observed at the first diagnosis, consistent with the so-called 'high-grade lymphoma arising in low-grade MALT lymphoma' or 'high-grade MALT lymphoma with a low-grade component' in the literature (Isaacson, 2001). After chemotherapy, the DLBCL responds well, whereas the MALT lymphoma persists and later causes relapse. It is also possible in the case of MALT lymphoma at the first diagnosis with DLBCL at relapse to have foci of DLBCL that were not obtained on the biopsy sample from pathologic examination. The large lymphoma cells in this case do not respond to chemotherapy and eventually cause relapse.

In the present series, we did not intend to

study the role of eradication of *H. pylori* infection to create regression of MALT lymphoma or other types of lymphoma as reported in the literature (Wotherspoon *et al*, 1993; Bayerdörffer *et al*, 1995; Roggero *et al*, 1995). Eradication of *H. pylori* infection in gastric lymphoma was widely accepted in our hospital after the period of this retrospective study.

In summary, GI lymphoma in Thai adults is mostly primary in nature, approximately 87% of cases. Mass lesions and advanced disease are quite common in the present series. Interestingly, LEL is not as specific as a defining feature of either MALT lymphoma or primary GI lymphoma whereas the presence of *H. pylori* highly suggests primary gastric lymphoma. Complete clinical information is crucial to distinguish between primary and secondary GI lymphoma. A prospective study to determine the treatment of choice in localized GI lymphoma is needed. Better terminology and classification of lymphoma are certainly needed for better agreement and understanding of GI lymphoma.

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