Original Article

Primary Gasterointestinal Lymphoma, Clinicopathologic Study of 49 Small Intestinal Lymphoma Casess and the Treatment Option of Choice

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Abstract

Introduction: A study was made conserning 142 patients who were suffering from gastrointestinal lymphoma, were seen at the department of Hematology and Oncology, Esfahan Medical School, during the period 1982-2002.
Method: All patients had laparotomy, and biopsy of the site lesion. Histopathological subtypes were done in the International Working Formulation. Stage groupings were done applying the Crowther and Blackledge staging system. The post-laparotomy was made depending on the patient's general condition, the completeness of surgery and histological subtype.
Results: There were 52 cases of gastrointestinal lymphoma in the stomach, 49 in the small intestine, 12 in the ileocecal region, 22 in the rectosigmoid and in seven of the cases, multiple sites in the gastrointestinal tract were involved.
Conclusion: The overall survival rate was 47.8% at 5 years. Early stage disease and high-grade lymphoma have a better prognosis if treated adequately. Patients who had complete surgical removal of primary tumour (befor any metastasis) had a longer survival.

Key words: Non Hodgkin's Lymphoma, Small Intestinal, Pimary, Treatment

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Introduction

The gastrointestinal (GI) tract is the predominant site of extranodal non-Hodgkin's lymphomas (NHLs).(1) Primary NHLs of the GI tract are rare, accounting for only 1 to 4 percent of malignancies arising in the stomach, small intestine or colon.(2) In contrast, secondary GI involvement is relatively common, occurring in approximately 10 percent of patients with limited stage NHL lymphomas at the time of diagnosis, and up to 60 percent of those dying from advanced NHL.(1,3) Despite their rarity, primary NHL lymphomas of the GI tract are significant, since their management and prognosis are distinct from that of adenocarcinomas of the GI tract. By definition, primary non-Hodgkin's gastrointestinal lymphomas are those which are present with gastrointestinal symptoms as a result of lymphomatous involvement or of a predominant alimentary tract lesion.(1,3) Primary GI lymphomas account for 40% of all primary extra nodal NH lymphomas.(2,3) This excludes patients whose GI involvment was detected following previously diagnosed extra-abdominal disease. There are two types of primary small intestinal NHLs, designated as immunoprolifrative small intestinal disease (IPSID) and non-IPSID. The first one, accounting for the high

incidence of small intestinal lymphoma in the Middle East and North Africa(5) is the IPSID. The second type, designated as the "Western type" or non-IPSID small, is characterized by localized lymphoma lesions, with a normal intestinal wall distinct from the tumor site.(4)

Extrnodal Marginal Zone B-Cell (MALT) Lymphoma: B-cell lymphomas of the MALT type (MALT-type lymphoma or MALT lymphoma), now called extranodal marginal zone B-cell lymphoma of the MALT type in the REAL/WHO classification, are the most common primary gastrointestinal lymphomas worldwide. In western countries, MALT lymphomas tend to occur most commonly in the stomach, followed in incidence by the small bowel, ileocecal area, colon and the esophagus.(1,6,7) Regardless of the site, these so-called "western" type lymphomas have an inclination to occur in individuals over the age of 50 and exhibit a slight male predominance.(8) Epidemiologic studies support a strong association between MALT type gastric lymphomas and chronic Helicobacter pylori infection.(9) In addition to its association with bacterial infection, MALT type intestinal lymphomas have been associated with various autoimmune, immunodeficiency syndromes,(10-14) and nodular lymphoid hyperplasia.

Immunoproliferative Small Intestinal Disease: Immunoproliferative small intestinal diseases (IPSID, alpha heavy- chain disease, Mediterranean lymphoma, diffuse small intestinal lymphoma) is a specialized subtype of MALT lymphoma that occurs almost exclusively in the Middle East and is characterized by the synthesis of an alpha heavy chain paraprotein. IPSID tends to be a disease of young adults, and also shows a slight male predominance. Primary western-type intestinal GI lymphomas of the MALT type may also present themselves as unifocal or, less commonly, multifocal ulcerated, protruding, or infiltrating mass lesions. The distal small intestine, particularly the ileocecal region, is a more frequent site of involvement than the proximal small intestine or colon.(5,8,18)

Diffuse large B-cell lymphoma: Diffuse large B-cell lymphoma (DLBCL) involving MALT sites, previously called "high-grade" MALT lymphoma, is characterized by the presence of confluent sheets or clusters of centroblastic or plasmablastic tumor cells outside of colonized follicles. Reactive lymphoid follicles and lymphoepithelial lesions may or may not be present; if absent, these tumors may be histologically and cytologically indistinguishable from DLBCLs arising at nodal sites.(5)

Mantle Cell Lymphoma: Mantle cell lymphoma (MCL) is a B-cell variant which may act clinically as an indolent or as an aggressive primary GI lymphoma. In the largest series reported to date, MCL accounted for only 9 percent of primary GI lymphomas accrued prospectively from multiple centers in France between 1984 and 1995.(30) The disease occurs more commonly in men, at a mean age of 55 to 64. Predisposing conditions have not yet been identified.

Burkitt's and Burkitt-Like Lymphomas: Burkitt's and Burkitt-like lymphomas are highly aggressive B-cell neoplasms with distinctive epidemiologies. Burkitt's lymphoma is endemic in parts of Africa, particularly central Africa, where malaria is also endemic; it tends to be a disease of childhood with a peak incidence at about eight years of age.(31,32) In contrast, "sporadic" Burkitt's lymphoma occurs in industrialized societies and exhibits a wider age distribution, with only 50 percent of cases involving children.(31,33) Epstein-Barr virus (EBV) infection has been implicated in the pathogenesis of endemic Burkitt's lymphoma; its role in the development of sporadic Burkitt's is uncertain.(31,34) The previous prognostic factors attributed in GI NHL are the site and stage of the disease, as well as histology. It has been noted that patients with localized GI lymphomas have better long term survival.(5,6) The treatment of these lymphomas includes surgery, radiation therapy and chemotherapy. In this paper, we are reporting our experience with forty nine patients of primary, small intestinal lymphoma.

Materials and Methods:

Five hundred ninety tow patients with non-Hodgkins lymphoma were treated at the Department of Medical Oncology, Esfahan Medical School, Sayed Al-Shohada Hospital, during the period 1982-2002. One hundred forty tow cases were identifide with primary gastro-intestinal lymphoma. The occurences were 52 cases in the stomach, 49 in the small intestine, 12 in the ileocecal region, 22 in the rectosigmoid and in seven cases, multiple sites in the gastrointestinaltract were involved. All patients had laparotomy and attempt was made at complete resection of the tumor. Histopathology slides were reviewed and all cases were classified according to the International Working Formulation. A pre-operative diagnosis was not made in these cases since they all presented as acute

Table 1. Staging of GI Lymphoma(8)

I	A	Single tumour confined to gut
	B	Multiple tumour confined to gut
II	A	Tumour with local lymph node involvment
	B	Tumour with local extension to adjacent tissue
	C	Tumour with perforation and peritonitis
III	A	Tumour with widespread lymphadenopathy
IV	A	Tumour with disseminated disease in non-lymphoid tissue

abdomen or abdominal pain, for which an exploratory laparotomy was done. Only 31 patients had a complete resection of the tumour. Of the remining eighteen patients, all were considered inoperable and only multi biopsies were done. Post-laparotomy treatment modality was decided on the base of the general condition of the patients, their histology and the extent of the surgical resection. All patients (49 cases) who had had complete surgical removal of the primary tumour were given chemotherapy using Cyclophosphamide 1000 mg/m^2, Vincristine 1.4 mg/m^2 Adriamycin 50 mg/m^2 Prednisolone 40mg/m^2 (CHOP), repeated once in 15 days. A total of 6 cycles were administered. Patients follow- up was in 3 months for the first year and therafter at increasing intervals. Overall survival analysis with respect to stage and histology was done using the Kaplan-Meier method.

Results

The frequency of primary GI-NHL in our series was 41.69% of all non-Hodgkin's lymphomas during same period. Small Intestinal lymphomas formed 34.50% of all GI NHL. The characteristics of the 49 patients are given in tables 2 and 3. Male preponderance was noted, with a sex ratio of 2:1 (Table- 2). Abdominal pain was the most common symptom followed by detection of palpable mass in abdomen and iron deficiency anemia. The overall 5-year survival rate was 47.8%. Early stages had a better prognosis. Stage I & IIA showed more than a 75% survival compared to IIB & III, where the survival was only 60 % and 33.3%, respectively (Table- 5). High-grade lymphomas have shown a relatively better rate of disease free survival of 43% at 5 years (Table- 5). The 4 cases in which the histological subtyping was not possible also behaved like the high-grade subtype with a 50% 5 years survival. The low-grade lymphomas have

Table 2 : Patients characteristics (n=49)

Sex	
Male	33
Female	16
Age	
Range	(15-67)
Mean	33

Table 3 : Patients Staging

I (A+B)	6
IIA	9
IIB	14
III	16
IV	4

Table 4: Subtype of patients histology

A- Low grade (13 cases)	
Follicular small cleaved	4
Diffuse small cleaved	9
B- Intermediate grade (14 cases)	
Diffuse large cleaved cell	14
C- High grade (17 cases)	
Lymphoblastic	8
D.L.C. Immunoblastic	4
Small non-cleaved	5
D- Unclassified (5 cases)	

Table 5: Five years Survival and Disease Free Survival rate according the subtype of lymphoma

Grade	No	5 years.survival rate	D.F.S
Low grade	13	17%	--
Intermediate grade	14	33%	33%
High grade	15	67%	43%
Unclassified	5	75%	50%

Table 6: 5 years Survival and Disease Free Survival rate according complete resection of the tumor

Patients	No.	5 years survival rates
patients how had complete resection	31	67%
patients how had not complete resection	18	27%

Discussion

GI-NHL is often misdiagnosed as carcinoma at first, until a histologic diagnosis has been established. The frequency of primary GI lymphoma in our series was similar to the reported frequency in western literature.(6,9) Abdominal pain, GI bleeding and perforation are the reported common presenting symptoms.(10,11)

The clinical picture was similar in our series except for a lower incidence of perforations. Among the various histological subtypes lymphocytic lymphomas predominant in the reported literature.(10,12) Our series of small intestinal lymphomas revealed a survival advantage for high-grade lymphomas. The unclassified group showing a better survival would have been in the high-grade subtype. Histological subtypes have not been shown to be a major determinant of survival in several series.(6,9,13) The stage of the disease correlates well with the prognosis.(9, 10, 11) We have used a classification prepared by Crowther and Blackledge.(8) Staging was done retrospectively with the information available from the case records and this may have resulted in a minor misclassification of stages. This might probably explain the lower survival observed in the stage I cases. The treatment options are surgery, radiation and chemotherapy. The initial treatment is almost always surgery and it is reported that surgical removal of the primary tumor significantly influences survival.(9) This may be due to the fact that the primary removal, the other modalities like radiation and chemotherapy are well tolerated without any danger of perforation. In our series of small intestinal lymphomas, all patients underwent an exploratory laparatomy. Since a preoperative diagnosis was not available in many cases, only a biopsy was done and the lesion was considered inoperable. Post-surgical treatment also varied depending on patient related factors and physician preferences. Shih-LY, et al(14) have reported an overall survival and disease-free survival rates for non-IPSID patients. Those who were treated with chemotherapy in locally advanced disease were 59% & 54%, respectively. In our study, most patients had widespread disease. Thus, the 5-year overall survival and disease free survival rates were 47.8% & 43.4%, which is similar to the reported results.(12, 13, 14, 15) . The conclusion is that intensive chemotherapy with CHOP protocol provides long-term survival and disease-free survival rates in advanced, non-IPSID, primary small intestinal lymphoma and patients who had complete resections of their tumors have shown a relatively better rate of disease free survival, 67% at 5 years (Table- 6).

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