Primary Gastric Lymphoma: Clinicopathologic Study of Gastric Lyphoma Casess and the Treatment Option of Choice

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Abstract
Introduction: Lymphoma may involve the gastrointestinal tract either primarily or as a manifestation of extensively disseminated systemic disease. Stomach being the most frequent site of primary gastrointestinal lyphoma, followed by the small bowel and colon respectively (1&2&3). For diagnosis of pimary small intestinal lymphoma (PSIL), one most satisfies the criteria specified by Dawson and coworkers.(5) Gastric lymphoma is a common presentation of non-Hodgkin's lymphoma. Controversy reigns about many aspects of its classification and management, especially regarding roles for surgical resection.The aim of this study is evaluation of 5 years survival and methods of treatment of primary gastric lymphoma in a group of Iranian patients.
Methods: The authors review the clinical features, staging, pathology, prognosis, and management of 30 patients with an emphasis on the role of chemotherapy, surgical resection and radiotherapy of 71 gastrointestinal lymphoma cases.
Results: A total of 30 patients (19 male and 11 female) with a mean age of 51 years and a range of 34 – 68 years were included in the study. The frequency of primary gastric lymphoma in our series was 42% of the total of primary gastrointestinal lymphoma. The overall survival rate was 47.8% at 5 years. Staging usually was completed using noninvasive techniques. Patients with stage I or II disease were treated with Surgery (gastric resection) and chemotherapy showed improved Free Disease Survival (FDS) of 67% at 5 years. The five-year survival for stage I, II, III and IV patients were 87%, 61%, 25%, and 11% respectively, and the five-year survival for low grade and high grade were 91% and 56%, respectively. Stage III or IV and inoperable primary gastric lymphoma were treated with chemotherapy and radiotherapy showed improved Free Disease Survival (FDS) of 67% at five years. The five-year survival for stage I, II, III, IV were 87%, 61%, 25% and 11% respectively, and the five year survival for low grade and high grade were 91% and 56% respectively.
Conclusion: Early stage disease and high-grade Lymphoma have a better prognosis and patients who have complete surgical removal of primary tumor and chemotherapy.

Key words: Primary gastric Lymphoma, Treatment

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Introduction
Lymphoma is generally classified as Hodgkin's disease or, for a lack of better term, a non-Hodgkin's type.(1,2) Lymphoma may involve the gastrointestinal tract either primarily or as a manifestation of extensively disseminated systemic disease.(1,2,3) The latter occurs more often and may be nodal or extranodal in origin. Primary extranodal lymphoma constitutes 25% of the non-Hodgkin's lymphoma cases in North America and up to 50% in parts of Europe and the Far East.(1,2,4) The most common site of extranodal non-Hodgkin's lymphoma is the stomach, which represents approximately 24% of all primary extranodal lymphoma in the End Results Groups Cancer Registries in the United States.(1,2,4) Compared with carcinoma incidence, non-Hodgkin's lymphoma is rare, representing 2% to 8% of all gastric malignancies, 2-5 but its incidence is increasing.(6-8) At least

60% of gastrointestinal lymphomas arise in the stomach. Gastric lymphomas are considered primary when the stomach is predominantly involved, and the intra-abdominal lymphadenopathy, if present, corresponds to the expected lymphatic drainage of the stomach. Patients with palpable subcutaneous nodes, mediastinal lymphadenopathy, or abnormal leukocytes on peripheral blood smear or bone marrow aspirate are excluded.[7] The criteria also exclude those with splenic or liver involvement. These strict criteria exclude many advanced cases, which can result in an underestimate of the frequency of the disease.[7,8] Other series have included patients with predominant gastric involvement in whom the stomach appears to be the primary site on clinical judgment,[8] thus including nodal lymphomas that have spread to the stomach. The definition of the Danish lymphoma group is predicated on the assumption that patients with primary gastric lymphoma have more than 75% of their disease volume in the stomach, based on clinical and radiological staging.[7,8,9] In the literature, almost every aspect of this entity is controversial, including its definition. Neither the staging system nor the histologic classification is uniform, and there are many types and subtypes with varying degrees of malignancy. The major controversy centers on the therapeutic options, and treatment continues to differ among major institutions. In 1961, criteria proposed by Dawson et al [10,11,12] to define intestinal lymphoma were subsequently applied to gastric lymphoma as well.[6,7,13]

Methods

In this study based on 71 patients who presented with gastrointestinal lymphoma, seen atthe department of Hematology and Oncology, Isfahan, Saied–al Shohada Medical center, during the period 1990-2000. The occurence was 30 in the Stomach, 24 in the Intestine, 8 in the Ileoccal region, 5 in the Rectosigmoid and in the 4 cases, multiple sites in the gastrointestinal tract were involved. Gastric lymphomas are considered primary when the stomach is predominantly involved, and the intra-abdominal lymphadenopathy, if present, corresponded to the expected lymphatic drainage of the stomach. Patients with palpable subcutaneous nodes, mediastinal lymphadenopathy, or abnormal leukocytes on peripheral blood smear or bone marrow aspirate were excluded. The criteria also excluded those with splenic or liver involvement. Evaluation of patients included physical examination, full blood counts, liver and renal function tests and bone marrow examination. Stage groupings were done retrospectively applling the Crowther and Blackledge[8] staging system (Table 1). All patients had gastroscopy and 23 patients of 30 had laparatomy and an attempt was made at complete resection of stomache (total gastrectomy). Histopathology slides were reviewed and all cases were classified according to International Working Formulation. Post diagnosis and staging treatment modality was decieded on the base of the patients, the type of histology of primary gastric lymphoma, staging, general condition, and extent of surgical resection. The goals of staging are to provide an insight into prognosis and a sound basis for the planning therapy. A combination of clinical, radiological, and surgical procedures may be required to define accurately the stage of each patient.

Table 1: Staging of GI Lymphoma (Crowther D A. Blackledge G)

I	A Single tumour confined to gut. B Multiple tumours confined to gut
II	A Tumour with local lymph node involvement. B Tumour with local extension to adjacent tissues.
III	C Tumour with proliferation and peritonitis. A Tumour with widespread lymphodenopathy.
IV	A Tumour with disseminated disease in non-lymphoid tissue

Results

A total of 30 patients (19 male and 11 female) with a mean age of 51 years and a range of 34 – 68 years were included in the study. Many patients experience symptoms, which are vague and nonspecific, for four to 10 months prior to diagnosis. Symptoms were mostly referable to the upper gastrointestinal tract and resemble peptic ulcer disease or gastritis. The most common complaints were epigastric pain (100%), weight loss (80%), nausea, and vomiting 74%.Occasionally, an abdominal mass is palpable. Lymphadenopathy is rare (3 of 30 cases), and patients often have no physical signs.Perforation, bleeding, or obstruction are

uncommon. Post-laparotomy and total gastroctomy (groupe 1) in 17 cases and in 13 of 30 (groupe 2) with no gastric resection. chemotherapy was made with CHOP (Cyclophosphamid 1000 mg/m, Adriamycin 50 mg/m. Vincristine 1.4 mg/m and Prednisolone 40 mg/m) repeated once in 15 days. A total of 6 cycle were administered protocol depending on the patient's general condition, completeness of surgery and histological subtype.The subtype of lymphoma were Low grade Lymphoma 17patients (57%) and high-grade Lymphoma 13 cases(43%).The frequency of primary gastric lymphoma in our series was 42% of all patients of primary gastrointestinal lymphoma. The stages were 7 cases in stage I (23%), 9 cases in stage II (30%), 9 cases in stage III (30%) and 5 cases in stage IV(17%).According to stage of patients, the overall survival rate was 47.8% at 5 years. Early stage disease and high-grade Lymphoma had a better prognosis and patients who had complete surgical removal of primary tumor and chemotherapy shown a relatively better of Free Disease Survival (FDS) of 67% at 5 years. the five-year survival for stage I, II, III and IV patients were 87% , 61%, 25% and 11% respectively. The five-year survival for low grade and high grade was 91% and 56%, respectively.

Discussion

The frequency of primary gastric lymphoma in our series was slightly more than the reported frequency in western literature.[11,12,13] The most common complaints are epigastric pain, weight loss, nausea, and vomiting. The prognosis of gastric lymphoma is more optimistic than that of gastric carcinoma or intestinal lymphoma.[8,14,15,16] Advocates of surgery argue that excision is necessary for accurate staging and histologic classification as the pathologist is given the whole specimen for examination rather than a small endoscopic biopsy specimen.[5,6,18] The stage of primary gastic lymphoma is one of the most important prognostic factors[7,17,18], Our report indicates a worse prognosis in disseminated disease (stage III and IV) than in localized disease (stage I and II). Involvement of regional lymph nodes are other prognostic factors associated with a decreased survival rate. The main concern with nonsurgical treatment is that chemotherapy and radiotherapy can lead to necrosis of the tumor with resultant gastric perforation or bleeding.[6,12,23] The incidence of chemotherapy-induced complications is variable and has been reported to be as high as 13% to 25%.[17,19,23] Surgical excision has been the mainstay of treatment[19,28]. Several reports show superior outcome with surgical resection in the early stages of disease.[28] Surgical intervention is not indicated for stage III or stage IV disease unless complications or limited residual disease occurs following chemoradiation.[19,23,28] Patients should undergo repeated endoscopic biopsies to confirm the diagnosis and accurately define the histology. Patients with a low-grade B-cell MALT-type lymphoma with H pylori infection can receive antibiotics with careful follow-up and reassessment.[20,21,22,25] Those with stage I and stage II disease if resection is performed, it should be conservative since residual disease can be managed with adjuvant therapy.[16,20-24] To define more accurately the indications of different therapeutic options in gastric lymphoma, more prospectively randomized studies are needed that involve a large number of cases and multi-institutional trials. Japan has the highest number of cases, but investigations there are refractory to performing prospective, randomized trials. Interestingly, while Europe and the United States report success for medical treatment of gastric lymphoma, a recent report from Japan advocates total gastrectomy for early gastric lymphoma and biopsy with no resection.[14,23] Six deaths were disease related, and two died of treatment complications.[19,25.28] Interestingly, two patients required surgery one for progressive disease and the other for treatment-induced cicatrization and obstruction. The five-year survival rate and disease-free survival rate for the whole group were 73% and 62%, respectively. Another report14 analyzed 50 patients with gastrointestinal lymphoma, of which 25 were gastric in origin. They were treated with radiotherapy, surgery, or both. The five-year survival rate was equivalent for those treated with radiotherapy alone or in combination with surgery (75%) and was superior to that of the group treated with surgery only. Many of our patients with gastric lymphoma had been treated for peptic ulcer disease in the past. The low specificity in endoscopic diagnosis of gastric lymphoma is mainly due to the

submucosal development of the lesion. Thus, it is necessary to obtain deep gastric biopsies if the macropscopic appearance of the stomach suggest the possibility of a lymphomatous lesion. Stage of the disease and grade of the lesion are the most significant prognostic factors that consistently and independently influence outcome and survival in gastric lymphoma. In one study,27. A report27,29 showed that relapse may be localized or generalized; it occurred in 22% of 244 patients who were followed for five years. Depth of invasion and serosal penetration are other adverse variables. the five-year survival rate for T1, T2, and T3 disease was 82%, 65%, and 24%, respectively.[19,28] T-cell lymphoma is less common but more aggressive than its B-cell counterpart. Superficial spreading and nodular types have better prognoses than other types.[16,28,29] Lesions with a higher index of cell proliferation as measured by monoclonal antibody Ki-67 or MIB1 are more aggressive.[5,6,18,28] Patients with aneuploid lymphoma have a poorer survival and disease-free survival than those with diploid tumors.[27,29] The concept of early gastric lymphoma has been introduced in Japan and defined as disease limited to the mucosa or submucosa, irrespective of lymph node status.[9,29] Kitamura et al9 described 10 cases and reviewed another 202 patients from the literature with this entity. They reported a five-year survival rate of 95% following resection. Stage I and stage II disease is usually amenable to curative resection, but the resectability rate in all patients regardless of stage ranges from between 52% to 76%.[16,28], Nonresectability is usually due to metastatic disease or coexistent morbid conditions. The aim of surgery is to excise all the tumor with negative margins, but this goal must be balanced against the morbidity of the operation and the resulting quality of life.[19,27] Thus, subtotal gastrectomy is preferable to total gastrectomy or more radical operations when the gross margins are negative.[27,28] Positive microscopic margins can be controlled later with adjuvant therapy.[4,23,17,28,29] In a prospectively randomized multicentric study from France[23], the incomplete resection status did not influence survival, relapse, or disease-free survival because all patients received adjuvant chemotherapy. Our policy is to try surgical resection for patients who are considred to surgical candidates, followed by adjuvant chemotherapy with or without radiotherapy, depending on stage and extent gastric B- Cell Mucosa Associated Lymphoid of the disease.[25,26,27]

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