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RESEARCH ARTICLE

Gastric and non-gastric marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue: A single-center experience

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ABSTRACT

Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) is a distinct lymphoma with specific clinical and pathological features that occurs in diverse anatomic locations. We conducted this retrospective study to demonstrate our experience in patients with MALT lymphomas and compare our results with the literature.

We studied 23 patients with histologically confirmed diagnosis of MALT lymphomas (12 with gastric, 11 with non-gastric localization) treated during the past 13 years. The female/male ratio of patients was 15/8 with a median age at presentation of 56 years (range 27-88 years). 16 patients (70%) with stage I and II, 7 patients (30%) with stage III and IV were admitted. At presentation 93% of patients had good performance status (ECOG<2) and 5 (22%) had B-symptoms.

There was no difference between gastric and non-gastric MALT lymphomas when compared with sex, age, ECOG performance status, stage of the disease. Patients were treated with different treatment modality; *H. Pylori* eradication only (8.6%), radiotherapy only (21.7%), surgery alone (4.%) or followed by radiotherapy (26%) or chemotherapy (21.7%). All the patients are alive with a median 33 months (range 8-153 months) of follow-up and the 5- year PFS in gastric lymphoma and non-gastric lymphoma were 86% and 84% respectively with no statistical difference (p=0.5).

Because of the indolent course the prognosis of MALT lymphoma was good regardless of the treatment modalities. The treatment choice should be patient-tailored, taking into account the site, stage, age and other clinical characteristic of patient.

Key Words: MALT, gastric, lymphoma, NHL

ÖZET

Mide ve mide dışı marjinal zon B-hücreli malt lenfoma olgularımız

MALT lenfomalar genellikle midede görülmekle birlikte tükürük bezleri, tiroid, deri, orbita, akciğer, meme, prostat, böbrek gibi çeşitli bölgelerde mide dışı yerleşim de gösterebilmektedir. Bu çalışmada, merkezimizde 1992-2006 yılları arasında tanı konulan MALT lenfomalı 23 olgu klinik bulguları ve tedavi yaklaşımları açısından retrospektif olarak değerlendirilmiştir. 15'i kadın, 8'i erkek olan hastaların medyan yaşı 55 (27-88) yıl olup, 12'si (%52) mide, 11'i (%48) mide dışı (7 parotis tükrük bezi, 2 akciğer, 1 tiroid, 1 kolon) yerleşimlidir. Her iki grup arasında medyan yaş ve cinsiyet açısından farklılık saptanmamıştır. Tanı anında olguların %93'ü iyi performans (ECOG<2) göstermektedir. %22'sinde B-semptomları eşlik eden olguların %70'inde erken evre (evre I-II) hastalık belirlenmiş; klinik evre ve B semptomları karşılaştırıldığında gruplar arasında fark bulunmamıştır. Hiçbir hastada kemik iliği tutulumu saptanmamıştır. Hastalara, hastalık yerleşimi, klinik evre ve tanı tarihine göre farklı tedaviler (1 olgu tedavisiz izlemde, 2 olgu sadece H.pilori eradikasyonu, 3 olgu antrasiklin içeren kombine kemoterapi rejimleri, 5 olgu sadece lokal radyoterapi, 12 olgu cerrahi bunların 5'i kemoterapi, 6'sı radyoterapi ile kombine) uygulanmıştır. Lokalize mide lenfomalı tüm hastalara helikobakter pilori eradikasyon tedavisi de başlanmıştır. Medyan 33 (8-153) aylık izlemde, tedavi alan tüm hastalarda tam remisyon sağlanmış, akciğer yerleşimi olan ve sadece cerrahi ile tedavi olan bir hastada oküler adnekste relaps (%4) gelişmiş olup, tüm hastalar yaşamdadır. 5 yıllık progresyonsuz sağkalım oranı mide-MALT lenfomalarda %92 iken, mide dışı lenfomalarda %86 olarak belirlenmiş, gruplar arasında anlamlı farklılık bulunmamıştır. Tedavi seçeneği ne olursa olsun MALT lenfomalar genellikle iyi seyirlidir: en uygun tedavi seçeneği net olmamakla birlikte, hastalığın yerleşimi, evresi, hastanın yaşı ve diğer klinik özellikleri göz önünde bulundurularak kararlaştırılmalıdır.

Anahtar Sözcükler: MALT, gastrik, lenfoma, NHL

INTRODUCTION

Mucosa-associated lymphoid tissue (MALT) lymphoma was first described by Isaacson and Wright in 1983 [1] and recognized as a distinct lymphoma with clinicopathologic features in the Revised European American Lymphoma (REAL) [2] and World Health Organization (WHO) classification systems of lymphoma [3]. Far from being rare, MALT lymphomas account for approximately 7% to 8% of all non-Hodgkin's lymphomas, being the third most frequent histologic subtype after diffuse large B-cell lymphoma and follicular lymphoma [4-6]. MALT lymphomas are mostly localized to the stomach but have also been described in various non-gastrointestinal sites such as salivary gland, thyroid, skin, orbit, lung, breast, liver, prostate and kidney [4-18]. In these sites, MALT lymphomas arise from extranodal sites, often in the setting of chronic inflammatory disorders in response to either infection such as *Helicobacter pylori* (HP) gastritis in the stomach, or autoimmune processes like Hashimoto's thyroiditis and Sjögren's syndrome [4,19-21].

The etiology, sites of presentation and clinical and biological behavior remain variable and heterogeneous. The optimal treatment in MALT lymphoma has not yet been clearly defined. Surgery alone or combined with chemotherapy or radiotherapy has been according to disease site, stage and clinical characteristics of the individual patient.

We conducted this study to demonstrate our experience in patients with MALT lymphomas and compare our treatment modality and results with those available in the literature.

MATERIALS and METHODS

We retrospectively and thoroughly researched the records of 618 patients with non-Hodgkin lymphoma (NHL) treated in our hematology unit between 1992 and 2005. Among these cases, 23 (3.7%) patients with biopsy-proven MALT lymphomas according to REAL / WHO classification criteria with different localizations were considered eligible for this study. Histologic materials were reevaluated by our hematopathologists, with appropriate immunophenotypic techniques establishing the diagnosis. Patients with transformed lymphoma (MALT lymphoma with areas of diffuse large-cell lymphoma) were not included in this study. Staging included complete blood count (CBC), serum lactate dehydrogenase (LDH) level, computed tomography of the neck, thorax, and upper and lower abdomen, and bone marrow biopsy examination. B-symptoms were defined as recurrent fever of more than 38°C, night sweats and unexplained weight loss of more than 10% of body weight within six months prior to diagnosis. Disease stage was defined according to Ann Arbor criteria [22], location of extranodal disease, and presence of B-symptoms. The distribution among the International Prognostic Index (IPI) risk groups was defined according to published criteria [23]. Upper gastrointestinal endoscopy and gastric biopsy were performed in all patients with gastric lymphoma, but not in the patients with non-gastric disease. HP was documented in biopsy specimens in 6 of 12 patients (50%) with gastric lymphoma.

Therapeutic approaches:

Patients were treated according to time of diagnosis, disease localization and the stage. Patients with localized lymphoma were treated with surgery, local radiotherapy, and/or single agent or anthracycline-combined chemotherapy. Some patients received adjuvant chemotherapy, radiotherapy or both after surgery. Patients with localized gastric lymphoma with HP infection were treated with antibiotics (amoxicillin and clarithromycin) and omeprazole. Patients with advanced disease were treated with multidrug regimen such as CHOP (standard dose of cyclophosphamide, doxorubicin, vincristine, and prednisone) or a CHOP-like regimen.

Response criteria:

Complete response (CR) was defined as the complete absence for at least six weeks of all clinical evidence of lymphoma, while reduction of at least 50% of known disease for at least six weeks was rated as partial response (PR). Overall survival (OS) was calculated from time of diagnosis to time of death or last follow-up. Progression free survival (PFS) was measured from time of diagnosis to time of treatment failure, relapse/progression or death from lymphoma.

Statistical analysis:

Descriptive analysis was made on computer using SPSS for Windows. Survival analysis was calculated using the life table method of Kaplan-Meier and differences between survival curves were estimated using the log-rank test. Differences of variables between two groups (gastric and non-gastric MALT lymphoma) were

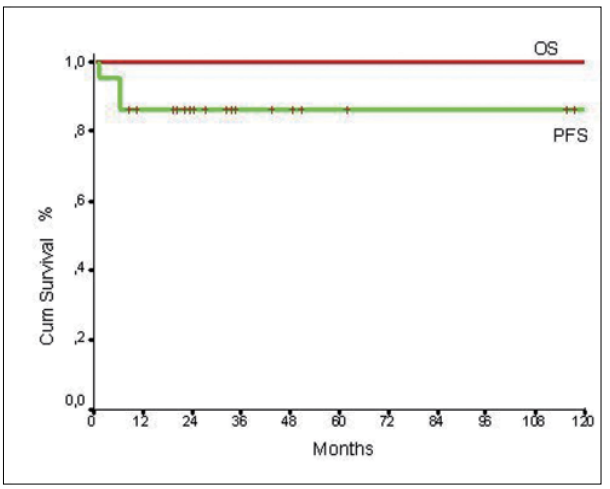

Figure 1. Overall survival (OS) and progression free survival (PFS) in all patients with MALT lymphoma.

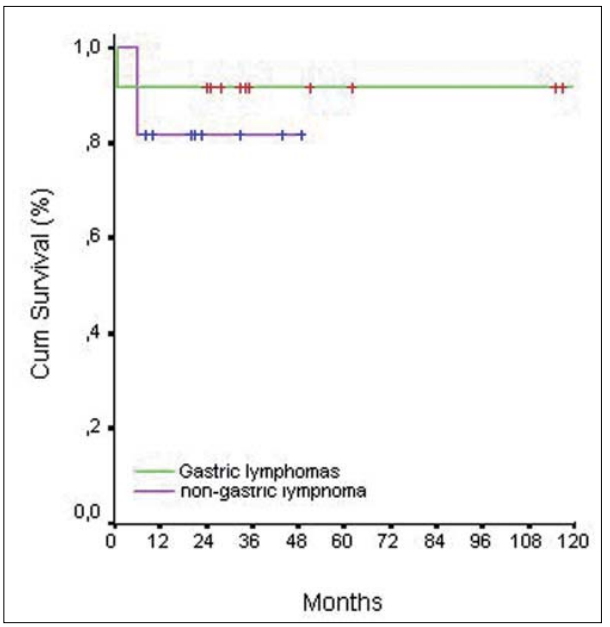

Figure 2. Progression free survival (PFS) in MALT lymphomas with gastric and non-gastric localization.

analyzed with X^2 test, Fisher's exact test and Mann-Whitney U test.

RESULTS

Twenty-three patients with MALT lymphoma were included in the study. The female/male ratio of patients was 15/8, with a median age of 56 years (range 27-88 years) at presentation. Localizations of MALT lymphoma were gastric in 12 (52%) and non-gastric in 11 (48%) (7 salivary gland, 2 lung, 1 thyroid, 1 colon). There was no statistically significant difference between the gastric and non-gastric groups with respect to median ages [51 years (range 27-88 years) and 60 years (range 31-77 years), respectively; p>0.1]. There was also no difference according to sex between groups (p=0.12). At presentation, 93% of patients had good performance status (Eastern Cooperative Oncology Group-ECOG<2) and 5

Table 1. Clinical characteristics of patients

Features	*No. of patients (%)*
Age	
Median	56 years
Range	27-88 years
Sex	
Male	8 (35%)
Female	15 (65%)
Performance status	
ECOG score 0-1	21 (92%)
ECOG score 2-4	1 (4.3%)
Unknown	1 (4.3%)
Serum LDH level	
Normal	5 (22%)
Elevated	12 (52%)
Unknown	6 (26%)
Ann Arbor Stage	
I-II	17 (74%)
III-IV	6 (26%)
B-symptoms	
Present	5 (22%)
Absent	18 (78%)
Disease site	
Stomach	12 (52%)
Salivary gland	7 (30%)
Lung + orbit	1 (4.3%)
Lung	1 (4.3%)
Thyroid	1 (4.3%)
Colon	1 (4.3%)
Diagnostic procedure	
Endoscopic biopsy	10* (44%)
Subtotal gastrectomy	3 (13%)
Subtotal thyroidectomy	1 (4.3%)
Lobectomy	1 (4.3%)
Parotidectomy	7 (30%)
Transthoracic biopsy	1 (4.3%)
Nodal involvement	
Present	6 (26%)
Absent	17 (74%)
IPI	
Low risk	19 (82.5%)
Low to intermediate risk	3 (13%)
High to intermediate risk	1 (4.3%)
Detection of *H. pylori*	6 (50%**)

*1 patient diagnosed with colonoscopic biopsy.
** 50% of patients with gastric localization.

Table 2. First-line treatment according to localization and stage in patients with MALT lymphoma

	Patient number (%)				
Therapeutic Modalities	*Gastric Lymphoma*		*Non-Gastric Lymphoma*		*Total (%)*
	Stage I-II	Stage III-IV	Stage I-II	Stage III-IV	
No treatment	1 (4.3%)	-	-	-	1 (4.3%)
Anti-HP treatment only	2 (8.6%)	-	-	-	2 (8.6%)
Chemotherapy (CT)			-		
With anthracycline	-	1 (4.3%)		2 (8.6%)	3 (13%)
Radiotherapy (RT) only	5 (21.7%)	-	-	-	5 (21.7%)
Surgery					
Surgery only	-	-	-	1 (4.3%)	1 (4.3%)
Surgery and RT	-	-	6 (26%)	-	6 (26%)
Surgery and CT	3 (13%)	-	-	2 (8.6%)	5 (21.7%)
Surgery and RT and CT	-	-	-	-	-

(22%) had B-symptoms. Sixteen patients (70%) with stage I and II and 7 patients (30%) with stage III and IV were admitted. No statistically significant differences in stage and B-symptoms were found between groups (p=0.5 for disease stage, p=0.18 for B-symptoms). Seven patients (30%) had anemia and 12 patients (52%) had elevated levels of LDH. There was no statistical difference in LDH levels and hemoglobin levels between the two groups (p=0.12, p=0.2). Most patients (82.5%) were at low risk according to IPI and 26% of patients had nodal involvement at presentation. None of the patients had bone marrow involvement.

Clinical characteristics of all patients are demonstrated in Table 1. Ten (44%) patients with gastric MALT lymphoma were diagnosed using endoscopic biopsy procedure. Subtotal gastrectomy was performed in 3 of the patients with gastric lymphoma (13%). Parotidectomy was performed for diagnosis and also first-line treatment in all patients with parotid gland lymphoma. One of 2 patients with lung involvement was diagnosed with transthoracic biopsy; the other was diagnosed and received first-line treatment with lobectomy. Subtotal thyroidectomy was performed in 1 patient with thyroid lymphoma.

All the patients were alive with a median of 33 months (range 8-153 months) of follow-up. Only 1 patient with lung involvement treated with surgery relapsed six months after diagnosis with the mass on ocular adnexa. He was treated with local radiotherapy to eye and achieved second CR and was followed-up in CR for 16 months. First-line treatment details according to disease localization and stage are presented in Table 2. One patient with stage I gastric MALT lymphoma declined the treatment and was alive with disease without progression at three-years' follow-up. HP was identified in 6 (50%) patients with gastric MALT lymphoma. Two patients with stage I and HP-positive lymphoma in stomach achieved CR with only antibiotic and proton pump inhibitor treatment for HP eradication and were in CR for 2 and 3 years, respectively. Three patients (13%) received doxorubicin-based systemic chemotherapy, 5 patients (21%) radiotherapy only and 12 patients (52%) were treated with complete surgical excision (3 stomach, 7 salivary gland, 1 lung, 1 thyroid) -- 5 of them combined with chemotherapy (3 stomach, 2 salivary gland) and 6 of them combined with radiotherapy (5 salivary glands, 1 thyroid). All the treated patients achieved CR (95%) except 1 who was in partial remission.

Figure 1 shows OS and PFS of all patients with MALT lymphoma. The five-year PFS was 86% in all patients. The estimated five-year PFS was 84% in patients with non-gastric MALT lymphoma. Patients with MALT lymphoma involving stomach had 92% five-year PFS. No statistically significant difference was found between gastric and non-gastric MALT lymphoma groups with respect to PFS (p=0.5). Different therapeutic modalities, stage of the disease, IPI risk status, serum LDH and hemoglobin levels had no signifi-

cant influence on OS and PFS. Figure 2 shows the PFS curves of the two groups.

DISCUSSION

In a NHL classification project, MALT lymphoma ranked third preceded by diffuse large B-cell and follicular lymphomas, constituting 4% to 13% of the cases seen in individual cancer centers [24,25]. MALT lymphoma of the stomach remains the most common organ of involvement followed closely by salivary gland, lung, and thyroid involvement, respectively [4-11]. Disease often presents as localized disease, rarely involving bone marrow [4,11,26-27]. Bone marrow involvement was reported as 2% in a recently published prospective study of a large series including 140 patients with gastric and non-gastric MALT lymphomas by Raderer *et al.* [28]. At presentation, the majority of patients (66%) had stage IE and IIE disease. In the majority of retrospective series, the median age was reported as 59 to 61 years, and 55% to 62% were female [4,8-11].

Clinical characteristics of the patients included in the study confirm the specific features of the MALT lymphoma as outlined in the previous reports [4,8-11,26-28]. MALT lymphomas accounted for 3.7% of all NHL evaluated in our hematology unit. The stomach was the most common site of involvement followed by salivary gland, mostly parotid gland. Median age of 56 years (range 27-88 years) and female dominance were similar with the reported series [4,8,9,27]. 74% of patients with MALT lymphoma presented with stage I and stage II disease and 92% of patients had good performance status. B-symptoms were absent in 78% of all presented patients. 82.5% of patients had low-risk disease according to IPI. Upper gastrointestinal endoscopic biopsy was mostly used as diagnostic procedure and was performed in 77% of patients with MALT lymphoma localized to stomach. In the past, surgery was thought to be necessary for the diagnosis, staging, and treatment of gastric lymphomas. Currently, most patients can be adequately diagnosed by endoscopic biopsy. 75% of patients with non-gastric MALT lymphoma were diagnosed with surgery. Surgery was also instituted as first-line treatment in these patients.

Several lines of evidence suggest that gastric lymphoma arises from MALT acquired as the result of HP infection. HP can be demonstrated in a majority of cases with gastric MALT lymphoma and therapy to eradicate this microorganism results in a 55% to 80% complete regression of the disease [29-32]. For MALT lymphomas arising in non-gastric locations, etiologic agents have not been identified. However, predisposing conditions to MALT lymphoma of some specific sites such as Hashimoto's thyroiditis for thyroid MALT lymphoma and Sjögren's syndrome for salivary gland MALT lymphoma have been reported [27,33-35]. In our retrospective study, HP was demonstrated in 50% of patients with gastric MALT lymphoma. We did not identify any etiological agents or predisposing conditions such as autoimmune diseases in patients with non-gastric MALT lymphoma.

Clinically, MALT lymphomas behave as an indolent disease with prolonged clinical course. Patients have a good outcome with a long PFS and OS. No superiority of one therapeutic modality has been demonstrated in previously reported retrospective series [4,8,11,26]. Our patients with MALT lymphoma localized to the stomach with different stagings were treated with different therapeutic modalities. The majority of all gastric lymphomas (42%) with stage I and II disease were treated with local radiotherapy. Even though we observed HP in half of the patients, eradication was instituted in all patients with gastric involvement. Two patients with stage I disease received HP eradication only, achieved CR and were followed-up in CR for 2 and 3 years, respectively. Doxorubicin-based systemic chemotherapy was given to 4 patients with gastric involvement, and 3 (25% of gastric lymphomas) of them had subtotal gastrectomy before chemotherapy. The majority of patients with non-gastric MALT lymphoma (55%) were treated with surgery followed by radiotherapy. At a median of 33 months of follow-up, all the analyzed patients were alive with one relapse. One patient with gastric lymphoma has been followed up with disease without treatment. One patient with lymphoma localized to ascending colon achieved PR after treatment. A 95% CR ratio was achieved in all patients with MALT lymphoma. Five-year PFS of all patients and patients with gastric involvement were 86% and 88%, respectively. No statistically significant difference was found between gastric and non-gastric MALT lymphoma groups with respect to PFS (p=0.5). Different therapeutic modalities, disease stage, IPI risk status, serum LDH and hemoglobin levels had no significant influence on OS and PFS.

Despite abundant literature on the clinical features of MALT lymphoma, results defining the

optimal therapy have not yet been published. A recently published prospective study by Aviles *et al.* [36] demonstrated that chemotherapy was an effective treatment in low-grade MALT lymphoma and was well tolerated, in contrast to reports advocating the effectiveness of radiotherapy [6,7,9,27]. Aviles *et al.* [36] randomized 241 patients to surgery alone, radiation alone, or chemotherapy alone, with a median follow-up of 7.5 years. Three cycles of CHOP-21 followed by four cycles of CVP (cyclophosphamide, vincristine prednisone) were applied to patients. All the patients achieved CR and five-year OS was slightly superior in the chemotherapy-treated group (87%) than the surgery (80%) and radiotherapy (75%) arms (p=0.04).

Reports have shown that in patients treated with a variety of combinations of surgery, radiotherapy and chemotherapy, OS rates range from 80% to 95% at five years (4,7-9,27). The prognosis of MALT lymphoma was excellent regardless of treatment. In a multicenter retrospective series of 93 patients with gastric MALT lymphoma, no statistically significant difference was obtained in OS or PFS between patients who received different initial treatments: chemotherapy alone, surgery alone, surgery with chemotherapy or radiotherapy, or HP eradication [31]. In this series, five-year OS was 82% and in 49 patients treated with antibiotics alone for HP eradication, histologic regression was achieved in 67% of patients.

Because of the indolent course, the prognosis of MALT lymphoma was good regardless of the treatment modalities. The treatment choice should be patient-tailored, taking into account the site, stage, age and other clinical characteristics of the patient.

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