·Clinical Research·

Clinical features and prognosis of mucosa-associated lymphoid tissue lymphoma: a report of 90 cases

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[**Abstract**] **Background and Objective**: Mucosa-associated lymphoid tissue lymphoma is a histological type of marginal zone non-Hodgkin's lymphoma (NHL). Its clinical features and prognosis have seldom been reported because of its indolent clinical course. This study was to explore the clinical features and prognosis of this disease. **Methods**: Clinical data of 90 pathologically confirmed mucosa-associated lymphoid tissue lymphoma patients, treated from December 1997 to February 2007, were analyzed. **Results**: Of the 90 patients, 23 (25.6%) had gastric lymphoma and 67 (74.4%) had non-gastric lymphoma, with a median age of 52 (range, 13–77); 75 (83.3%) had stage I-II disease and 15 (16.7%) had stage Ⅲ–Ⅳ disease; 31 (34.4%) had multiple organ involvement and 40 (44.4%) had nodal involvement. The percentage of nodal involvement was significantly higher in non-gastric group than in gastric group (P=0.040). The complete remission (CR) rate after treatment was 72.1%. The patients were followed up for a median of 31.4 months. The 5-year overall survival rates of patients with and without nodal involvement were 58.7% and 88.4%, respectively (P=0.012). The median time to progression was significantly longer in patients with IPI score of 0–2 than in those with IPI score of > 2 (61.9 months vs. 5.2 months, P=0.005), and was significantly longer in patients who got CR after initial treatment than in those without CR (not reached vs. 15.0 months, P=0.030). In non-gastric lymphoma group, IPI score was an independent prognostic variable of overall survival (P=0.023). **Conclusions**: Mucosa-associated lymphoid tissue lymphoma should be considered as a kind of disseminated indolent lymphoma. The patients with non-gastric lymphoma are likely to have nodal involvement. Patients with poor prognostic factors should be treated more aggressively.

Key words: non-Hodgkin's lymphoma, mucosa-associated lymphoid tissue lymphoma, clinical features, prognosis

The definition of mucosa-associated lymphoid tissue (MALT) lymphoma was first made by Isaacson and Wright in 1983.[1] It is a kind of extra-nodal marginal zone B-cell lymphoma that derived from mucosa-associated lymphoid tissue, and is also classified as MALT lymphoma. MALT lymphoma accounts for approximately 7.6% of NHL,[2] whereas in domestic report, the percentage is 6.1%.[3] MALT lymphoma may derive from extensive anatomic sites

and the presenting symptoms are various, thus it is difficult to investigate clinical features and prognosis of this tumor. The domestic reports with large number of patients diagnosed as MALT lymphoma have been rare. This study was to explore the clinical features and prognosis of this disease retrospectively.

Materials and Methods

Clinical data. Tumor tissues of 90 patients with MALT lymphoma treated from August 1996 to February 2007 at the Cancer Center and the First Affiliated Hospital of Sun Yat-sen University were analyzed. The results of HE and immunohistochemical analysis were interpreted by pathologists in the Cancer Center of Sun Yat-sen University. All cases were classified according to the World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues. The collected data included sex, age, presence of systemic symptoms, bone marrow involvement, stage, PS score, hemoglobin, LDH level, HBV, nodal involvement, process of treatment, and so on.

Methods. To be consistent with the previous clinical studies,[4-6] we divided 90 patients into gastric group and non-gastric group. Statistical differences in patients' clinical parameters were evaluated by chi-square tests for categorical parameters and Mann-Whitney U test for continuous variables. Responses to treatment were categorized according to the criteria defined by the World Health Organization in 1999.[7] The WHO criteria for CR, PR, SD, and PD were used. Survival curves were constructed according to the method of Kaplan and Meier and compared with using the log-rank test. A Cox proportional hazard regression model was used in multivariate analysis. A two-tailed P value of less than 0.05 was considered significant. Overall survival (OS) was measured from the date of diagnosis to death or the date of the last contact. Progression-free survival (PFS) for all patients was taken from the time of diagnosis until disease progression or death. Time to progression (TTP) was defined from the time of diagnosis until disease progression. The analysis was carried out using the SPSS 13.0 software.

Results

Patients characteristics. The primary involved sites included stomach (23 cases, 25.6%), bowels (27 cases, 30.0%) and other organs, including lung, thoat-ring, conjunctiva and orbit, thyroid and salivary (40 cases, 44.4%). The median age was 52 years (13-77 years). Of the 90 patients, 48 were men and 42 were women, with a ratio of 1.1:1; 75 (83.3%) were at stage I-II, and 15 (16.7%) at stage III-IV. The nodal and multiple-organ involvement were found in 40 (44.4%) and 31 (34.4%) patients, respectively. Clinical characteristics of the 90 patients were shown in Table 1.

More patients in the non-gastric group had nodal involvement than that in the gastric group (χ^2=4.217, P=0.040). With respect to physical

Table 1 Clinical features of 90 mucosa-associated lymphoid tissue lymphoma patients

Item	Total [cases(%)]	Gastric group [cases (%)]	Non-gastric group [cases (%)]	*P* value
Sex				
Male	48(53.3)	10 (43.5)	38(56.1)	0.272
Female	42(46.7)	13 (56.5)	29(43.9)	
Age				
<60	60(66.7)	14 (60.9)	46(68.7)	0.494
≥60	30(33.3)	9 (39.1)	21(31.3)	
ECOG score				
0-1	86(95.6)	23(100)	63(94.0)	0.540
≥2	4 (4.4)	0 (0)	4 (6.0)	
Ann Arbor stage				
Ⅰ-Ⅱ	75(77.8)	22 (95.7)	53(79.1)	
Ⅲ-Ⅳ	15(22.2)	1 (4.3)	14(20.9)	0.130
LDH elevation	13(14.4)	5 (21.7)	8(11.9)	
IPI				
0-2	81(90.0)	22(95.7)	59(88.1)	0.468
>2	9(10.0)	1 (4.3)	8(11.9)	0.295
B symptoms	35(38.9)	13(56.6)	22(32.8)	0.044
Bone marrow involvment	1 (1.1)	0 (0)	1 (1.5)	1.000
Multiple organ involvment	31(34.4)	6(26.1)	25(37.3)	0.328
Nodal involvement	40(44.4)	6(26.1)	34(50.7)	0.040
Bulky disease	11(12.2)	3(13.0)	8(11.9)	1.000
Hemoglobulin <120 g/L	21(23.3)	13(56.5)	8(11.9)	<0.001
HBsAg positive	9(10.0)	3(13.0)	6 (9.0)	0.872

fitness and nutritional state, gastric MALT lymphoma was prone to have B symptom (χ^2=4.042, P=0.044) and lower hemoglobin level (χ^2=14.356, P<0.001) than the non-gastric group.

According to different stages, the initial treatments of 90 patients were shown in Table 2. For patients belonged to stage I-II, the treatment which was shown in sequence included chemotherapy (73.3%), surgery (65.3%), radiotherapy (14.7%) and anti- Helicobacter pylori infection treatment (4 gastric MALT lymphomas, 5.3%). For patients of stage III-IV, anthracycline-based chemotherapy, particularly the CHOP regimen, were the major treatments (93.3%). In the whole group, 7 patients received anti-CD20 antibody treatment and 2 patients underwent fludarabine involved regimen. Only 1 patient received interferon treatment.

Efficacy. Of the 90 patients, 4 did not receive any treatment. Among the other patients, 62 got CR or CRu, including 57 in stage I-II and 5 in stage III-IV. The total CR rate was 72.1%. Sixteen patients achieved PR and the total PR rate was 90.1%. In the gastric group, 18 patients got CR or CRu and the CR rate was 81.8%; while in the non-gastric group, CR or CRu was acquired in 44 patients with the CR rate of 71.0%. The CR rate between two groups was almost the same (χ^2=0.989, P=0.320). All 4 patients who received anti-Helicobacter pylori infection treatment achieved CR.

Survival analysis. Till March 2007, 8 patients (5.9%) were lost to follow-up. The follow-up rate was 91.1%. The median follow-up time was 31.4 months. Totally 17 patients were died of the tumor including 2 gastric cases and 15 extra-gastric cases; 34 experienced relapse including 7 gastric cases and 27 extra-gastric cases. The total rate of progression was 37.8%.

The 5- and 10-year OS rates for all patients were 75.7% and 70.3%, respectively. The median survival time was not reached. The 5- and 10-year PFS rates for all patients were 49.6% and 44.6%, with a median TTP of 58.9 months (95%CI: 25.6-92.3 months).

The 5-year OS rates of gastric and extra-gastric groups were similar (94.4% vs. 69.7%, P=0.173). The median OS of both groups were not reached. In addition, the TTP of gastric group was not reached and that of extra-gastric group was 40.9 months (95%CI: 12.5-69.3 months) (P=0.215).

Table 2 Initial treatments of 90 mucosa-associated lymphoid tissue lymphoma patients

Treatment	Total [cases(%)]	Stage Ⅰ-Ⅱ group [cases(%)]	Stage Ⅲ-Ⅳ group [cases (%)]
Chemotherapy	69(76.7)	55(73.3)	14(93.3)
Only chemotherapy	22(24.4)	14(18.7)	8(53.3)
Radiotherapy	16(17.8)	11(14.7)	5(33.3)
Only radiotherapy	1 (2.2)	1 (1.3)	0 (0)
Radiotherapy and chemotherapy	5 (5.6)	3 (4.0)	2(13.3)
Surgery	54(60.0)	49(65.3)	5(33.3)
Only surgery	12(13.3)	12(16.0)	0 (0)
Surgery and chemotherapy	33(36.7)	31(41.3)	2(13.3)
Surgery and radiotherapy	2 (2.2)	2 (2.7)	0 (0)
Surgery and chemoradiotherapy	7 (7.8)	4 (5.3)	3(20.0)
Anti-*Helicobacterpylori*(*Hp*) treatment	4 (4.4)	4 (5.3)	0 (0)
Only anti-*Hp* treatment	1 (1.1)	1 (1.3)	0 (0)
Anti-*Hp* and chemotherapy	2 (2.2)	2 (2.7)	0 (0)
Anti-*Hp* and chemoradiotherapy	1 (1.1)	1 (1.3)	0 (0)
No treatment	4 (4.4)	4 (5.3)	0 (0)

Prognostic factors analysis. The following characteristics were involved in the univariate analysis: sex, age, presence of systemic symptoms, Ann Arbor stage, multiple-organ involvement, PS score, IPI , LDH level, nodal involvement, bulky disease, efficacy of treatment, and so on. The results showed Ann Arbor stage, PS score, IPI, efficacy of treatment and nodal involvement were clinical features that contributed mostly to the OS or PFS (Table 3).

Considering Ann Arbor stage and PS score were factors involved in the IPI, we only brought IPI, efficacy of treatment and nodal involvement into the Cox proportional hazard regression model for multivariate analysis. The results showed nodal involvement was independently associated with poor OS (P=0.012). The 5-year OS in patients with or without nodal involvement was 88.4% and 58.7%, respectively (Fig. 1); IPI (P=0.005) and efficacy of treatment (P=0.030) were independently negative

Table 3 Univariate prognostic analysis of 90 mucosa-associated lymphoid tissue lymphoma patients

Variate		Overall survival		Progression-free survival	
		χ^2	*P* value	χ^2	*P* value
Age	>60	0.634	0.426	0.727	0.394
	≤60				
Sex	Male	1.263	0.261	0.111	0.739
	Female				
B symptoms	Yes	1.029	0.310	0.159	0.690
	No				
Albumin level	≥35 g/L	0.439	0.507	0.509	0.476
	<35 g/L				
Ann Arbor stage	Ⅰ-Ⅱ	9.397	0.002	24.068	<0.001
	Ⅲ-Ⅳ				
Multiple-organ involvement	Yes	1.001	0.317	0.564	0.453
	No				
ECOG score	≥2	30.514	0.000	118.749	<0.001
	<2				
IPI	>2	6.786	0.009	11.967	0.001
	≤2				
LDH level	Elevated	2.008	0.156	1.276	0.259
	Normal				
Hemoglobin	≥120 g/L	0.184	0.668	0.010	0.922
	<120 g/L				
Nodal involvement	Yes	6.06	0.014	3.949	0.047
	No				
Bulky disease	Yes	0.002	0.963	0.14	0.708
	No				
Efficacy of initial therapy	CR	5.931	0.015	4.993	0.025
	Not CR				

predictors for PFS. The median PFS in patients with IPI 0-1 and with CR was 61.9 months and not reached, while the median PFS in patients with IPI >2 and without CR was 5.2 months and 15.0 months (Figs. 2 and 3).

Due to the relatively small number of patients (23 cases), statistical analysis was not conducted in gastric group. In the univariate analysis for extra-gastric group, Ann Arbor stage, PS score, efficacy of treatment, nodal involvement and IPI were factors associated with OS. When efficacy of treatment, nodal involvement and IPI were involved in the multivariate analysis, results showed that IPI >2 contributed most to poor OS (P=0.023) (Fig. 4). The following factors were associated with PFS: Ann Arbor stage, PS score and IPI.

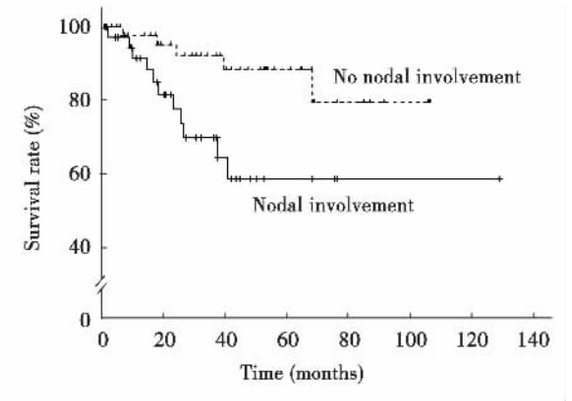

Figure 1 Overall survival curves of mucosa-associated lymphoid tissue lymphoma patients with or without nodal involvement

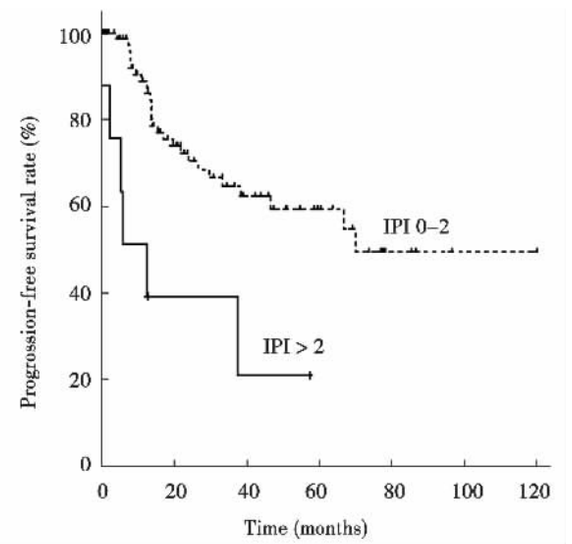

Figure 2 Progression-free survival curves of mucosa-associated lymphoid tissue lymphoma patients with IPI score of 0–2 or > 2

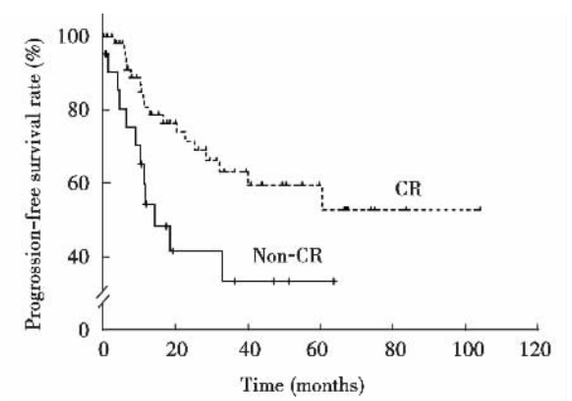

Figure 3 Progression-free survival curves of mucosa-associated lymphoid tissue lymphoma patients who got complete remission (CR) or not after initial treatment

Considering Ann Arbor stage and PS score were factors involved in the IPI, no multivariate analysis was conducted.

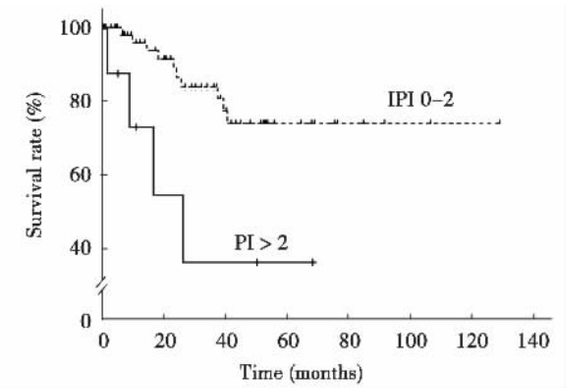

Figure 4 Overall survival curves of non-gastric mucosa-associated lymphoid tissue lymphoma patients with IPI score of 0–2 or > 2

Discussion

After more than 20 years of clinical research, MALT lymphomas are now recognized as a distinct subtype of indolent NHL with unique pathogenic, histological, and clinical features. Both the Revised European-American Lymphoma (REAL) classification in 1994 and the World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues in 2001 recognized MALT lymphoma as a discrete entity. This kind of tumor occurs in a number of anatomic sites including gastrointestinal tract, lung, conjunctiva and orbit, salivary gland and thyroid. Stomach is the most frequently involved organ,[1] but tumors derived from other organs are rare. Most of the previous clinical studies divided cases into gastric group and non-gastric group,[4-6] while several researchers still investigated this tumor as a whole group.[8, 9]

With respect to the clinical features of MALT lymphoma, the most controversial point is its nature of dissemination. In terms of traditional point of view, MALT lymphoma is rated as an located disease,[10] which is consistent with its indolent nature. Several recent studies with large number of patients challenged this point. In Lyons study,[11] 52% of patients were in advanced stage and 25% of them had bone marrow involvement. In Arcainis study,[4] 39% of cases had nodal involvement. The patients with advanced stage and bone marrow involvement accounted for 44% and 28%. Previous reports showed this character might reflect a special homing pattern.[12] In our report, cases with multiple-organ and bone marrow involvement accounted for 34.4% and 44.4%, which was consistent with the view that MALT lymphoma was a kind of systemic disease. Therefore all patients with MALT lymphoma should undergo extensive staging to evaluate the disease before initiation of therapy.

The percentage of nodal involvement in gastric MALT lymphoma was about 24%～38% in previous reports,[5, 9] similar to that in extra-gastric MALT lymphoma (21%～39%).[4, 6] To the best of our knowledge, this was the first study to disclose that the percentage of nodal involvement was significantly higher in non-gastric group than in gastric group (50.7% and 26.1%, P = 0.040). Considering the limited number of cases in the gastric group, further study with larger number of patients was warranted.

In the prognosis analysis, nodal involvement was an independent factor associated with OS in the whole group, similar to Thieblemonts[9] and Arcains[4] reports. A 2-stage dissemination of MALT lymphomas could be postulated in Zuccas study:[6] one phase in which the disease first disseminated to other MALT sites and the second in which lymph node involvement occurred. The higher rate of multiple extranodal localizations in cases with nodal involvement and a worse prognosis in the presence of both nodal involvement and multiple-organ involvement appeared in keeping with this hypothesis. In the 40 cases with nodal involvement in the current study, 21 had multiple-organ involvement (52.5%). In 50 cases without nodal involvement, only 10 developed multiple-organ involvement (20.0%). The difference was significant (P=0.001). The PFS in cases who had multiple-organ involvement with or without nodal involvement

was 28.6% and 48%, but was not significant. Therefore the result in our report supported Zuccas conclusion. Furthermore, the involvement of supradiaphragmatic lymph nodes in patients with gastrointestinal lymphoma was classified as stage IV in Lugano staging system,[13] which also indicated the importance of the nodal involvement. Thus, nodal involvement should be considered as a presentation of advanced disease, and this subset of patients should undergo more active treatment to improve the efficacy.

CR or not after initial treatment was an independent factor associated with OS in the whole group, which was consistent with Thieblemont's report.[8] The purpose of treatment was different in patients with MALT lymphoma of different stages. For patients in stage I-II and some in stage III, the treatment was curable and CR was important. For patients in stage IV, the treatment was incurable and the purpose for treatment was to delay the progression. In our study, patients who achieved CR underwent a longer TTP, which was more meaningful to patients in stage IV. Therefore, in spite of the stage, patients should be fully treated according to the treatment guideline to improve the efficacy.

The IPI score was used extensively as a prognostic score system in aggressive lymphoma. Other score systems, such as the FLIPI system for follicular lymphoma,[14] were all evolved from the IPI score. Now there has not been score system which can be used specially for MALT lymphoma. Zucca et al.[6] firstly brought the IPI score into the analysis of the prognosis MALT lymphoma and found patients with IPI in intermediate/high and high risk had a shorter TTP. In the current study, IPI score was an independent prognostic variable of PFS in the whole group and OS in the extra-gastric group. Ann Arbor stage and PS score, two factors involved in the IPI score, contributed most to the significance of IPI score. In the present studies, Ann Arbor stage and PS score were both significantly associated with OS and PFS, no matter in the whole group or in the extra-gastric group in the univariate analysis. Ann Arbor staging system was worked out initially for Hodgkins disease by Smithers et al.[15] in 1971 and was also proved refer to NHL. The prognostic value of PS score was confirmed in several aggressive lymphomas, suggesting patients with a good PS score could tolerate the treatment better and benefit from the treatment. In indolent lymphoma such as follicular lymphoma, the prognostic value of PS score was not obvious.[14] However, MALT lymphoma often involved important vital organs, and was different from follicular lymphoma which mostly derived from peripheral lymph nodes. For MALT lymphoma, a poor PS score often reflected the impaired function of organs. But for follicular lymphoma, the lymph nodes were not likewise associated closely with vital movement. Thus PS score was a prognostic factor in MALT lymphoma but not in follicular lymphoma. To better the general condition of patients with MALT lymphoma may improve the prognosis of this tumor. Further study was warranted.

To conclude, mucosa-associated lymphoid tissue lymphoma should be considered as a kind of disseminated indolent lymphoma. The patients with non-gastric lymphoma are likely to have nodal involvement. Patients with poor prognostic factors such as nodal involvement, not CR after initial treatment and IPI score > 2 should be treated more aggressively.

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