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Original Article

C-MYC overexpression predicts aggressive transformation and a poor outcome in mucosa-associated lymphoid tissue lymphomas

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Abstract: Mucosa-associated lymphoid tissue (MALT) lymphoma is a relatively common, indolent B-cell lymphoma. MALT lymphoma with large tumor cells (LTCs) is believed to have the potential to transform to aggressive diffuse large B-cell lymphoma (DLBCL) which may have a poor prognosis. *C-MYC* is a transcription factor. Its translocation and overexpression predicts an inferior prognosis and poor response to therapy in cases of DLBCL. In the current study, C-MYC expression was detected in MALT lymphomas, and its relationship to the occurrence of LTCs, clinicopathological parameters and prognosis was assessed. A total of 69 cases were enrolled in the study, including 42 cases of MALT lymphoma without LTCs, 20 cases of MALT lymphoma with LTCs and 7 cases of DLBCL with a MALT lymphoma component (DLBCL+MALT). Immunohistochemistry and fluorescent in situ hybridization analyses were performed. In total, 15/42 (35.7%) cases were nuclear positive for C-MYC expression in the group without LTCs, whereas 15/20 (75.0%) and 4/7 (57.1%) cases were positive in the group with LTCs and in the group with DLBCL+MALT, respectively (P=0.004). Univariate and multivariate analysis were used to determine the correlations of C-MYC expression and clinicopathological parameters with overall survival (OS). C-MYC expression, Ann Arbor stage, LDH level and IPI were considerably associated with OS according to the univariate analysis. However, only C-MYC expression ≥20% showed a statistical significance in the multivariate analysis (HR=20.604, 95% CI: 1.909-222.412, P=0.013). Therefore, C-MYC overexpression may play an important role in aggressive transformation and is an independent prognostic factor in MALT lymphoma.

Keywords: C-MYC, MALT lymphoma, prognosis, immunohistochemistry, fluorescent in situ hybridization

Introduction

Extranodal marginal zone lymphoma of the mucosa-associated lymphoid tissue is a relatively common extranodal lymphoma, accounting for 7-8% of all B-cell lymphomas [1, 2]. MALT is predominantly composed of morphologically heterogeneous small tumor cells admixed with variable numbers of transformed centroblast- and immunoblast-like cells [1]. Although MALT lymphomas have an indolent natural clinical course and are slow to disseminate, a small number of them evolve into aggressive DLBCLs [3-5], which have a poor prognosis. Three different subgroups of MALT were mentioned in the 2008 World Health Organization (WHO) classification of hematopoietic and lymphoid tissues tumors [1]: MALT lymphoma, MALT lymphoma with LTCs and DLBCL+MALT. However, in spite of the distinct histological features of each subgroup described by WHO, no definitive number of transformed large cells was included in order to make a diagnosis of MALT lymphoma with LTCs. Due to lack of quantitative diagnostic criterion, diagnosis of the subtype of MALT lymphoma is sometimes poorly reproducible in daily clinical practice, especially the cases with atypical morphologic features. In addition, differences in prognosis between MALT lymphoma with and MALT lymphoma without LTCs remain controversial [6, 7].

Recurrent chromosomal abnormalities, including *API2-MALT1*, *IGH-MALT1*, *IGH-BCL10* and *IGH-FOXP1* translocation, are well known that they seem to be closely related to MALT lym-

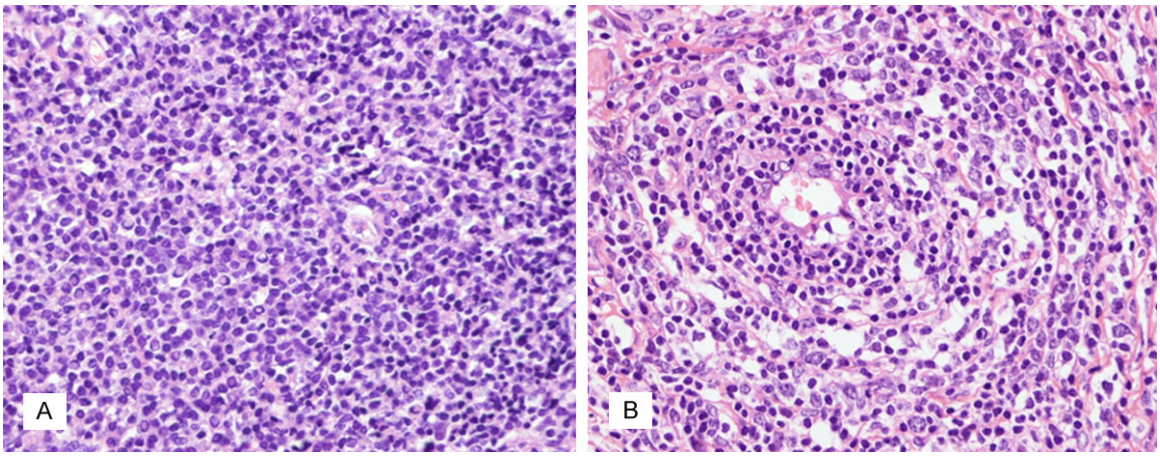

Figure 1. A. MALT lymphoma without large tumor cells (×400). B. MALT lymphoma with large tumor cells showing centroblast- or immunoblast-like large cells scattered among the small tumor cells (×400).

phoma [8-12]. A few previous studies have discussed the current insights into the mechanisms underlying the transition from MALT lymphoma into aggressive DLBCL [4, 6, 7, 13, 14], as well as the molecular prognostic signatures of MALT lymphoma. Some studies have reported that *FOXP1* may play a role in the aggressive transformation and that overexpression of FOXP1 predicted an inferior prognosis [6, 7, 15]. In addition, several studies performed global microRNA (miRNA) expression profiling of MALT lymphomas and reported that the MYC and NF-κB pathways were involved in dysregulation of miRNA expression in aggressive disease [16, 17] and 20% of MALT lymphoma showed C-MYC overexpression [17], which may be caused by posttranscriptional regulation of miRNAs exerted by regulation of its target *FOXP1*.

C-MYC is a transcription factor [18]. It has been determined that *C-MYC* translocation predicts an inferior prognosis and poor response to therapy in cases of DLBCL [19-25]. Few studies found that *C-MYC* and its target genes were involved in the transformation of follicular lymphoma to DLBCL [26, 27]. However, to the best of our knowledge, few studies have been performed [17], which have investigated the role of *C-MYC* in the transformation and prognostic assessment of MALT lymphoma.

In the current study, the expression of C-MYC was examined in a series of MALT lymphomas. The relationship between C-MYC expression and cellular components was analyzed and the relationship between these effects and prognosis in cases of MALT lymphomas were compared in order to determine a possible role of C-MYC in the prognostic evaluation of MALT lymphoma and/or the transition of MALT lymphoma to aggressive DLBCL.

Materials and methods

Patient selection and clinical information

A total of 69 MALT lymphomas samples including 42 MALT lymphoma without LTCs, 20 MALT lymphoma with LTCs and 7 DLBCL+MALT samples were collected at the Cancer Institute and Hospital, Chinese Academy of Medical Sciences (CICAMS) in Beijing, between May 2004 and January 2013. All samples were formalin-fixed paraffin embedded (FFPE) and reviewed to confirm for the diagnoses based on hematoxylin and eosin (H&E)-stained sections and immunohistochemical staining by two experienced pathologists. Other types of B-cell lymphomas, such as small lymphocytic lymphomas, follicular lymphomas and mantle cell lymphomas, were excluded. The clinicopathological parameters of these patients were recorded, including age at diagnosis, gender, primary site, Ann Arbor stage, the International Prognostic Index (IPI) and follow-up data. This study protocol was approved by the ethics committee of the Cancer Hospital, Chinese Academy of Medical Sciences. And the ethics document number was NCC2013RE-047.

IHC analysis

Immunohistochemical staining was performed on 4-μm-thick FFPE tissue sections. Briefly, the

Table 1. Demographic, clinical characteristics and C-MYC expression of all patients

Characteristics	MALT lymphoma without LTCs	MALT lymphoma with LTCs	DLBCL+ MALT	*P* value
Total	42	20	7	
Age (years)				>0.05
Mean age	57	53	60	
Median age	60	52	59	
Gender				0.123
Male	24	6	4	
Female	18	14	3	
Primary Site				0.081 (**0.027**[a])
GI tract	**31**	**9**	4	
Stomach	24	6	3	
Intestine	7	3	1	
Non-GI tract	**11**	**11**	3	
Lung	8	1	0	
Oral cavity	1	3	0	
Thyroid	0	4	1	
Breast	0	1	1	
Tonsil	0	2	0	
Ocular adnexa	1	0	0	
Salivary gland	1	0	1	
Ann Arbor stage[b]				0.083
I	26	7	3	
II	6	6	3	
III	1	0	1	
IV	3	4	0	
IPI[b]				0.281
Low (0, 1)	31	11	5	
Intermediate (2)	3	3	2	
High (3, 4)	2	3	0	
LDH[b]				0.515
Normal	30	12	5	
High	6	5	2	
C-MYC expression				**0.004**[a]
Negative (<10%)	**27**	**5**	**3**	
Positive (≥10%)	**15**	**15**	**4**	

[a]Significant differences are highlighted in bold. [b]The Ann Arbor Stage, IPI and LDH level of 9 patients were not known.

slides were deparaffinized and antigen retrieval was performed for 1.5 min in 1 mM EDTA (pH 8.0) (Beijing Zhongshan Golden Bridge Biotechnology Co. Ltd., Beijing, China) using a pressure cooker. The slides were then incubated for 1 h in C-MYC rabbit monoclonal anti-human antibody (catalog #1472-1, Epitomics, Inc., Burlingame, CA, USA) plus SignalStain® antibody diluent, at a concentration of 1:100 (Cell Signaling Technology, Danvers, MA, USA). Slides were then incubated in universal secondary antibody (DAKO) for 15 min. Diaminobenzidine (DAB) was the chromogen used and slides were counterstained with hematoxylin before mounting.

The staining pattern for C-MYC was nuclear staining. The expression level of C-MYC was evaluated independently, by 2 'masked' pathologists, for the proportion of positively staining tumor cells in, regardless of the staining intensity [7, 17], and recorded in 10% increments. Grades the percentage of positive tumor cells as follows: <10%, 10%, 20%, 30%, 40%, 50% and >50% [28]. Grades <10% were defined as "negative expression" [17, 29] and ≥10% were defined as "positive expression". The diagnostic accordance rate between the two pathologists was 84.06% (58/69). Cases with different diagnoses were discussed by the two pathologists until agreement was reached.

FISH analysis

FISH was done on 3-μm-thick FFPE tumor tissue samples, using a break-apart probe specific to the *C-MYC* locus (Vysis LSI *C-MYC* Dual Color, Break Apart Rearrangement Probe; Abbott Molecular, Abbott Park, IL, USA), according to the manufacturer's instructions. FISH signals were scored with a Zeiss AxioImager M2 epifluorescence microscope (Carl Zeiss, Oberkochen, Germany) equipped with ×100 oil

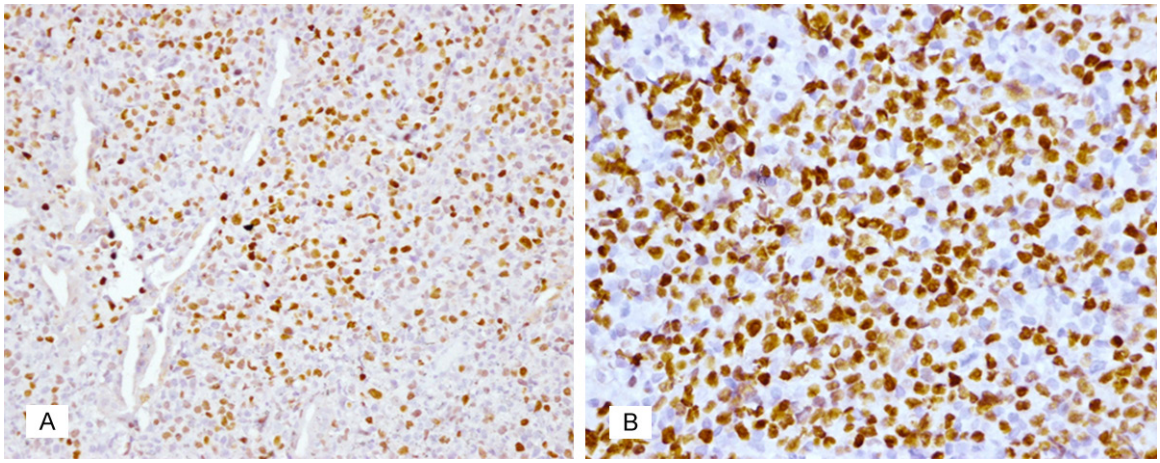

Figure 2. A. Staining shows that both large and small tumor cells were positive for C-MYC in MALT lymphoma (×400). B. In one of the DLBCL+MALT cases, 80% of tumor cells show strong nuclear staining for C-MYC (×200).

immersion objectives and 4', 6'-diamidino-2-phenylindole (DAPI)/Spectrum Green/Orange single and triple band pass filters. Tumor cells, which had nuclei with one or more FISH signals of each color, were enumerated. A positive cell was defined as one in which the nucleus had split signals (three or more signal diameters apart) [17, 22, 23].

Statistical analysis

Clinical pathological characteristics of different groups were compared using the Fisher's exact test or chi-square test. The correlations between the various variables and overall survival (OS) were estimated using the Kaplan-Meier analysis and the survival distributions were compared using the log-rank test. Cox regression analysis was performed to determine independent prognostic factors. All statistical analyses were two-sided, and *P* values less than 0.05 were considered statistically significant. Data were analyzed using the SPSS 16.0 statistical software program (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

The demographic and clinical characteristics of all patients enrolled in this study were listed in **Table 1**. Patients ranged in age from 16 to 80 years (median 60), 23 to 77 years (median 52) and 36 to 78 years (median 59) in the MALT lymphoma without LTCs, MALT lymphoma with LTCs and DLBCL+MALT groups, respectively. There was a significant difference in the primary site between the MALT lymphoma without LTCs and the MALT lymphoma with LTCs groups (P=0.027). In the MALT lymphoma without LTCs group, 31/42 (73.8%) cases occurred primarily in the gastrointestinal tract, whereas in the MALT lymphoma with LTCs group only 9/20 (45%) cases had gastrointestinal tract involvement. No significant differences were found between the two groups with respect to age, gender, Ann Arbor stage and IPI (P>0.05).

Morphology and immunohistochemistry

The H&E-stained sections were reviewed. 42 cases of MALT lymphoma without LTCs predominantly showed small B cells, including centrocyte-like cells, monocytoid cells and small lymphocyte-like cells. 20 cases of MALT lymphoma with LTCs displayed a variable number of transformed centroblast- or immunoblast-like large cells, which were scattered among the small tumor cells (**Figure 1A** and **1B**). The DLBCL+MALT cases presented as solid or sheet-like proliferations of large tumor cells in part of the area of each of the 7 samples.

The expression of C-MYC was examined in all 69 cases (**Table 1**). C-MYC positive cells were predominantly large tumor cells with strong to moderate nuclear staining, which were prominent among a large amount of inflammatory cells. In addition to the large tumor cells, it is worthwhile to note that some of the small tumor cells also displayed variable intensities of C-MYC expression (**Figure 2A**).

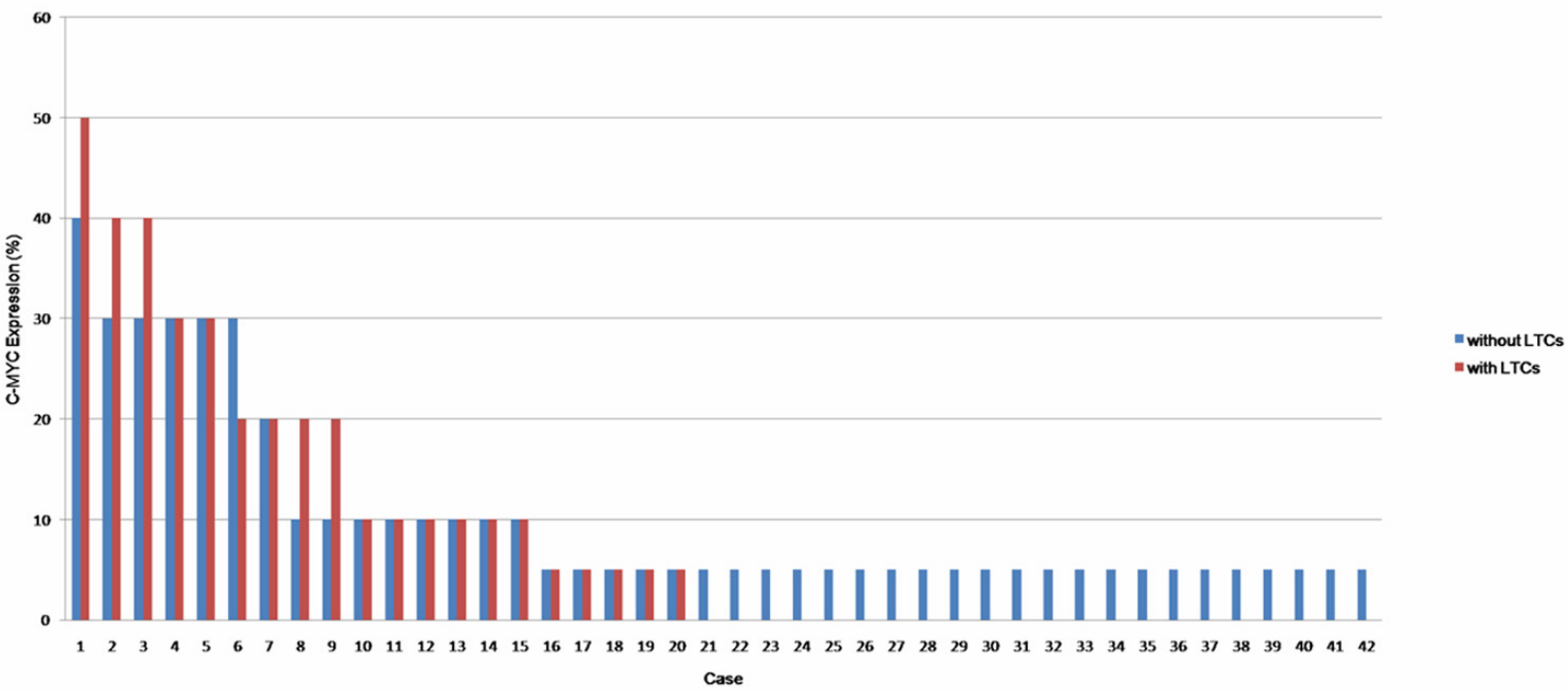

Figure 3. It shows the C-MYC expression of each case in all 62 MALT lymphomas.

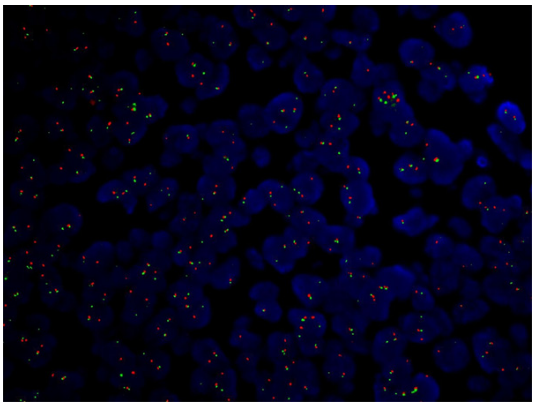

Figure 4. *C-MYC* translocation in a DLBCL+MALT case as shown by split fluorescent in situ hybridization (FISH) signals.

In the group without LTCs, 15/42 (35.7%) cases appeared to be nuclear positive for C-MYC vs. 15/20 (75.0%) cases in the group with LTCs (**Figure 3**). Thus, the expression of C-MYC was significantly higher in the MALT lymphoma with LTCs group compared to the group without LTCs (P=0.004). The percentage of samples with C-MYC expression was also higher in the DLBCL+MALT group compared to the MALT lymphoma without LTCs group (4/7, 57.1%). In fact, in one positive case, 80% of tumor cells exhibited nuclear staining in a partial area of the tumor (**Figure 2B**).

There were no significant differences between the groups when comparing the relationship between the expression levels of C-MYC and any of the clinicopathological features, including age, gender, primary site, Ann Arbor stage, IPI and LDH level.

FISH analysis

None of the 62 cases of MALT lymphoma had *C-MYC* translocation. *C-MYC* translocation was found in the case of DLBCL+MALT that had positive C-MYC expression in 80% of tumor cells (**Figure 4**).

Prognostic analysis

Among the 62 MALT lymphoma cases, follow-up data was available for 49 patients (79%). Of these, follow- up was done in 87.8% (43/49) of patients for at least 3 years and in 38.8% (19/49) of patients for at least 5 years. A total of 9 patients died, 6 from lymphoma progression or recurrence; 5 of these occurred within 3 years of diagnosis. Lymphoma recurrence and dissemination occurred in 3 of the 40 living patients more than 3 years after the initial diagnosis. The mean OS time was 43.2 months (range of 1 to 84 months) and the overall 3-year and 5-year survival rates were 89.31% and 85.42%, respectively. According to the Kaplan-Meier analysis shown in **Figure 5**, OS was significantly associated with C-MYC expression, Ann Arbor stage, LDH level and IPI (**Table 2**), whereas age, gender, primary site and cellular composition were not associated with OS. The correlation between OS and C-MYC expression was even more obvious when looking at C-MYC expression values of ≥20%. However, only C-MYC expressions of ≥20% were found to be significant in the multivariate analysis (multivariate HR=20.604, 95% CI: 1.909-222.412, P=0.013) (**Table 3**).

One of the 7 DLBCL+MALT patients died approximately one year after diagnosis and one progressed to DLBCL after seven months.

Discussion

Although MALT lymphomas are generally considered to be indolent diseases, they can transform to DLBCL on rare occasions [1]. For this reason, patients diagnosed with MALT lymphoma with LTCs are usually considered to be at risk for developing DLBCL and should be treated with an aggressive therapy regimen similar to DLBCL [30-32], which are differ from the patients of MALT lymphoma without LTCs. However, the diagnostic criteria for MALT lymphomas with LTCs are not clear. Even the 2008 WHO classification of hematopoietic and lymphoid tissues tumors did not specify the number of the scattered large tumor cells necessary to make a definitive diagnosis of MALT lymphomas with LTCs. To some extent, the diagnosis of MALT lymphoma with LTCs may be subjective in clinical practice, especially for the cases lack of atypical morphological features. In addition, the differences in prognoses between MALT lymphoma patients with LTCs and without LTCs remain controversial [6, 7, 32, 33]. In the current study, there was no significant difference in the prognosis between these two groups (P=0.355). We presumed that the inconsistent results of these studies may be attributed to the lack of definitive diagnostic criteria, leading to imprecise classification of

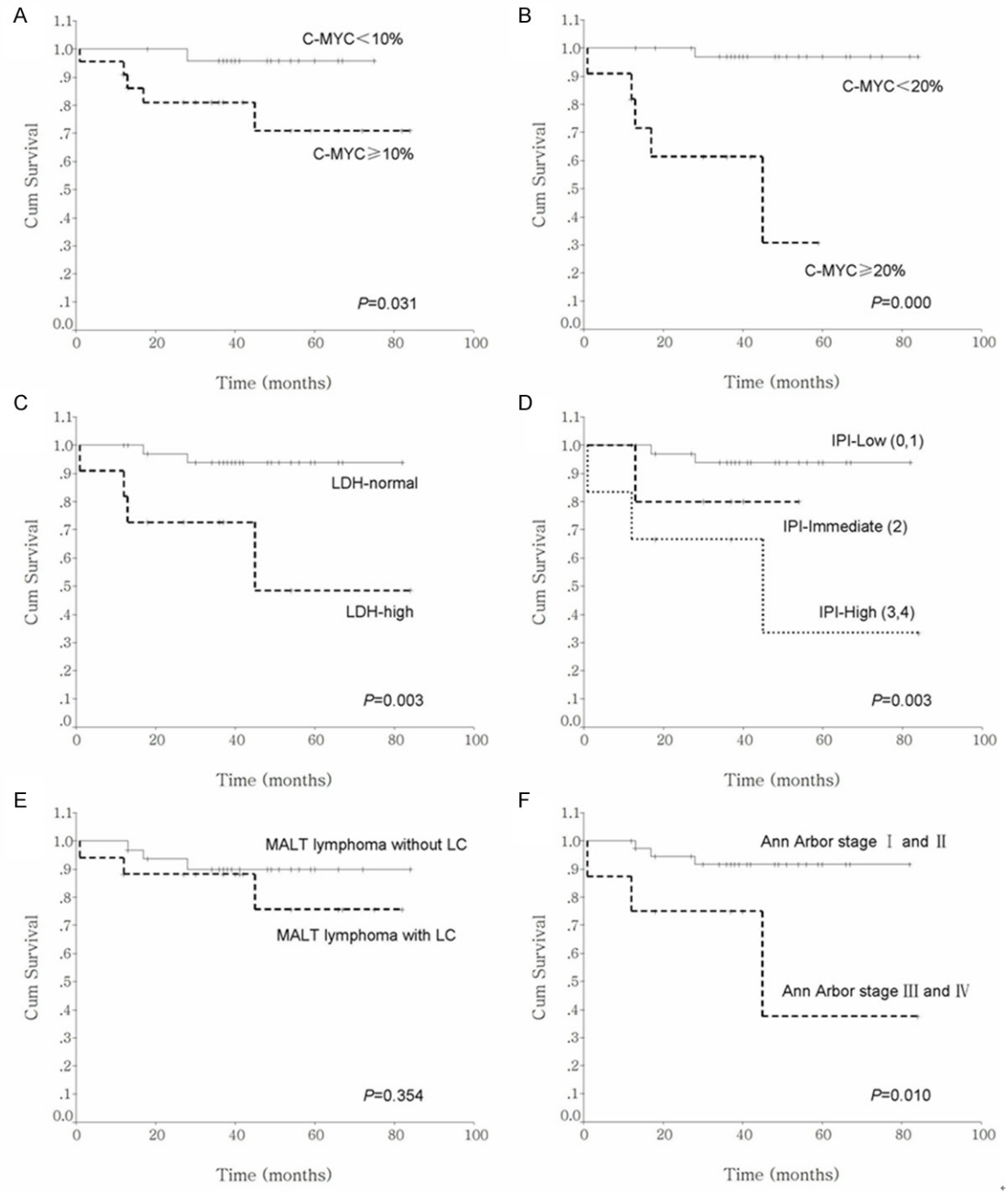

Figure 5. Kaplan-Meier survival curves with respect to C-MYC expression (A and B), LDH level (C), IPI (D), cellular composition (E) and Ann Arbor stage (F).

the cases, as well as the relatively low number of the samples in the study. Therefore, objective molecular markers for assessing the prognosis in cases of MALT lymphoma are necessary.

Previous reports have shown that *C-MYC* deregulation in lymphoma was typically associated with aggressive clinical behavior [20, 34] and that the overexpression of C-MYC or *C-MYC* translocation in DLBCL was predictive of inferior prognosis, poor response to therapy, and was an independent predictor of outcome [19, 21, 35-37]. In the current study, the expression of C-MYC in MALT lymphoma was determined and the role of C-MYC in the transformation of

Table 2. Variables associated with C-MYC expression, tumor cellular composition, primary site, clinicopathological parameters and OS by univariate analysis in 62 MALT lymphomas

Variables	N	Log-rank test	*P* value
C-MYC expression ≥10%	30	4.64	**0.031**[a]
C-MYC expression ≥20%	16	19.31	**0.000**[a]
Gender		2.12	0.145
Male	30		
Female	32		
Primary site		0.02	0.902
GI tract	40		
Non-GI tract	22		
IPI[b]		11.62	**0.003**[a]
Low (0, 1)	42		
Intermediate (2)	6		
High (3, 4)	5		
LDH[b]		8.78	**0.003**[a]
Normal	42		
High	11		
Ann Arbor stage[b]		6.59	**0.010**[a]
I-II	45		
III-IV	8		
Cellular composition		0.86	0.355
Without LTCs	42		
With LTCs	20		

[a]Significant differences are highlighted in bold. [b]The Ann Arbor Stage, IPI and LDH level of 9 patients were not known.

large tumor cells was investigated. A total of 30 out of 62 MALT lymphoma cases had C-MYC expression and the C-MYC positive cells were predominantly large tumor cells. C-MYC staining may help to identify large tumor cells in lymphomas with obviously inflammatory background. In the current study, the expression level of C-MYC in the MALT lymphoma with LTCs group was higher than in the group without LTCs (75.0% vs. 35.7%, *P*=0.004). In the DLBCL+MALT group, 4/7 (57.1%) cases were positive for C-MYC. From this, it could be perceived that the positive rate of C-MYC expression increased as well as the increase in large tumor cells. Therefore, we speculate that C-MYC might play a role in the transformation of large tumor cells in MALT lymphoma. Furthermore, it is worthwhile to note that some small tumor cells were also positive for C-MYC, which is similar to Jiang's research [7]. We hypothesized that the C-MYC positive small tumor cells may precursors of the large tumor cells and that the two different sizes of C-MYC expressing tumor cells may be derived from the same clone.

Only one DLBCL+MALT case displayed *C-MYC* translocation, in which 80% of tumor cells showed nuclear expression of C-MYC. In all other cases, nuclear staining was present in less than 50% of tumors and no *C-MYC* aberrations were found. The concordance between C-MYC expression and *C-MYC* translocation was consistent with previous studies [24, 38, 39]. The cases of MALT lymphoma with LTCs were found to be significantly more likely to occur outside the gastrointestinal tract compared with cases of MALT lymphoma without LTCs. There was no significant difference between C-MYC expression and different clinicopathological parameters, including different primary sites, IPI, Ann Arbor stage and LDH level.

In the present study, C-MYC expression level was significantly associated with OS according to univariate analysis of prognostic factors. OS was inferior in cases with C-MYC expression in ≥10% of tumor cells compared to those with C-MYC expression in <10% of tumor cells (*P*=0.031). When the cut off value for C-MYC expression was set at 20%, the difference in OS between the two groups became more remarkable (*P*=0.000). In addition, we found that Ann Arbor stage III-IV, higher IPI score and elevated LDH level also appeared to have a significantly adverse impact on OS. However, when the variables that were significant according to the univariate analysis were analyzed using a multivariate analysis, only C-MYC expression ≥20% was statistically significant (multivariate HR=20.604, 95% CI: 1.909-222.412, *P*=0.013). Therefore, an inferior prognosis may be indicated when ≥20% of tumor cells are positive for C-MYC in MALT lymphoma.

In conclusion, C-MYC staining may be contributed to recognize the large tumor cells, especially in an obviously inflammatory background. The positive rate of C-MYC expression was higher in the group of MALT lymphoma with LTCs and in the group of DLBCL+MALT than that in the group of MALT lymphoma without LTCs, which suggested that C-MYC would play an important role in aggressive transformation in MALT lymphoma. And according to the Cox

Table 3. Correlation between C-MYC expression, clinicopathological parameters and OS by multivariate analysis in 62 MALT lymphomas

	Variables	Hazard ratio	95% CI	*P* value
(A)	C-MYC ≥10%	4.351	0.468-40.431	0.196
	IPI	1.824	0.138-24.169	0.648
	LDH	2.594	0.129-52.266	0.534
	Ann Arbor stage	0.968	0.033-28.073	0.985
(B)	C-MYC ≥20%	20.604	1.909-222.412	**0.013**[a]
	IPI	0.820	0.037-18.389	0.900
	LDH	7.169	0.244-210.341	0.253
	Ann Arbor stage	0.799	0.012-52.410	0.916

[a]Significant differences are highlighted in bold.

regression analysis, C-MYC overexpression appeared to be an objective independent prognostic factor in MALT lymphoma.

However, it should be noted that the cohort of patients with outcome data was small in the current study and the results need to be further validated in larger patient cohorts.

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Disclosure of conflict of interest

None.

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