CD5-Positive Marginal Zone Lymphoma: Clinicopathological Features And Survival Outcomes

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Research Article

Keywords: MZL, CD5, Prognostic factor, Transformation, DLBCL

Posted Date: October 19th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-948719/v1

Version of Record: A version of this preprint was published at Leukemia Research on April 1st, 2022. See the published version at https://doi.org/10.1016/j.leukres.2022.106840.

CD5-positive marginal zone lymphoma: clinicopathological features and survival outcomes

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Funding: This work was supported by the National Natural Science Foundation of China (Grant No. 81970184) and the National Science and Technology Major Project of China (Grant No.2020ZX09201-009).

Conflict of interest statement
The authors declare no conflicts of interest.

Abstract

Background CD5 expression in diffuse large B-cell lymphoma has a poor prognosis but the prognostic value of CD5 expression in marginal zone lymphoma is undefined**.**

Methods Clinicopathological features, survival outcomes, and prognostic implications of marginal zone lymphoma were retrospectively analyzed in 204 patients. We classified patients into (i) CD5-positive marginal zone lymphoma (ii) CD5-negative marginal zone Lymphoma, Fisher's exact test was used to compare the CD5-positive and CD5-negative marginal zone lymphoma. Progression-free survival (PFS) and overall survival (OS) curves were summarized by Kaplan-Meier method and compared using the log-rank test, The Cox proportional hazard regression model was used for univariate and multivariate analyses.

Results： CD5 expression is rare in marginal zone lymphoma, of 204 patients, only 48 (23.53%) had CD5-positive. Due to the characterized of slow growth and locally

aggressive nature, the prognosis is favorable after treatment. at the end of the follow-up 179 patients were still alive,163 patients never progressed. The 5-year PFS and OS rates for marginal zone lymphoma were 65.10% and 77.30% respectively, the 5-year PFS and OS rates for CD5-positive marginal zone lymphoma were 64.80% and 84.10%, there is no significant difference between CD5-positive and CD5-negative (*P*=0.829, *P*=0.521). Diffuse large B-cell lymphoma (DLBCL) transformation was pathologically indicated in 6 patients, of which 5(83.33%) patients were CD5-positive marginal zone lymphoma.

Conclusion： CD5 expression in marginal zone lymphoma is not independently prognostic for PFS and OS. But CD5-positive marginal zone lymphoma seems more likely to transformation to diffuse large B-cell lymphoma.

Keywords: MZL, CD5, Prognostic factor, Transformation, DLBCL

Introduction

Marginal zone lymphoma (MZL) is the second most common subtype of indolent B cell non-Hodgkin's lymphoma (iNHL). It is derived from post-germinal center memory B cells present in the marginal zone of lymphoid organs(Maes and De Wolf-Peeters 2002) MZL comprises approximately 6% of all lymphoid malignancies (Armitage and Weisenburger 1998). According to the World Health Organization classification, there are three different MZL subtypes with specific diagnostic criteria, genetic features, clinical course and therapeutic implications: extra nodal MZL of mucosa-associated lymphoid tissue (MALT), splenic marginal zone lymphoma (SMZL) and nodal marginal zone lymphoma (NMZL) (Arber et al. 2016, Arcaini et al. 2016) representing 50%–70%, 20% and Marginal zone lymphoma 10% of all MZL, respectively. (Denlinger et al. 2018, Conconi et al. 2020, Zucca et al. 2020) The 5-years OS of MZL has been reported to be 61%(Smith et al. 2015)–84% (Vaughn et al. 2021) for overall MZL over the past two decades.

CD5 is a membrane glycoprotein that is normally found on T cells but is also expressed on normal B cells in cord blood, a few adult peripheral blood, spleen, and

lymph nodes. (Dalloul 2009) In some B lymphocyte malignancies, the aberrant expression of CD5 has been reported, including DLBCL, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL)/SLL and mantle cell lymphoma (MCL) in which this condition is observed. A study from China (Zhao et al. 2019) showed that CD5 expression in DLBCL has a poor prognosis, associated with more invasive clinical course, and even resistance to treatment. In rare cases of MZL, the aberrant CD5 expression is also reported(Ferry et al. 1996, Wenzel et al. 2001, Mutreja et al. 2014), Whether CD5 expression is relevant to the prognosis of patients with MZL is controversial. In order to explore the relationship between the expression of CD5 and clinical characteristics and survival in MZL, we report a series of 204 cases diagnosed.

METHODS AND MATERIALS

Study population

After obtaining approval from the Institutional Review Board of our institution, we retrospectively analysis 204 patients with a confirmed diagnosis of MZL between January 2010 and December 2019 in the First Affiliated Hospital of Zhengzhou University. Initial diagnostic evaluations included a complete blood count, serum lactate dehydrogenase (LDH), serum β2–macroglobulin（β2-MG）, Hepatitis B viral panels, and bone marrow biopsy. Computed tomography of the chest, abdomen, and pelvis are usually obtained. For GALT lymphoma, endoscopy should be per-formed.

Variables of interest

The following clinical data were collected from the patients' medical records: age at diagnosis; gender; the area of tumor; complete blood analysis; serum lactate dehydrogenase (LDH) ; serum β2–macroglobulin; Ann Arbor stage at diagnosis; mucosa-associated lymphoid international prognostic index (MALT-IPI); the follicular lymphoma international prognostic index (FLIPI); pathological report; bone marrow biopsy; B symptom; type of treatment; therapeutic evaluation; follow-up results and survival. OS was defined as the time between diagnosis and death or the last follow-up. PFS was defined as the time from initial diagnosis to the date of the first relapse or disease progression or last follow-up. Progression was defined as a

relapse for patients in complete response, or as the appearance of a new lesion. Efficacy evaluation including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), were evaluated according to the Lugano classification. ORR is the total of CR and PR. Application of the original international prognostic index IPI in MZL has been proposed from small retrospective studies, (Cortelazzo et al. 2002, Heilgeist et al. 2013) but FLIPI and MALT-IPI efficiently discriminates patients with good, intermediate and poor PFS and OS (Solal-Céligny et al. 2004, Thieblemont et al. 2017).The MALT-IPI with three parameters (age ≥ 70 years, elevated LDH level, Ann Arbor stage III or IV)(Thieblemont et al. 2017) .The FLIPI with five parameters (age ≥60 years, elevated LDH level, Ann Arbor stage III or IV， Nodal areas ≥5,Hemoglobin<12g/dl)(Solal-Céligny et al. 2004).the patients in three groups: low, intermediate, and high risk (corresponding to the presence of 0, 1, or ≥2 of these factors, respectively).

Immunohistochemistry for CD5

In clinical practice, CD5 expression on lymphoma cell surfaces can be evaluated by immunohistochemistry (IHC) or IHC on formalin-fixed, paraffin-embedded sections is the most common evaluation method by flow cytometry (FCM). IHC on formalin-fixed, paraffin-embedded sections is the most common evaluation method, representative formalin-fixed paraffin-embedded tissue blocks from each case were cut into 3μm sections. The slides were stained for anti-CD5 antibody (Ber-H2, dilution 1: 100; Dako, Glostrup, Denmark), CD5 expression was evaluated in a representative tumor area.

Statistical analysis

Statistical analyses were performed using SPSS 26.0. Survival was analyzed using the Kaplan–Meier method and compared using the log-rank test. Prognostic factors at diagnosis independently associated with OS were identified through multivariate analysis with Cox proportional hazards regression modeling. Comparisons between subgroups of patients according to CD5-expression were performed using a chi-square test or Fisher exact test for categorical variables. In this study, $P < 0.05$ was considered statistically significant.

Results

Clinical features of MZL in this study

The clinical characteristics of the 204 MZL at the time of diagnosis are summarized in **Table 1**. Their median age was 56.5 years (range7–83years), and the study population demonstrated a male-to-female ratio of 1: 1. there are 3 subtypes, MALT is the most common subtype of MZL, accounting for 69.60% of all MZL, while SMZL and NMZL make up the remaining 30.4%. MALT can arise at any extra nodal site with the stomach as the most common, followed by ocular adnexal, lung, skin and salivary glands and so on. In this study, 91 patients from the stomach, 24 patients from the ocular adnexal, and 27 patients from the other mucosal tissues. A total of 23 patients presented bone marrow invasion. Our data show that 48(23.53%) patients were CD5-positive ,156（76.47%） patients were CD5-negative, CD5-positive patients were older than CD5-negative(*P*=0.045), they were more likely to transformation to DLBCL(*P*=0.003), and it is not easy to get ORR(*P*=0.019).

In 204 patients, 25 patients had hepatitis B,1 patient had rheumatoid arthritis, 1 patient had Sjogren's syndrome,1 patient had systemic lupus erythematosus, 1 patient had lung squamous cell carcinoma.

Table 1. clinical features of MZL

Clinical feature	**CD5-positive N=48**	**CD5-negative N=156**	***P***
Gender			0.741
Male	23	79	
Female	25	77	
Age			0.045
>60	25	56	
《60	23	100	
B symptom			1.000
Yes	4	14	
No	40	140	
Ann Abor stage			0.295
I/II	18	46	
III/IV	30	110	
Serum LDH（U/L）			0.141
Elevated（＞300）	8	14	
Normal（100～300）	37	130	
Serum β2-MG（μg/L）			0.108

Elevated（＞2.6）	9	15	
Normal（1.0～2.6）	37	128	
Ki-67			0.365
》10%	31	89	
<10%	16	63	
BM involvement			0.212
Yes	8	15	
No	33	112	
Transformation to DLBCL			0.003
Yes	5	1	
No	43	153	
Efficacy evaluation			0.019
ORR	24	96	
SD+PD	8	8	
HBV infection			0.117
Yes	9	16	
No	39	140	
MALT：MALT-IPI			0.379
Low	23	66	
Intermediate	5	27	
High	7	14	
SMZL: FIL score			0.739
Low	0	3	
Intermediate	1	2	
High	2	2	
NMZL: FIL score			0.180
Low	1	7	
Intermediate	2	11	
High	7	24	

BM: bone marrow

Clinical features of CD5-positive MZL

Among the 204 total cases, 48 cases of CD5-positive MZL were found, these included 35(24.65%) cases of MALT,10 (19.23%) cases of NMZL, and 3(30.00%) cases of SMZL (**Table 2**). In this study CD5-positive MZL was more common in SMZL. CD5-positive MZL patients were older than CD5-negitive MZL patients, they were more likely to transformation to DLBCL, and it is not easy to get ORR. However there was no significant association between CD5 expression and specific clinical characteristics such as BM (P=0.255) involvement, Ann Abor stage (P=0.450) and MALT-IPI(P=0.379), SMZL: FIL score(P=0.739), NMZL: FIL score(P=0.180).

Table 2. subtypes of MZL

Subtype	**CD5-positive**	**CD5-negative**	**Total**
	N=48	**N=156**	**N=204**
MALT	35	107	142
EMZL	10	42	52

SMZL	3	7	10

Initial treatment and response

MZL is a type of indolent lymphoma, and individualized treatment is adopted according to the patient's condition. The initial treatment modalities and responses of MZL patients are summarized in **table 3**. For localized disease, local therapy is used such as therapy for H.pylori in gastric extra nodal MZL, splenectomy for splenic MZL, and radiotherapy for nodal MZL. For disseminated disease with low tumor burden or patients refuse treatment, a watch and wait be used. and chemoimmunotherapy for disseminated disease with high tumor burden.

Table 3 Treatment modalities and responses of MZL patients

Therapy	CD5-postive			CD5-negative		
	N	**ORR(%)**	**Relapse (%)**	**N**	**ORR(%)**	**Relapse (%)**
ISC	3	3(100.00)	0	21	21(100.00)	3(14.29)
RT	0	0	0	2	2(100.00)	0
cit	21	18(85.71)	2(9.52)	102	93 (91.18)	23(22.55)
therapy for HP	2	2(100.00)	0	4	3(75.00)	0
watch and wait	8	-	0	9	-	2(22.22)
ISC+ RT	1	1 (100.00)	0	1	1(100.00)	1(100.00)
ISC+ cit	6	5 (83.33)	2 (33.33%)	9	9(100.00)	1(11.11)
RT+cit	7	5 (71.43)	2 (28.57)	7	6(85.71)	3 (42.86)
ISC+RT+cit	0	0	0	1	0	0

RT: radiotherapy; cit: chemoimmunotherapy; ISC: Inpatient and Surgical Care

Survival outcomes of MZL

The follow-up periods ranged from 2 to 124 months (median follow-up, 26.5months), Due to the number of deaths was too small to calculate the median survival time, the mean survival time could be used instead, which was 98 months. Until the end of follow-up, 24 patients died. 179 patients were still alive. One of the 6 patients who transformed to DLBCL died and was CD5-positive. The 5-year PFS and OS rates were 78.6% and 77.3% respectively (**Fig1**). patients of MALT had better prognosis with the 5-years OS rates was 81.10% and patients of SMZL had poor prognosis with the 5-years OS rates was 65.60% (**Fig2**).

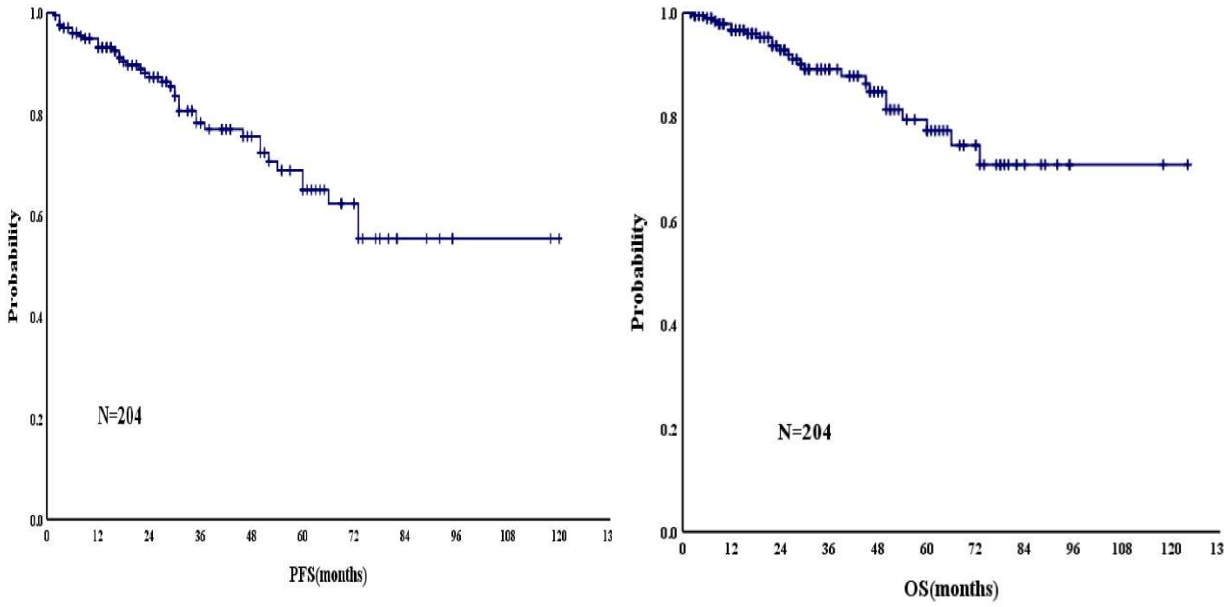

Fig. 1 Survival of MZL patients (A) PFS and (B) 0S.

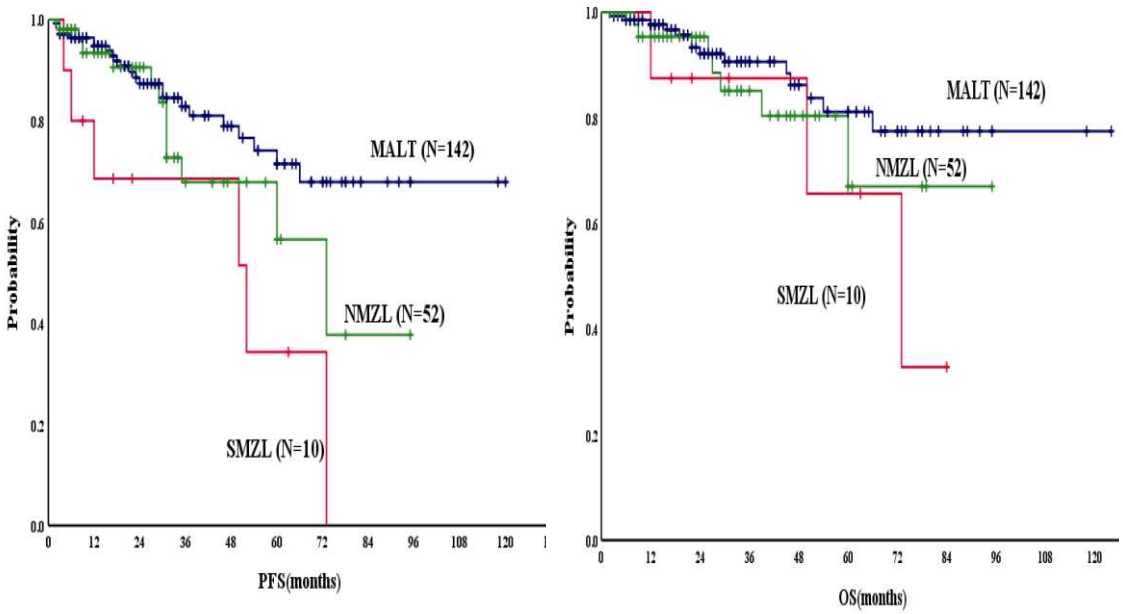

Fig. 2 Survival of three subtypes MZL patients (A) PFS and (B) OS.

Univariate analysis identified that serum LDH was prognostic factor for OS and PFS (all P<0.05). BM involvement, Efficacy evaluation were prognostic factors for PFS (all P<0.05). Age, Serum β2-MG were prognostic factors for OS (all P<0.05)

(**Table 4**). Multivariate analysis identified that BM involvement (HR 0.165, 95% CI 0.049-0.555, *P*=0.004) and Efficacy evaluation (HR 11.139,95% CI 3.233-38.379, *P*=0.000) were independent prognostic factors for PFS, Independent prognostic factors for OS was age (HR 4.718, 95% CI 1.776-12.536, *P*=0.002) (**Table 5**).

Table 4 Univariate analysis of predictors of PFS and OS (by Cox regression)

Clinical factor	PFS			OS		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age	1.665	0.758-3.657	0.204	4.010	1.726-9.313	0.001
Sex	1.202	0.548-2.638	0.646	1.137	0.510 -2.533	0.754
B symptom	2.464	0.841-7.217	0.100	1.826	0.542-6.151	0.331
Ann Abor stage	1.425	0.629-3.229	0.397	1.327	0.584-3.016	0.500
Serum LDH	3.854	1.519-9.782	0.005	3.541	1.300-9.646	0.013
Serum β2-MG	1.759	0.596-5.191	0.307	3.151	1.129-8.797	0.028
Ki-67	1.013	0.443 -2.318	0.976	0.938	0.410-2.147	0.880
BM involvement	4.320	1.609-11.602	0.004	2.117	0.705-6.357	0.181
Transformation to DLBCL	2.328	0.541-10.026	0.257	1.515	0.312-7.357	0.606
Efficacy evaluation	0.281	0.098-0.806	0.018	1.434	0.186-11.046	0.730
HBV infection	1.097	0.373-3.226	0.866	0.365	0.084-1.587	0.179

Table 5 Multivariate analysis of predictors of PFS and OS (by Cox regression)

Clinical factor	PFS			OS		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age	-	-	-	4.718	1.776-12.536	0.002
Serum LDH	0.344	0.109 -1.089	0.069	2.242	0.792-6.351	0.128
Serum β2-MG	-	-	-	2.708	0.959-7.647	0.060
BM involvement	0.165	0.049-0.555	0.004	-	-	-
Efficacy evaluation	11.139	3.233-38.379	0.000	-	-	-

Survival outcomes of CD5-positive MZL

During the follow-up period, only 3 of the 48 patients died and 45 were still alive, the 1-year, 3-year and 5-year PFS rates for CD5-positive patients were 95.10%,72.30% and 72.30%, the 1-year, 3-year and 5-year OS rates for CD5-positive patients were 97.10%, 84.10% and 84.10%, there is no statistical difference in the PFS and OS rates of CD5-positive and CD5-negative patients (*P*=0.828, *P*=0.521) (**Fig.4**). patients of CD5-positive MALT had better prognosis with the 5-years OS rates was 100.00% and patients of CD5-positive NMZL and SMZL had poor prognosis with the 5-years OS rates was 50.00% **(Fig.3**.)

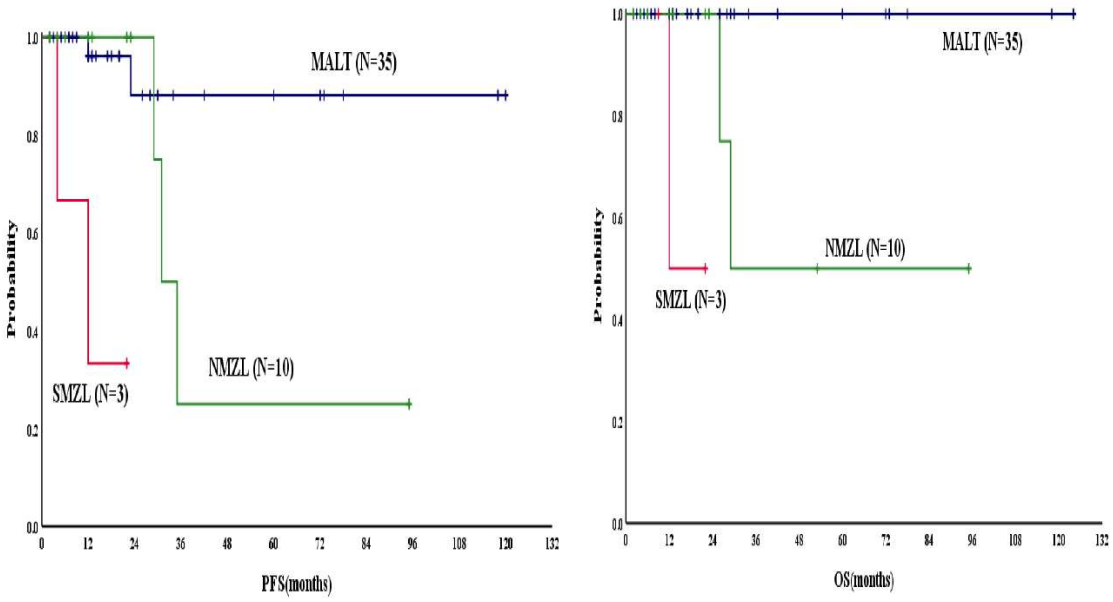

Fig. 3 Survival of three subtypesCD5-positive MZL patients (A) PFS and (B) OS

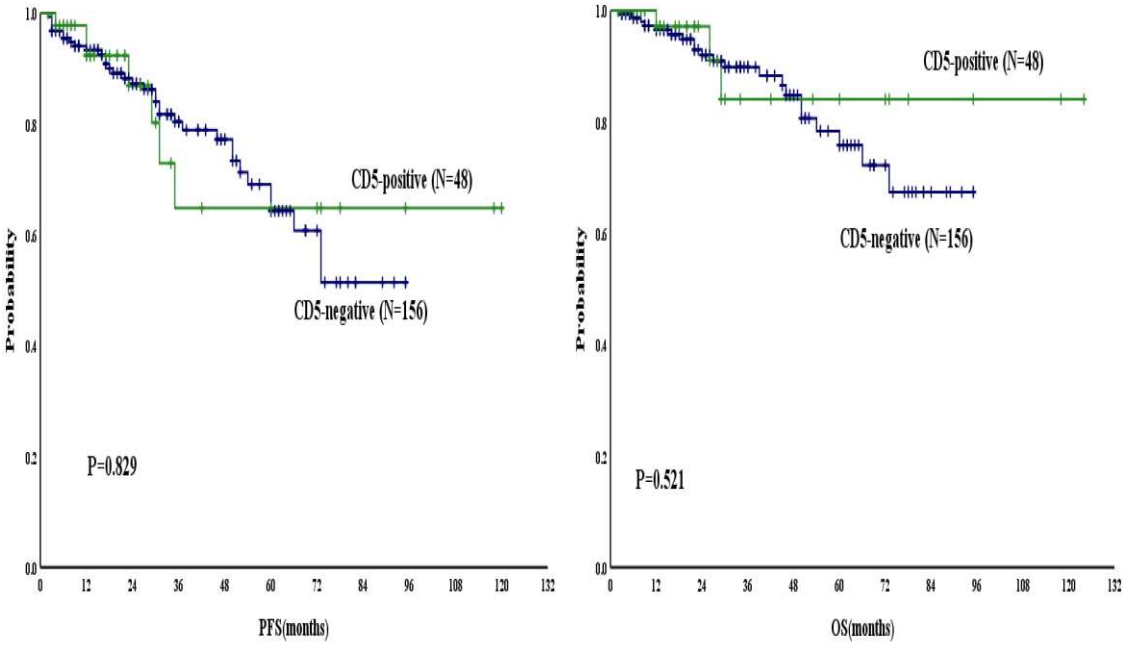

Fig. 4 Survival of CD5-positive MZL patients. (A) OS and (B) PFS of all CD5-positive MZL patients

Histologic transformation

Histological transformation to DLBCL is reported to occur in about 30-40% of Follicular lymphoma (FL) patients, at a rate of about 3% each year,(Takata et al. 2014) 37 and the risk of Histological transformation to DLBCL across all MZL types appeared lower than FL(Conconi et al. 2015) .In this study, 6 patients transformation to DLBCL, 5 of which were CD5-positive (**Table 6**).

Table 6 Histologic transformation of MZL patients

Subtype	CD5-positive N=5	CD5-negative N=1
MALT	3	1
NMZL	2	0
SMZL	0	0

Discussion

The CD5 molecule is a glycoprotein, Since its discovery, over 30 years ago, CD5 has been used as a marker to identify T cells, a subset of B cells, and B cell chronic lymphocytic leukemia/small lymphocytic lymphoma cells (CLL/SLL) (Reinherz et al. 1979, Boumsell et al. 1980). CD5-positive B cells produce higher amounts of IL-10 than CD5-negative B cells, and that the ectopic expression of CD5 in B cells induces the production of IL-10, which is known can cause immunosuppressive thereby promoting tumor growth(Mageed et al. 2012, Xu-Monette et al. 2015, Garaud et al. 2018).

MZL represent approximately 5%-15% of all non-Hodgkin lymphomas in the world，represent approximately 9.04% of all non-Hodgkin lymphomas in our center. It has a nonspecific B-cell immunophenotype, positive for monotypic immunoglobulin and pan B cell markers, but usually negative for CD5. In recent years, it has been recognized that a subset of DLBCL patients expresses CD5 with a particularly poor prognosis.(Zhao et al. 2019) However the role in MZL is unclear, Scattered cases of CD5-positive MZL lymphoma have been reported in small numbers(Ferry et al. 1996, Kubota et al. 2010). Some authors have suggested that

CD5 expression is associated with an aggressive clinical course marked by widespread dissemination(Wenzel et al. 2001, Batstone et al. 2003), but others suggested that CD5 expression has nothing to do with aggressiveness.(Ueda et al. 1996, Heuring et al. 2001, Tasaki et al. 2007) Thus, the clinical features of the CD5-positive subgroup of MZL lymphoma are not well defined.

In fact, these CD5-positive MZL cases have many similarities with classical CD5-negative MZL cases, including their clinical presentation, cytological, morphological and immunological features, cytogenetics(Ballesteros et al. 1998)，which suggests that they could arise from a common B cell of the marginal compartment differing only by CD5 expression. Previous studies have shown that, Histologic transformation to DLBCL occurs in 7.5% of cases, with the majority (73.5%) from EMZL, followed by NMZL (14.7%)(Conconi et al. 2015, Alderuccio et al. 2018). For this study, Histologic transformation to DLBCL occurs in 2.94% of cases, most of them were MALT (66.67%), others (33.33%) were NMZL, low than previous research. It may be caused by different regions and too little data. Moreover, we found that CD5-positive of MZL was easier to evolute to DLBCL (P<0.05), DLBCL transformation occurred in 6 of 204 patients, and 5 of them were CD5-positive. But the reliability of this conclusion needs further verification, because of our study is single-center retrospective analysis, and the number of patients was limited.

Although CD5-positive MZL is more easily transformation to DLBCL, CD5 expression does not appear to have an impact on prognosis. There is no statistical difference in the OS rates of CD5-positive and CD5-negative. the 5-year PFS and OS rates for CD5-positive marginal zone lymphoma were 64.80% and 84.10%, there is no significant difference between CD5-positive and CD5-negative (P=0.829, P=0.521). The 5-years OS of all MZL was 77.30% in our study, which is similar to those reported from other population-based studies revealing 5-years OS rates/estimates of 61% (UK's HMRN, 2004–2014), (Smith et al. 2015) 72% (SEER, 1995–2009) (Olszewski and Castillo 2013) and 84% (SEER, 2009–2017), (Vaughn et al. 2021) respectively. In this study, SMZL has the lowest 5-years OS rates, but the

number of cases of SMZ is small, so the 5-years OS rates of SMZL needs further study.

In summary, our findings indicate that CD5 expression occurs in a significant subset of MZL. Patients with CD5-positive MZL appear to have a higher frequency of transformation to DLBCL, although CD5 expression has no effect on the prognosis. the mechanism that is more likely to be DLBCL needs further study.

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