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Original Article

Clinicopathological and molecular genetic abnormalities associated with the prognosis of angioimmunoblastic T-cell lymphoma

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Abstract: Objective: To explore the clinicopathological and molecular genetic correlations of angioimmunoblastic T-cell lymphoma (AITL) with the Epstein-Barr virus (EBv) and to analyze the related prognostic factors. Methods: Paraffin-embedded samples of 16 cases of AITL and detailed clinicopathological information were obtained and studied using the immunohistochemistry EnVision method for the CXCL13, PD-1, CD10, BCL-6, CD2, CD3, CD5, CD7, CD20, CD79a, PAX5, CD4, CD8, CD21, CD23, and Ki-67 markers. The expression of EBER mRNA was quantified by in situ hybridization. BCL-2, BCL-6, and C-MYC gene abnormalities were determined with interphase fluorescence in situ hybridization (FISH). Results: Sixteen cases were examined, including 11 males (68.8%) and 5 females (31.2%), for a sex ratio of 2.2:1, an age range from 38-78 years, and a median age of 65.5 years. AITL typically presented at an advanced stage, with enlargement of the body and some lymph nodes, fever, splenomegaly and rash. Patient data: polyclonal hypergammaglobulinemia, 75.0% (12/16); high-risk of the International Prognosis Index (IPI), 56.3% (9/16); high level of lactate dehydrogenase (LDH), 20% (2/10); bone marrow involvement, and 81.3% (13/16); IIIb-IV of clinical stage. The tumor cells positive for CXCL13 were (93.8%, 15/16), PD-1 (75.0%, 12/16), CD10 (50.0%, 8/16), BCL-6 (81.3%, 13/16), CD2 (100.0%, 16/16), CD3 (100.0%, 15/16), CD5 (62.5%, 10/16), CD7 (18.8%, 3/16), CD20 (12.5%, 2/16), CD79a (18.8%, 3/16), PAX5 (6.3%, 1/16), CD4 (81.3%, 13/16), CD8 (18.8%, 3/16), CD21 (87.5%, 14/16), CD23 (87.5%, 14/16), Ki-67 (≥ 30.0%, 16/16), and EBER (56.3%, 9/16). The genetic alterations of BCL2, BCL6, and C-MYC were not detected using the FISH method. All of the patients had follow-up results, with a follow-up ranging from 1-84 months, and the median survival time was 17 months (1-84 months). Five cases died within a year, so the one-year survival rate was 68.75% (11/16). All data were used for the statistical analysis. Six patients died (mortality rate 37.5.0%, 6/16). A univariate analysis showed that male, ≥ 65 years old, the IPI score risk group, and LDH level led to a poor prognosis. Conclusions: AITL is a common lymphoma in elderly patients with an advanced stage and a poor prognosis. CXCL13, PD-1, CD10, and BCL-6 play an important role in the diagnosis of the tumor. Additionally, gender, age, IPI score, and LDH levels are important prognostic factors.

Keywords: Lymphoma, AITL, immunohistochemistry, fluorescence in situ hybridization, prognosis

Introduction

Angioimmunoblastic T-cell lymphoma (AITL) is a peripheral T-cell lymphoma (PTCL) that is characterized by T-cell hyperplasia, accompanied by high endothelial vessels and follicular dendritic cell hyperplasia It accounts for 1-2% of all non-Hodgkin's lymphoma (NHL) and 15-20% of PTCL [1]. Its features include systemic disease with polymorphous infiltration, branching high endothelial vessels, and follicular dendritic cell hyperplasia. The main clinical manifestations of AITL are fever, systemic lymphadenopathy, hepatomegaly, splenomegaly, weight loss, skin rash, and polyclonal hyperglobulinemia, and its prognosis is poor. AITL needs to be discriminated from reactive hyperplasia and non-specific PTCL in its pathological diagnosis. AITL overlaps with PTCL (non-specific) follicular subtypes in pathological and immunological phenotypes, which increases the difficulty of AITL pathological diagnosis. We performed a retrospective analysis of clinicopathologic data of 16 patients with AITL to analyze its clinical manifestations,

Table 1. Antibodies used for immunohistochemistry

Antigen	Clone	Source	Location	Dilution
CXCL13	GAB-0616	Fuzhou Maixin Biotech. Co., Ltd	Beside nucleus or/and in cytoplasm	1:100
PD-1	MRQ-22	Zhongshan Biotechnology Co., Ltd	Cell cytoplasm	1:50
CD10	56C6	Shanghai Gene Tech Co., Ltd	Cell membrane	1:30
BCL-6	GI191E/A8	Zhongshan Biotechnology Co., Ltd	Cell nucleus	1:80
CD2	UMAB6	Zhongshan Biotechnology Co., Ltd	Cell membrane	1:40
CD3	LN10	Zhongshan Biotechnology Co., Ltd	Cell membrane	1:50
CD5	SP19	Zhongshan Biotechnology Co., Ltd	Cell membrane	1:100
CD7	MRQ-56	Shanghai Gene Tech Co., Ltd	Cell membrane	1:50
CD20	L26	Shanghai Gene Tech Co., Ltd	Cell membrane	1:150
CD79a	EP82	Zhongshan Biotechnology Co., Ltd	Cell membrane	1:100
PAX5	SP34	Shanghai Gene Tech Co., Ltd	Cell nucleus	1:50
CD4	1F6	Zhongshan Biotechnology Co., Ltd	Cell membrane	1:40
CD8	SP16	Zhongshan Biotechnology Co., Ltd	Cell membrane	1:50
CD21	EP3093	Fuzhou Maixin Biotech. Co., Ltd	Cell membrane	1:50
CD23	EP75	Zhongshan Biotechnology Co., Ltd	Cell membrane	1:100
Ki-67	MIB-1	Shanghai Gene Tech Co., Ltd	Cell nucleus	1:150

pathological characteristics, specific markers and prognosis. Additionally, we reviewed the literature to better understand this tumor.

Materials and methods

Materials

Specimens from 16 patients with AITL were collected from the First Affiliated Hospital of Xinjiang Medical University between January 2003 and December 2012. All sections were reviewed by two independent professional lymphoma pathologists (Xinxia Li and Wenli Cui) who referred to the *WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues* (2008) and followed up, with the patients' informed consent. Complete clinical and follow-up data were obtained. The deadline for the first follow-up visit was September 30, 2015. The follow-up content included age, gender, lactate dehydrogenase (LDH) level, clinical staging, international prognostic index (IPI) score, and overall survival (OS) time. The OS time was calculated from the date of diagnosis to death or termination of follow-up caused by lymphoma. Death irrelevant to this disease was considered an end.

Immunohistochemistry markers and criteria: All submitted tissues were lymph gland tissues. The tissue sections were embedded in paraffin. The primary antibodies, clone, manufacturer, and dilutions are listed in **Table 1**. The EnVision method was applied to examine CXCL13, PD-1, CD10, BCL-6, CD2, CD3, CD5, CD7, CD20, CD79a, PAX5, CD4, CD8, CD21, CD23, and Ki-67. Among them, CXCL13 and CD21 were purchased from Fuzhou Maixin Biotech. Co., Ltd. PD-1 and Ki-67 were purchased from Danish Dako. Other antibodies were purchased from Zhongshan Biotechnology Co., Ltd. The immunohistochemical analysis was performed using a Ventana BenchMark XT auto-immunostainer (Ventana Medical System, Tucson, AZ). Using known positive tissues as the positive control and omitting primary antibodies as the negative control, DAB color development and hematoxylin contrast staining were conducted. The results indicated that CXCL13 was localized near the nuclei or/and in the cytoplasms [2, 3]. BCL-6, PAX5 and Ki-67 were localized in the cell nuclei. PD-1, CD10, CD2, CD3, CD5, CD7, CD20, CD79a, CD4, CD8, CD21 and CD23 were localized in the cell membranes.

EBV-coded small RNA (EBER) in situ hybridization detection

Paraffin-embedded sections of the specimens from the 16 patients were processed using an EBER *in situ* hybridization kit (the EBER probe was produced by Danish Dako). Positive expression was localized in the nucleus (digoxin was applied to label EBER1/2 DNA probes and detect EBER1 and EBER2 expression in the tis-

Table 2. Clinical features of AITL (N = 16)

Case No	Sex/Age (yr)	Nation	Size (cm)	Stage	IPI	Elevated LDH	Hypertension	Bone marrow biopsy	Follow-up period (mo)	Status
1	M/47	Hui	5	IIIB	Low	172	No	Without	45+	Alive
2	M/75	Han	2.5	IIIA	Low	168	Grade 3	No	60+	Alive
3	M/75	Han	4	IVB	High	356	No	Without	28	Dead
4	F/67	Han	1.5	IVA	High	286	Grade 3	No	34+	Alive
5	M/74	Han	1	IVB	High	549	No	Without	1	Dead
6	M/54	Han	2	IVA	H-int	233	No	Without	24+	Alive
7	M/78	Han	2	IVA	High	81	Grade 3	Without	4	Dead
8	F/78	Han	1.5	IVB	High	387	Grade 3	Without	2	Dead
9	F/47	Dongxiang	2.4	IVB	High	198	Grade 2	No	19+	Alive
10	M/75	Han	1.3	IIIB	High	206	Grade 3	Invasion	2	Dead
11	F/64	Han	2	IA	Low	214	No	Invasion	17+	Alive
12	M/68	Han	2	IVA	High	299	Grade 2	Without	6+	Alive
13	M/67	Mongols	2.9	IVA	High	432	No	No	3	Dead
14	M/38	Han	0.6	IIIA	High	289	No	No	2	Drop out
15	F/62	Han	1.5	IVA	H-int	217	No	No	84+	Alive
16	M/46	Han	3	IIIB	Low	212	No	Without	8+	Alive

M, male; F, female; IPI, International Prognostic Index; H-int, high-intermediate; LDH, lactate dehydrogenase.

sues). The in situ hybridization procedures were performed as previously described [4], with lymph glands containing infectious mononucleosis used as positive controls.

Fluorescence in situ hybridization (FISH)

The probes used in the present study included dual color break apart rearrangement probes (including the BCL-6 probe: 30-231050, and the C-MYC probe: 30-191096) and dual color, dual fusion translocation probes (IgH/BCL-2 probe: 30-191018). All probes were purchased from the U.S. Vysis-Abbott Company. The FISH procedures were performed as previously described [5, 6]. FISH 2.0 Software was used to analyze the results. The interpretation of the results was performed as previously described [7, 8]. For each case, 10 fields of view (FOVs) were selected, and 100 cells were counted for each FOV. The percentage of positive cells in 10 FOVs was calculated. If red and green signals overlapped in > 5% of the tumor cell nuclei, then BCL-2/IgH was considered positive. If red and green signals were not overlapped in > 5% of the tumor cell nuclei, BCL-6 and C-MYC were considered positive.

Statistical processing

SPSS 19.0 statistical software was used for statistical analysis. The results were expressed as the means ± standard deviations, as the medians and ranges for continuous variables, and as proportions for categorical variables. The associations between pathologic variables were tested using the chi-square test. The Kaplan-Meier method was adopted for single factor analysis to draw survival curves. The results were considered significant at the 5% level ($P < 0.05$).

Results

Clinical features

The primary clinical data on the 16 patients are listed in **Table 2**. Among the 16 patients, there were 11 males and 5 females. The male to female ratio was 2.2:1. The median age was 65.5 (range: 38-78) years. Nine patients (56.3%) were more than 65 years old. All patients had systemic or partial lymphadenopathy. Nine cases (56.3%) showed extranodal organ involvement. The spleen was affected in 43.8% (7/16) of the cases. Among the 10 cases that underwent a bone marrow needle biopsy, 2 cases (20%) had bone marrow involvement. Seven cases (43.8%) had a history of hypertension. Seventy-five percent (12/16) of the patients had B symptoms (fever of unknown origin > 38°C, night sweats, weight loss > 10% in half a year). Fever was present in 62.5% (10/16), and 37.5% (6/16) of the patients had a rash. The LDH levels were normal (109-245 IU/L) in 8 cases, higher than normal (> 245 IU/L) in 7

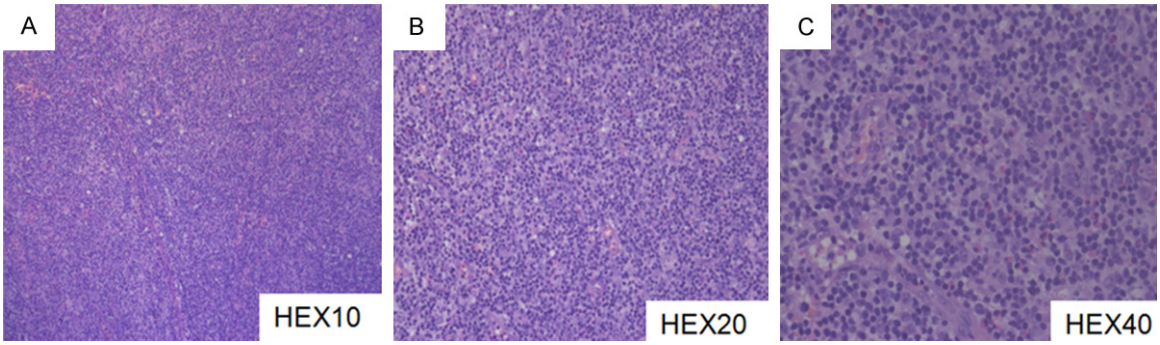


Figure 1. AITL. A. The lymph node structure was damaged. Tumor cells infiltrated the envelope. H/E stain, low-power magnification. B. A large number of heterotypic small lymphocytes exhibited diffusion and infiltration. Branching high endothelial venules and follicular dendritic cells were significantly hyperplastic. H/E stain, medium-power magnification. C. The infiltrated lymphocytes were medium to large cells. The cytoplasm was lucent or light. The karyotheca was clear. H/E stain, high-power magnification.

cases, and lower than normal (< 109 U/L) in 1 case. According to the Ann-Arbor staging criteria, there was 1 case (6.25%) at Stage IA, 2 cases (12.5%) at Stage IIIA and 13 cases (81.3%) at Stage IIIB-IV. The international prognostic index (IPI) score showed that there were 4 cases (25.0%) at low risk and 12 cases (75.0%) at a moderately high-risk or high-risk.

Histopathological features

All specimens of the 16 patients with AITL were surgically resected. The lymph node structures were damaged to varying degrees. Parts of the marginal sinus and lymphoid follicle remained. The paracortex increased in size and was accompanied by polymorphous tumor cellular infiltration. The cells were small to medium sized. The cytoplasm was lucent or light. The karyotheca was clear. The heterotypic lymphocytes intermixed with small reactive lymphocytes, eosinophils, plasmocytes, histiocytes, and increased follicular dendritic cells (**Figure 1A-C**). The branching high endothelial venules and follicular dendritic cells were significantly hyperplastic.

Immunohistochemistry and in situ hybridization detection

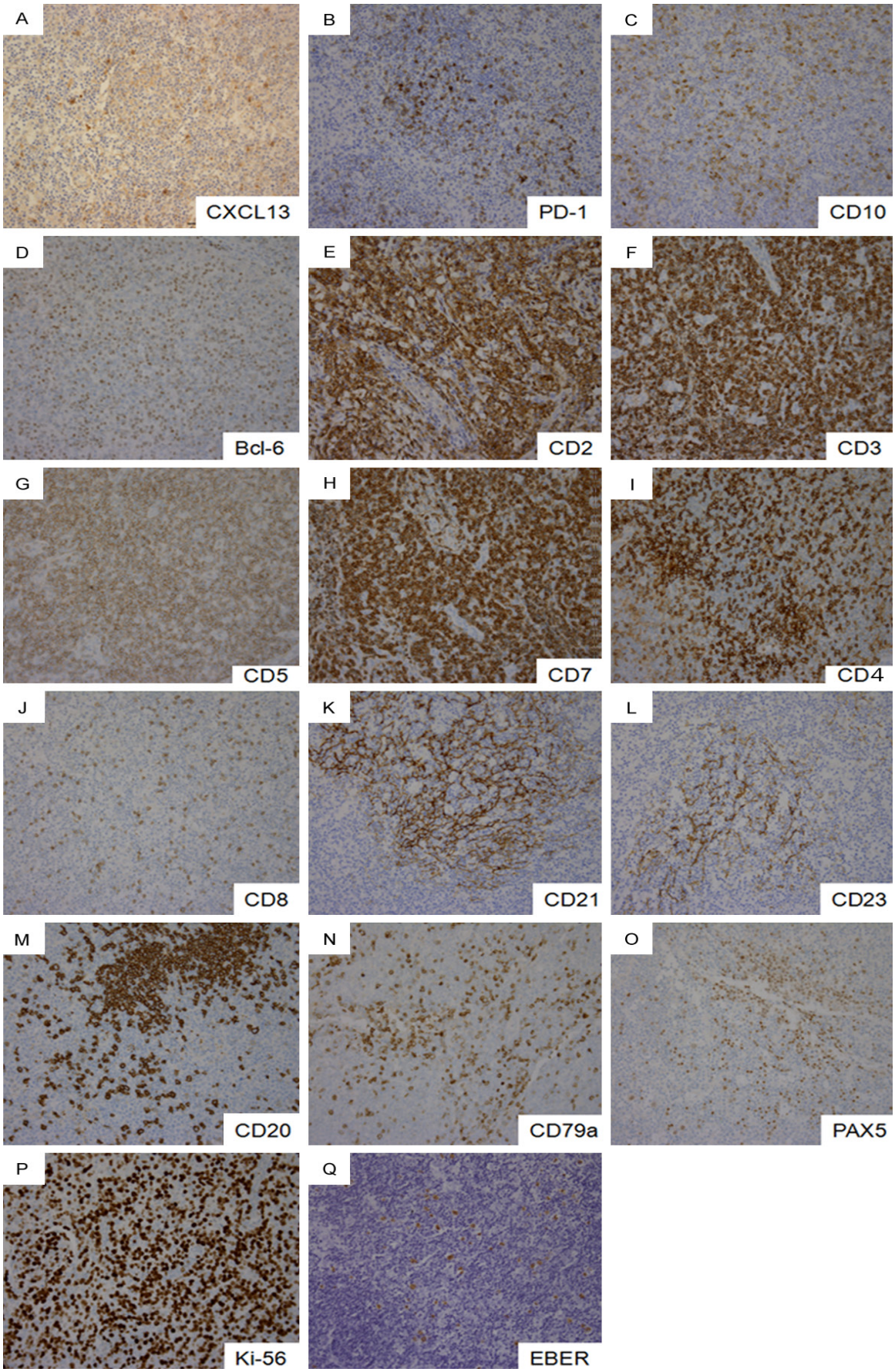
The specific markers for tumor expression were CXCL13, PD-1, CD10, and BCL-6. 15 of the 16 patients (93.8%) had positive CXCL13 expression. The one negative case had positive PD-1 expression. Twelve of the 16 patients (75.0%) had positive PD-1 expression. Four negative cases had positive CXCL13 expression. The CD10 positive rate was 50.0% (8/16). The BCL-6 positive rate was 81.3% (13/16) (**Figure 2A-D**). Regarding the T-lymphocyte markers for tumor expression: the CD2 positive rate was 100.0% (16/16), the CD3 positive rate was 100.0% (16/16), the CD5 positive rate was 62.5% (10/16), and the CD7 positive rate was 18.8% (3/16) (**Figure 2E-H**). The CD4 positive rate was 81.3% (13/16). CD8 was not expressed. The positive rate of reactive small lymphocytes with mature morphology was 18.8% (3/16) (**Figure 2I**, **2J**). AITL showed characteristic CD21 and CD23 follicular dendritic cell meshwork hyperplasia. The positive rate of both was 87.5% (14/16) (**Figure 2K**, **2L**). The EBER in situ hybridization positive rate was 56.3% (9/16) (**Figure 2Q**). The positive expression observed was in the nucleus. The EBER positive cells expressed CD20, CD79a, and PAX5 but did not express the T-cell phenotype; they were B immunoblastic cells, with positive rates of 25.0% (4/16), 12.5% (2/16), and 18.8% (3/16), respectively (**Figure 2M-O**). All Ki-67 were positively expressed. The median positive rate was 60.0% (30.0%-95.0%), with an average of 59.1%. All Ki-67 positive rates were 30.0% (16/16) or higher (**Figure 2P**).

FISH detection

BCL-2/IgH, BCL-6, and C-MYC gene rearrangement did not occur in the tumor cells (**Figure 3A-C**).

Prognostic analysis

All the patients in the present study were followed up on the phone. The survival time was calculated from the date of pathological diag-


A
CXCL13
B
PD-1
C
CD10
D
Bcl-6
E
CD2
F
CD3
G
CD5
H
CD7
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CD4
J
CD8
K
CD21
L
CD23
M
CD20
N
CD79a
O
PAX5
P
Ki-56
Q
EBER

Figure 2. Immunohistochemical results (EnVision method, low-power magnification). A. CXCL13 expression on oncocyte; B. PD-1 expression on oncocyte; C. CD10 expression on oncocyte; D. BCL-6 expression on oncocyte; E. CD2 expression on oncocyte; F. CD3 expression on oncocyte; G. CD5 expression on oncocyte; H. CD7 expression on oncocyte; I. CD4-positive oncocytes; J. CD8-positive small reactive lymphocytes; K. CD21 labelling showed increased degenerated FDC networks; L. CD21 labelling showed increased degenerated FDC networks; M. CD20 expression on oncocyte; N. CD79a expression on oncocyte; O. PAX5 expression on oncocyte; P. Ki-67-positive oncocytes; Q. EBER-positive oncocytes.

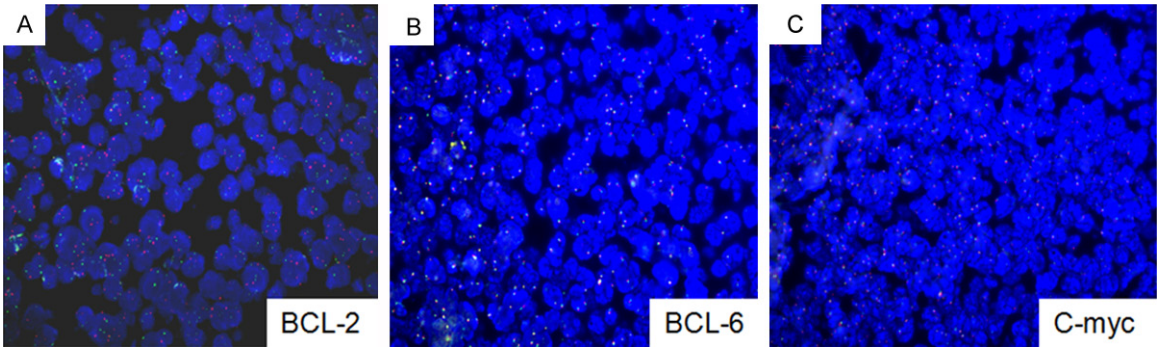

Figure 3. FISH results (×1000). A. BCL-2/IgH translocation rearrangement did not occur in oncocytes; B. BCL-6 gene rearrangement did not occur in oncocytes; C. C-MYC gene rearrangement did not occur in oncocytes.

Table 3. The disease-free survival of 16 patients with AITL by prognostic factor grouping

Factor		Number of Cases	Overall Survival [% (cases)]		
			1-year	2-year	3-year
Gender	Male	11	63.6 (7)	63.6 (7)	45.5 (6)
	Female	5	80.0 (4)	80.0 (4)	80.0 (4)
Age (yrs)	< 65	7	100.0 (7)	100.0 (7)	100.0 (7)
	≥ 65	9	44.4 (4)	44.4 (4)	33.3 (3)
IPI	Low-risk	4	100.0 (4)	100.0 (4)	100.0 (4)
	High-risk	12	58.3 (7)	58.3 (7)	50.0 (6)
LDH	Normal	8	87.5 (7)	87.5 (7)	87.5 (7)
	Abnormal	8	50.0 (4)	50.0 (4)	37.5 (3)
Clinical Staging	I-IIIA	3	100.0 (3)	100.0 (3)	100.0 (3)
	IIIB-VI	13	61.5 (8)	61.5 (8)	53.8 (7)
Bone Mallow Needle Biopsy	Uninvolved	8	62.5 (5)	62.5 (5)	50.0 (4)
	Involved	2	50.0 (1)	50.0 (1)	50.0 (1)
Hypertension	No	9	77.8 (7)	77.8 (7)	66.76
	Yes	7	57.1 (4)	57.1 (4)	57.1 (4)

nosis. The last included follow-up visit was set for October 30, 2015. Among the 16 patients, 15 had systematically traceable follow-ups, but 1 case was lost to follow-up. The median survival time of the whole group was 17 months (1-84 months) in **Table 3**. After treatment, the 1-year OS rate was 66.67% (5/15). A total of 6 patients died, accounting for 40.0% of the whole group. The times of death were 1, 2, 2, 3, 4, and 28 months after diagnosis, respectively. Within 1 year was the peak time for death (**Figure 4A**). A group analysis was performed according to the factors of the lymphoma international prognostic index (IPI). According to the prognostic factor grouping, the survival curves are shown in **Figure 4B-H**.

A single factor prognostic analysis showed that the OS of the males was better than that of the females (**Figure 4B**). The OS of the patients aged < 65 was better than that of the patients aged ≥ 65 (**Figure 4C**). The OS of the patients

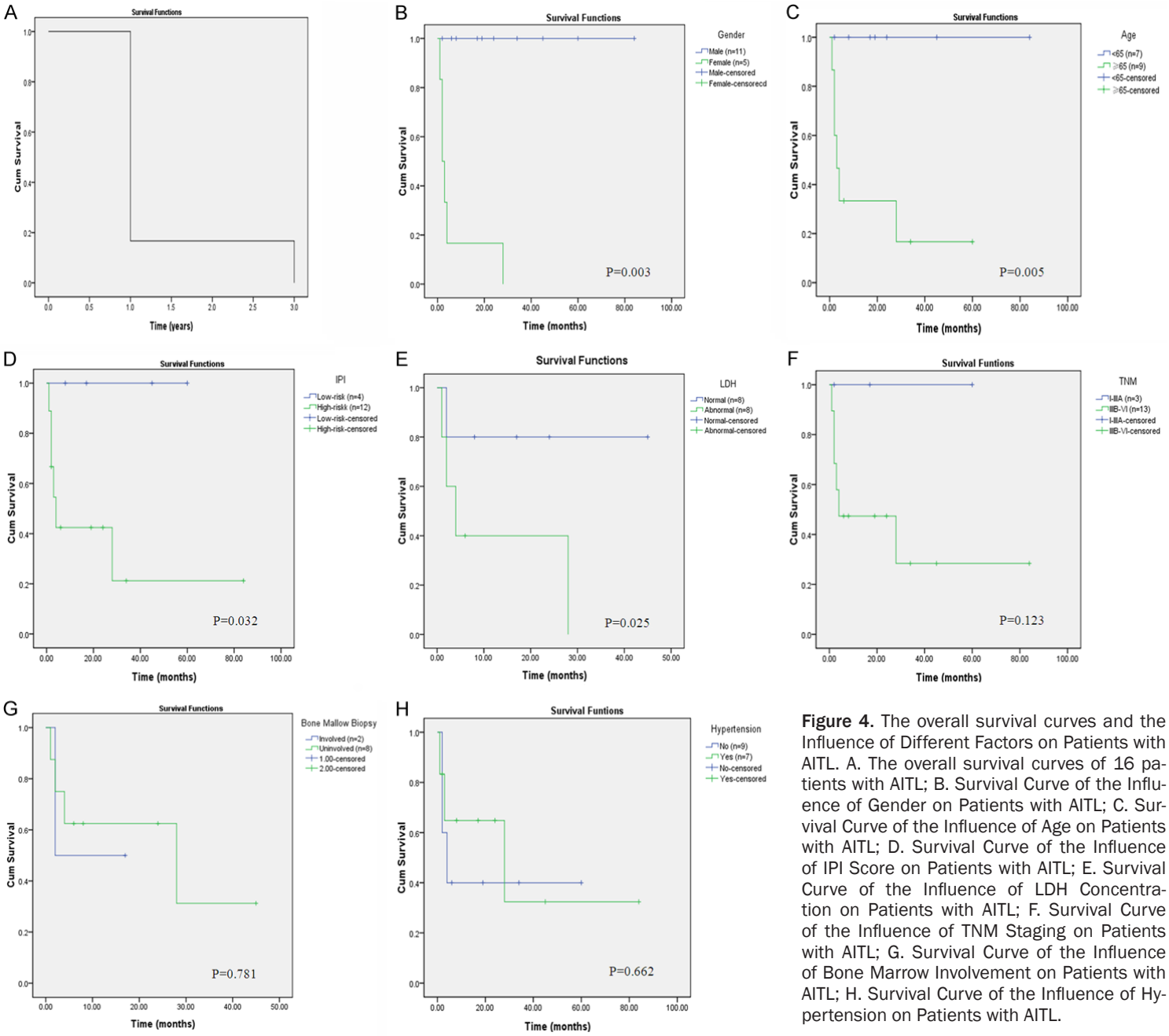

Figure 4. The overall survival curves and the Influence of Different Factors on Patients with AITL. A. The overall survival curves of 16 patients with AITL; B. Survival Curve of the Influence of Gender on Patients with AITL; C. Survival Curve of the Influence of Age on Patients with AITL; D. Survival Curve of the Influence of IPI Score on Patients with AITL; E. Survival Curve of the Influence of LDH Concentration on Patients with AITL; F. Survival Curve of the Influence of TNM Staging on Patients with AITL; G. Survival Curve of the Influence of Bone Marrow Involvement on Patients with AITL; H. Survival Curve of the Influence of Hypertension on Patients with AITL.

who scored as low-risk in IPI was better than the OS of those who scored as high-risk (**Figure 4D**). A normal LDH level also determined the level of OS (**Figure 4E**), which was consistent with the IPI score. The OS of patients with stages IIIb-VI disease was lower than the OS of those in stages III or above (**Figure 4F**). TNM, bone marrow involvement (**Figure 4G**), and hypertension (**Figure 4H**) showed no association with patient prognosis ($P > 0.05$).

Discussion

Angioimmunoblastic T-cell lymphoma (AITL) is an invasive lymphoma that accounts for 1-2% of non-Hodgkin's lymphoma (NHL) cases and 15-20% of PTCL cases [1]. AITL is characterized by systemic disease and polymorphous infiltration, branching high endothelial vessels and follicular dendritic cell hyperplasia. A total of 16 AITL cases treated in our hospital between January 2003 and December 2012 were retrospectively analyzed. The clinical manifestations, pathological characteristics, specific markers and prognosis-related factors of AITL were analyzed. The relevant literature was reviewed to deepen our understanding of this tumor.

AITL often occurs in elderly patients. In our study, there were 16 patients with AITL, including 11 males and 5 females. The male to female ratio was 2.2:1. The average age was 57.9 years. The median age was 65.5 (38-78) years. Nine cases (56.3%) were more than 65 years old, similar to data seen observed in previous reports [9-11]. Most patients with AITL were in a progressive stage when they first visited a doctor. The main clinical manifestations were fever, systemic lymphadenectasis, hepatomegaly, splenomegaly, weight loss, rash and polyclonal hyperglobulinemia. This group of patients did not have specific clinical manifestations other than systemic or partial lymphadenectasis. The LDH levels were higher than normal (> 245 IU/L) in 7 cases and lower than normal (< 109 U/L) in 1 case. The patients' clinical biological behaviors were highly invasive. Overall, 75.0% (12/16) of the patients had B symptoms. The patients in stages IIIB-IV accounted for 81.3% (13/16). The patients who scored as moderately high- and high-risk in IPI accounted for 75.0% (12/16). Further, 43.8% (7/16) of the patients had a history of hypertension, and 56.3% (9/16) had extranodal organ involvement. The incidence of extranodal organ involvement was consistent with the literature. Therein, the spleen involvement rate was 43.8% (7/16), and the bone marrow involvement rate was 20% (2/10), rates lower than those found by GELA (Groupe d'Etude des Lymphomes de l'Adulte) [12] but consistent with reports by Chinese scholars [11, 13], suggesting that the AITL biological behaviors of Chinese patients may differ from those in Europe and America. However, the present study was a monocentric, retrospective analysis that must be further confirmed with more studies.

AITL mainly occurs in the lymph nodes. Among all of the 16 cases in this group, it occurred in glands. The pathomorphological features of this tumor included the following: (1) The lymph node structure was damaged to varying degrees, but part of the marginal sinus and lymphoid follicle remained; (2) The paracortex increased in size and showed polymorphous tumor cellular infiltration. The cells were small to medium sized. The cytoplasms were transparent or light in color. The karyotheca was clear; (3) The branching high endothelial venules and follicular dendritic cells were significantly hyperplastic; (4) Many background cells were present, including small reactive lymphocytes, eosinophils, plasmocytes, histocytes, and epithelioid cells. The specific markers for oncocyte expression were CXCL13, PD-1, CD10, and BCL-6. Fifteen of the 16 patients (93.8%) had positive CXCL13 expressions. One negative case had positive PD-1 expression. Twelve of the 16 patients (75.0%) had positive PD-1 expression. Four negative cases had positive CXCL13 expressions. The CD10 positive rate was 50.0% (8/16). The BCL-6 positive rate was 81.3% (13/16). The positive rates of CD2 and CD3, T-lymphocyte markers for oncocyte expression, in the 16 patients in our study, were 100%. The CD5 positive rate was 62.5%, suggesting that this tumor was a T-cell lymphoma. The B immunoblasts expressed CD20, CD79a, or PAX5 but did not express the T-cell phenotype. Among the patients, 81.3% (13/16) had oncocytes expressing CD4. Because CD4 indicated that cytotoxicity was associated with T cells, its high expression may be related to the effect of cytotoxicity. Neither CD7 nor CD8 exhibited a loss. However, scattered small reactive T-lymphocytes can express CD7 and CD8. AITL indicated characteristic CD23 and CD21 follicular dendritic cell hyperplasia. Their posi-

tive rates were 87.5% (14/16), and they usually grew around high endothelial veins. All Ki-67 were positively expressed. The median positive rate was 60.0% (30.0%-95.0%), with an average of 59.1%.

Research has shown that BCL-2/IgH, BCL-6 and C-MYC gene rearrangement is present in diffuse large B-cell lymphoma (DLBCL) [14-16]. Chromosomal and gene loci changes are associated with the genesis, development and outcome of lymphoma. One study found that 10% of all AITL cases progress to DLBCL [17]. The present study used fluorescence in situ hybridization to detect abnormalities in the BCL-2/IgH, BCL-6, and C-MYC genes in tissue specimens of 10 patients with AITL to study their molecular genetic features and thereby understand its pathogenesis and find better treatments. The BCL-2 gene is located on 18q21, and the BCL2 protein has anti-apoptotic functions. BCL2 is widely expressed in immature B cells and memory B cells but not in germinal centre B cells. The BCL-6 gene is located on 3q27, at the end of chromosome 3. The BCL-6 protein is a zinc-finger protein in which the N-terminus carries a POZ domain. BCL-6 is expressed only in the germinal centre B cells in various human tissues, suggesting that the formation of the germinal center depends on the expression of the BCL-6 protein. The C-MYC gene is located on 8q24, and the MYC protein is a transcription factor that regulates the expression of many genes, including those involved in cell cycle regulation, metabolism, DNA repair, protein synthesis, and other genes. BCL-2, BCL-6, and C-MYC are all involved in the genesis of B cells lymphomas. Our findings showed that gene rearrangement of BCL-2/IgH, BCL-6 and C-MYC did not occur in AITL oncocytes, suggesting that the above genes were not involved in the genesis and development of this specific type of tumor.

At present, some scholars believe that the pathogenesis of AITL is associated with latent EBV infections. EBV-infected B cells display EBV proteins on their surface to T cells through major histocompatibility complex class II molecules, up-regulate CD28 ligand expression, provide antigens and stimulating signals for T-cell activation and prompt T-cells to secrete the chemokine CXCL13. At the same time, CXCL13 can activate B cells to become hyperplasic, thus forming a feedback loop. The EBER in situ hybridization positive rate in our group was 56.3% (9/16), which further confirms this hypothesis. It may also explain why AITL can progress to DLBCL [17, 18].

AITL is a type of invasive lymphoma. The medial survival time is estimated to be less than 3 years. The 5-year survival rate was 30%-35%. Thus, the prognosis is poor [13]. Our study included 16 systematically traceable follow-up cases. The median survival time of the whole group was only 17 months (1-84 months). After treatment, the 1-year OS rate was 68.75% (11/16). Within 1 year was the peak time for death. A total of 6 patients died, accounting for 37.5% of the cohort (6/16). AITL prognostic factors have been a research hotspot in recent years, and IPI has been used for the prognostic evaluation of patients with lymphoma [11]. The present study used the lymphoma international prognostic index (IPI) factor. The prognosis of patients scored as low-risk in IPI was better than the prognosis of those who scored as high-risk, which suggests that the IPI score was an important and reliable prognostic measure for AITL. The present study then compared other prognosis-related factors. The results showed that males, age of 65 or higher, the IPI score high-risk group, and abnormal LDH levels were associated with the patients' poor prognosis [11]. The results of the present study suggest that TNM and bone marrow involvement is not associated with AITL prognosis. This could be attributed to the small sample size used in the present study. The sample size must be enlarged for further study and confirmation.

In summary, AITL often occurs in elderly patients and is a highly invasive lymphoma with a poor prognosis. CXCL13, PD-1, CD10 and BCL-6 play important roles in the diagnosis of this tumor. Gender, age, IPI score, and LDH levels are all important factors affecting the prognosis of patients. The present study deepened our understanding of this tumor, but because of its small sample size, further studies are needed.

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Disclosure of conflict of interest

None.

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