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Original Article

Correlation between the clinicopathological features and prognosis in patients with extranodal natural killer/T cell lymphoma

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Abstract

Objective: To investigate the correlation between the clinicopathological features and prognosis in patients with extranodal natural killer (NK)/T-cell lymphoma (ENKTCL).

Methods: One hundred and four patients diagnosed with ENKTCL at the Department of Pathology, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China from November 1991 to September 2011 were included in the study. The clinicopathological features and their correlations with disease prognosis were evaluated in these patients.

Results: The number of effective follow-up cases was 56 (53.8%) by the end of last follow-up in October 2015. Univariate survival analysis showed that granzyme B, perforin, and Bcl-2 expression was significantly associated with a poor prognosis in ENKTCL ($P = 0.033$, 0.004, and 0.034, respectively), whereas platelet-derived growth factor receptor-alpha (PDGFRA) expression was significantly associated with a better prognosis ($P = 0.034$). Ki-67 overexpression (≥50%) was significantly associated with a poor prognosis ($P = 0.017$). Different treatment approaches were also associated with prognosis ($P = 0.014$); specifically, the efficacies of combination treatments including chemotherapy and radiotherapy, and autologous hematopoietic stem cell transplantation were significantly better than those involving radiotherapy and chemotherapy alone. Patient gender, age, tumor location, staging, the presence of B symptoms, pretreatment lactate dehydrogenase levels, and β2-microglobulin levels were not associated with the prognosis of ENKTCL ($P > 0.05$). However, multivariate analyses showed that the treatment approach and all the immune markers were not independent prognostic factors for ENKTCL.

Conclusion: Granzyme B, perforin, and Bcl-2 expression and Ki-67 overexpression (≥50%) might be adverse prognostic factors for ENKTCL, whereas PDGFRA-positivity suggested a better disease prognosis. In addition, different treatment approaches might be closely related to patient prognosis.

Keywords: Extranodal natural killer/T-cell lymphoma; Pathology; Immunohistochemistry; Prognosis

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Introduction

Extranodal natural killer (NK)/T-cell lymphoma (ENKTCL) is a rare type of non-Hodgkin's lymphoma (NHL) that accounts for 5%−18% of all NHL. There are significant regional and racial differences in its prevalence, and the cases in Asia, Mexico, and South America account for about 70% of the total number of cases.[1] With the aid of morphological traits, immunohistochemistry and Epstein−Barr virus (EBV)-encoded RNA (EBER) *in situ* hybridization test, diagnosis of ENKTCL is no longer difficult. However, there are no standard treatment guidelines for this disease. While some previous retrospective analyses have shown that ENKTCL has a poor prognosis, some others have reported different findings.[2,3] The quest for molecular markers for the treatment and prognosis of ENKTCL has, therefore, become an active area of research.

We performed a retrospective analysis of the clinicopathological features of patients with ENKTCL from the Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China and evaluated the correlations between these features, immunophenotypes, and the disease prognosis.

Methods

Cases and clinical data

One hundred and four patients pathologically diagnosed with ENKTCL in the Department of Pathology, Cancer Hospital, Chinese Academy of Medical Sciences between November 1991 and September 2011 were included in this study. The samples were collected from patients during routine diagnostic procedures after obtaining their informed consent. The study was approved by the Independent Ethics Committee of the Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China and was performed in accordance with the Declaration of Helsinki. The clinical data collected included patient's age, gender, disease course, primary site, the extent of disease involvement, B symptoms, lactate dehydrogenase (LDH) levels, β2-microglobulin (β2-MG) levels, clinical staging, treatment approaches, therapeutic efficacy, recurrence, and metastasis. All cases were followed up by phone, starting from the date of pathological diagnosis. The reasons for discontinuing follow-up included death, withdrawal, or termination of follow-up (October 2015). The followings were recorded during follow-up: the disease course, B symptoms, treatment, recurrence, status when follow-up was terminated (death, survival, or withdrawal), cause of death, and survival time (in months).

Histopathology

All specimens were fixed in 10% neutral formalin, paraffin-embedded, and sectioned into 4 μm-thick sections for hematoxylin and eosin (H&E) staining. The hematopoietic lymphoid tumors from the 56 patients were classified according to the World Health Organization criteria under a light microscope. The number of tumor cells, tumor cell distribution (diffused or scattered), size and morphology of tumor cells, vascular invasion, and the pro-epithelial or mucosal infiltration of tumor cells were all observed under the microscope. Finally, some cases associated with tissue necrosis, pseudoepitheliomatous hyperplasia of the mucosa, granulomas, and fungal infections were also recorded.

Immunohistochemistry and EBV detection

Immunohistochemical staining by the EnVision System (Dako Cytomation, Carpinteria, CA, USA) was used to detect various antigenic markers in all cases. Positive controls were used for the immunohistochemical staining. Phosphate buffer saline (PBS) was used as negative control. All the primary antibodies used are listed in Table 1. The semi-quantitative analyses were scored as follows: (1) Positive intensity scoring: 0, no staining; 1, light yellow staining; 2, brownish yellow staining; and 3, brown staining. (2) Scoring based on the proportion of positive cells: 0, <5%; 1, 5−25%; 2, 26−50%; 3, 51−75%, and 4, >75%. The sum of the two scores was used as the final score for each case and ranked as follows: 0, negative (−); 1−4, weak expression (+); 5−8, moderate expression (++); and 9−12, strong expression (+++). Table 1 also shows the corresponding location (e.g., nuclei, cell membrane, and cytoplasm) of the cells that were stained positive with different antibodies.

The presence of Epstein−Barr virus (EBV) RNA was analyzed by nonisotopic *in situ* hybridization with EBER 1 and 2 oligonucleotide probes (Dako Cytomation, Carpinteria, CA, USA) in paraffin-embedded tissue sections. Staining of the nuclei was considered as positive staining, whereas cytoplasmic and cell membrane staining was considered negative. Samples of EBER-positive nasopharyngeal carcinoma diagnosed in our department were used as the positive control and PBS as the negative control. Tumor cell staining was determined according to the criteria described by Weiss et al.[4]

Table 1
Source of primary antibodies used in immunohistochemistry and the antigen recognition sites.

Antibody name	Clone number	Company	Positive location
CD3	SP7	Fuzhou Maixin Biotech. Co., Ltd., Fujian, China	Cell membrane
CD56	UMAB83	Beijing Zhong Shan-Golden Bridge Biotechnology Co., Ltd., Beijing, China	Cell membrane
CD30	Ber-H2	Dako Cytomation, Carpinteria, CA, USA	Cell membrane/cytoplasm
TIA-1	TIA-1	Fuzhou Maixin Biotech. Co., Ltd., Fujian, China	Cytoplasm
Granzyme B	Rabbit polyclonal antibody	Dako Cytomation, Carpinteria, CA, USA	Cytoplasm
Perforin	ZM44	Dako Cytomation, Carpinteria, CA, USA	Cytoplasm
Bcl-2	124	Dako Cytomation, Carpinteria, CA, USA	Cell membrane/cytoplasm
nm23	37.6	Dako Cytomation, Carpinteria, CA, USA	Cytoplasm
VEGF	Rabbit polyclonal antibody	Beijing Zhong Shan-Golden Bridge Biotechnology Co., Ltd., Beijing, China	Cytoplasm
PDGFRA	Rabbit polyclonal antibody	Beijing Zhong Shan-Golden Bridge Biotechnology Co., Ltd., Beijing, China	Cell membrane/cytoplasm
Ki-67	MIB-1	Fuzhou Maixin Biotech. Co., Ltd., Fujian, China	Nuclei

CD: cluster of differentiation; TIA-1: T cell intracellular antigen 1; VEGF: vascular endothelial growth factor; PDGFRA: platelet-derived growth factor receptor-alpha.

Statistical analysis

SPSS 19.0 software (SPSS Inc., Chicago, IL) was used for data analysis and processing. Survival analyses were performed using the Kaplan−Meier method to prepare a survival curve. Cox proportional hazard regression and binary Logistic regression models were used to perform multivariate analysis of potential prognostic factors. Differences with a $P < 0.05$ were considered significant.

Results

Clinical features and follow-up

Among the 104 cases pathologically diagnosed with ENKTCL, the number of effective follow-up cases was 56 (53.8%) by the end of last follow-up in October 2015. Table 2 shows the clinical data of these 56 patients. The age of the patients was 12−85 years, with a median age of 44 years. ENKTCL was more commonly seen in men, with a men to women ratio of 1.8:1. Most tumors were localized in the upper aerodigestive tract (52/56, 92.9%) and most commonly in the nasal cavity (37/56, 66.1%), followed by the nasopharynx (8/56, 14.3%), oropharynx (6/56, 10.7%), and tonsils (1/56, 1.8%). Among the regions outside the aerodigestive tract, ENKTCL was found in the gastrointestinal tract (2/56, 3.6%), skin (1/56, 1.8%), and soft tissues (1/56, 1.8%). According to the Ann Arbor staging system, 51 (91.1%) of the 56 patients had stage IE−IIE ENKTCL, and the remaining 5 patients (8.9%) had stage IIIE−IVE disease. Among the 56 ENKTCL patients, 27 (48.2%) had no B symptoms, and

Table 2
Clinical characteristics and univariate analysis of prognostic factors for 56 extranodal NK/T cell lymphoma patients.

Characteristics	*n*	χ^2	*P*-value
Gender		0.612	0.434
Male	36		
Female	20		
Age		0.349	0.555
≤45 years old	34		
>45 years old	22		
Primary Site		0.493	0.483
Upper aerodigestive tract	52		
Other	4		
Ann Arbor stage		1.902	0.168
IE−IIE	51		
IIIE−IVE	5		
LDH range		0.616	0.433
<240 UI/L	38		
≥240 UI/L	18		
β2-MG		0.111	0.739
<1.8 mg/L	19		
≥1.8 mg/L	37		
B symptoms		1.178	0.278
Absent	27		
Present	29		
Treatment approach		12.431	0.014
No treatment	4		
Radiotherapy	16		
Chemotherapy	4		
Combination of chemotherapy and radiotherapy	31		
AHSCT	1		

NK: natural killer; LDH: lactate dehydrogenase; β2-MG: β2-microglobulin; AHSCT: autologous hematopoietic stem cell transplantation.

29 (51.8%) had B symptoms (e.g., fever, night sweats, and progressive weight loss). Laboratory examinations revealed that 18 patients (32.1%) had elevated serum LDH levels (≥240 UI/L), and 37 patients (66.1%) had elevated β2-MG levels (≥1.8 mg/L). While 31 patients (55.4%) underwent a combination of chemotherapy and radiotherapy, 16 (28.6%) underwent only radiotherapy, 4 (7.1%) underwent only chemotherapy, 4 (7.1%) died without receiving any treatment, and 1 (1.8%) patient achieved complete remission (CR) after an autologous hematopoietic stem cell transplantation (AHSCT). Among the 35 patients who received chemotherapy, 25 received Cytoxan, Hydroxyrubicin, Oncovin, Prednisone (CHOP)-based chemotherapy, while the others received personalized treatment. After treatment, CR was seen in 66.1% (37/56) of patients. There were 10 recurrent cases (17.9%) and 9 metastatic cases (16.1%). Thirty-seven (66.1%) of the 56 patients survived and 19 (33.9%) died. The survival time of the 56 patients ranged from 0 to 287 months. The mean survival time was 88.4 months. The 1-, 2- and 3-year survival rates were 85.7% (48/56), 82.1% (46/56) and 80.3% (45/56), respectively.

Univariate Kaplan−Meier analysis and Log-rank tests were used to analyze the correlations between patient gender, age, primary site, staging, the presence of B symptoms, pretreatment LDH and β2-MG levels, treatment approaches, and prognosis. The results showed that only treatment approaches ($P = 0.014$) were significantly associated with patient prognosis (Table 2). The treatment efficacies of a combination of chemotherapy and radiotherapy, and AHSCT were significantly better than that of radiotherapy and chemotherapy alone (Fig. 1A).

Histopathological features

Microscopy revealed that the morphology of ENKTCL from various sites was similar. Against a background of coagulation necrosis and mixed infiltration of a variety of inflammatory cells (e.g., small lymphocytes, tissue cells, eosinophils, and plasma cells), atypical lymphoid cells (ALCs) were scattered or diffusely distributed. Small vessel fibrinoid necrosis and vasculitis occurred adjacent to regions of ulceration and tissue necrosis.

The cytology of the ENKTCL samples was diverse. ALCs varied in size, with a mix of small, medium, and large cells. Most of the samples had medium sized cells or a mixture of small and large cells. Most ALCs were round in shape with moderately, weakly, or unstained cytoplasm. The ALC nuclei were irregular in shape or elongated with granular chromatin; however, large ALC nuclei exhibited a vacuolar shape. Most nucleoli were not obvious or were of a small size. Mitotic figures were commonly seen, even in small cell-based ENKTCL samples.

Immunophenotype and EBV detection

As shown in Table 3, cluster of differentiation (CD) 56, CD3, and cytotoxic-related proteins T cell intracellular antigen 1 (TIA-1), granzyme B, and perforin were highly expressed, with staining rates of 73.2% (41/56), 80.4% (45/56), 85.7% (48/56), 75.0% (42/56), and 46.4% (26/56), respectively. On the other hand, B cell markers, including CD20 and CD79a, were not expressed in the ENKTCL specimens. Some samples also expressed Bcl-2 (14.3%), nm23 (28.6%), vascular endothelial growth factor (VEGF) (25.0%), and platelet-derived growth factor receptor-alpha (PDGFRA) (7.1%). In this study, 50% was used as the threshold to divide the Ki-67-positive specimens into the under-expression group (<50%) and the overexpression group (≥50%). Eighteen of the evaluated samples (32.1%) overexpressed Ki-67. EBV *in situ* hybridization showed that 34 patients with ENKTCL (60.7%) were EBER-positive.

Univariate Kaplan−Meier analysis and Log-rank tests were applied to analyze the correlation between all positively expressed immune markers and prognosis in the 56 patients with ENKTCL. Granzyme B, perforin, and Bcl-2 expression was significantly associated with a poor prognosis ($P = 0.033$, 0.004, and 0.034, respectively; Fig. 1B−D), whereas PDGFRA expression was significantly associated with a better prognosis ($P = 0.034$; Fig. 1E). Ki-67 overexpression (≥50%) was also significantly associated with a poor prognosis ($P = 0.017$; Fig. 1F).

Multivariate analyses

The Cox proportional hazard regression and binary Logistic regression models were used for multivariate prognostic analyses, which showed that treatment approach was not an independent prognostic factor for ENKTCL. In addition, none of the immune markers were independent prognostic factors for ENKTCL ($P > 0.05$) (Table 4).

Discussion

Most patients with ENKTCL were relatively young, with a median age at onset of 46 years and more men were affected than women (men to women ratio of 2:1). ENKTCL commonly presents in the nasal regions

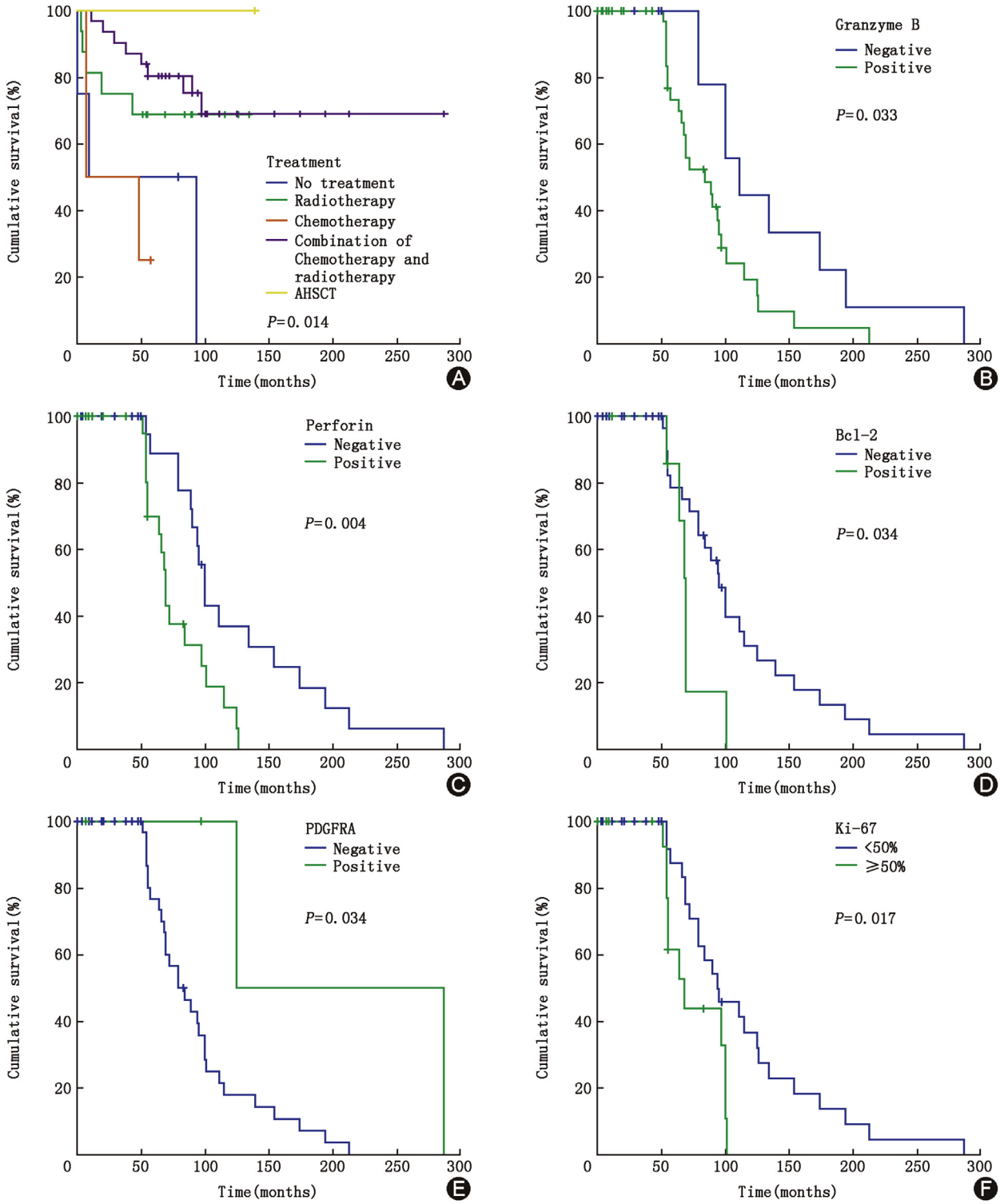

Fig. 1. Kaplan–Meier survival curves. (A) Survival following different treatment approaches is shown. The effects of expression of (B) Granzyme B, (C) Perforin, (D) Bcl-2, (E) PDGFRA and (F) Ki-67 on survival are also compared. AHSCT: autologous hematopoietic stem cell transplantation; PDGFRA: platelet-derived growth factor receptor-alpha.

Table 3
The immunohistochemical expression and univariate analysis of prognostic factors for 56 extranodal NK/T cell lymphoma patients.

Markers	*n*	χ^2	*P*-value
CD3			
Positive	45	0.045	0.832
Negative	11		
CD56			
Positive	41	0.903	0.342
Negative	15		
CD30			
Positive	5	2.992	0.084
Negative	51		
TIA-1			
Positive	48	0.842	0.359
Negative	8		
Granzyme B			
Positive	42	4.547	0.033
Negative	14		
Perforin			
Positive	26	8.279	0.004
Negative	30		
Bcl-2			
Positive	8	4.496	0.034
Negative	48		
nm23			
Positive	16	0.881	0.348
Negative	40		
VEGF			
Positive	14	0.084	0.773
Negative	42		
PDGFRA			
Positive	4	4.501	0.034
Negative	52		
Ki-67			
Overexpression (≥50%)	18	5.670	0.017
Underexpression (<50%)	38		
EBER			
Positive	34	0.251	0.616
Negative	22		

NK: natural killer; CD: cluster of differentiation; TIA-1: T cell intracellular antigen 1; VEGF: vascular endothelial growth factor; PDGFRA: platelet-derived growth factor receptor A; EBER: Epstein–Barr virus-encoded RNA.

Table 4
The multivariate survival analyses of 56 extranodal NK/T cell lymphoma patients.

Item	*HR*	95% *CI*	*P*
Treatment approaches	1.943	0.511–7.385	0.329
Granzyme B	0.327	0.069–1.550	0.159
Perforin	1.534	0.414–5.676	0.522
Bcl-2	2.377	0.275–20.514	0.431
PDGFRA	0.787	0.158–3.927	0.770
Ki-67	0.719	0.227–2.280	0.575

NK: natural killer; *HR*: hazard ratio; *CI*: confidence interval; PDGFRA: platelet-derived growth factor receptor A.

as nasal-type ENKTCL, which is most commonly found in the nasopharynx and jaw, followed by the oropharynx, throat, and tonsils. In addition to the nasal regions, ENKTCL also occurs in the skin, gastrointestinal tract, testes, and salivary glands.[5] Consistent with the previous report, most of the cases enrolled in our study occurred at the nasal cavity.

The clinical manifestation of patients varies with the involvement of different organs. Progressive destruction in the nose or midline of the face is the most common feature.[6] Fevers, night sweats, weight loss, and other B symptoms may also occur. A previous study indicated that B symptoms are prognostic indicators for lymphoma in Korean patients according to the Korean lymphoma prognostic index (KPI), and are also adverse prognostic factors for ENKTCL.[7] The results of this study showed that B symptoms were not associated with prognosis in patients with ENKTCL ($P > 0.05$), suggesting that fever and other B symptoms at an early stage of the disease in addition to being caused by the tumor, could also be associated with local infection.

A study by Hanakawa et al[8] showed that an LDH level ≥350 UI/L and a serum C-reactive protein (CRP) level ≥ 1.0 mg/dl were associated with the prognosis of patients with ENKTCL. Another study demonstrated that a serum β2-MG concentration ≥3.0 mg/L was an independent poor prognostic factor for ENKTCL.[9] However, the current study showed no association between levels of LDH and serum β2-MG and prognosis in patients with ENKTCL ($P > 0.05$). This could be related to the different cutoff levels used in the different studies.[8,10,11]

ENKTCL tumors from different sites have similar morphological features under a light microscope, characterized by diffused and infiltrating tumor cells and an angiocentric and destructive growth pattern.[12,13] Previous immunohistochemistry studies have shown that these tumors express CD3ε, CD45RO, CD56, cytotoxin-associated proteins (i.e., TIA-1, granzyme B, and perforin), as well as CD2, CD16, CD30, and CD43.[14] However, the B cell marker CD20 is not expressed in ENKTCL cells. Consistent with these earlier findings, the current study also shows an overexpression of CD56, CD3, TIA-1, granzyme B, and perforin in ENKTCL specimens, whereas B cell markers CD20 and CD79a were not expressed. The tumors also exhibited positive staining for Bcl-2, nm23, VEGF, and PDGFRA.

CD56, a nerve cell adhesion factor, increases the ability of tumor cells to firmly adhere to and destroy blood vessel walls, resulting in the extensive infiltration and destruction of blood vessels.[15] CD56 is commonly

found in ENKTCL accounting for the invasive nature of these cells. Thus, CD56 might be associated with poor disease prognosis. CD30 expression is found in a variety of lymphoproliferative disorders.[16] A previous study showed that CD30 expression has no impact on the therapeutic outcomes of ENKTCL; however, it is an independent prognostic factor for overall survival (OS) and progression-free survival (PFS).[17] CD30 plays a role in the pathogenesis of ENKTCL, and therefore could be a useful therapeutic target. However, in the current study, there was no association between CD56 and CD30 expression and the prognosis of patients with ENKTCL. This could be due to the small sample size in the current study, as well as the fact that most patients were at an early stage of the disease (IE–IIE, 91.1%) and therefore achieved a better therapeutic outcome (CR, 66.1%).

Univariate analyses showed that the results of immunohistochemical staining in the current study showed that the expression of cytotoxin-associated proteins granzyme B and perforin was significantly associated with a poor prognosis in patients with ENKTCL. However, multivariate analyses indicated that they were not independent prognostic factors. Since the sample size of the current study is small, a large-scale study is needed to verify the current findings further.

Bcl-2 enhances the stability of the mitochondrial membrane and inhibits apoptosis. Ma et al[18] have demonstrated that patients with tumors expressing Bcl-2 had a significantly poorer OS and event-free survival compared to those with tumors without Bcl-2 expression. Although our univariate analyses indicate that Bcl-2 expression is significantly associated with poor patient prognosis, multivariate analyses show that it is not an independent prognostic factor.

PDGFR, a member of the tyrosine kinase family, promotes cell chemotaxis, division, and proliferation, and also plays an important role in growth, development, repair, and other physiological processes. Huang et al[19] have demonstrated overexpression of PDGFRA in ENKTCL and imatinib-induced inhibition of PDGFRA expression in MEC04 cells, suggesting that PDGFRA could be a therapeutic target. In the current study, patients with PDGFRA expression had a better prognosis in the univariate analysis, suggesting that PDGFRA-expressing ENKTCL might be more sensitive to treatment, consistent with the study by Huang et al.[19]

Recently, Huang et al[20] showed that Ki-67 overexpression (≥50%) was negatively associated with OS and PFS, suggesting that Ki-67 overexpression could be a prognostic factor for ENKTCL. In the current study, Ki-67 overexpression (≥50%) was significantly associated with poor prognosis in patients with ENKTCL in the univariate analysis, but not associated with prognosis in the multivariate analysis.

The incidence of ENKTCL is known to be associated with EBV infection. In a previous study, *in situ* hybridization revealed that 68%–100% of tumor cells expressed EBER, with an average positive rate of 89.9%.[21] Therefore, EBV detection may contribute to disease diagnosis. In the current study, 60.7% of the 56 patients with ENKTCL expressed EBER, which is consistent with the previous report. Studies by Suzuki et al[22] and Wang et al[23] demonstrated that the EBV DNA copy number in the peripheral blood of patients is a good indicator of the tumor load and therefore, could be used to predict the tumor response and potential adverse reactions to chemotherapy in ENKTCL. However, the current study showed that EBER had no significant effect on prognosis.

Li et al[24] conducted a meta-analysis of 11 randomized controlled trials including 871 ENKTCL Chinese patients with early-stage (IE–IIE) disease. They showed that the therapeutic effects of radiotherapy alone in the early clinical stages of ENKTCL (I/IIE) were good. In addition, extended field radiotherapy combined with 50 Gy intensity-modulated radiation therapy (IMRT) resulted in good survival and regional control.[25] However, concurrent radiochemotherapy further enhanced long-term survival of the patients.[24] In the current study, single-factor survival analysis and Log-rank tests showed that different treatment approaches were associated with patient prognosis. Specifically, the therapeutic effects of concurrent radiochemotherapy and AHSCT were better than radiotherapy or chemotherapy alone. These findings are consistent with previous reports.[26,27]

In conclusion, the expression of many immunohistochemical markers, such as granzyme B, perforin, Bcl-2, and overexpression of Ki-67 (≥50%), might be associated with poor prognosis in patients with ENKTCL. In contrast, PDGFRA expression correlated with better prognosis. Different treatment approaches may be also closely associated with patient prognosis. However, these findings need to be confirmed in the large-scale studies.

Conflicts of interest

The authors declare no competing financial interests.

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