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Original Article

Tumor cell nuclear diameter and CD30 expression as potential prognostic parameter in patients with extranodal NK/T-cell lymphoma, nasal type

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Abstract: Extranodal natural killer/T-cell lymphoma, nasal type (nasal ENKTL) is a distinct clinicopathologic entity of lymphoid tumors with variable size and differentiation of tumor cells. Nasal ENKTL is related to infection of the tumor cells with Epstein-Barr virus (EBV) and virtually all cases contain monoclonal episomal EBV DNA and detectable EBV encoded small nuclear RNAs (EBERs). Several clinical factors are known for their relation to the prognosis, but histopathologic prognostic factors of nasal ENKTL have not yet been well established. We evaluated the prognostic value of the longest nuclear diameter of EBER+ tumor cells (NDTC) along with the result of CD30 expression. Twenty two patients with newly diagnosed nasal ENKTL were evaluated regarding clinicopathologic characteristics. NDTC was measured using a computerized image analysis system. The results were expressed as the mean diameter of ≥ 50 cells in a patient. Median of the mean NDTC of the patients was 7.32 μm (5.15-11.27). Patients with larger mean NDTC (≥ 7.35 μm) had a poorer event-free survival (EFS) than those with smaller mean NDTC (<7.35 μm; $p = 0.024$) and had a tendency of inferior overall survival (OS) ($p = 0.08$). Patients with CD30 expression had a inferior EFS ($p = 0.018$) and OS ($p = 0.011$) compared those without CD30 expression. The NDTC of EBV infected tumor cell and CD30 expression had relation to survival in the current exploratory analysis.

Keywords: Extranodal NK/T-cell lymphoma, nasal type, epstein-barr virus, CD30, prognosis, nuclear diameter

Introduction

Extranodal natural killer/T-cell lymphoma, nasal type (nasal ENKTL) is usually derived from natural killer (NK) cells or, rarely, from cytotoxic T-cells. Characteristically, Epstein-Barr virus (EBV) latently infects tumor cells in nearly all nasal ENKTLs. Nasal ENKTL is common in Asia and South America but is very rare in North America and Europe [1-3]. Nasal ENKTL most frequently presents in the upper aerodigestive tract (UAT); however, it can also involve variable extranodal sites [4]. The overall prognosis of this disease is poor because of frequent relapse or resistance to treatment [5, 6]. However, most patients initially have low international prognostic index (IPI) scores, as they usually present as a localized disease involving the head and neck with good performance status [7, 8]. Therefore, evaluating risk prognostic factors specific to nasal ENKTL is of paramount importance for the appropriate management of the disease.

The cytologic spectrum of nasal ENKTL is very broad. Cells may be small, medium-sized, large, or anaplastic [4]. In most cases, the lymphoma is composed of medium-sized cells or a mixture of small and large cells [4]. The correlation between tumor size and genetic status or clinical outcome is not clear to date. In one study, survival analysis failed to show significant difference in survival among the different histologic subtypes [9]. However, Quintanilla-Martinez et al. reported that nasal ENKTL with large cell morphology were more likely to be

associated with p53 mutation [10], even though these findings were not confirmed by other study [11]. Here, we measured the nuclear diameter of tumor cells and CD30 expression to evaluate their prognostic value.

Materials and methods

Study sample

Clinical data and biopsied tissue of the patients with nasal ENKTL treated at a single institution, Gachon University Gil Hospital (GUGH), between February 2000 and June 2011 were retrospectively analyzed. The patients were included if they had histologic confirmation of nasal ENKTL according to the World Health Organization criteria [4]; the NK/T-cell type as proven by immunohistochemical, flow cytometry, or EBV in situ hybridization analysis. The enrolled patients were without any previous treatment for lymphoma and received at least one of the following therapies: concurrent chemo-radiotherapy, chemotherapy alone, or radiotherapy alone. Patients with extranodal NK/T-cell lymphoma without lymphomatous lesion on the upper aerodigestive tract (UAT) were excluded from the analysis. The patients underwent pre-treatment staging evaluation, including computed tomography (CT) or magnetic resonance imaging (MRI) of the head and neck, chest radiography, abdominopelvic CT, upper endoscopy for the evaluation of upper aerodigestive tract, and bilateral bone marrow trephine biopsy. The Institutional Review Board of GUGH approved the acquisition, analysis, and reporting of patient data (grant number: GIRBA 2583).

Measurement of EBER-positive tumor cells

The nuclear diameter of EBER-positive tumor cells were measured using a computerized image analysis system (IMT i-Solution, Vancouver, British Columbia, Canada) that included a DP70 Digital camera (Olympus, Tokyo, Japan) installed on an Olympus BX51 light microscope and attached to a personal computer. More than 50 tumor cells were selected randomly for the measurement of the longest nuclear diameter of tumor cells (NDTC) in each case. The results of each patient were expressed as the mean diameter of the evaluated tumor cells. The mean diameter was used for statistical analysis.

Histopathologic examination and evaluation of EBV infection

Representative formalin-fixed paraffin-embedded tissues obtained from surgical resections or biopsies were submitted to immunohistochemistry and EBV study. Sections of the paraffin-embedded tissues were cut at 4μm, placed on slides, deparaffinized in xylene, and hydrated in a graded series of alcohol. Sections were stained with antibody to CD30 (Dakopatts, Copenhagen, Denmark). Immunohistochemical study was performed using a modified avidin-biotin peroxidase complex amplification and detection system. CD30 expression was considered positive when more than 50% of tumor cells showed strong membranous staining. EBV RNA was detected by an ISH (in situ hybridization) technique. Paraffin sections were pretreated with xylene followed by treatment with proteinase K and hybridized with fluorescein isothiocyanate-conjugated EBV oligonucleotides (Novocastra, Newcastle, UK) complementary to the mRNA portion of the EBER-1 and EBER-2 genes.

Statistical analyses

The relationships of mean NDTCs with clinical variables were evaluated using Fisher's exact test. Event-free survival (EFS) was defined as survival free of progression, relapse, or death from lymphoma or treatment toxicity. Overall survival (OS) was defined as survival free of death from any cause. Survival was calculated using Kaplan-Meier method and compared by log rank test or Cox proportional hazard model. Probability values < 0.05 were considered significant. All values were two-sided and statistical significance was accepted at the $P < 0.05$ level.

Results

Patient characteristics and treatment outcomes

Twenty-two patients satisfied the inclusion criteria for the current study. The clinical characteristics of the 22 patients are presented in **Table 1**. The median age of the patients was 48 years (range 15-81 years). The most common primary tumor site was the nasal cavity (17 patients). Nine patients (40.9%) showed involvement of cervical lymph nodes, and 6

Table 1. Patient characteristics

Characteristics		N	%
Gender	Male	20	90.9
	Female	2	9.1
Age (year)	Median	48	
	Range	15-81	
Primary site	Nasal cavity (NC)	15	68.2
	Nasopharynx or Oropharynx	5	22.7
	Both NC and naso- or oropharynx	2	9.1
Local tumor invasion	No	16	72.7
	Yes	6	27.3
ECOG performance status	0	5	22.7
	1	12	54.5
	2	4	18.2
	3	1	4.5
Lactose dehydrogenase	Not elevated	13	59.1
	Elevated	9	40.9
B symptom	No	18	81.8
	Yes	4	18.2
Cervical lymph node(s)	Not involved	13	59.1
	Involved	9	40.9
Bone marrow involvement	No	21	95.5
	Yes	1	4.5
Splenomegaly at diagnosis	No	15	60
	Yes	10	40
Ann Arbor staging	I	7	31.8
	II	6	27.3
	III	3	13.6
	IV	6	27.3
Type of therapy	Concurrent chemo-radiotherapy	16	72.7
	Chemotherapy alone	5	22.7
	Radiotherapy alone	1	4.5

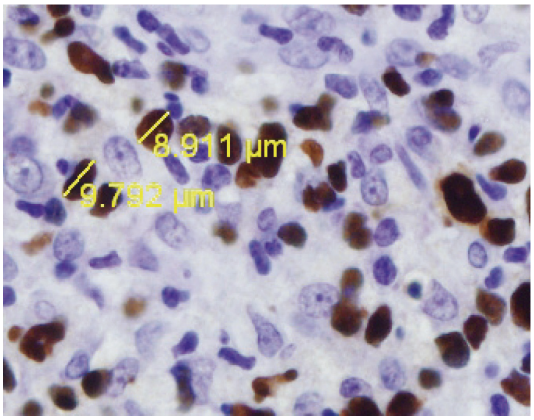

Figure 1. Representative captured image of EBER-positive tumor cells (EBV in situ hybridization, x400).

patients (27.3%) had local tumor invasion (LTI), which is defined as bony invasion or perforation or invasion of the skin in a previous study [7]. Thirteen patients (59.1%) were Ann Arbor stage I or II. Most patients (16; 72.7%) received concurrent chemo-radiotherapy whereas 5 and 1 received only chemotherapy and radiotherapy, respectively. Of the 20 evaluable patients, 14 patients responded to initial therapy (complete remission in 9 patients, partial remission in 5, stable disease in 3, and progressive disease in 3). During the median follow-up duration of 19.9 months, 13 patients (59.1%) had significant events and 11 patients (50.0%) died (Ten patients were died of lymphoma progression and one for treatment-related mortality). The median EFS was 9.7 months and EFS rate of 1-year and 3-year were 45.4% and 37.8%, respectively. The median OS was 28.2 months and OS rate of 1-year and 3-year were 75.9% and 43.6%, respectively.

Measurement of the nuclear diameter of tumor cells

Representative captured images are provided in **Figure 1**. The mean nuclear diameter of EBER-positive tumor cells ranged from 5.15 µm to 11.27 µm among the 22 patients. The median and mean value of the mean NDTCs of the patients were 7.32 µm, and 7.27 µm (± 1.30 as standard deviation), respectively. Patients were separated into two groups according to the mean NDTC, larger NDTC (≥ 7.35 µm) and smaller NDTC group (<7.35 µm).

Table 2. Comparison of clinical characteristics according to nuclear diameter of tumor cells

	Smaller cell (<7.35 μm)	Larger cell (≥7.35 μm)	*P*-value
Gender			
Male	10	10	0.481
Female	2	0	
Age (year)			
< 60	10	5	0.172
≥ 60	2	5	
Local tumor invasion			
No	10	8	1.0
Yes	2	2	
ECOG* performance status			
0 and 1	11	6	0.135
≥ 2	1	4	
Lactose dehydrogenase			
Not elevated	8	5	0.666
Elevated	4	5	
B symptom			
No	10	8	1.0
Yes	2	2	
Cervical lymph node(s)			
Not involved	6	7	0.415
Involved	6	3	
Bone marrow involvement			
No	11	10	1.0
Yes	1	0	
Splenomegaly at diagnosis			
No	9	4	0.192
Yes	3	6	
Ann Arbor staging			
I and II	9	5	0.378
III and IV	3	5	
Type of therapy			
CCRT†	10	6	0.348
Not CCRT	2	4	
CD30 expression			
Yes	3	5	0.378
No	9	5	

*ECOG, Eastern Cooperative Oncology Group; †CCRT, concurrent chemo-radiotherapy.

Clinical feature and survival according to the nuclear diameter of tumor cells

The relationships of NDTC group with clinical characteristics are summarized in **Table 2**. No statistically significant association was reported between NDTC group and clinical characteristics.

By Kaplan-Meier analysis, patients of larger NDTC group had a inferior EFS (median 2.87 months, 95% confidence interval [CI] 2.67-3.06) compared to smaller group (median 43.37 months, 95% CI 14.10-72.6; $p = 0.024$ by log-rank test). Patients with larger NDTC group had a tendency of inferior OS compared to those with smaller NDTC group ($p = 0.08$ by log-rank test; **Figure 2**), although failed to reach statistical significance.

CD30 expression and patient survival

The membranous staining pattern of CD30 expression was noted. Of 22 cases, 8 (36.4%) cases were positive for CD30 (**Figure 3**). Patients with CD30 expression showed inferior EFS (median 2.2 vs. 43.36 months, $p = 0.018$ by log-rank test) and OS (median 5.2 vs. 43.0 months, $p = 0.011$ by log-rank test; **Figure 4**).

Univariate and multivariate analyses for event-free survival according to the clinicopathologic factors

In the univariate analysis, CD30 expression and NDTC were associated with EFS along with age, LTI, type of therapy, performance status, and splenomegaly at the time of diagnosis (**Table 3**). Only LTI (Hazard Ratio [HR] 30.59,

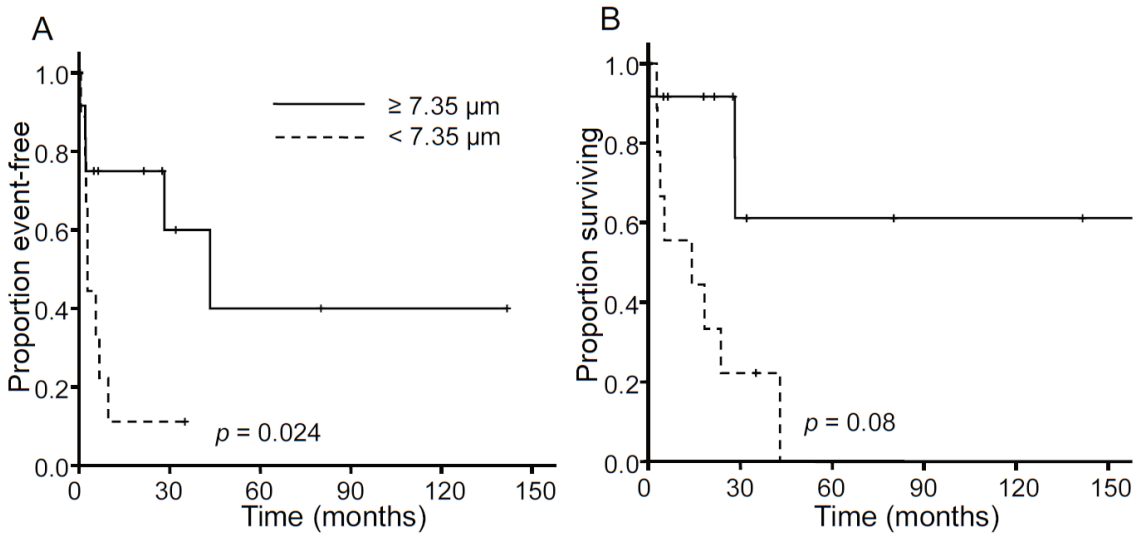

Figure 2. Kaplan-Meier curve of event-free survival and overall survival according to nuclear diameter of tumor cells (NDTC) group.

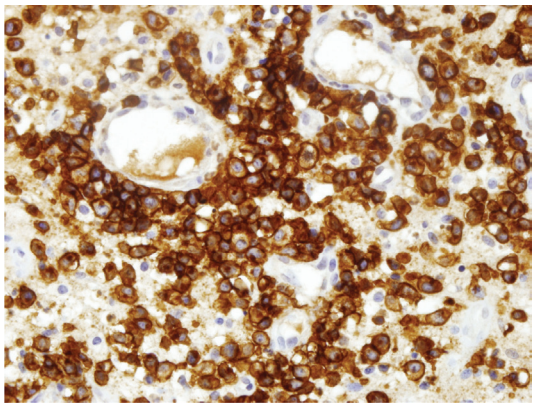

Figure 3. Representative image of CD30-positive tumor cells showing strong membranous staining (HE, x400).

95% CI 3.69-253.5, p = 0.002), splenomegaly (HR 4.61, 95% CI 1.16-18.27, p = 0.03), and performance status (2.45, 95% CI 2.10-73.7, p = 0.005) were associated with EFS in the multivariate analysis. NDTC group and CD30 expression did not show statistical significance in the multivariate analysis, along with patient age (>60 vs. ≤ 60 years) and type of therapy (concurrent chemo-radiotherapy or not).

Discussion

Many clinical and pathological efforts have been made to identify prognostic markers in nasal ENKTL. Clinically, two major clinical prognostic models are applied in NK/T-cell lymphoma: IPI and prognostic index for peripheral T-cell lymphoma-unspecified (PIT). The IPI has been widely used for both predicting prognosis and selecting therapeutic options in patients with aggressive non-Hodgkin's lymphoma. However, its value has been challenged by nasal ENKTL because it has failed to predict prognosis in retrospective analyses [12, 13]. Recently, PIT has been carried out in other subtypes T-cell lymphoma and its improved prognostic value were recognized [14-16]. However, these prognostic models are based primarily on pre-treatment clinical characteristics; the pathological or molecular factors that may predict the prognosis of nasal ENKTL have not yet been well defined. Ki-67 proliferation rate was reported to be correlated with a shorter disease-free survival and OS ($P < 0.05$), while Ann Arbor stage and IPI failed to predict prognosis of the patients with nasal ENKTL [17]. Recently, loss of the granzyme B protease inhibitor 9, cyclooxygenase-2 expression and decreased quantity of tumor-infiltrating FOXP3-positive regulatory T-cells have been associated with poor prognosis of nasal or UAT-ENKTL [18-20].

Nasal ENKTL is associated with various histologic changes. According to the predominant lymphoma cells in the infiltrates, they could be classified into four histologic subtypes; small cell type, medium-sized cell type, large cell type, and pleomorphic cell type [9]. The majority consists of polymorphous infiltrations of small, medium, and large atypical lymphocytes with accompanying inflammatory cells, plasma cells, macrophages, and neutrophils. The asso-

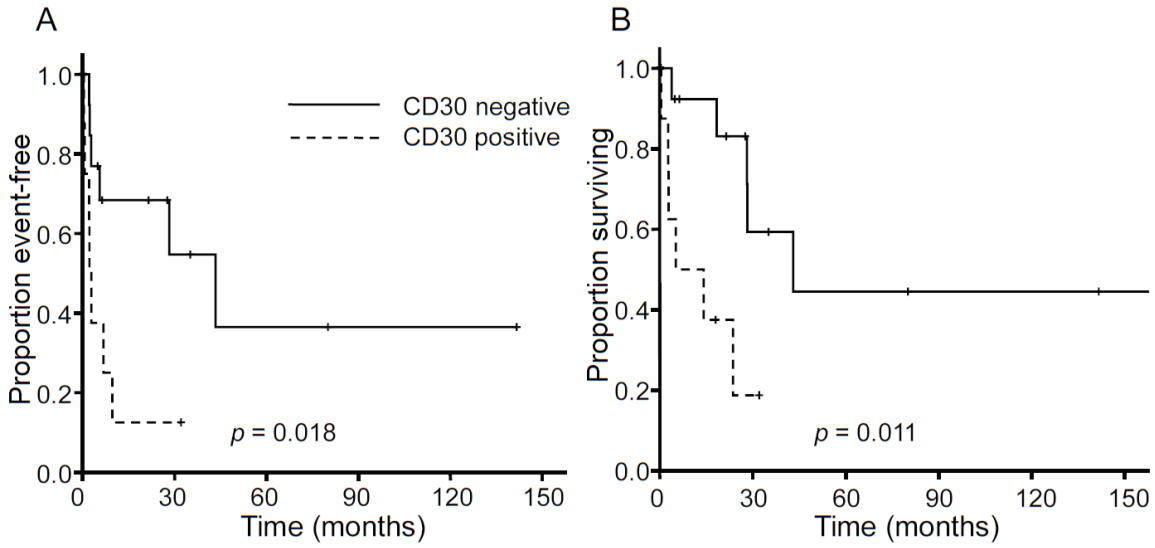

Figure 4. Kaplan-Meier graph of event-free survival and overall survival according to CD30 expression.

Table 3. Prognostic factors affecting event-free survival in univariate and multivariate analysis

	Univariate analysis		
Parameters	HR	95% CI	*P*
Age (> 60 years)	4.97	1.33-18.58	0.017
Local tumor invasion (present)	10.4	2.24-48.19	0.003
Cervical nodes (involved)	1.62	0.54-4.90	0.389
ECOG* Performance status (2, 3, and 4)	11.86	2.73-51.58	0.001
CCRT† (not done)	3.99	1.30-12.22	0.015
Lactose dehydrogenase (elevated)	2.05	0.68-6.13	0.201
B symptom (present)	2.13	0.56-8.10	0.270
Splenomegaly (present)	4.63	1.37-15.66	0.014
CD30 (expressed)	3.68	1.16-11.74	0.027
NDTC‡ group (≥7.35 μm)	3.75	1.10-12.77	0.035

*ECOG, Eastern Cooperative Oncology Group; †CCRT, concurrent chemo-radiotherapy; ‡NDTC, Nuclear diameter of tumor cells.

ciation of tumor cell type with prognosis has not been clear until now. In one study, survival analysis failed to demonstrate significant difference among the histologic subtypes [9]. The neoplastic cells often consist only of small lymphocytes lacking atypia and necrosis, and are easily overlooked, resulting in a misdiagnosis as chronic inflammation [21]. We experienced several cases of nasal ENKTL with favorable prognosis that consisted of small infiltrating lymphocytes lacking cytological atypia and necrosis. Therefore, we hypothesized that the small cell type of nasal ENKTL might be associated with favorable prognosis and the current study showed that nasal ENKTL cases with smaller size had favorable EFS. However, most cases of nasal ENKTL consist of polymorphous infiltrations of various tumor cells. Therefore, it is nearly impossible to segregate histologic subtypes exactly. The authors measured the nuclear diameter of the EBER positive tumor cells as a surrogate for tumor cell size to avoid subjective histologic classifications. EBV in situ hybridization is a commonly used technique that can be easily applied to formalin-fixed, paraffin-embedded tissue sections and image analyzer is also a commonly used computerized system. Therefore, these techniques allow for the differentiation of larger tumor cells from smaller tumor cells with convenience.

CD30 (Ki-1) molecule is a member of the tumor necrosis factor receptor super-family and preferentially expressed in activated CD8+T-cell and NK-cell [22, 23]. In nasal ENKTL, the positivity for CD30 has been reported in some sporadic reports (range 20-64%) [24-28]. In one study (n = 30), patients with CD30 expression tend to have more favorable outcome [29], but other studies conducted by Kuo et al (n = 22) [9] and Gaal et al (n = 15) [24] revealed that there was no difference of survival according to CD30 expression, although it seemed to be that CD30 expression correlated with vascular

destruction, thrombosis, or pleomorphic cell type [9, 24]. In our study, patients with CD30 expression (≥ 50%) had inferior EFS and OS. Further study with larger patient number would define the actual relationship of CD30 expression to the prognosis of nasal ENKTL.

Relatively small patient number can be a limitation of the current study. However, since the rarity of nasal ENKTL, not a few of the studies on pathologic or molecular prognostic markers on nasal ENKTL were performed with small numbers (15 to 30) of patients [9, 10, 24, 29]. Several biomarker studies on nasal ENKTL had larger patient numbers but in those studies patients' tissues were collected over fifteen to even more than twenty-five years [18-20, 30]; in those studies, the development of optimal chemo-radiotherapy strategy, the advance of diagnostic technology including positron emission tomography, and the improved supportive care could not be considered enough, opposite our study, which only dealt with patients in a decade recently.

Because of limited sample size, the result of multivariate analysis in the current study has only an auxiliary value and does not exclude the necessity of further investigation on NDTC and CD30 expression. Even multivariate analyses shows conflict results according to the studies. For Example, elevated serum lactose dehydrogenase was an independent prognostic factor in several studies [6, 8, 30], but other studies do not support it [7, 12].

We measured the longest nuclear diameter of EBER-positive tumor cells for economy of time and it was the simplest method for evaluating tumor cells as many as possible (≥ 50 cells in a patient). Other parameters such as nuclear area or circumference may improve the prognostic value of tumor cell size in later studies. Furthermore, the nuclear diameter of tumor cells in paraffin sections may vary from case to case and there are many factors that could affect the cell size in formalin-fixed and paraffin-embedded tissue. When measuring the mean NDTCs again within the case and among different cases, the values were well reproducible. To use a size standard such as the size of red blood cells or nuclei of small lymphocytes might be better method to ensure the reproducibility in future studies.

In conclusion, the measurement of NDTC of EBV infected tumor cell and assessment of CD30 expression had relation to survival in the current exploratory analysis. Further larger scale study to define the prognostic value of them is warranted.

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