Original paper

Evaluation of the role of Epstein-Barr virus in cases of nodal or extranodal T- and NK-cell lymphoma using EBER *in situ* hybridization

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Various racial and geographic differences have been observed in studies questioning the role of Epstein-Barr virus (EBV) infection in the etiology of T- and NK-cell lymphomas. The aim of this study was to evaluate the relationship of EBV with nodal or extranodal (skin excluded) T- and NK-cell lymphoma subtypes encountered in our geographic area. Sixty-two cases of peripheral T-cell lymphoma were included in the study. EBV-encoded early RNA (EBER) was detected by *in situ* hybridization. The distributions of T- and NK-cell lymphoma subtypes were as follows: 32 peripheral T-cell lymphomas, unspecified (PTCL, NOS), 13 anaplastic large-cell lymphomas (ALCL), 8 angioimmunoblastic T-cell lymphomas (AITCL), 4 extranodal NK/T-cell lymphomas, nasal type (NKTCL), 3 enteropathy-type T-cell lymphomas (ETTCL), 1 hepatosplenic T-cell lymphoma (HSTCL), and 1 subcutaneous panniculitis-like T-cell lymphoma (SPTCL). Using a cut-off value of > 25% of EBER-positive neoplastic lymphoid cells, EBV was positive in 22.6% of all cases. According to subtype, the neoplastic cells of 31.3% of PTCL, NOS and 100% of extranodal NKTCL, nasal type were EBER positive, whereas some cases of ALCL, AITCL, and ETTCL presented EBER-positive non-neoplastic cells, and all cells of HSTCL and SPTCL were EBV negative. Extranodal NKTCL, nasal type, presented the strongest association with EBV, followed by PTCL, NOS.

Key words: lymphoma, T-cell, extranodal NK-T-cell, EBV, EBER, *in situ* hybridization.

Introduction

Since "natural killer" (NK) cells are closely related to T-cells, their neoplasms were integrated into "mature T- and NK-cell neoplasms" in the WHO classification [1]. T- and NK-cell lymphomas, which comprise 12-15% of all non-Hodgkin's lymphomas (NHL), are a group of NHL with aggressive clinical behaviour [2-5]. T- and NK-cell neoplasms are more common in Asia [5, 6]; indeed, the incidences of nasal and nasal type NK/T-cell lymphomas and aggressive NK/T-cell lymphomas are highest in Asians [7, 8].

While Epstein-Barr virus (EBV) has been mostly linked to B-cell neoplasms, some EBV-associated T- and NK-cell lymphomas have been reported, especially those with a cytotoxic phenotype and aggressive behaviour [9]. Various racial and geographic differences have been reported in studies of the role of EBV infection in the etiology of T- and NK-cell lymphomas. Most reported cases are from Asia and Latin America, consistent with the higher incidence in these regions. It has been proposed that EBV-encoded RNA promotes the proliferation and transformation of T-cells [10, 11]. An association between EBV and

nasal NK/T-cell lymphomas has been demonstrated [5, 11-17]. Recent studies on various other subtypes of T- and NK-cell lymphomas, such as peripheral T-cell lymphoma, unspecified (PTCL, NOS) [18, 19], angioimmunoblastic T-cell lymphoma (AITCL) [20], enteropathy type T-cell lymphoma (ETTCL) [21, 22], and hepatosplenic T-cell lymphoma (HSTCL) [23], have also reported a possible role for EBV as an aetiopathogenetic factor. In most T- and NK-cell neoplasms, EBV latency type II has been reported expressing the latency proteins LMP-1, 2a, 2b, EBNA1 and EBERs [24].

The aim of this study was to evaluate the relationship of EBV with nodal or extranodal (excluding the skin) T- and NK-cell lymphoma subtypes encountered in our geographic area. We evaluated the incidence of EBV latency in our archival material using chromogenic *in situ* hybridization to demonstrate EBV-encoded early RNA (EBER), which is the most reliable method reported to date [25].

Material and methods

Tissue samples from cases diagnosed as nodal or extranodal T- and NK-cell lymphomas during a seven-year period between 1997 and 2004 were retrieved from the archives. Cases with cutaneous or leukaemic presentation were excluded from the study. Sixty-two cases with available paraffin-embedded tissue were studied. Tissue sections, 4 μm thick, were prepared from formalin-fixed, paraffin-embedded tissues and were placed on electrostatic-charged slides (X-tra, Surgipath Medical Industries, Richmond, IL, USA). EBER was detected by *in situ* hybridization using an automated system (Benchmark XT, Ventana Medical Systems, Tucson, USA), an EBER probe (INFORM EBER Probe, Ventana Medical Systems, Tucson, USA) and a ready-to-use *in situ* hybridization kit (ISH iVIEW Blue Detection Kit, Ventana Medical Systems, Tucson, USA). Samples from five cases of Hodgkin's lymphoma known to be positive for EBV LMP-1 by immunohistochemical methods and a lymph node from a case of infectious mononucleosis were included as positive controls. A positive reaction was identified by the appearance of a greyish-blue precipitate detected by examination under a light microscope. This evaluation was performed by two pathologists (SK, MH) and scored as below according to the percentage of positive cells (Fig. 1).

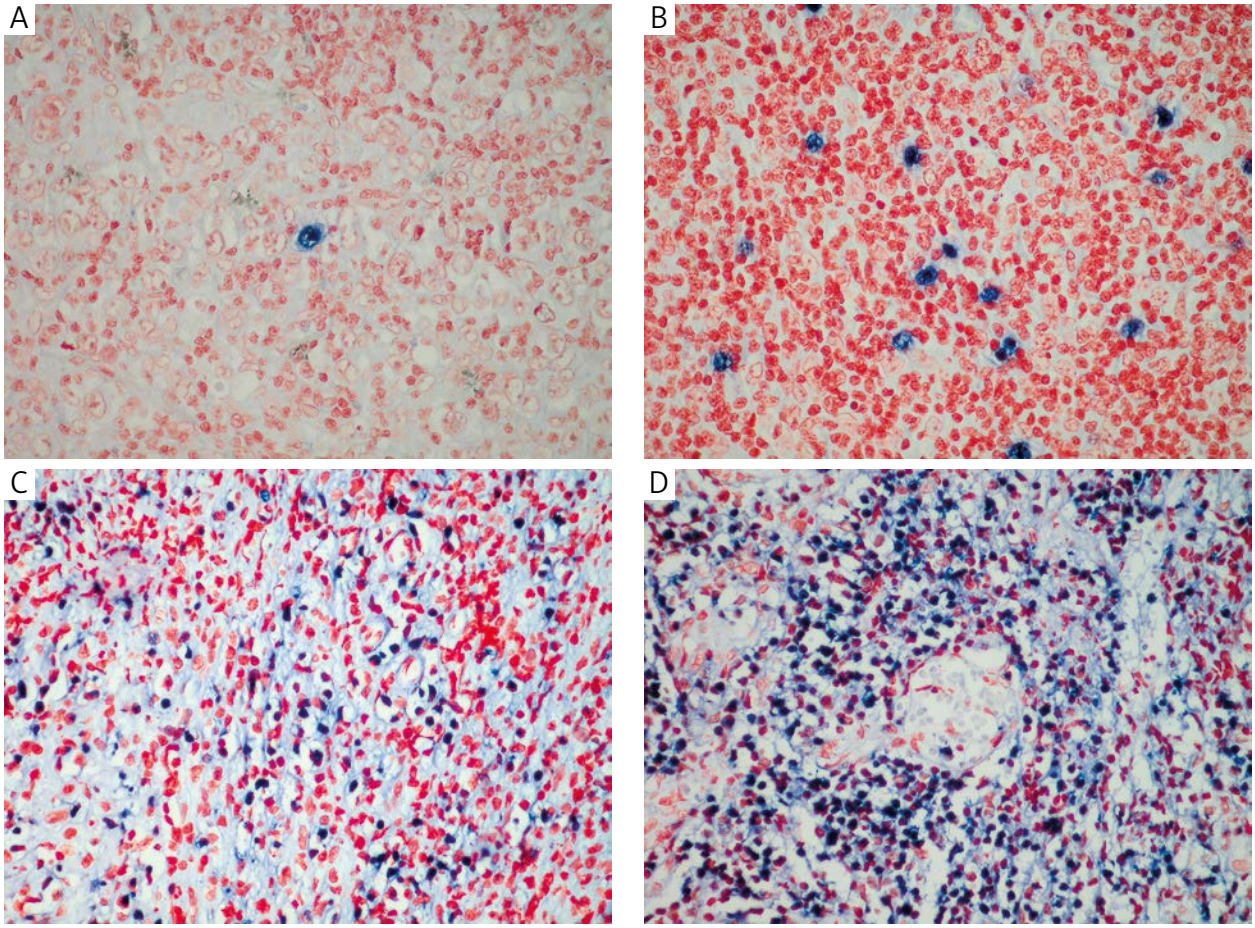

Fig. 1. Grading of EBER reaction (*in situ* hybridization, NBT). A) Grade 1+, magnification 40×. B) Grade 2+, magnification 40×. C) Grade 3+, magnification 20×. D) Grade 4+, magnification 20×

Criteria used in grading the EBER staining pattern:
0: No reaction in any cell.
1+: Scarce EBER-positive cells (< 5%), suggestive of isolated reactive or activated lymphoid cells and/or immunoblasts.
2+: Few EBER-positive cells (5-25%), discordance with the morphology of neoplastic cells, consistent with reactive or activated lymphoid cells and/or immunoblasts.
3+: Some neoplastic cells (26-75%) EBER positive.
4+: All neoplastic cells (> 75%) EBER positive.

Only grade 3+ and 4+ cases, with a cut-off value > 25% EBER-positive neoplastic cells, were accepted as being EBV positive.

Statistical analysis

Statistical analyses were conducted using the SPSS software (version 14.0). Pearson's χ^2 and Fisher's exact tests were used to compare the associations between the histological subtypes and EBER positivity. A p value < 0.05 was accepted to indicate statistical significance.

Results

Of the 62 cases studied, the subtypes, in order of decreasing frequency, were as follows: 32 PTCL, NOS (51.6%), 13 anaplastic large-cell lymphomas (ALCL) (21.0%), 8 AITCL (12.9%), 4 extranodal NK/TCL, nasal type (6.5%), 3 ETTCL (4.8%), 1 HSTCL (1.6%), and 1 subcutaneous panniculitis-like T-cell lymphoma (SPTCL) (1.6%). The age and sex distributions of the cases are summarised in Table I.

Of the subtypes known to present with nodal involvement (n = 53), most were diagnosed by analysing lymph node biopsies (74.0%), and some cases using the skin (38.4%). All subtypes known to present in extranodal sites (n = 9) were diagnosed in their specific locations. A total of 39 lymph nodes were examined in 22 cases of PTCL, NOS, 9 cases of ALCL, and 8 cases of AITCL. The remaining 23 samples comprised cases that involved various extranodal locations. These included skin (n = 3), bone marrow (n = 2), spleen (n = 1), spleen and liver (n = 1), thorax (n = 1), tonsil and root of tongue (n = 1), and nasopharynx (n = 1) in PTCL, NOS. Extranodal ALCL cases were sampled from the thymus and lung (n = 1), skin (n = 2), and perirectal area (n = 1). Extranodal NK/T-cell lymphomas presented with involvement of the nasal cavity (n = 2), maxilla and orbits (n = 1), and nasopharynx (n = 1). All cases of ETTCL (n = 3) were diagnosed from biopsies and/or small intestinal material obtained during surgery. As expected, the only case of HSTCL presented with involvement of the spleen, liver, and lymph nodes, while subcutaneous soft tissue was involved in the case diagnosed as SPTCL.

Neoplastic cells in 14 cases (22.6%) were determined to be EBER positive. As a result, of the 14 EBV-positive nodal or extranodal (noncutaneous) T- and NK-cell lymphomas, only PTCL, NOS and extranodal NK/T-cell lymphoma, nasal type were positive, which constituted 71.4% and 28.6%, respectively, of the positive cases. The EBER staining pattern intensity of these subtypes is presented in Table II.

Peripheral T-cell lymphomas, NOS was found to be EBER positive in 10 of 32 cases, and the staining pattern was diffuse in most samples, although an intense staining pattern was observed in 2 cases graded as 4+. All 13 cases of ALCL, characterised by large, pleomorphic, often horseshoe-shaped nuclei, were EBV negative, but 2 cases exhibited grade 1 and 2 positivity that was confined to rare, small lymphoid cells, which may be bystander B-cells (Fig. 2).

AITCL is characterised by a polymorphous lymphoid infiltrate, florid vascular proliferation, and follicular dendritic cell proliferation. Five of 8 cases of AITCL examined in this study were graded as 1+

Table I. Age and sex distribution of various histopathological subtypes

Histopathologic subtype	n (%)	Median age (age range)	Sex (M : F ratio)
PTCL, NOS	32 (51.6)	46.6 (11-75)	3 : 1
ALCL	13 (21.0)	38.7 (13-79)	10 : 3
AITCL	8 (12.9)	50.6 (33-80)	1 : 3
Extranodal NK/TCL, nasal type	4 (6.5)	44.7 (22-66)	3 : 1
ETTCL	3 (4.8)	45.3 (27-63)	1 : 2
HSTCL	1 (1.6)	19	-
SPTCL	1 (1.6)	34	-
TOTAL	62	44.6 (11-75)	2.1 : 1

PTCL, NOS – peripheral T-cell lymphoma, not otherwise specified; ALCL – anaplastic large cell lymphoma; AITCL – angioimmunoblastic T-cell lymphoma; ETTCL – enteropathy type T-cell lymphoma; HSTCL – hepatosplenic T-cell lymphoma; SPTCL – subcutaneous panniculitis-like T-cell lymphoma

Table II. Comparison of the intensity of EBER positivity on various histopathologic subtypes

Histopathologic Subtype	EBER Grade					EBER (+) n (%)
	0	1+	2+	3+	4+	
PTCL, NOS	20	–	2	8	2	10/32 (31.3)
ALCL	11	1	1	–	–	0/13 (0)
AITCL	3	1	4	–	–	0/8 (0)
Extranodal NK/TCL, nasal type	–	–	–	–	4	4/4 (100)
ETTCL	2	1	–	–	–	0/3 (0)
HSTCL	1	–	–	–	–	0/1 (0)
SPTCL	1	–	–	–	–	0/1 (0)
TOTAL	38	3	7	8	6	14/62 (22.6)

PTCL, NOS – peripheral T-cell lymphoma, not otherwise specified; ALCL – anaplastic large cell lymphoma; AITCL – angioimmunoblastic T-cell lymphoma; ETTCL – enteropathy type T-cell lymphoma; HSTCL – hepatosplenic T-cell lymphoma; SPTCL – subcutaneous panniculitis-like T-cell lymphoma

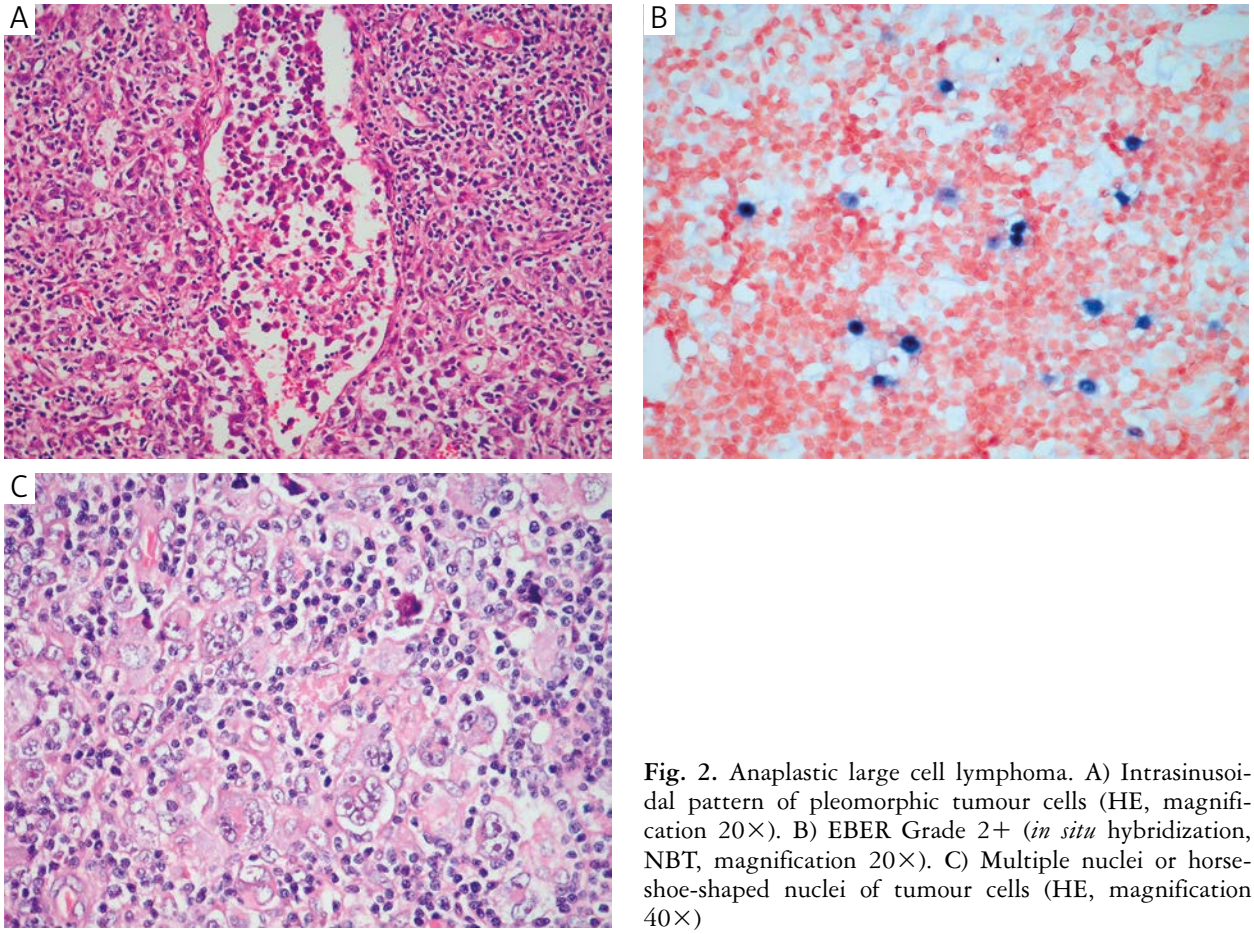

Fig. 2. Anaplastic large cell lymphoma. A) Intrasinusoidal pattern of pleomorphic tumour cells (HE, magnification 20×). B) EBER Grade 2+ (*in situ* hybridization, NBT, magnification 20×). C) Multiple nuclei or horseshoe-shaped nuclei of tumour cells (HE, magnification 40×)

or 2+ for EBER, on non-neoplastic large B-cells and immunoblasts, as seen in Fig. 3.

Four cases of extranodal NK/T-cell lymphoma, nasal type, presented with a typical angiocentric and angiodestructive infiltration and the associated prominent necrosis. All 4 of these cases exhibited a high level of EBER-positive staining in almost all of the neoplastic cells (Fig. 4). Extranodal NK/T-cell lymphoma, nasal type expressed significantly higher levels of EBER-positive staining ($p = 0.019$). In contrast, EBER-positive staining in the other histopathological subtypes did not result in significant results.

Enteropathy-type T-cell lymphoma, an aggressive tumour of intraepithelial T lymphocytes common in areas with a high prevalence of coeliac disease, consisted of only 3 cases in this study. One of these cases

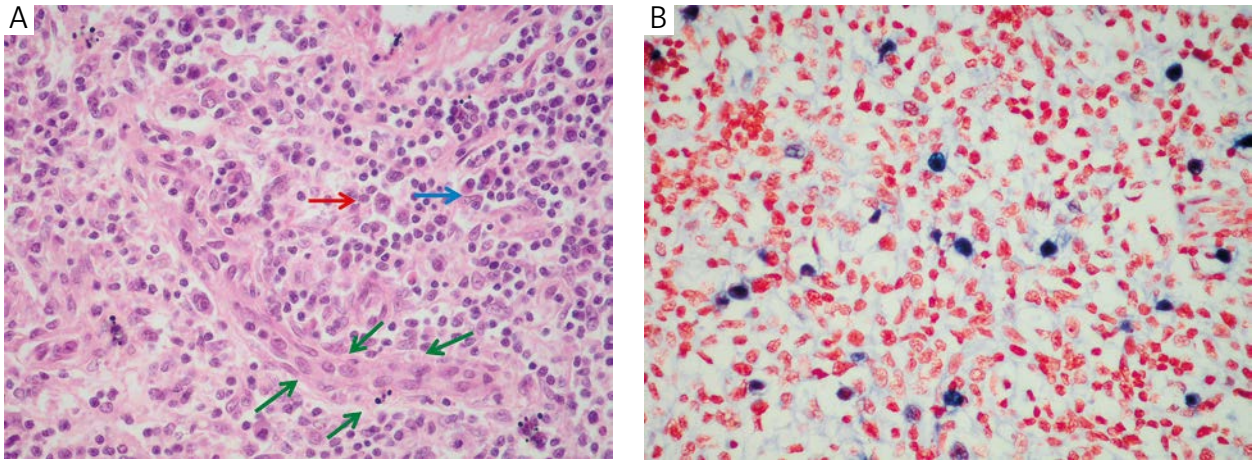

Fig. 3. Angioimmunoblastic T-cell lymphoma. A) Medium sized cells with clear cytoplasm (red arrows), reactive plasma cells (blue arrow), and immunoblasts, eosinophils, mature lymphocytes, and high endothelial proliferation (green arrows) (HE, magnification 20×). B) EBER Grade 2+ (*in situ* hybridization, NBT, magnification 20×)

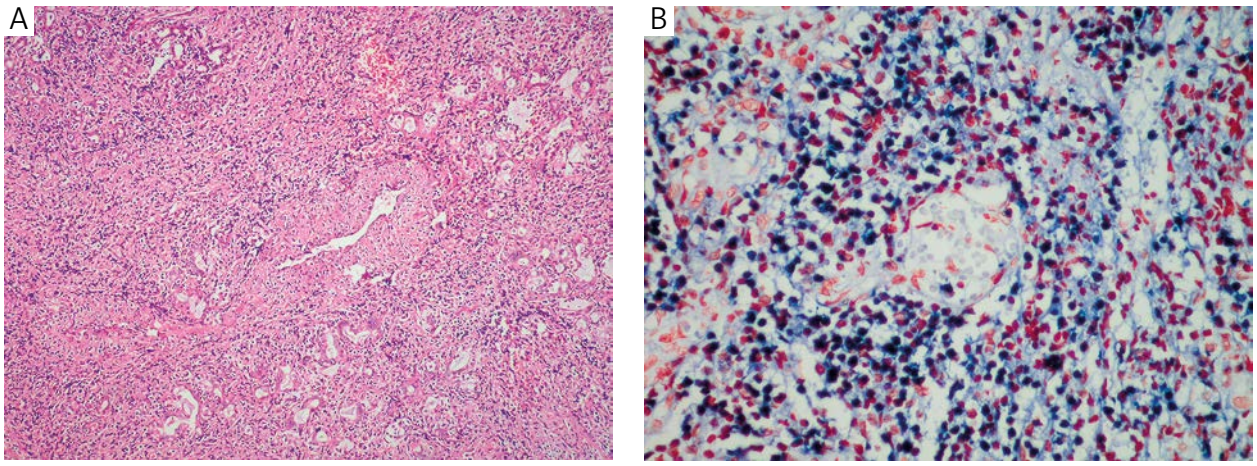

Fig. 4. Extranodal NK/T-cell lymphoma, nasal type. A) Angiocentric infiltration of medium sized cells (HE, magnification 10×). B) EBER Grade 4+ (*in situ* hybridization, NBT, magnification 20×)

contained rare EBER-positive cells, which were probably reactive or exhibited an activated phenotype; notably, this finding was observed in a post-transplant patient.

There was only 1 case of HSTCL, characterised by hepatosplenomegaly and cytopenia, which was not associated with EBV, as was the other post-transplant patient included in the study, who presented with SPTCL.

Discussion

Although EBV-related lymphoproliferative diseases consist mostly of B-cell neoplasms, some T- and NK-cell lymphoproliferative diseases, especially those with a more aggressive clinical behaviour, have been etiologically linked to chronic, active EBV infection [26]. Since most T- and NK-cell neoplasms exhibiting EBER-positive staining have a cytotoxic T-cell phenotype, it has been proposed that proliferation of cytotoxic T-cells in response to EBV-infected B-cells plays a role in the pathogenesis of these tumours [10, 27]. However, the exact mechanisms of EBV infection and transformation of T-cells are unknown at this time.

The distribution of various subtypes of NHL shows wide geographic variations between the Western and Eastern parts of the world [8]. Studies gathering information from different geographic areas, including America, Europe, Asia, and South Africa, have documented that mature T- and NK-cell neoplasms comprise about 12% to 15% of all NHLs [2, 3]. The percentage of T- and NK-cell neoplasms among all NHLs is 7% to 10% in Western countries [2, 28], 25% in Korea [29], 21% in Osaka [30], a region of Japan not endemic for adult T-cell leukaemia/lymphoma, and 18% in South Taiwan [31]. According to these studies, PTCL, NOS is the most frequent subtype, followed by ALCL, AITCL, and extranodal NK/T-cell lymphoma, nasal type, which comprise 3.7%, 2.4%, 1.2%, and 1.4%, respectively, of all NHLs. In con-

trast, ETTCL, HSTCL, and adult T-cell leukaemia/lymphoma each comprise < 1% of all NHLs. PTCL, NOS comprises 9% to 10% of NHL cases in the East and 3% to 4% of NHL cases in the West [8]. Similarly PTCL, NOS was the most prevalent subtype in our patient population, followed by ALCL. However, the second most prevalent type reported was extranodal NK/T-cell lymphoma, nasal type in Eastern countries, accounting for 4% to 8% of all cases of NHL [5, 8, 30, 31]. The extranodal NK/T-cell lymphoma, nasal type was scarce in our dataset, and adult T-cell leukaemia/lymphoma was not found, which is more similar to Western case series.

Table III. Distribution of EBER positivity in various series of NK/T cell lymphomas

Author, country and reference	Distribution
Harabuchi, Japan 1996 [35]	16/18 (89%)
Nakamura, Japan 1997 [36]	27/32 (84%)
Cuadra-Garcia, USA 1999 [37]	13/14 (93%)
Quintanilla-Martinez, Peru 1999 [15]	27/28 (96%)
Gaal, USA 2000 [38]	14/14 (100%)
Ko, Korea 2004 [39]	39/51 (76%)
Kim, Korea 2003 [40]	25/35 (71%)
Kuo, Taiwan 2004 [41]	22/22 (100%)
Ng, Singapore 2004 [42]	41/42 (98%)
Miyazato, Japan 2004 [30]	23/34 (68%)
Tai, Malaysia 2004 [43]	19/20 (95%)
Kitamura, Japan 2005 [44]	31/31 (100%)
Oshimi, Japan 2005 [34]	123/126 (98%)

The results of our study, presented in Table II, revealed that extranodal NK/T-cell lymphoma, nasal type, exhibited the most significant association with EBV, followed by PTCL, NOS. Some cases of AITCL, ALCL, and ETTCL showed evidence of EBV-positive non-neoplastic cells, discordant with the morphology of neoplastic cells, but consistent with reactive or activated lymphoid cells and/or immunoblasts. All cases of extranodal NK/T-cell lymphoma, nasal type included in this study presented with predominant infiltration of the nasal cavity and a high-grade EBER staining pattern determined by *in situ* hybridization. A type II latency expressing the latent EBV proteins LMP1, EBNA1, and EBERs has been reported in this entity [32]. Most large series have been reported from Asia and Central and South America

Table IV. Distribution of EBER positivity in various series of T and NK cell lymphomas and comparison with the present study.

Histopathological Diagnosis	Chan ACL Hong Kong 1999	Huh J Korea 1999	Jung CK Korea 2001	Ohshima K Japan 2002	Lu D Taiwan 2004	Noorali S Pakistan 2004-5	Kim DH Korea 2005	Au W-Y China 2005	Hirose Y Japan 2006	Karaarslan S Turkey 2008
Extranodal NK/TCL, nasal type	24/24 (100%)	47/51 (92%)	9/13 (69%)	18/18 (100%)	14/14 (100%)		6/6 (100%)	56/56 (100%)	11/11 (100%)	4 /4 (100%)
ETTCL	3/6 (50%)			5/13 (38%)	1/2 (50%)			0/3 (0%)		0/3 (0%)
HSTCL				4/5 (80%)				0/1 (0%)		0/1 (0%)
SPTCL					0/1 (0%)			0/1 (0%)		0/1 (0%)
PTCL, NOS	11/27 (41%)	26/66 (39%)	5/17 (29%)		4/22 (18%)		5/11 (45%)	16/24 (68%)	18/37 (49%)	10/32 (31.3%)
ALCL	0/6 (0%)	3/13 (23%)	0/2 (0%)	0/6 (0%)	1/11 (9%)	2/12 (16%)	0/13 (0%)	0/25 (0%)		0/13 (0%)
AITCL	6/7 (86%)	3/4 (75%)	1/1 (100%)		6/9 (67%)	8/9 (89%)		16/19 (84%)	14/20 (70%)	0/8 (0%)
TOTAL	44/70 (63%)	79/137 (58%)	15/33 (45%)	27/42 (64%)	26/59 (44%)	10/21 (48%)	5/24 (21%)	88/129 (68%)	43/68 (63%)	14/62 (22.6%)

PTCL, NOS – peripheral T-cell lymphoma, not otherwise specified; ALCL – anaplastic large cell lymphoma; AITCL – angioimmunoblastic T-cell lymphoma; ETTCL – enteropathy type T-cell lymphoma; HSTCL – hepatosplenic T-cell lymphoma; SPTCL – subcutaneous panniculitis-like T-cell lymphoma

[33], and Table III presents a summary of those studies, which used Southern blotting or *in situ* hybridization techniques to detect viral genomes in extranodal NK/T-cell lymphomas. The incidence of EBV latency has been reported to be 68-100%, including a few reports with a small number of cases from the East. The largest series of extranodal NK-cell lymphoma published to date is by Oshimi *et al*., who reported 98% EBER positivity [34].

Miyazato *et al.* [30] identified EBER-positive staining by *in situ* hybridization in 83%, 36%, and 25% of nasal, non-nasal, and nodal NK/T-cell lymphomas, respectively. The largest series by Oshimi *et al.* [34] found EBER-positive cells in 100% of nasal and 88% of extranasal cases. In a similar study from Korea [35], 82% of nasal and 54% of extranasal NK/T-cell lymphomas and 50% of PTCL were found to be EBV positive.

In other studies using *in situ* hybridization for the detection of EBER-positive staining, extranodal NK/T-cell lymphoma, nasal type has been found to exhibit a significantly higher correlation with EBV-positive cells. A comparison of previous studies with the current work is shown in Table IV.

A few studies have reported an association between EBV and ETTCL by PCR and *in situ* hybridization. EBER positivity was reported to be 38% in a Japanese series with 13 patients [36] and 30% in two different series from Hong Kong comprising a total of 9 patients [7, 9]. Of the 3 ETTCL cases in the present study, 1 post-transplant patient exhibited EBER-positive staining that was limited to isolated cells resembling reactive or activated lymphocytes and some with immunoblast morphology.

A few studies have reported an aetiological role of EBV using Southern blot and *in situ* hybridization in patients with HSTCL [23, 37]. The largest series was a study from France that reported 2 EBER-positive cases of a total of 20 [38]. These 2 cases with pleomorphic cytological features were both of the βF1-negative, γTCR-positive γδT-cell phenotype. The series of Ohshima *et al.* [36] from Japan consisted of 4 EBER-positive cases out of a total of 5 with a γδT-cell phenotype. The only case in the present study was EBER negative.

SPTCL, a very rare entity, was found to be unrelated to EBV in 2 patients from two different series [5, 7], and 1 patient in the present study (Table IV).

AITCL, a systemic lymphoproliferative disease involving the lymph nodes, spleen, and bone marrow, is especially problematic for inexperienced pathologists, because it is characterised by a polymorphous infiltrate of a neoplastic T-cell population and accompanying reactive B-cells. This challenging disease is diagnosed more frequently after the observation of aberrant CD10 expression on neoplastic T-cells [39]. Some EBV-positive cells were detected in 67-100% of the cases in previous studies and 62.5% of our cases [5, 7, 9, 40, 41]; however, the reaction with EBER was restricted to the reactive B-cell population, rather than neoplastic T-cells. While the latency pattern is unknown, LMP1 and EBERs reflect latency pattern II in these cases.

EBER-positive staining was found in 31.3% of cases in the heterogeneous PTCL, NOS group, while this group has been reported to exhibit 18-68% positivity in other studies [5, 7, 9, 41, 42].

ALCL has been reported as positive for EBER *in situ* hybridization in 0% to 23% of cases in several studies [5, 7, 9, 36, 40, 42]. However, none of the 13 cases of ALCL were positive in the present study, although 2 cases presented EBER expression that was limited to rare non-neoplastic lymphoid cells.

Conclusions

The present study of T- and NK-cell lymphomas, which includes the rare and aggressive subtypes of NHL, has demonstrated that PTCL, NOS is the most prevalent type in our geographic area. In parallel with this finding, most of our EBER-positive cases were PTCL, NOS. Extranodal NK/T-cell lymphoma was limited to only 4 cases in this study; however, EBER-positive staining was increased to a statistically significant level and exhibited a more robust staining pattern in this lymphoma subtype ($p = 0.019$). We have concluded that *in situ* hybridization is a sensitive method for the identification of EBV in lymphomas and that EBV infection plays an important role in the pathogenesis of nodal or extranodal T- and NK-cell lymphomas in our area, which is consistent with the findings in Western countries.

The authors declare no conflict of interest.

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