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Original Article

Histological type distribution and expression of nm23, VEGF, TOP2A and MUM-1 in peripheral T-cell and NK-cell lymphomas in Chinese: analysis of 313 cases

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Abstract: Peripheral T cell and natural killer cell lymphomas (PT/NKCLs) are rare malignant tumors of lymphoid tissue. The incidence varies by geographical region and race. We reclassified 313 cases of PT/NKCLs based on the 4th edition of the World Health Organization (WHO) classification to demonstrate the distribution of each histologic type of PT/NKCLs in Chinese populations. In our series, extranodal NK/T-cell lymphoma (ENKT) was the most common (37.1%) type, followed by peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) (31.3%) and angioimmunoblastic T-cell lymphoma (AITL) (12.8%). Also, we investigated the expression level of nm23, VEGF, TOP2A, and MUM-1 in all 313 cases. The positive rate of nm23, VEGF, TOP2A, and MUM-1 expression was more than 50% in most histologic types. Among the five common types, the expression rate of nm23 (34.5%) and TOP2A (27.6%) in ENKT were the lowest ($P<0.05$). VEGF expression was also lowest in ENKT (26.7%), but it was much higher in PTCL-NOS (54.1%), AITL (70.0%), and ALCL-ALK- (56.5%) and ALCL-ALK+ (42.9%). The difference of VEGF expression between ENKT and PTCL-NOS and AITL was significant ($P<0.05$). Fourteen of 23 (60.9%) cases of ALCL-ALK- and 9 of 14 (64.3%) cases of ALCL-ALK+ were positive for MUM-1, which was much higher than in ENKT (19.8%), PTCL-NOS (26.5%) and AITL (35.0%) ($P<0.05$). Although the significance of their expression in PT/NKCLs is not clear, we suggested that they may be novel tumor markers for developing targeted therapy in the future.

Keywords: Lymphoma, T-cell, NK-cell, epidemiology, immunohistochemistry

Introduction

Peripheral T cell and natural killer cell lymphomas (PT/NKCLs) are relatively rare, and account for about 12% of non-Hodgkin lymphomas (NHLs) [1]. The frequency of each type of PT/NKCLs varies according to different geographic regions and race around the world [2]. Compared to western countries, PT/NKCLs are more prevalent in Asia as previously reported [3, 4]. Even in Asia, the distribution of each type of PT/NKCLs is also geographically different.

PT/NKCLs consist of a group of biologically distinct histologic types with heterogeneous clinical, histologic, immunophenotypic, cytogenetic, and molecular features. The diagnosis of PT/NKCLs is mostly made depending on immunophenotype [5-9]. Although the characteristic expression of pan-T markers and cytotoxic molecules of tumor cells is useful to make the right diagnosis according to the WHO classification of lymphoid neoplasms, the ability of hematopathologists to reproducibly diagnose PT/NKCLs is still low.

Many biomarkers play a crucial role in cellular proliferation, differentiation, oncogenesis, and tumor metastasis. Therefore, they were used for monitoring the progression of tumors and guiding targeting therapies. nm23 was originally identified as a protein that was expressed at a lower level in metastatic cancer cells. So far, a few studies showed that nm23 was detected in diffuse large B-cell lymphoma (DLBCL) and PTCL-NOS, and the expression of nm23 might suggest poor prognosis [10, 11].

Topoisomerase IIa (TOP2A) is a key enzyme in DNA replication and a molecular target for many anticancer drugs. Overexpression of TOP-2A in all acute lymphoblastic leukemia suggested that *TOP2A* induces the development of leukemia [12]. Vascular endothelial growth factor (VEGF) can stimulate angiogenesis and lymphangiogenesis, which is an important process in the growth and metastasis of tumor cells. It regulates the progression of cutaneous T-cell lymphoma by increasing vasculature [13]. However, the expression level of nm23, TOP2A and VEGF in PT/NKCLs is not clear.

In addition, interferon regulatory factor 4 (IRF)/multiple myeloma oncogene-1 (MUM-1) is a member of the interferon regulatory factor family of transcriptional factors. It usually is expressed in aggressive B-cell lymphomas. A recent study suggested MUM-1 expression might be associated with poor survival outcomes in patients with PTCL [14].

In this study, we analyzed all 313 cases of PT/NKCLs diagnosed in the last 12 years in our hospital to demonsrate the distribution of each histologic type of PT/NKCLs in Chinese populations. We also performed immunohistochemical staining of nm23, TOP2A, VEGF and MUM-1 to investigate their expression level in PT/NKCLs.

Materials and methods

Patients and clinical data

A total of 313 cases of *de novo* PT/NKCLs were collected at National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union (CICAMS) in Beijing, between Oct. 1999 and Oct. 2011. All the patients were native Chinese.

All the samples were formalin-fixed, paraffin embedded (FFPE). We reclassified these cases according to the 4th edition of the WHO classification of tumors of haematopoietic and lymphoid tissues [8] by two experienced hematopathologists (H.W. and F.X.) based on hematoxylin and eosin (H&E)-stained sections and immunohistochemical staining. The cases with different opinions were discussed and finally diagnosed consistently.

The clinical parameters of these patients were recorded, including age at the diagnosis, gender, and primary site. Laboratory data including serum lactate-dehydrogenate (LDH) and β macroglobulin (β2-MG) levels were collected.

Tissue microarray and immunohistochemistry

All the specimens were assembled into nine blocks of tissue microarrays. Three tumor cores of 1.0 mm diameter were taken from each FFPE sample.

Immunohistochemical staining was performed on 4 μm-thick FFPE tissue microarrays using an autostainer, a Ventana Benchmark XT (Ventana Medical systems, Tucson, AZ, USA) according to the manufacturer's instruction. The primary antibodies included nm23, VEGF, TOP2A and MUM1. Positive controls were used, and phosphate buffer saline (PBS) was used as negative controls to replace the primary antibody. TOP2A and MUM1 were both nuclear staining, and nm23 and VEGF were both cytoplasm staining. 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 as follows: 0, negative (-); 1-4, weakly positive expression (1+); 5-8, moderately positive expression (2+); and 9-12, strongly positive expression (3+).

T-cell clonality analysis

Genomic DNA was extracted from FFPE tumor tissues using QIAamp® DNA Mini Kit (Qiagen, Germany), according to the manufacturer's instructions. The quality of the DNA was assessed. BIOMED-2 polymerase chain reaction (PCR) was performed to analyze the clonal expansion of T cells using IdentiClone™ T Clonality Assays (Invivoscribe, USA) in 63 selected cases with better block preservation. T-cell clonal expansion was detected by analysis of TCRβ and TCRγ gene rearrangement. The PCR products were analyzed using fluorescence capillary electrophoresis (FCE) on an ABI 3500XL genetic analyzer (Applied Biosystems) [15, 16]. Appropriate positive and negative controls were included in all experiments.

Statistical analysis

SPSS18.0 software (SPSS Inc., Chicago, IL) was used for data analysis and processing. Clinical

Table 1. Clinicopathologic features of 313 cases of PT/NKCL

Histologic Type	Number of cases (%)	Male to Female Ratio	Median Age (range)	Primary Site		β2-MG Elevated (%)	LDH Elevated (%)
				Extranodal	Nodal		
ENKT	116 (37.1)	1.8:1	42 (13-88)	113	3	37.7	28.4
PTCL-NOS	98 (31.3)	2.5:1	51 (4-78)	26	72	52.6	40
AITL	40 (12.8)	3:1	57 (16-80)	3	37	50	36
ALCL-ALK-	23 (7.3)	2.8:1	53 (23-77)	4	19	40	20
ALCL-ALK+	14 (4.5)	1:1	28 (10-80)	1	13	44.4	30
MF	7 (2.2)	6:1	47 (29-72)	7	0	25	60
EATL	6 (1.9)	2:1	47 (41-69)	5	0	60	40
SPTCL	6 (1.9)	1:2	42 (23-55)	6	0	25	25
C-ALTL	3 (1.0)	2:1	33 (16-50)	3	0	0	0

Table 2. Expression of nm23, VEGF, TOP2A, and MUM-1 in 313 cases of PT/NKCL

Marker	Number of Positive cases (%)								
	ENKT (n=116)	PTCL-NOS (n=98)	AITL (n=40)	ALCL-ALK- (n=23)	ALCL-ALK+ (n=14)	MF (n=7)	EATL (n=6)	SPTCL (n=6)	C-ALTL (n=3)
nm23	40 (34.5)*	61 (62.2)	27 (67.5)	16 (69.6)	9 (64.3)	5 (71.4)	4 (66.7)	5 (83.3)	2 (66.7)
VEGF	31 (26.7)#	53 (54.1)	28 (70.0)	13 (56.5)	6 (42.9)	0	2 (33.3)	4 (66.7)	2 (66.7)
TOP2A	32 (27.6)*	60 (61.2)	30 (75.0)	17 (73.9)	9 (64.3)	4 (57.1)	3 (50.0)	4 (66.7)	2 (66.7)
MUM-1	23 (19.8)	26 (26.5)	14 (35.0)	14 (60.9)▲	9 (64.3)▲	2 (28.6)	1 (16.7)	2 (33.3)	1 (33.3)

*Compared to PTCL-NOS, AITL, ALCL-ALK- and ALCL-ALK+, the positive rate of nm23 and TOP2A expression in ENKT was the lowest ($P<0.05$). #Compared to PTCL-NOS and AITL, the positive rate of VEGF expression in ENKT was lower ($P<0.05$). ▲Compared to ENKT, PTCL-NOS and AITL, the positive rate of MUM-1 expression in ALCL-ALK- and ALCL-ALK+ was higher ($P<0.05$).

pathological characteristics of different groups were compared using the Fisher's exact test or chi-square test. All statistical analyses were two-sided, and *P* values less than 0.05 were considered significant.

Results

Histologic type distribution

According to the standards of the 4th edition of the WHO classification, all 313 cases were reclassified into 9 histologic types as shown in **Table 1**. ENKT was the most common (116 cases, 37.1%) type in PT/NKCLs, the second was PTCL-NOS (98 cases, 31.3%), and the third was AITL (40 cases, 12.8%). ALCL-ALK- (23 cases, 7.3%) and ALCL-ALK+ (14 cases, 4.5%) accounted for fewer than 10% of the total. While, MF (7 cases, 2.2%), EATL (6 cases, 1.9%), SPTCL (6 cases, 1.9%) and C-ALTL (3 cases, 1.0%) were all rare in Chinese populations.

Clinical features

The age of the total 313 patients ranged from 4 to 88 years (median 47). **Table 1** shows the patients of AITL were the eldest with a median age of 57 years, and the patients of ALCL-ALK+ were the youngest with the median age of only 28 years. Male to female ratio of the total was 2.10:1. There was a male predominance in many histologic types, especially in MF (6:1) and AITL (3:1). Extranodal sites were more common, and accounted for 53.7% of the total, mostly in nasal cavity, followed by nasopharynx, oropharynx, tonsils, skin, gastrointestinal tract, and testis. Almost all the cases of ENKT (113/116) primarily occurred in extranodal sites, while AITL mainly involved lymph nodes (34/37, 91.9%). This showed a statistically significant difference between primary sites and ENKT and AITL ($P<0.05$). All the cases of EATL were occurred in gastrointestinal tract, and MF, SPTCL, C-ALCL were only in skin.

The level of serum β2-MG and LDH were variably elevated in PT/NKCLs, most frequently in EATL (3/5, 60%) and MF (3/5, 60%), but there was no difference between different histologic types ($P>0.05$).

Immunohistochemical characteristics

As seen from **Table 2**, the positive rate of nm23, VEGF, TOP2A, and MUM-1 expression was more than 50% in most histological types, respec-

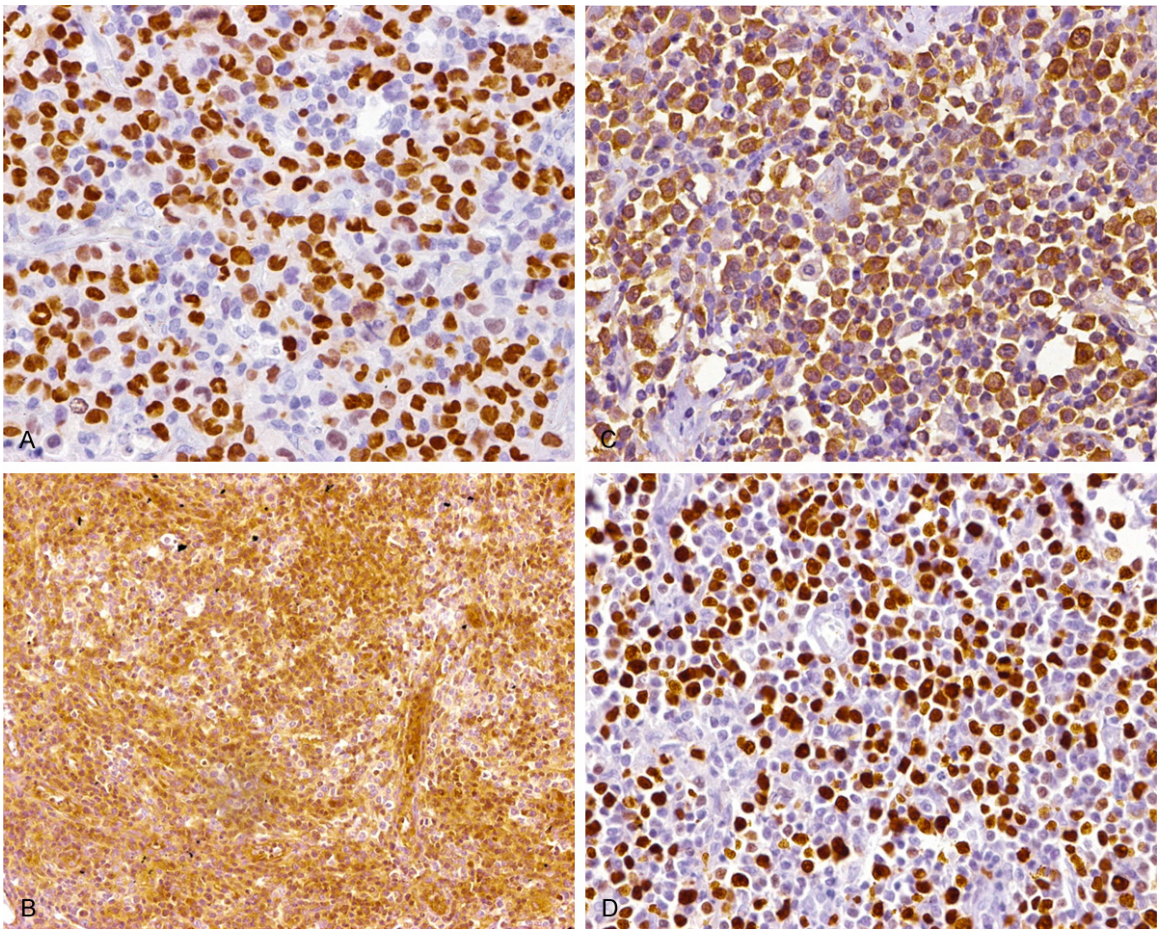

Figure 1. Immunohistochemical staining of ALCL, ALK- for MUM1 (A, IHC ×400) and VEGF (B, IHC ×200); Immunohistochemical staining of PTCL-NOS for nm23 (C, IHC ×400) and TOP2A (D, IHC ×400).

tively. Among the five common types, the expression rate of nm23 (34.5%) and TOP2A (27.6%) in ENKT were the lowest ($P<0.05$). VEGF expression was also lowest in ENKT (26.7%), as it was much higher in PTCL-NOS (54.1%), AITL (70.0%), and ALCL-ALK- (56.5%) and ALCL-ALK+ (42.9%). The difference of VEGF expression between ENKT and PTCL-NOS and AITL was significant ($P<0.05$). Fourteen of 23 (60.9%) cases of ALCL-ALK- and 9 of 14 (64.3%) cases of ALCL-ALK+ were positive for MUM-1, which were much higher than ENKT (19.8%), PTCL-NOS (26.5%) and AITL (35.0%) ($P<0.05$) (**Figure 1A-D**).

T-cell receptor gene rearrangement analysis

63 cases were assessed for T-cell receptor gene rearrangement. Except for 13 cases of ENKT, the positive rate was only 38.5%; the remaining 50 cases of other types were all detected through TCR gene rearrangement.

Discussion

PT/NKCLs are heterogeneous lymphoid neoplasms, originating from T or NK-cells, with marked geographic variation [17-19]. An international collaborative study of 1153 cases of T/NK-cell lymphomas from 22 centers worldwide showed that PTCL-NOS was the most common type (25.9%), followed by AITL (18.5%), ALCL (12%), NK/T-cell lymphoma (10.4%) and EATL (4.7%) [18]. It found that PTCL-NOS was the most common type in both North America and Europe, while ENKT and ATIL were the most common type in Asia. Whereas, the frequency of each histologic type of PT/NKCLs was varied from different geographic regions even in Asia. Recently, a study in the Far East (FE), including China (Hong Kong and Shanghai), Indonesia, and Thailand, showed that the FE had a significant higher frequency of T-NHL, especially in Hong Kong and Shanghai [20]. As reported, MF was the most common type (43.4%) in South of

Iran [21], whereas PTCL-NOS in Far East (FE) [20] and ENKT, nasal type in China [22, 23]. The distribution of our group was similar to the previous study in China. ENKT was the most common type (37.1%), followed by PTCL-NOS (31.3%) and AITL (12.8%).

The clinicopathologic characteristics of our 313 cases of PT/NKCLs were consistent with previous reports [18, 24]. We also showed a male predominance in many histological types except for ALCL-ALK+ and SPTCL. Moreover, we found that the patients with ALCL-ALK+ were the youngest and the patients of AITL were eldest in our study. We also provided an evidence that PT/NKCL mainly involved extranodular sites. Certainly, there were great differences between each type. All ENKT were almost occurred in extranodular sites, whereas almost all AITL involved lymph nodes.

The results of T-cell rearrangements in our study showed 38.5% cases of ENKT were identified with TCR gene rearrangments, which was much higher than most previous studies [25], but was similar with Au et al. and Hong et al. [26, 27]. It might be that ENKT more frequently originate from T-cells rather than NK-cells [27]. Due to the few cases of ENKT in our group detected by TCR, the conclusion needs to be proven in more numerous cases in the future.

In recent years, several hot genes including *nm23*, *TOP2A*, *VEGF* and *MUM-1*, were extensively explored in many tumors such as nasopharyngeal carcinoma, colorectal carcinoma, breast cancer, and renal cell carcinoma [14, 28-34]. Several studies confirmed that nm23, TOP2A, VEGF and MUM-1 not only played an important role in the tumorigenesis, invasion and metastasis, but also were associated with inferior prognosis. To the best of our knowledge, there were only a few studies focusing on the relationship between those genes and PT/NKCLs [11, 35-37]. A study by Niitsu et al. found that 78.4% of cases of PTCL-NOS overexpressed nm23-H1 and its expression could be an independent prognostic factor in PTCL-NOS [11]. Also, overpression of TOP2A indicated shorter survival of patients with nodal PTCL [35].

In our series, we investigated the expression of nm23, VEGF, TOP2A, and MUM-1 in all 313 cases. Although the positive rate of nm23 expression was a little lower in our study than that reported previously [11], we showed more than 60% cases of PTCL-NOS, AITL, ALCL-ALK- and ALCL-ALK+ were positive for nm23. However, only 34.5% cases of ENKT expressed nm23. There was a difference in the expression of nm23 between ENKT and other four common types of PT/NKCLs ($P<0.05$).

The expression of TOP2A in our series was same as the expression of nm23; except for the cases of ENKT, most of the cases of PTCL-NOS, AITL, ALCL-ALK- were positive. The difference was significant ($P<0.05$).

The positive rate of VEGF expression in PTCL-NOS was high, similar to previous studies [38, 39]. In our study, AITL had the highest positive rate of VEGF expression, followed by ALCL-ALK-, as ENKT was the lowest.

MUM-1 is a well-known biomarker of activated B-cell like DLBCL. It contributes to cell proliferation and aggressiveness. In our results, 60.9% cases of ALCL-ALK- and 64.3% cases of ALCL-ALK+ were positive for MUM-1, which is much higher than ENKT, PTCL-NOS and AITL ($P<0.05$).

Although the significance of the expression of nm23, VEGF, TOP2A, and MUM-1 in PT/NKCLs is not clear, the positive rate was high in most types. As their role was detected in other tumors, we suggested that they might serve as novel tumor markers for developing targeted therapy in the future.

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Disclosure of conflict of interest

None.

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