RESEARCH COMMUNICATION

Pathological and Clinical Characteristics of 1,248 Non-hodgkin's Lymphomas from a Regional Cancer Hospital in Shandong, China

Jie Liu[1,2&], Bao Song[3&], Tingyong Fan[1,2&], Chengsuo Huang[2], Chao Xie[2], Jing Li[5], Weixia Zhong[4], Sheng Li[1], Jinming Yu[2*]

Abstract

Introduction: Non-Hodgkin's lymphomas (NHL) in China appear to have many characteristics different from those Western countries, but clinical studies to provide details have been rare so far. Methods:This study retrospectively analyzed the characteristics of clinical and pathological data for the 1248 NHL patients in the Shandong region of China between 2002 and 2010. Results: From 2002 to 2010, the number of clinical cases of NHL increased year by year. Among the total, 64.7% were B-cell NHL, 30.3% were T-cell NHL, including: diffuse large B cell lymphoma (DLBCL) (40.9%), extranodal NK/T-cell lymphoma, nasal type (NK/T) (10.0%); peripheral T cell lymphoma, unspecified (PTL) (9.2%); follicular lymphoma (FL) (6.4%); extranodal marginal zone B cell lymphoma (MALT) (5.4%); precursor T lymphoblastic leukemia/lymphoma (T-LBL) (4.5%); and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (3.2%). The average age of onset was 47.7 ± 16.3 (18-85), and the male to female ratio was 1.57:1. Compared with Shanghai and Shanxi in China, the proportion of NK/T cell lymphoma in this region was higher. In comparison with other countries, the FL and CLL/SLL in this region were significantly lower, while the incidence of T-cell lymphoma was significantly higher than that in the United States and Europe. Conclusions:The clinical and pathological distribution of NHL in Shandong region of China is consistent with that of Asian populations, but with significant difference from the Western countries. The NK/T cell lymphoma in this region was significantly higher.

Keywords: Non-Hodgkin's lymphoma - distribution - 2001 WHO diagnostic criteria - retrospective study

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Introduction

Non-Hodgkin's lymphoma (NHL) is a malignancy originated in lymphatic hematopoietic tissue, and is also currently the fastest-growing malignant tumor in the world. The incidence of NHL has been rising greatly in the last 30 years. Especially in the past 10 years, the growth rate increased significantly. From 1973 to 1997, the overall incidence of NHL in the United States increased by 80%, with average annual increase of approximately 3%. In 2000, there were 55,000 cases of newly diagnosed NHL in the United States; and in 2010, there were 66,120 cases of newly diagnosed NHL in the United States, ranking as the sixth most common cancer (Baris et al., 2000; Siegel et al., 2011). Although the incidence of NHL in China was significantly lower than that in the United States and Europe, this incidence has significantly increased in recent years. According to the published data from the 2008 Shanghai World Lymphoma Awareness Day, the incidence rate was 3.5/100,000 and the number of newly diagnosed cases was 45,000 every year, with more than 20,000 deaths, ranking from the 10th to the 9th in the malignant tumor incidence(HYPERLINK "http://baike.baidu.com/view/2102969.html" http://baike.baidu.com/view/2102969.html).

The etiology of lymphoma has not yet been fully elucidated. It is a disease caused by the abnormal differentiation and proliferation of cells with immunological activity in different developmental stages, affected by both the internal factors and external factors. Its occurrence and development is related to viruses, genetic susceptibility, immune status, ethnicity, and geographic factors (Aisenberg et al., 1997; Alexander et al., 2007; Nogai et al., 2011). NHL is divided into B-cell lymphoma and T-cell lymphoma. According to the pathology, immunophenotype, genetic characteristics, and clinical characteristics of the immune cells, each type of NHL also includes more than ten different pathological subtypes. Compared with the European and American countries, the distribution of the pathological subtypes for Chinese NHL is obviously different. The follicular lymphoma (FL) is significantly lower, with only 3-10%,

*[1]Medical College, Shandong University, [2]Department of Oncology, [3]Shandong Provincial Key Laboratory of Radiation Oncology, [4]Department of Pathology, Shandong Cancer Hospital & Institute, [5]Department of Oncology, the Fourth People's Hospital of Jinan city, Jinan, China [&]Equal contributors *For correspondence: yu_jinming@126.com*

while the proportion of T-cell lymphoma is significantly higher, which is up to ~30%(No authors listed, 1985; Yang et al.,1993; Yin et al., 2003; Wang et al., 2005; Wang et al., 2006; Zhou et al., 2006; Gross et al., 2008).

Previous studies have shown that the distributions of a variety of pathological types of NHL in the United States were similar(Anderson et al., 1998; Cocco et al., 2000; Groves et al., 2 000; Wang et al., 2007). A project by the Surveillance, Epidemiology and End Results (SEER) program analyzed the data of 60,057 NHL patients between 1978 and 1995 in the United States, and the results showed that the distributions of all NHL pathological subtypes in 9 U.S. regions (San Francisco–Oakland, Seattle–Puget Sound, Metropolitan Detroit, Connecticut, Hawaii, Iowa, Metropolitan Atlanta, Utah, New Mexico) were basically the same(Groves et al., 2000). However, the distributions of various NHL pathological subtypes in different parts of China had some differences. The the Nationwide Lymphoma Pathology Coopsrative Group (NLPCG) project based on the statistics of 8572 cases of patients with NHL in 13 provinces of China from 1972 to 1981 showed that, the proportion of B-cell NHL was higher in the central and western regions of China, while the proportion of T-cell NHL was higher in the eastern region of China (No authors listed, 1985). The difference in the distribution of various NHL pathological types in different parts of China may be related to the quite different environment and lifestyle in different parts of China. This also suggested that it is necessary to understand the distribution of pathological types of NHL in the specific regions of China.

Shandong is an eastern coastal province of China. Shandong Cancer Hospital is a cancer hospital mainly responsible for the diagnosis and treatment of cancer patients from Shandong province and the surrounding areas. In this study, the clinical and pathological data of 1248 cases of NHL patients in Shandong Cancer Hospital from January 2002 to December 2010 were investigated. And its comparisons were carried out with other regions of China including Shanghai and Shanxi province, other Asian countries including Japan, Korea, and Thailand, and other European and American countries such as the United States and the Netherlands. It was expected to provide some information for the changing trends of NHL in recent years in China.

Materials and Methods

Clinical data collection

In this study, the clinical data of patients diagnosed with lymphoma in Shandong Cancer Hospital continuously from January 2002 to December 2010 were retrospectively analyzed. All cases were diagnosed based on the clinical characteristics, the pathological morphology of the tissue samples, and the immunohistochemical results. The patients only with bone marrow smears were excluded. This study was approved by the IRB of the hospital. The clinical data and pathological tissue sections of the patients with NHL were re-reviewed.

The clinical data of patients included gender, age, pathological type and immunohistochemistry, clinical stage, lesion location, date of diagnosis, family history, personal history. The section of biopsy from each case was reviewed by three clinical pathologists, with consistent diagnosis for all cases. The pathological diagnostic criterion was the "2001 WHO classification for hematopoietic and lymphoid neoplasms" (Jaffe et al., 2001). The pathological classification was determined based on the tissue section with haematoxylin-eosin (H&E) staining and immunohistochemistry as well as the clinical characteristics. The detected immune phenotype markers included CD3, CD5, CD15, CD20, CD23, CD30, CD43, CD45, CD45RA, CD45RO, CD56, CD68, CD79α, EMA, bcl-2, TIA21, and cyclinD1, etc. In general, the main antibodies used in immunohistochemistry were: CD20 and CD79α as B cell markers; CD45RO, CD3, CD4, and CD5 as T cell markers; CD56 and CD3ε as NK cell marker. additional immunophenotypic study involved the use of monoclonal antibodies for CD30, CD43, CD56, cyclin D1 and MIC2, as necessary. EBER-1 in-situ hybridization was performed in cases suspected to be angiocentric lymphoma and in all nasal/nasopharyngeal lymphoma cases. Leukaemia and plasmacytoma were excluded from this study.If the application of immunophenotyping finally failed to confirm the type, it would be identified as "unclassified". Clinical staging was determined according to the Ann Arbor staging method.

Statistical analysis

Clinical data of all patients including gender, age, lesion location, pathological type, and clinical stage were counted or measured. The proportions or the averages were used for processing and analysis. Significant differences between data were analyzed using chi-square test or t test. The statistical software SPSS 13.0 was used for all statistical analyses.

Results

General information of NHL

From 2002 to 2010, a total of 1447 cases of malignant lymphoma patients, all belonging to the Han ethnic group, were treated in Shandong Cancer Hospital, including 104 cases of Hodgkin's lymphoma (7.2%) and 1343 cases of NHL (92.8%). For the NHL patients, the 95 patients less than 18 years old were excluded, and the remaining 1248 cases were included in the data being analyzed (due to its unique clinical characteristics, the multiple myeloma was not included in this set of data). Among the included patients, 762 cases were male (61.1%) and 486 cases were female (38.9%), with the male to female ratio of 1.57:1. The mean age was 47.7 ± 16.3 (18-85), with 336 cases (26.9%) over 60 years old, and 912 cases (73.1%) younger than 60 years old. There were 109 cases (8.7%) with family history of cancer. For the classification according to pathological type, there were 807 cases of B-cell NHL, accounting for 64.7%; 378 cases of T-cell NHL, accounting for 30.3%; and 63 unclassified cases, accounting for 5.0%. For the staging according to Ann Arbor staging, there were 168 cases of stage I (13.5%), 317 cases of stage II (25.4%), 409 cases of stage III (32.8%), and 306 cases of stage IV (24.5%). There were 799 cases

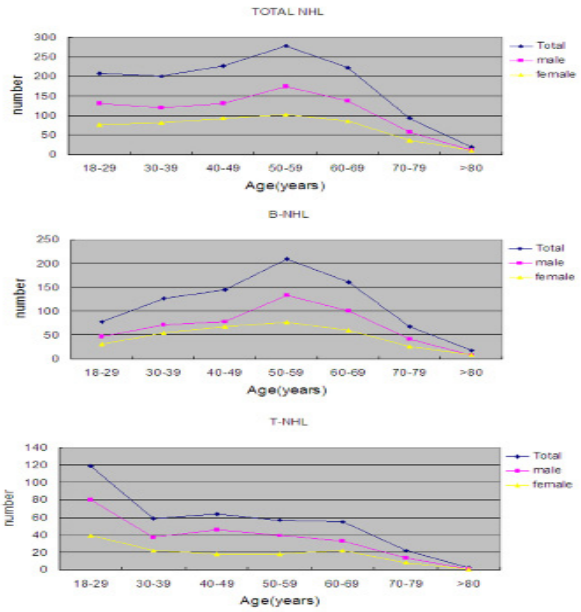

Figure 1. Age and Gender Distribution for Both Males and Females Diagnosed with: A, All NHL; B, B cell NHL; C, T cell NHL in Shandong, China

with the primary nodal lymphoma (64.0%), and 449 cases with the extranodal lesions (36.0%). There were 705 cases (56.5%) with normal expression level of LDH (≤ 250U/L), 508 cases (40.7%) with LDH level higher than normal (> 250U/L), and missing data in 35 cases (2.8%) (Table 1).

The main pathological types of NHL

The pathological subtypes of the patients included in this study were classified according to the Revised European-American Lymphoma (REAL)/World Health Organization lymphoma classification scheme(2001). There were 807 cases of B-cell lymphoma (64.7%); 378 cases of T-cell lymphoma (30.3%). Among them, the pathological types were mainly: 510 cases of diffuse large B cell lymphoma (DLBCL) (40.9%); 125 cases of extranodal NK/T-cell lymphoma, nasal type (NK/T) (10.0%); 115 cases of peripheral T cell lymphoma, unspecified (PTL) (9.2%); 80 cases of follicular lymphoma (FL) (6.4%); 68 cases of extranodal marginal zone B cell lymphoma (MALT) (5.4%); 56 cases of precursor T lymphoblastic leukemia/lymphoma (T-LBL) (4.5%); 40 cases of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (3.2%); 29 cases of mantle-cell lymphoma (MCL) (2.3%); 19 cases of plasma cell neoplasms (PCN) (1.5%); 14 cases of anaplastic large cell lymphoma (ALCL) (1.1%); 14 cases of Burkitt lymphomas (BL) (1.1%); 11 cases of precursor B lymphoblastic leukemia/lymphoma (B-LBL) (0.9%); 10 cases of angioimmunoblastic T-cell lymphoma (AITL) (0.8%); 10 cases of mycosis fungoides (MF) (0.8%); 8 cases of subcutaneous panniculitis-like T-cell lymphoma (SPTCL) (0.6%); 36 cases of unclassified B-cell NHL or other types of B-cell NHL (2.9%); and 40 cases of unclassified T-cell NHL or other types of T-cell NHL (3.2%) (Table 2).

Distribution of pathological types by age and gender

The mean age of patients with B-cell NHL of 50.7 ± 15.2 was significantly higher than that of the patients with T-cell NHL of 42.0 ± 17.1, with significant difference between the two groups (P<0.001). In B-cell NHL, the average onset ages of BL and B-LBL were low, which were 24.1 ± 6.8 and 23.8 ± 5.3, respectively, and the average onset ages of DLBCL, FL, MALT, CLL/SLL and MCL were around 50 to 56 years old. In T-NHL, the average onset age of T-LBL was the lowest, which was 24.0 ± 5.6, while the average onset age of AITL was the highest, which was 61.5 ± 7.5, and the average onset ages of PTL, NK/T, ALCL, and SPTCL were between 40 and 47 years old (Table 2).

Table 1. The General Clinical Data of NH

	Number of cases	Proportion
Gender		
Male	762	61.1%
Female	486	38.9%
Age		
≥60	336	26.9%
<60	912	73.1%
Family history		
Yes	109	8.7%
No	1139	91.3%
Pathological type		
B-cell NHL	807	64.7%
T-cell NHL	378	30.3%
unclassified NHL	63	5.0%
Clinical stage		
I	168	13.5%
II	317	25.4%
III	409	32.8%
IV	306	24.5%
missing	48	3.8%
Lesion location		
nodal	799	64.0%
extranodal	449	36.0%
LDH level		
<250U/L	705	56.5%
>250U/L	508	40.7%
missing	35	2.8%

When grouping the patients according to their onset ages, there were 208 cases of 18 ~29 years old (16.7%), 200 cases of 30~39 years old (16.0%), 226 cases of 40~49 years old (18.1%), 278 cases of 50~59 years old (22.3%), 222 cases of 60~69 years old (17.8%), 94 cases of 70~79 years old (7.5%), and 20 cases of over 80 years old (1.6%). Overall, the peak of onset ages of the NHL was 50 to 59. When grouping according to gender, the peaks of onset ages were 50~59 for both male and female patients. In the group of B-cell NHL, the peaks of onset ages were 50 to 59 for both male and female; in the group of T-cell NHL, the peaks of onset ages were less than 18-29 for both male and female (Figure 1).

Commonly, more males were in each pathological type of NHL. The male to female ratio of B-cell NHL patients (1.4:1) was significantly lower than that of T-cell NHL patients (2.0:1). The male to female ratios of ALCL and MCL were relatively high, and were 3.7:1 and 3.8:1, respectively (Table 2).

Analysis of NHL lesions

In the 1248 cases of NHL in this study, the lesions of

Table 2. The Main Pathological Subtypes of NHL and their Distribution by Gender and Age

B-cell NHL n=807 (64.7%)				T-cell NHL n=378 (30.3%)			
Subtype	N (%)	Gender (male:female)	Average age	Subtype	N (%)	Gender (male:female)	Average age
DLBCL	510 (40.9)	1.4:1	50.9±15.1	NK/T	125(10.0)	2.6:1	44.4±15.7
FL	80 (6.4)	1.1:1	51.8±13.9	PTL	115 (9.2)	2.2:1	46.4±16.5
MALT	68 (5.4)	1.6:1	50.3±13.4	T-LBL	56 (4.5)	1.5:1	24.0±5.6
CLL/SLL	40 (3.2)	1.8:1	55.3±14.3	ALCL	14 (1.1)	3.7:1	40.8±20.2
MCL	29 (2.3)	3.8:1	53.6±12.4	AITL	10 (0.8)	2.3:1	60.5±7.5
PCN	19 (1.5)	1.4:1	53.3±13.8	MF	10 (0.8)	1:1	42.7±15.5
BL	14 (1.1)	2.5:1	24.1±6.8	SPTCL	8 (0.6)	1.7:1	43.0±18.6
B-LBL	11 (0.9)	1:1.2	23.8±5.3				
Other and unknown type B-cell NHL	36 (2.9)	1.4:1	54.5±14.4	Other and unknown type T-cell NHL	40 (3.2)	1.4:1	42.3±15.9

Table 3. Location of NHL Lesions

Location	Number of cases	proportion
nodal	799	64.0%
digestive system	127	10.2%
nasal cavity	116	9.3%
Waldeyer's ring	101	8.1%
(including tonsils)	45	3.6%
skin	38	3.0%
central nervous system	16	1.3%
bone and soft tissue	14	1.1%
liver and spleen	12	1.0%
genitourinary system	10	0.8%
breast	7	0.6%
lung	4	0.3%
thyroid	4	0.3%

Table 4. Comparison of Pathological Subtypes with the Regions of Shanghai and Shanxi in Mainland China

	Shandong n=1248 (%)	Shanghai n=728 (%)	Shanxi n=385 (%)
B-cell NHL	807 (64.7)	568 (78.0)	263 (68.3)
DLBCL	510(40.9)	212 (29.1)*	135 (35.1)
FL	80(6.4)	51 (7.0)	33 (8.6)
MALT	68(5.4)	18 (2.5)*	45 (11.7)#
CLL/SLL	40(3.2)	71(9.8)**	14(3.6)
MCL	29(2.3)	14 (1.9)	10 (2.6)
PCN	19(1.5)	21 (2.9)	5 (1.3)
BL	14(1.1)	12 (1.6)	1 (0.3)
B-LBL	11(0.9)	140(19.2)**	4(1.0)
Other and unknown type B-cell NHL	36(2.9)	/	/
T-NHL	378 (30.3)	151 (20.7)	119 (30.6)
PTL	115 (9.2)	40 (5.5)**	46 (12.0)
NK/T	125 (10.0)Δ	4 (0.6)	5 (1.3)
T-LBL	56 (4.5)	/	27(7.0)
ALCL	14 (1.1)	15 (2.1)	16 (4.2)
AITL	10 (0.8)	26 (3.6)	9 (2.3)
MF	10(0.8)	/	1 (0.3)
SPTCL	8 (0.6)	/	2(0.5)
Other and unknown type T-NHL	36 (2.9)	/	/
Unknown type of NHL	63(5.0)	18 (2.5)	4 (1.0)

*P<0.05 compared to Shandong; **P<0.001 compared to Shandong and Shanxi; #P<0.001 compared to Shandong and Shanghai; ΔP <0.001 compared to Shanghai and Shanxi

799 cases were lymph nodes (64.0%). The lesions of 449 cases were extranodal sites (36.0%), including 127 cases

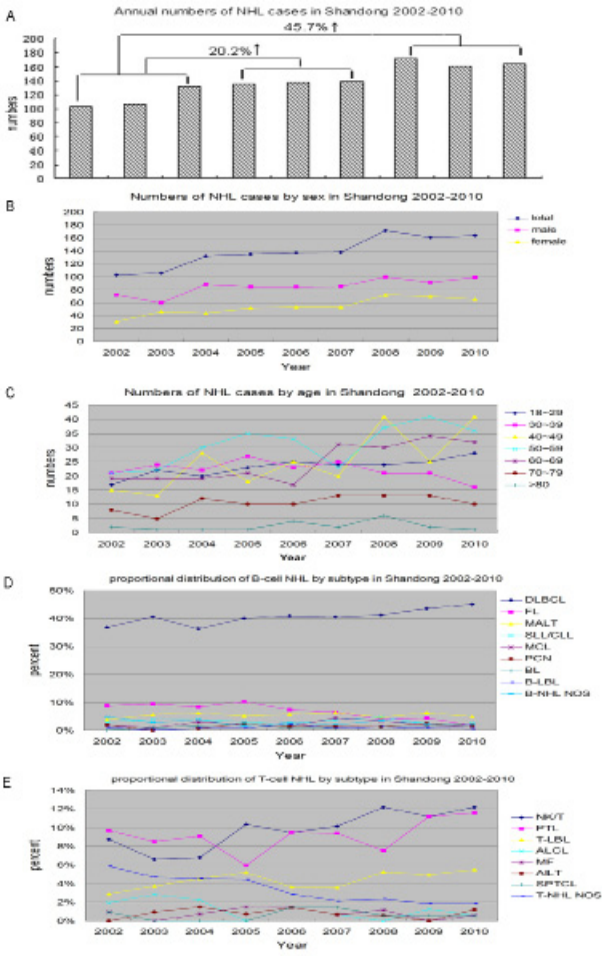

Figure 2. Annual Numbers of NHL Cases in Shandong 2002-2010. A, the changes in annual number of total cases of NHL; B, the changes in the number of cases for groups by gender in each year; C, the changes in the number of cases for groups by age in each year; D, the changes in the percents of cases for groups by pathological type of B-cell NHL in each year; E, the changes in the percents of cases for groups by pathological type of T-NHL in each year

in digestive system (10.2%), 116 cases in the nasal cavity (9.3%), 101 cases in Waldeyer's ring (8.1%), 38 cases in skin (3.0%),16 cases in central nervous system (1.3%), 14 cases in bone and soft tissue (1.1%), 12 cases in liver and spleen (1.0%), and rare in genitourinary system, breast, lung, and thyroid (Table 3).

The changing trend of NHL cases from 2002 to 2010

From 2002 to 2010, the number of NHL patients

Table 5. Comparison of Pathological Subtypes with Other Countries and Regions

subtypes	Caucasian Americans	Netherlands	Chinese-Americans	Thailand	Japan	Korean	Taiwan	Hong Kong	Shandong
N (%)	67715	55069	1451	1983	3025	501	303	197	1248
Period	1992-2001	1989-2007	1996-2004	1993-2002	1994-1996	1990-1996	1995-2007	1988-1990	2002-2010
B-cell NHL									
DLBCL	20628 (30.4)	16079(29.2)	411 (36.5)	922 (46.5)	1065 (35.2)	243 (48.5)	137 (45.2)	71 (36.0)	510 (40.9)
FL	12640 (18.7)	7167 (13.0)	117 (10.4)	153 (7.7)	214 (7.1)	27 (5.4)	24 (7.9)	16 (8.0)	86 (6.4)
CLL/SLL	15157 (22.4)	12478(22.7)	112 (10.0)	47 (2.4)	42 (1.4)	8 (1.6)	18 (5.9)	6 (3.0)	40 (3.2)
MALT	2636 (3.9)	1945 (3.5)	99 (8.8)	76 (3.8)	270 (8.9)	19 (3.8)	12 (3.9)	6 (3.0)	68 (5.4)
MCL	1507 (2.2)	2333 (4.2)	16 (1.4)	19 (1.0)	89 (2.9)	11 (2.2)	13 (4.3)	6 (3.0)	29 (2.3)
B-LBL	/	/	/	16 (0.8)	75 (2.5)	/	4 (1.3)	/	14 (1.1)
T-cell NHL									
PTL	744 (1.0)	1438 (2.6)	20 (1.8)	240 (12.1)	213 (7.0)	57 (11.4)	32 (10.6)	20 (10.0)	115 (9.2)
NK/T	1206 (1.8)	104 (0.2)	34 (3.0)	/	83 (2.7)	59 (11.8)	4 (1.3)	16 (8.0)	125 (10.0)
T-LBL	/	/	/	75 (3.8)	55 (1.8)	25 (5.0)	9 (3.0)	/	56 (4.5)
ALCL	702 (1.0)	604 (1.1)	9 (0.8)	67 (3.3)	77 (2.5)	7 (1.4)	6 (2.0)	6 (3.0)	14 (1.1)
MF	1306 (1.9)	790 (1.4)	31 (2.9)	23 (1.6)	37 (1.2)	/	1 (0.3)	/	10 (0.8)

receiving treatment was increasing year by year. Compared with the years between 2002 and 2004, the number of cases increased by about 20.2% between 2005 and 2007, and the number of cases grew by about 45.7% between 2008 and 2010 (Figure 2A). In each year, the numbers of cases for both male and female were gently rising, with the ratio remaining stable (male to female ratio of about 1.5:1) (Figure 2B). The proportions of annual incidence for all ages were also relatively stable, with higher proportions at the two age groups of 40~49 and 50~59, and the proportion of incidence in the age group of >80 was the lowest (Figure 2C). The analysis of pathological type for each year showed that, the numbers of cases of DLBCL, PTL and NK/T receiving treatment were gradually increasing, and the numbers of cases of other pathological types were relative stable (Figure 2D, E).

Comparison with other regions in China

The comparison results with the regions of Shanghai and Shanxi in China showed that, the distributions of the pathological subtypes of NHL in different regions had some similarities, as well as some differences (see Table 4). For B-cell NHL, the proportions of CLL/SLL (9.8%) and B-LBL (19.2%) in the Shanghai region were significantly higher than those in the other two regions; the proportion of DLBCL was lower than those in Shandong and Shanxi, but with significant differences only for Shandong. The proportion of MALT lymphoma was the highest in Shanxi (11.7%), followed by Shandong (5.4%), and Shanghai was the lowest (2.5%), with significant differences in between. In T-cell NHL, PTL was 9.2% in Shandong, and 12.0% in Shanxi, which were both significantly higher than that in Shanghai (5.5%); while the NK/T cell lymphoma in Shandong (10.0%) was significantly higher than those in Shanghai (0.6%) and Shanxi (1.3 %). The regional distributions of other subtypes were similar.

Comparison with other countries and regions

The analysis for other countries and regions in the world (Anderson et al., 1998; Lee et al., 1999; No authors listed, 2000; Sukpanichnant et al., 2004; Lindsay et al., 2006; Chen et al., 2010; van et al., 2011) (USA, Netherlands, Thailand, Japan, South Korea, Taiwan, Hong Kong) and Chinese-Americans (Carreon et al., 2008) showed that, DLBCL was the pathological subtype with the highest incidence rate in the world (see Table 5). The FL and CLL/SLL in the regions in our study were similar to those in the Asian regions, which were significantly lower than those in the United States, the Netherlands and Chinese-Americans. The PTL and NK/T in the regions of this study were also similar to those in other Asian regions, which were significantly higher than those in the United States, the Netherlands and Chinese-Americans. However, the distributions of NK/T in the Asian regions were different, with higher rates in the regions in this study and South Korea and Hong Kong, and lower rates in Japan and Taiwan.

Discussion

In this study, a detailed retrospective analysis was performed for the clinical and pathological data from the medical records of patients with lymphoma in Shandong Cancer Hospital, China, from 2002 to 2010. The 1248 patients with NHL included 807 cases of B-cell lymphoma (64.7%), 378 cases of T-cell lymphoma (30.3%). The analysis of pathological subtypes showed that, the 6 subtypes with the highest proportions were DLBCL (40.9%), NK/T (10.0%), PTL (9.2%), FL (6.4%), MALT (5.4%), and T-LBL (4.5%). No adult T-cell leukemia/lymphoma (ATLL) was found in any patients in this study. Regarding the gender ratio, the male to female ratio of B-cell NHL patients of 1.4:1 was lower than that of T-cell NHL patients of 2.0:1. The average ages were 47.7±16.3 (18-85 years old) for all NHL patients, 50.7±15.2 for B-cell NHL patients, 42.0±17.0 for T-cell NHL patients. The peak onset age showed as a single peak at age group of 50 to 59, which is similar to the previous report in China. The onset age is slightly lower than that reported in the United States (58.8 ± 20.9) (Han et al., 2008). Regarding the location of the lesions, about 64% of the incidences were inside the lymph node, and 36% were extranodal. According to the 6th edition of AJCC,

the lesion in Waldeyer's ring was proposed to be a lesion inside the lymph nodes. But in order to compare with other literature, it was considered as extranodal in this study. The most common sites of extranodal NHL were the digestive system, nasal cavity, and Waldeyer's ring, which is similar to the domestic reports. The international literatures showed that the most common extranodal lesions were the digestive system, Waldeyer's ring (mainly tonsils), and skin (Groves et al., 2000).

The result of this study also showed that, from 2002 to 2010, the number of NHL cases increased year by year. Comparing with the years between 2002 and 2004, the number of cases between 2005 and 2007 increased by 20%, and the number of cases between 2008 and 2010 increased by about 45%. The reasons for this phenomenon may be: (1), increase of NHL incidence. Due to the current serious environmental pollution in China and the changes in diet and lifestyle, the immune dysfunction, bacterial infections, and other factors are all likely to lead to an increased prevalence of NHL. (2), improvement in diagnostic methods. Currently, the technologies of biopsy morphology, immunohistochemistry, and flow cytometry are applied in the pathological diagnosis, which have greatly enhanced the diagnosis and its confirmation for NHL. (3), increase in the number of patients visiting for NHL. Due to the improvement of the medical insurance system in China, even people at a low economic level intend to seek medical attention, resulting in an increase in the number of cases.

In addition, our results showed that, in recent years, the numbers of cases with DLBCL, PTL, and NK/T cell NHL were rising, while the number of case with FL was decreasing. Similarly, the report in the Shanghai area also showed a decreasing trend for FL (Gross et al., 2008). This study also showed that, in Shandong Cancer Hospital, the ratio of the number of patients with NHL in rural areas to that in urban areas was up to about 1.5:1 (data not shown). This result is inconsistent with the previous reports in China, which had shown that the incidence number of NHL in the city of Shanghai was higher than that in rural areas. This is a very interesting phenomenon. Considering the high proportion of T-cell lymphoma, especially high proportions of NK/T and peripheral T-cell lymphoma in this region, the region-specific environmental factors such as the large agricultural population, high exposure to farm chemical and pesticides, and environmental pollution may play an important role in its pathogenesis, which is worth further study for this area.

When searching the published articles in English journal for NHL in China, we found that in recent years, only Shanghai and Shanxi in China had relatively complete clinical data. By the comparative analysis, we found that the incidence rates of CLL/SLL (9.8%) and B-LBL (19.2%) in Shanghai were significantly higher than those in Shandong and Shanxi, while the incidence rates of PTL and NK/T were significantly lower than those in the other two regions. MALT was the highest in the Shanxi region (11.7%), while NK/T in the Shandong region (10.0%) was significantly higher than those in Shanghai (0.6%) and Shanxi (1.3%). Thus, the distributions of NHL subtypes in different parts of China have some similarities, as well as some differences. This may be mainly related to the uneven regional economic development, different diet and lifestyle in different regions of mainland China.

We also compared the worldwide distribution of NHL subtypes. Overall, the B-cell lymphoma accounted for a high proportion worldwide, the T-cell lymphoma in Asia was however higher than that in European and American countries. DLBCL is the pathological subtype with the highest rate of incidence all around the world, accounting for 25%-50% of NHL. The incidence proportions of FL and CLL/SLL in the United States, the Netherlands and Chinese-Americans were significantly higher than those in Asia. T-cell lymphomas (especially PTL, NK/T, and T-LBL) in European and American countries was significantly lower than that in Asia. However, in different areas of Asia, the distribution of NHL pathological subtypes also showed some significant regional differences. For examples, the reports for FL and CLL/SLL were inconsistent in various regions; the incidence rates of NK/T lymphoma in Japan and Taiwan were significantly lower than those in South Korea and Shandong region, and were not reported in the literature of Thailand. In addition, we found that the proportions of FL and CLL/SLL for Chinese-Americans were less than those for Caucasian Americans, showing a difference in the incidence of different racial groups. However, the proportions of FL and CLL/SLL for Chinese-Americans were higher than those for the Chinese in Asia, indicating the environmental factor is an important factor of influence. In addition, the proportions of PTL and NK/T for Chinese-Americans were similar to those for Caucasians in the United States and Netherlands, which were significantly lower than those in Asian countries, indicating the occurrence of T-cell lymphoma is closely related with the environmental factors. Similar findings were found in two other reports(Herrinton et al., 1996; Clarke et al., 2011). Therefore, based on the above observations, it can be inferred that, the genetic susceptibility of different ethnic groups, and the environmental factors caused by the social and geographical environment in different areas may be related to the occurrence of specific subtypes of NHL.

In this study, the clinical and pathological data of NHL patients in Shandong Cancer Hospital in China were analyzed. The advantages are: as a large cancer hospital in Shandong province, the organization treated cancer patients across the province. The clinical and pathological data of our NHL patients could reflect the characteristics of the incidence of NHL in the region, and all patients belong to the Han ethnic group. The disadvantage is that, only one research institute was involved in the analysis of this study, and not all the cases in the region were included in a detailed and systematic analysis. So the results might show only the changes in the attendance rate of patients, but not reflect the accurate incidence of NHL in this region.

This study suggests that the clinical and pathological distribution of NHL in Shandong province, China, is consistent with that for Asian populations, but significantly different from that in the Western countries, with higher proportion of NK/T lymphoma in this region. We hope this study can provide a reference for the etiology and epidemiological studies of NHL in China.

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