Genetic characteristics of non-Hodgkin lymphoma in ethnic Uighur people, and their clinical significance

L. Xu[1], X.G. Zou[1], X. Wang[1], A.B.L.M.T. Hairesa[1] and J.J. Liu[2]

[1]Department of Hematology,
First People's Hospital in Kashgar (Kashi) Prefecture, Xinjiang, China
[2]Department of Hematology,
The Third Affiliated Hospital of Sun Yat-sen University, Guangdong, China

Corresponding author: J.J. Liu
E-mail: lixuvbn@sina.com

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ABSTRACT. The incidence of non-Hodgkin lymphoma (NHL) in China is increasing and is attracting attention as a topic of research. The percentage of NHL cases in ethnic Uighur people is also gradually increasing. We therefore recruited Uighur people with NHL to investigate the correlation between genetic alternations and clinical/pathological features in an attempt to determine their clinical significance. A total of 60 NHL patients were recruited from our hospital for a microscopic examination of their tumor cell morphology. Further analysis of chromosome karyotypes revealed the relationship between genetic alternations and clinical/pathological features. Microscopic examination revealed increased numbers of tumor cells with altered morphology. The recruited patients all exhibited abnormal karyotypes. Chromosomal breakages were detected at 14q32, 18q21, 6q21-25, +3,

+, +18, and short tandem repeat 17 (str17) in 18.3, 25, 25, 18.3, 15, and 21.7% of patients, respectively. Karyotype change was not related to age, gender, performance status score, or pathological type ($P > 0.05$), but was correlated with clinical stage, average lactate dehydrogenase (LDH) level, extra-lymphatic metastasis, median survival time, and efficacy of radio- or chemotherapy ($P < 0.05$). Independent risk factors for genetic change in Uighur NHL patients included clinical stage, average LDH level, extra-lymphatic metastasis, median survival time, and efficacy of radio- or chemotherapy ($P < 0.05$). Uighur NHL patients exhibited genetic changes including t(14:18), 6q21-25, +3, +7, +18, and str17. Clinical stage, average LDH level, extra-lymphatic metastasis, median survival time, and efficacy of radio- or chemotherapy were all independent risk factors for NHL.

Key words: Uighur ethnic group; Non-Hodgkin lymphoma; Chromosome mutation

INTRODUCTION

Malignant lymphoma is a common tumor in humans. Its incidence is increasing significantly worldwide, and it accounts for 3-4% of all malignant tumors. The incidence of and mortality from lymphoma are higher in the Uighur ethnic group of Xinjiang than in people from eastern coastal regions. With a male to female ratio of 2.3:1, lymphoma has two peaks of incidence at younger than 10 years and 31-50 years in the population (Pervez et al., 2009). Malignant lymphoma has highly homogenous features but has various subtypes and classifications. To improve diagnosis and treatment efficacy, the clinical and pathological classification criteria for lymphoma are continuously updated with precise guidelines (Stewart et al., 2009). Non-Hodgkin lymphoma comprises a group of heterogeneous diseases with different etiologies and biological features (Rossi et al., 2009). Based on the hematological tumor and lymphoma classification system stipulated by the World Health Organization (WHO), a confirmed diagnosis of malignant lymphoma requires descriptions of the morphology, immune phenotype, genetics, and clinical features (Smedby et al., 2006). Owing to its migration and heterogeneous characteristics, the major clinical manifestations and biological features of NHL are difficult to describe precisely under the current pathological classification system. Therefore, its clinical diagnosis and treatment are compromised (Wang et al., 2013). Recently, the examination of chromosome karyotypes has attracted a great deal of attention from researchers. The investigation of chromosome change in malignant tumors for purposes of prognosis has achieved certain outputs. Previous studies on malignant hematological tumors have established the chromosome assay as an important and independent technique for guiding a patient's prognosis (Yoon et al., 2008). Another study on NHL showed that certain featured chromosome translocations may be valuable for patient prognosis prediction and for improving diagnosis accuracy and treatment compared with histology classification, which may have significant implications for clinical work (Basso et al., 2010). Therefore, in this study, we recruited Uighur NHL patients from our hospital to investigate the correlation between genetic change and clinical efficacy, prognosis, and the subtypes of Uighur NHL patients to provide evidence for treatment plan selection and overall evaluation.

MATERIAL AND METHODS

General information

We recruited 60 Uighur NHL patients from the First People's Hospital in Kashi Prefecture between January 2015 and January 2016. The patients were evaluated according to history of primary diagnosis, body examination, imaging, and bone marrow biopsy. All recruited patients were primary patients who received pathological examination of the lymph nodes or extra-node tumors, plus bone marrow smear slide and chromosome examination. The diagnosis and staging of NHL followed the hematology guidelines for diagnosis and treatment efficacy. The Ann Arbor system was used for the staging of intra-node NHL patients, and the Lugano system was used for patients with NHL derived from gastrointestinal or other extra-node sites. The NHL patients comprised 22, 18, and 20 cases of B cell, T cell, and NK/T cell origin, respectively. There were 30 males and 30 females in the patient group, with an average age of 50.2 ± 3.5 years (20-80 years). Clinical staging assessment revealed 5, 25, 19, and 11 cases with stage I, stage II, stage III, and stage IV NHL, respectively. The treatment plan and focal radiotherapy were employed using the CHOP plan [CHOP is named after the initials of the drugs used, namely: cyclophosphamide, doxorubicin (hydroxydaunomycin), vincristine (Oncovin®), and prednisolone (a steroid)]. The evaluation of treatment efficacy and survival period followed the WHO guidelines. There were 19, 15, 16, and 10 cases of complete remission, partial remission, stable disease, and progressed disease, respectively.

This study was pre-approved by the Ethical Committee of the First People's Hospital in Kashi Prefecture. All subjects signed consent forms before recruitment to the study.

Reagents and instruments

We used a CytoVision™ chromosome imaging system produced by Applied Imaging (Rochester, NY, USA). Reagents for hematoxylin and eosin stain, and Giemsa stain were bought from Beisuo Biotech (Zhuhai, Guangdong, China).

Chromosome analysis

Samples were collected from all NHL patients to prepare chromosome and R bands. Cell suspensions were prepared and placed in a 37°C incubator for 24 h, vortexing twice in the morning and evening. NSC-3096 was added to arrest the cells at the metaphase of mitosis. The incubation was stopped after 1 h, with a final concentration at 0.05 mg/mL. The mixture was then centrifuged at 1000 *g* for 10 min. The supernatant was removed, 6 mL KCl buffer (0.075 M) was added, and the cells were incubated at 37°C for 30 min. Iced methanol-acetic acid solution (3:1) was added to fix the cells, which were then centrifuged at 132 *g* for 10 min in triplicate. A disposable dropper was used to apply the cell suspension to glass slides (2 drops each), followed by drying, addition of Earle's solution, and heating in a warm bath (87.5°C) for 60 min. Freshly prepared 10% Giemsa stain was used for 10 min.

The judgement criteria were as follows. A total of 20 mitotic phases were analyzed in individuals with normal karyotypes, whereas 10 phases were analyzed in patients with abnormal karyotypes. Those individuals with two or more identical karyotype abnormalities were identified as abnormal clones.

Data processing

The SPSS 17.0 software was used for data analysis. The enumeration data were investigated using the chi-square test, whereas the measurement data were investigated using analysis of variance (ANOVA); both sets of data are reported as means ± standard deviation. A logistic regression model was used for multivariate analysis. Statistical significance was defined as $P < 0.05$.

RESULTS

Morphology of Uighur NHL patients viewed under a microscope

The tumor cells showed diffused and infiltrative growth, with a partial increase of volume and oval or round nuclei. Two or three nucleoli were observed adjacent to the nuclear membrane, which exhibited thickening (Figure 1).

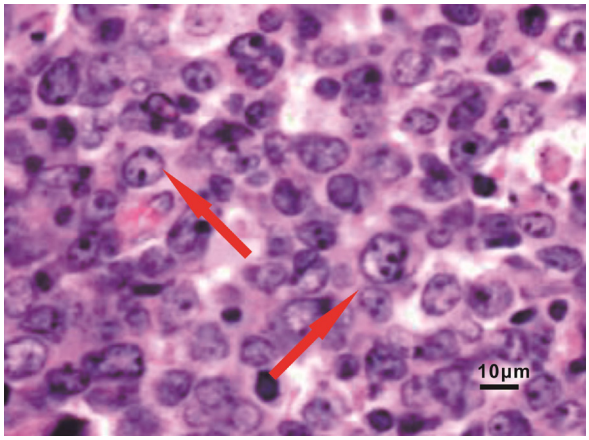

Figure 1. Cell morphology of Uighur NHL patients (200X).

Genetic alternation in Uighur NHL patients

The chromosome karyotype was examined in all the recruited Uighur NHL patients. The results showed abnormal karyotypes in the patients. There were 11 cases (18.3%) of chromosome breakage at 14q32 or 18q21, 15 cases (25%) at 6q21-25, 15 cases (25%) at +3, 11 cases (18.3%) at +7, 9 cases (15%) at +18, and 13 cases (21.7%) at short tandem repeat 17 (str17).

Correlation between genetic change and clinical/pathological features of Uighur NHL patients

Correlation analysis was carried out between genetic change in NHL patients and clinical/pathological features including age, gender, performance status (PS) score, pathological type, clinical stage, average lactate dehydrogenase (LDH) level, extra-node metastasis, median survival period, efficacy of radio- and chemotherapy, and efficacy evaluation. The

results showed no correlation between genetic changes such as t(14:18), 6q21-25, +3, +7, +18, and str17 and age, gender, PS score, or pathological type ($P > 0.05$). However, these genetic changes were correlated with clinical stage, average LDH level, extra-node metastasis, median survival period, radio- or chemotherapy efficacy, and efficacy evaluation ($P < 0.05$, Table 1).

Table 1. Relationship between genetic change of Uighur NHL patients and clinical/pathological features.

Item	N	t(14;18)	6q21-25	+3	+7	+18	str17
Age							
<45	29	5(17.2)	7(24.1)	7(24.1)	5(17.2)	4(13.8)	6(20.7)
≥45	31	6(19.3)	8(25.8)	8(25.8)	6(19.3)	5(16.1)	7(22.1)
P value		>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
Gender							
Male	30	6(20)	8(26.7)	7(23.3)	5(16.7)	5(16.7)	7(23.3)
Female	30	5(16.7)	7(23.3)	8(26.7)	6(20)	4(13.3)	6(20)
P value		>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
PS							
≤1	28	5(17.8)	7(25)	8(25)	5(17.8)	4(14.3)	6(21.4)
>2	32	6(18.7)	8(25)	7(25)	6(18.7)	5(15.6)	7(21.8)
P value		>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
Pathology							
T cell	22	4(18.2)	6(27.3)	5(22.7)	4(18.2)	3(13.6)	5(22.7)
B cell	18	3(16.7)	4(22.2)	5(27.8)	3(16.7)	3(16.7)	4(22.2)
NK/T	20	4(20)	5(25)	5(25)	4(20)	3(15)	4(20)
P value		>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
Clinical stage							
I	6	1(16.7)	1(16.7)	1(16.7)	1(16.7)	0(16.7)	0(16.7)
II	24	4(16.7)	4(16.7)	3(12.5)	3(12.5)	3(12.5)	3(12.5)
III	19	3(15.8)	5(26.3)	6(31.5)	3(15.8)	3(15.8)	5(26.3)
IV	11	3(27.2)	5(45.5)	5(45.5)	4(36.4)	3(27.2)	5(45.5)
P value		<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Average LDH							
≤225 U	25	3(12)	4(16)	5(20)	4(16)	2(8)	3(12)
>225 U	35	8(22.9)	11(31.4)	10(28.6)	7(20)	7(20)	10(28.6)
P value		<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Metastasis							
Single	28	3(10.7)	4(14.3)	5(17.9)	4(14.3)	2(7.1)	3(10.7)
Multiple	32	8(25)	11(34.3)	10 (31.3)	7(21.9)	7(21.9)	10 (31.3)
P value		<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Median survival time (months)							
>12	27	4(14.8)	4(14.8)	4(14.8)	3(11.1)	3(11.1)	4(14.8)
≤12	33	7(21.2)	11(33.3)	11(33.3)	8(90.9)	6(18.2)	9(27.3)
P value		<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Radiotherapy							
No	26	3(11.5)	4(15.4)	3(11.5)	4(15.4)	2(7.7)	3(11.5)
Yes	34	8(23.5)	11(32.4)	12(35.3)	7(20.6)	7(20.6)	10(29.4)
P value		<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Chemotherapy							
No	31	4(93.5)	5(16.1)	4(12.9)	3(9.7)	2(6.5)	4(12.9)
Yes	29	7(24.1)	10(34.5)	11(37.9)	8(27.6)	7(24.1)	9(31)
P value		<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Efficacy							
CR	19	0(0)	1(16.7)	1(16.7)	1(16.7)	0(16.7)	0(16.7)
PR	15	3(20)	3(20)	3(20)	2(13.3)	2(13.3)	3(20)
SD	16	4(25)	5(31.3)	6(37.5)	4(25)	4(25)	5(31.3)
PD	10	4(40)	6(60)	5(50)	4(40)	3(30)	6(60)
P value		<0.05	<0.05	<0.05	<0.05	<0.05	<0.05

Multivariate analysis of correlation between genetic change in Uighur NHL patients and clinical/pathological features

We carried out multivariate analysis on the correlation between genetic change in the

Uighur NHL patients and clinical/pathological features. The results revealed that clinical stage, average LDH level, extra-node metastasis, median survival period, radio- and chemotherapy efficacy, and efficacy evaluation were independent risk factors for genetic alternation in the Uighur NHL patients ($P < 0.05$, Table 2).

Table 2. Multi-variant analysis between genetic change of Uighur NHL patients and clinical/pathological features.

	Clinical stage	Average LDH	Extra-node metastasis	Median survival time (months)	Radiotherapy	Chemotherapy	Efficacy evaluation
t(14;18)							
Regression coefficient	0.724	0.613	0.801	0.697	0.733	0.821	0.992
P	0.003	0.002	0.004	0.003	0.003	0.002	0.001
Relative risk	2.125	2.003	2.228	2.015	2.142	2.068	2.272
6q21-25							
Regression coefficient	1.132	1.124	1.275	1.233	1.214	1.083	1.171
P	0.002	0.001	0.001	0.002	0.001	0.002	0.002
Relative risk	2.027	2.015	2.852	2.325	2.453	2.501	2.244
+3							
Regression coefficient	1.007	1.014	1.018	1.124	1.024	0.869	1.426
P	0.001	0.002	0.001	0.002	0.001	0.002	0.004
Relative risk	2.004	2.027	2.812	2.623	2.087	2.683	2.022
+7							
Regression coefficient	1.113	1.213	1.004	1.015	1.044	1.075	1.403
P	0.002	0.004	0.001	0.001	0.002	0.001	0.003
Relative risk	2.892	2.367	2.730	2.457	2.716	2.452	2.028
+18							
Regression coefficient	0.748	0.892	0.952	0.878	1.116	0.813	0.91
P	0.002	0.003	0.003	0.002	0.002	0.002	0.003
Relative risk	2.156	2.368	2.376	2.054	2.211	2.103	2.208
Str17							
Regression coefficient	1.005	1.017	1.008	1.104	1.153	1.162	1.203
P	0.001	0.002	0.002	0.001	0.002	0.003	0.001
Relative risk	2.247	2.127	2.502	2.273	2.034	2.214	2.104

DISCUSSION

The WHO has stipulated a classification system for malignant hematological and lymphatic tumors, for which differential diagnoses should be made from morphology, immune phenotype, genetics, and clinical features (Ferlay et al., 2010; Roman and Smith, 2011; Siegel et al., 2014). Currently, the epidemiology and geographical distribution of NHL varies across countries. In Uighur regions of China, the incidence of NHL of different subtypes is relatively high and is similar to that found in Japan or Korea, but differs greatly from Western countries (Luminari et al., 2007; Kim et al., 2011). Therefore, the stipulation of individualized treatment strategies based on prognostic parameters is critical for improving treatment efficacy and patient survival.

For this study, we recruited NHL patients from the Uighur people of China. Microscopic observation revealed diffused infiltrative growth with partially dilated volume and oval/round shape. Two or three nucleoli were visible adjacent to the nuclear membrane, which was thickened. Chromosome karyotype investigation revealed abnormal karyotypes, with 18.3% of chromosome breakage at 14q32 or 18q21, 25% at 6q21-25, 25% at +3, 18.3% at +7, 15% at +18, and 21.7% at str17.

This study revealed genetic changes in Uighur NHL patients including t(14:18), 6q21-25, +3, +7, +18, and str17. Such genetic alternations were correlated with clinical stage, average LDH level, extra-node metastasis, median survival period, radio- and chemotherapy efficacy, and efficacy evaluation, but not with age, gender, PS score, or pathology type. For those patients

at an advanced clinical stage, it is easier to demonstrate correlation between genetic change and elevated LDH level, occurrence of extra-node metastasis, shortened median survival period, efficacy of radio- or chemotherapy, or unfavorable treatment efficacy. Histological examination is important for predicting survival period and evaluating treatment efficacy, and is correlated with patient prognosis. However, the change of chromosome karyotype is an important independent risk factor for NHL prognosis in addition to its histological implications (Chen et al., 2013). One study has shown multiple critical chromosome karyotype changes in NHL patients, and their significant effect on patient treatment efficacy and median survival period (Zhang et al., 2013). Certain complex changes in chromosome karyotype or rearrangement, and some special chromosome genesis abnormalities such as t(8:14)(q24:q32) translocation and +7, are unfavorable prognostic factors for NHL (Kahl and Yang, 2008; Zhang et al., 2010. Certain basic studies have shown no dysfunction of known genes located in the 6q21-25 region in NHL patients. In lymphocyte leukemia, however, certain gene dysfunctions occur in known genes in the 6q21-25 region (Klein et al., 2003; Streubel et al., 2003). Previous studies have shown that (t14:18), chromosome 7 abnormalities, and polyploidy chromosomes have the most significant effects on NHL patient survival periods (Kyle and Rajkumar, 2006). It has been reported that NHL patients with chromosome 7 abnormalities have unfavorable prognoses, chemo-resistance, and relatively higher mortality (Isaacson and Du, 2004). Moreover, NHL patients with abnormal chromosome 7 and 17 also have high serum LDH levels (João et al., 2007). The authors of previous studies have also reported close correlation between chromosome abnormalities including str17, +3, and +18 and median survival period in NHL patients (Han et al., 2011). Analysis of the clinical data has revealed correlation between +3 and highly malignant NHL, mainly including diffused mixed type NHL. Those patients with str17 abnormalities cannot reach CR even after receiving systemic anti-tumor treatment, and have a shortened survival period. Researchers believe that the abnormal number of sex chromosomes in some NHL patients might be due to cell aging, because there is a more frequent occurrence of sex chromosome abnormalities in elderly patients. Unfortunately, in the present study, the number of sex chromosomes in the NHL patients was not evaluated, making it impossible to assess the relationship between age and sex chromosome abnormalities, which is the main limitation of the current study. The increased number of +3, +5, and +18 chromosome abnormalities and other clonal abnormalities (Swerdlow et al., 2008), are consistent with the results of this study.

Further logistic analysis revealed clinical stage, average LDH level, extra-node metastasis, median survival period, radio- and chemotherapy efficacy, and efficacy evaluation as independent risk factors for genetic alterations in Uighur NHL patients.

In conclusion, the occurrence of genetic changes including t(14:18), 6q21-25, +3, +7, +18, and str17 is correlated with clinical stage, average LDH level, extra-lymphatic metastasis, median survival time, and efficacy of radio- or chemotherapy. Those patients with advanced clinical stage, elevated LDH level, extra-node metastasis, shortened median survival period, and those who had received chemo- or radiotherapy, or experienced unfavorable treatment efficacy, were more susceptible to genetic change. Therefore, the analysis of patient genetics provides a novel approach to individualized treatment or optimization of treatment plans, and may provide novel treatment targets.

Conflicts of interest

The authors declare no conflict of interest.

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