Analysis of Clinicopathologic Characteristics and Prognostic Factors of Nasal Type NK /T Cell Lymphoma

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Abstract **Objective** Nasal type NK/T cell lymphoma is a disease with low incidence and its behaviors are different from other lymphoma, and its early diagnosis is difficult. The objective of this study was to investigate the clinical and pathological features and prognostic factors of this disease. **Methods** The clinical data of 31 patients with this disease admitted from January 1993 to October 2003 in the Second Hospital and the First Hospital of Xian Jiaotong University were analyzed retrospectively. The diagnosis of the 31 patients was confirmed histopathologically. **Results** The misdiagnosis of nasal type NK/T cell lymphoma is often encountered both in clinic and pathology. Of all 31 cases, the overall 3- year survival rate and the overall 5-year survival rate were 58.1% (18/31) and 33.3% (5/15), respectively. The survival rates decreased with the progression of the clinical stages; B symptoms and international prognostic factors index (IPI) were statistically negative in relation with prognosis. Compared with chemotherapy alone, there was a higher 3-year survival rate in combined modality therapy (CMT) group. **Conclusion** Effective measures to avoid misdiagnosis lie in the mastering of the clinical features, morphology, immunology and genetics of this disease. Ann Arbor staging, IPI and B symptoms are important prognostic factors and CMT may be an optimal selection for treatment of nasal type NK/T cell lymphoma.

Key words non-Hodgkins lymphoma; chemotherapy; radiation therapy; combined modality therapy; prognosis

Nasal type NK/T cell lymphoma belongs to outer node type lymphoma, more frequently occurs in east and south Asia, middle and south America [1], race of Spanish language [2]. The incidence of NK/T lymphoma is also high in China, accounting for nearly 10% of the total lymphoma [3]. This disease is usually characterized by angioinvasive growth, necrosis and expressions of natural killer cell and cytotoxic T lymphocytes. Evidences indicated that this disease was associated with Epstein-Barr virus infection. Lots of studies had shown that the nasal type NK/T cell lymphoma resisted the chemotherapy and radiotherapy. Compared with other types of lymphoma, this disease was prone to reoccurrence locally and metastasis and has poor outcome. Here we have studied 31 patients with this disease confirmed pathologically and the results may benefit for diagnosis and treatment of this disease.

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MATERIALS AND METHODS

Patient population A total of 31 patients were treated from Jan 1993 to Oct 2003 in the second and the first Hospital of Xian Jiaotong University. The age of patients ranged from 6 to 73 years old with a median age of 42.6 years. There were 22 cases (71.0%) originating in nasal cavity, 4 cases (12.9%) in nasopharynx, 3 cases (9.7%) in nasal sinus, 2 cases (3.2%) in pharyngeal tonsil. Primary lesion invasion of adjacent tissue and other organs: nasal septum 8 cases (25.8%), paranasalsinuses 6 (19.4%), facial nerve 5 (16.1%), contralateral nasal cavity 3 (9.7%), uvula 3 (9.7%), bone marrow involvement (29.0%); encephalic invasion 5 (16.1%), liver metastasis 1 (3.2%), lung metastasis 1 (3.2%). Details were shown in table 1.

Histopathological diagnosis Of the 31 cases, 10 have undergone more than 2 times of biopsies and some were firstly diagnosed as inflammation, reactive hyperplasia, necrosis, differentiaional atypia, etc, respectively and the remaining were suspicious of malignancies but primary lesions were not found. All patients were ex-

Table 1 Clinical characteristics of 31 patients with nasal type NK/T cell lymphoma

Clinical data		No. of patients (%)
Gender	male	21 (67.7)
	female	10 (32.3)
Age	≤60 years	22 (71.0)
	>60 years	9 (29.0)
EB virus (+)(using PCR technique)		23(74.2)
Performance status	ECOG 0~1	21(67.7)
	ECOG 2~4	10 (32.3)
B symptom		10 (32.3)
Ann Arbor stage	I+II	14 (45.2)
	III+IV	17 (54.8)
IPI score	0~1	14 (45.2)
	2	17 (54.8)
Pathology	Angiocentric type	31(100.0%)
	T-cell associated antigen	31(100.0%)
	CD56 (+)(n=23)	11(49%)

amined by immunohistochemistry and the phenotypes of immunology and genetics were similar to type of NK/T cell lymphoma.

Treatment Patients of stage I were treated with radiation alone or combined modality (radiotherapy plus chemotherapy). Stage III or IV patients were treated with chemotherapy alone or combined modality (seen in Table 2). Radiotherapy was delivered using a 6mV~8mV X-ray. According to invasive areas, the radiotherapy fields of primary lesions of tumors included single anterior nasal and anterior ear fields. The median dose was 50 Gy (30~60Gy) in single anterior nasal and anterior ear fields and 45Gy (35~50Gy) in the neck. The chemotherapy regimen adopted CHOP consisting of Adriamycin, Epirubicin, Methotrexate, Mitoxantrone, Pirarubicin etc. The patients of stage I received chemotherapy for 2 cycles, stage II 4 cycles; III/IV 6 cycles.

Follow-up and statistical analysis Survival time was calculated from the day of the disease confirmed histopathologically to the day of death. All of the patients underwent a period of 3 years observation, 15 of whom observed for 5 years. The SPSS software package (Version 11.5, SPSS Inc Chicago IL) was used for the data calculating, $P<0.05$ were considered to be statistically significant.

RESULTS

The overall 3-year and 5-year survival rates were 58.1% and 73.3% respectively. Table 3 showed the relationship between the survival rate and age, gender, EB virus conditions, ECOG scores, B symptoms, Ann Arbor stages, IPI score, regimens respectively.

Relationship between B symptoms and survival rate The 3-year survival rate in patients with B symptoms and without B symptoms was 66.7% and 41.3% respectively and there was a significant difference between them ($P<0.001$). The 5-year survival rates between them were not significantly difference.

Stages and survival rate The 3-year survival rate of stage I/II and stage III/IV were 85.7% and 45.5% respectively and there was not a statistical difference between the two groups. Moreover, the 5-year survival rates between the two groups were 42.9% and 0 respectively and there was not a statistical difference.

IPI and survival rate Recording 1 score respectively according to the 5 influenced prognostic factors which were age of over 60, the amount of lactate dehydrogenase higher than normal value, scores 2-4 of ECOG, stage of Ann Arbor Ⅲ-Ⅳ and more than 1 organs involved. The total scores were acquired by accumulating the number of influenced prognostic factors. The cases in this group were 14 with 0-1 score and 17 with ≥2 scores respectively. The overall 3-year survival rate in the two groups were 78.6% and 45.5% respectively, and there was a significant difference ($P<0.05$); the overall 5-year survival rate were 41.2% and 0 respectively and there was no significant difference ($P>0.05$).

Treatment regimen and survival rate The number

Table 2 Treatment methods of nasal type NK/T cell lymphoma (n=31)

Treatment methods	Stage I + II	Stage III +IV	Total
Radiation alone	6	1	7
Chemotherapy alone	0	13	13
Combined modality therapy	8	3	11

of patients undergone different treatment regimens was 7 with chemotherapy alone, 13 with radiation alone and 11 with combined modalities respectively. The overall 3−year and 5−year survival rate in the three groups was 28.6% and 0, 53.8% and 20.0%, 81.8% and 50.0% respectively. The statistical comparison of the overall 3−year survival rate between the group with chemotherapy alone and the group with combined modality indicated that there was a significant difference ($P<0.05$), but there was no significant difference between the chemotherapy group and the radiation group, the radiation group and the combined modality group ($P>0.05$). The comparisons of the 5−year survival rate between any two groups were not significantly different neither ($P>0.05$).

Other factors and survival rate The statistical analysis on the 3−year survival rate and 5−year survival rate according to age, gender, EB virus positive rate and ECOG scores indicated that there were no significant

Table 3 Relationship between clinical features and survival rates in 31 cases with nasal type NK/T cell lymphoma

Clinical features		3−year survival (%)	5−year survival (%)
Gender	male	57.1(12/21)	40.0(4/10)
	female	60.0(6/10)	20.0(1/5)
	P value	>0.05	>0.05
Age	≤60	68.2(15/22)	45.5(5/11)
	>60	33.3(3/9)	0(0/4)
	P value	>0.05	>0.05
EB virus examination	negative	50.0(4/8)	0(0/3)
	positive	60.9(14/23)	41.7(5/12)
	P value	>0.05	>0.05
ECOG score	0~1	66.7 (14/21)	40.0(4/10)
	≥2	40.0(4/10)	20.0(1/5)
	P value	>0.05	>0.05
B symptom	no	81.0(17/21)	41.7(5/12)
	yes	10.0(1/10)	0(0/3)
	P value	<0.001	>0.05
Ann Arbor stage	I+II	85.7(12/14)	45.5(5/11)
	III+IV	42.9(6/17)	0(0/4)
	P value	<0.005	>0.05
IPI score	0~1	78.6(11/14)	45.5(5/11)
	≥2	41.2(7/17)	0(0/4)
	P value	<0.05	>0.05
Treatment therapy	Radiation alone	46.2(6/13)	20.0(1/5)
	Chemotherapy alone	28.6(2/7)	0 (0/2)
	Combined modality therapy	90.9(10/11)	50.0(4/8)
	P value	<0.05	>0.05

difference ($P>0.05$).

DISCUSSIONS

The histopathology of nasal type NK/T cell lymphoma manifests obvious atypia of cell, angioinvasive growth, visible thrombus in blood vessel and frequently causing ischemic necrosis. There are considerable patients who were misdiagnosed or missed diagnosis although histopathological examinations were performed. Zhou et al. [4] reported that the misdiagnosis rate of nasopharynx malignant lymphoma reached up to 35.8% (43/120). 10 cases (32.3%) in this group were not correctly diagnosed at the first pathological examination. Chen et al. [5] believed all resected tissue mass in nasal cavity and paranasal sinuses must be examined by pathologist because of the difficult discrimination between NK/T lymphoma and other benign or malignant neoplasms. We think doctors should not blindly follow pathological results and more pathological slices should be performed and immunological markers such as CD3, CD56, CD4, CD8 etc should be, at best, detected using immunohistochemistical method simultaneously in order to make definitive diagnosis when the patients who was reported as "inflammation" are highly suspicious of nasal type NK/T cell lymphoma for repeated rhinostenosis, blood snivel, unhealing nasal cavity erosion and ulcer, facial swelling, fetor smell and so on. This disease is closely related to EB virus, the positive rate of EB virus examination reaching up to 95% [6]. The positive rate of EB virus in this group using PCR technique is 74.2%.

The overall 3-year rate and 5-year survival rate of patients in this group were 58.1% and 33.3% respectively, similar to documentations [7, 8, 9]. This results showed that the 3-year survival rate of stage Ⅰ and Ⅱ patients reached up to 85.7% and 45.5% respectively which were significantly higher than that of stage Ⅲ and Ⅳ patients ($P<0.05$), which suggested that clinical stage was an important prognostic factor. Clinical study manifested that long-term treatment effects of patients with B symptom were inferior to that of patients with non-B symptom, which were similar to this study. IPI were used to evaluate prognosis of patients with intermediate and high-grade malignant non-Hodgkin lymphoma at the earliest stage. Recently the study result from Yuan et al. [10] applying IPI to nasopharynx NHL patients suggested that IPI was an important prognosis factor of nasopharynx NHL but its value in nasal type NK/T cell lymphoma was still unclear at present. Our study indicated that the 3-year survival rate of patients with IPI $\leqslant 1$ was significantly higher than that of patients with IPI $\geqslant 2$ and the 5-year survival rate of patients was 0 when IPI $\geqslant 2$, which suggested IPI possibly had a certain value in prognostic estimation of nasal type NK/T cell lymphoma.

Currently evidence-based medicine studies have obviously showed the advantage of comprehensive treatment on NHL. Miller et al. [11] reported the random and prospective study results of 401 patients of intermediate and high-grade malignant NHL with stage Ⅰ and Ⅱ, the 5-year overall survival rate and disease free survival time in comprehensive treatment group was significantly superior to the radiotherapy group and the chemotherapy respectively. The reports with size of sample more than 50 on clinical study of nasal type NK/T cell lymphoma had only several articles at the present time [7, 8, 9]. Most studies [8,9] indicated that although the rate of complete remission of radiotherapy alone of patients with stage Ⅰ and Ⅱ could reach up to 60%-80%, the 5-year survival rate still lingered around 30% because of local recurrence, remote metastasis and rapid progress. Chemotherapy alone was inferior to radiotherapy alone. This study suggested that the 3-year survival rate in the combined modality group was significantly superior to the chemotherapy group ($P<0.05$); the 3-year and the 5-year survival rate in the combined modality group was also superior to the radiotherapy group, but the difference was not significant, possibly because the size of sample to be relatively smaller ($P>0.05$). Based on our results and relevant documents, we believe that the combined modalities on nasal type NK-T cell lymphoma may benefit patients for long-term survival.

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