

Characteristics of Extranodal NK/T-Cell Lymphoma, Nasal Type, Compared with Nasal Diffuse Large B-cell Lymphoma

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ABSTRACT

BACKGROUND: Extranodal NK/T-cell lymphoma, nasal type (ENKL), is an aggressive tumour with poor prognosis. Its early diagnosis may improve the prognosis of patients; however, it is often overlooked in many cases and misdiagnosed as an inflammatory sinus disease during its initial stage. Identifying the clinical characteristics of ENKL may aid otorhinolaryngologists in indicating cases early for a pathologic examination. In this study, we aimed to investigate the clinical characteristics of ENKL compared with that of diffuse large B-cell lymphoma (DLBCL), which is the most common nasal malignant lymphoma.

METHODS: The backgrounds, clinical symptoms, blood test results, and computed tomography images of patients with nasal/paranasal malignant lymphoma in our hospital between 2012 and 2017 were investigated. The characteristics of ENKL and nasal DLBCL were compared to differentiate them.

RESULTS: A total of 27 patients with nasal cavity and/or paranasal sinus lymphoma were included. Extranodal NK/T-cell lymphoma, nasal type, was diagnosed in 10 patients, while DLBCL was diagnosed in 17 patients. The median age of patients with ENKL was significantly lower than that of patients with DLBCL. All patients with ENKL had a unilateral lesion in the nasal cavity, with most located at the inferior turbinate. They also experienced nasal symptoms with significantly higher incidence of nasal obstruction and tendency of bleeding.

CONCLUSION: ENKL was often unilateral and caused nasal obstruction, unlike DLBCL. Those who are younger in age and have sinonasal tumour with unilateral nasal obstruction and bleeding should be considered for early and repeated biopsies at multiple sites, with ENKL taken into consideration.

KEYWORDS: Early diagnosis, lymphoma, B-cell, lymphoma, extranodal NK/T-cell, nose neoplasms, paranasal sinus neoplasms

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Introduction

Malignant lymphoma involving the nasal cavity and paranasal sinuses is rare and comprises less than 1% of head and neck cancers.^{1,2} Diffuse large B-cell lymphoma (DLBCL) is the most common type and accounts for approximately 80% of all sinonasal lymphomas.³ However, fast-growing malignant lymphomas, such as extranodal NK/T-cell lymphoma, nasal type (ENKL), must be considered as a differential diagnosis.^{4,5}

Extranodal NK/T-cell lymphoma, nasal type, an aggressive type of non-Hodgkin lymphoma (NHL), is derived from NK cells or $\gamma\delta$ T-cells. It has a poor prognosis, with only a 5-year overall survival (OS) of 50% in the early clinical stages.^{6,7} Its incidence is high in Asia, Mexico, and Central and South America,⁸ constituting approximately 3% to 10% of all NHL cases in these countries.⁹ In contrast, its incidence is less than 1% in Western countries,¹⁰ constituting approximately 0.2% of all NHL cases in a recent European study.¹¹ Extranodal NK/T-cell lymphoma, nasal type, has a male predilection, and patients

were usually in their 40s or 50s at the time of diagnosis,⁹ which was slightly lower than those who have other types of lymphoma. Extranodal NK/T-cell lymphoma, nasal type, frequently occurs within the nasal cavity and pharynx: 80% of nasal/paranasal ENKLs involve the nasal cavity, followed by the maxillary sinus (6%).¹² Furthermore, ENKL involving the nasal cavity was often misdiagnosed as an inflammatory sinus disease during its initial stage and detected only after progression.^{4,13} Moreover, histopathologic examination is required to achieve a definitive diagnosis.¹⁴ Polymorphic tumour cell and inflammatory cell infiltration against a background of necrosis and granulation tissue and infiltration of the reticular fibres of blood vessels within the blood vessel wall are typically observed in ENKL.⁹

As ENKL is an aggressive tumour with a poor prognosis, early diagnosis and treatment are desired; hence, an early biopsy is required. However, as its clinical symptoms and examination findings are often similar to those of inflammatory sinus



disease,⁴ an early biopsy may often not be performed, resulting in a delay in diagnosis. It is difficult to clinically diagnose based on the symptoms during the initial stage. Moreover, a single biopsy may not lead to a definitive diagnosis, necessitating repeated biopsies in suspicious cases.¹³

If the characteristic signs of ENKL can be observed, otorhinolaryngologists can ensure a prompt diagnosis and facilitate early intervention. Thereby, identifying the characteristic features of ENKL may be useful in determining whether to perform a pathologic examination early. Therefore, this study aimed to identify the characteristic clinical findings of ENKL in relation to nasal and paranasal DLBCL.

Materials and Methods

Ethics approval and consent

This study was approved by the ethics committee of Jikei University School of Medicine (Approval No. 32-428[10517]). The need for informed consent was waived due to the retrospective nature of the study.

Study design and participants

The clinical records of patients histopathologically diagnosed with nasal and paranasal malignant lymphomas at the Department of Otorhinolaryngology, Jikei University School of Medicine, from January 2012 through December 2017 were retrospectively analysed. Patient inclusion was determined as follows: 'lymphoma' was set as the search code based on the pathologic diagnosis results, and the search codes, 'nasal cavity / nose / sinus / paranasal sinus', were set as sampling sites. The exclusion criteria were as follows: (a) insufficient patient and treatment information and (b) patients aged under 20 years.

Outcomes

The primary outcomes were the characteristic clinical manifestations and laboratory findings of ENKL compared with those of DLBCL. The secondary outcomes were OS in ENKL and DLBCL involving the nasal cavity and paranasal sinuses.

Procedures

The following data were obtained from the clinical records: patient age (at the time of biopsy), sex (male or female), medical history, family history, smoking status (at the first visit), chief complaints and symptoms (at the first visit), presence of systemic symptoms (symptoms during the first visit), blood test findings (lactate dehydrogenase [LDH], albumin, soluble interleukin-2 receptor [*s*-IL2R], white blood cell, haemoglobin, platelet, peripheral blood lymphocyte), computed tomography (CT) findings, treatment information, OS (from the date of first visit to the date of last visit or death), and progression-free survival (PFS) (from the date of first visit to the date of last visit until progression or death). The periods from the

first visit until the biopsy and from the first visit until the start of treatment were also noted to examine their relationship with patient prognosis.

The diagnosis and classification of malignant lymphoma were performed according to the 2017 World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues.¹⁴ The clinical staging of malignant lymphoma was determined according to the Ann Arbor staging system.¹⁵

Determination of the tumour location

The location of the malignant lymphoma was determined using sinus CT images. These CT images were examined by 3 otorhinolaryngologists based on the following points:

- (i) The distribution area in the nasal cavity (olfactory cleft, superior turbinate, middle turbinate, inferior turbinate, and nasal septum) and paranasal sinuses (maxillary sinus, ethmoid sinus, frontal sinus, and sphenoid sinus) with the largest soft tissue concentration were identified;
- (ii) If the soft tissue concentration involved multiple regions and occupied 50% or more of that region, it was considered as involved; and
- (iii) If there were disagreements regarding the location among the 3 otorhinolaryngologists, the location was selected by a majority vote. If all 3 were different, the opinion of the most experienced otorhinolaryngologist was chosen.

As examples, Figure 1A was a nasal cavity tumour (1 of the slices of the inferior turbinate tumour image) and Figure 1B was a paranasal sinus tumour (1 of the slices of the ethmoid sinus tumour image).

Statistical analysis

Continuous and categorical variables are presented as means (standard deviation) and count (%), respectively. The Mann-Whitney *U* test and Fisher's exact test were used to compare the differences between ENKL and DLBCL. Differences between the Kaplan-Meier survival curves were analysed using log-rank tests. A 2-sided α value of less than .05 was considered as statistically significant. Statistical analyses were performed using GraphPad Prism version 8.4.3 (Graphpad Software Inc., San Diego, CA, USA).

Results

Patient characteristics

A total of 29 patients who were diagnosed with nasal cavity and/or paranasal sinus lymphoma during the 6-year period were reviewed. Diffuse large B-cell lymphoma was the most common malignant lymphoma involving the nasal cavity and/

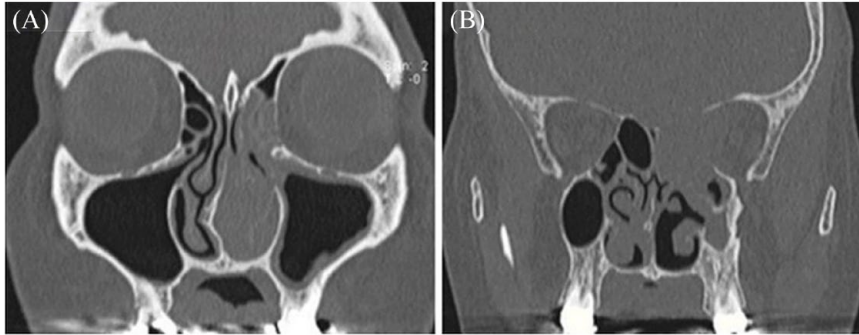


Figure 1. Sinus computed tomography images of nasal and paranasal lymphoma. (A) Nasal cavity tumour. (B) Paranasal sinus tumour.

or paranasal sinuses and diagnosed in 17 cases (58.6%). The second most common was ENKL, which was diagnosed in 10 patients (34.5%). B-cell lymphoblastic leukaemia and high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements were diagnosed in 1 case each (3.4%).

Characteristics of ENKL

Ten patients with ENKL were identified (Table 1). The median age at diagnosis was 46 years (range, 28–75 years), and half of the patients were in the 40 to 50 age group. The patients included 6 men and 4 women. The most common chief complaints and symptoms were unilateral nasal obstruction (8 cases) and unilateral nasal bleeding (2 cases). Nasal discharge, intranasal pain, cheek swelling, eyelid swelling, and neck swelling were observed in 1 case each. Systemic symptoms (B symptoms), which comprised fever over 38°C, night sweats, and/or unintentional weight loss, were observed in 4 cases. All ENKLs involved only one side of the nasal cavity, with most located at the inferior turbinate (60.0%), followed by the middle turbinate (30.0%), and nasal septum (10.0%). The clinical stages were IE, IIE, and IVE, in 5 (50%), 3 (30%), and 2 cases (20%), respectively, and 80% were diagnosed with early-stage disease.

Regarding the laboratory findings, the median LDH and s-IL2R levels were 187.5 IU/L and 370.5 U/mL, respectively. As for the tissue biopsies, the cell surface markers, CD3, CD56, granzyme B, and Epstein–Barr virus-encoded small RNA in situ hybridisation (EBER-ISH), were positive in 9 cases. Meanwhile, the markers were perforin in 5 cases and T-cell intracytoplasmic antigen in another 5 cases. Bone marrow biopsy showed bone marrow infiltration in 2 cases.

Characteristics of DLBCL

A total of 17 patients with DLBCL were identified. The median age at diagnosis was 66 years (range, 36–83 years). The patients included 12 men and 5 women. The most common chief complaints and symptoms were double vision (5 cases) and unilateral nasal obstruction (4 cases). Cheek symptoms were observed in 3 cases. Eye pain and visual field loss were observed in 2 cases each. B symptoms were found in 1 case.

Most DLBCL cases involved the paranasal sinuses, with most located at the ethmoidal sinus (35.3%), followed by the maxillary (23.6%), sphenoidal (17.6%), and frontal (5.9%) sinus. The clinical stages were IE, IIE, and IVE, in 13 (76.5%), 1 (5.9%), and 3 (17.6%) cases, respectively, and 82.4% were diagnosed with early-stage disease.

Regarding the laboratory findings, the median LDH and s-IL2R levels were 186 IU/L and 480 U/mL, respectively. As for the tissue biopsies, the cell surface markers, CD20 and CD79a, were positive in all cases, CD10 in 6, BCL2 in 11, and BCL6 in 10. As for the cell of origin, 12 cases were under the germinal centre B-cell type, and 5 were under the activated B-cell type. Bone marrow biopsy showed bone marrow infiltration in 3 cases.

Comparison between ENKL and DLBCL

A total of 27 lymphoma cases were identified (Table 2). Male patients accounted for 60.0% and 70.6% of the patients with ENKL and DLBCL, respectively. Sex distribution did not vary significantly between the 2 groups. The median age at diagnosis of ENKL was significantly lower than that of DLBCL (46.00 ± 13.83 years vs 66.00 ± 13.63 years, $P < 0.05$). The presence of systemic symptoms was significantly higher in patients with ENKL (40.0% vs 5.9%, $P < 0.05$). The Ann Arbor stages at the diagnosis of ENKL and DLBCL did not reach statistical significance (IE, IIE, IIIIE, and IVE, respectively). Regarding the lesion distribution within the nasal cavity and paranasal sinuses (maxillary, ethmoidal, frontal, and sphenoidal sinus), most ENKLs originated from the nasal cavity ($P < 0.05$), with most involving the inferior turbinate (60.0%), followed by the middle turbinate (30.0%) and nasal septum (10.0%). In contrast, two-thirds of DLBCL cases were located within the paranasal sinuses ($P < 0.05$), with most involving the ethmoidal sinus (35.3%), followed by the maxillary (23.6%), sphenoidal (17.6%), and frontal (5.9%) sinus. Most DLBCL cases that involve the nasal cavity originated from the middle turbinate (17.6%), followed by the inferior turbinate (5.9%).

Table 2 shows the chief complaints of the patients during their initial visit to our hospital. Patients with ENKL tended to

Table 1. Characteristics and outcomes of 10 patients with extranodal NK/T-cell lymphoma.

CASE NO.	AGE (YEAR)	SEX	CHIEF COMPLAINT			B SYMPTOM			SMOKING STATUS	CLINICAL STAGE
			NASAL OBSTRUCTION	NASAL BLEEDING	OTHER SYMPTOMS	FEVER	NIGHT SWEAT	WEIGHT LOSS		
1	40-49	2	+	-	Cheek pain	-	-	-	Never	I
2	40-49	2	+	-	-	+	-	-	Never	I
3	50-59	2	+	-	-	-	-	-	Unknown	II
4	70-79	1	+	-	-	-	-	+	Current	II
5	20-29	2	+	+	-	-	-	-	Never	I
6	40-49	1	+	-	-	+	+	+	Current	I
7	30-39	1	-	-	Intranasal pain	-	-	-	Unknown	II
8	60-69	1	+	-	-	-	-	-	Never	I
9	30-39	1	+	+	Nasal discharge	+	-	+	Never	IV
10	50-59	1	-	-	Eyelid/neck swelling	-	-	-	Current	IV

CASE NO.	MEDICAL HISTORY	LOCATION	RESPONSE	OUTCOME	
				OS (MONTH)	PFS (MONTH)
1	Hypertension	Inferior turbinate	CR	30	30
2	-	Middle turbinate	PD	17	17
3	-	Inferior turbinate	CR	9	9
4	Hypertension, dyslipidaemia, atrial fibrillation	Inferior turbinate	CR	10	10
5	-	Inferior turbinate	CR	3	3
6	-	Middle turbinate	CR	5	5
7	-	Inferior turbinate	CR	58	58
8	Hypertension, dyslipidaemia	Nasal septum	CR	53	53
9	Arrhythmia	Inferior turbinate	PR	10	10
10	Hypertension	Middle turbinate	PD	3	3

Abbreviations: CR, complete response; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response.

complain of nasal symptoms, with nasal obstruction being significantly higher ($P < .05$). Nasal bleeding was also more frequent in ENKL, although the difference was not significant. Eye symptoms (eg, double vision) were more common in DLBCL; however, this difference was not statistically significant ($P = .091$).

In the blood test results, the number of peripheral blood lymphocytes was significantly higher in DLBCL than in ENKL ($1.90 \pm 0.79 \times 10^3/\mu\text{L}$ vs $1.20 \pm 0.59 \times 10^3/\mu\text{L}$, $P = .013$), although the other results were not significantly different.

In addition, there was no significant difference between ENKL and DLBCL in terms of the interval from the first visit until biopsy (15.0 ± 24.39 days vs 1.00 ± 24.41 days, $P = .179$). In all cases, a biopsy was performed only once, with no cases requiring multiple biopsies to obtain a diagnosis.

Patient survival

Figure 2 depicts the Kaplan–Meier survival curve for ENKL and DLBCL. The median observation periods of ENKL and DLBCL were 11.5 and 27.0 months, respectively, and the OS rates were 80% and 100%, respectively. For ENKL, 3 cases had a complete response, 1 had a partial response, and 2 had progressive disease. The OS and PFS rates for ENKL were significantly lower than those for DLBCL (10.0 ± 20.5 months vs 26.0 ± 18.4 months, hazard ratio = 29.23, 95% confidence interval = 1.385–616.8, $P < .05$). However, no significant difference was observed regarding staging. There was also no correlation observed between the period until biopsy and OS for ENKL. All patients with ENKL were treated with chemotherapy, and 80% were treated with combined radiation therapy.

Table 2. Demographic/histopathologic characteristics and chief complaints of ENKL and DLBCL.

	TOTAL (N=27)	ENKL (N=10)	DLBCL (N=17)	P VALUE
Age (y, median, SD)				
	59.00 ± 16.05	46.00 ± 13.83	66.00 ± 13.63	.003*
Sex (no.)				
Male	18	6	12	.683
Female	9	4	5	
Smoking status (no.)				
Smoking	9	3	6	.650
Non-smoking	10	5	5	
Unknown	8	2	6	
B symptoms (no.)				
Present	5	4	1	.047*
Absent	22	6	16	
Ann Arbor stage (no.)				
IE	18	5	13	.219
IIE	4	3	1	.128
IIIE	0	0	0	
IVE	5	2	3	>.999
Original sites (no.)				
Nasal cavity	16	10	6	.001*
Paranasal sinus	12	0	12	.0004*
Maxillary sinus	4	0	4	
Ethmoidal sinus	6	0	6	
Frontal sinus	1	0	1	
Sphenoidal sinus	3	0	3	
Chief complaints				
Nasal symptoms (no.)				
Nasal obstruction	12	8	4	.007*
Nasal bleeding	2	2	0	.128
Nasal discharge	2	1	1	>.999
Intranasal pain	1	1	0	.370
Eye symptoms (no.)				
Double vision	5	0	5	.124
Eye pain	2	0	2	.516
Visual field loss	2	0	2	.516
Eyelid swelling	2	1	1	>.999
Blurred vision	1	0	1	>.999
Cheek symptoms (no.)				
Cheek pain	2	1	1	>.999
Cheek swelling	1	0	1	>.999
Cheek discomfort	1	0	1	>.999
Others (no.)	3	1	2	>.999
Blood test (median, SD)				
LDH (U/L)	186 ± 76	188 ± 105	186 ± 56	.421
s-IL2R (U/mL)	444 ± 1445	371 ± 2260	480 ± 287	.856

Abbreviations: DLBCL, diffuse large B-cell lymphoma; ENKL, extranodal NK/T-cell lymphoma, nasal type; LDH, lactate dehydrogenase; s-IL2R, soluble interleukin-2 receptor.

*Age and blood test results were analysed using the Mann–Whitney *U* test. The other factors were analysed using Fisher's exact test. Statistical significance was set at *P* < .05.

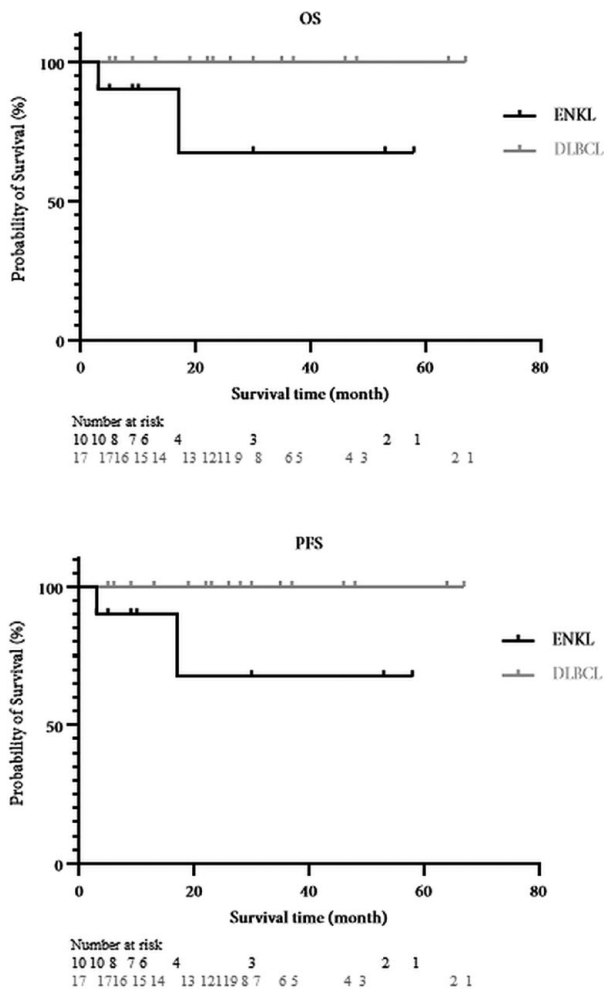


Figure 2. Survival curves for ENKL and DLBCL. DLBCL indicates diffuse large B-cell lymphoma; ENKL, extranodal NK/T-cell lymphoma, nasal type; OS, overall survival; PFS, progression-free survival.

Discussion

This study provided 2 important findings. First, ENKL exhibited the following characteristics in comparison with DLBCL: younger patient age, distinctive tumour location within the nasal cavity, nasal obstruction symptoms, and B symptoms. Second, the OS and PFS rates in ENKL were worse than those in DLBCL.

Characteristics of ENKL in comparison with DLBCL

The age at diagnosis of ENKL was generally 40s to 50s in Asia, suggesting that our patient population was similar to that of previous epidemiologic studies.⁹

Extranodal NK/T-cell lymphoma, nasal type, more commonly involves the nasal cavity than the paranasal sinuses; however, possible causes have not been reported. A unique characteristic of the development of ENKL is the infection of NK/T cells with Epstein–Barr virus,^{9,16} unlike other lymphomas. The heterogeneous distribution of NK/T cells within the nasal/paranasal mucosa may be associated with the apparent

localisation of ENKL. As there was a report that NK cells were major immune cells in the nasal lavage fluid,¹⁷ ENKL might develop more often in the nasal cavity. Nevertheless, there are no reports comparing the NK/T-cell distribution in the nasal/paranasal mucosa or major immune cells in the paranasal lavage fluid; thus, further studies are required to investigate the cause of this localisation.

Extranodal NK/T-cell lymphoma, nasal type, often presents with nasal symptoms, particularly nasal obstruction and bleeding.¹⁸ Given the fact that ENKL is common within the nasal cavity, nasal symptoms may likely occur more than eye and/or cheek symptoms. In this study, there was no significant difference regarding nasal bleeding; however, it was more prevalent in ENKL. Therefore, ENKL must be considered in the diagnosis of nasal tumours with nasal obstruction and bleeding.

B symptoms were also significantly higher in patients with ENKL because the OS and PFS rates were significantly worse. B symptoms are characteristic systemic symptoms of lymphoma and observed in 30% to 50%⁹ of cases with ENKL in Asia, which is consistent with the percentage observed in our study.

Furthermore, 31% of lymphomas manifest with eye symptoms, which was observed in the DLBCL cases in our study. In another case series of sinonasal lymphomas,^{4,5} eye symptoms were present in approximately 20% to 40% of cases, which was less than that of nasal symptoms, such as nasal obstruction; however, these symptoms were remarkable. Two-thirds of the other lymphomas in this study were localised in the paranasal sinuses, especially in the ethmoid and maxillary sinuses, which are present around the orbit; hence, this may account for many of the eye symptoms.

Prognosis of ENKL in comparison with DLBCL

Extranodal NK/T-cell lymphoma, nasal type, has a relatively poor prognosis among malignant lymphomas. Dubal et al¹⁹ compared sinonasal ENKL and DLBCL and reported that the overall 1-, 5-, and 10-year disease-specific survival was significantly lower in ENKL, with no significant difference in Ann Arbor staging. Our results were similar to those of previous studies, in which there was no significant difference in the time to diagnosis. Therefore, ENKL is likely to have a worse prognosis than DLBCL. In our study, all cases were diagnosed after a single biopsy; however, if the diagnosis was delayed due to inappropriate or repeated biopsies, the results could have been different.

The blood test results showed a significant decrease only in the peripheral blood lymphocyte count in patients with ENKL, which might also reflect the poor OS and PFS rates. As no previous report showed a significant decrease in peripheral blood lymphocyte count in ENKL, it may be difficult to consider this decrease as a characteristic of ENKL based on our results alone as the number of ENKL cases in this study was small, and 1 patient was in extremely poor health at the time of diagnosis.

Epidemiology of lymphoma in Asia in comparison with European studies

The patients included in this study were all Asians, and their epidemiology was similar to that of previous reports in Asia and Latin America.^{9,10} However, some differences were observed in comparison with a recent large-scale cohort study in Europe.¹¹ First, the median age of the patients in ENKL in Europe was 65.7 years, which was higher than that of the patients in our study and previous reports in Asia and Latin America.^{9,10} Extranodal NK/T-cell lymphoma, nasal type, is a rare disease in Europe, and race, Epstein–Barr virus strain mutations, and environmental factors are considered as some of the reasons for this geographical difference.⁹ These elements may also partly account for the delayed age of onset in Europe. Second, pain and swelling were more frequently seen than nasal bleeding and B symptoms with patients in ENKL in Europe. In an Asian report, the most common symptoms of ENKL were nasal obstruction, nasal bleeding, and B symptoms,⁹ suggesting that there may be some regional differences in the symptoms. In addition, patients with sinonasal DLBCL in Europe also had other different characteristics in other aspects from our results. In Europe,³ the median age was higher than in our results (72.8 years), and nasal symptoms were more frequent than eye symptoms. Thus, additional research is needed to further elucidate the epidemiologic differences between ENKL and sinonasal DLBCL.

Limitations

One limitation of our study was that lymphoma distribution was determined only through CT imaging. A more accurate evaluation of the location could be achieved if there were detailed medical records describing the distribution and transnasal endoscopic images. Another limitation was that the evaluation of the presence or absence of symptoms was based on the patient's chief complaints. As the presence or absence of all major nasal and eye symptoms could not be confirmed retrospectively, the frequency of the symptoms could not be evaluated accurately. The retrospective and single-centre design of the study was also a limitation. Although the number of cases in this study was small and the treatment and prognostic findings were limited, our study focused on determining the characteristics of ENKL, which may facilitate its early diagnosis. In addition, because this study only included Asian patients, the results may not apply to some regions, such as Europe.

Conclusion

Extranodal NK/T-cell lymphoma, nasal type, has a worse prognosis than DLBCL; therefore, performing diagnostic methods earlier if ENKL is suspected must be considered. In particular, younger patients who have sinonasal tumour with unilateral nasal obstruction and bleeding should be considered for an early biopsy and repeated biopsies at multiple sites, with ENKL taken into consideration.

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Author Contributions

Hirota Tanaka: Conceptualisation, data collection and analysis, funding acquisition, investigation, methodology and resources.

Eri Mori: Conceptualisation, investigation, methodology, writing, review, and editing of the manuscript, and total project administration and supervision.

Taisuke Akutsu: Writing, data collection, and analysis,

Shota Saito: Data collection.

Masayoshi Tei: Review and editing of the manuscript.

Nobuyoshi Otori: Supervision, review, and editing of the final manuscript.

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