Evaluation of Central Nervous System Involvement in Nasal Lymphomas

Naoto Shikama[1], Masahiko Oguchi[2], Sigeru Sasaki[1], Atsunori Shinoda[1], Atsushi Nishikawa[1], Kazukiyo Arakawa[1], Keiichirou Koiwai[1], Kentarou Mochizuki[1], Akira Yamada[1], Tomoharu Watanabe[1], and Masumi Kadoya,[1]

1) Department of Radiology, Shinshu University, School of Medicine
2) Department of Radiation Oncology, Cancer Institute Hospital

鼻腔原発非ホジキンリンパ腫における中枢神経浸潤の評価

鹿間　直人　小口　正彦　佐々木　茂　篠田　充功
西川　敦　荒川　和清　小岩井慶一郎　望月健太郎
山田　哲　渡辺　智治　角谷　眞澄

【目的】鼻腔原発非ホジキンリンパ腫の病期診断における中枢神経系への進展の評価の重要性と，病期I-II期における中枢神経系再発に対する予防的治療の意義を明らかにする．
【対象】1973年から1999年までに治療された43例の鼻腔原発非ホジキンリンパ腫を対象とした．病期診断としてCT，超音波検査，ガリウムシンチ，上部消化管検査，骨髄生検、MRIなどを用いた．42例に放射線治療が，また25例に化学療法が行われた．病期I-II期の全38例には中枢神経再発の予防的治療である抗癌剤の髄注や全脳照射は行わなかった．平均経過観察期間は73カ月であった．
【結果】病期診断の段階で，4例に中枢神経系への進展が確認された．3例はMRIのみで確認され，このうちCTでも進展が確認されたのは1例のみであった．また1例はMRIおよびCTで中枢神経浸潤が確認できなかったが，髄液細胞診で確認された．この4例は前頭部の痛みや脳神経症状を示していた．病期I-II期の38例で中枢神経系の再発は見られなかった．
【結論】鼻腔リンパ腫の中枢神経浸潤を評価するため，病期診断にMRIおよび髄液検査を用いるべきであり，特に前頭部の痛みや脳神経症状を示す症例においては重要と思われる．病期I-II期においては中枢神経再発の予防的治療は不要と思われた．

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信州大学放射線科

別刷請求先
3-1-1 Asahi Matsumoto, 390-8621 Japan
Department of Radiology, Shinshu University, School of Medicine
Naoto Shikama

Objectives: To clarify the usefulness of evaluating central nervous system (CNS) involvement in patients with nasal lymphomas at the initial staging procedure, and of CNS prophylaxis for patients with clinical stage I/II.
Patients and Methods: We retrospectively reviewed 43 patients with nasal lymphomas who had been treated from 1973 through 1999. The staging procedure included mainly computed tomography (CT), ultrasonography, gallium scintigraphy, upper gastrointestinal study, magnetic resonance (MR) imaging, and bone marrow biopsy. Forty-two patients received radiotherapy, and 25 patients received chemotherapy. All 38 patients with stage I/II were not subjected to CNS prophylaxis.
Results: Four patients demonstrated CNS involvement at the staging procedure. MR imaging demonstrated the tumor had directly infiltrated the skull base in 3 patients, but CT demonstrated CNS infiltration in only one patient. In another patient, cerebrospinal fluid (CSF) cytologic analyses demonstrated CNS involvement, but MR imaging and CT did not. These 4 patients complained of frontonasal pain and/or cerebral nerve dysfunction. No patient with stage I/II developed CNS relapse.
Conclusions: MR imaging and CSF cytologic analyses should be performed at the initial staging of nasal lymphomas, especially in patients with frontonasal pain and/or cerebral nerve dysfunction. Patients with stage I/II might not need CNS prophylaxis.

INTRODUCTION

Non-Hodgkin's lymphoma arising in the nasal cavity is an aggressive tumor, and the patients with nasal lymphomas have been treated with radiotherapy or combination therapy consisting of radiotherapy and cytotoxic agents[1)-4)]. However, central nervous system (CNS) relapse after treatment has been often documented, and the incidence of CNS relapse is said to range from 1% to 29%[1),3),4)]. The causes of CNS relapse

after treatment may include CNS involvement at presentation, local recurrence at the base of skull and systemic relapse. Although it is essential to evaluate CNS involvement before treatment, it is usually difficult to detect minimal CNS involvement. The Cotswolds Staging Classification, which is the revised version of the Ann Arbor Staging Classification, recommends the use of multi-modality techniques, including cranial computed tomography (CT), isotope scanning, and other imaging techniques for pretreatment evaluation, and magnetic resonance (MR) imaging should be performed under special circumstances[5].

The purposes of this study were to clarify the usefulness of evaluating CNS involvement in patients with nasal lymphoma at the initial staging procedure, and of CNS prophylaxis for patients with clinical stage I/II.

PATIENTS AND METHODS

We treated 43 patients with nasal lymphomas from 1973 through 1999 (Table 1). The male to female ratio was 28: 15, and the median age was 56 years (range, 19 to 86 years). The initial staging procedure included history, physical examination, complete blood cells counts, liver and renal function, and chest roentgenogram in all patients. Cranial CT was performed in 37 patients (86%), ultrasonography of neck and abdomen in 29 patients (67%), chest CT in 29 patients (67%), abdominal and pelvic CT in 29 patients (67%), gallium scintigraphy in 37 patients (86%) and upper gastrointestinal radiographic examination in 32 patients (74%), MR imaging in 22 patients (51%) and bone marrow biopsy in 28 patients (65%). We performed cerebrospinal fluid (CSF) cytologic analyses in only 6 patients (13%), which included 2 patients (stage I) with a complaint of frontonasal pain, 3 patients (stage IV) who were found to present CNS involvement by MR imaging and/or CT, and one patient (stage IV) with testicular involvement.

Table 1　Clinical characteristics of the study population

	(n)	CNS involvement (n)	p value
Median age 56			
Genders			
Male	28	2	0.505
Female	15	2	
Stage			
I	34	–	
II	4	–	–
IV	5	4	
Phenotype			
T or NK	32	4	
B	8	0	0.468
Unknown	3	0	
Tumor size			
<5 cm	14	0	
>=5 cm	28	4	0.137
Unknown	1	0	
Symptoms at presentation			–
Nasal obstruction	28	4	
Nasal bleeding	15	0	
Fever	7	2	
Frontonasal pain	6	3	
Nasal swelling	5	1	
Nasal discharge	5	1	
Double vision	1	1	
Exophthalmos	1	1	

Histological subtype was classified using the International Working Formulation for Non-Hodgkin's lymphomas. Four patients were low-grade group and 39 patients were intermediate-grade group. The phenotypes of 40 patients were determined. Thirty-two patients (80%) had T-lineage or NK cell lymphomas, and 8 patients (20%) had B-lineage lymphomas.

Forty-two patients received radiotherapy and the total radiation dose of the primary site ranged from 9 Gy to 60 Gy (median; 43 Gy). Ten patients received ipsilateral neck irradiation, and the total radiation dose ranged from 9 Gy to 50 Gy (median; 30 Gy). Multi-agents chemotherapy, including the MACOP-B [methotrexate (MTX), doxorubicin hydrochloride (Adriamycin; Adria Laboratories, Columbus, OH), cyclophosphamide (Endoxan; ASTA-Medica, Dresden, Germany), vincristine (Oncovin; Eli Lilly, Indianapolis, Ind), prednisone, and bleomycin], and CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone], and CHOP like regimens was used in 25 patients. No patient with stage I or II received CNS prophylaxis with intrathecal MTX and cytosine arabinoside (Ara-C) or cranial irradiation.

Difference between two groups was assesed by chi-square test. The survival rate was calculated by the Kaplan-Meier method. Difference between the curves was assessed by the log-rank test. The median follow-up period was 73 months (range; 1 to 241 months).

RESULTS

There were three patients, in whom MR imaging demonstrated the tumor had directly infiltrated the skull base at the initial staging procedure. CT disclosed CNS involvement in only one of 3 patients. Incidentally, we had one patient, in whom neither CT nor MR imaging disclosed CNS involvement, but CSF cytologic analysis at the staging procedure demonstrated lymphoma cells in CSF.

The clinical stage according to the Cotswolds Stag-

ing Classification, tumor size, and chief complaint were shown in Table 1. As for the size of the primary tumor and the phenotype, all 4 patients with CNS involvement had large primary tumors of the T-lineage or NK cell lymphomas. The chief complaints of these 4 patients were mainly nasal obstruction and frontonasal pain.

The 8-year cause-specific survival rates of patients without CNS involvement and that of patients with CNS involvement were 75% and 25% ($p = 0.0007$), respectively (Fig. 1). The relapse sites after treatment were nose, neck lymph nodes and small intestine. No patient with stage I or II developed CNS relapse during the follow-up period. Three of the 4 patients with CNS involvement died due to lymphoma within 6 months despite combination therapy, and only one patient is alive at present without evidence of disease more than 8 years since the end of treatment. The patient with testicular involvement (stage IV) was administered combination therapy including intrathecal MTX and Ara-C and cranial irradiation, and at present, that is, he is alive without evidence of disease more than one year since the end of treatment.

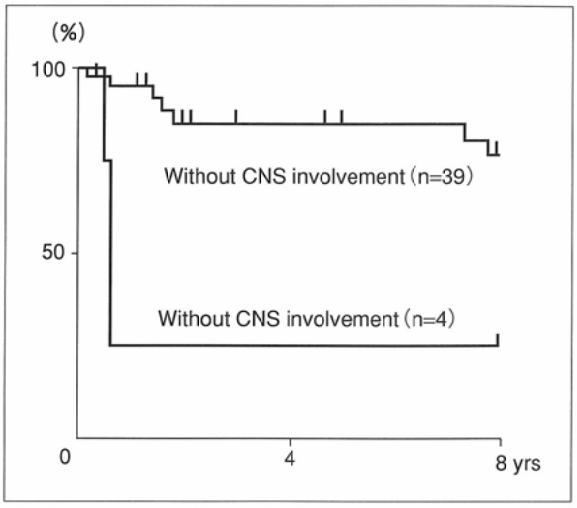


Fig. 1 Cause-specific survival curves according to clinical stage

The clinical features of the 3 patients in whom CT at the time of the staging procedure did not disclose CNS involvement, but MR imaging or CSF cytologic analyses were positive are presented.

Case 1

The patient, a 27-year-old woman, presented with a complaint of nasal obstruction and headache of one-month duration. The histopathological finding of a biopsy specimen from the nasal cavity were compatible with the diagnosis of non-Hodgkin's lymphoma, peripheral T cell type, unspecified, T or NK lineage (positive for UCHL-1 [anti-human T cell], negative for L 26 [anti-human B cell]) according to the Revised European-American Classification of Lymphoid neoplasms (REAL)[6]. CT and gallium scintigram showed the tumor filling the bilateral nasal cavity, but did not show infiltration of the skull base by the tumor (Fig. 2A). No malignant cell was found in CSF cytologic analyses, and the bone scintigram showed no abnormal accumulation. The coronal contrast-enhanced T1-weighted MR imaging, however, showed the tumor had infiltrated the skull base through the cribriform plate (Fig. 2B). The patient was administered systemic chemotherapy consisting 6 cycles of CHOP, intrathecal MTX and Ara-C, and radiotherapy using 46 Gy in 23 fractions over 4.5 weeks. Radiation field included the gross tumor volume. That was detected by MR imaging, and 2 cm margin. Unfortunately one month later the patient died due to systemic relapse.

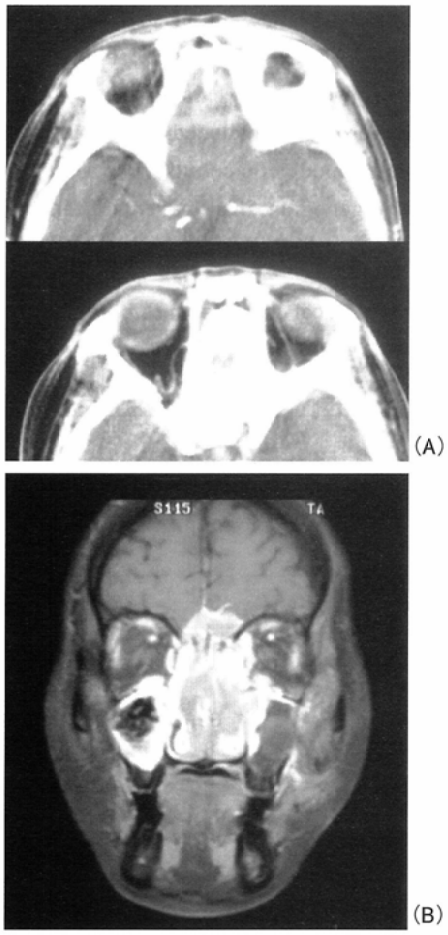


Fig. 2 Case 1, a 27-year-old woman
A: Axial contrast-enhanced CT image showing a slightly high-density area in the frontal lobe. Infiltration of the skull base could not be diagnosed because of the partial volume effect of the skull base.
B: Coronal contrast-enhanced T1-weighted MR image showing the large tumor of the nasal cavity that infiltrated the skull base through the cribriform plate and extended along the dura.

Case 2

The patient, a 35-year-old woman, presented with a complaint of nasal obstruction of five-months duration, and exophthalmos and double vision of one-month duration. The ophthalmic symptoms were due to intraorbital growth of the tumor. The histopathological findings were compatible with the diagnosis of angiocentric type

of T or NK lineage (positive for LCA [anti-human leukocyte common antigen], UCHL-1, CD3 and CD56, negative for L-26 and CD57). The tumor filled the right nasal cavity, and the lymphoma involved the bilateral neck lymph nodes and paraaortic lymph nodes. Cranial CT did not demonstrate infiltration of the skull base by the tumor. However, the MR imaging showed the tumor had infiltrated the skull through the cribriform plate and the left foramen ovale reaching the cavernous sinus (Fig. 3A, B). Soon she was administered radiotherapy with 18 Gy in 9 fractions over 2 weeks for the primary site during the staging procedure. But her visual activity and eye movement did not improve. The patients was administered, high-dose systemic chemotherapy and intrathecal MTX and Ara-C and radiotherapy (30 Gy/10 fractions). However, complete remission was not achieved, and she died due to systemic relapse after 6 months of the start of chemotherapy.

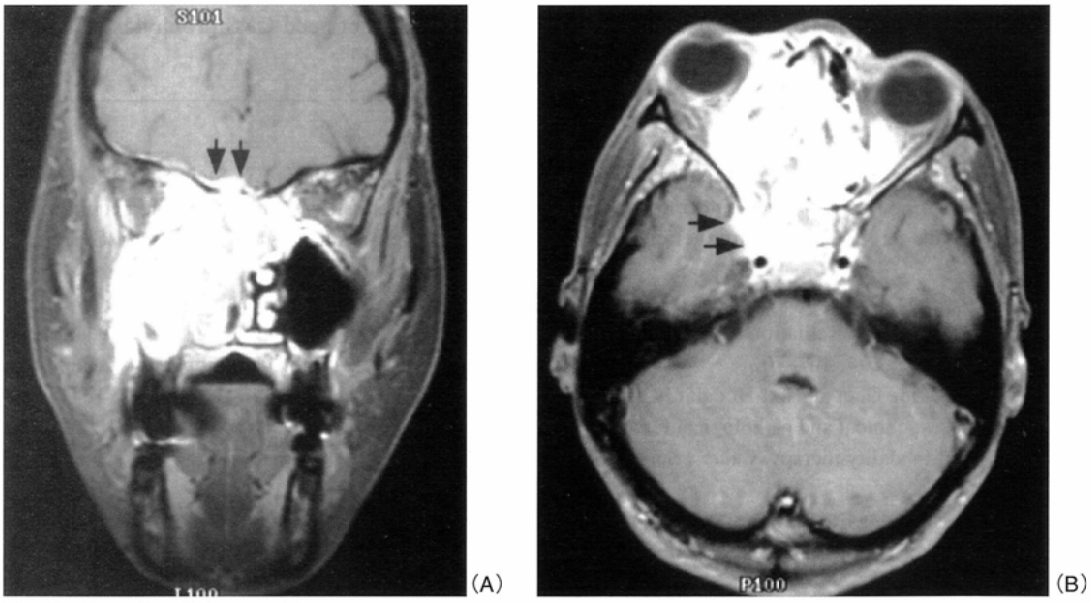
Case 3

The patient, a 60-year-old man, presented with a complaint of nasal obstruction and headache of 7-months duration. The histopathological findings of a biopsy specimen from the nasal cavity were compatible with the diagnosis of peripheral T cell type, unspecified, T or NK lineage (positive for LCA and UCHL-1, negative for L-26). CT, MR imaging and gallium scintigraphy showed the tumor filled the bilateral nasal cavity, but did not show infiltration of the skull base by the tumor. However, since his headache and neck pain worsened, then we performed CSF cytologic analyses, and lymphoma cells were found in CSF. The patient was administered systemic chemotherapy, intrathecal MTX and Ara-C, and radiotherapy using 35.4 Gy in 18 fractions over 4 weeks. But 3 months later he died due to CNS dissemination.

DISCUSSION

The incidence of CNS relapse after treatment in patients with nasal lymphomas has not been clarified. In an early Stanford study involving 20 patients who were treated with radiotherapy, 5 patients developed CNS relapse after treatment[4]. Whereas a subsequent Stanford study showed that combination therapy plus CNS prophylaxis decreased the occurrence of CNS relapse and improved the outcome[3]. Incidentally, in a retrospective MD Anderson Cancer Center study involving 70 patients who had been treated with combination chemotherapy and radiotherapy, only one patient developed CNS relapse[1]. The reasons of this discrepancy are not known. The occurrence of CNS relapse might depend on the proportion of T lineage or NK cell lymphomas in the study population, the presence of minimal CNS involvement before treatment, and local recurrence at the base of the skull. In Asian studies the proportion of T-lineage or NK cell lymphomas was from 70% to 80%[2),3)]. Incidentally, in the MD Anderson Cancer Center study, the proportion of T-lineage or NK cell lymphomas was about 40%. T-lineage or NK cell lymphomas are aggressive tumors, and their clinical feature might be different from that of B-cell lymphomas[7].

The pathway to the CNS seems to be direct infiltration or hematogenous spread. There are some pathways from the nasal



(A)　(B)

Fig. 3　Case 2, a 35-year-old woman
A: Coronal contrast-enhanced T1-weighted MR image showing the tumor of the nasal cavity that infiltrated the skull base through the cribriform plate (arrows).
B: Axial contrast enhanced MR image showing the tumor that infiltrated the cavernous sinus (arrows) through the foramen ovale.

cavity, paranasal sinuses, or nasopharynx through the skull base to the CNS. Some of them are the cribriform plate, the foramen ovale and the foramen lacerum[8]. The latter leads to the cavernous sinus. Because of the complex anatomy of the skull base, skull base infiltration is difficult to detect at an early time. CT is superior to plain radiography and bone scintigraphy. However, skull base infiltration is difficult to assess clearly on CT because of the obscure demarcation of the anatomic landmark. The contrast resolution of MR imaging is better than that of CT. Incidentally, CT seems to be superior to MR imaging in detecting skull base erosion, but most lymphomas generally infiltrate without destroying tissues, thus MR imaging is more useful to evaluate infiltration of the skull base by lymphomas. And also the coronal view of MR imaging and CT is superior to the axial view to evaluate the skull base infiltration. The Cotswolds Staging Classification recommended the use of multi-modality techniques, including CT, isotope scanning MR imaging, and other imaging techniques for pretreatment evaluation. In our experience MR imaging and CSF cytologic analyses are more useful than plain radiography, CT and isotopic scanning to detect minimal CNS involvement by nasal lymphomas.

Should all patients with nasal lymphomas be subjected to MR imaging and CSF cytologic analyses at the initial staging procedure? Since our study included a small number of patients, we could not provide an adequate answer for this question. Burton recommended that the patients with a tumor above the pterygopalatine line should be subjected to examination for CNS involvement and CNS prophylactic therapy[9]. Our 4 patients with CNS involvement had a large primary tumor of more than 5 cm of T-lineage or NK cell lymphoma. But there was no statistical significance. Moreover of the 6 patients with a complaint of frontonasal pain, three patients demonstrated CNS involvement at presentation. The patient without a complaint of frontonasal pain complained of double vision and exophthalmos. The staging procedure, including MR imaging and CSF cytologic analyses, should be performed for patients with frontonasal pain and/or cerebral nerve dysfunction.

The proportions of Epstein-Barr virus (EBV) infection and CD56 expression have been high incidence in nasal lymphomas[10]. Cheung et al. reported that a patient with nasal T/NK-cell lymphomas with CD56 expression had a very poor outcome[7]. CD56 represents the neural cell adhesion molecule (NCAM), and may induce tumor-cell migration and dissemination. It was reported that some nasal lymphomas had a multidrug resistance (P-glucoprotein-positive) phenotype. P-glucoprotein may be correlated with chemotherapy resistance. In a previous study, that did not evaluate P-glucoprotein, chemotherapy did not improve the treatment outcome of nasal lymphomas[2]. CD56 positive lymphomas tend to invade surrounding tissue, and therefore a multi-modalities staging procedure might be considered to evaluate the patient for minimal CNS involvement. To draw meaningful conclusions on the optimal staging procedure and treatment strategy for nasal lymphomas, further phenotypic studies including the examination of CD56 and P-glucoprotein should be performed.

CONCLUSIONS

MR imaging and CSF cytologic analyses should be included in the initial staging procedure for the patients with nasal lymphomas, especially the patients with frontonasal pain and/or cerebral nerve dysfunction. The patients with stage I and II might not need CNS prophylaxis.

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