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REVIEW ARTICLE

Primary Nasal Lymphoma

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ABSTRACT

Primary nasal lymphoma is a rare disease. It shows significant variability in incidence and immunophenotypic characteristics among different geographic areas. It is relatively common, among the Chinese people and more than half of the lesions are of the aggressive natural killer-/T-cell immunophenotype. Except for those patients with stage IE disease confined to the nasal cavity, the prognosis of patients with primary nasal lymphoma is unsatisfactory with current treatment. The optimal treatment for the disease remains unknown. The clinical features, pathology, prognostic factors, and treatment results for this disease are reviewed, and possible approaches to improving treatment are discussed.

Key Words: *Chemotherapy, Immunophenotype, Lymphoma, Nasal cavity, Radiotherapy*

INTRODUCTION

Primary nasal lymphoma may be defined as lymphoma with exclusive or predominant involvement of the nasal cavity, presenting with nasal symptoms.[1] There is significant variability in the incidence and immunophenotypic characteristics among different geographic areas. Primary nasal lymphoma is rare in western populations, but is more common among Chinese and Japanese populations.[2-12] Primary nasal lymphoma comprises 3% to 10% of cases of non-Hodgkin's lymphoma in the Chinese population.[2,8] In Hong Kong, assuming an annual incidence of 8.5 cases of non-Hodgkin's lymphoma per 100 000 population[13] and a total population of 7 million, about 20 new cases of primary nasal lymphoma are expected each year. Immunophenotypically, primary nasal lymphomas of Asian patients are mostly of natural killer (NK)- or T-cell lineage,[2,3,6,8,10,14-16] whereas in western series of sino-nasal lymphoma, it is not clear which immunophenotype is most common.[4,7,12]

Although the nasal cavity is adjacent to the nasopharynx, primary nasal lymphoma appears to carry a worse prognosis than lymphomas arising from the Waldeyer's ring, probably because of differences in tumour cell lineage.[17-20] Except for those with stage IE disease confined to the nasal cavity, the prognosis of patients with primary nasal lymphoma is unsatisfactory with current treatment.[2,3,5,8] In this article, the clinical features, pathology, prognostic factors, and treatment results for primary nasal lymphoma will be reviewed, and possible approaches to improving treatment will be discussed.

CLINICAL FEATURES

The clinical features of patients with primary nasal lymphoma at presentation are highlighted in Table 1. While most patients have a short duration of symptoms

Table 1. Clinical characteristics of patients with primary nasal lymphoma at presentation

Sex	
M:F	1.2 – 2.1:1
Median age (years)	44 – 50
Karnofsky performance status	90 – 100
Presenting symptoms	
Common:	
Epistaxis	
Nasal obstruction	
Nasal swelling	
B symptoms	
Uncommon:	
Proptosis	
Hard palate perforation	
Cranial nerve palsy	
Ann Arbor stage (%)	
IE	52 - 81
IIE	15 - 28
IIIE – IV	0 - 33

Abbreviation: B symptoms = fever, night sweats, weight loss.

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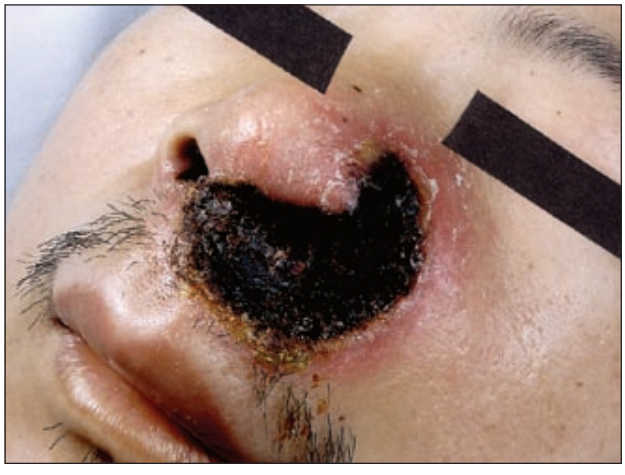

Figure 1. Clinical photograph of a 32-year-old man with stage IE primary nasal natural killer-/T-cell lymphoma. He received four cycles of epidoxorubicin-containing chemotherapy but the disease progressed. He declined salvage radiotherapy and subsequently developed a large ulcerative necrotic lesion. He eventually died.

before diagnosis, some patients may have experienced long-standing symptoms with initial examination failing to reveal the lymphoma.

The local tumour typically appears as a diffuse erythematous swelling inside the nasal cavity covered with exudate and crust, and in some advanced cases, there may be extensive ulceration and necrosis, producing midfacial destructive disease (Figure 1).[3,10] The full local tumour extent is best assessed with endoscopy complemented with computed tomography (CT) and magnetic resonance imaging (MRI).[2,5,21] MRI of the local tumour site may be used to differentiate between tumour involvement of the paranasal sinuses and benign mucosal thickening and fluid retention.[21] The local tumour extends to the maxillary sinus, ethmoid sinuses and nasopharynx in 42%, 36%, and 25% of patients, respectively (Figure 2).[2] Involvement of the base of the skull and cranial nerve palsies are very uncommon.[8]

PATHOLOGY

According to the Working Formulation, 61% to 84% of non-Hodgkin's lymphomas are intermediate-grade, 10% are high-grade, and 25% to 28% are unclassifiable.[2,6,8] A recent study showed that primary nasal lymphomas frequently express the NK-cell marker CD56.[3] In the study, NK/T-, T- and B-cell immunophenotype was revealed in 55%, 16%, and 29% of lymphomas that arose from the nasal cavity, respectively. The designation 'NK/T-cell' lymphoma is used for CD56-expressing tumours because, while they probably represent genuine NK-cell lymphomas,[14] some T-cell-associated antigens are expressed. In the revised European-American classification of lymphoid neoplasms (REAL) and new World Health Organization (WHO) classification of haematological malignancies, the entity 'extranodal NK/T-cell lymphoma, nasal type' is used to describe this lymphoma with midfacial presentation.[22] Histologically, NK/T-cell lymphoma shows a polymorphous infiltrate. Apoptosis is prominent. Angiocentric or angio-invasive infiltration is common, with marked tissue necrosis. Of interest, the subset of nasal lymphoma with NK/T-cell lineage is frequently associated with the Epstein-Barr virus (EBV), which may play a role in tumour causation.[14,23,24]

In clinical practice, it is important to distinguish CD56-positive NK/T-cell tumours from CD56-negative peripheral T-cell lymphomas,[25] because they carry different prognoses.[3]

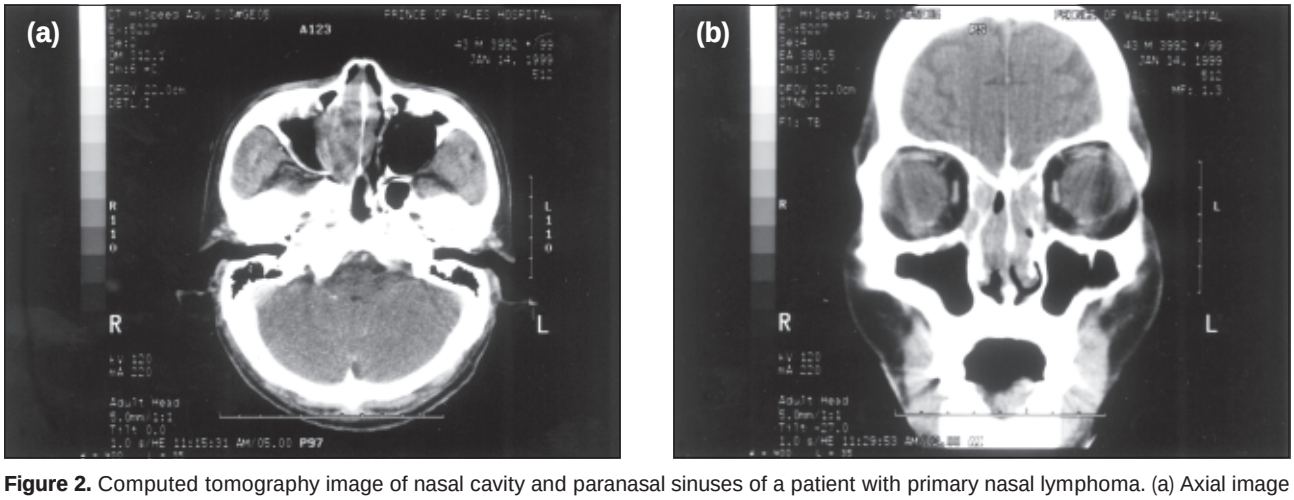

Figure 2. Computed tomography image of nasal cavity and paranasal sinuses of a patient with primary nasal lymphoma. (a) Axial image shows a soft tissue mass in the nasal cavity eroding the medial wall of the right maxillary sinus; (b) coronal image demonstrates tumour invasion into the ethmoidal sinuses and encroachment on the orbits, which may pose difficulty in radiotherapy planning.

PROGNOSTIC FACTORS

Ann Arbor stage is an independent prognostic factor for survival in patients with primary nasal lymphoma,[2,3,8] as is immunophenotype.[3] NK/T-cell lymphomas carry the worst prognosis, with a median overall survival of 12.5 months.[3] The reasons for the high aggressiveness of nasal NK/T-cell lymphomas are not clear. One possible contributing factor is their frequent expression of P-glycoprotein, an energy-dependent efflux pump for multiple chemotherapeutic drugs including doxorubicin and vincristine, which may account for their poor response to conventional chemotherapy.[26,27] Tumour hypoxia resulting from angioinvasion has been postulated to be a mechanism for their low chemosensitivity and perhaps low radiosensitivity, but features of angiocentric lymphoma were not shown to be a prognostic factor in a large study.[8]

Since 52% to 81% of patients have stage IE disease, it would be useful to identify different prognostic groups among them to guide treatment. A large study showed that paranasal extension was an independent prognostic factor in patients with stage IE disease.[2] However, the significance of tumour volume has not been determined for primary nasal lymphoma. While the International Prognostic Index has been found to predict survival for patients with aggressive non-Hodgkin's lymphoma in general,[28] its significance in the subset of patients with primary nasal lymphoma has not been well studied.[2-6,8,10]

TREATMENT RESULTS

Table 2 provides a summary of the treatment results of three large retrospective clinical studies in Chinese patients with primary nasal lymphoma.

Stage IE and IIE

Most of the patients with stage IE or IIE disease have been treated with radiotherapy with or without doxorubicin-containing chemotherapy.[2,3,5,6,8-11] In general, the outcome of patients with even early stage disease is unfavourable; the 5-year overall survival rates for patients with stage IE and IIE disease are 25% to 75% and 33% to 35%, respectively.[2,5,8,10]

Stage IIIE and IV

Chemotherapy, with or without local radiotherapy, has resulted in complete response rates of 30% and survival rates of 7% to 31% at 5 years for stage IIIE or IV disease.[2,8]

Patterns of Failure

Of patients who relapse after an initial complete response, 70% do so within 2 years.[2] Overall, local failure, nodal failure and extranodal failure occur as a component of failure in 24%, 27%, and 78% of patients, respectively.[2]

Lymphomas with different immunophenotypes show different patterns of failure. In a large series, NK/T-cell tumours had a local relapse rate of 21%, while 5% of T-cell tumours and none of the B-cell tumours relapsed locally.[3] As for systemic involvement, skin is the most common site for NK/T- and T-cell lymphomas, while distant lymph nodes are the most common site for B-cell tumours.

Treatment for Refractory or Relapsed Disease

A second course of radiotherapy has been used to treat patients with limited local relapse. In one report, salvage treatment by re-irradiation was successful for 5

Table 2. Summary of three large retrospective clinical studies of Chinese patients with primary nasal lymphoma

Reference	Ann Arbor stage (no. of patients)	Treatment (no. of patients)	5-year overall survival rate (%)	Remarks
Li et al. 1998[2]	IE (133) IIE (28) IIIE (4) IV (10)	RT (65) RT + CT (103) CT (7)	Whole series 65 Stage IE 75 IIE 35 IIIE/IV 31	Prognosis was stage-dependent. Among patients with stage IE disease, paranasal extension was an adverse prognostic factor. Addition of chemotherapy did not improve survival of patients with stage IE disease.
Liang et al. 1995[8]	IE (52) IIE (15) IIIE (4) IV (29)	RT (39) CT ± RT (61)	Stage IE 66 IIE 33 IIIE 0 IV 9	Survival was significantly better in patients with stage IE disease. Use of chemotherapy did not significantly improve clinical outcome.
Cheung et al. 1998[3]	IE (61) IIE (29) IIIE (8) IV (15)	RT (25) CT ± RT (86)	Whole series 38 NK/T-cell 31 T-cell 58 B-cell 35	Patients with nasopharyngeal lymphoma were also included. Advanced stage and NK/T-cell immunophenotype were adverse prognostic factors for overall survival.

Abbreviations: CT = chemotherapy; RT= radiotherapy.

Table 3. Suggested treatment approaches to primary nasal non-Hodgkin's lymphomas

NK/T-cell lymphoma (CD56-positive)
• Doxorubicin-based chemotherapy (followed by involved field radiotherapy to 50-54 Gy for patients with early stage disease).
• Consider high-dose chemotherapy with autologous haemopoietic stem cell transplantation as consolidation therapy for young patients with chemo-responsive tumours and poor prognostic factors (e.g. bulky local or nodal disease, advanced stage).
• Early switch to radiotherapy for patients with localised disease and poor chemotherapy response.
• Primary radiotherapy for patients with early stage disease who are unfit for chemotherapy.
Peripheral T-cell lymphoma (CD56-negative) and B-cell lymphoma
• CHOP for 3 to 6 cycles depending on stage (followed by involved field radiotherapy for patients with early stage disease; dose 40-50 Gy depending on chemotherapy response).
• Primary radiotherapy for patients with early stage disease who are unfit for chemotherapy.

Abbreviation: CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone.

patients, who remained disease-free for 45 to 187 months after salvage therapy.[3] Salvage chemotherapy has been used to treat patients with refractory or relapsed disease.[5,8] A complete response was achieved in 16% of patients with refractory disease, and a second complete response was observed in 36% of those who relapsed.[8] In another report, high-dose chemotherapy with autologous bone marrow rescue was given to three patients with relapse of nasal NK/T-cell lymphoma, and two remained in complete remission at 12 and 44 months post-transplant.[29]

TREATMENT RECOMMENDATIONS

Table 3 outlines suggested treatment approaches based on currently available information. The importance of immunophenotyping to identify NK/T-cell lymphomas which warrant intensive systemic and local therapy is emphasised. It should be noted that the optimal chemotherapy regimens and radiotherapy doses for NK/T-cell and peripheral T-cell nasal lymphomas remain unknown.

At least three retrospective studies failed to show an improved outcome for patients with early stage disease treated with combined chemotherapy and radiotherapy when compared with those treated with radiotherapy alone.[2,3,8] However, the apparent lack of benefit in these studies may be due to the use of suboptimal chemotherapy, patient selection bias, or inadequate patient numbers. In view of the potential effect of chemotherapy on both local tumour and systemic micrometastases, chemotherapy followed by local radiotherapy is a reasonable approach even in stage IE disease — provided that tumour response is carefully monitored during chemotherapy and non-responders receive early radiotherapy. This approach also allows evaluation of the efficacy of specific chemotherapy regimens.

For radiotherapy, limited data suggest that doses of 50 Gy or more are required to achieve in-field control for T- or NK-cell nasal lymphomas, when treated with radiotherapy with or without chemotherapy.[6,30]

FUTURE DIRECTIONS

Since primary nasal lymphoma is a rare disease, only prospective multicentre studies are likely to yield conclusive information. As this disease is relatively common in the Chinese population, centres in Hong Kong and China are well-placed to conduct studies.

To improve treatment outcome, prospective studies are required to identify more effective and less toxic chemotherapy and radiotherapy regimens, and the optimal combined modality approach. Known prognostic factors such as stage, the presence of extranasal extension in stage IE disease, and NK/T-cell immunophenotype, should be used to stratify patients. Cytological and molecular studies may elucidate the heterogeneity of primary nasal lymphomas, and identify more prognostic factors to guide treatment and research strategies.

To improve the efficacy of systemic treatment, investigation of the use of chemotherapeutic drugs independent of the multidrug resistance gene-related efflux pump may be useful. High-dose chemotherapy with autologous haematopoietic stem cell transplantation may also be studied as a primary therapy for patients with poor prognostic factors.[31] Immunotherapy with EBV as a target may be investigated in NK/T-cell lymphomas, as most of them contain the virus. Research on gene therapy may lead to development of treatment that can reverse multidrug resistance in this aggressive lymphoma.[32]

Radiotherapy planning for primary nasal lymphomas may be difficult because these lymphomas often encroach on such radiosensitive critical structures as the optic chiasma, optic nerves, and eyeballs,[21] and the

exact dose-tumour response relationship is unknown. Studies should be conducted to investigate the optimal treatment portal, dose, and fractionation. Technological advances may improve treatment results — for example, new imaging methods for better delineation of local tumour extent and intensity modulated radiotherapy (IMRT) for highly conformal treatment with maximal sparing of adjacent critical normal structures.

To conclude, primary nasal lymphoma remains a challenge to the oncologist and it is hoped that well-organised multi-disciplinary studies will benefit future patients.

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