Specific Soft-Tissue Invasion and LMP1 Expression Are Potential Indicators of Extranodal NK/T Cell Lymphoma, Nasal Type

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Background: Extranodal NK/T cell lymphoma, nasal type (ENKTL-NT) is difficult to distinguish from nasal polyps and inverted papilloma, leading to its high misdiagnosis ratio. The aim of this study was to investigate its potential prognostic indicators.

Material/Methods: Kaplan-Meier method was used to calculate overall survival (OS) rate. Cox proportional hazards regression was used to analyze risk ratios (ORs) with 95% confidence intervals (CIs).

Results: Nasal ala infiltration and nasal floor thickness >2.0 mm or nasal septum thickness >2.5 mm were potential prognostic factors for OS (p=0.0323 and 0.0072, respectively). Cox proportional-hazards regression indicated that high LMP1 expression and the nasal floor thickness >2.0 mm or nasal septum thickness >2.5 mm were the independent risk factors for poor OS of ENKTL-NT (HR=3.0655, p=0.028; HR=2.3650, p=0.0452, respectively). In the subgroup analysis, the OS rate was lower when the nasal floor thickness >2.0 mm or nasal septum thickness >2.5 mm in the patients who had high expression of LMP1 (p=0.0651), whereas high LMP1 expression increased the risk of worse prognostic outcome in patients with deep infiltration thickness. Thus, high LMP1 expression may contribute to the tissue invasion of ENKTL-NT.

Conclusions: Any patient with nasal ala soft-tissue invasion, nasal floor thickness >2.0 mm/nasal septum thickness >2.5 mm on CT imaging or high LMP1 expression should prompt immediate histopathologic diagnosis to rule out ENKTL-NT in clinical practice.

MeSH Keywords: Leukemia-Lymphoma, Adult T-Cell • Lymphoma, Extranodal NK-T-Cell • TNF Receptor-Associated Factor 2

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Background

Extranodal NK/T cell lymphoma is a rare and aggressive non-Hodgkin’s lymphoma, which is accompanied by poor survival [1]. It is more prevalent in Southeast Asia and in South and Central America, and is less common in Africa and Europe [2,3]. ENKTL accounts for 6–7% of all non-Hodgkin lymphoma in Southeast Asia and is associated with Epstein-Barr Virus (EBV) infection [4,5]. In addition, compared with females, males are more susceptible to ENKTL [3]. ENKTL can affect extra-nasal areas such as skin, soft tissue, and testes, as well as the gastrointestinal and upper respiratory tracts [3]. However, it resembles other destructive nasal diseases, thereby leading to the failure of diagnosis and treatment [6,7]. Thus, it is very difficult to distinguish between nasal type (ENKTL-NT) and other benign nasal diseases in clinical symptoms [6,8]. If not treated promptly, it can lead to total destruction of the nasopharyngeal region, including the midface, nasopalatine, and orbital wall. Accordingly, the diagnosis of ENKTL-NT is a challenge because of its nonspecific clinical history. Therefore, early diagnosis and treatment will help increase the overall quality of life and survival of patients with this disease [6].

Plain radiography of the paranasal sinuses is widely used in the diagnosis of paranasal sinus diseases. However, it is very limited because of the minimal information about delicate bony structures and mucosal changes of the ostiomeatal complex [9]. Computed tomography (CT) is the first imaging modality in use to differentiate sinusonal disease of the head and neck, which contributes to evaluating the size, morphology, and extent of ENKTL locally, distant metastases, and pre-treatment staging after the histopathologic diagnoses [8]. Due to its ability to display bone and soft tissues, CT is the current diagnostic modality of choice for evaluating the ostiomeatal complex, but MRI [2,10] is the first choice for detecting the extent of disease progression [11,12]. Moreover, CT is used both as a diagnostic tool to identify anatomical anomalies and mucosal pathology and to preoperatively map and guide through the challenging, convoluted, and variable anatomy of the area [13].

Epstein-Barr virus (EBV) has been recognized as a “class I cancer-causing virus” by the WHO [14]. Various lymphomas (e.g., Burkett’s lymphoma, Hodgkin’s lymphoma, Lymphoepithelioma-like carcinoma, and NK/T cell lymphoma) have been demonstrated to be associated with EBV [15]. In particular, there is a very strong relationship between EBV infection and ENKTL [16]. Multiple molecules are involved in EBV latent infection, including latent membrane protein (LMP) 1. LAMP1 regulates proliferation and invasion of lymphoma cells, playing oncogenic roles in the progression of lymphomas [17–19].

In the present study we investigated the specific prognostic indicators of ENKTL-NT by analysis of CT imaging and LMP1 expression of the patients, thereby providing valuable references for accurate clinical diagnosis of ENKTL-NT.

Material and Methods

Patients and samples

From 2010 to 2015, we enrolled 52 patients with histologically proven ENKTL-NT, 134 patients with diagnosis of nasal polyps, and 24 patients with inverted papilloma. The background data of the patients is presented in Table 1. Patients with previously untreated, histologically diagnosed disease of the nasopharynx without coexisting disease were selected. The included patients had no previous history of head and neck cancer. Informed consent was obtained from all participating patients in clinical trials. The study was conducted with approval of the Zhenjiang First People’s Hospital, Affiliated People’s Hospital of Jiangsu University’s Review Board. Biopsy tissue examination was used to diagnose of ENKTL, nasal polyps, and inverted papilloma. The staging of ENKTL was performed according to the Ann Arbor classification system [20]. Clinical history, pathological report, and CT image with report were collected and retrospectively reviewed.

Treatment of ENKTL-NT patients and the evaluation criteria of efficacy

All the ENKTL-NT patients in this study received combined CHOP regimen therapy and radiation therapy: cyclophosphamide (750 mg/m²), intravenous drip, day 1; epirubicin (80 mg/m²), intravenous drip, day 1; vincristine sulphate (1.4 mg/m²), intravenous drip, day 1; prednisone acetate (40 mg/m²), intravenous drip, days 1–5. After 2 cycles of chemotherapy, radiation therapy was administered. The radiation dose was...
The TaqMan probe sequence for LMP1 DNA was as follows: 5′-FAM-TGATCTCCTTTGGCCTCTCTGTTT-TAMRA-3′. The primer used was sense primer 5′-AAAAACTGGTGACCTCTATTG-3′; antisense primer 5′-TCGTTGAGTTGAGTCAGA-3′. The ABI 7700 Sequence Detection System was used to perform the PCR reactions. The plasmid-containing LMP1 fragment was used to run a calibration curve. The concentration (copies/ml) was calculated according to the following equation [23]:

$$C = Q \times \left(\frac{V_{DNA}}{V_{PCR}}\right) \times \left(\frac{1}{V_{ext}}\right)$$

$$V_{PCR} =$$ volume of DNA solution used for PCR; $$V_{DNA} =$$ volume of plasma extracted. Four copies/ml of LMP1 DNA level were set as the lower limits of detection for LMP1 DNA. Values below the detection limit were regarded as zero.

**CT imaging**

All patients underwent standard CT scans before treatment. The CT images were evaluated by head and neck specialist radiologists. Patients were examined with standard CT scan of the nasal, accessory nasal sinuses, and nasopharynx region in the axial and coronal planes on either of the 2 scanner machines. Parameters were as below:

I. Siemens Somatom sensation 64 (Siemens, Germany):
   - 120 kVp, 150–200 mAs, collimation of 64*0.625 mm, pitch of 0.8 and primary reconstruction of 0.4 mm, 1.5 ml/kg of intravenous contrast medium, and flow rate of 3 ml/s.
   - A 3-mm-thick axial reconstruction and a 3-mm coronal multiplanar reconstruction (MRP) were obtained with bone and soft tissue.

II. Brilliance iCT 256 slice (Philips Medical Systems, USA):
   - 120 kVp, 300 mAs, pitch of 0.391 with 100 ml of intravenous contrast medium, flow rate of 1.0 ml/s +50 mL saline flush, collimation of 256 * 0.5 mm, 3-mm axial thickness reconstruction, and 3-mm coronal thickness reconstruction.

Patients were placed in a supine position and scans were obtained parallel to the occlusal line from the hard palate to the end of the frontal sinus in paranasal sinus (PNS) setting in axial plane and coronal plane, followed by reconstruction.

**Interpretation of CT images**

CT images were retrospectively reviewed by 2 head and neck specialist radiologists in a double-blind manner. The interpretation of results included the description of tumor location (unilateral vs. bilateral nasal cavity), morphological pattern of the tumor (polypoidal vs. infiltrative lesion), tumor signal intensity (homogeneous vs. heterogeneous), bone destruction/erosion, bone sclerosis, involvement of the sinuses (maxillary, ethmoid, frontal and sphenoid), involvement of the soft-tissue and nasal vestibule, involvement of the nasopharynx and surrounding structures, and nasal turbinate and nasal septum destruction.

**LMP1 expression detection**

The blood samples from ENKTL-NT patients were collected and stored for further examinations. DNA were isolated with a QiAamp Blood kit (Qiagen, Germany) following the manufacturer’s instructions. Real-time quantitative DNA PCR for LMP1 DNA levels was carried out according to previous studies [22]. The TaqMan probe sequence for LMP1 DNA was as follows:
polyps, and inverted papilloma. There was no significant difference between ENKTL-NT vs. nasal polyp (p=0.339) and ENKTL vs. inverted papilloma (P=1.000). Bone erosion was more common in ENKTL-NT (Figure 1C) than in nasal polyps (p=0.016). Polypoidal tumor lesion was often noticed both in ENKTL-NT (Figure 1D) and inverted papilloma. Sinus involvement was found in most cases of ENKTL-NT, inverted papilloma, and nasal polyps (Figure 1E). Moreover, sinus involvement was more common in nasal polyps (p=0.025) compared to ENKTL-NT. Soft-tissue infiltration (except for infiltration of choana and nasopharynx) was the special feature for ENKTL-NT. Infiltration of nasal vestibule was most common in patients with ENKTL-NT or nasal polyps. Over half of the patients with ENKTL-NT had infiltration of nasal ala (Figure 1F), whereas minor cases were found in nasal polyps (p=0.000) and inverted papilloma (p=0.000). Some cases of nasopharyngeal wall infiltration were noticed in ENKTL-NT and nasal polyps, whereas no patients with inverted papilloma had this infiltration (p=0.05). Furthermore, 53.8% of patients with ENKTL-NT had either nasal floor thickness >2.0 mm or nasal septum thickness >2.5 mm. In contrast, 8 of 134 patients with nasal polyps and no patients with inverted papilloma had nasal mucosal thickening.

**Association between LMP1 expression and clinicopathological characteristics**

All ENKTL patients received combined chemotherapy and radiation therapy. Twenty-seven patients (51.9%) experienced CR, 27 patients (51.9%) experienced CR, and 27 patients (51.9%) experienced CR. 

**Table 2. Difference in CT imaging finding between ENKTL and nasal polyps.**

| Tumor location       | ENKTL (n=52) | Nasal polyps (n=134) | p Value |
|----------------------|--------------|----------------------|---------|
| Unilateral           | 43           | 39                   | p=0.000 |
| Bilateral            | 9            | 95                   |         |
| Tumor density        |              |                      |         |
| Heterogeneous        | 21           | 48                   | p=0.339 |
| Homogeneous          | 31           | 86                   |         |
| Bone remodeling      |              |                      |         |
| Bone sclerosis       | 8            | 13                   | p=0.305 |
| Bone erosion         | 10           | 9                    | p=0.016 |
| Tumor morphology     |              |                      |         |
| Polypoid             | 35           | 46                   | p=0.000 |
| Infiltrative         | 17           | 88                   |         |
| Sinus involvement    |              |                      |         |
| Maxillary            | 50           | 130                  | p=0.673 |
| Ethmoid              | 48           | 113                  | p=0.205 |
| Frontal              | 28           | 96                   | p=0.025 |
| Sphenoid             | 16           | 59                   | p=0.133 |
| Soft tissue infiltration |          |                      |         |
| Nasal vestibule      | 47           | 58                   | p=0.000 |
| Choana & nasopharynx | 1            | 50                   | p=0.000 |
| Nasal ala            | 28           | 2                    | p=0.000 |
| Nasopharyngeal wall  | 9            | 1                    | P=0.000 |
| Nasal floor thickness >2.0 mm or nasal septum thickness >2.5 mm | 28 | 8 | P=0.000 |
21 patients (40.4%) experienced partial remission (PR), and 4 patients (7.7%) had no response (NR) (Table 4). LMP1 is implicated in EBV-mediated invasion in lymphoma cells [25]. Thus, the expression of LMP1 was evaluated next. The expression of LMP1 was divided into 2 groups: a high LMP1 expression group and a low expression group, based on a previous study [22]: 40 copies/ml was the cut-off value to define the low (<40 copies/ml) and high (>40 copies/ml) expression. There were 29 patients with ENKTL-NT who were determined to have high LMP1 expression. IHC was conducted to further estimate the expression of LMP1 in ENKTL-NT tissues. Notably, the distribution of LMP1 was mainly located in cell membrane and cytoplasm. Furthermore, high expression of LMP1 was observed in 27 of 52 ENKTL-NT tissues (51.9%) and 48.1% presented low LMP1 expression (Figure 2A–2C). The association of LMP1 expression with the clinicopathological characteristics with ENKTL-NT patients is displayed in Table 5. No significant relationship was found between LMP1 expression and sex, age, or IPI. Poor prognosis was strongly associated with high expression of LMP1.

**Patient survival and multivariate analyses**

Kaplan-Meier analysis was used to analyze the survival rate of ENKTL-NT patients. The overall (OS) survival probability was significantly lower in patients with nasal ala infiltration, the nasal floor thickness >2.0 mm, or nasal septum thickness >2.5 mm, or high LMP1 expression (p<0.01, Figure 3A–3C).
Clinical features that were statistically significant risk factors of ENKTL-NT and poor prognosis (p<0.05) were included in the multivariate analysis. Multivariate analysis showed that high LMP1 expression and the nasal floor thickness >2.0 mm or nasal septum thickness >2.5 mm were the independent risk factors for the prognostic outcome of ENKTL-NT patients (Table 6, HR=3.0655, p=0.028; HR=2.3650, p=0.0452, respectively).

**Subgroup analysis**

In consideration of the tight relationship between LMP1 expression and tissue invasion, a subgroup analysis was performed to determine the association of LMP1 expression with nasal ala infiltration and infiltration thickness. The analysis showed that the OS was slightly lower in patients with high LMP1 expression when the nasal floor thickness was >2.0 mm or nasal septum thickness was >2.5 mm (p=0.0581, Figure 4A). There were no poor outcomes observed in patients with high LMP1 expression when the nasal ala infiltration occurred (p=0.303). On the other hand, worse prognostic outcome was noticed in patients with high LMP1 expression when the nasal floor thickness was >2.0 mm or nasal septum thickness was >2.5 mm, although the difference was not significant (p=0.0651, Figure 4B).

**Discussion**

ENKTL is the most aggressive malignant disease of the nasal cavity. It progresses rapidly and has a poor prognosis, which can only be improved by early diagnosis and early management. However, the clinical phenotype of ENKTL is very similar to nasal polyps and inverted papilloma, which are the most common benign diseases occurring in the nasopharynx [11]. Thus, the misdiagnosis rate of ENKTL-NT is extremely high [26]. Accurate clinical diagnosis is desirable for choosing timely and optimal treatment modalities. Compared to conventional plain radiography, CT scanning has become a valuable tool for diagnosing, comparing, and staging of ENKTL [14]. Many studies have pointed out that LMP1 may serve as a potential indicator for ENKTL [27–29]. Therefore, we aimed to investigate whether ENKTL can differentiate between nasal polyps and true ENKTL.

| Response to treatment | Total number of patients | Percentage (%) |
|-----------------------|--------------------------|----------------|
| CR                    | 27                       | 51.9           |
| PR                    | 21                       | 40.4           |
| NR                    | 4                        | 7.7            |

CR – complete remission; PR – partial remission; NR – no response.
and inverted papilloma arising in the nasal cavity by comparison of the CT imaging and the expression of LMP1.

In the present study, most of the lesions in ENKTL-NT were present in only 1 nasal cavity, which was similar to unilateral nasal cavity lesions found by previous studies [2,30]. Unilateral nasal cavity was also found in most cases of inverted papilloma, but the situation was the opposite in nasal polyps patients. Sclerosis and bone erosion have been observed in ENKTL [31,32]. More cases of ENKTL-NT had bone erosion, with a significant

Figure 2. (A) Negative IHC staining of adjacent normal tissue. (B) Weak IHC staining for LMP1 in ENKTL-NT samples. (C) Strong IHC staining for LMP1 in ENKTL-NT samples.
difference with nasal polyps but no significant difference with inverted papilloma. In terms of tumor morphology, about 70% of patients had a polypoidal tumor pattern in ENKTL-NT. There was a significant difference with the nasal polyps, but polypoidal pattern were also observed in many inverted papilloma patients. As for sinus involvement, ethmoid sinus was reported as the most commonly involved in ENKTL [32]. However, in the present study, maxillary sinus involvement was the most commonly involved in ENKTL-NT patients, which was identical to a previous finding [33]. There was no significant difference in

Table 5. Association of LMP1 expression with clinical features.

|                | High | Low  | χ²  |
|----------------|------|------|-----|
| Gender         |      |      |     |
| Male           | 15 (14) | 13 (14) | 1.000 (0.788) |
| Female         | 14 (13) | 10 (11) |
| Age            |      |      |     |
| ≤50            | 9 (6) | 7 (6) | 1.000 (1.000) |
| >50            | 20 (21) | 16 (19) |
| IPI            |      |      |     |
| Low/Low-intermediate | 21 (22) | 16 (19) | 0.548 (0.74) |
| High-intermediate/High | 8 (5) | 7 (6) |
| Prognosis      |      |      |     |
| Live           | 6 (5) | 16 (20) | 0.001 (<0.001) |
| Dead           | 23 (22) | 7 (5) |

Data in ”( )” were from IHC for LMP1 expression.

Table 6. Results of multivariate analyses of prognostic factors for OS in patients with ENKTL-NT.

|                          | Multivariate analysis |
|--------------------------|-----------------------|
|                          | HR (95% CI)           | p Value   |
| High LMP1 expression     | 3.0655 (1.1344 to 0.82841) | 0.028     |
| Nasal ala infiltration   | 1.1875 (0.5095 to 2.7678) | 0.692     |
| Nasal floor thickness >2.0 mm or nasal septum thickness >2.5 mm | 2.3650 (1.0229 to 5.4683) | 0.0452    |
| Nasopharyngeal wall      | 0.4520 (0.115 to 1.1708)  | 0.2565    |
| Nasal vestibule          | 1.1708 (0.2268 to 6.0438) | 0.8514    |

Figure 3. Kaplan-Meier analysis of overall survival for patients with ENKTL-NT according to nasal ala infiltration at CT imaging (A), infiltration thickness > or < at CT imaging (nasal floor thickness >2.0 mm or nasal septum thickness >2.5 mm) (B) and high/low LMP1 expression (C).
sinus involvement between ENKTL-NT and nasal polyps or inverted papilloma, but a significant difference was observed in the frontal sinus compared to nasal polyps. A major difference between ENKTL-NT and nasal polyps or inverted papilloma was noted in soft-tissue infiltration. Choana and nasopharynx infiltration was rare in ENKTL-NT patients. Higher incidence of infiltration into nasal ala and nasopharyngeal wall and the deeper infiltration thickness (nasal floor thickness >2.0 mm or nasal septum thickness >2.5 mm) were common in ENKTL-NT compared to nasal polyps or inverted papilloma. These results are supported by previous studies [33,34]. Taken together, these results confirm the aggressive features of ENKTL-NT and indicate that the soft-tissue infiltration (except from choana and nasopharynx infiltration) observed from CT imaging may predict the risk of ENKTL-NT. Moreover, as a most important oncogenic factor in EBV-induced transformation and invasion [35], the expression of LMP1 was estimated as well. The results showed that high LMP1 expression was highly associated with poor prognosis of patients with ENKTL-NT. It was previously reported that patients with nasal polyps and inverted papilloma tend to be EBV-negative [36]. It was suggested that the soft-tissue invasion may be related to the high expression of LMP1. This mechanism needs further investigation for a deeper understanding of the pathogenesis of ENKTL-NT.

There is a lack of consensus among experts in the treatment protocol of ENKTL. No therapy is considered standard and various treatment methods are used for this disease [37]. Radiotherapy is initiated for patients with localized disease [3]. Common anthracycline (called as CHOP regimen) is used for chemotherapy [38]. However, there is a significant relapse of the disease in patients receiving chemotherapy treatment, which may be due to the expression of multi-drug resistant 1 (MDR1) gene, leading to overproduction of p-glycoprotein [39]. Chemotherapy followed by radiotherapy is the best choice to decrease relapse rate [38,39], but the result is far from satisfactory. Recently, combination regimens of dexamethasone (a steroid), methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) have been tried on different relapsed or refractory cases [3]. The outcomes of this new therapy were quite remarkable. In addition, multiple therapy regimens such as Gelox [40], Gemox [41], DDGP [31], and AspaMet Dex [42] were reported. However, definitive long-term results are not yet available [39].

Kaplan-Meier survival analysis revealed that nasal ala infiltration and the nasal floor thickness >2.0 mm or nasal septum thickness >2.5 mm, or higher LMP1 expression can independently predict low overall survival rate. However, a previous study found no significant difference between LMP1 expression and prognosis in ENKTL-NT [43]. These conflicting results may be due to differences in sample origin, detection methods for LMP1, and sample size. In addition, to predict the independent risk factors of ENKTL-NT, clinical factors that were significant for OS (HR=3.0655, p=0.028; HR=2.3650, p=0.0452, respectively), ENKTL-NT patients who had high expression of LMP1, nasal ala infiltration, the nasal floor thickness >2.0 mm/nasal septum thickness >2.5 mm were independent prognostic factors for OS (p=0.028; p=0.058, respectively). ENKTL-NT patients who had high expression of LMP1, nasal ala infiltration, the nasal floor thickness >2.0 mm/nasal septum thickness >2.5 mm had higher possibility of poor OS. Although no significant difference was found and further exploration is still needed, the subgroup analysis revealed that high LMP1 expression may be related with nasal ala infiltration and deeper infiltration thickness. The distinction in CT imaging and the detection of LMP1 expression may be beneficial to the timely diagnosis for ENKTL-NT.

However, further investigations with larger samples of ENKTL-NT patients are needed to confirm our results, and it is also required to gain a better understanding of the mechanisms

**Figure 4.** (A) Kaplan-Meier analysis of overall survival for the ENKTL-NT patients with nasal floor thickness > 2.0 mm or nasal septum thickness >2.5 mm according to LMP1 expression; (B) Kaplan-Meier analysis of overall survival for the ENKTL-NT patients with high LMP1 expression according to infiltration thickness.
underlying the association of soft-tissue infiltration and clinical outcomes. In addition, MRI has a good resolution in differentiating various soft-tissue structures and also has a multiplanar scanning function [11,12,44]. It was reported that PET/CT was useful in staging and detecting ENKTL in patients that were missed by conventional staging methods [45–47]. Therefore, CT/MRI or PET/CT may be included in diagnosis and routine staging modality [11,48,49].

Conclusions

In conclusion, infiltration of nasal ala and the infiltration thickness (nasal floor thickness >2.0 mm/nasal septum thickness >2.5 mm) were the independent risk factors of ENKTL compared to nasal polyps and inverted papilloma. If any patient has these symptoms in adjacent nasal soft-tissue invasion on CT imaging, prompt histopathologic diagnosis is needed. Our study may provide an early diagnostic indicator for patients with ENKTL.

Conflict of interest

None.

References:

1. Ooi GC, Chim CS, Liang R et al: Nasal T-cell/natural killer cell lymphoma: CT and MR imaging features of a new clinicopathologic entity. Am J Roentgenol, 2000; 174(6): 1141–45
2. Ou CH, Chen CC, Ling JC et al: Nasal NK/T-cell lymphoma: Computed tomography and magnetic resonance imaging findings. J Chin Med Assoc, 2007; 70(5): 207–12
3. Al-Hakeem DA, Fedele S, Carlos R, Porter S: Extranodal NK/T-cell lymphoma, nasal type. Oral Oncol, 2007; 43(5): 4–14
4. Au WY, Ma SY, Chim CS et al: Clinicopathologic features and treatment outcome of mature T-cell and natural killer-cell lymphomas diagnosed according to the World Health Organization classification scheme: A single center experience of 10 years. Ann Oncol, 2005; 16(2): 206–14
5. Chan JK, Yip TT, Tsang WY et al: Detection of Epstein-Barr viral RNA in malignant lymphomas of the upper aerodigestive tract. Am J Surg Pathol, 1994; 18(9): 938–46
6. Miyake MM, Oliveira MW, Garcia JO, Granato L: Clinical and otorhinolaryngological aspects of extranodal NK/T-cell lymphoma, nasal type. Braz J Otorhinolaryngol, 2014; 80(4): 325–29
7. Kidwai SM, Parasher AK, Lin FY: An unusual presentation of NK/T-cell lymphoma, nasal-type in the United States. Am J Otolaryngol, 2015; 36(1): 80–83
8. Coba H, Vucinic I, Mahovne I, Vukovic-Arar Z: Extranodal lymphomas of head and neck with emphasis on NK/T-cell lymphoma, nasal type. J Craniomaxillofac Surg, 2014; 42(2): 149–52
9. Friedman I: The pathology of malignant granuloma of the nose. J Laryngol Otol, 1955; 69(5): 331–41
10. Spear GS, Walker WG Jr: Lethal midline granuloma (granuloma gangraenosum) at autopsy: report of a case and review of literature. Bull Johns Hopkins Hosp, 1956; 99(6): 313–32
11. Gu Y, Yu B, Zhang Y et al: MRI appearances of stage IE/IIIE extranodal NK/T-cell lymphoma, nasal type, in the upper aerodigestive tract. Eur Rev Med Pharmacol Sci, 2014; 18(3): 404–12
12. Liang R: Advances in the management and monitoring of extranodal NK/T-cell lymphoma, nasal type. Br J Haematol, 2009; 147(1): 13–21
13. Lopes De Faria J, Cutin M et al: Malignant granuloma of the face; Contribution to its nosology. AMA Arch Otolaryngol, 1957; 65(3): 255–62
14. Listed N: Proceedings of the IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Epstein-Barr Virus and Kaposi’s Sarcoma Herpesvirus/Human Herpesvirus 8. Lyon, France, 17–24 June 1997. Iarc Monographs on the Evaluation of Carcinogenic Risks to Humans, 1997; 70: 1
15. Uner A, Akyurek N, Saglam A et al: The presence of Epstein-Barr virus (EBV) in diffuse large B-cell lymphomas (DLBCLs) in Turkey: Special emphasis on ‘EBV-positive DLBCL of the elderly’. PMIS, 2011; 119(4–5): 309–16
16. Takahashi E, Ohshima K, Kimura H et al: Clinicopathological analysis of the age-related differences in patients with Epstein-Barr virus (EBV)-associated extranasal natural killer (NK)/T-cell lymphoma with reference to the relationship with aggressive NK cell leukaemia and chronic active EBV infec. Histopathology, 2011; 59(4): 660–71
17. Kieff E: Epstein-Barr virus and its replication. Fields Virology, 2001: 2343–96
18. Shair KH, Bendit KM, Edwards BH et al: EBV latent membrane protein 1 activates Akt, NFkappaB, and Stat3 in B cell lymphomas. PLoS Pathog, 2007; 3(1): e166
19. Vrzalkova K, Vockerodt M, Leonard S et al: Down-regulation of BLIMP1 by the EBV oncogene, LMP-1, disrupts the plasma cell differentiation program and prevents viral replication in B cells: Implications for the pathogenesis of EBV-associated B-cell lymphomas. Blood, 2011; 117(22): 5907–17
20. Carbone PP, Kaplan HS, Musshoff K et al: Report of the Committee on Hodgkin’s Disease Staging Classification. Cancer Res, 1971; 31(1): 1860–61
21. Johnson SA, Kumar A, Matasar MJ et al: Imaging for staging and response assessment in lymphoma. Radiology, 2015; 276(2): 323–38
22. Ishii H, Ogino T, Berger C et al: Clinical usefulness of serum EBV DNA levels for evaluating the response to chemotherapy in nasal type NK/T-cell lymphoma. J Med Virol, 2007; 79(5): 562–72
23. Lo YM, Chan LY, Chan AT et al: Quantitative and temporal correlation between circulating cell-free Epstein-Barr virus DNA and tumor recurrence in nasopharyngeal carcinoma. Cancer Res, 1999; 59(2): 5452–55
24. Mao Y, Zhang DW, Zhu H et al: LMP1 and LMP2A are potential prognostic markers of extranodal NK/T-cell lymphoma, nasal type (ENKTL). Diagn Pathol, 2012; 7(1): 178
25. Yang QX, Pei X, Tian XY et al: Secondary cutaneous Epstein-Barr virus-associated diffuse large B-cell lymphoma in a patient with angioimmunoblastic T-cell lymphoma: A case report and review of literature. Diagn Pathol, 2012; 7: 7
26. Wu X, Li P, Zhao J et al: A clinical study of 115 patients with extranodal natural killer/T-cell lymphoma, nasal type. Clin Oncol, 2008; 20(8): 619–25
27. Yuan M, Zhang DW, Zhu H et al: LMP1 and LMP2A are potential prognostic markers of extranodal NK/T-cell lymphoma, nasal type (ENKTL). Diagn Pathol, 2012; 7: 178
28. Shi C, Yang X, Ni Y et al: High Rab27A expression indicates favorable outcome in patients with extranodal NK/T-cell lymphoma-NT. PLoS One, 2013; 8(9): e76120
29. Wang TS, Hu Q, Shao S et al: LMP1 and LMP2A overexpression is associated with more aggressive clinical features and worse survival in patients with nasal type extranodal NK/T-cell lymphoma. Oncotarget, 2017; 8(14): 23105–16
30. Mao Y, Zhang DW, Zhu H et al: LMP1 and LMP2A are potential prognostic markers of extranodal NK/T-cell lymphoma, nasal type (ENKTL). Diagn Pathol, 2012; 7: 178
31. Quintanilla-Martinez L, Franklin JL, Guerrero I et al: Histological and immunophenotypic profile of nasal NK/T-cell lymphomas from Peru: High prevalence of p53 overexpression. Hum Pathol, 1999; 30(7): 849–55

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32. Au WY, Weisenburger DD, Intragumtornchai T et al: Clinical differences between nasal and extranasal natural killer/T-cell lymphoma: A study of 136 cases from the International Peripheral T-Cell Lymphoma Project. Blood, 2009; 113(17): 3931–37
33. International Non-Hodgkin's Lymphoma Prognostic Factors Project: A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med, 1993; 329(14): 987–94
34. Barrionuevo C, Zaharia M, Martinez MT et al: Extranodal NK/T-cell lymphoma, nasal type: Study of clinicopathologic and prognosis factors in a series of 78 cases from Peru. Appl Immunohistochem Mol Morphol, 2007; 15(1): 38–44
35. Takahashi E, Ohshima K, Kimura H et al: Clinicopathological analysis of the age-related differences in patients with Epstein-Barr virus (EBV)-associated extranasal natural killer (NK)/T-cell lymphoma with reference to the relationship with aggressive NK cell leukemia and chronic active EBV infection-associated lymphoproliferative disorders. Histopathology, 2011; 59(4): 660–71
36. Sham CL, To KF, Chan PK et al: Prevalence of human papillomavirus, Epstein-Barr virus, p21, and p53 expression in sinonasal inverted papilloma, nasal polyp, and hypertrophied turbinate in Hong Kong patients. Head Neck, 2012; 34(4): 520–33
37. Kohrt H, Advani R: Extranodal natural killer/T-cell lymphoma: Current concepts in biology and treatment. Leuk Lymphoma, 2009; 50(11): 1773–84
38. Li YX, Fang H, Liu QF et al: Clinical features and treatment outcome of nasal-type NK/T-cell lymphoma of Waldeyer ring. Blood, 2008; 112(8): 3057–64
39. Kwong YL: The diagnosis and management of extranodal natural killer/T-cell lymphoma: A case with nasal involvement. Diagn Pathol, 2017; 12(1): 46
40. Wu HB, Wang QS, Wang MF et al: Utility of 18F-FDG PET/CT for staging NK/T-cell lymphomas. Nucl Med Commun, 2010; 31(3): 195–200
41. Wu LM, Chen FY, Jiang XX et al: 18F-FDG PET, combined FDG-PET/CT and MRI for evaluation of bone marrow infiltration in staging of lymphoma: A systematic review and meta-analysis. Eur J Radiol, 2012; 81(2): 303–11
42. Fujiwara H, Maeda Y, Nawa Y et al: The utility of positron emission tomography/computed tomography in the staging of extranodal natural killer/T-cell lymphoma. Eur J Haematol, 2011; 87(2): 123–29
43. Gao X, Li B, You Q, Peng X: Primary extranodal marginal zone B-cell lymphoma with diffuse uveal involvement and focal infiltration of the trabecular meshwork: A case report and review of literature. BMC Ophthalmol, 2015; 15: 48
44. Quintanilla-Martinez L, Kremer M, Keller G et al: p53 Mutations in nasal natural killer/T-cell lymphoma from Mexico: Association with large cell morphology and advanced disease. Am J Pathol, 2001; 159(6): 2095–105
45. Hongyo T, Hoshida Y, Nakatsuka S et al: p53, K-ras, c-kit and beta-catenin gene mutations in sinonasal NK/T-cell lymphoma in Korea and Japan. Oncol Rep, 2005; 13(2): 265–71
46. Zhao S, Liu WP, Zhang WY, Li GD: Extranodal nasal type NK/T-cell lymphoma: the expression of Epstein-Barr virus latent membrane protein 1 and its significance of prognosis. Journal of Sichuan University (Medical Sciences Edition), 2005; 36(3): 338 [in Chinese]
47. Jin X, Xu Y, Zhang J et al: Aggressive natural killer cell leukemia or extranodal NK/T-cell lymphoma? A case with nasal involvement. Diagn Pathol, 2017; 12(1): 46