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## Extranodal nasal-type NK/T-cell lymphoma of the palate and paranasal sinuses

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### Summary

#### Background:

Extranodal nasal-type natural killer (NK)/T-cell lymphoma represents a rare entity, typically originating in the nasal cavity, palate or midfacial region. Signs and symptoms include non-specific rhinitis and/or sinusitis, nasal obstruction, epistaxis, facial swelling and development of deep necrotic ulceration in the midline of the palate, causing an oronasal defect. Differential diagnosis includes fungal infections, Wegener's granulomatosis, tertiary syphilis, other non-Hodgkin's lymphomas and malignant epithelial midline tumors.

#### Case Report:

We present a case of a 40-year-old man complaining of headache, facial pain, nasal congestion and fever. Examination revealed a large deep necrotic ulcer in the middle of the palate, presenting as an oronasal defect. Endoscopic rhinoscopy revealed crusts in the nasal cavities, moderate perforation of the nasal septum cartilage and contraction of the middle and inferior conchae. Computer tomography showed occupation of the maxillary sinuses, ethmoidal cells and sphenoidal sinus by a hyperdense soft tissue mass. Laboratory investigation revealed increased erythrocyte sedimentation rate. A wide excision of the lesion was performed. Histopathological and immunohistochemical evaluation established the diagnosis of extranodal nasal-type NK/T-cell lymphoma. The patient was treated with CHOP chemotherapy, involved-field radiotherapy and autologous bone marrow transplantation. A removable partial denture with obturator was fabricated and inserted to relieve problems caused by the oronasal defect.

#### Conclusions:

Extranodal nasal-type NK/T-cell lymphoma is a very aggressive, rapidly progressing malignant neoplasm with a poor prognosis, which can be improved by early diagnosis and combined treatment.

#### key words:

**extranodal NK/T-cell lymphoma • oral midline malignant tumors**

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## BACKGROUND

Extranodal nasal-type NK/T-cell lymphoma represents a rare malignant entity, characterized by progressive and relentless destruction of the affected tissues. Typically, this type of lymphoma originates in the nasal cavity, the palate or midfacial region. Its main characteristics are vascular invasion and destruction, accompanied by unremitting destruction of the midline structures of the palate and nasal fossa [1–3]. The exact etiopathogenesis of these tumors remains unknown. Nevertheless, Epstein-Barr virus (EBV) is demonstrated in practically all extranodal nasal-type NK/T-cell lymphomas, suggesting an important pathogenetic role [4–6].

Extranodal nasal-type NK/T-cell lymphoma is very rare in industrialized Western populations, with an estimated prevalence of 0.4–2.2% of all non-Hodgkin's lymphomas (NHL). It is more common in Asia and Central and South America, accounting for 6–7% of all NHLs. The median

age of patients is 53, with a wide range of 3 to 94 years and a male-to-female ratio of approximately 3:1 [1,3].

The initials signs and symptoms of this entity are often localized to the nasal region. Patients often complain of pain and present with non-specific rhinitis and/or sinusitis and nasal obstruction, while in later stages epistaxis and facial swelling can occur [7,8]. Other clinical features include swelling of the soft palate or posterior hard palate [9–11]. Further progression of the lesion can lead to the formation of a deep necrotic ulceration in the midline of the palate, which enlarges and destroys the palatal tissues, creating an oronasal fistula. This type of lymphoma can lead to painful midfacial destruction. The lesion may be secondarily infected, complicating the course of the disease, and life-threatening hemorrhage is a possible significant complication in some cases [9–11].

The aim of this report is to present a case of extranodal nasal-type NK/T-cell lymphoma, emphasizing its clinical and histopathological differential diagnosis, treatment and maxillofacial prosthodontic rehabilitation of the patient.

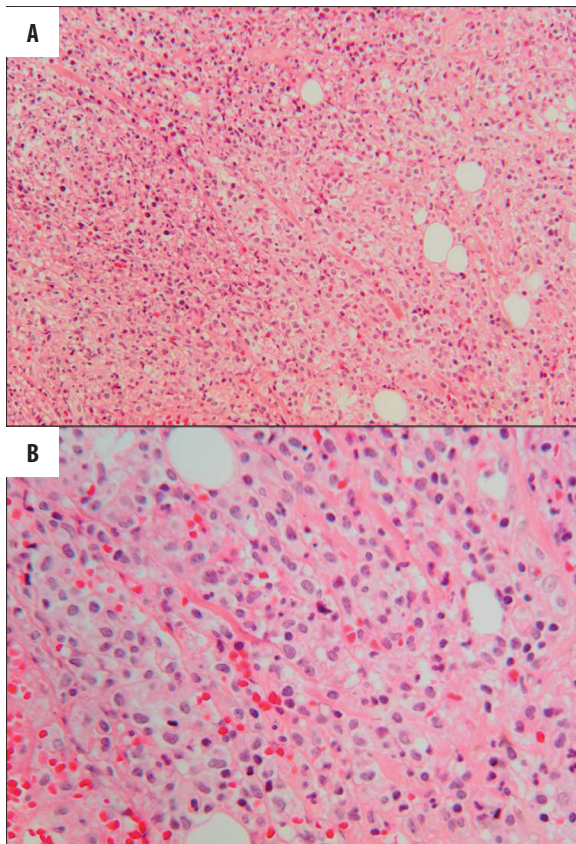
## CASE REPORT

In September 2004, a 40-year-old Greek man was referred to the otorhinolaryngology clinic of the University of Patras, Greece complaining of headache (temporal and occipital), facial pain, nasal congestion and fever. Examination revealed a deep necrotic elliptical ulcer measuring 6x4 cm in the middle of the palate, creating an oronasal defect. The lesion was fetid and hemorrhagic. Endoscopic rhinoscopy revealed yellow fetid crusts in the nasal cavities, moderate perforation of the nasal septum cartilage and contraction of the middle and inferior conchae.

The patient was initially treated with ciprofloxacin and metronidazole. Because of fever elevation and after examination



**Figure 1.** Computed tomography showing occupation of the maxillary sinuses, ethmoidal cells and sphenoidal sinus by a hyperdense soft tissue mass. (A) Coronal plane. (B) Sagittal plane. (C) Axial plane.



**Figure 2.** Photomicrographs demonstrating a dense polymorphous cellular infiltrate consisting of small and medium-sized lymphocytes with atypical nuclear characteristics (irregular nuclear outline and absence of nucleoli), abundant reactive macrophages, plasma cells, neutrophils, eosinophils and new blood vessels. (Hematoxylin and Eosin, (A) 100 $\times$ , (B) 200 $\times$ ).

by an infectious disease specialist, antibiotic treatment was modified to IV teicoplanin and meropenem. Laboratory investigation revealed increased erythrocyte sedimentation rate. White blood cell count, platelets, PT and PTT were within reference rates and the patient was found to be HIV-negative. A computed tomography (CT) scan was performed, showing occupation of the maxillary sinuses, ethmoidal cells and sphenoidal sinus by a hyperdense soft tissue mass (Figure 1).

A biopsy of the lesion was performed and histopathologic examination revealed extensive necrosis with abundant fungal and bacterial colonies. Non-necrotized segments showed extensive ulceration of the covering epithelium and a dense polymorphous infiltration consisting of lymphoid cells such as small and medium-sized lymphocytes with atypical nuclei characteristics (irregular nuclear outline and absence of nucleoli), abundant reactive macrophages, plasma cells, new blood vessels, neutrophils and eosinophils (Figure 2). This infiltrate showed focal necrosis and apoptotic activity and appeared to extend among the surrounding mucous glands. Necrosis and infiltration of small capillary and larger blood vessels by the cellular infiltrate was prominent.

Immunohistochemical analysis (Table 1) revealed that the atypical lymphoid cells were positive for the T-cell markers

**Table 1.** Immunochemical analysis.

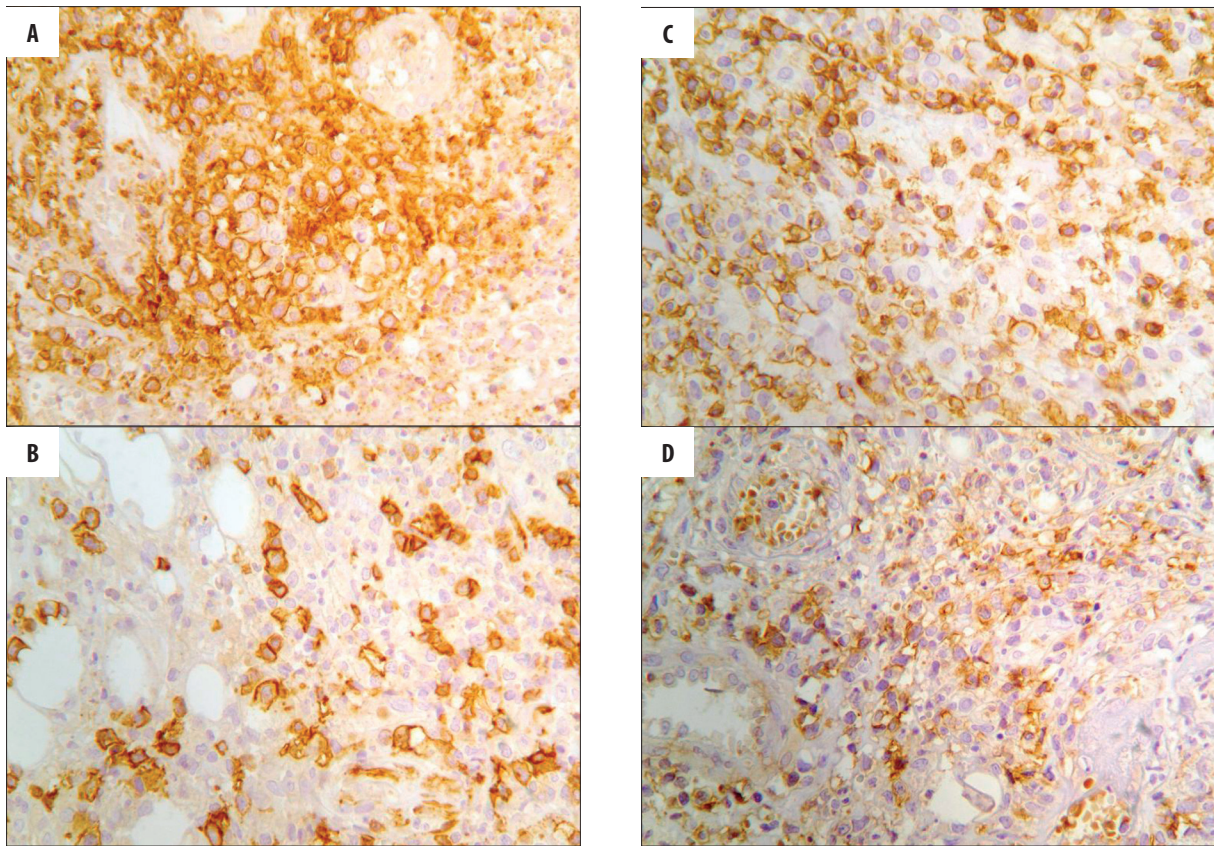
	Positive	Negative
B-cell markers		
L26		✓
CD10		✓
CD23		✓
T-cell markers		
CD2	✓	
CD3		✓
CD4		✓
CD5		✓
CD7	✓	
CD8		✓
CD43	✓	
NK-cell markers		
CD56	✓	
Granzyme B	✓	
Perforin	✓	
Monocytes markers		
PGM1	✓	
Other markers		
CD30		✓
Fas (CD95)	✓	
LMP1	✓	
Bcl - 2		✓
Ki67	✓	

CD43, CD2 and CD7, and many of these cells were also positive for the NK-cell markers CD56, perforin and granzyme B, as well for EBV LMP1 and CD95 (Figure 3). Small lymphocytes detected at the periphery of the lesion were positive only for T-cell markers. A high proportion of neoplastic cells were Ki67-positive. A final diagnosis of extranodal nasal-type NK/T-cell lymphoma was rendered.

Thorough clinical and imaging examination ruled out the presence of other site involvement. Initial treatment consisted of surgical debulking of the tumor for functional purposes, including sinus trephination, intranasal ethmoidectomy, sphenoidectomy, frontal sinus trephination and extensive nasal cavity debridement. The patient was treated with 6 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy, repeated every 2 weeks. Following chemotherapy, he received radiotherapy (4000 cGY in total) followed by autologous bone marrow transplantation.

Thirty months after treatment, a removable partial denture with obturator was fabricated and inserted to relieve





**Figure 3.** Immunohistochemical analysis. The neoplastic lymphocytes are positive for the T-cell markers CD43 (A), CD2 (B) and CD7 (C), as well as for the NK cell marker CD56 (D).

problems of regurgitation of food and fluids into the nasal cavity caused by the oronasal fistula (Figure 4). During a 5-year follow-up period, no recurrence was noted.

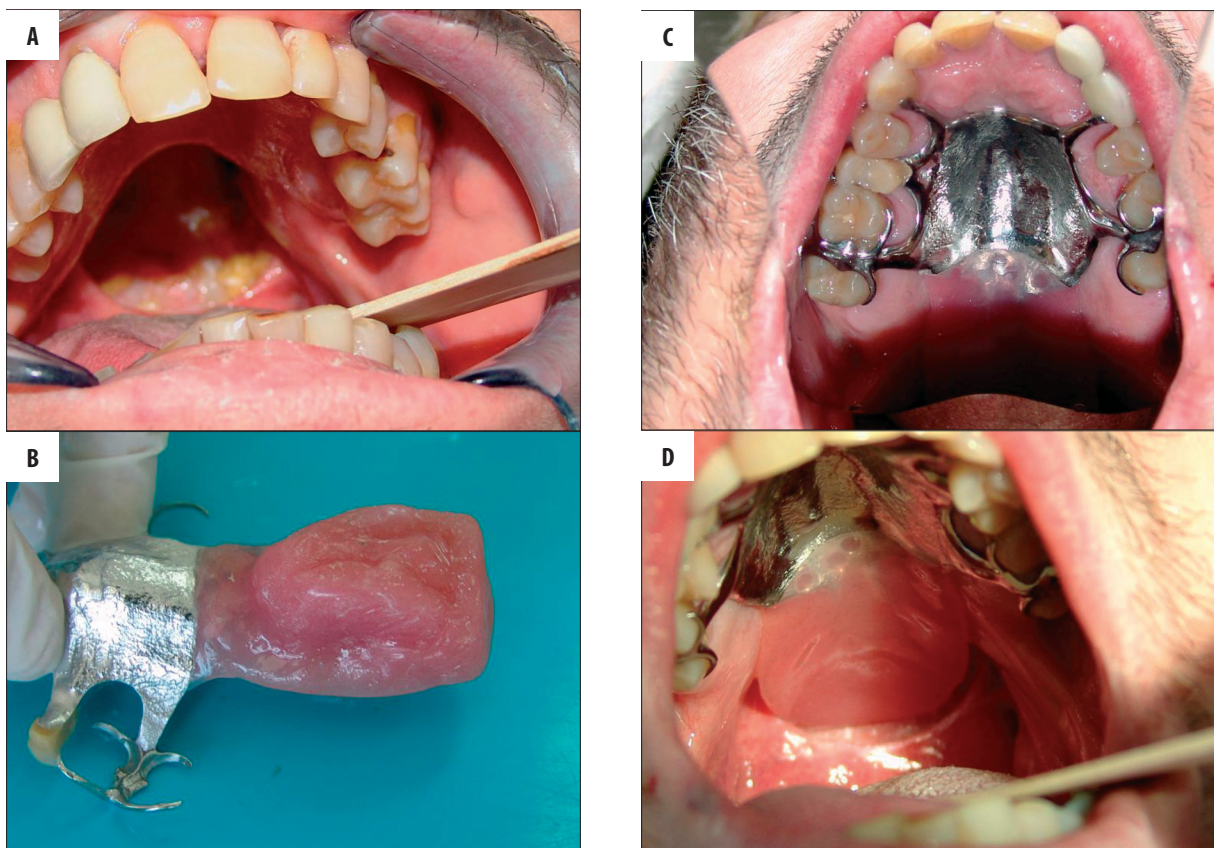
## DISCUSSION

Extranodal nasal-type NK/T-cell lymphoma was recognized as a distinct clinicopathological entity by the International Lymphoma Study Group and was included in the latest classification of lymphoproliferative diseases by the World Health Organization [12–15]. This tumor was previously known as lethal midline granuloma, polymorphic reticulosis, or midline malignant reticulosis, reflecting the uncertainty about its origin [1,7]. Recently, there has been an effort to classify extranodal NK/T cell lymphomas into subtypes due to their clinical heterogeneity, treatment outcomes and prognosis [16,17].

Extranodal nasal-type NK/T-cell lymphoma demonstrates a characteristic geographical distribution, with predominance in Asia and Central and South America, whereas it is rare in industrialized Western populations [18]. This distinctive racial pattern may to some extent imply genetic factors, but is also closely associated with high incidence of infection by EBV [4]. This fact and the detection of EBV genome in practically all studied nasal NK/T-cell lymphomas suggests that EBV infection plays an important role in the pathogenesis of this type of lymphoma [5,8]. It appears that chronic active EBV infection is a borderline condition with a high risk of evolution into aggressive NK/T-cell lymphoma [6].

The term ‘nasal-type’ is used to emphasize the predominant but not exclusive site of involvement. Other sites of spreading include maxillary sinus, nasopharynx, oropharynx, palate, oral cavity, hypopharynx and tonsils; however, it may also affect other sites, such as skin, gastrointestinal tract, larynx, testicles, liver, spleen, central nervous system, and even lymph nodes [19–21].

Differential diagnosis includes deep fungal infections, Wegener’s granulomatosis, tertiary syphilis, cocaine abuse, other non-Hodgkin’s lymphomas and malignant epithelial midline tumors [11]. Disseminated deep fungal infection is found in severely immunocompromised patients. In our case, there were no signs, history or blood laboratory test results suggestive of compromised immunity. Oral manifestations of Wegener’s granulomatosis, in addition to destructive midline lesions, include florid-granular hyperplasia of gingiva with hemorrhage, known as strawberry gingivitis, relatively superficial ulcerations and enlargement of 1 or more major salivary glands. Typical manifestations of upper or lower respiratory system and renal involvement as well as appropriate laboratory investigations (notably c-ANCA positivity) point to the correct diagnosis. In cases of tertiary syphilis, a positive history of previously diagnosed disease or an anamnesis of typical signs and symptoms of the primary and secondary stages, such as chancre, regional lymphadenopathy, mucous patches, rosette and syphilitic plaques, would raise suspicion. History of cocaine abuse should be evaluated. Finally, other midline malignant tumors such as carcinoma of the maxillary sinus, sinonasal



**Figure 4.** Removable partial denture with obturator was fabricated to relieve functional problems caused by the oronasal defect. (A) A 6×4cm postoperative oronasal defect creating problems of regurgitation of food and fluids into the nasal cavity. (B) Removable partial denture with obturator. (C and D) Insertion of the partial denture in the maxilla and the oronasal defect.

undifferentiated carcinoma and nasopharyngeal carcinoma could be possible and would be ruled out on the basis of specific microscopic features.

Considering that early clinical signs and symptoms are not specific, histological and immunohistochemical evaluation of the lesion is crucial in order to establish the diagnosis. Wu et al reported a misdiagnosis rate of 44% in their clinical study of 115 patients with extranodal NK/T cell lymphomas; in 22.5% of these cases, 3 or more biopsies were needed to reach the correct diagnosis [1]. Possible explanations for the difficulties in the microscopic diagnosis of these tumors include their tendency for angioinvasion and angiodestruction, causing vascular occlusion, massive tissue necrosis and secondary infections, so that collection of adequate tumor tissue becomes challenging [22]. It is characteristic that in the case presented here biopsy material consisted mainly of necrotized tissues segments including abundant fungal and bacteria colonies. Therefore, multiple biopsies are advised for confirmation when a neoplastic process is clinically suspected.

Histopathologic features show a dense polymorphous infiltrate of inflammatory cells, often arranged around blood vessels (angiocentricity). This infiltrate consists of atypical lymphoid cells of a broad-pleomorphic cytological spectrum, such as large, small or medium-sized cells, admixed with other inflammatory cells such as reactive lymphocytes, histiocytes, plasma cells and, more rarely, eosinophils and

neutrophils. The cell infiltrate invades and destroys existing structures in the area, noticeably causing vascular invasion and occlusion and tissue necrosis [11,19].

Immunohistochemical evaluation reveals tumor cells expressing both NK cell-related marker CD56 and some T-cell-related antigens such as CD2, CD7, CD8, CD43 and cytoplasmic CD3, while surface CD3 and the NK markers CD16 and CD57 are negative. Cytotoxic granule-associated proteins granzyme B and perforin are also expressed. CD54 shows lower expression on primary cutaneous cases compared to other primary affected sites [23–25]. The tumor has a predominant EBV+ phenotype in about 85% of patients [25].

Staging of the disease, similar to NHLs, is based on the results of peripheral blood count and smear, liver function tests, chest radiography, and CT scans of the skull, chest and abdomen. Ultrasonography of the kidneys, bone marrow biopsy and bone scan may also be needed [2]. In general, Ann Arbor staging and International Prognostic Index have limitations and their prognostic value remains unclear [26–29].

Today, there is no consensus regarding the optimal treatment for extranodal nasal-type NK/T-cell lymphoma. Despite diagnostic advantages, the rarity of the tumor and the absence of large randomized controlled trials have hindered therapeutic progress, as is reflected by the poor overall survival rates [1,30]. The mechanisms of extranodal nasal-type NK/T-cell lymphoma resistance to conventional



chemotherapy are not fully understood, but might be due to P-gp expression by lymphoma cells, which is responsible for multidrug resistance [31]. The mainstay of treatment is the combination of locoregional radiotherapy and CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy, with better results than radiotherapy alone [1]. Autologous hematopoietic stem cell transplantation (HSCT) seems to confer a survival benefit in patients who attained complete remission as post-remission consolidation therapy [32]. Localized NK/T-cell lymphomas often respond to radiotherapy, which, however, is not effective against extensive disease or relapses [33]. L-asparaginase-containing therapies seem to be effective in refractory extranodal nasal-type NK/T-cell lymphoma and should be considered as a salvage treatment, especially for patients with disseminated disease [34,35]. The role of surgery is limited in gaining biopsic material and tumor debulking for functional purposes [1,16]. In case of oronasal fistulas/defects, an obturator can be fabricated and inserted to relieve the problem of regurgitation of food and fluids into the nasal cavity, improving speech, food intake and quality of life [36–39].

This type of lymphoma is extremely aggressive in comparison to B-cell NHL and anaplastic T-cell lymphomas [28]. Patients with extranodal nasal-type NK/T-cell lymphoma show significantly lower survival rates than patients with mucosa-associated lymphoid tissue (MALT) lymphoma, follicular lymphoma, or diffuse large B-cell lymphomas. Prognosis depends upon whether the disease is small and confined to the nasal area as opposed to disseminated disease [30]. Variables associated with poor survival include B symptoms (defined as unexplained fever with temperature above 38°C, night sweats, and unexplained weight loss of more than 10% of the usual body weight in the 6 months before diagnosis), advanced stage, elevated lactate dehydrogenase (LDH), and regional lymph node invasion [36]. It appears that locoregional and systemic disease recurrence is more likely in patients with angiocentric lymphomas of the head and neck, positive for granzyme B. These patients also have a lower survival rate [23]. Molecular markers may also be related to prognosis; CD56 positivity increases the risk of metastasis and tumor spreading.<sup>1</sup> Furthermore, Ki67 and COX2 high expression levels are correlated with lower survival rates [26,27].

The 5-year overall survival rate reported in the literature ranges from 10% to 60% and the majority of the progression, presenting as locoregional and distant relapse, occurs within 2 years [36,37].

## CONCLUSIONS

Extranodal nasal-type NK/T-cell lymphoma represents a rare clinico-pathological entity. It is very aggressive, it progresses rapidly and has a poor prognosis, which can be improved by early diagnosis and treatment. Considering the non-specific nature of the early clinical signs and symptoms, histological and immunohistochemical evaluation of the lesion is crucial to diagnosis. The mainstay of therapy is a combination of locoregional radiotherapy and CHOP chemotherapy. Additionally, autologous hematopoietic stem cell transplantation can be performed. Prosthetic treatment of possible oronasal fistulas/defects can significantly improve the patient's quality of life.

## REFERENCES:

1. 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 (R Coll Radiol)*, 2008; 20: 619–25
2. Tsang WM, Tong AC, Lam KY et al: Nasal T/NK cell lymphoma: report of 3 cases involving the palate. *J Oral Maxillofac Surg*, 2000; 58: 1323–27
3. Meng W, Zhou Y, Zhang H et al: Nasal-type NK/T-cell lymphoma with palatal ulcer as the earliest clinical manifestation: a case report with literature review. *Pathol Oncol Res*, 2010; 16: 133–37
4. Arber DA, Weiss LM, Albujaq PF et al: Nasal lymphomas in Peru, high incidence of T-cell immunophenotype and Epstein-Barr virus infection. *Am J Surg Pathol*, 1993; 17: 392–99
5. Ott G, Kalla J, Ott MM et al: The Epstein-Barr virus in malignant non-Hodgkin's lymphoma of the upper aerodigestive tract. *Diagn Mol Pathol*, 1997; 6: 134–39
6. Ohtsuka R, Abe Y, Sada E et al: Adult patient with Epstein-Barr virus (EBV)-associated lymphoproliferative disorder: chronic active EBV infection or *de novo* extranodal natural killer (NK)/T-cell lymphoma, nasal type? *Intern Med*, 2009; 48: 471–74
7. Rodrigo JP, Suárez C, Rinaldo A: Idiopathic midline destructive disease: fact or fiction. *Oral Oncol*, 2005; 41: 340–48
8. Ketharanathan N, van Kipshagen PJ, Vasmel W et al: T/NK cell lymphoma presenting as a "blocked nose". *Eur Arch Otorhinolaryngol*, 2008; 265: 1131–34
9. Takahashi E, Asano N, Li C et al: Nodal T/NK-cell lymphoma of nasal type: a clinicopathological study of six cases. *Histopathology*, 2008; 52: 585–96
10. Huang KJ, Wang LF, Lee KW et al: Sinonasal NK/T-cell lymphoma with upper gastrointestinal bleeding: a case report. *Kaohsiung J Med Sci*, 2003; 19: 639–43
11. Neville B, Damm D, Allen C, Bouquot J: *Oral and Maxillofacial Pathology*. 3<sup>rd</sup> ed. Saunders Elsevier, St.Louis, 2009: 602–4
12. Jaffe ES, Chan JK, Su JJ et al: Report of the workshop on nasal and related extranodal angiocentric T/natural killer cell lymphomas. Definitions, differential diagnosis, and epidemiology. *Am J Surg Pathol*, 1996; 20: 103–11
13. Harris NL, Jaffe ES, Stein H et al: A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood*, 1994; 84: 1361–92
14. Jaffe ES, Harris NL, Stein H et al: Tumours of haematopoietic and lymphoid tissues. World Health Organization classification of tumours. Lyon: IARC, 2001; 204–7
15. Swerdlow SH, Campo E, Harris NL et al: World Health Organization classification of tumours of haematopoietic and lymphoid tissues. Lyon: IARC, 2008; 285–88
16. Kim TM, Heo DS: Extranodal NK/T-cell lymphoma, nasal type: New staging system and treatment strategies. *Cancer Sci*, 2009; 100: 2242–48
17. Li YX, Liu QF, Fang H et al: Variable clinical presentations of nasal and Waldeyer ring natural killer/T-cell lymphoma. *Clin Cancer Res*, 2009; 15: 2905–12
18. Aozasa K, Takakuwa T, Hongyo T et al: Nasal NK/T-cell lymphoma: epidemiology and pathogenesis. *Int J Hematol*, 2008; 87: 110–17
19. Greer JP, Mosse CA: Natural killer-cell neoplasms. *Curr Hematol Malig Rep*, 2009; 4: 245–52
20. Yang C, Ma J, Yang X et al: Natural killer/T-cell nasal-type lymphoma: unusual primary spinal tumor. *Spine*, 2008; 33: 929–32
21. Tardío JC, Moreno A, Pérez C et al: Primary laryngeal T/NK-cell lymphoma, nasal-type: an unusual location for an aggressive subtype of extranodal lymphoma. *Eur Arch Otorhinolaryngol*, 2008; 265: 705–8
22. Kim TM, Lee SY, Jeon YK et al: Clinical heterogeneity of extranodal NK/T-cell lymphoma, nasal type: a national survey of the Korean Cancer Study Group. *Ann Oncol*, 2008; 19: 1477–84
23. Kim GE, Yang WI, Lee S et al: The significance of granzyme B expression in patients with angiocentric lymphoma of the head and neck. *Cancer*, 2001; 91: 2343–52
24. Au WY, Pang A, Choy C et al: Quantification of circulating Epstein-Barr virus (EBV) DNA in the diagnosis and monitoring of natural killer cell and EBV-positive lymphomas in immunocompetent patients. *Blood*, 2004; 104: 243–49
25. Schwartz EJ, Molina-Kirsch H, Zhao S et al: Immunohistochemical Characterization of Nasal-Type Extranodal NK/T-Cell Lymphoma Using a Tissue Microarray. An Analysis of 84 Cases. *Am J Clin Pathol*, 2008; 130: 343–51

26. Kim SJ, Kim BS, Choi CW et al: Ki-67 expression is predictive of prognosis in patients with stage III extranodal NK/T-cell lymphoma, nasal type. *Ann Oncol*, 2007; 18: 1382–87
27. Shim SJ, Yang WI, Shin E et al: Clinical significance of cyclooxygenase-2 expression in extranodal natural killer (NK)/T-cell lymphoma, nasal type. *Int J Radiat Oncol Biol Phys*, 2007; 67: 31–38
28. Lee SY, Park K, Ryou BR et al: Korean multicenter study of extranodal NK/T-cell lymphoma: failure of Ann Arbor staging in predicting prognosis. *Int J Hematol*, 2002; 76: 27
29. Kim TM, Park YH, Lee SY et al: Local tumor invasiveness is more predictive of survival than International Prognostic Index in stage I(E)/II(E) extranodal NK/T-cell lymphoma, nasal type. *Blood*, 2005; 106: 3785–90
30. Greer JP: Therapy of peripheral T/NK neoplasms. *Hematology*, 2006: 331–37
31. Yamaguchi M, Kita K, Miwa H et al: Frequent expression of P-glycoprotein/MDR1 by nasal T-cell lymphoma cells. *Cancer*, 1995; 76: 2351–56
32. Lee J, Au WY, Park MJ et al: Autologous hematopoietic stem cell transplantation in extranodal natural killer/T cell lymphoma: a multinational, multicenter, matched controlled study. *Biol Blood Marrow Transplant*, 2008; 14: 1356–64
33. Isobe K, Uno T, Tamaru J et al: Extranodal natural killer/T-cell lymphoma, nasal type: the significance of radiotherapeutic parameters. *Cancer*, 2006; 106: 609–15
34. Yong W, Zheng W, Zhang Y et al: L-asparaginase-based regimen in the treatment of refractory midline nasal/nasal-type T/NK-cell lymphoma. *Int J Hematol*, 2003; 78: 163–67
35. Jaccard A, Petit B, Girault S et al: L-Asparaginase-based treatment of 15 western patients with extranodal NK/T-cell lymphoma and leukemia and a review of the literature. *Ann Oncol*, 2009; 20: 110–16
36. Lee J, Suh C, Park YH et al: Extranodal natural killer T-cell lymphoma, nasal-type: a prognostic model from a retrospective multicenter study. *J Clin Oncol*, 2006; 24: 612–18
37. Zhang XX, Xie CH, Xu Y et al: Salvage Treatment Improved Survival of Patients with Relapsed Extranodal Natural Killer/T-Cell Lymphoma, Nasal Type. *Int J Radiat Oncol Biol Phys*, 2009; 74: 747–52
38. Jewers WM, Rawal YB, Allen CM et al: Palatal perforation associated with intranasal prescription narcotic abuse. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, 2005; 99: 594–97
39. Serrano-Sánchez P, Bagán JV, Jiménez-Soriano Y et al: Palatal perforations secondary to inhaled cocaine abuse. Presentation of five cases. *J Clin Exp Dent*, 2010; 2: 105–9