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Primary natural killer/T-cell lymphomas of the oral cavity are aggressive neoplasms

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Abstract Thirty-four cases of primary non-Hodgkin's lymphoma of the oral cavity were investigated for their clinical findings, histopathological features, immunophenotypes and association with Epstein-Barr virus (EBV). Four cases (12%) were natural killer/T-cell lymphomas, 3 (9%) were T-cell lymphomas and 27 (79%) were B-cell lymphomas. Compared with T- and B-cell lymphomas, NK/T-cell lymphomas had a male predominance (M:F 4:0), and most presented as ulceration of the palate and/or maxillary gingiva. Histologically, the lesions showed diffuse infiltration of medium-sized or large lymphoid tumour cells. Angiocentricity and/or angioinvasion were found in all 4 cases. The immunophenotypes of the NK/T-cell lymphomas were CD3+, CD43+, CD45RO+, CD56+ and TIA-1+. EBV was detected in 2 NK/T-cell lymphomas by in situ hybridization (ISH) and polymerase chain reaction (PCR) methods, and was not detected in T- and B-cell lymphomas. The survival rate of patients with NK/T-cell lymphoma was zero, but the survival rates for patients with T-cell and B-cell lymphomas were 67% and 38%, respectively. It appears that NK/T-cell lymphomas of the oral cavity have a predilection for originating in the palate and maxillary gingiva and are aggressive neoplasms. EBV positivity might be associated with more aggressive behaviour.

Key words NK/T-cell lymphoma · Oral cavity · Epstein-Barr virus

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Introduction

NK/T-cell lymphoma is a lymphoma of the putative natural killer (NK) cell lineage. Recently, NK/T-cell lymphoma has been reported, but little is understood about its origin and behaviour [2, 17–21, 23, 26, 32]. It is more common among Orientals, Mexicans and South Americans than in Western populations [2, 7] and is strongly associated with Epstein-Barr virus (EBV), which has been thought to have a role in the aetiology. Most NK/T-cell lymphomas occur in the nasal or nasopharyngeal regions [2, 9, 17, 19, 21, 23, 26]. Our study was designed to determine the relative frequency of *NK/T-cell lymphoma of the oral cavity, its clinical and histopathological features, its immunophenotypes* and its association with EBV. Comparisons were made with T- and B-cell lymphomas.

Materials and methods

Between 1977 and 1997, 34 patients with non-Hodgkin's lymphoma of the oral cavity were registered at the Department of Laboratory Medicine and Oral Pathology, Faculty of Dentistry, Tokyo Medical and Dental University. Pertinent clinical information and follow-up data on the patients were obtained from hospital charts for all patients. The Ann Arbor clinical staging system was used [4].

Biopsy specimens were fixed in 10% neutral buffered formalin, embedded in paraffin, and stained with haematoxylin and eosin. Lymphomas were classified according to the Revised European-American Lymphoma (REAL) classification [14, 20]. For case 4, the first two biopsies were taken within 1 week and the third biopsy was done 1 month later.

The immunophenotypic study was performed on paraffin sections (4 μm) by streptavidin-biotin immunoperoxidase staining methods with various monoclonal antibodies (Table 1). The antibodies used were CD45RO (UCHL-1; Dako, 1:50), CD43 (MT-1; Bio-Science, 1:50), CD3/HRP (Dako EPOS), CD56 (123C3; Zymed, 1:120), TIA-1 (Coulter, 1:80), CD34 (Biosource, 1:10), CD20 (L26; Dako, 1:50), MB-1 (Bio-Science, 1:50). Appropriate positive controls were included and, as a normal control, normal mouse serum and phosphate-buffered saline were substituted for the primary antibody. For better detection of CD56 and TIA-1, sections were pretreated with microwave oven heating (three cycles of 5 min in 0.01 M citrate buffer, pH 6.0).

Table 1 Specificity, source and dilution of antibodies used in this study

Antibody	Specificity	Source	Dilution
CD45RO (UCHL-1)	T-cells	Dako	1:50
CD43 (MT-1)	T-cells, histocytes	Bio-Science	1:50
CD3/HRP	T-cells, NK/T-cells	Dako	EPOS
CD56 (123C3)	Neuroectodermal cells, NK cells	Zymed	1:120
TIA-1	Cytotoxic T-cells, NK cells	Coulter	1:80
CD34	Human lymphoid and myeloid hematopoietic progenitor cells	Biosource	1:10
CD20 (L26)	B cells	Dako	1:50
MB-1	B cells	Bio-Science	1:50

Table 2 Clinical features of NK/T- and T-cell lymphomas (*CHOP* cyclophosphamide, doxorubicin, vincristine and prednisolone, *COP* cyclophosphamide, vincristine and prednisolone, *RT* radiation therapy)

Case no.	Age	Sex	Initial symptoms and signs	Primary sites	Clinical stages	Involvement of other sites during the courses	Therapy	Outcome[a]
NK/T-cell lymphomas								
1	51	M	swelling, ulceration, pain	soft palate	III	submandibular lymph nodes	RT; COP	Dead of disease (20 months)
2	51	M	mass, ulceration pain, paresthesia	upper incisal gingiva & hard palate	I	nose (8 mon)	RT; CHOP	Dead of disease (14 months)
3	5	M	swelling	hard palate	IV	bone marrow, spleen (13 mon)	CHOP	Dead of disease (35 months)
4	59	M	mass, induration, ulceration	hard & soft palates	IV	cervical lymph nodes	RT	Dead of disease (2 months)
T-cell lymphomas								
5	45	M	swelling, pain, paresthesia	upper molar gingiva	I		RT; CHOP	Alive, disease free (10 years 2 months)
6	76	F	induration, ulceration	hard & soft palates	I		RT	Alive, disease free (4 years 6 months)
7	83	M	swelling, pain	lower molar gingiva	I	upper molar gingiva & orbital cavity (6 mon)	RT	Dead of disease (15 months)

[a] The numbers in parentheses show the time of involvement of other sites or duration of survival after initial symptoms

Epstein-Barr virus was detected by immunohistochemistry, in situ hybridization (ISH) and polymerase chain reaction (PCR). For detection of EBNA2 and EBV-encoded LMP-1, we used streptavidin-biotin immunoperoxidase staining, using monoclonal antibodies PE2 (Dako), which is specific for EBNA2 (1:20), and CS 1-4 (Dako) recognizing LMP-1 (1:25) were employed on paraffin sections from all 34 cases. For detection of EBNA2, microwave oven heating was used (three cycles of 5 min in 0.01 M citrate buffer, pH 6.0). For LMP-1 antibody, proteinase K digestion (10 μg/ml, 37°C, 30 min) was used for antigen retrieval.

Formalin-fixed, paraffin-embedded sections from 32 cases were studied for the presence of EBV by ISH, using EBER oligonucleotides. A Novocastra hybridization kit was used with fluorescein isothiocyanate (FITC)-conjugated EBV oligonucleotide cocktail (Novocastra Laboratories, Newcastle-upon-Tyne, UK). Hybridization products were detected using rabbit F (ab′) anti-FITC/AP (alkaline-phosphatase-conjugated antibody). Colorimetric detection was performed by incubation with enzyme substrate [5-bromo-4-chloro-3-indolylphosphate and nitroblue tetrazolium (BCIP/NBT)]. The negative control probe was a fluorescein-labelled random oligonucleotide cocktail. Positive tissue sections in the ISH kit were used as a positive control.

DNA was extracted from the formalin-fixed, paraffin-embedded sections by TaKaRa DEXPAT™ for PCR. The EBV-specific primer pair (forward: 5′-CGGTCGCCCAGTCCTACCAG-3′, position 45451-45470; reverse: 5′-CCTGGAGAGGTCAGGTTACT-3′ position 45556-45575) was used for the amplification of 125 base pairs (bp) in BamHI-W [16]. Thirty-four cycles of denaturation (94°C, 1 min), annealing (58°C, 1 min) and extension (72°C, 2 min) were carried out in a minicycler. Lymphoma specimens positive for EBV BamHI-W were used as a positive control. Double-distilled water was used as a negative control. The PCR products were visualized on ultraviolet fluorescence by staining with ethidium bromide, after electrophoresis in 3% agarose gel (Nippon Gene Co.).

Results

Clinical findings

NK/T-cell lymphomas

All 4 patients with such tumours were men, with a mean age of 41.5 years (range 5–59 years). The clinical features are summarized in Table 2. A mass, swelling, ulceration and/or pain were the most frequently recorded initial symptoms and signs. The primary sites of the 4 tumours were: the soft palate; the upper incisal gingiva and hard palate; the hard palate; and the soft and hard palate. Nasal extension was observed in case 2 8 months after the oral tumours, while the other 3 showed no nasal involvement. According to the Ann Arbor clinical staging system, 1 was in stage I, 1 was in stage III and 2 were in stage IV. As

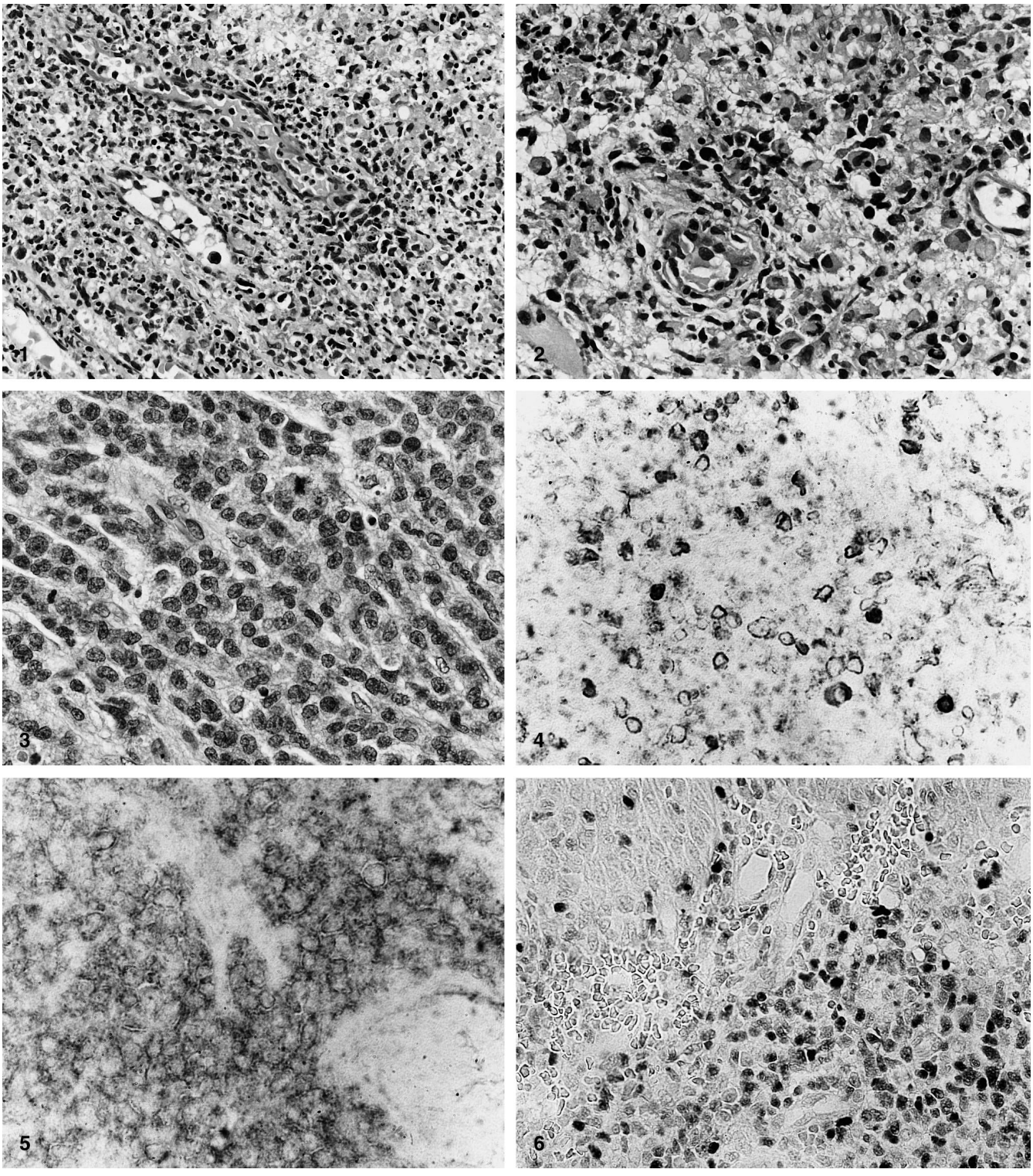

Fig. 1 Case 4(3): angiocentricity and necrosis can be seen. H&E, ×280

Fig. 2 Case 4(3): the tumour is composed of pleomorphic lymphoma cells intermingled with small lymphoid cells, plasma cells, histiocytes and polymorphonuclear leukocytes. H&E, ×464

Fig. 3 Case 3: large monotonous proliferation of fairly uniform cells is seen. H&E, ×464

Fig. 4 CD3(+) tumour cells in case 2. Counterstained with Methyl Green, ×650

Fig. 5 CD56(+) tumour cells in case 2. Counterstained with Methyl Green, ×620

Fig. 6 Case 2: EBV-RNAs in situ hybridization. Note the positive signal restricted to the nuclei of the atypical cells. Positive cells infiltrating in the squamous cell epithelium can be seen. ×400

treatment, 1 patient received radiotherapy, 1 received chemotherapy, and 2 received both radiotherapy and chemotherapy. All patients died, and the duration of the disease from onset to death ranged from 2 to 35 months.

T-cell lymphomas

The patients with T-cell lymphomas were 2 men and 1 woman, with a mean age of 68 years (range 45–83 years). The clinical features are summarized in Table 2. The initial symptoms were swelling and pain. The primary sites were: the upper molar gingiva; the hard and soft palate; and the lower molar gingiva. All 3 were in stage I. As treatment, 2 patients received radiotherapy and 1 received both radiotherapy and chemotherapy. One patient died of the disease 15 months after onset and the other 2 patients are currently still alive. The period of follow-up was from 4 years 6 months to 10 years 2 months.

B-cell lymphomas

The 27 B-cell lymphomas studied were in 18 men and 9 women, with a mean age of 61.0 years (range 18–86 years). The primary sites were: gingiva in 18 (upper 12, lower 6), upper gingiva and palate in 1, hard palate in 5, cheek in 2 and lower lip in 1. The clinical stages were recorded for 26 patients: 8 were in stage I, 9 in stage II and 9 in stage IV. The treatments recorded for 25 patients were: 9 patients received radiotherapy, 5 received chemotherapy and 11 received both radiotherapy and chemotherapy. Sixteen patients died; 10 patients are alive; and the survival information was not available for 1 patient. Of the 10 surviving patients, the duration of follow-up ranged from 6 months to 7 years 2 months.

Histopathological findings

NK/T-cell lymphomas

All 4 cases had diffuse invasion of the tumour cells under the oral mucosa. The minor salivary gland was also frequently involved. Angiocentricity and angioinvasion were found in all 4 tumours (Fig. 1), and necrosis in 2 cases (cases 1 and 4). In cases 1 (CD56+, EBV–) and cases 2 and 4 (CD56+, EBV+), morphological examination showed pleomorphic lymphoid cell proliferation, mainly of large or medium-sized lymphoid cells. The tumour cells were intermingled with small lymphoid cells, plasma cells, histiocytes and polymorphonuclear leucocytes (Fig. 2). In case 3 (CD56+, EBV–), the lymphoma population appeared homogeneous; the tumour cells were uniformly "lymphoblastoid" cells, which had large, round to moderately irregular nuclei, fine chromatin and inconspicuous nucleoli (Fig. 3).

T-cell lymphomas

T-cell lymphomas were classified as peripheral T-cell lymphoma, unspecified, according to the REAL classification. The cytological categories were medium-sized cell type and large cell type. The lymphoma cells usually possessed a moderate amount of cytoplasm and had angulated and irregularly folded nuclei, moderately dense chromatin and inconspicuous nucleoli. The atypical lymphoma cells diffusely infiltrated the mucosa propria. Angiocentricity, angioinvasion and necrosis were not observed.

B-cell lymphomas

B-cell lymphomas were classified as diffuse large cell type (92%), lymphoplasmacytoid type (4%) and small lymphocytic type (4%).

Immunohistochemical study

The immunophenotypic features of the NK/T– and T-cell lymphomas are summarized in Table 3. Both NK/T-cell lymphomas and T-cell lymphomas were positive for CD45RO, CD43 and CD3 (Fig. 4) and negative for CD34, CD20 and MB-1. All 4 cases of NK/T-cell lymphoma showed CD56 and TIA-1 positivity (Fig. 5). All 3

Table 3 Summary of immunohistochemical, EBV RNA in situ hybridization and PCR results. 4(1), 4(2), 4(3) show the results of three different biopsies of case 4

Case No	CD45RO	CD43	CD3	CD56	TIA-1	CD34	CD20	MB-1	LMP-1	EBNA2	ISH EBERs	PCR DNA
1	+	+	+	+	+	–	–	–	–	–	–	–
2	+	+	+	+	+	–	–	–	+	–	+	+
3	+	+	+	+	+	–	–	–	–	–	–	–
4(1)	+	+	+	+	+	–	–	–	–	–	–	–
4(2)	+	+	+	+	+	–	–	–	–	–	–	–
4(3)	+	+	+	+	+	–	–	–	+	+	+	+
5	+	+	+	–	–	–	–	–	–	–	–	–
6	+	+	+	–	–	–	–	–	–	–	–	–
7	+	+	+	–	–	–	–	–	–	–	–	–

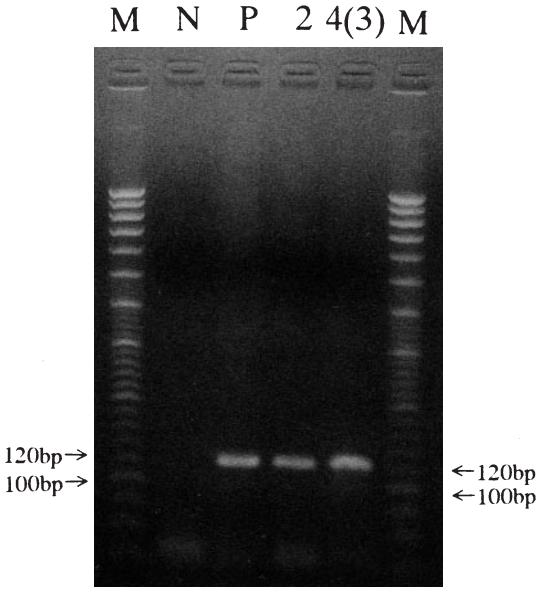

Fig. 7 Polymerase chain reaction products obtained after amplification with EBV-specific primer are run on 3% agarose gel, stained with ethidium bromide, and visualized with ultraviolet fluorescence (*lane M* DNA markers, *N* negative control, *P* positive control; *2* and *4*(*3*) on *top* are case numbers)

cases of T-cell lymphoma were negative for CD56 and TIA-1. B-cell lymphomas were positive for CD20 or MB-1, and all were negative for CD45RO, CD43 and CD3.

EBV Detection

The results of the EBV study on the NK/T– and T-cell lymphomas are summarized in Table 3. LMP-1 immunostaining of the tumour cells was positive in two cases (cases 2 and 4 (the third specimen)). EBNA2 was weakly positive in case 4 (third specimen). Both LMP-1 and EBNA2 were negative for all cases of T- and B-cell lymphoma.

EBER mRNA was abundant in the tumour cells of cases 2 and 4 (third specimen) (Fig. 6). The cells that were positive for EBV were lymphoid cells with cytological atypia and polymorphism. Occasionally, EBER-positive cells infiltrated into the epithelial layers (Fig. 6). In case 4, EBV-positive cells were observed only in the third biopsy specimen. EBER mRNA was not found in the B-cell lymphomas.

EBV DNA was amplified by PCR for cases 2 and 4 (third specimen), in which ISH was also positive for EBV (Fig. 7). EBV DNA was not amplified by PCR for any B- or T-cell lymphomas.

Discussion

The oral cavity is an uncommon site for the occurrence of non-Hodgkin's lymphoma [1, 10]. Non-Hodgkin's lymphomas are classified into T- and B-cell lymphomas, but recently NK/T-cell lymphoma has been recognized as a distinct clinicopathological entity [17–21, 23, 26, 32]. It is referred to as angiocentric NK/T-cell lymphoma in the REAL classification [20]. In our study, immunohistochemically, NK/T-cell lymphomas expressed CD56 (neural cell adhesion molecule) and TIA-1 (T-cell intracellular antigen-1), CD45RO, CD43, and CD3 [3, 5, 29]. T-cell lymphomas expressed CD45RO, CD43, and CD3, but not CD56 and TIA-1. B-cell lymphomas were positive for CD20 and MB-1, but were negative for CD45RO, CD43 and CD3. NK/T-cell lymphomas differed from T-cell lymphomas in their histopathological features, preferential sites, prognosis, geographical distribution and relationship with EBV. Histopathologically, they were characterized by angiocentricity, angioinvasion and necrosis. It can be difficult to make a firm histopathological diagnosis, because some of these tumours are composed predominantly of small cells with minimal atypia, and reactive inflammatory cells are frequently admixed. Immunostaining and EBER-labelling positivity are useful for the correct diagnosis.

The preferential site of NK/T-cell lymphomas in certain extranodal areas is the nasal cavity, but they also occur in the central nervous system, gastrointestinal tract, skin, salivary gland and testis [6, 8, 22, 25, 31, 32]. The oral cavity is a rare site of occurrence. In the reports of oral malignant lymphoma in Japanese individuals by Fukada et al. and Takahashi et al. [11, 27, 28], NK/T-cell lymphomas were not classified. In the series of 34 non-nasal NK/T-cell lymphomas reported by Chan et al. [7], oral cavity involvement was seen in 2 cases, and in the series of 16 cases reported by Emile et al. [9], 2 originated primarily in the palate. All 4 tumours in our study originated in the palate and/or maxillary gingiva. Nasal involvement was found in case 2, but we considered that the gingiva was the primary site because the nasal tumour occurred 8 months later. There was no nasal involvement in the other 3 cases. NK/T-cell lymphoma of the oral cavity should be considered to be separated from that of the nose. Our study suggests that NK/T-cell lymphomas originate more frequently in the palate and maxillary gingiva, with a male predominance, and occur relatively frequently among oral lymphomas in Japan.

It is known that NK/T-cell lymphomas are associated with EBV in a high proportion of cases. Recent studies have revealed that a higher percentage (50–100%) of nasal T-cell lymphomas are associated with EBV, regardless of the geographic origin of the patients [2, 12, 13, 15, 17, 21, 24, 30]. Chan et al. reported 94.1% EBV positivity of non-nasal NK/T-cell lymphomas, and they emphasized an aetiological role for EBV in NK/T-cell lymphoma [7]. In our study, 2 of 4 NK/T-cell lymphomas were shown by ISH and PCR to be associated with EBV. Although three separate biopsies were taken for case 4, the first and second biopsies were negative for EBV and only the last biopsy, after a month, was positive. We are interested in the change in the tumour cells from EBV negativity to EBV positivity. It suggests the possibility

that this patient was infected with EBV after NK/T-cell lymphoma had developed. However, the specimens were not adequate for further analysis.

In cases 2 and 4, the tumour cells tended to be more variable and irregular in size and/or shape, and they were positive for EBV. EBV association and pleomorphic morphology appeared to be correlated. In case 3 (EBV–) the tumour cells were characterized by a monomorphic proliferation, but they could be differentiated from cells of blastoid NK-cell lymphoma by CD34 negativity. It is suggested that two subcategories of NK/T-cell lymphomas might be distinguished; one group is pleomorphic and usually positive for EBV; another group is monomorphic and usually negative for EBV.

Another characteristic of the NK/T-cell lymphoma is its poor prognosis. This is thought to be related to local diffuse infiltration accompanied by necrosis, metastasis to the whole body at an early stage, and the high resistance to treatment. In our study, 4 patients died of the tumour, and the 2 patients positive for EBV died within 14 months. The 2 who were negative for EBV died within 35 months. It seems that EBV positivity may be associated with an accelerated clinical course.

In conclusion, NK/T-cell lymphomas of the oral cavity appear to have a male predominance, to originate more frequently in the palate and maxillary gingiva, and to pursue a more aggressive course than T-cell or B-cell lymphomas.

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