ORIGINAL ARTICLE

Nasal and Nasal-type Natural Killer (NK)/T-cell Lymphoma: Immunophenotype and Epstein-Barr Virus (EBV) Association

S C Peh, FRCPath, Q W Danielle Quen, BSc

Department of Pathology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur

Summary

Epstein-Barr virus (EBV) is believed to have a pathogenic role in lymphomas of the upper-aerodigestive tract. This study aims to elucidate the virus association pattern in nasal and nasal-type NK/T-cell lymphomas, and in sequential biopsies of these tumours. A total of 31 cases of previously diagnosed as lethal midline granuloma, Stewart's granuloma, nasal T-cell non-Hodgkin's lymphoma (T-NHL) and NK/T-cell lymphomas from all anatomical sites were retrieved from the files for the study. Reviews of these cases confirm 8 nasal T-NHL, 19 nasal and 4 extranasal lymphomas of NK/T-cell phenotype from 10 Malays, 18 Chinese, 2 Indian and 1 Kadazan. The male: female ratio was 2.4: 1. All T- and NK/T-cell lymphomas strongly expressed TIA-1 and 63% expressed CD2. The majority of NK/T-cell lymphoma occurred in Chinese (13/23), of which 12/13 (92%) of these cases were associated with EBV. Of the 15 nasal and 9 tonsillar B-cell lymphomas included for a comparison study, only 3 (20%) of the nasal cases were associated with EBV (1 male Chinese, 1 female Chinese and 1 male of other ethnic group). Eight cases of NK/T-cell tumours with sequential biopsies show persistence of EBV, irrespective of the interval and sites of subsequent presentations. This study confirms the cytotoxic nature of NK/T-cell tumour and that EBV is strongly associated with the disease regardless of the anatomical site of presentation and ethnicity. However, nasal and paranasal lymphomas of all phenotypes appear to show higher predilection of EBV association in the ethnic Chinese when compared to non-Chinese.

Key Words: Epstein-Barr virus, Nasal, Nasal-type, NK/T-cell lymphoma

Introduction

Nasal lymphoma accounts for 4% - 7% of all lymphomas in Asian populations in Hong Kong, Japan, Taiwan, China and Malaysia [1-6], and approximately 90% of these show natural killer (NK)/T-cell phenotype [7,8]. A high frequency of nasal lymphomas (8%) with a demonstrable NK/T-cell phenotype of 88% is also seen in the native American in Peru and Mexico [8]. In contrast, the Western populations show an estimation of only 1.5% of all non-Hodgkin's lymphoma (NHL) occuring in the nasal and paranasal area [5,9,10]. The majority of lymphomas of the nasal and paranasal areas in Western populations have been shown to

This article was accepted: 13 November 2002

Corresponding Author: S C Peh, Department of Pathology, University of Malaya, 50603 Kuala Lumpur.

express B-cell phenotype [5,11,12]. This finding suggests an ethnic and/or geographical predisposition for the disease.

The atypical cells in nasal NK/T-cell lymphom a frequently express the NK-cell-associated CD56 (neural cell adhesion) molecule, and other markers such as CD57 and CD16 are generally not expressed [13]. CD2 is often but not always expressed. In most cases, these tumour cells do not express surface CD3, but show the presence of cytoplasmic epsilon chain of CD3 molecule. Cytolytic granule proteins such as T-cell intracellular antigen-1 (TIA-1), granzyme B, and perforin are also highly expressed [14,15]. Genotypically, these tumours lack T-cell receptor (TCR) gene rearrangement, and this supports the notion that these tumours are derived from NK cells [13,15,16].

Lymphomas with NK/T phenotype are not restricted to the nasal or midline facial presentations. Tumours with identical phenotype and genotype as nasal NK/T-cell lymphoma has been reported in other extranasal sites, such as the skin and soft tissue, lung, testis, upper respiratory tract, gastrointestinal tract and central nervous system [7,13,17-22]. The term *'nasal-type'* has been adopted to recognise this group of lymphomas. Lymph node involvement is rare in both clinical progression and presentation of nasal and nasal-type NK/T-cell lymphoma [7,23].

Studies report consistent presence of Epstein-Barr virus (EBV) in nasal NK/T-cell lymphoma and the virus was demonstrated to be clonal [24]. These findings strongly support the pathogenic role of EBV [15], although the mechanism of malignant transformation remains undefined. Nasopharyngeal carcinoma, another cancer in a similar anatomical region is also associated with EBV. Hence, it strongly suggests that perhaps the anatomic site is important for the development of EBV-related neoplasms [25].

This study aims to demonstrate the cytotoxic nature and elucidate the association of EBV in lymphomas of upper-aerodigestive tract, the nasal and nasal-type NK/T cell lymphomas, and the status of the virus in sequential biopsies of these tumours.

Materials and Methods

Biopsy material/ Case selection

The archival material of all cases previously diagnosed and confirmed as lethal midline granuloma, Stewart's granuloma, nasal T-cell non-Hodgkin's lymphoma (NHL) and NK/T-cell lymphomas from all sites were retrieved from the files in the Department of Pathology, University of Malaya, Kuala Lumpur in a period of 20 consecutive years. A total of 41 formalin-fixed and paraffin-embedded biopsy tissues from 31 patients were available for further study. In addition, 15 nasal and 9 tonsillar B-cell lymphomas from the same period were retrieved for comparison study.

Immunohistochemistry

Paraffin-embedded sections were stained with haematoxylin and eosin and a panel of antibodies (names are shown in parentheses). Briefly, 4μm-thick paraffin sections were mounted on salinized slides, deparaffinization in xylene and rehydration in alcohol was performed, followed by microwave treatment for antigen retrieval. The sections were first incubated with the primary antibodies, then with biotinylated rabbit anti-mouse or biotinylated swine anti-rabbit immunoglobulins for monoclonal and polyclonal antibodies respectively. The monoclonal antibodies used were: CD20cy clone L26 (DAKO, Denmark), CD2, CD56 (Novocastra, Newcastle, UK), TIA-1 (ImmunoTech) and CD57 (Leu-7 Becton Dickinson, Mountain View, CA). Polyclonal T-cell specific antigen CD3 (DAKO, Denmark) antibody was used for confirmation of T-phenotype. Three, 3'-diaminobenzidine tetrahydrochloride (DAB) chromogens (Dako, Denmark) were employed for colour development for most of the antibodies except CD56 and TIA-1, where ENVISION$^+$ system was applied. A tumour was categorized as NK/T phenotype when both CD3 and CD56 expression were present in the tumour cells.

In situ hybridisation

The presence of EBV was detected by in situ hybridization (ISH) technique, using fluoroisothiocynate (FITC)-conjugated EBV oligonucleotide probe (NCL-EBV, Novocastra, Newcastle, UK) for EBV early RNAs (EBER). Alkaline phosphatase-conjugated rabbit anti-FITC was then added followed by introduction of a substrate, 4-nitro-blue-tetrazolium chloride/ 5-bromo-4-chloro-3-indolyl-phosphate (NBT/BCIP). The tissues were counterstained with Meyer's haematoxylin. A known EBV-positive nasopharyngeal carcinoma was used as an external positive control.

Results

Of the 31 patients' material studied, 8 are nasal T-NHL, 19 are nasal and 4 nasal-type lymphomas of NK/T-cell phenotype. The latter were tissue obtained one each from the pleura, testes, jejunum, and colon. These cases were from 22 male and 9 female patients (male: female = 2.4: 1). Their ages ranged from 8 to 77 years (mean age is 46.1 years). Among the 19 nasal NK/T cell lymphomas, there are 7 Malays, 11 Chinese, 1 Kadazan and in the group of nasal-type NK/T cell lymphoma, there are 1 Malay, 2 Chinese and 1 Indian (Table I). The ethnic distribution of T-NHL are 2 Malay, 5 Chinese and 1 Indian. The majority of the NK/T-cell lymphoma cases were in Chinese males (10/23, 43%), followed by Malay males (4/23, 17%), Malay females (4/23, 17%), and Chinese females (3/23, 13%). There are 9 males and 6 females in the group of nasal B-cell NHL (Table II), from 6 Malay, 6 Chinese, 1 Indian, and 2 of other ethnic origin. In the group of tonsillar B-cell NHL, there are 6 males and 3 females, from 3 Malay and 6 Chinese patients.

All nasal and nasal-type NK/T-cell lymphoma cases expressed CD3 (Figure 1A) and CD56 (Figure 1B) in a large number of the tumour cells. CD57 expression was observed only in 1 case (Figure 1C). Of the nasal NK/T-cell lymphoma cases, 12/19 (63%) express CD2 (Figure 1D), but none in the 3 cases of nasal-type NK/T-cell lymphoma. There was insufficient tissue from the 4th case of the latter group for immunostaining. TIA-1 is equally and strongly expressed by all of the nasal, nasal-type and T-cell NHL cases (Figure 1E).

EBER is detected in 18/19 (95%) of the nasal NK/T-cell lymphoma (Figure 1F), 2/4 (50%) of the nasal-type and 2/8 (25%) of nasal T-NHL (Table I). In the nasal B-cell lymphomas group, 3/15 (20%), from 2 Burkitt's and 1 diffuse large B-cell type, also express EBER (Table II). There is higher EBV association rate in Chinese cases, with frequencies of 11/11 (100%), 1/2 (50%), 2/5 (40%) and 2/3 (67%) for nasal, nasal-type, T-cell and B-cell NHL respectively, whereas for the non-Chinese, the frequencies are 7/8 (88%), 1/2 (50%), 0/3 (0%) and 1/3 (33%). The EBV association rate of nasal and paranasal lymphomas of all phenotypes combined appeared to be higher in the ethnic Chinese (15/22, 68%) than that for non-Chinese (8/20, 40%). However, this difference is statistically not significant (p-value = 0.127). Eight cases (6 nasal, 1 nasal-type NK/T-cell and 1 T-cell NHL) with sequential biopsies show persistence of EBV, irrespective of the interval and sites of subsequent presentations (Table III).

Table I : Expression of CD3, L26, CD56, CD57, CD2, TIA-1 and EBER in nasal, nasal-type NK/T- and T-cell non-Hodgkin's lymphoma (NHL).

	n	CD3+	L26+	CD56+	CD57+	CD2+	TIA-1+	EBER (%)
T-cell NHL								
Males : Malay	1	1	0	-	-	-	-	0/1 (0)
Chinese	4	4	0	0	0	-	4	2/4 (50)
Indian	1	1	0	0	0	-	1	0/1 (0)
Others	0	0	0	0	0	-	0	0/0 (0)
Females : Malay	1	1	0	0	0	-	1	0/1 (0)
Chinese	1	1	0	0	0	-	1	0/1 (0)
Indian	0	0	0	0	0	-	0	0/0 (0)
Others	0	0	0	0	0	-	0	0/0 (0)
Total	8	8	0	0	0	-	8	2/8 (25)
Nasal NK/T- cell								
Males : Malay	3	3	0	3	0	3	3	2/3 (67)
Chinese	8	8	0	8	0	4	8	8/8 (100)
Indian	0	0	0	0	0	0	0	0/0 (0)
Others	1	1	0	1	1	1	1	1/1 (100)
Females: Malay	4	4	0	4	0	2	4	4/4 (100)
Chinese	3	3	0	3	0	2	3	3/3 (100)
Indian	0	0	0	0	0	0	0	0/0 (0)
Others	0	0	0	0	0	0	0	0/0 (0)
Total	19	19	0	19	1	12	19	18/19 (95)
Nasal-type NK/T-cell								
Males : Malay	1	1	0	1	0	-	-	1/1 (100)
Chinese	2	2	0	2	0	0	2	1/2 (50)
Indian	1	1	0	1	0	0	1	0/1 (0)
Others	0	0	0	0	0	0	0	0/0 (0)
Total	4	4	0	4	0	0	3	2/4 (50)

- = Not done

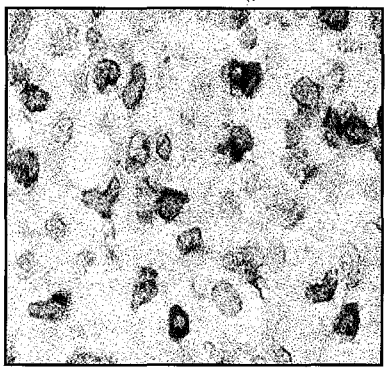
Table II : Expression of EBER in nasal B-cell lymphoma and tonsils of B-cell type

	EBER (%)				
	Malay	Chinese	Indian	Others	Total
Nasal B-cell NHL					
Male	0/4 (0)	1/3 (33)	0/0 (0)	1/2 (50)	2/9 (22)
Female	0/2 (0)	1/3 (33)	0/1 (0)	0/0 (0)	1/6 (17)
Total	0/6 (0)	2/6 (33)	0/1 (0)	1/2 (50)	3/15 (20)
Tonsils B-cell NHL					
Male	0/3 (0)	0/3 (0)	0/0 (0)	0/0 (0)	0/6 (0)
Female	0/0 (0)	0/3 (0)	0/0 (0)	0/0 (0)	0/3 (0)
Total	0/3 (0)	0/6 (0)	0/0 (0)	0/0 (0)	0/9 (0)

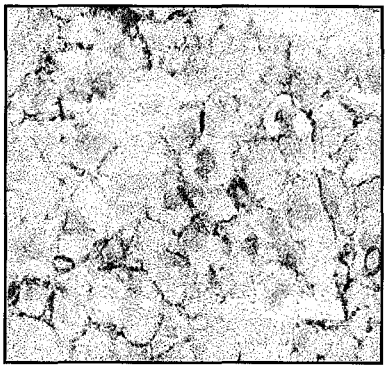
Table III : Expression of EBER in nasal-, nasal-type NK/T- and T-cell NHL cases with sequential biopsies.

Age/Sex/Race	Biopsy		EBER
	Site of biopsy	Month/ Year	
Nasal NK/T-cell lymphoma			
38/m/M	Nasal septum	05/91	+
	Pleural	06/94	+
	Right maxilla sinus	07/94	+
48/m/C	Inferior turbinate	02/93	+
	Nose	02/94	+
34/m/C	Lateral wall of Nose	02/94	+
	Nose	06/94	+
56/f/M	Nose	03/99	+
	Nose	04/99	+
40/f/M	Maxilla	07/97	+
	Left post-nasal space	03/98	+
58/f/C	Inferior turbinate	09/82	+
	Nasopharynx	05/83	+
Nasal-type NK/T-cell lymphoma			
48/m/C	Lymph Node	09/96	+
	Bowel	11/96	+
T-cell NHL			
38/m/C	Tonsil ulcer	04/92	+
	Epiglottis	07/92	+
	Epiglottis	09/92	+

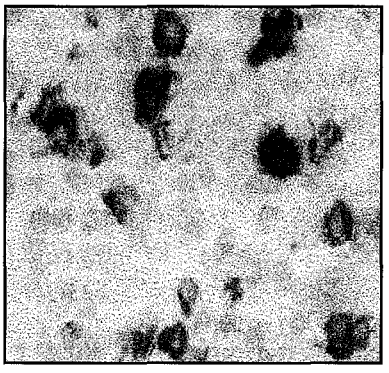
*m = male, f = female, M = Malay, C = Chinese



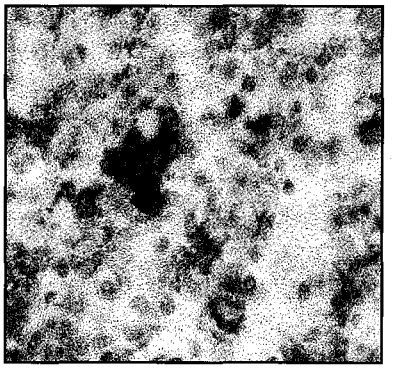
A: CD3



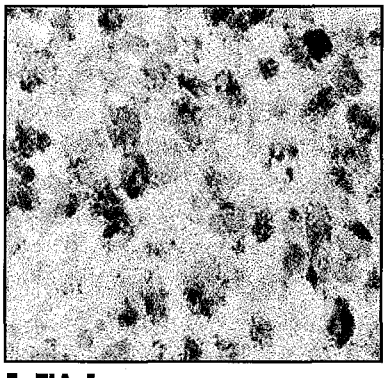
B: CD56



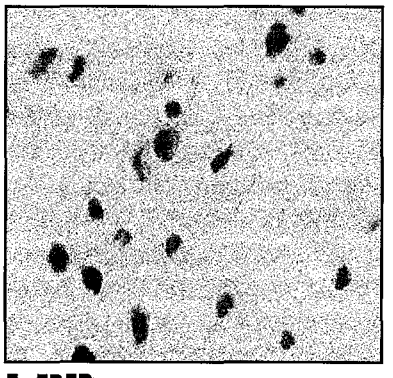
C: CD57



D: CD2



E: TIA-1



F: EBER

Fig. 1: Immunophenotypic expressions of NK/T-cell lymphoma: A) CD3+ (600X) B) CD56+ (600X) C) CD57+ (400X) D) CD2+ (400X) E) TIA-1+ (600X). F) In situ hybridisation for EBER (600X).

Discussion

Nasal NK/T-cell lymphoma is a unique tumour. Terms such as polymorphic reticulosis, lethal midline granuloma, angiocentric lymphoma and angiocentric immunoproliferative lesions have been used to describe this type of lymphoma [26-28] because morphologically, this lymphoma often shows histologic features of polymorphic cellular infiltration, necrosis, angiocentricity and angioinvasion. The tumour cells express NK-cell phenotype. NK-cells are related to T-cells, but at some point in the differentiation process, they branch off to form a separate lineage [29] and are characteristically cytotoxic, by using effector mechanisms of killing their target via the release of cytotoxic proteins such as TIA-1, a 15-kd cytotoxic granule-associated RNA-binding protein [30]. All (28/28) of the T- and NK/T-cell lymphomas express TIA-1 in this series, concurring with other observations [8,14,15,31,32]. Chiang et al, 1997 [32] also demonstrated by using dual labelling of TIA-1 and EBER that the protein granules were localised in the neoplastic cells. In contrast, TIA-1 cytotoxic proteins are not expressed in B-cell tumours in the same anatomic region as seen in this series, and also reported by Chiang et al, 1997 [32]. The universal expression of cytotoxic proteins in nasal lymphomas, irrespective of T- or NK-cell lineage argues for a selection for cytotoxic transformation of lymphocytes in this region. It is plausible that cytotoxic lymphocytes generated during the cellular immune response to primary EBV infection or subsequent re-activation at the nasal region themselves become targets for EBV infection and subsequent transformation, since they are the primary effector cells in host immune surveillance. Tao *et al*, 1996 [33] and Chiang *et al*, 1997 [32]have observed that normal nasal and nasopharyngeal mucosal tissues frequently harboured EBV-infected B- and T- lymphocytes, and can act as reservoirs for the virus. Hence this may provide a local setting for the emergence of EBV-associated tumours.

In our study, all, but 1, of the nasal NK/T-cell lymphoma are EBV infected whereas only 50% of nasal-type and 25% of nasal T-cell NHL cases demonstrated EBV-positive tumour cells. Tao et al (1995) reported the localisation of EBER RNA in all the nasal lymphoma cases of NK- and T-cell phenotype in their study, confirming an association between the virus and this disease [34]. Many other reports have documented EBV infection in NHLs in the nasal area [9,25,35-39], and particularly in nasal NK/T-cell lymphomas [7-8, 13,16,32,40-42]. On the other hand, only 3 (20%) of the nasal B-cell lymphoma in our study is EBV-associated. This lower EBV association rate when compared to T- or NK/T-cell lymphoma is supported by Chiang et al, 1997 [32]. The only one nasal NK/T-cell lymphoma case which is not EBV-infected is from a non-Chinese patient. Hence, concurring with findings from previous studies that reported the predilection of EBV-associated nasal and paranasal lymphomas of T-phenotype in Chinese is higher when compared to non-Chinese [6,43].

The reason for the East-West difference in the frequency of nasal NK/T-cell lymphomas is still not entirely clear. The more frequent occurrence of T- and NK-cell neoplasms in less developed countries, where EBV infection tends to occur at an earlier age [9] may explain the differences observed between the Eastern and Western series. However, irrespective of ethnicity and geography, EBV is consistently observed to be highly associated with this group of tumours, and also in the sequential biopsies as confirmed in this study. This overwhelming association is strongly suggestive of the involvement of virus in tumour formation, and that it is not a mere innocent passenger. It appears likely that the virus can enter cells of diverse lineages and, by conferring some growth advantage, lead to their clonal expansion [34].

Acknowledgements

This study was supported by the Malaysian Ministry of Science, Technology and Environment Top Down Biotechnology Research grant: 26-02-03-0586.

References

1. Ho FCS, Todd D, Loke SL, Ng RP, and Khoo RKK. Clinico-Pathologic Features of Malignant Lymphomas in 294 Hong Kong Chinese Patients, Retrospective Study Covering an Eight-year Period. Int J Cancer 1984; 34: 143-8.
2. Lee SH, Su IJ, Chen RL et al. A Pathologic Study of Childhood Lymphoma in Taiwan With Special Reference to Peripheral T-Cell Lymphoma and the Association with Epstein-Barr Viral Infection. Cancer 1991; 68: 1954-62.
3. Ng CS, Chan JKC, Lo STH, and Poon YF. Immunophenotypic Analysis of Non-Hodgkin's Lymphomas in Chinese. A Study of 75 cases in Hong Kong. Pathology 1986; 18: 419-25.
4. Harrington DS, Ye Y, Weisenburger DD et al. Malignant Lymphoma in Nebraska and Guangchou, China: A Comparative Study. Hum Pathol 1987; 18: 924-8.
5. Frierson HF Jr, Innes DJ Jr, Mills SE, and Wick MR. Immunophenotypic Analysis of Sinonasal Non-Hodgkin's Lymphomas. Hum Pathol 1989; 20: 636-42.
6. Peh SC. Host ethnicity influences non-Hodgkin's lymphoma subtype frequency and Epstein-Barr virus association rate: the experience of a multi-ethnic patient population in Malaysia. Histopathology 2001; 38: 458-65.
7. Jaffe ES. Nasal and nasal-type T/NK Cell Lymphoma: a unique form of lymphoma associated with the Epstein-Barr Virus. Histopathology 1995; 27: 581-3.
8. 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: 849-55.
9. Arber DA, Weiss LM, Albujar PF, Chen YY, and Jaffe ES. Nasal Lymphomas in Peru. High Incidence of T-cell Immunophenotype and Epstein-Barr Infection. Am J Surg Pathol 1993; 17: 392-9.
10. Frierson HF, Mills SE, and Innes DJ. Non-Hodgkin's Lymphomas of the Sinonasal Region: Histologic Subtypes and their Clinicopathologic Features. Am J Clin Pathol 1984; 81: 721-7.
11. Ferry JA, Sklar J, Zukerberg LR, and Harris NL. Nasal Lymphoma. A Clinicopathologic Study with Immunophenotypic and Genotypic Analysis. Am J Surg Pathol 1991; 15: 268-79.
12. Campo E, Cardesa A, Alos L et al. Non-Hodgkin's Lymphomas of Nasal Cavity and Paranasal Sinuses. An Immunohistochemical Study. Am J Surg Pathol 1991; 96: 184-90.
13. Jaffe ES, Chan JKC, Su IJ et al. Report of the Workshop on Nasal and Related Extranodal Angiocentric T/Natural Killer Cell Lymphomas. Definitions, Differential Diagnosis, and Epidermiology. Am J Surg Pathol 1996; 20: 103-11.
14. Felgar RE, Macon WR, Kinney MC, Roberts S, Pasha T, and Salhany KE. TIA-1 Expression in Lymphoid Neoplasms. Identification of Subsets with Cytotoxic T Lymphocyte of Natural Killer Cell Differentiation. Am J Pathol 1997; 150: 1893-1900.
15. Kinney MC. The Role of Morphologic Features, Phenotype, Genotype, and Anatomic Site in Defining Extranodal T-cell of NK-cell Neoplasms. Am J Clin Pathol 1999; 111 Suppl 1: 104-18.
16. van Gorp J, de Bruin PC, Sie-Go DMDS et al. Nasal T-cell Lymphoma: A Clinicopathologic and immunophenotypic analysis of 13 cases. Histopathology 1995; 27: 139-48.
17. Wong KF, Chan JKC, Ng CS, Tsang WYW, and Cheung MMC. CD56 (NKH1)-Positive Hematolymphoid Malignancies: An Aggressive Neoplasm Featuring Frequent Cutaneous/Mucosal Involvement, Cytoplasmic Azurophilic Granules, and Angiocentricity. Hum Pathol 1992; 23: 798-804.
18. Jaffe ES. Classification of Natural Killer (NK) Cells and NK-like T Cell Malignancies. Blood 1996; 87: 1207-10.
19. Chan JKC, Sin VC, Wong KF et al. Nonnasal Lymphoma Expressing the Natural Killer Cell Marker CD56: A Clinicopathologic Study of 49 Cases of an Uncommon Aggressive Neoplasm. Blood 1997; 89, 4501-13.
20. Chan JKC, Ng CS, Ngan KC, Hui PK, Lo STH, and Lau WH. Angiocentric T-Cell Lymphoma of the Skin. Am J Surg Pathol 1988; 12: 861-76.
21. Nakamura S, Suchi T, Koshikawa T et al. Clinicopathologic Study of CD56 (NCAM)-Positive Angiocentric Lymphoma Ocurring in Sites Other than the Upper and Lower Respiratory Tract. Am J Surg Pathol 1995; 19: 284-96.

22. Yeh KH, Lien HC, Hsu SM, and Cheng AL. Quiescent Nasal T/NK Cell Lymphoma Manifested as Primary Central Nervous System Lymphoma. Am J Hematol 1999; 60: 161-3.

23. Takeshita M, Akamatsu M, Ohshima K et al. Angiocentric Immunoproliferative Lesions of the Lymph Node. Am J Clin Pathol 1996; 106: 69-77.

24. Yoon TY, Lee HT, and Chang SH. Nasal-type T/Natural Killer cell angiocentric lymphomas, Epstein-Barr virus-associated, and showing clonal T-cell receptor (gene rearrangement. British Journal of Dermatology 1999; 140: 505-8.

25. Weiss LM, Gaffrey MJ, Chen YY, and Frierson HF. Frequency of Epstein-Barr viral DNA in "Western" Sinonasal and Waldeyer's Ring non-Hodgkin's Lymphomas. Am J Surg Pathol 1992; 16: 156-62.

26. Ho FCS, Choy D, Loke SL et al. Polymorphic Reticulosis and Conventional Lymphomas of the Nose and Upper Aerodigestive Tract: A Clinicopathologic Study of 70 Cases and Immunophenotypic Studies of 16 Cases. Hum Pathol 1990a; 21: 1041-50.

27. Chan JKC, Ng CS, Lau WH, and Lo STH. Most Nasal/Nasopharyngeal Lymphomas are Peripheral T-cell Neoplasms. Am J Surg Pathol 1987; 11: 418-29.

28. Yoshifumi I, Yamanaka N, Ogawa K et al. Nasal T-cell Lymphoma as a Type of So-Called "Lethal Midline Granuloma". Cancer 1982; 50: 2336-44.

29. Spits H, Lanier LL, and Phillips JH. Development of Human T and Natural Killer Cells. Blood 1995; 85: 2654-70.

30. Kawakami A, Tian Q, Duan X, Streuli M, Schlossman SF, and Anderson P. Identification and functional characterization of a TIA-1 related nucleolysin. Proc Natl Acad Sci USA 1992; 89: 8681-5.

31. Ohsawa M, Nakatsuka SI, Kanno H et al. Immunophenotypic and Genotypic Characterization of Nasal Lymphoma with Polymorphic Reticulosis Morphology. Int J Cancer 1999; 81: 865-70.

32. Chiang AKS, Chang ACL, Srivastava G, and Ho FCS. Nasal T/Natural Killer (NK)-Cell Lymphomas are Derived From Epstein-Barr Virus-Infected Cytotoxic Lymphocytes of Both NK and T-Cell Lineage. Int J Cancer 1997; 73: 332-8.

33. Tao Q, Srivastava G, Dickens P, and Ho FCS. Detection of Epstein-Barr Virus-Infected Mucosal Lymphocytes in Nasal Polyps. Am J Pathol 1996; 149: 1111-8.

34. Tao Q, Ho FCS, Loke SL, and Srivastava G. Epstein-Barr Virus is Localized in the Tumour Cells of Nasal Lymphomas of NK, T or B Cell Type. Int J Cancer 1995; 60: 315-20.

35. Ho FCS, Srivastava G, Loke SL et al. Presence of Epstein-Barr Virus DNA in Nasal Lymphomas of B and T Cell Type. Hematol Oncol 1990b; 8: 271-81.

36. Harabuchi Y, Yamanaka N, Kataura A et al. Epstein-Barr Virus in Nasal T-cell Lymphomas in patients with Lethal Midline Granuloma. Lancet 1990; 335: 128-30.

37. Medeiros LJ, Jaffe ES, Chen YY, and Weiss LM. Localization of Epstein-Barr Viral Genomes in Angiocentric Immunoproliferative Lesions. Am J Surg Pathol 1992; 16: 439-47.

38. Kanavaros P, Lescs M-C, Briere J et al. Nasal T-cell Lymphoma: A Clinicopathologic Entity Associated with Peculiar Phenotype and With Epstein-Barr virus. Blood 1993; 81: 2688-95.

39. Borisch B, Hennig I, Laeng RH, Waelti ER, Kraft R, and Laissue J. Association of the Subtype-2 of the Epstein-Barr virus with T-cell Non-Hodgkin's Lymphoma of the Midline Granuloma type. Blood 1993; 82: 858-64.

40. Boulland M-L, Meignin V, Leroy-Viard K et al. Human Interleukin-10 Expression in T/Natural Killer Cell Lymphomas. Association with Anaplastic Large Cell Lymphomas and Nasal Natural Killer Cell Lymphoma. Am J Surg Pathol 1998; 153: 1229-37.

41. Cuadra-Garcia I, Proulx GM, Wu CL et al. Sinonasal Lymphoma. A Clinicopathologic Analysis of 58 Cases From the Massachusetts General Hospital. Am J Surg Pathol 1999; 23: 1356-69.

42. Chiang AKS, Tao Q, Srivastava, G and Ho FCS. Nasal NK- and T-Cells lymphomas share the same type of Epstein-Barr virus latency as Nasopharyngeal carcinoma and Hodgkin's Disease. Int J Cancer 1996; 68: 285-90.

43. Peh SC, Sandvej K, and Pallesen G. Epstein-Barr Virus (EBV) in Malaysian Upper-Aerodigestive Tract Lymphoma: Incidence and Sub-Type. Int J Cancer 1995; 61: 327-33.