A Case of NCAM-positive Nasal Type T/NK-Cell Lymphoma

Jae Wang Kim, M.D., Sang Ho Nam, M.D., Kwang Joong Kim, M.D.,
Jong Min Kim, M.D., Chong Ju Lee, M.D.

Department of Dermatology, College of Medicine, Hallym University
Seoul, Korea

We herein report a case of nasal type T/natural killer(NK)-cell lymphoma(TNKCL). This lymphoma is characterized by the expression of CD2, CD43 and NCAM(CD56) antigen, an aggressive clinical course, frequent extranodal spreading, a strong association with Epstein-Barr virus(EBV), and the absence of T-cell receptor(TCR) gene rearrangement. NCAM antigen is known to be a possible determinant of extranodal dissemination of peripheral T-cell lymphoma(PTCL). The patient is a 70-year-old male with skin lesion on his forearm. Histopathological and immunohistochemical studies were diagnostic of EBV-associated TNKCL. Untill now, he has failed to respond to anticancer therapy.
(Ann Dermatol 10:(3) 190~194, 1998).

Key Words : Nasal type T/NK-cell lymphoma, NCAM, EBV

Recently, non-epidermotrophic PTCL encompassing varied subtypes, has been conceptualized as a distinctive disease category, compared with classical[1] mycosis fungoides/Sézary syndrome[1]. The NCAM-positive nasal type of TNKCL is especially regarded as a separate subtype among spectra of PTCL due to different biological behavior[2-4]. Moreover, this type is more frequently reported in Oriental areas than the Western world[5]. Additionally, NCAM expression is likely to play a role in the behavior and localization of lymphomas[2]. We herein report one case of EBV-associated, NCAM-positive nasal type of TNKCL showing extranodal localization without upper aerodigestive tract involvement.

CASE REPORT

A 70-year-old male had had skin lesion on his right forearm for 9 months. Easy fatigue, intermittent fever and weight loss were experienced over the 2 months before his visit. An examination demonstrated a well-defined erythematous figurate and circinate plaque on his right forearm(Fig. 1). Hepatomegaly was noted but peripheral lymphadenopathy were not found. Labaratory data showed a hemoglobin of 7.2 gm/dl, a hematocrit of 27%, a leukocyte count of 2,990/mm^3, and a platelet count of 90,000/mm^3. The liver function test profiles were as follows: AST 58 IU/L(normal range 5-35 U/L), ALT 59 IU/L(normal range 5-35 IU/L), LDH 4480 IU/L(normal range 260-460 IU/L). No atypical lymphocytes were found in peripheral blood and on bone marrow aspiration. A head and neck CT scan did not reveal any abnormal findings. Although he is currently alive, he is not recovering from systemic symptoms despite combined chemotherapy with a CHOP regimen(cyclophosphamide, doxorubicin, vincristine and prednisone). Also, his skin lesion does not show any remission.

Morphological Studies

A skin biopsy specimen taken from his forearm showed a dense infiltration of atypical lymphoid cells in the whole dermis. The overlying epidermis

Received March 30, 1997.
Accepted for publication January 17, 1998.
Reprint request to : Jae Wang Kim, M.D., Department of Dermatology, College of Medicine, Hallym University Seoul, Korea

showed severe necrotic degeneration, leading to intraepidermal pustular cavities. The vessels were permeated and destroyed by infiltrative cells with fibrinoid deposits(Fig. 2-A). The atypical cells which were small to medium sized, polymorphic cleaved lymphoid types, caused the manifestation of glomeruloid concentration and degeneration of the vessels(Fig. 2-B). The vessels also showed endothelial hyperplasia and fibrinoid occlusion of the lumens(Fig. C). Hair follicles disclosed necrotic changes by infiltrative cells(Fig. 2-D). Active mitotic figures were also found.

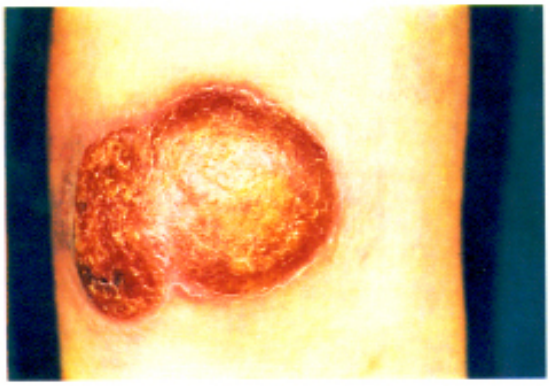

Fig. 1. A well-defined erythematous figurate and circinate plaque on his right forearm.

Immunophenotypic Studies

The standard avidin-biotin complex immunoperoxidase technique was performed to identify the immunophenotypes of infiltrative cells in paraffin-embedded sections with a wide panel of monoclonal antibodies. T-cell markers such as CD2(Leu5a, Becton & Dickinson, Sunnyale,

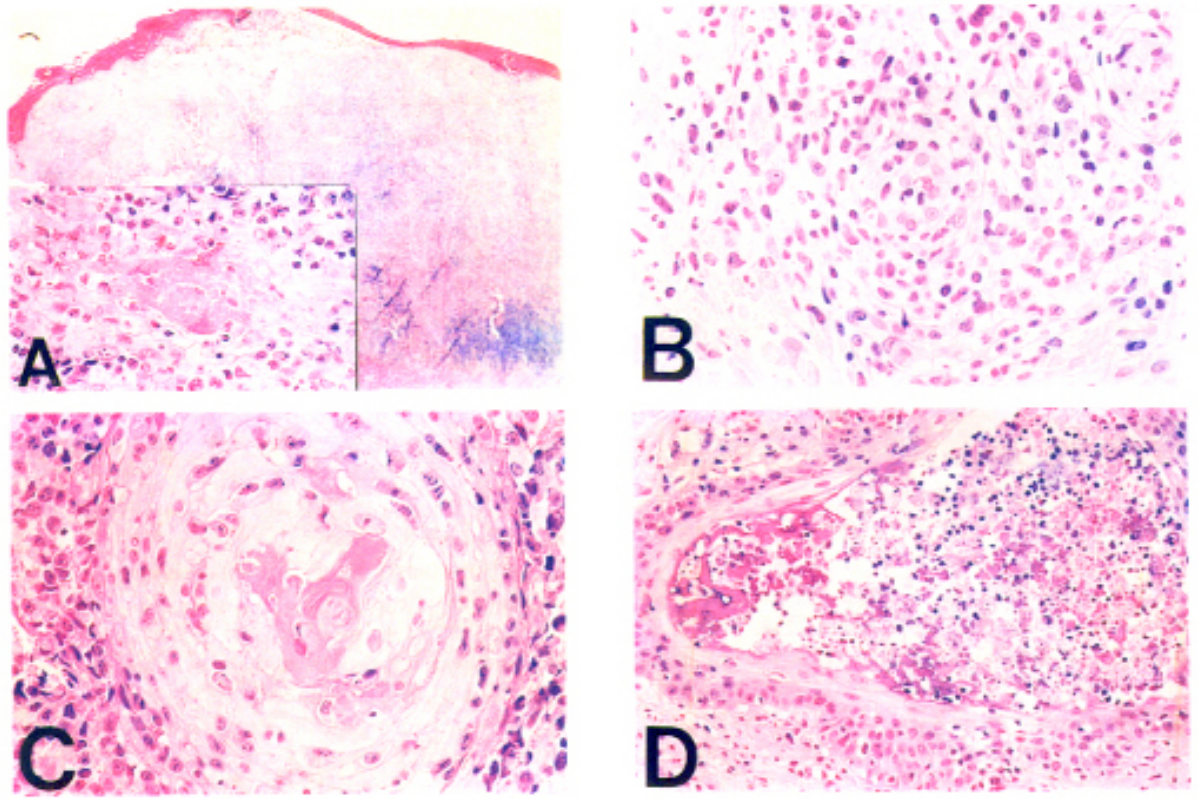

Fig. 2. A skin biopsy specimen showing a degenerating epidermis with pustular cavity and diffuse cellular infiltration in the dermis(H & E, ×100, Right, A). The vessels were permeated and destroyed by atypical cells with fibrinoid deposits(H & E, ×400, Left, A). Angiocentricity and angioinvasion by polymorphic cleaved lymphoid cells(center) and glomeruloid degeration of vessels(2 o'clock in direction)(H & E, ×400, B). The vessel showing concentric endothelial hyperplasia and luminal fibrinoid occusion(H & E, ×400, C). Hair follicle representing severe necrotic changes(H & E, ×400, D).

Annals of Dermatology
Vol. 10, No. 3, July 1998

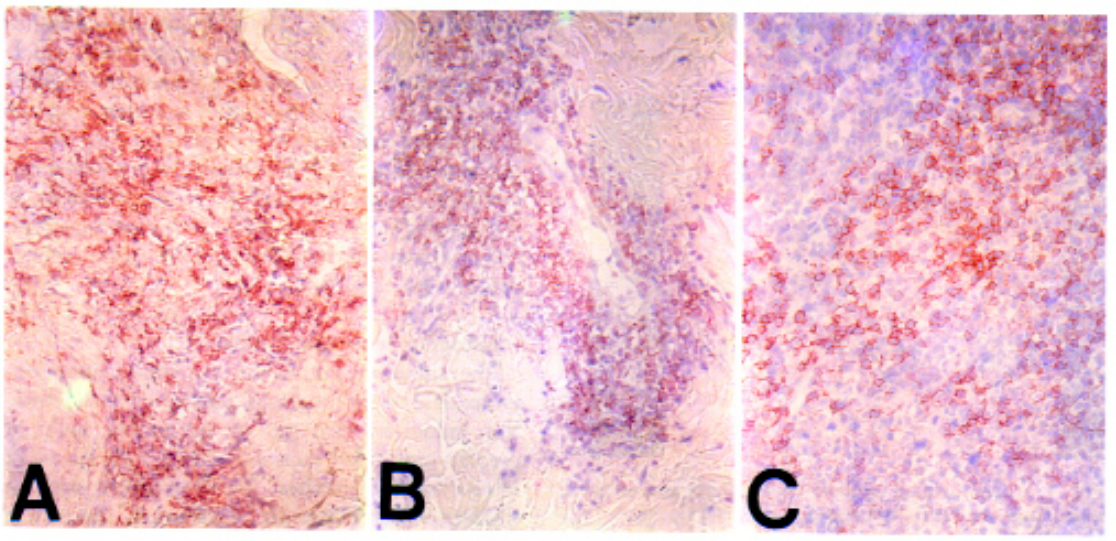

Fig. 3. Immunohistochemical findings of tumor cells reacting with CD2(PAP, ×200, A), CD43(PAP, °ø200, B) and NCAM(PAP, ×200, C).

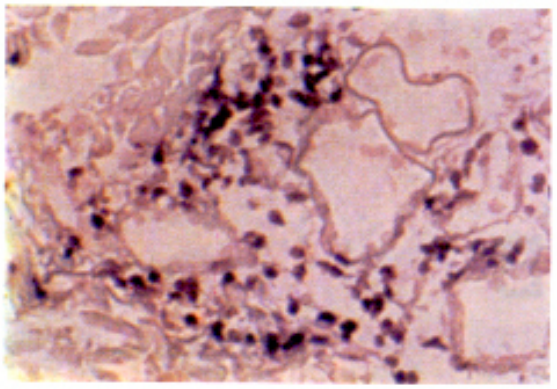

Fig. 4. Positive signals by in situ hybridization for EBV genomes(×400).

U.S.A), CD43(Becton & Dickinson), and an NK-cell surface marker, NCAM(CD56, NKH-1, Zymed, San Francisco, CA, U.S.A.) were positive(Fig. 3-A, B, C). However, CD45RO(UCHL-1, Dako, Carpinteria, CA, U.S.A.) CD4(Becton & Dickinson), CD8(Becton & Dickinson), CD20(Dako), CD30(Ki-1, Dako) and CD68(Kp-1, Dako) were negative for tumor cells. In the CD3 marker(Dako), cytoplasmic CD3 was focally positive but surface CD3 was not expressed on the tumor cells.

DNA Hybridization Studies for EBV

We performed in situ hybridization for EBV nuclear genomes from paraffin-embedded tissues of the skin biopsy with a fluorescein-conjugated oligonucleotide probe(EBER-1, EBV encoded RNA, Dako, Japan). After the deparaffinized tissue specimens were processed with proteinase K(3 ug/ml) over 30 minutes, they were reacted with EBER-1 probe and alkaline phosphatase-conjugated FITC antibody sequentially. There were positive hybridization signals corresponding to EBV transcripts(Fig. 4).

T-cell Receptor(TCR)-ß, γ, Gene Rearrangement Study

For identification of TCR-ß, γ chain gene rearrangement, tumor DNA was digested with restriction endonuclease Bam HI, Eco RI, and Hind III, and was hybridized with a probe of constant region of TCR-ß, γ gene(Cß, Cγ). However, we could not detect gene rearrangement in our case because he did not show clonality of TCR gene but a germline pattern through TCR rearrangement analysis.

DISCUSSION

Nasal type(or non-nasal) TNKCL was recently

designated in the case of an angiocentric T-cell lymphoma(ACTCL) that showed positiveness to both some T-cell markers(e.g. CD43, CD2) and NK-cell marker(NCAM), not accompanied by the involvement of the nasal or upper respiratory tract[3,4]. Conversely, nasal TNKCL invades the mid-line facial area, nasal cavity, sinus and upper respiratory tract though it shares the immunophenotype, genotype, and histopathological findings with the nasal type[4]. However, the nomination of the nasal or nasal type of TNKCL has recently given intricate conceptional confusion in differentiating from other various PTCL such as NCAM-negative ACTCL, previously named as lymphomatoid granulomatosis or angioimmunoproliferative lesions, blastic/monomorphic NK-cell lymphoma/leukemia, aggressive NK-cell leukemia, enteropathy-associated T-cell lymphoma(ETCL), and NCAM-positive true T-cell lymphoma[6,7], besides other five PTCL subclassified by Su[8].

The nasal type of TNKCL has distinct biological behavior, compared with other types of lymphoma[3,5,9,10]. First, it clinically exhibits a striking predilection for unusual anatomic sites of involvement(except for the upper respiratory tract or nasal cavity); the skin, muscle, central nervous system, pituitary gland, pancreas and adrenal gland[2,11-13]. Second, there is histologically prominent angiocentricity, angiodestruction, tissue necrosis and dense dermal infiltration by small-to-medium sized, polymorphic atypical lymphoid cells[3-5,9]. Third, in immunophenotypical profiles, it invariably shows positiveness to NCAM, CD2, and CD43[2,4,9]. However, other NK-cell markers, such as CD16 and CD57, and other T-cell markers including CD3, CD4, CD5, CD7, and CD8, are all negative[2-4,6,12,13]. Fourth, there is no clonally rearranged TCR-ß, γ, δ or genes[2,4]. Fifth, it pursues an aggressive and resistant clinical course, comparable with a rapidly fatal course of NCAM-negative EBV-associated PTCL[2,4,6,10]. Finally, it has a strong association with EBV[4,5,13]. In this case, there was no involvement of the upper respiratory tract or nasal cavity. Histological findings included angiocentricity, angiodestruction and necrosis of the epidermis and skin appendages. The immunophenotypes were CD2+, CD3-, CD4-, CD5-, CD8-, NCAM+ and CD43+. There was no rearrangement of TCR-ß, γ, δ chain gene. The clinical course did not respond to conventional anticancer therapy, and there was EBV positiveness in situ hybridization. All these features were manifestly diagnostic of typical nasal type TNKCL.

NCAM(neural cell adhesion molecule, CD56) is a member of the immunoglobulin superfamily glycoprotein found in cells of a variety of tissues; brain, nerve, muscle, and large granular lymphocytes(LGL) such as NK-cells and non-MHC restricted cytotoxic T-cells[10,11,14]. NCAM has been described on neuroblastoma, small cell carcinoma of the lung, malignant melanoma, myelocytic leukemia and multiple myeloma[3]. An overall expression rate of NCAM in PTCL is estimated by about 24%[2]. NCAM on the surfaces of tumor cells might direct those cells into other tissues that also express NCAM[2,10] because NCAM antigen characteristically exhibits homophilic(like-to-like) binding[2,10,11]. Accordingly, it is possible that NCAM might have a role in determining the biological behavior of PTCL, in that the nasal type of TNKCL pursues a more aggressive clinical course and frequent extranodal spreading, compared with its NCAM-negative counterpart[2]. Takeshita et al[9]. reported that atypical LGL expressing NCAM might produce angiocentric and/or angiodestructive features and lobular panniculitis by enhanced expression of IL-2, IL-2 ß receptors, and perforin on cell surfaces. However, it is not confirmatory that these lymphomas may represent NK cell or indeterminate LGL possessing biphenotypes rather than true T-cell neoplasms[2,4,6,10,12,15]. In this case, we could identify NCAM+ phenotype on tumor cells.

In addition, EBV may play an etiological role in the tumorigenesis of this lymphoma[4]. There is a recent report that EBV might activate secretion of varied cytokines such as TNF-α, ß from atypical lymphoid cells to lead to tissue necrosis, angiodestruction and hemophagocytosis syndrome[3]. Many reports showed that EBV was strongly correlated with NCAM positivity[4,5,13]. However, there was also a correlation between EBV positivity and CD3 negativity, independent of the NCAM positivity[4]. Our case with NCAM+ CD3- phenotypes revealed the nuclear positiveness to EBV genomes.

A differential diagnosis of the nasal type of TNKCL from other varied PTCL is possible only through immunophenotyping by a wide panel, TCR gene rearrangement analysis and EBV in situ hybridization because these lymphomas have near-

ly the same histological findings. NCAM-negative ACTCL is usually clonal TCR rearrangement(TCRr)-, CD2+, CD3-, CD4 +/-, CD8 +/- and EBV+[3,15]. Blastic/monomorphic NK-cell lymphoma/leukemia is characterized by the finding of CD2- and EBV- though it is TCRr-, CD3-, and NCAM+ as in the nasal type of TNKCL[3]. Aggressive NK-cell leukemia is considered as a leukemic variant of the nasal type of TNKCL[6]. Although it invariably exhibits identical immunophenotypical findings with TNKCL, it is distinguishable from the nasal type of TNKCL in that the former reveals atypical cells having large azurophilic cytoplasmic granules in the peripheral blood and bone marrow[6,13]. ETCL, accompanied by gastrointestinal symptoms as in ulcerative colitis, is TCRr+, CD3+, NCAM- and EBV-[3,7]. NCAM-positive true T-cell lymphoma shows TCRr+, CD3+, and EBV+[3].

In summary, we report a case of the NCAM-postive nasal type of TNKCL showing EBV association. We propose that especially in Asia, where PTCL is relatively common, thorough immunophenotypical studies including NK-cell marker and in situ hybridization of EBV genome in tissues, should be performed for the accurate prognostic evaluation in PTCL patients.

REFERENCES

1. Leboit PE: Cutaneous lymphomas and leukemia. In Elder D, Elentsas R, Jaworsky C, Johnson JB(eds); Lever's histopathology of the skin(8th Ed). Lippincott-Raven, New York, 1997, pp805-843.
2. Kern WF, Spier CM, Hanneman EH: Neural cell adhesion molecule-positive peripheral T-cell lymphoma; a rare variant with a propensity for unusual sites of involvement. Blood 79:2432-2437, 1992.
3. Jaffe ES, Chan JK, Su IJ: Report of the workshop on nasal and related extranodal angiocentric T/natural killer cell lymphomas; definitions, differential diagnosis, and epidemiology. Am J Surg Pathol 20:103-111, 1996.
4. Tsang WY, Chan JK, Yip TT, Wong KF: In situ localization of Epstein-Barr virus encoded RNA in non-nasal/nasopharyngeal CD56-positive and CD56-negative T-cell lymphoma. Hum Pathol 25:758-765, 1994.
5. Cho KH, Yang SG, Kim CW: Angiocentric T-cell lymphoma of the skin. Kor J Dermatol 34:953-960, 1996.
6. Imamura N, Kusunoki Y, Kawa-Ha K, Yumura K: Aggressive natural killer cell leukaemia/lymphoma; report of four cases and review of the literature, possible existence of a new clinical entity originating from the third lineage of lymphoid cells. Br J Haematol 75:49-59, 1990.
7. Son HJ, Rhee PL, Kim JJ: Primary T-cell lymphoma of the colon. Kor J Int Med 12;238-241, 1997.
8. Su IJ, Tsai TF: Cutaneous manifestations of Epstein-Barr virus-associated T-cell lymphoma. J Am Acad Dermatol 29:685-692, 1993.
9. Takeshita M, Akamatsu M, Ohshima K: Angiocentric immunoproliferative lesions of the skin show lobular panniculitis and are mainly disorders of large granular lymphocytes. Hum Pathol 26:1321-1328, 1995.
10. Wong KF, Chan JK: CD56(NKH-1)-positive hematolymphoid malignancies; an aggressive neoplasm featuring frequent cutaneous/mucosal involvement, cytoplasmic azurophilic granules, and angiocentricity. Hum Pathol 23:798-804, 1992.
11. Lanier LL, Chang C, Azuma M, Ruitenberg JJ: Molecular and functional analysis of human natural killer cell-associated neural cell adhesion molecule(NCAM/CD56). J Immunol 146;4421-4426, 1991.
12. Nakamura S, Suchi T, Koshikawa T, Kitoh K: Clinicopathologic study of CD56(NCAM)-positive angiocentric lymphoma occurring in sites other than the upper and lower respiratory tract. Am J Surg Pathol 19:284-286, 1995.
13. Chan JK, Sin VC, Wong KF, Ng CS: Nonnasal lymphoma expressing the natural killer cell marker CD56: a clinicopathologic study of 49 cases of an uncommon aggressive neoplasm. Blood 89:4501-4503, 1997.
14. Tsang WY, Chan JK: Utility of a paraffin section-reactive CD56 antibody(123C3) for characterization and diagnosis of lymphomas. Am J Surg Pathol 20:202-210, 1996.
15. Ansai S, Macda K, Yamakawa M, Matsuda M: CD56-positive(nasal type T/NK-cell) lymphoma arising on the skin; report of two cases and review of the literature. J Cutan Pathol 24:468-476, 1997.