J Clin Exp Hematopathol
Vol. 50, No. 1, May 2010

Case Study

A Unique Case of Nasal NK/T Cell Lymphoma with Frequent Remission and Relapse Showing Different Histological Features During 12 Years of Follow Up

Kazuko Watanabe,[1] Akitoshi Hanamura,[2] and Naoyoshi Mori[3]

Nasal natural killer (NK)/T cell lymphoma is an aggressive subtype of non-Hodgkin lymphomas, usually with a broad morphological spectrum, necrosis and angioinvasion, and is closely associated with Epstein-Barr virus (EBV) infection. We herein report a unique case of nasal NK/T cell lymphoma with frequent complete remission and relapse 12 years of follow up. A 9-year-old girl was diagnosed as having nasal NK/T cell lymphoma in 1995. The histological features were typical with diffuse lymphoid cell infiltration and angiocentric destruction. At the time of third relapse, however, biopsy showed infiltration of small sized lymphoid cells without necrosis and ulceration. These lymphoid cells were positive for both NK/T cell phenotype and EBV-encoded small RNAs. The tumor regressed spontaneously after biopsy and her clinical symptoms subsided. When she was admitted to the hospital in 2006 she had an extensive destructive lesion in the nasal cavity. These findings represent a rare case, in which histological findings changed in each time of relapse. 〔*J Clin Exp Hematopathol 50(1) : 65-69, 2010*〕

Keywords: localized natural killer/T cell lymphoma, Epstein-Barr virus-associated lymphoma, Epstein-Barr virus-encoded small RNA

INTRODUCTION

The extranodal natural killer (NK)/T cell lymphoma, nasal type is a distinct clinicopathologic entity which is very rare in Western countries and is relatively common among Asians, Mexicans and South Americans.[1,2] Clinically, it is localized to the nasal cavity, however, other upper aero tracts can also be involved. The histological features are characterized by diffuse or patchy infiltration of atypical lymphoid cells with angiodestrcutive growth pattern. The cytological spectrum is very broad, from small to large sized with anaplastic features. In most cases, lymphoma cells are medium sized or are a mixture of various sized cells, and frequently show irregular folding and granular chromatin. Immunohistochemically, the lymphoma cells have NK/T cell phenotypes. Most cases are also positive for cytotoxic molecules and show a striking association with Epstein-Barr virus (EBV).[3,4] Patients who present with stage III/IV NK/T cell lymphoma exhibit more aggressive behavior and poor prognosis compared with patients of nasal stage I/II.[5]

We herein present an atypical case of NK/T cell lymphoma in a 9-year-old girl. Although the histological features at her first admission were that of typical NK/T cell lymphoma, when she had a relapse, the lymphoma was localized and composed of small sized lymphoid cells without any atypism or necrosis. The histological features resembled reactive lymphocyte proliferation ; however, these lymphocytes had NK/T cell phenotypes and cytotoxic molecules, and were positive for EBV-encoded small RNAs (EBERs). To the best of our knowledge, such a case in which the histological features have changed after chemotherapy has not previously been reported.

Received : October 23, 2008
Revised : July 18, 2009
Accepted : September 14, 2009
[1]Department of Pathology and [2]Department of Hematology, Gifu Prefectural Tajimi Hospital, Tajimi, Gifu, Japan
[3]Department of Pathology, Nakatsugawa Municipal Central Hospital, Nakatsugawa, Gifu, Japan
Address correspondence and reprint request to Dr. Kazuko Watanabe, Department of Pathology, Gifu Prefectural Tajimi Hospital, 5-161 Maehata, Tajimi, Gifu 507-8522, Japan. E-mail : watanabe-kazuko 1@.pref.gifu.lg.jp

CASE REPORT

A 9-year-old girl presented at our hospital with complaints of nasal hemorrhage and obstruction in 1995. On physical examination, the patient had a mass in the left nasal cavity without lymph node swelling or bone-marrow infiltration. She was diagnosed as having NK/T cell lymphoma (Stage I) by punch biopsy and underwent chemotherapy according to the T-cell acute lymphoblastic leukemia protocol. The re-

sponse was good and she was discharged from the hospital. She was again admitted to our hospital due to the tumor in the left nasal cavity in 1998. The relapse was confirmed by punch biopsy from nasal cavity (in the case of the first relapse). Any other sites of recurrence were not found. Salvage therapy was performed followed by autologous peripheral blood stem cell transplantation. One month after chemotherapy, the computed tomography scan did not show the mass and she left the hospital. In 2001, she presented with a tumor of the tonsil (this being the second relapse). She was treated with combination chemotherapy (DeVIC ; dexamethasone, etoposide, ifosfamide, and carboplatin ; three times). The response was good and she recovered completely. From 2002 to 2004, she had been followed up as an outpatient with medication of Chinese herbal medicine. In 2004, she had a left nasal mass again. Punch biopsy revealed a proliferation of small sized lymphoid cells with no atypia and no necrosis in the nasal mucosa. Image findings also did not show necrosis and invasion. The histological findings were different from those of typical NK/T cell lymphoma. The lymphoid cells were positive for CD3 and CD56 and showed a signal of EBV gene by *in situ* hybridization. She was diagnosed as having relapse (third relapse) ; however, the size of tumor decreased spontaneously after surgical resection and her clinical symptoms subsided. She was discharged from the hospital and followed from then. During follow up periods, when a new mass was detected, the tumor resolved only by local excision. When she came to the hospital on March in 2006, she had an extensive destructive lesion in the nasal cavity. Biopsy specimen revealed typical NK/T cell lymphoma. At this time, lymph node was not swelling and bone-marrow infiltration was not found, similar to the previous relapse. Combination chemotherapy (90% dose of DeVIC) was started, and total 50.5 Gy of irradiation was given. She showed marked improvement after 2 courses of therapy and was discharged from the hospital. To date, the patient has remained well without any evidence of recurrence.

PATHOLOGICAL FINDINGS

The histological features of the initial and two subsequent recurrent lesions were quite similar. Medium to large sized lymphoid cells with irregular nuclei showed extensive infiltration into the nasal mucosa with angiocentric growth pattern and coagluative necrosis was present (Fig. 1). These lymphocytes were immunostained for CD3ε and CD56, and showed a signal of EBV encoded RNA by *in situ* hybridization technique.

In 2004, she had left a nasal mass again (second relapse). Punch biopsy and local excision were performed. The nasal mucosa was diffusely infiltrated by non atypical lymphoid cells without ulceration and necrosis. In high power view, the lymphoid cells were small sized without nuclear irregularity. These were similar to reactive lymphocytes ; however, the lymphoid cells were positive for CD3ε, CD56, CD2, cytotoxic molecules such as granzyme B and T-cell intracellular antigen-1, and EBERs (Fig. 2).

When she had a relapse again in 2006 (third relapse), the histological findings showed typical NK/T cell lymphoma, quite similar to the initial tumor (Fig. 3).

DISCUSSION

NK/T cell lymphoma has a broad cytological spectrum varying from pleomorphic mixed, small, medium, or large cells to predominantly large cells.[1] Small cell variants such as this case, however, may mimic a reactive inflammatory process. Recently, Robert *et al*. reported similar cases with predominantly small lymphoid cells and remained indolent for 10 years prior to recurrence.[6] This study also described that it was difficult to diagnose such cases with proliferation of only small sized lymphoid cells without atypia and necrosis, even if the lymphoid cells expressed typical NK cell immunophenotypes. Finally, they diagnosed their case as malignant because the lymphoid cells infiltrated into the bone of the nasal septum. In our case, the tumor was localized in the nasal mucosa and tonsil without invasion into any other regions. Furthermore, to our knowledge, there have been no reports that aggressive typical NK/T cell lymphoma changed into indolent lymphoma after chemotherapy, so the diagnosis was more difficult than their case. Kitamura *et al*. studied the immunophenotypes on primary lymphomas arising from the nasal cavity.[7] They reported that the lymphoma cells were mostly of NK/T cell derivation and *in situ* hybridization for EBERs was positive in 31/31 cases. We consider that to be an important clue to the diagnosis of NK/T cell lymphoma, where having low-grade appearance resembling reactive lymphocytes is the demonstration of being both positive for NK/T cell antigen and EBERs. There have many attempts to evaluate of prognostic factors of nasal NK/T cell lymphoma, but so far no specific factors have been identified.[5,8,9] We should make a diagnosis of such an atypical case like this cautiously.

De novo NK/T cell lymphomas occur less frequently in childhood. We must consider whether our case was a *de novo* case or a case occurring in the context of chronic active EBV infection (CAEBV). CAEBV is characterized by chronic or recurrent infectious mononucleosis like symptoms, such as fever, hepatosplenomegaly, persistent hepatitis and extensive lymphadenopathy, which normally occurs between the ages of 2 to 20 years old.[10] The prognosis of CAEBV is generally poor, because the patient often develops malignant lymphoma, including T/NK-cell lymphoma, or EBV-associated hemophagocytic syndrome. Watanabe *et al*. reported the spontaneous regression of EBV associated T-cell lymphoma of the stomach in a patient with CAEBV.[11] In our case, both EBV antibody titers and EBV DNA determination have not been

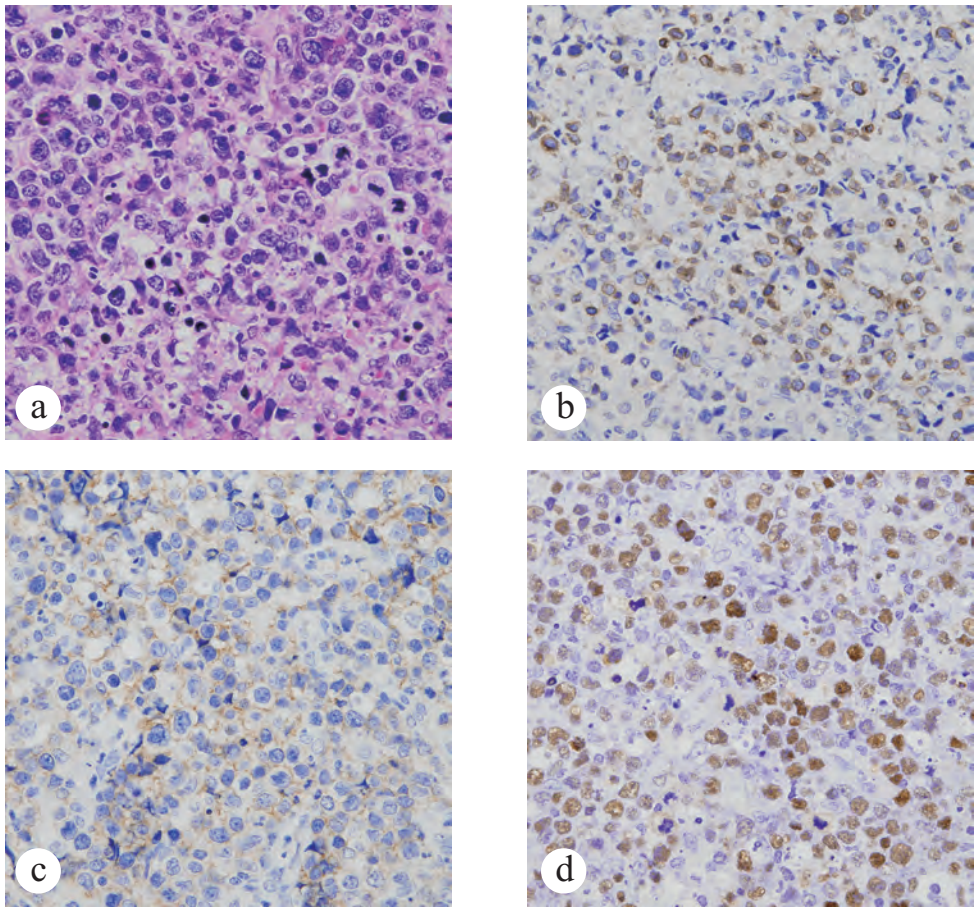

Fig. 1. Histological and immunohistochemical features of nasal tumor in 2001. (***1a***) H&E stain. (***1b***) Lymphoma cells are positive for CD3. (***1c***) Lymphoma cells are positive for CD56. (***1d***) *In situ* hybridization for Epstein-Barr virus-encoded small RNAs reveals positivity. (***1a***) ×400, (***1b***)-(***1d***) counterstained with hematoxylin, ×400.

performed though the all clinical course. However, we did not have information that the patient had extensive lymphaenopathy, pancytopenia and hepatosplenomegaly, nor did she have mosquito allergy or photosensitivity reaction. We consider that this case can not confirm NK/T cell lymphoma associated with CAEBV. Even if the patient was affected with CAEBV, this clinical course of repeated relapse and remission of NK/T cell lymphoma was rare.

Recently, there were several reports that local radiation therapy before systemic chemotherapy may be effective for localized NK/T cell lymphoma (I/II disease).[12,13] In our case, the patient was 9-years old, and the doctor at the time of first onset, did not treat with irradiation in consideration of possible side effects. During the indolent stage of third relapse, any radiation therapy or chemotherapy was not done because her tumor disappeared by surgical resection alone. But the tumor has relapsed as an aggressive lymphoma after two years. Further studies of treatment for such a case like this are required to understand the proper treatment and evaluation of such cases.

REFERENCE

1 Chan JKC, Quintanilla-Martinez L, Ferry JA, Peh S-C : Extranodal NK/T-cell lymphoma, nasal type. In : Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, *et al*. (eds) : World Health Organization Classification of Tumours, WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed, International Agency for Research on Cancer (IARC), Lyon, pp. 285-288, 2008

2 Chan JK, Sin VC, Wong KF, Ng CS, Tsang WY, *et al*. : Nonnasal lymphoma expressing the natural killer cell marker CD56 : a clinicopathologic study of 49 cases of an uncommon aggressive neoplasm. Blood 89 : 4501-4513, 1997

3 Kanavaros P, Lescs MC, Briere J, Divine M, Galateau F, *et al*. : Nasal T-cell lymphoma : a clinicopathologic entity associated

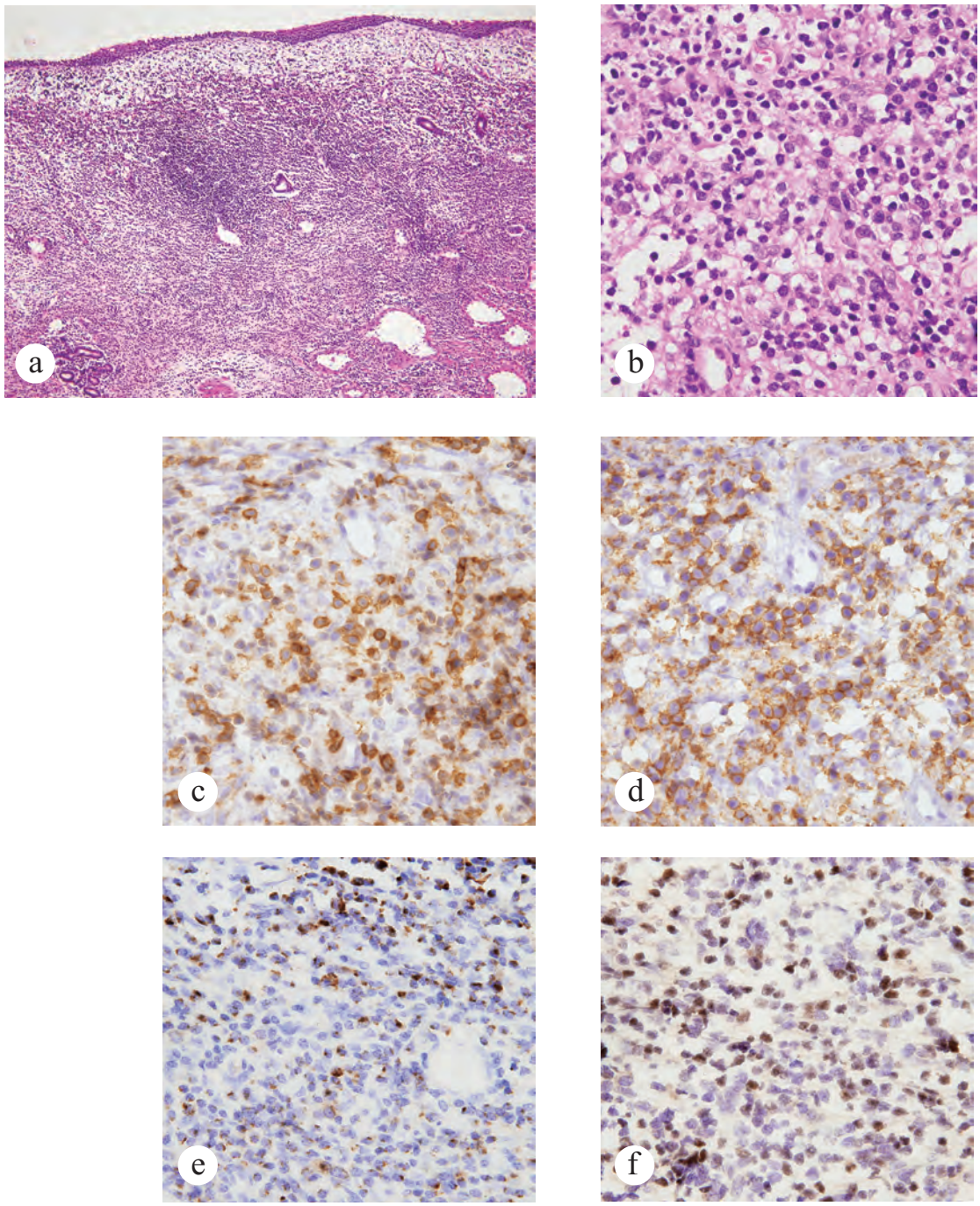

Fig. 2. Histological and immunohistochemical findings at the time of relapse in 2004. (***2a***) The nasal mucosa is diffusely infiltrated by small lymphoid cells. H&E stain. (***2b***) The lymphoid cells are small sized without atypia. H&E stain. (***2c***) Lymphoid cells are positive for CD3. (***2d***) Tumor cells are positive for CD56. (***2e***) Tumor cells are positive for granzyme B. (***2f***) The lymphoid cells are positive for Epstein-Barr virus-encoded small RNAs. (***2a***) ×40, (***2b***) ×400, (***2c***)-(***2f***) counterstained with hematoxylin, ×400.

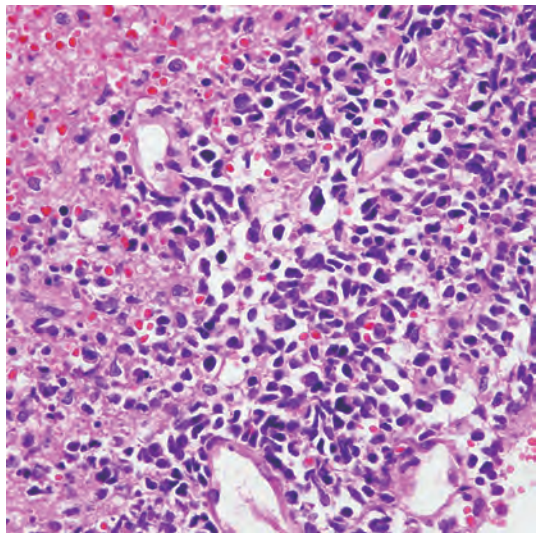

Fig. 3. Histological findings at relapse in 2006. Lymphoid cells have pleomorphic feature with necrosis, similar to the initial tumor. H&E stain, × 400.

with peculiar phenotype and with Epstein-Barr virus. Blood 81 : 2688-2695, 1993

4 Jaffe ES, Chan JK, Su IJ, Frizzera G, Mori S, *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 20 : 103-111, 1996

5 Na II, Kang HJ, Park YH, Lee SS, Yoo HJ, *et al.* : Prognostic factors for classifying extranodal NK/T cell lymphoma, nasal type, as lymphoid neoplasia. Eur J Haematol 79 : 1-7, 2007

6 Hasserjian RP, Harris NL : NK-cell lymphomas and leukemias : a spectrum of tumors with variable manifestations and immunophenotype. Am J Clin Pathol 127 : 860-868, 2007

7 Kitamura A, Yamashita Y, Hasegawa Y, Kojima H, Nagasawa T, *et al.* : Primary lymphoma arising in the nasal cavity among Japanese. Histopathology 47 : 523-532, 2005

8 Kim SJ, Kim BS, Choi CW, Choi J, Kim I, *et al.* : Ki-67 expression is predictive of prognosis in patients with stage I/II extranodal NK/T-cell lymphoma, nasal type. Ann Oncol 18 : 1382-1387, 2007

9 Kim TM, Park YH, Lee SY, Kim JH, Kim DW, *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 106 : 3785-3790, 2005

10 Kimura H : Pathogenesis of chronic active Epstein-Barr virus infection : is this an infectious disease, lymphoproliferative disorder, or immunodeficiency ? Rev Med Viol 16 : 251-261, 2006

11 Watanabe N, Okazaki K, Yazumi S, Ohana M, Uchida K, *et al.* : Spontaneous regression of Epstein-Barr virus-associated T-cell lymphoma of the stomach. Gastrointest Endosc 57 : 414-417, 2003

12 Huang MJ, Jiang Y, Liu WP, Li ZP, Li M, *et al.* : Early or up-front radiotherapy improved survival of localized extranodal NK/T-cell lymphoma, nasal-type in the upper aerodigestive tract. Int J Radiat Oncol Biol Phys 70 : 166-174, 2008

13 Tamai Y, Imataki O, Abe Y, Hagiwara S, Ito I, *et al.* : Case series of localized nasal NK/T-cell lymphoma treated with preceding intensified local radiation therapy before systemic chemotherapy. Gan to Kagaku Ryoho 33 : 687-690, 2006 (*in Japanese*)