A Case of Nasal NK Cell Lymphoma

Takeshi AKISADA, Yozo ORITA, Tsuyoshi YOSHIHIRO, Hideho WADA* and Yoshito SADAHIRA* *

Departments of Otorhinolaryngology, Hematology, Pathology* *, Kawasaki Medical School, Kurashiki 701-0192, Japan*

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ABSTRACT. A case of nasal lymphoma derived from natural killer (NK) cells is presented. A 72-year-old woman complaining of left epistaxis visited our hospital. Anterior rhinoscopy revealed a light-red colored mass. Histopathological findings were indicative of malignant lymphoma (diffuse mixed, small and large cell type). Azurophilic granules were disclosed by Giemsa staining. Immunohistochemically, the tumor cells were positive for CD56, CD3 ε, and TIA-1, but negative for surface CD3. Genotypic analysis revealed no rearrangement of TCR β, γ, δ gese. Based on these findings, the tumor cells were suspected of NK cell lineage. We then performed combination chemotherapy and radiation therapy (46Gy). Her tumor was resolved on anterior rhinoscopy, CT and MRI examinations, and recurrence has not been observed during the 20 months to date. Our present study suggest that some nasal lymphomas are of NK cell lineage and radiation therapy may be effective for this type of lymphomas.

Key words: nasal lymphoma — NK cell

The head and neck region is one of the most common sites of extranodal non-Hodgkin's lymphoma.[1] However, malignant lymphomas arising in the nasal cavity and paranasal sinuses are unusual.[2-4] A relatively high incidence of sinonasal lymphoma has been observed in Asian countries.[1,5] Most of the cases have been considered an nasal T-cell lymphomas because they express markers of T cells.[6,7] We also encountered six Japanese patients with primary sinonasal lymphoma at Kawasaki Medical School Hospital over an 18-year period.[8] These lymphomas arose from the nasal cavity in three cases and from the paranasal sinuses in three cases. Immunohistochemical studies revealed the atypical cells to be T cells in two cases, and B cells in two cases. Two other cases were of undetermined origin.

Recently, there have been reports of cases with nasal lymphoma cells of NK cell lineage.[9-12] The NK cell lineage of the cases was suggested on the basis of the presence of cytoplasmic azurophilic granules, immunohistochemical NK cell markers, and no rearrangement of T cell receptor gene. However, no definitive existence of NK cell lymphoma has been widely accepted. In this paper, we describe a case of nasal lymphoma derived from NK cells and discussed distinctions from T cell lymphoma.

秋定 健，折田洋造，吉弘 剛，和田秀穂，定平吉都

CASE

A 72-year-old woman who had been complaining of left epistaxis since October, 1995 visited our hospital on November 24, 1995. Anterior rhinoscopy revealed a light-red colored mass in the left nasal cavity, and a nasal biopsy was performed (Fig 1). She was admitted to our hospital on January 10, 1996 with a diagnosis of malignant lymphoma.

An enhanced CT scan showed a tumor in the area from the left nasal cavity to the left ethmoid sinus (Fig 2). MRI examination revealed a tumor of low intensity by T1 weighted imaging and of high intensity by T2 weighted imaging. There was slight enhancement with Gadolinium diethylenetriaminepentacetic acid(Gd-DTPA) (Fig 3).

The patient's peripheral blood count values and screening data were normal. Measurements of the antibody to the Epstein-Barr virus (EBV), viral capsid antigen (VCA) IgG and EBV-asociated nuclear antigen (EBNA) were

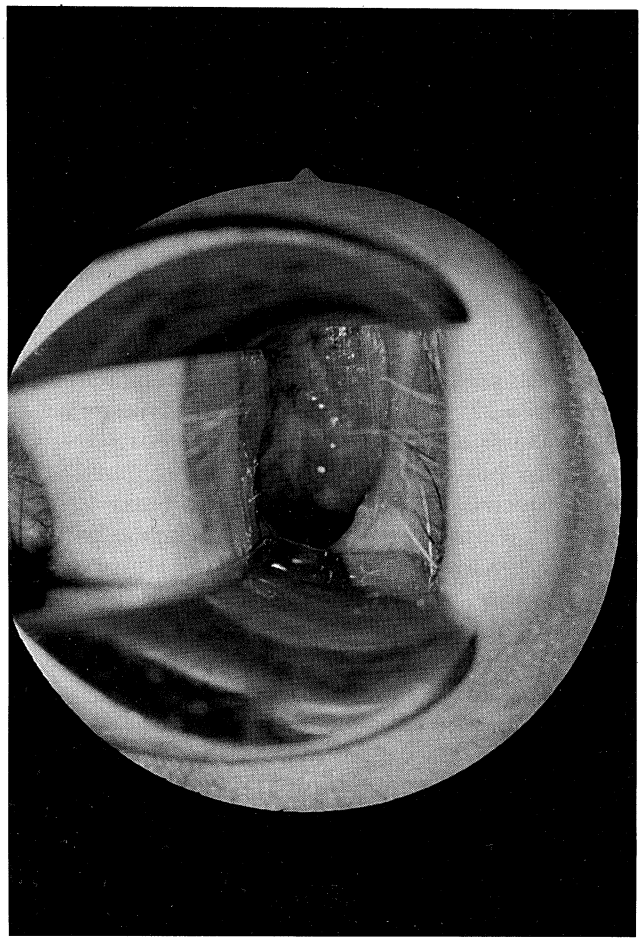

Fig 1. Anterior rhinoscopy showed a light-red colored mass in the left nasal cavity and lateral movement of the inferior turbinate.

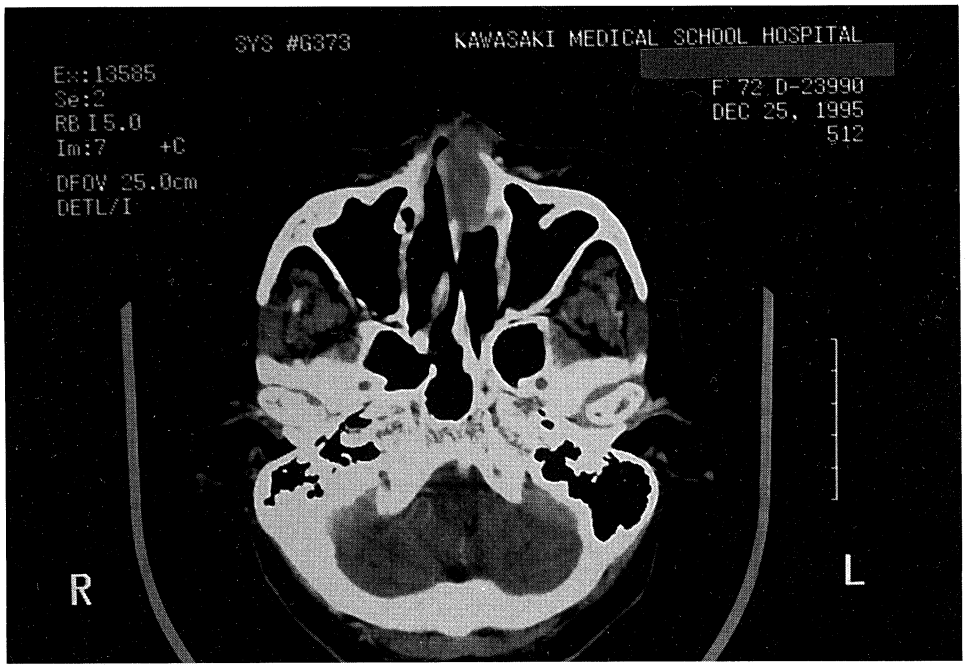

Fig 2. Enhanced computed tomographic scans showed a large mass in the left nasal cavity.

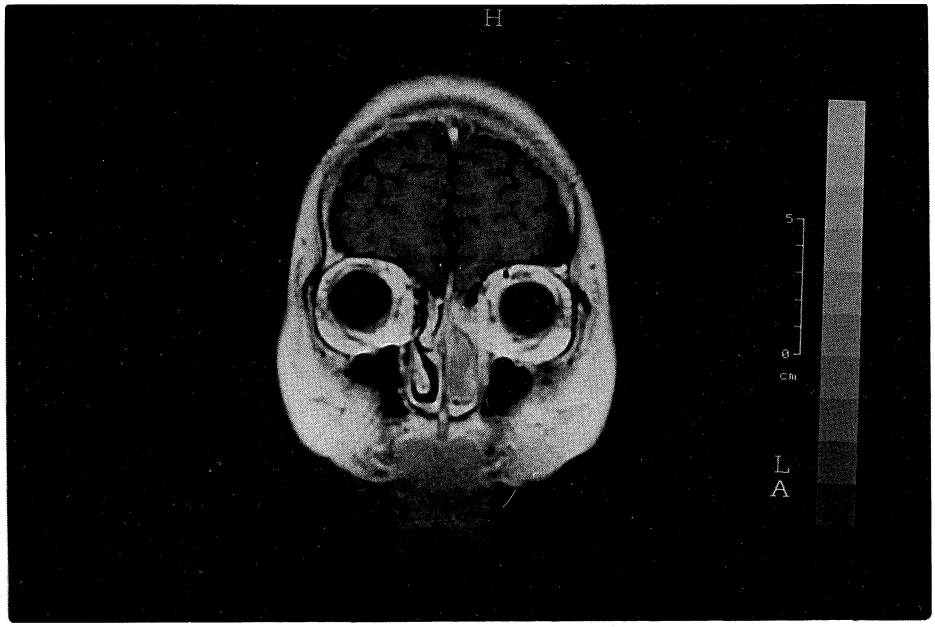

Fig 3. MRI(coronal view) showed a tumor filling the left nasal cavity and ethmoid sinus.

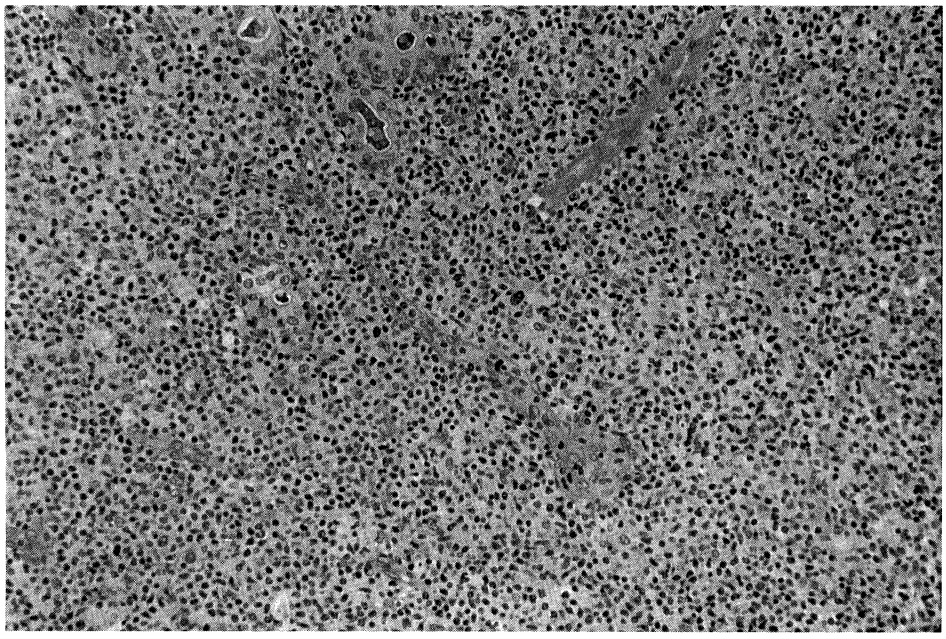

Fig 4A. A nasal biopsy showed a non-Hodgkin's lymphoma (diffuse mixed, small and large cell type).

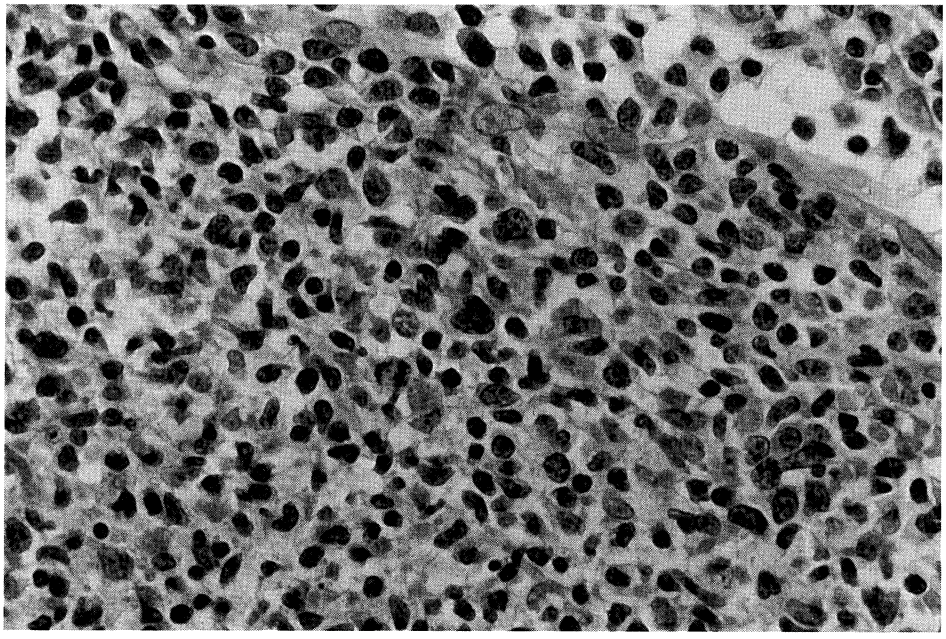

Fig 4B. Histopathological findings (HE staining).

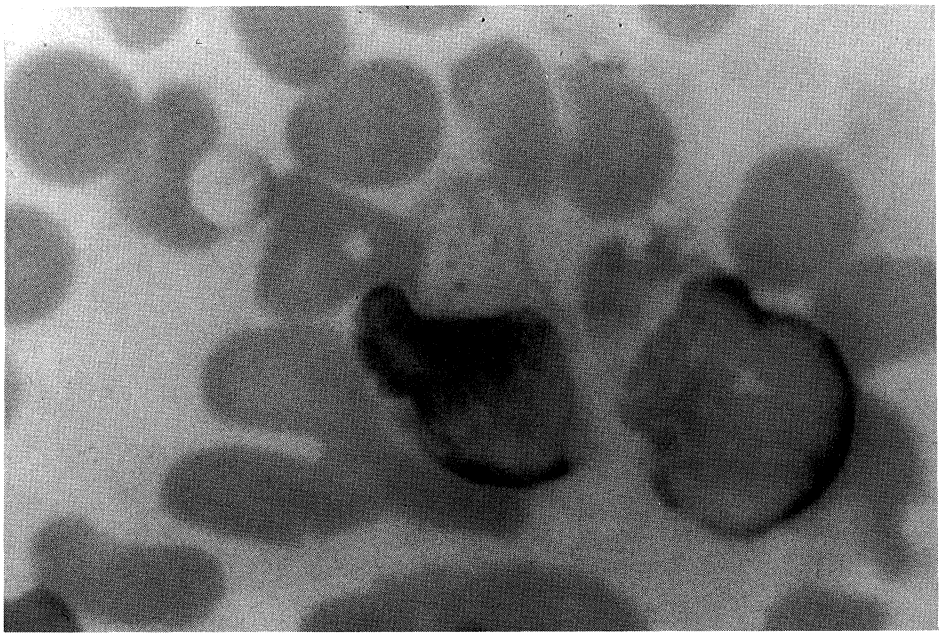

Fig 4C. Azurophilic granules in the cytoplasm (May-Grünwald-Giemsa staining).

high. These findings were indicative of that her EBV past infection.

^{67}Ga scintigraphical examination revealed a slightly increased hot spot in the nasal region. Bone scintigraphy, a bone marrow biopsy, and echography of the abdomen were normal. The patient's clinical stage was IEA according to the Ann Arbor classification.[13]

Histopathological study revealed pleomorphic lymphoid proliferation composed mainly of small-sized cells intermingled with a variable number of slightly large cells, histiocytes, and swelling of epithelial cells. The tumor cells had invaded and destroyed the squamous epithelium, but invasion of the blood vessels by the tumor cells was not evident. The histological subtype was diffuse mixed, small and large cell type, according to the Working Formulation[14] (Fig 4A, B). Azurophilic granules were detected in the cytoplasm by May-Grünwald-Giemsa staining (Fig 4C).

Surface marker of tumor tissue analyzed with flow cytometry is shown in Table 1. In particular, CD2 was 73.9%, but no diagnostic information was

TABLE 1. Surface marker of tumor tissue analyzed with flow cytometry

T cell lineage		B cell lineage		Others	
CD1	0.6%	CD10	3.3%	HLA-DR	62.5%
CD2	73.9%	CD19	8.1%		
CD3	46.2%	CD20	5.2%		
CD4	10.0%	Myeloid lineage			
CD5	41.5%	CD13	12.4%		
CD7	54.5%	CD14	6.8%		
CD8	38.4%	CD33	2.7%		

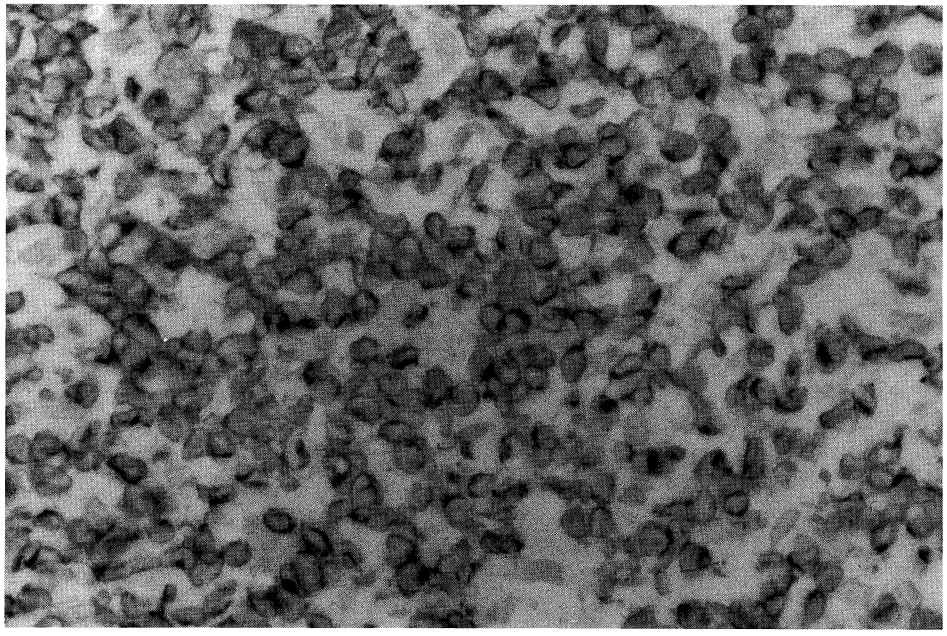

Fig 5A. CD3 cytoplasmic-positive (frozen sections) staining.

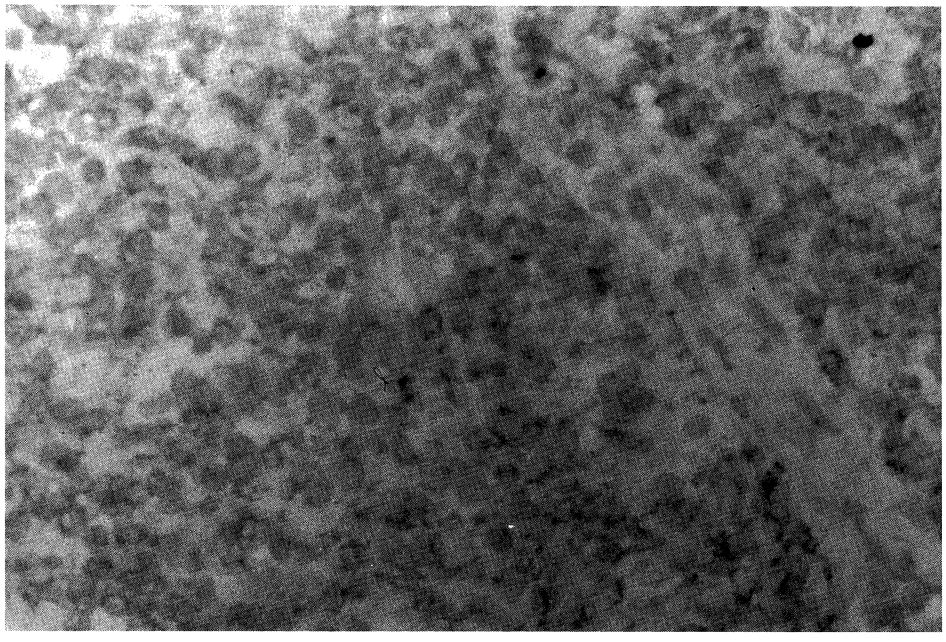

Fig 5B. CD56-positive (frozen sections) staining.

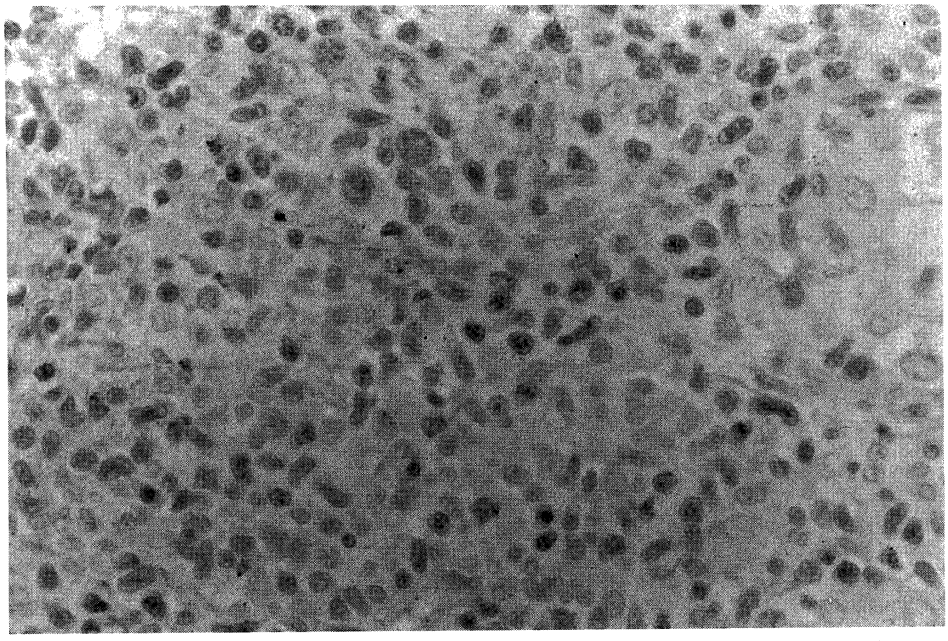

Fig 5C. EB virus-encoded RNA in situ hybridization. Note the positive signal in the nuclei of tumor cells.

available. In immunohistochemical studies of frozen and paraffin sections of the tumor, atypical cells displayed a CD3−, CD3 cytoplasmic+(Fig 5A), CD19−, CD20−, CD45+, CD45RO+, CD56+(Fig 5B), and CD57− phenotype. In addition, cytolytic protein and TIA-1 were detected in the cytoplasm.

Fresh frozen tissue was available for Southern blot hybridization. Genotypic analysis revealed no evidence of clonal rearrangements of the β, γ, δ chain genes of the T-cell receptor (TCR) (date not shown). An EBV infection was detected using the method df EBV-encoded RNA (EBER) in situ hybridization (Fig 5C).

Initially, we performed combination chemotherapy (THP-COP) with pirarubicin 40mg, cyclophosphamide 650mg, vincristine 1mg, and predonisolone 40mg.[15] However anterior rhinoscopy showed no change in tumor size after the one course of this THP-COP regimen, so we considered the chemotherapy to have had no beneficial effect on her tumor. Therefore we started irradiation with 46 Gy, and this was effective. Anterior rhinoscopy showed no mass in the left nasal cavity, and CT and MRI after treatment showed no tumor. No recurrence of her nasal tumor has been observed during the 20 months to date.

DISCUSSON

Morphologically, NK cells are large granular lymphocytes with azurophilic granules in the cytoplasm. Phenotypically, they do not express CD3 or TCR antigen, although they commonly express CD16 and CD56 antigen. Functionally, they mediate the major histocompatibility complex-unrestricted cytolytic reaction on target cells; e.g., tumor cells and viral infected cells.

When all these criteria are fulfilled, such lymphocytes are defined as NK cells.[16] Thus, the diagnosis of NK cell lymphoma is extremly difficult without functional assay of the tumor cells. However, it has been recognized that NK-cell lymphoma is a distinct clinicopathologic entity.[17] Clinically, it commonly presents with midfacial destructive disease. In other cases, it presents with a mass effect. Morphologically, the disease is characterized by a broad cytologic spectrum. The atypical cells may be small or medium-sized cells, large atypical and hyperchromatic cells, or a mixture of these types. In situ hybridization studies with probes to EBV-encoded small nuclear RNA may be very helpful in the diagnosis and can detect even small numbers of neoplastic cells. Necrosis is a virtually constant feature. Vascular invasion and destruction are also common. The tumor cells are frequently positive for the NK-cell associated marker CD56, although there are generally negative for other markers of NK cells, such as CD16 and CD57. The cells may express some T-cell-associated antigen, most often CD2. There is no expression of surface CD3. Cytoplasmic CD3 can often be detected using polyvalent antisera to CD3 in paraffin sections. The tumors do not show clonal T-cell receptor β chain gene rearrangement. Not only the surface markers, but also Giemsa staining and genotypic analysis are important in the diagnosis of NK lymphomas.

In our case, a broad cytologic spectrum and necrosis were noted, but angiocentricity and angioinvasion were not evident. Azurophilic granules were detected in the cytoplasm by Giemsa staining. Immunophenotypic analysis showed the tumor cells to be dimly positive for surface CD3 and in contradistinction, to be strongly positive for cytoplasmic CD3. The cells were brightly positive for CD56, but were negative for CD19 and CD20 with B cell markers. Genotypic analysis revealed no evidence of clonal rearrangements of the β, γ or δ chain genes of the TCR. The above findings would indicate that the tumor cells were of NK cells lineage.

The EBV infection in this tumor was demonstrated by EBV-encoded RNA in situ hybridization. An etiological link between EBV infection and nasal NK lymphomas has also been suggested. Kaneko *et al*,[18] reported the presence of the EBV receptor CD21 antigen in nasal lymphoma cells and normal NK cells, and the possibility exists that EBV gains entry into NK cells via the CD21 molecule and transforms them. EBV may play a role in the pathogenesis of nasal lymphomas.

The therapy for early stage nasal lymphomas is radiation alone or in combination with chemotherapy. For patients in the advanced stage, combination chemotherapies; for example, CHOP (cyclophpsphamide, doxorubicin, vincristine, and prednisolone), BACOP (bleomycin, doxorubicin, cyclophosphamide, vincristine, and prednisolone), and m-BACOP (methothrexate and folinic acid rescue, bleomycin, doxorubicin, cyclophosphamide, vincristine, and predonisolone) have been selected.[5] However, chemotherapies has been reported to have little effect.[5] Expression of multi drug resistance (MDR) P-glycoprotein has been reported to be one reason for the ineffectiveness of chemotherapy.[19] Yamamoto *et al*,[20] reported that every nasal NK lymphoma in their study had P-glycoprotein. In our case, although expression of MDR was not measured, THP-COP was not effective, but radiation was very effective. As for radiation therapy, notwithstanding the

fact that normal NK cells are comparatively resistant to radiation, nasal NK lymphoma is usually sensitive to radiation therapy.[17]

Nasal lymphomas are classified into two group, expanding type and infiltrative type, according to the mode of proliferation. They are also classified into four cell types; B cell type, T cell type, NK cell type and Null cell type, according to their surface markers and evidence of clonal rearrangement.[21] Most so-called lethal midline granulomas are infiltrative, T cell or NK cell type.[21] The present case was of the expanding, NK cell type. In the future, this classification shoud be useful in the choice of treatment and presumption of prognosis.

In conclusion, we encountered a very rare care of nasal lymphoma derived from NK cells. Radiation therapy was very effective for this case and the posttherapic course has been uneventful. However, this case must be followed up very closely and further studies are reguired to elucidate a detailed understanding of nasal NK cell lymphoma.

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