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CASE REPORT

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Nasal NK/T cell lymphoma presenting as transverse myelopathy

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Abstract A case of nasal NK/T cell lymphoma with central nervous system (CNS) involvement is reported. A 56-year-old man presented with eyelid edema and transverse myelopathy. Cerebrospinal fluid examination revealed atypical lymphoid cells with azurophilic granules, which were positive for CD2, CD8, and CD56, and negative for CD3 and CD5 by flow cytometry. Because a tumor mass was found involving the ethmoid and maxillary sinuses, CNS involvement was considered to have resulted from local invasion by the nasal lymphoma. In spite of intensive chemotherapy including intrathecal infusion, the patient died 6 months after the initial diagnosis. Autopsy revealed that lymphoma cells were positive for cytotoxic molecules, granzyme B and TIA-1, and EB virus-encoded RNA-1 (EBER-1), and they showed no rearrangement of TCR-β, -γ, or -δ genes, suggesting an NK-cell origin of the lymphoma cells. They showed an angiocentric and angiodestructive pattern in the subarachnoid space, focally extending to the cerebral cortex and cranial and spinal nerve roots. Marked demyelination was found in the lateral and posterior funiculi of the spinal cord. Thus, the pathogenesis of this spinal demyelination might be attributed to ischemia secondary to angiocentric and angiodestructive infiltration by lymphoma cells.

Key words NK cell · Lymphoma · Myelopathy · Demyelination · CNS

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Introduction

NK/T cell lymphoma is a distinct clinicopathologic entity identified by proliferation of atypical cells with cytoplasmic azurophilic granules, immunopositivity for CD56, CD2, and cytotoxic molecules, and no rearrangement of T-cell receptor genes [3]. It affects mostly middle-aged adults, who often present with fever, skin rash and hepatosplenomegaly in the absence of peripheral lymphadenopathy. Histologically, the lymphoma cells often show an angiocentric and angiodestructive infiltrating pattern with focal tissue necrosis. This lymphoma is divided into two types by location of the primary tumor [3]: nasal NK/T cell lymphoma and nonnasal NK/T cell lymphoma. The former develops primarily in the nasosinusoidal region and has been known to be a lethal midline granuloma or polymorphic reticulosis [8]. The latter is recognized as NK/T cell lymphoma occurring in nonnasal sites such as the skin, subcutis, gastrointestinal tract, and testis [1].

Local progression of nasal NK/T cell lymphoma may result in involvement of the central nervous system (CNS) [13, 15, 16]. Although this may be an important clinicopathological issue, precise information about such cases has not been provided. The present study aimed to describe an autopsy case of a patient with nasal NK/T cell lymphoma with CNS involvement.

Clinical history

A 56-year-old man had become aware of left eyelid swelling and nummular eczema-like eruptions of the extremities. A few weeks later, he was admitted to a local hospital because of numbness and incomplete paralysis of the left lower extremity. Cytologic examination of CSF revealed many atypical lymphoid cells. He was transferred to our hospital in June 1997. On physical examination, nummular eczema-like eruptions were scattered over the upper and lower extremities. He also exhibited eyelid edema. There was no hepatosplenomegaly. The pupils were anisocoric (right smaller than left); bilateral facial palsies were present; a manual muscle test showed flaccid paralysis of the lower extremities; deep tendon reflexes were decreased; there were no patho-

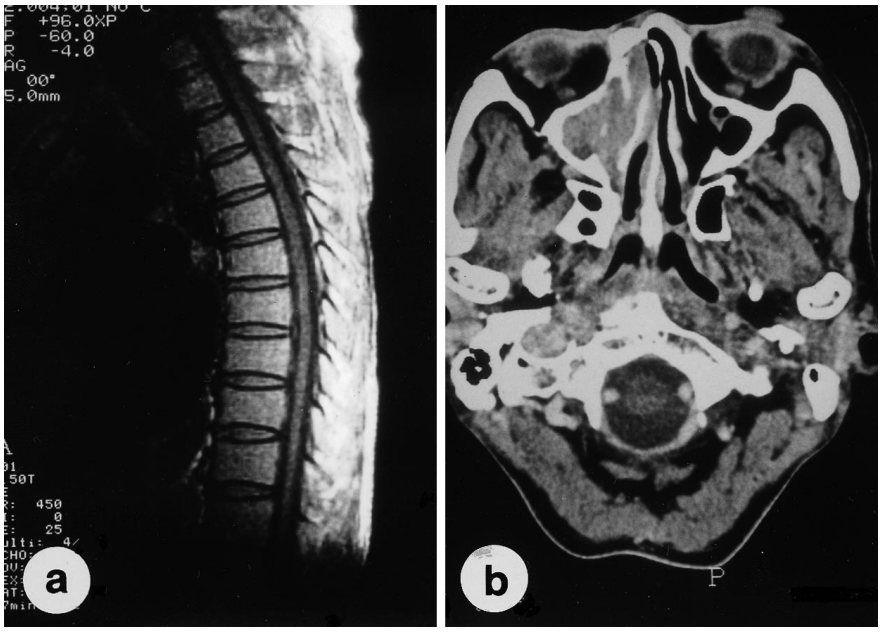


Fig. 1 **a** Magnetic resonance imaging shows no mass lesion in the vertebrae or spinal canal. **b** Computed tomography scan shows a mass lesion occupying the right maxillary sinuses

Table 1 Flow-cytometric analysis of cerebrospinal fluid. The percentage of reactivity for each antibody was determined after gating mononuclear cells by forward scatter and side scatter. The reactivity of negative control antibody was less than 0.5%

Antibody	Positivity (%)
CD1	0.0
CD2	98.4
CD3	2.5
CD4	0.7
CD5	3.5
CD7	99.8
CD8	96.2
CD10	0.1
CD13	0.4
CD14	0.2
CD19	0.2
CD20	0.2
CD25	0.3
CD30	3.1
CD56	95.9
HLA-DR	2.9

logical reflexes; superficial and deep sensations were decreased below the umbilical level of the abdominal wall and in both lower extremities; sphincter disturbance was noted. Thus, the presence of transverse myelopathy at T-10 level and cranial nerve disturbance was suspected.

Magnetic resonance imaging (MRI) did not show any lesions in the vertebrae or spinal canal (Fig. 1a). Computed tomography (CT) scan revealed an extensive mass lesion occupying an area from the right ethmoid to the right maxillary sinus with destruction of the bone (Fig. 1b) and mass lesions of both adrenal glands. In the CSF, the protein concentration was 9.96 g/l, glucose was 0.31 g/l, and the leukocyte count was 1.79×10^9/l and consisted exclusively of neoplastic cells with cytoplasmic azurophilic granules. Flow-cytometric analysis showed that these neoplastic cells expressed CD2, CD7, CD8, and CD56, but not CD3 or CD5 (Table 1). The EBV genome was also detected by PCR. A test was negative for serum anti-HTLV-I antibody. The titers of anti-EBV antibodies were as follows: VCA IgG, 160; VCA IgM <10; VCA IgA <10; EA-DR IgG, 160; EA-DR IgA <10; EBNA 80. HIV antibodies were not examined.

A skin biopsy specimen showed that pleomorphic lymphoid cells had infiltrated the dermis and subcutaneous tissues with angiocentric infiltration. In the subcutis, the lymphoma cell infiltration was accompanied by fat necrosis. Immunohistochemically, these cells reacted with CD45RO, CD3e, CD56, granzyme B, and TIA-1, but not with CD20, CD30, CD57 or CD68. Peripheral blood showed pancytopenia without atypical lymphocytes. Bone marrow showed marked hemophagocytosis by CD68-positive macrophages, indicating the presence of lymphoma-associated hemophagocytic syndrome. No megaloblastic changes were found. On biochemical examination, the levels of LDH and ferritin were 1.680 IU/l and 32.460 ng/ml, respectively. According to the above findings, the patient was diagnosed as having NK/T cell lymphoma; CS: IVB_{NOD}, PS: IV_{D+M-}. Immediately after admission, he underwent CHOP chemotherapy [6] and intrathecal infusion therapy with methotrexate, followed by ESHAP chemotherapy [14]. He died of adrenal gland failure on 29 November 1997.

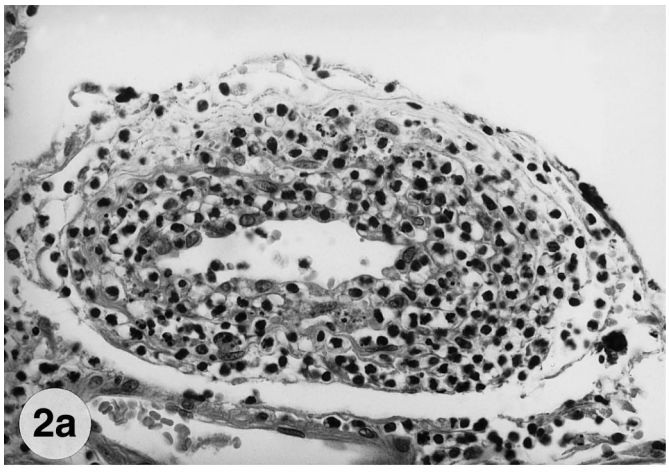
Materials and methods

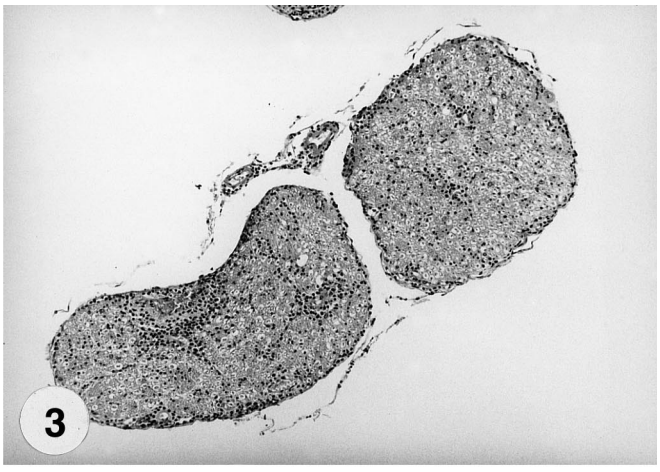
Flow-cytometric analysis

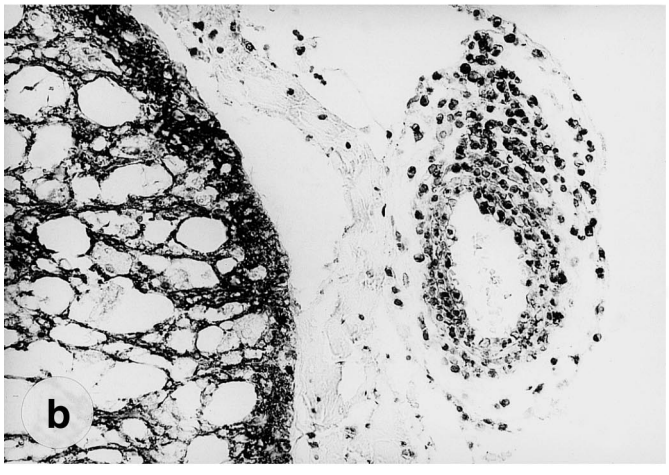
Single-cell suspension of cerebrospinal fluid (CSF) was examined by flow cytometry using a direct immunofluorescence method. The monoclonal antibodies (mAb) used in this study were CD1 (OKT6, Ortho Pharmaceutical Co., Raritan, N.J.), CD2 (OKT11, Ortho), CD3 (OKT3, Ortho), CD4 (OKT4, Ortho), CD5 (Leu1, Becton Dickinson, Mountain View, Calif.), CD7 (Leu9, Becton Dickinson), CD8 (OKT8, Ortho), CD10 (J5, Coulter Immunology, Hialeah, Fla.), CD13 (MCS-2, Nichirei, Tokyo, Japan), CD14 (My4, Coulter), CD19 (B4, Coulter), CD20 (B1, Coulter), CD25 (anti-IL-2R, Becton Dickinson), CD30 (Ki-1, Dako, Kyoto, Japan), anti-HLA-DR (Becton Dickinson) , and CD56 (NKH-1, Coulter).

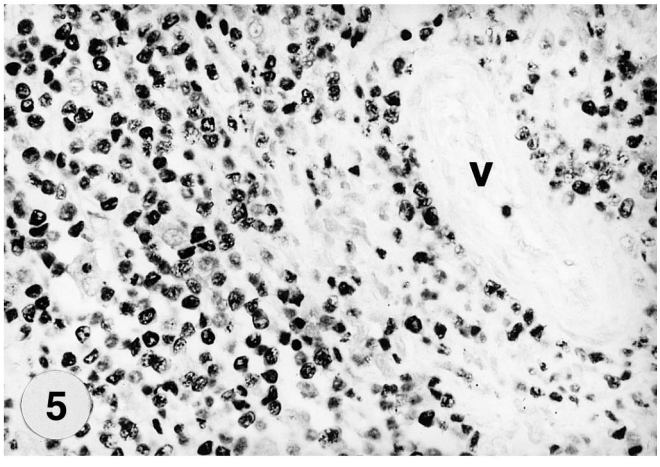
Immunohistochemistry

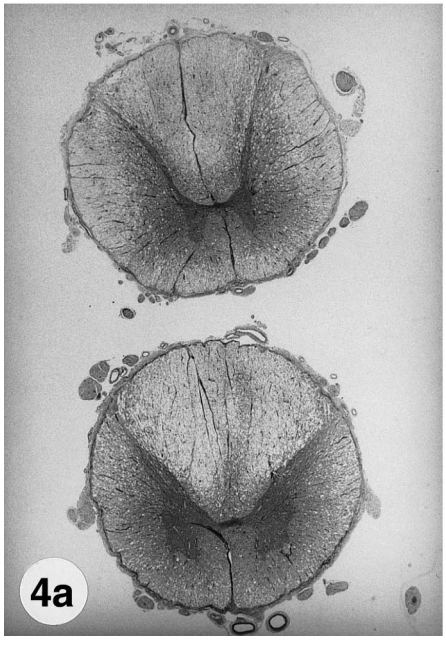
Paraffin sections cut 4 mm thick were immunostained by the Envision system (Dako), preceded by microwave antigen retrieval of tissue sections in a Dako antigen retrieval solution. The following antibodies were used: CD3 (rabbit polyclonal anti-CD3ε antiserum, Dako), CD8 (Dako), CD20 (L-26, Dako), CD30 (Ber-H2, Dako), CD45 (leukocyte common antigen, Dako), CD45RO (UCHL-1, Dako), CD56 (123C3, Zymed, San Francisco, Calif.), CD57 (Leu-7, Becton-Dickinson), CD68 (PG-M1, Dako), gran-

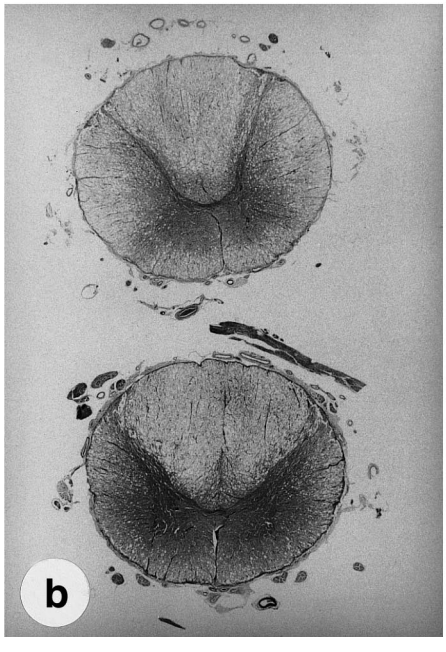












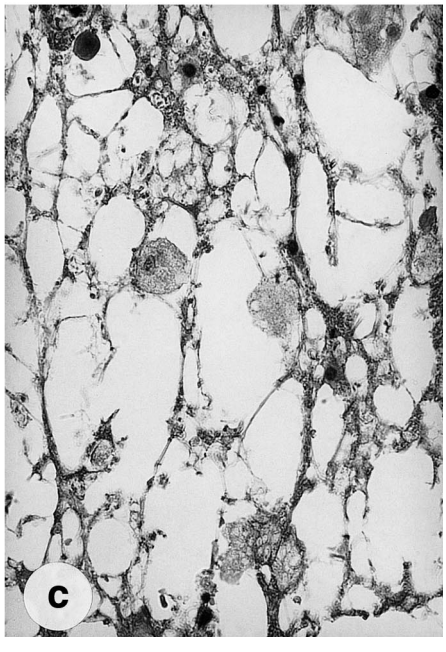


Fig. 2 **a** Lymphoma cells show angiocentric infiltration of subarachnoidal vessels with fibrin exudation. H-E stain, original magnification ×100 **b** CD56 expression on lymphoma cells showing angiocentric infiltration. Parenchyma of spinal cord with spongiotic change is also positive for CD56. Immunoperoxidase staining, original magnification ×50

Fig. 3 Lymphoma cell infiltration of spinal nerve roots. Interestingly, lymphoma cells are seen around small vessels in the nerve roots. H-E stain, original magnification ×25

Fig. 4a,b Prominent demyelinization in lateral and posterior funiculi (T-7 and T-11). **a** H-E stain, original magnification ×1.0 **b** Luxol-Nissl-PAS stain, original magnification ×1.0 **c** Severe demyelination with spongiosis and macrophage infiltration is seen. H-E stain, original magnification ×100

Fig. 5 EBER-1 expression in nuclei of lymphoma cells (paraortic lymph node; *V* blood vessels). Original magnification ×100

zyme B (GrB-7, Pharmacell, Paris, France), and T-cell intracellular antigen (TIA)-1 (Coulter).

DNA analysis

DNA was extracted from lymph node cells by treating them overnight with lysis buffer/proteinase K and extracting them from the mixture with phenol/chloroform. For rearrangement analysis, Southern blot hybridization was performed to detect the T-cell receptor (TCR) β-, γ-, and δ-chain [12]. DNA (5 mg) was digested with restriction endonucleases, separated by electrophoresis in 0.8% agarose gel, and then transferred to activated nylon membranes. The DNA fragments on the membranes were hybridized with nick-translated ^{32}P-labeled probes and examined by autoradiography. The restriction endonucleases used were *Bam*HI or *Eco*RV for the TCR-Cβ1, *Eco*RI or *Bam*HI or *Hin*dIII for the TCR-Jγ and *Bgl*II or *Hind*III for the TCR-Jδ1 gene probe.

Serum DNA was amplified by polymerase chain reaction (PCR) for detection of the EBV genomes as described elsewhere [12].

In situ hybridization of EBER-1 (Epstein-Barr-encoded RNA 1) was performed on the paraffin sections using an FITC-labeled EBER-1 30-base oligonucleotide probe, as described elsewhere [12].

Pathologic findings

Macroscopically, there was no mass lesion in the vertebral canal. The spinal cord was swollen from levels T-10 level to L-1. Microscopically, lymphoma cells were medium in size. They infiltrated the subarachnoidal space of the cerebrum, cerebellum, brain stem, and spinal cord, accompanied by an angiocentric infiltration pattern (Fig. 2a). Immunohistochemically, they were positive for CD56 (Fig. 2b). They extended focally into the cerebral cortex along the Virchow-Robin space. The lymphoma cell infiltration was also found in cranial and spinal nerve roots (Fig. 3). The spinal cord showed severe demyelination with spongiosis, mild gliosis, and macrophage infiltration, especially in the lateral and posterior funiculi (Fig. 4a–c). These lesions were distributed throughout the spinal cord and were most evident at the lower thoracic level. In addition, the pancreatic tail, retroperitoneal, and paraaortic lymph nodes, bilateral adrenal glands, liver, lungs, pericardium, pleura, pancreas, kidneys, spleen, testes and skin were involved by the lymphoma cells. In these tissues, the lymphoma cells showed an angiocentric infiltration pattern. In a section of a paraaortic lymph node, EBV was detected in neoplastic cells by EBER-1 in situ hybridization (Fig. 5). Genotypic analysis of the lymph node showed no clonal rearrangement of TCR Cβ1, Jγ, or Jδ1 genes.

Discussion

In this report, we describe an autopsy case of patient with nasal NK/T cell lymphoma with special attention paid to CNS involvement. The route of CNS involvement in the patient was considered to have been direct invasion from a sinusoidal lesion.

Compared with leukemia, secondary CNS involvement of malignant lymphomas is relatively uncommon [4]. It has two distinct patterns: one is predominantly leptomeningeal and the other is restricted to the epidural space [2]. The former often occurs late in the course of diffuse high-grade lymphomas. The lymphoma cells proliferate in the leptomeninges, extend along perivascular (Virchow-Robin) spaces, and penetrate into the nerve roots. The latter is frequently accompanied by spinal cord compression. In these cases, transverse myelopathy can be induced by cord compression or ischemia resulting from thrombosis of the radicular arteries.

Although our patient was initially thought to have transverse myelopathy, no tumor mass was found in the epidural space. The spinal cord was found to be affected by severe demyelination with spongiosis, associated with angiocentric infiltration of the lymphoma cells into relatively small vessels. Because angoicentric infiltration by NK/T cell lymphoma cells is often accompanied by coagulation necrosis of the tissues [3], it is possible that the destruction of small vessels by lymphoma cells resulted in ischemia of the spinal cord, followed by spongiotic changes. Hence, the patient's initial clinical manifestation as a patient with transverse myelopathy might have been induced by a combination of ischemic spinal changes secondary to angiocentric infiltration by lymphoma cells and lymphoma cell infiltration into the spinal nerve roots. The pattern of demyelination of spinal changes in this case resembled subacute combined degeneration, a pattern of degeneration that is associated with megaloblastic anemia [9] and vacuolar myelopathy in patients with acquired immunodeficiency syndrome (AIDS) [10].

CD56 expressed on NK cell lymphoma is a neural adhesion molecule and mediates adhesion through homophilic binding [11]. This adhesion molecule is also expressed on nerve tissues [7], and NK cell malignancies could therefore have an affinity for nerve tissues [5]. In our case, lymphoma cells also showed a preferential infiltration of spinal nerve roots.

In conclusion, we report a case of nasal NK/T cell lymphoma with CNS involvement. The findings described here should contribute to the future management of patients with this aggressive lymphoma.

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References

1. Chan JK, Sin VC, Wong KF, Ng CS, Tsang WY, Chan CH, Cheung MM, Lau WH (1997) Non-nasal lymphoma expressing the natural killer cell marker CD56: clinicopathologic study of 49 cases of an uncommon aggressive neoplasm. Blood 89:4501–4513
2. Grant JW, Kaech D, Jones DB (1986) Spinal cord compression as the first presentation of lymphoma-a review of 15 cases. Histopathology10:1191–1202
3. Jaffe ES, Chan JK, Su IJ, Frizzera G, Mori S, Feller AC, Ho FC (1996) Report of the workshop on nasal and related extran-

odal angiocentric T/Natural Killer cell lymphomas. Am J Surg Pathol 20:103–111
4. Jellinger K, Radaszkiewicz T (1976) Involvement of the central nervous system in malignant lymphomas. Virchows Arch [A] 370:345–362
5. Lackowski D, Koberda L, deLoughery TG, So Y (1998) Natural killer cell leukemia as a cause of peripheral neuropathy and meningitis: case report. Neurology 51:640–641
6. Mckelvey EM, Gottlieb JA, Wilson HE, McKelvey EM, Gottlieb JA, Wilson HE, Haut A, Talley RW, Stephens R, Lane M, Gamble JF, Jones SE, Grozea PN, Gutterman J, Coltman C, Moon TE (1976) Hydroxydaunomycin (Adriamycin) combination chemotherapy in malignant lymphoma. Cancer 38: 1484–1493
7. Mechterscheimer G, Staudter M, Moller P (1991) Expression of the natural killer cell-associated antigens CD56 and CD57 in human neural and striated muscle cells and in their tumors. Cancer Res 51:1300–1307
8. Nakamura S, Suchi T, Koshikawa T, Kitoh K, Koike K, Komatsu H, Iida S, Kagami Y, Ogura M, Katoh E et al. (1995) Clinicopathologic study of CD56 (NCAM)-positive angiocentric lymphoma occurring in sites other than the upper and lower respiratory tract. Am J Surg Pathol 19:284–296
9. Pant SS, Asbury AK, Richardson EP Jr (1968) The myelopathy of pernicious anemia. Acta Neurol Scand [Suppl] 44:4–36
10. Petito CK, Navia BA, Cho ES, Jordan BD, George DC, Price RW (1985) Vacuolar myelopathy pathologically resembling subacute combined degeneration in patients with the acquired immunodeficiency syndrome. N Engl J Med 312:874–879
11. Ranheim TS, Edelman GM, Cunnigham BA (1996) Homophilic adhesion mediated by the neural cell adhesion molecule involves multiple immunoglobulin domains. Proc Natl Acad Sci USA 93:4071–4075
12. Sadahira Y, Ohmoto K, Yamamoto S, Nishihara H, Wada H, Yawata Y, Manabe T (1998) Expression of cytotoxic molecule TIA-1 in malignant lymphomas mimicking fulminant hepatitis. Pathol Int 48:695–704
13. Van Gorp J, De Bruin PC, Sie-Go DM, Heerde P van, Ossenkoppele GJ, Rademakers LH, Meijer CJ, Tweel JG van den (1995) Nasal T-cell lymphoma: a clinicopathological and immunophenotypic analysis of 13 cases. Histopathology 27:139–148
14. Velasquez WS, McLaughlin P, Tucker S, Hagemeister FB, Swan F, Rodriguez MA, Romaguera J, Rubenstein E, Cabanillas F (1994) ESHAP – an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. J Clin Oncol 12:1169–1176
15. Wong KF, Chan JK, Ng CS (1994) CD56 (NCAM)-positive malignant lymphoma. Leuk Lymphoma 14:29–36
16. Yeh K, Lien H, Hsu S, Cheng A (1999) Quiescent nasal T/NK cell lymphoma manifested as primary central nervous system lymphoma. Am J Heamtol 60:161–163