

Case Report

Extranodal NK/T-cell lymphoma, nasal type, manifesting as rapidly progressive dementia without any mass or enhancing brain lesion

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Among the many potential etiologies for rapidly progressive dementia (RPD), primary central nervous system extranodal NK/T-cell lymphoma, nasal-type (ENKL) is a rare entity. We present the first reported case of autopsy-proven RPD due to ENKL without any mass or enhancing lesion of the brain. A 54-year-old immunocompetent man presented with RPD, myoclonus and ataxia. The mini-mental state examination (MMSE) score was 22/30. His brain MRI revealed progressive brain atrophy without gadolinium enhancement or mass lesion. Five months after the initial evaluation, cognitive impairment further worsened with an MMSE score of 3/30. At the advanced stage, lumbar MRI showed swollen *cauda equina* with gadolinium enhancement. The number of Epstein-Barr virus (EBV) DNA in cerebrospinal fluid had gradually increased. Twelve months after onset, the patient died of respiratory failure. Pathological findings revealed that lymphoma cells had diffusely invaded the meninges, parenchyma of the brain, spinal cord and *cauda equina*. Cells were positive for CD3, CD56 and EBV-encoded small RNAs and negative for CD20. No evidence of malignancy was identified in the visceral organs. This report indicates that ENKL should be recognized as one of the rare causes of RPD. Early testing for EBV-DNA in cerebrospinal fluid and imaging of *cauda equina* would be useful diagnostic tools.

Key words: *cauda equina*, epstein-barr virus, extranodal NK/T-cell lymphoma, nasal type, rapidly progressive dementia.

INTRODUCTION

Rapidly progressive dementia (RPD) is relatively uncommon in patients with dementia. The pathophysiological mechanism of RPD is broad, including neurodegenerative, autoimmune, infectious and toxic-metabolic processes.¹ Early and accurate diagnosis is crucial because many of the etiologies are treatable.

Primary central nervous system lymphoma (PCNSL) is a rare entity among malignant lymphoid neoplasms. It typically presents with progressive encephalopathy or focal neurological deficits accompanied by enhancing abnormalities on brain imaging.² Quantitative polymerase chain reaction (qPCR) for the detection of Epstein-Barr virus (EBV) in cerebrospinal fluid (CSF) can provide a clue to diagnose PCNSL in immunocompromised patients such as those with acquired immune deficiency syndrome (AIDS).³ However, PCNSL has rarely been associated with EBV in immunocompetent patients,⁴ which often leads to failure of recognition of the disease.

We encountered an immunocompetent patient with extranodal NK/T-cell lymphoma, nasal type (ENKL), whose brain imaging studies lacked any pathognomonic features suggesting PCNSL. Moreover, this case highlights that testing for EBV DNA in CSF using qPCR should be considered for immunocompetent patients if PCNSL is suspected or etiology for RPD is undetermined.

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CLINICAL SUMMARY

A 54-year-old man with a 9-year history of type 2 diabetes mellitus was referred to our hospital for RPD, tremulous movement and clumsiness of the right hand, which had manifested over the previous 2 months. On initial physical examination, no splenomegaly, lymphadenopathy, skin lesion or fever was observed. Sinonasal involvement was not identified based on the clinical history, symptoms or physical examination results. On neurological examination, he was irritable and reported an inability to use a personal computer at work. Memory disturbance and verbal memory impairment were evident. The scores of the mini-mental state examination (MMSE) and frontal assessment battery were low at 22/30 and 8/18, respectively. Mild ataxia and myoclonus were observed in the right hand. Bilateral hypoactive Achilles tendon reflexes and mild loss of vibratory sensations were evident.

The patient's symptoms rapidly progressed. Five months after the initial evaluation, cognitive impairment further

worsened with an MMSE score of 3/30. Two months later, he required 24-h nursing support because of global aphasia and inability to change clothes, feed himself or walk.

The blood and CSF findings are summarized in Table 1. Six months after the initial evaluation, laboratory work-up yielded a white cell count of 7500/ mm³, a CD4 count of 1037/ mm³ (reference range: 500–1200/ mm³). Brain MRI revealed mild atrophy with a few scattered white matter lesions mainly in the left frontal and temporal lobes. The diffusion-weighted imaging result was unremarkable. Brain atrophy had progressed with no evidence of a mass or an enhancing lesion (Fig. 1). Contrast-enhanced computed tomography and ⁶⁷Ga-scintigraphy revealed neither a mass nor high-uptake lesion. Bone marrow and random skin biopsy samples were negative for any malignant cells.

With a presumptive diagnosis of inflammatory disease and neoplasm such as neuro-Sweet disease, multiple sclerosis, sarcoidosis, paraneoplastic syndrome or malignant lymphoma, intravenous methylprednisolone and subsequent

Table 1 CSF and blood laboratory results on the initial evaluation

	Initial evaluation	Reference range
Blood tests		
White-cell count (per mm ³)	9100	4000–9000
Neutrophils (%)	31.5	—
Lymphocytes (%)	60.5	—
Hemoglobin (g/dL)	13.7	14.0–17.0
Platelet count (per mm ³)	154 000	150 000–350 000
Lactate dehydrogenase (U/L)	151	110–220
Hemoglobin A1c (%)	6.3	4.6–6.2
C-reactive protein (mg/dL)	<0.05	<0.3
Soluble interleukin-2 receptor level (U/mL)	258	220–530
β2-microglobulin, serum (mg/L)	2.08	<1.7
IgG (mg/dL)	1025	870–1700
IgA (mg/dL)	244	110–410
IgM (mg/dL)	47	33–190
Anti-nuclear antibody	1:80	<1:40
HIV antigen/antibody	Negative	Negative
Angiotensin-converting enzyme (IU/mL)	<1.0	7.7–29.4
Anti-GAD antibody (U/mL)	0.8	<1.5
EBV-VCA-IgG	1:320	<1:10
EBV-VCA-IgA	<1:10	<1:10
EBV-VCA-IgM	<1:10	<1:10
EBV-EADR-IgG	<1:10	<1:10
EBV-EADR-IgA	<1:10	<1:10
EBV-EBNA	1:40	<1:10
Human leukocyte antigen (HLA) typing	B54 Cw1	—
Cerebrospinal fluid		
Cell count (per mm ³)	14/3	0–15/3
Protein level (mg/dL)	35	<42
IgG index	0.56	<0.73
Oligoclonal band	Positive	Negative
Myelin basic protein (pg/mL)	<31.3	<102
Soluble interleukin-2 receptor level (U/mL)	<54.5	<54.5
β2-microglobulin (mg/L)	3.60	<1.9

The complete blood counts were almost within the reference range. A serological examination demonstrated almost normal amounts of lactate dehydrogenase and soluble interleukin-2 receptor. Antibodies for EBV showed the pattern of a previous infection. EADR: early antigen-diffuse and restricted antibody, EBNA: EB nuclear antigen, VCA: viral capsid antigen.

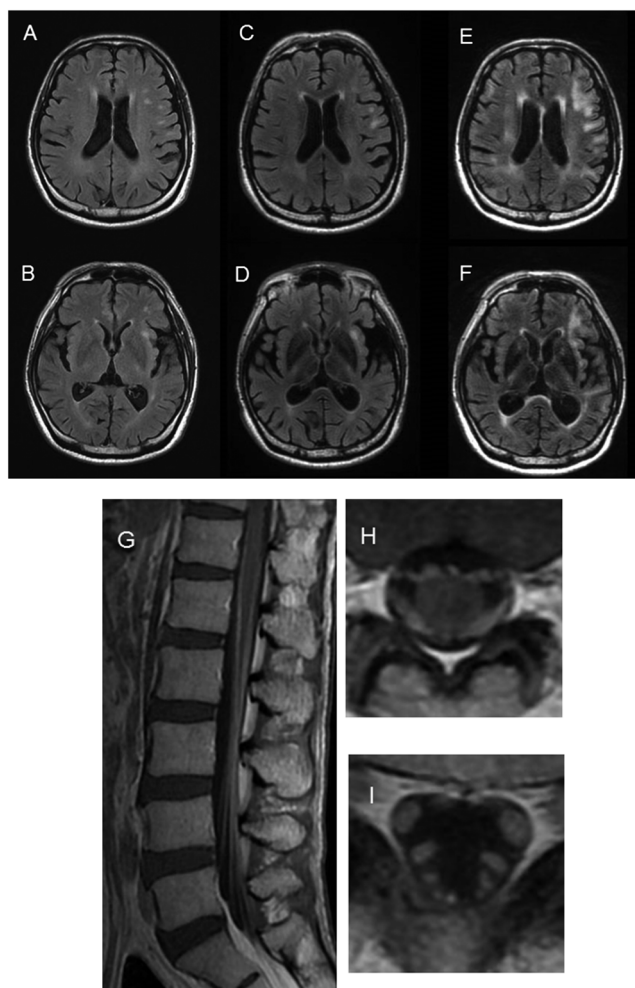


Fig. 1 Brain and lumbar MRIs. (A, B) Fluid-attenuated inversion recovery (FLAIR) images on initial evaluation. Diffuse brain atrophy with mild subcortical lesions was evident. These lesions were hyperintense on T2-weighted and FLAIR images. No enhancement effect with gadolinium (Gd) administration was observed on the T1-weighted images (not shown). (C, D) FLAIR images obtained 5 months after the initial evaluation. Brain atrophy had progressed without a mass or an enhancing lesion. (E, F) FLAIR images obtained 7 months after the initial evaluation. Brain atrophy had progressed without a mass or an enhancing lesion. (G–I) Lumbar MRI with Gd administration on T1-weighted images obtained 9 months after initial evaluation. The *cauda equina* was swollen and showed Gd enhancement.

oral prednisolone were administered but had no apparent effect. Eight months after the initial evaluation, a brain biopsy of the parenchyma of the right frontal lobe showed nonspecific changes, which included increased numbers of microglia and astrocytes. Lumbar MRI revealed a swollen *cauda equina* with gadolinium enhancement (Fig. 1). The patient eventually died of respiratory failure. The disease duration was 12 months. General autopsy was conducted after informed consent was obtained from his guardian.

MATERIAL AND METHODS

The autopsy specimens were fixed with formalin. Paraffin-embedded, 5- μ m-thick sections were evaluated. Immunohistochemical studies were performed with a variety of

antibodies as described below, using heat-induced antigen retrieval on the Nichirei Bioscience Histostainer and Leica Microsystems Bond-III autostainers according to the manufacturer's instructions. The sections were immunostained with mouse monoclonal antibodies against the T-cell-associated antigen CD3 (Nichirei, Tokyo, Japan; diluted and ready for use), CD4 (Nichirei; diluted and ready for use), CD5 (Nichirei; diluted and ready for use), CD8 (Nichirei; 1:2), CD56 (Nichirei; diluted and ready for use), CD20 (Nichirei; diluted and ready for use), granzyme B (DAKO, Glostrup, Denmark; 1:40), TIA-1 (Beckman Coulter, Marceille Cedex, France; 1:100), perforin (Leica, Newcastle, United Kingdom, 1:20).

Molecular diagnoses of lymphoma and EBV infection were performed as follows: genome DNA was extracted from frozen sections. T-cell receptor γ -chain (TCRG) gene

rearrangement was analyzed by using multiplex PCR.⁵ Southern blotting was performed to detect the EBV genome and to measure clonality.⁶ The copy number of the EBV DNA was retrospectively analyzed in frozen serum and CSF samples by using real-time qPCR.⁷ To detect EBV-encoded small RNAs (EBER), EBV-RNA *in situ* hybridization was performed on the paraffin-embedded sections using EBER probe (BondTM Ready-to-Use ISH, Leica Microsystems).

PATHOLOGICAL FINDINGS AND RESULTS

The brain weighed 1200g. The leptomeninges were opaque along with the sulci. Atrophy of the brain could not be precisely assessed due to the swelling; however, the inferior horn of lateral ventricle was slightly enlarged. The nerve roots of *cauda equina* were swollen with various thicknesses (Fig. 2). Histologically, sparse infiltration of atypical lymphocytes spread diffusely throughout parenchyma of the brain, spinal cords and nerve roots without focal mass lesions (Fig. 3). In the brain, the atypical cells were found everywhere in the

cerebral cortex, white matter, basal ganglia, brain stem and cerebellum. The cells had distorted or lobulated nuclei, and expressed CD3, CD56, TIA-1, granzyme B and perforin, but not CD4, CD5, CD8 or CD20. An *in situ* hybridization study revealed that almost all of the atypical cells were strongly positive for EBER (Fig. 4).

Most severe infiltration of the lymphoma cells was observed in the nerve roots of *cauda equina*, where perivascular cuffing of mature reactive lymphocytes were also prominent. The tumor cells densely infiltrated in the dorsal nerve roots of the spinal cord. In the cerebrum, diffuse infiltration of the tumor cells were found in the cortex and white matter, with proliferation of gemistocytic astrocytes in the cortico-medullary junction. These changes were accentuated at entorhinal cortex, subiculum and hippocampal formation. Occasionally, the tumor cells invaginated into the neuronal cells at the anterior horn and locus ceruleus. In addition, neuronal loss was obvious in pyramidal cell layer of the CA1-2 in the hippocampus. Routine neuropathological examination revealed minimal age-related changes; a few neurofibrillary tangles (NFT) were observed in the transentorhinal cortex without



Fig. 2 Macroscopic feature of the *cauda equina*. Nerve roots with different diameters.

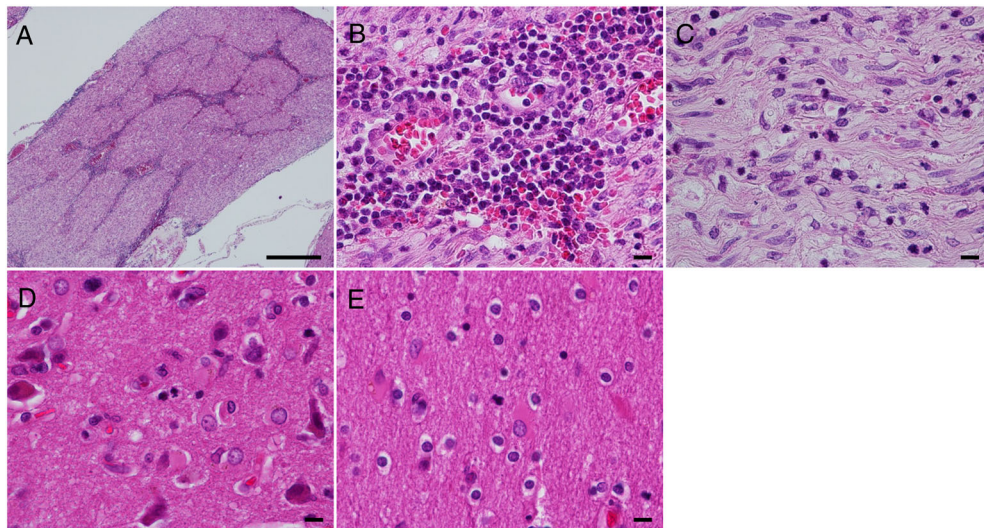


Fig. 3 Microscopic evaluation of the *cauda equina*. Lymphocytes infiltrating around vessels were markedly visible (a). The lymphocytes did not show pleomorphism. The cells showed two immunohistochemical patterns. One set was positive for CD3, CD4, CD5 and CD8, and the other was positive for CD20. Both cell types were negative for EBV-encoded small RNAs (EBER). T- and B-cells seemed to be induced by malignant cells (b). At the parenchyma, some scattered lymphoid cells were observed in addition to the Schwann cells, almost all of which had distorted nuclei (c). The lymphomatoid cells diffusely infiltrated into the neocortex (d) and white matter (e) of frontal lobe. Bar = 500 μ m (a) and 10 μ m (b-e).

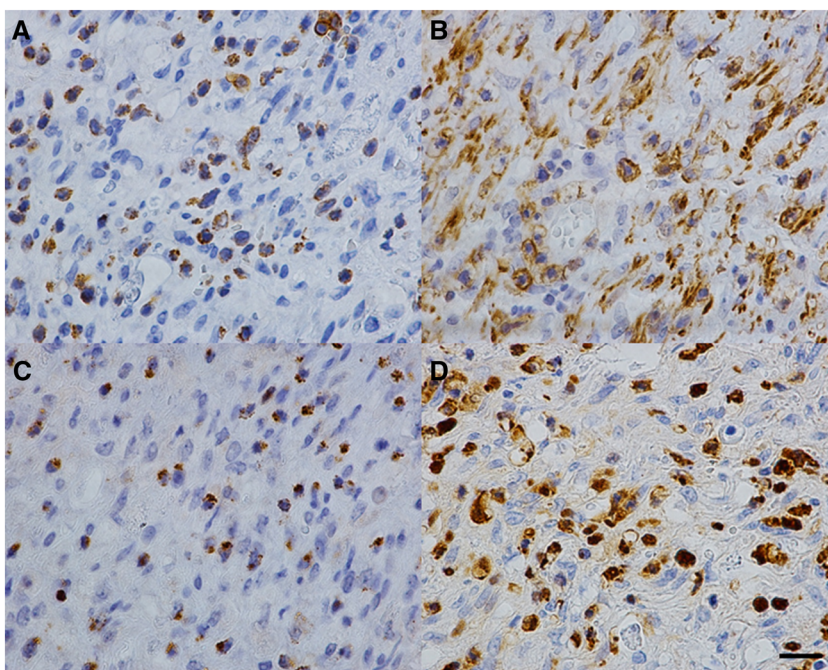


Fig. 4 Immunohistochemical evaluation of the *cauda equina*. The lymphoid cells were positive for CD3 (a), CD56 (b) and granzyme B (c). These cells showed the EBV-encoded RNA signals in the nuclei (d). Bar = 20 μ m (a–d).

amyloid-deposits (Braak NFT stage 1, Braak Amyloid stage 0, Consortium to Establish a registry for Alzheimer's Disease (CERAD) 0, Thal A Phase 0).^{8–10} Other senile changes were not detected.

No evidence of malignancy was identified in the visceral organs, including the lymph nodes, liver, spleen, testis, bone marrow or sural nerve at the ankle level. TCRG gene analysis demonstrated a monoclonal pattern, indicating that the lymphomas were derived from a single T cell. Southern blotting revealed a single band, indicating that EBV infection preceded the clonal expansion of the tumor cells. EBV-DNA was detected in the *post hoc* analysis of the CSF samples, although not in the analysis of the serum samples. Although no EBV DNA was detected in the first month after initial

evaluation, the copy number of EBV DNA increased with the clinical course thereafter (Tables 1, 2).

DISCUSSION

To our knowledge, this is the first autopsy-confirmed case of ENKL restricted to the CNS and *cauda equina*. In the patient's clinical course, brain MRI revealed no mass or enhancing lesions. The pathological findings had unusual features, and we identified the pattern of progression of the tumor cells. This report indicates that studying EBV DNA in CSF and imaging of the *cauda equina* might lead to early diagnosis and potential therapy.

ENKL is described as a distinct entity in the World Health Organization classification of hematopoietic and

Table 2 Transition of cerebrospinal fluid (CSF) results, β 2- microglobulin, EBV DNA load and cytodiagnosis of CSF

Months after initial onset	3	4	8	10	11	12
Number of cells in CSF (/3 μ L)	14	30	119	106	118	131
Protein level in CSF (mg/dL)	35	35	128	64	1069	1274
β 2-microglobulin (mg/L) in serum	2.01	ND	1.67	ND	ND	ND
β 2-microglobulin (mg/L) in CSF	3.6	ND	6.8	ND	ND	13.3
Soluble interleukin-2 receptor level (U/mL) in CSF	<54.5	ND	83	578	1440	ND
Cytological grade	I	ND	III	III	III	III
EBV DNA copy/mL in serum	ND	<100	ND	<100	ND	ND
EBV DNA copy/mL in CSF	ND	<100	ND	8400	ND	14000

Abnormal data are in bold. On initial evaluation, the patient showed normal cell count in CSF and normal protein level. In CSF, the β 2-microglobulin level was slightly elevated at 3.60 mg/L on initial evaluation. The number of cells and levels of protein, β 2-microglobulin and soluble interleukin-2 receptor in CSF increased with clinical course. Increasing EBV-DNA load was compatible with disease severity. The β 2-microglobulin serum level had not increased, and the EBV-DNA load in serum was normal throughout the clinical course. Repeated cytodiagnosis of CSF showed class I to III findings. Reference range: EBV DNA copy/mL (in serum and CSF) < 100.

Table 3 Summary of the reported cases of ENKL restricted to the CNS, including the present case

Report	Ethnicity	Age /sex	Past history	Distribution	Mass lesion of the brain	Enhancement lesion of the brain	EBV	CSF abnormalities	Methods of diagnosis	TCR gene rearrangement	Autopsy	Survival (months)
Kaluza <i>et al.</i>	Korean	53/ M	None	Left frontal	+	ND	+	Not performed	Operation	Germline	-	2
Coba <i>et al.</i>	Spanish	43/ M	HCV, HIV	Left parietal	+	ND	+	Not performed	Biopsy	Monoclonal appearance ND	-	1
Liu <i>et al.</i>	Spanish	26/ M	None	Pituitary gland	+	+	+	Not performed	Operation	ND	-	6
Guan <i>et al.</i>	Chinese	25/ M	None	Right hemisphere	+	+	+	Not performed	Operation	Monoclonal appearance Rearranged	-	18
Ng <i>et al.</i>	Chinese	40/ M	ND	ND	ND	ND	+	ND	ND	ND	-	7
Liao <i>et al.</i>	African-American	68/F	Breast cancer	Leptomeninges, temporal lobe	+	+	-	Cell ↑, protein ↑, β2-MG ↑ atypical lymphoid cells	Cytology, flow cytometry of CSF	ND	-	Undefined
Prajapati <i>et al.</i>	African-American	60/F	None	Left frontal	+	+	+	Protein ↑	Biopsy	ND	-	3.5
Present case	Japanese	54/ M	DM	Leptomeninges, diffuse brain, spinal cord, <i>cauda equina</i>	-	-	+	Cell ↑, protein ↑, β2-MG ↑	Autopsy	Monoclonal appearance	+	12

Ours was the only case proven by autopsy. DM, diabetes mellitus; F, female; HCV, hepatitis C virus; M, male; MG, microglobulin; ND, not described; TCR, T-cell receptor; ↑, increased.

lymphoid neoplasms.¹¹ It is immunophenotypically distinct from B- and T-cell non-Hodgkin lymphomas. Malignant cells are derived either from activated natural killer (NK) cells or rarely from cytotoxic T-cells. The nearly invariable presence of EBV is a distinguishing feature of the lymphoma. The nasal cavity is the most common and prototypic site of involvement, but other primary sites have also been reported, including the paranasal sinuses, pharynx, skin, gastrointestinal tract, testis and CNS.^{12–14} Metastasis to the brain from nasal NK/T-cell lymphomas has been reported in less than 3% of cases.¹⁵ ENKL developing within the CNS is rare (Table 3).^{14,16}

A previous study of clinicopathological and genotypic correlations in 42 cases with ENKL showed that the mean survival time was 30 months, and better survival rate was seen in patients with low (0–1) international prognostic index (IPI)¹³. Our case had IPI of 0. There is a tendency toward poor prognosis in cases confined to the CNS (Table 3).

Almost all patients with PCNSL had enhancing lesions.^{2,17} Only a few patients have been reported with white matter lesions without enhancement on T2-weighted images.^{17,18} As for the reported cases of primary CNS ENKL, all showed a mass in the parenchyma with an enhancing lesion (Table 3), one of whom presented leptomeningeal change with brain parenchymal involvement.¹⁴ The images of our patient showed that the case was unlikely to be a CNS lymphoma or have any similarity to the reported cases of primary CNS ENKL. On the other hand, lumbar MRI of the present case revealed abnormalities in the *cauda equina* in the advanced stage. This finding is important in retrospect because biopsy of the *cauda equina* can be diagnostic of B-cell lymphoma if suspicious symptoms are present, even without brain imaging abnormalities.¹⁹

The present case shared some features with lymphomatosis cerebri, a rare form of PCNSL. Lymphomatosis cerebri commonly presents with cognitive decline, gait disturbance and behavioral changes,²⁰ which were also observed in our case. MRI findings of lymphomatosis cerebri are characterized by diffuse bilateral leukoencephalopathy, with no or patchy enhancement;²⁰ however, in our case diffuse white matter lesions were absent. Histologically, lymphomatosis cerebri shows no cohesive mass lesion, rarely accompanies necrosis, but typically has perivascular infiltration of tumor cells.²⁰ In the present case, diffuse infiltration of atypical lymphocytes was also observed in the brain, spinal cord and nerve roots, without mass lesions.

This case showed symptoms of dementia. In pathological examination, senile change was mild and an ischemic lesion was not evident in the cerebral cortices, while infiltration with the lymphoma cells was shown in the entorhinal cortex. The initial brain MRI did not show any ischemic or space-occupying lesion. Taken together,

symptoms of dementia in the case might be due to diffuse infiltration of lymphoma cells in the cortex and white matter, rather than ischemic lesions or senile changes in the hippocampus.

Measurement of EBV DNA copy number is useful to diagnose, monitor and prognosticate ENKL cases, generally by using peripheral blood samples.^{21,22} Cell-free, fragmented EBV DNA is released from lymphoma cells during apoptosis in the serum.²³ EBV has been associated with the development of PCNSL in immunocompromised patients, typically those with AIDS; in such conditions, qPCR for detecting EBV DNA in CSF has been proposed as a diagnostic tool.² Our case underlines that measurement of EBV DNA copy number in CSF is also feasible in immunocompetent patients.

In summary, we present an immunocompetent patient who presented with RPD, in which an autopsy confirmed ENKL restricted to the CNS and *cauda equina*. Imaging of the *cauda equina* and evaluation of EBV DNA in CSF should provide a clue to the diagnosis of this potentially treatable condition.

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DISCLOSURES

The authors report no disclosures.

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