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CASE REPORT

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Central nervous system Hodgkin's lymphoma without systemic manifestation: case report and review of the literature

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Abstract A 66-year-old woman treated for ocular myasthenia gravis with azathioprine for 12 years presented with a left fronto-parietal mass. Histology revealed primary Hodgkin's lymphoma of the central nervous system with CD30, Epstein-Barr virus (EBV) latent membrane protein and CD20-positive, CD45 (LCA)-negative Reed-Sternberg cells surrounded by T cells. Moreover, EBV-encoded RNA-1 (EBER-1) sequences and a monoclonal rearrangement of the immunoglobulin heavy chain CDR2 locus were detected.

Key words Hodgkin's lymphoma · Primary central nervous system lymphoma · Immunosuppression · Epstein-Barr virus · Immunoglobulin rearrangement

Introduction

Primary central nervous system lymphoma (PCNSL) is a tumor which arises in the brain and remains restricted to the brain in more than 90% of cases. Pathologically, the vast majority of PCNSL are highly malignant B cell non-Hodgkin's lymphomas (NHL). In contrast, Hodgkin's lymphoma (HL) of the CNS is rare. Secondary involvement of the CNS by HL occurs in 0.2–0.5% of all cases [21, 23], but CNS involvement at the time of initial presentation has rarely been reported [2, 11, 17]. Primary CNS HL without a detectable systemic lymphoma at initial presentation has been reported in only six patients (Table 1) [1, 4, 6, 10, 15, 24]. An association of primary CNS HL with immunosuppression and Epstein-Barr virus (EBV) infection has been reported in one of these cases [15].

The differentiation of HL from NHL is based on the demonstration of Reed-Sternberg cells in conventional pathology as well as positive immunohistochemistry for the CD30 antigen in conjunction with negative staining for leukocyte common antigen (LCA, CD45), and negative or weak staining for B and T cell markers [7]. Here we report an immunosuppressed patient with EBV-associated primary CNS HL.

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Case report

A 66-year-old woman was admitted to the hospital because of two focal seizures. She had suffered from severe frontal headache for 4 weeks. Other symptoms were not reported; in particular, B symptoms like fever, weight loss or night sweat were absent. She had been diagnosed with ocular myasthenia gravis in 1983 and had had a thymectomy in 1985. Histological workup did not reveal pathology in the thymus. For 12 years, from 1986 to 1998, she was treated with 100 mg azathioprine/day. Neurological examination revealed mild hemiparesis of the right arm and discrete non-fluent aphasia. The general physical status was normal. Lymphadenopathy, splenomegaly, or hepatomegaly were absent. HIV test was negative. Cranial computed tomography (CT) and magnetic resonance imaging (MRI) scans showed a left fronto-parietal cortical mass with solid, cystic, and necrotic areas with rim enhancement (Fig. 1). A craniotomy was carried out and the tumor was resected. Tissue with a total diameter of 15 mm was submitted for pathological analysis.

After the diagnosis of an HL, mixed-cell type, was made extensive staging ensued. Further laboratory tests (blood count, ESR, liver enzymes, serum uric acid) were unrevealing. Thoracic, abdominal and pelvic CT scan did not show any enlarged lymph

Table 1 Clinicopathological features of patients with primary Hodgkin's lymphoma of the CNS (*RS cells* Reed-Sternberg cells, *pos.* positive, *neg.* negative, *mo.* months, *rearr.* rearrangement, *nd* not done, *WBRT* whole brain radiotherapy, *MTX* methotrexate, *COPP* cyclophosophamide/vincristine/procarbazine/prednisone, *PCV* procarbazine, *CCNU* vincristine, *LCA* leukocyte common antigen, *EBV* Epstein-Barr virus, HHV8 human herpes virus 8, EBER-1 EBV-encoded RNA, *LMP* latent membrane protein, *EMA* epithelial membrane antigen)

Authors	Doorly et al. [10]	Ashby et al. [1]	Sickler et al. [24]	Clark et al. [4]	Deckert-Schlueter et al. [6]	Klein et al. [15]	This case
Age, gender	51, male	62, male	84, female	53, female	62, female	54, male	67, female
Localization	cerebellar	fronto-temporal and meningeal	parieto-occipital	cerebellar	fronto-parietal	occipital	fronto-parietal
Histology	RS cells, mixed cellularity	RS cells, nodular sclerosing	RS cells, no sub-classification	RS cells, nodular sclerosing	RS cells, no sub-classification	RS cells, nodular sclerosis	RS cells, mixed cellularity
Immunohisto-chemistry of RS cells and DNA analysis	nd	pos. for CD15, LN2 neg. for LCA	pos. for IRac and CD30 neg. for CD3, CD4, CD8, CD15, CD22, kappa and lambda IgG	pos. for CD15 and CD30 neg. for LCA	pos. for CD30 neg. for LCA, CD20, bcl2, EBV LMP	pos. for CD30, CD15, CD20 (<10% of cells), EBV LMP neg. for LCA, CD3, CD45RO, EMA	pos. for CD30, EBV LMP neg. for LCA, CD3, CD15, CD20, MB2, EMA monoclonal CDR2 rearr., nested PCR pos. for EBV, neg. for HHV8, pos. EBER-1 in situ hybridization
Systemic disease	none	none	none	none	mediastinal involvement 3 mo. after diagnosis	none	none
Treatment	Complete resection, 4 × intrathecal MTX WBRT 45 Gy	Complete resection, WBRT 40 Gy, 2 × intrathecal MTX	Complete resection, WBRT 35 Gy + 5 Gy tumor boost	Complete resection, neuroaxis irradiation 36 Gy + 9 Gy tumor boost	Complete resection, alexan, MTX and dexamethasone, 45 Gy WBRT	Complete resection, WBRT 36 Gy + 14 Gy tumor boost, 5 × COPP	Complete resection, 45 Gy WBRT, 2 × PCV
Response to therapy	CR (12 mo+)	CR (14 mo+)	CR (8 mo+)	CR (6 mo+)	CR (13 mo+)	CR (12 mo+)	CR (18 mo+)

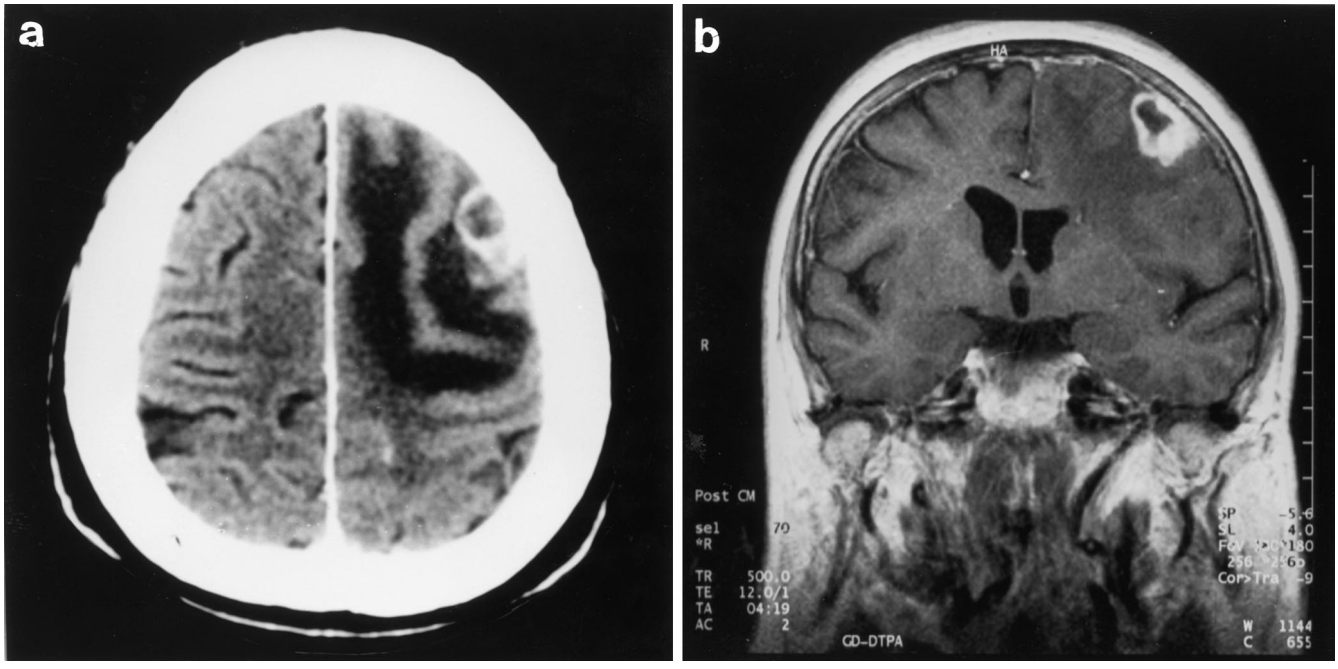

Fig. 1 a, b Radiographic findings. **a** Contrast-enhanced computed tomography scan showing a left fronto-parietal cortical mass with solid, cystic, and necrotic areas. Contrast enhancement was paritcularly prominent at the tumor margins. **b** Contrast-enhanced T1-weighted cranial magnetic resonance imaging of the fronto-parietal cortical mass lesion

nodes or mass lesions. ^{99m}Tc scintigraphy of skeleton and a bone marrow biopsy were normal.

The patient received whole-brain radiotherapy with a total dose of 45 Gy and a tumor boost of 15 Gy and PCV polychemotherapy (CCNU, procarbazine, and vincristine) comprising two complete cycles and one additional application of CCNU. Eighteen months after primary diagnosis, the patient is in complete clinical and radiographic remission. Restaging including cranial MRI, abdominal ultrasound, chest CT scan, and slit lamp examination of the eyes did not disclose any pathological findings.

Material and methods

Immunohistochemistry

Tissue was fixed in 4% buffered paraformaldehyde solution and embedded in paraffin. Tissue sections were stained with hematoxylin and eosin, periodic acid Schiff, Gomori silver impregnation, Elastica van Gieson (EvG) and Giemsa. Immunohistochemistry was carried out by the avidin-biotin-peroxidase complex method [12] using antibodies against CD3 (Novocastra, Newcastle, UK), CD15 (M1; Dako, Hamburg, Germany), CD20 (L26; Dako), CD30 (Ber-H2; Dako), CD45 (LCA-RB; Dako), latent membrane protein of EBV (LMP, Dako), MB2 (Biotest; Dreieich, Germany), epithelial membrane antigen (EMA; Dako), and MIB1 (Dianova, Hamburg, Germany). 3,3-Diaminobenzidine (Sigma, Deisenhofen, Germany) was used as chromogen.

In situ hybridization

Paraffin-embedded tissue was cut into 4-µm sections, deparaffinated and digested for 15 min at 37 °C in 1 µg/ml proteinase K (Sigma). Each section was covered with a hybridization solution containing the digoxigenin-labeled EBV-encoded RNA-1 (EBER-1) probe (2 ng/µl, 550 bp) in 10 mM TRIS-HCl, pH 7.4/50% (vol/vol) deionized formamide/600 mM NaCl/1 mM EDTA/0.02% polyvinylpyrrolidone/0.02% Ficoll/0.05% bovine serum albumin/10% dextrane sulfate/10 mM dithiothreitol/denatured sonicated salmon sperm DNA at 200 µg/ml/rabbit liver tRNA at 100 µg/ml at 42 °C for 18 h. As negative control, duplicate sections were hybridized with a digoxigenin-labeled RNA probe specific for the detection of enteroviral RNA. After stringent washings, tissue slide preparations were incubated with an alkaline phosphatase-conjugated antibody specific to digoxigenin (1 : 500, Boehringer Mannheim), developed by NBT and X phosphate and counterstained with hematoxylin.

PCR analysis

Total DNA was isolated from deparaffinated tissue sections by treatment with proteinase K followed by phenol/chloroform/isoamyl alcohol extraction. Enzymatic amplification for the detection of EBV EBNA-1 DNA was performed as a nested PCR on a Perkin-Elmer GeneAmp System 9600 with a first 35 and a second 40 cycle program consisting of denaturation at 94 °C for 30 s, annealing at 56 °C for 30 s, and extension at 72 °C for 45 s. Each reaction mixture contained PCR buffer (10 mM TRIS pH 8,3), 50 mM KCl, 1.5 mM $MgCl_2$, 15 pmol primers, 200 mM each dNTP, and 2.5 U Taq polymerase (Perkin-Elmer) and 200 ng of total extracted DNA. The nucleotide sequence of the outer primers specific for EBV EBNA-1 DNA was AAG GAG GGT GGT TTG GAA AG and AAC AGA CAA TGG ACT CCC TTA G and of the inner primers ATC GTG GTC AAG GAG GTT CC and ACT CAA TGG TGT AAG ACG AC, respectively. Successful extraction of DNA was confirmed by amplification of a 248-bp product of the human glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene using primers specific to nucleotides (nt) 3932–3949 and nt 4355–4372 of GAPDH DNA. The specificity of the amplification products was confirmed by automatic sequencing on a 373 DNA Sequencer (ABI, Weiterstadt, Germany). In addition, the tissue samples were investigated for the presence of human herpervirus-8 DNA-specific sequences by nested PCR [3] using the conditions described for amplification of EBV DNA sequences except that 50 °C was used as annealing temperature.

PCR amplification of monoclonal rearrangements of the immunoglobulin heavy chains were performed as described by Diss et

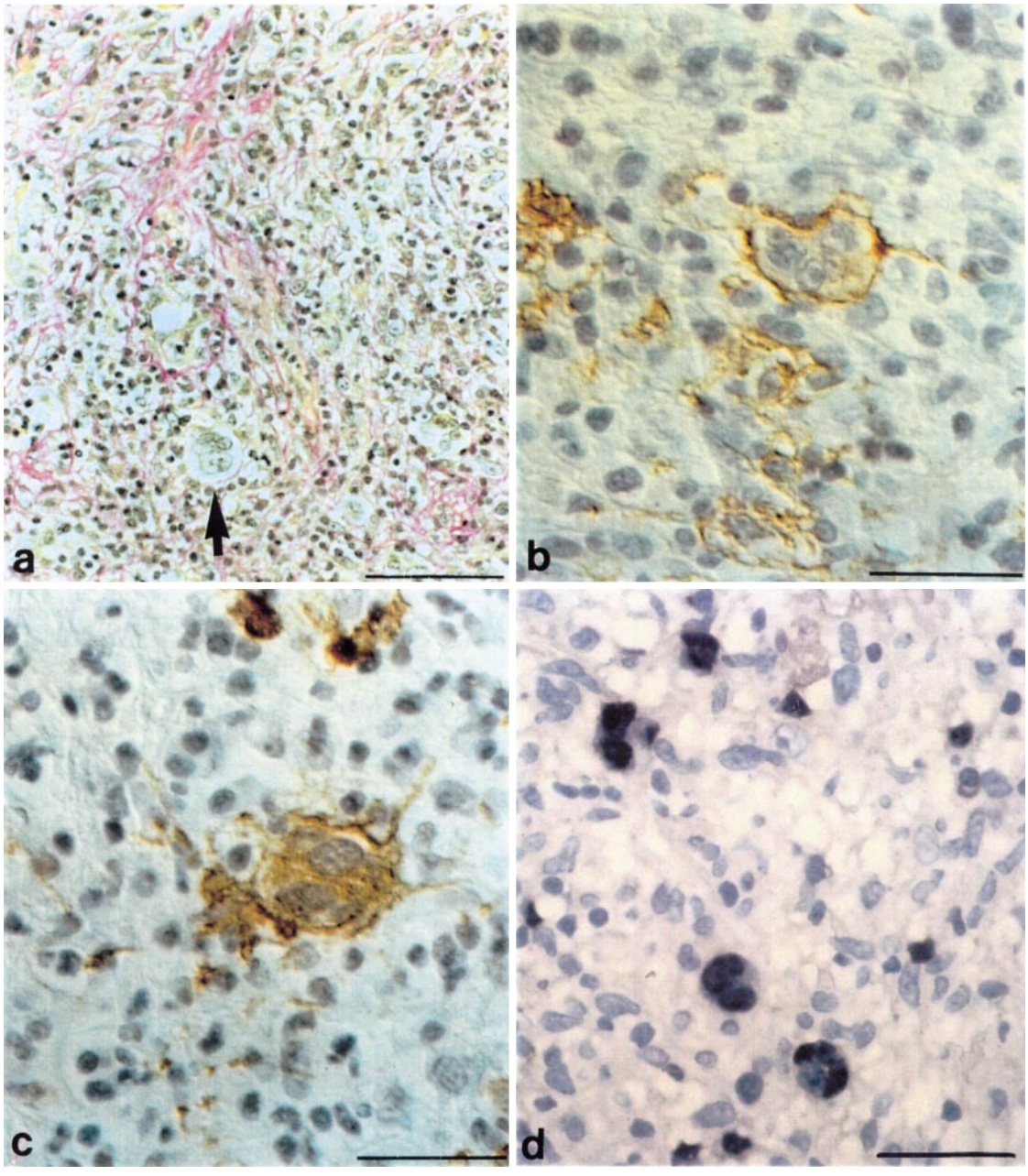

Fig. 2 a–d Histology of the left temporo-parietal cortical mass lesion showing characteristics of HL. **a** Polynuclear Reed-Sternberg cells *(arrow)* within the sclerotic lesion; Elastica van Gieson staining. **b** Reed-Sternberg cells staining positive for CD30 antigen; avidin-biotin-peroxidase labelling for CD30, hematoxylin counterstaining. **c** Reed-Sternberg cells also staining positive for EBV LMP; avidin-biotin-peroxidase labelling for LMP, hematoxylin counterstaining. **d** Positive in situ hybridization in Reed-Sternberg cells using a probe for EBV EBER-1-specific nucleic acid sequences; hematoxylin counterstaining (*HL* Hodgkin's lymphoma, *EBV* Epstein-Barr virus, *LMP* latent membrane protein). *Bars* **a, d** 100 μm; **b, c** 50 μm

al. [8] using the primer pairs FR3/LJH (external PCR) and FR3/VLJH (nested PCR) (CDR3 region) or the primer pairs FR2/LJH (external PCR) and FR2/VLJH (nested PCR) (CDR2 region), respectively. To identify monoclonal rearrangements of the T cell receptor (TCR) γ gene, primers and PCR conditions were applied as previously reported by Diss et al. [9]. PCR products were separated on a 2% agarose gel (CDR2) or on a 7% agarose gel (CDR3, TCR-γ).

Pathological findings

Standard preparations (H&E, EvG, PAS, reticulin staining, and Giemsa staining) showed polymorphic lymphatic tumor cells which diffusely infiltrated the brain parenchyma but were mainly grouped perivascularly. They formed partially sclerotic nodules with a dense network of collagen and reticulin fibers (Fig. 2 a). Few mitoses were seen. Large tumor cells with slightly eosinophilic cytoplasma bore nuclei with prominent central nucleoli. Some polynuclear cells with features of Reed-Sternberg cells were found (Fig. 2 a). Some centrally clustered larger areas of necrosis and astrogliosis were observed. The lesions were surrounded by reactive gliosis and prominent perivascular lymphocytic cuffs.

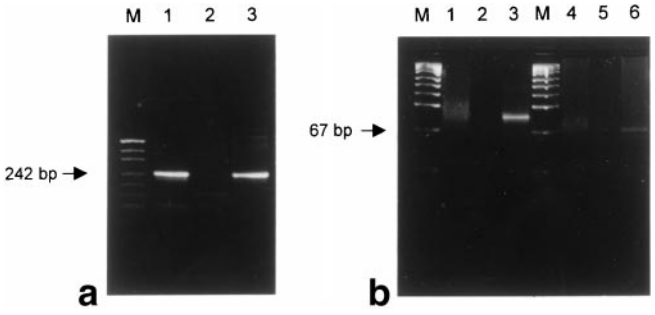

Fig. 3 a, b PCR amplification products of the immunoglobulin heavy chain regions CDR2 and CDR3, and of the T cell receptor γ. **a** CDR2 immunoglobulin heavy chain region. The presence of a single band of about 250 bp shows monoclonality of the CDR2 rearrangement in the primary CNS HL of this case *(lane 1)* and in a positive control (B-cell lymphoma, *lane 3*). *Lane 2* Negative control without DNA; *M* molecular weight marker, 2% agarose gel stained with ethidium bromide. **b** CDR3 immunoglobulin heavy chain region [*lane 1* this case, *lane 2* negative control, *lane 3* positive control (B cell lymphoma)] and T cell receptor γ [*lane 4* this case, *lane 5* negative control, *lane 6* positive control (T cell lymphoma), *M* molecular weight marker]. Single bands indicating monoclonal rearrangements were only detected in the positive controls (7% agarose gel stained with ethidium bromide)

CD30-positive (Ki1), LMP-positive polymorphic cells (Reed-Sternberg cells) were frequently found in the population of polymorphic tumor cells. These cell stained positive for CD30 in the cytoplasm and more prominently in the cell membrane (Fig. 2 b). LMP was also prominently stained on the cell membrane (Fig. 2 c). Only a small minority of these cells also expressed the B cell marker CD20 (L26). These cells were negative for CD3, CD45 (LCA-RB), CD15, MB2 and EMA. The majority of non-polymorphic cells were positive for the T cell antigen CD3, suggesting a non-neoplastic T cell infiltration especially in the periphery of the tumor. Staining with MIB-1 for the Ki67 antigen was predominantly positive in the polymorphic cells; 30–40% of cells stained positive with MIB1. In situ hybridization revealed the presence of EBV EBER-1 nucleic acid sequences in the nuclei of Reed-Sternberg cells and some lymphoid cells (Fig. 2 d).

Nested PCR analysis for the detection of the immunoglobulin heavy chain gene rearrangement revealed a single amplification product for the CDR2 region, indicating monoclonality of the tumor cells (Fig. 3 a). The TCR γ and the CDR3 region were found to be polyclonally rearranged (Fig. 3 b). Nested PCR analysis also confirmed the association of this lymphoma with EBV infection. HHV-8-specific sequences were not detected by nested PCR.

Discussion

Hodgkin's disease (HD) primarily restricted to the CNS parenchyma is rare. Only seven well-documented cases have been published, as summarized in Table 1. In these cases, classic disease with mixed cellularity ([10] and this case) or nodular sclerosis prevailed [1, 4, 15]. In all cases, histological examination disclosed Reed-Sternberg cells. Additionally, five out of seven publications fulfilled the criteria of CD30-positive staining of Reed-Sternberg cells ([4, 6, 15, 24] and this case). This summary does not include cases that primarily presented with an additional non-CNS manifestation [2, 11] or cases that presented with a primarily dural manifestation [17].

Primary CNS HL appears to be different from secondary seeding of the CNS. All seven patients with primary CNS HL developed their tumor beyond the age of 50 years. This is similar to the age of onset for primary NHL of the CNS (median age 57 years) but in contrast to the age of onset for secondary seeding of HL (median age 21 years) [20]. Also, the distribution pattern of the CNS lesions in the patient presented and in the six previously published cases with intraparenchymal mass lesions is distinct from secondary seeding of the CNS with predominantly dural or diffuse leptomeningeal deposits [21, 23].

The distinction of primary CNS HL from primary CNS NHL, particularly anaplastic large cell lymphoma and diffuse large cell lymphoma, poses some diagnostic problems. Some cases previously diagnosed as HL of the CNS without immunohistochemical confirmation [24] had to be reclassified as B cell NHL upon re-evaluation and application of immunohistochemistry [20, 25]. Even now, HD and NHL of the above-mentioned subtypes are difficult to distinguish since they share some properties. First, CD30-positive cells, although relatively specific for Reed-Sternberg cells, can also be found in CD30 (Ki1)-positive large cell anaplastic lymphoma. So far, seven CD30-positive primary CNS NHL, mainly T cell NHL, have been reported [19]. Second, positive staining for the B cell marker CD20 [22] and demonstration of a monoclonal rearrangement for a variable heavy chain locus [13] are found in Reed-Sternberg cells of HD and in B cell NHL. In the present case with CD30-positive cells and monoclonal CDR2 rearrangement, and in four of the six previously published cases [1, 4, 6, 15], the diagnosis of HL was finally made on the base of lack of CD45 (LCA)-positive staining on Reed-Sternberg cells, a prerequisite for the diagnosis of NHL.

Concerning the pathogenesis of primary CNS HL, an association with EBV infection could be demonstrated by LMP immunohistochemistry in Reed-Sternberg cells, nested PCR, and in situ hybridization using an EBV EBER-1-specific probe. So far, only one previous case has been published with positive LMP staining in Reed-Sternberg cells [15]. In another previous case LMP expression was not detected [6], other cases were not tested for EBV DNA or LMP expression. However, expression of EBV LMP has so far been demonstrated in 48% of patients with HD [18]. Moreover, association with EBV infection is rarely reported in primary CNS NHL in immunocompetent patients but for virtually all primary CNS NHL in immunodeficient patients [14, 16]. HHV-8 DNA sequences, which have been found in primary CNS non-HD in some patients [5], were not detected in the present case. It may be speculated that the presence of EBV in the present case is associated with immunosuppression caused by treatment with azathioprine for 12 years.

It is not clear whether the biological behavior, especially the systemic spreading, or primary CNS HL significantly differs from that of primary CNS NHL. In the presented case, no systemic tumor deposits were found at initial staging and 18 months later. However, in one of the previously seen cases [6], secondary systemic dissemina-

tion was observed early in the course of the disease. This is different from primary CNS NHL, where systemic spread is observed only in very late stages of the disease and usually remains clinically insignificant. Given the scarce data on primary CNS HD, with one of seven patients developing systemic deposits early in the course of the disease, it seems appropriate to follow the staging procedures suggested for systemic HD. This includes routine laboratory tests, chest X-ray abdominal and pelvic CT scan, and bone marrow biopsy [7]. Statements about efficacy of treatment in primary CNS HD are preliminary with reports on only seven patients published and short follow-up times. With complete resection, whole brain radiotherapy, or CNS penetrating chemotherapy, no local or systemic recurrences have been reported for the seven cases of primary CNS HL after a median follow-up time of 12 months (range 6–18 months).

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