

Diffuse large B-cell lymphoma of the central nervous system presenting as “lymphomatosis cerebri” and dementia in elderly man

Case report and review of the literature

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Abstract

Rationale: *Lymphomatosis cerebri* is a rare form of PCNSL, characterized by diffuse infiltration of lymphoma cells in cerebral parenchyma, without mass-formation and mild or no contrast enhancement on magnetic resonance (MR) imaging. There are less than 50 cases described in the literature under the term *Lymphomatosis cerebri*.

Patient concerns: A 74-year-old man presented to our service with progressive dementia for 12 months and accelerated cognitive decline within the last two months. Brain magnetic resonance imaging showed areas of hyperintensity involving predominantly the white matter of frontal lobes and knee of the corpus callosum, along with areas of blood-brain barrier disruption and areas of restricted diffusion. Stereotaxy brain surgery was indicated into contrasting areas and histologically there was heterogeneous foci of discreet infiltration of rare medium-large lymphoid cells intermingled with inflammatory cells and these atypical lymphoid cells were placed on breakdown neuropil and did not form tumor mass or sheets of cells, but occasionally displayed perivascular distribution. Immunohistochemically, these atypical lymphoid cells expressed CD20, Bcl2, Bcl6 and, heterogeneously, IRF4/MUM1.

Diagnosis: The diagnosis of a primary CNS diffuse large B-cell lymphoma manifested as *lymphomatosis cerebri* was performed.

Interventions: The treatment of choice was: temozolomide 100 mg/m² (D1 to D5), methotrexate 3g/m² (D1, D10, and D20) and rituximab 375 mg/m².

Outcomes: The patient evolved with progressive neurological deterioration, regardless of the improvement on neuroimaging.

Lessons: We described the diagnostic dilemma we faced with an elderly man with rapid cognitive impairment and a myriad of differential diagnoses, diagnosed with primary CNS diffuse large B-cell lymphoma with a *lymphomatosis cerebri*-like pattern.

Abbreviations: AGNA-1 = antibody glial type 1, CBC = complete blood count, CNS = central nervous system, CSF = cerebrospinal fluid, CT = computed tomography, DLBCL = diffuse large B-cell lymphomas, ECOG = eastern cooperative oncology group, KPS = Karnofsky performance status, LDH = lactate dehydrogenase, MR = magnetic resonance, MRI = magnetic resonance imaging, NHL = non-Hodgkin lymphomas, NR = normal range, OS = overall survival, PCA = Purkinje cell cytoplasmic autoantibody, PCNSLs = primary central nervous system lymphomas, PET-CT = positron emission tomography.

Keywords: dementia, diffuse lymphoma, large B-Cell, lymphoma, nervous system neoplasms

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1. Introduction

Primary central nervous system lymphomas (PCNSLs) are rare extranodal non-Hodgkin lymphomas (NHL) restricted to the central nervous system (CNS), that is, brain parenchyma, spinal cord, neural part of the eyes, the most proximal portions of cranial nerves, and/or meninges. Most often PCNSLs are represented by diffuse large B-cell lymphomas (DLBCL), which are characterized radiologically by single or multiple contrast-enhancing lesions, usually at supratentorial location.^[1] They represent 2% to 3% of all brain tumors and less than 1% of all non-Hodgkin lymphomas.^[2] *Lymphomatosis cerebri* is a rare form of PCNSL, first described by Bakshi et al in 1999,^[3] and it is characterized by diffuse infiltration of lymphoma cells in cerebral parenchyma, without mass-formation and mild or no contrast enhancement on magnetic resonance (MR) imaging.^[4,5] Clinically, progressive dementia is among the most frequent manifestation.^[6,7]

According to the best of our knowledge, there are less than 50 cases described in the literature under the term *Lymphomatosis cerebri*. However, when we include in the search patients with CNS lymphomas who presented, at some point of the disease, diffuse infiltration of sparse neoplastic cells and non-enhancing

lesions, we can find at least 66 reported cases. Herein, we report the diagnostic dilemma of a puzzling case of an elderly man who presented progressive dementia and *lymphomatosis cerebri*. We reviewed the literature, the main differential diagnoses and discussed the imaging and histopathological aspects of this pattern of CNS involvement by a DLBCL in comparison with other forms of CNS lymphomas.

2. Case report [Methods]

A 74-year-old man, a farmer with a previous history of hypertension, type II diabetes, and diabetic peripheral neuropathy, presented to our service on March, 2016 with progressive dementia for 12 months. He had also had accelerated cognitive decline within the last two months, characterized by recent memory loss, labile emotion, behavior changes, apathy, and confusion. At that moment, he was unable to carry on some daily activities, like bathing without assistance, and to perform instrumental activities without assistance.

The Karnofsky Performance Status (KPS) was 60%, and the neurologic examination confirmed the impairment of memory, dysexecutive syndrome, and attention deficits. Diabetic peripheral neuropathy was also noted. Strength was 5/5 in the upper

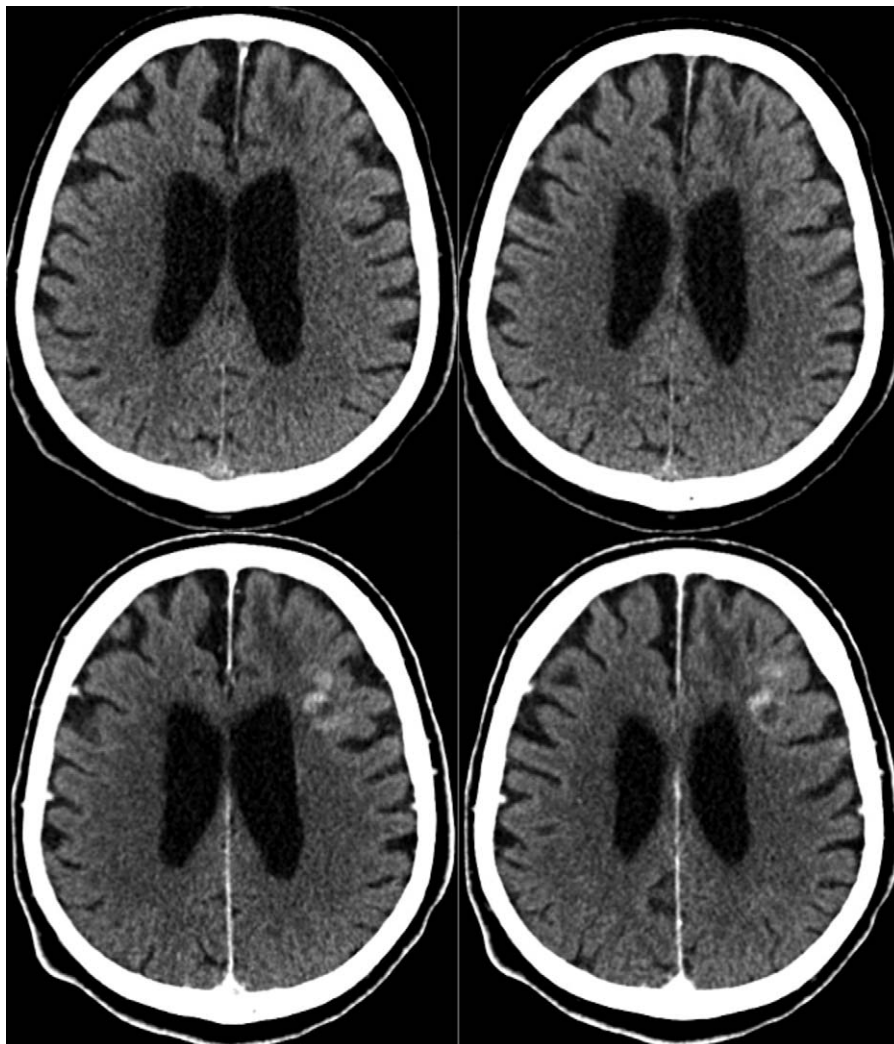


Figure 1. Axial computed tomography (CT) images show left frontal lobe heterogeneous hypodensity in the white matter with areas of abnormal contrast enhancement.

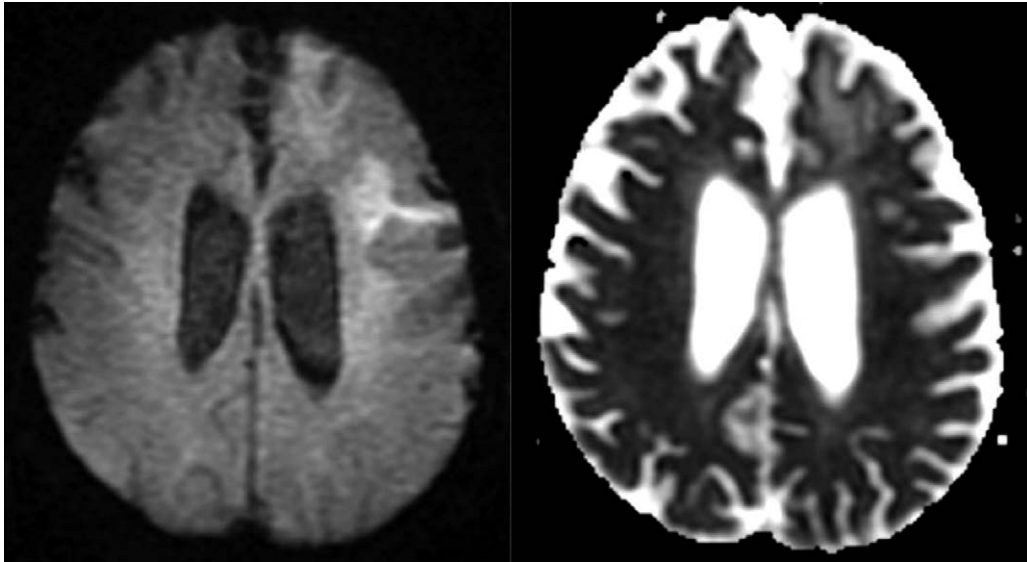


Figure 2. Axial diffusion and apparent diffusion coefficient (ADC) map magnetic resonance images show areas of diffusion hyperintensity, some with restricted diffusion.

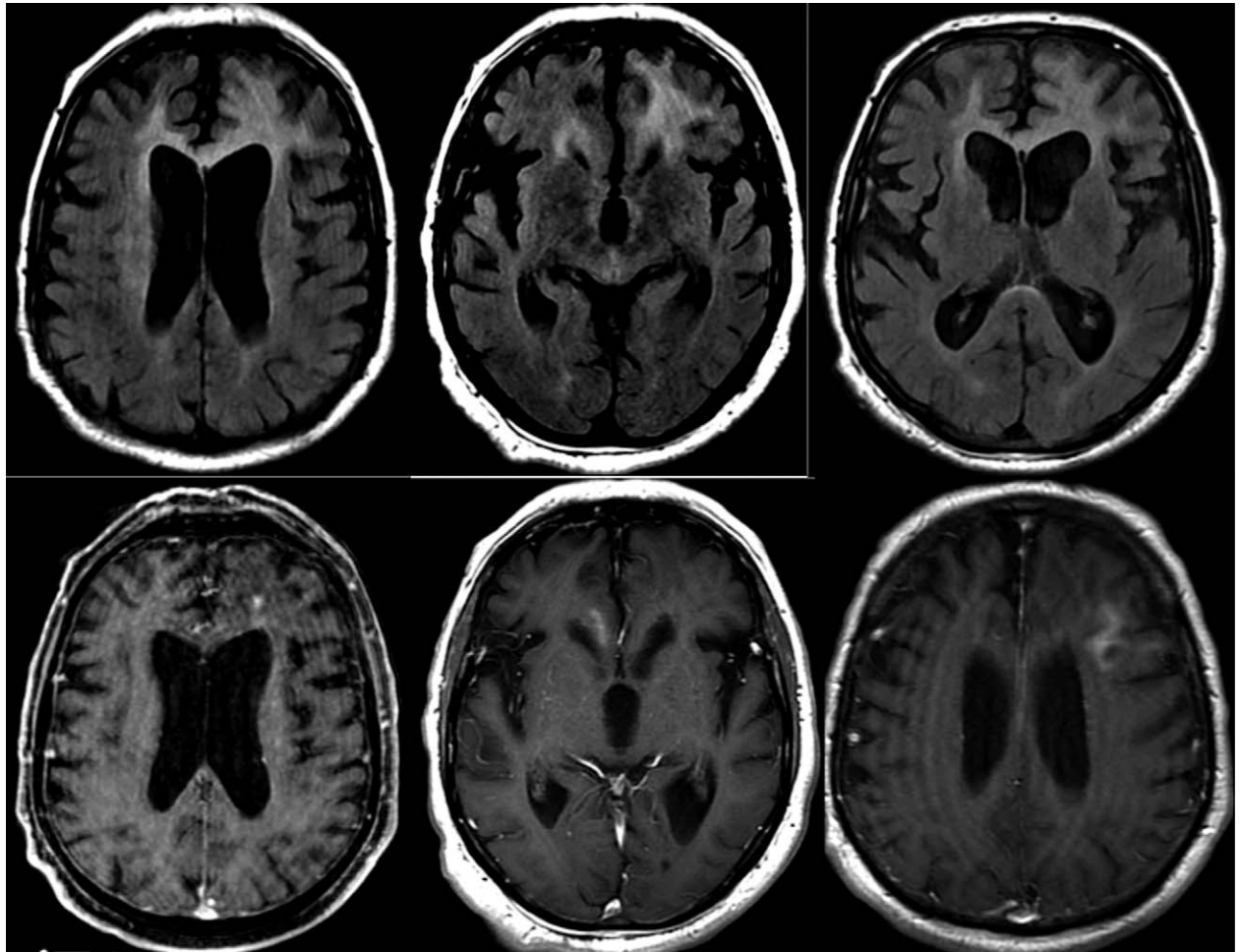


Figure 3. Axial FLAIR (above) and axial T1 post gadolinium (below) magnetic resonance images show areas of signal abnormality in both frontal lobes and corpus callosum with areas of contrast enhancement.

and lower extremities, respectively. We did not observe sensitive changes or gait abnormalities, and the Romberg sign was negative. Fundoscopy was also unremarkable.

Initial laboratory studies, like the complete blood count (CBC), C-reactive protein, liver and renal functions evaluations, were within normal range (NR). Lactate dehydrogenase (LDH) concentration was 614 U/L (NR: 313 – 618 U/L), beta-2 microglobulin was 1.9 mg/L (NR: 0.80–2.19 mg/L), and serology for HIV, hepatitis B and C and HTLV were negative.

Computed tomography (CT) scans of the brain revealed hypodensity in the white matter of the cerebral hemispheres and corpus callosum, most evident at left frontal lobes. This area of hypodensity showed more irregular and discontinuous contrasting areas with undefined borders, more evident at the left side and septal region. Effacement of the cortical sulci in the frontoparietal cortex and enlargement of other intracranial spaces were observed, suggesting a disturbance of cerebrospinal fluid (CSF) flow. Brain magnetic resonance imaging (MRI) showed areas of hyperintensity involving predominantly the white matter of frontal lobes and knee of the corpus callosum, mainly on the left side, along with areas of blood-brain barrier disruption (similar to CT findings) and areas of restricted diffusion (Figs. 1–3).

Positron emission tomography (PET-CT) scans, performed to rule out proliferative disease, disclosed areas of increased metabolism (SUVmax of 48.5) at the left frontal lesion, extending throughout the corpus callosum and superior frontal and right anterior cingulate gyri. Focal areas of increased FDG uptake were observed in the left superior and middle frontal gyri, corpus callosum and right superior frontal gyrus, which correspond to the areas of hyperintensity described at MR imaging. Additionally, hypometabolic areas were seen at frontal lobes and posterior temporoparietal region (more pronounced at the left), *cingulum*, basal ganglia, and thalamus.

CSF analyses showed an initial pressure of 23 cmH₂O and final pressure of 15 cmH₂O, 2 leucocytes/mm³ and absence of erythrocytes. Protein, glucose and lactic acid were within normal ranges, and no neoplastic cells were observed. Electrophoresis of proteins and immunofixation demonstrated an absence of monoclonal spike. Total Tau, beta-amyloid and phospho-Tau protein concentrations were 751 ng/L (NR for patient's age: 170.00 – 512.00 ng/L), 628 ng/L (NR for patient age: 567.00–1,027.00 ng/L) and 33.00 ng/L (NR < 61 ng/L), respectively. Screening for infectious disease was negative for aerobic and anaerobic bacteria, Zika virus, herpes, toxoplasmosis, tuberculosis, syphilis, cysticercosis, cytomegalovirus and fungal infections. NMDA-R, GAD 65, GABA-B-R, AMPA-R, anti-nuclear neuronal antibody types 1, 2 and 3, anti-nuclear antibody glial type 1 (AGNA -1), Purkinje cell cytoplasmic autoantibody types 1 and 2 (PCA- 1 and 2) and Purkinje cell cytoplasmic antibody type Tr, and CRMP-5-IgG were all negative. Immunophenotyping of CSF by flow cytometry failed to reveal any proliferation of abnormal lymphoid cells.

Due to the unspecific clinical and laboratory findings, stereotaxy brain surgery was indicated into contrasting areas in depth of the left frontal lobe. Histologically, the evaluation of stereotactic brain sections disclosed heterogeneous foci of discreet infiltration of rare medium-large lymphoid cells intermingled with inflammatory cells, composed of small lymphocytes, vacuolated macrophages, reactive astrocytes and activated microglia. These atypical lymphoid cells were placed on breakdown neuropil and did not form tumor mass or sheets of cells, but occasionally displayed perivascular distribution (Fig. 4). Immunohistochemically, these atypical lymphoid cells expressed

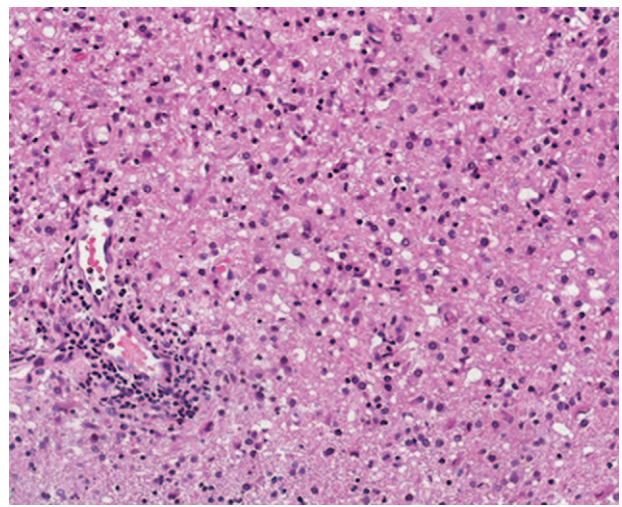


Figure 4. Heterogeneous discreet infiltration of rare atypical lymphoid cells without formation of mass or sheets of cells, in a background of small lymphocytes, macrophages and microglia. Mild perivascular infiltration, predominantly composed by small reactive lymphocytes (hematoxylin and eosin, 20 X).

CD20 (Fig. 3), Bcl2, Bcl6 and, heterogeneously, IRF4/MUM1. They were negative for CD3, CD10, CD30, and c-myc. The Ki-67 proliferation index was around 60%. The immunohistochemical evaluation for herpes simplex virus 1 and 2, varicella-zoster virus, cytomegalovirus, and Toxoplasma was negative. Additionally, abnormal amyloid deposits, plaques and/or neurofibrillary tangles were not observed (Fig. 5).

Therefore, the diagnosis of a primary CNS diffuse large B-cell lymphoma manifested as *lymphomatosis cerebri* was done. Complete workup and screening with PET-CT discarded any extracerebral or systemic lymphoma.

The patient exhibited a score of 3 according to the International Extranodal Lymphoma Prognostic Assessment [age greater than 60 years, involvement of deep regions of the brain and Eastern Cooperative Oncology Group (ECOG) performance status >1]. The treatment of choice was based on Omuro protocol: temozolomide 100 mg/m² (D1 to D5) and methotrexate 3 g/m² (D1, D10, and D20).¹⁸¹ High doses of corticosteroids were avoided due to the patient's history of diabetes, and rituximab 375 mg/m² was added in the induction and maintenance periods. Since the first dose of methotrexate, a worsening of renal function was observed, as well as raising of the liver enzymes and grade III mucositis. Because of this, the methotrexate dose was reduced to 1 g/m² on D10 and D20.

As the patient achieved partial response on neuroimaging after the induction period (first 45 days of treatment), the maintenance cycle was initially performed with methotrexate 1 g/m², temozolomide 100 mg/m², and rituximab 375 mg/m². However, since the patient developed renal dysfunction and infectious complications, the other five maintenance cycles were performed without systemic methotrexate, which was replaced by intrathecal chemotherapy with methotrexate and dexamethasone.

Concerning the neurological follow-up, the patient showed progressive neurological deterioration, regardless of the improvement on neuroimaging, which exhibited a significant size reduction at the left frontal lesion and in the brain edema (Figs. 6 and 7). At present, after 18 months of treatment, the patient remains entirely dependent for all his activities of daily living

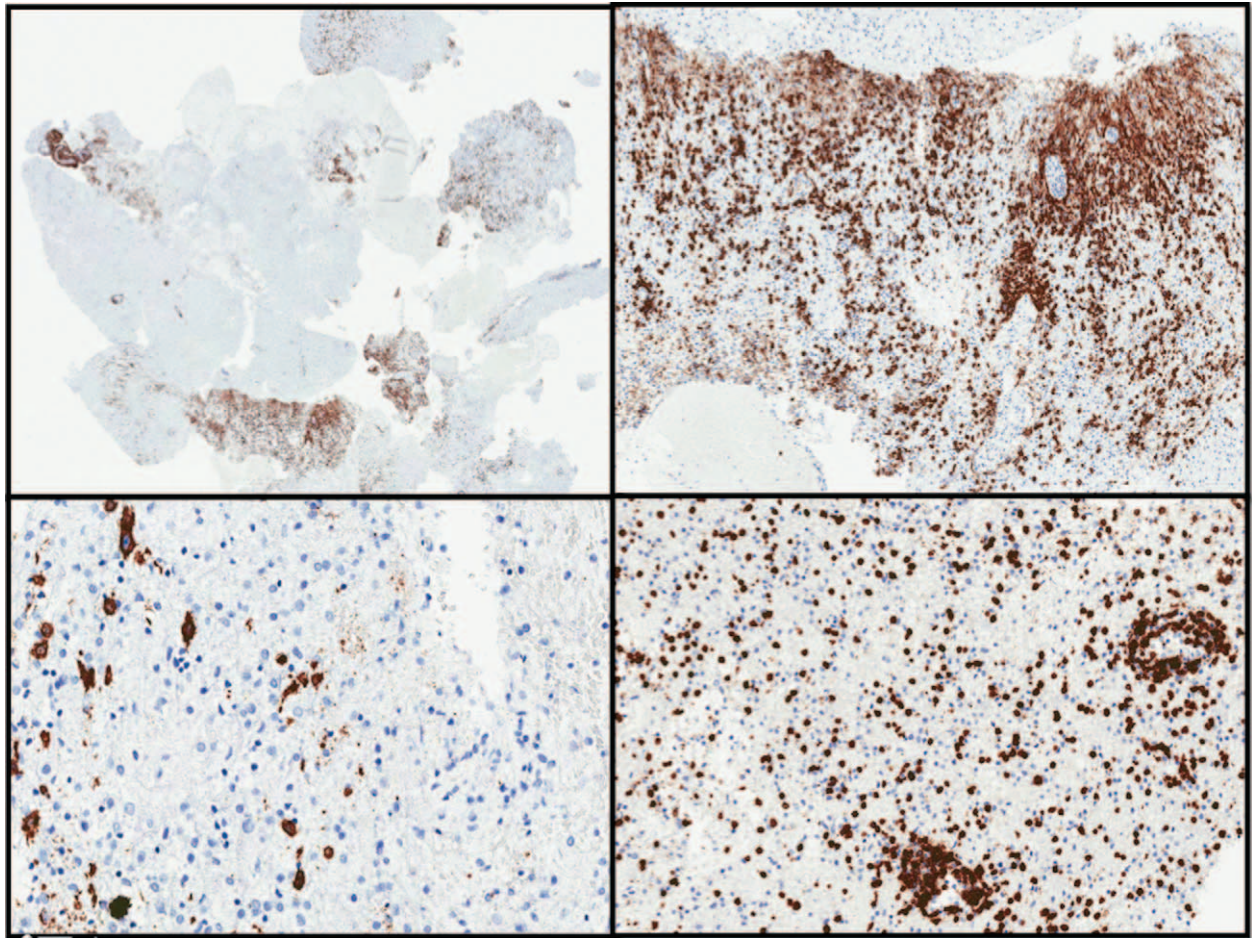


Figure 5. A. low power view of CD20 staining showing heterogeneous distribution of neoplastic B cells among different fragments of tissue (CD20, 4 X); B. Area of more dense staining of CD20 (CD20, 10 X); C. area with rare CD20-positive neoplastic cells distributed within numerous reactive lymphocytes and macrophages (CD20, 20 X); D: CD3 staining highlighting the significant permeation of brain tumor by reactive small lymphocytes and perivascular infiltration (CD3, 20 X).

(KPS of 40) and intense apathy, only expressing few words, but walks unsteadily with assistance.

This study was formally reviewed by the local Ethics Committee (Hospital Israelita Albert Einstein Ethics Board) that concluded it does not require ethical approval as it does not attend the criteria of research. The patient's family signed a written informed consent for this publication.

3. Discussion

Diffuse involvement of the brain parenchyma by lymphoma is an unusual but well-recognized pattern of infiltration by large diffuse cell CNS lymphomas.^[9–17] The term *lymphomatosis cerebri* was first used in 1999 by Bakshi et al^[3] who described two patients with rapidly progressive dementia and diffuse parenchymal infiltration by lymphoma cells. After this first description, 46 other cases of *lymphomatosis cerebri* were documented.^[4–7,18–50] On MR imaging, the typical findings are non-enhancing, T2 hyper-intense diffuse lesions without forming any distinct mass in the subcortical white matter.^[6] PET scans may demonstrate hypermetabolism in the areas of MR abnormalities.^[38] The median age of patients with *lymphomatosis cerebri* is 57 years (ranging from 14–81 years), with a mild male predilection (58%). The most common clinical manifestations were a cognitive decline, behavioral changes and/or abnormal gait.^[7] The absence

of enhancing lesion on MR is thought to occur due to the absence of disruption of the blood-brain barrier.^[3]

The unusual radiological finding, associated with clinical presentation of rapidly progressive dementia, opens a wide list of differential diagnosis that includes Creutzfeldt-Jakob disease;^[5,6,18,25,41] infectious and inflammatory encephalitis;^[4,5,16,19,21,24,25,41,45–48] autoimmune encephalopathy;^[22,36,38,47] hypertensive encephalopathy;^[47] demyelinating diseases;^[4,16,18,21,40,43,45] Binswanger disease (subcortical ischemic vascular dementia)^[5,19] and other vascular disorders;^[5,21,25] gliomatosis;^[5,17,19,27,37,45,50] tumor metastases;^[21] toxic and metabolic processes;^[5,6,18,30,45] and neurodegenerative diseases.^[6,40]

Additionally, the histopathological findings are atypical for the usual CNS lymphoma, that is, deep-seated tumor masses adjacent to the ventricular system with homogeneous contrast enhancement. Indeed, the paucity of neoplastic lymphoma cells intermingled with overwhelming inflammatory infiltrate and the absence a tumor mass makes *lymphomatosis cerebri* a challenging diagnosis for hematologists, neurologists, pathologists, and radiologists.

In a meta-analysis of clinical presentation of cases of CNS lymphomas with rapidly progressive dementia from 1950 to 2013, Deutsch and Mendez^[51] described 20 patients, 14 of which presented *lymphomatosis cerebri*. When they compared these 14 patients with those with other causes of rapidly progressive

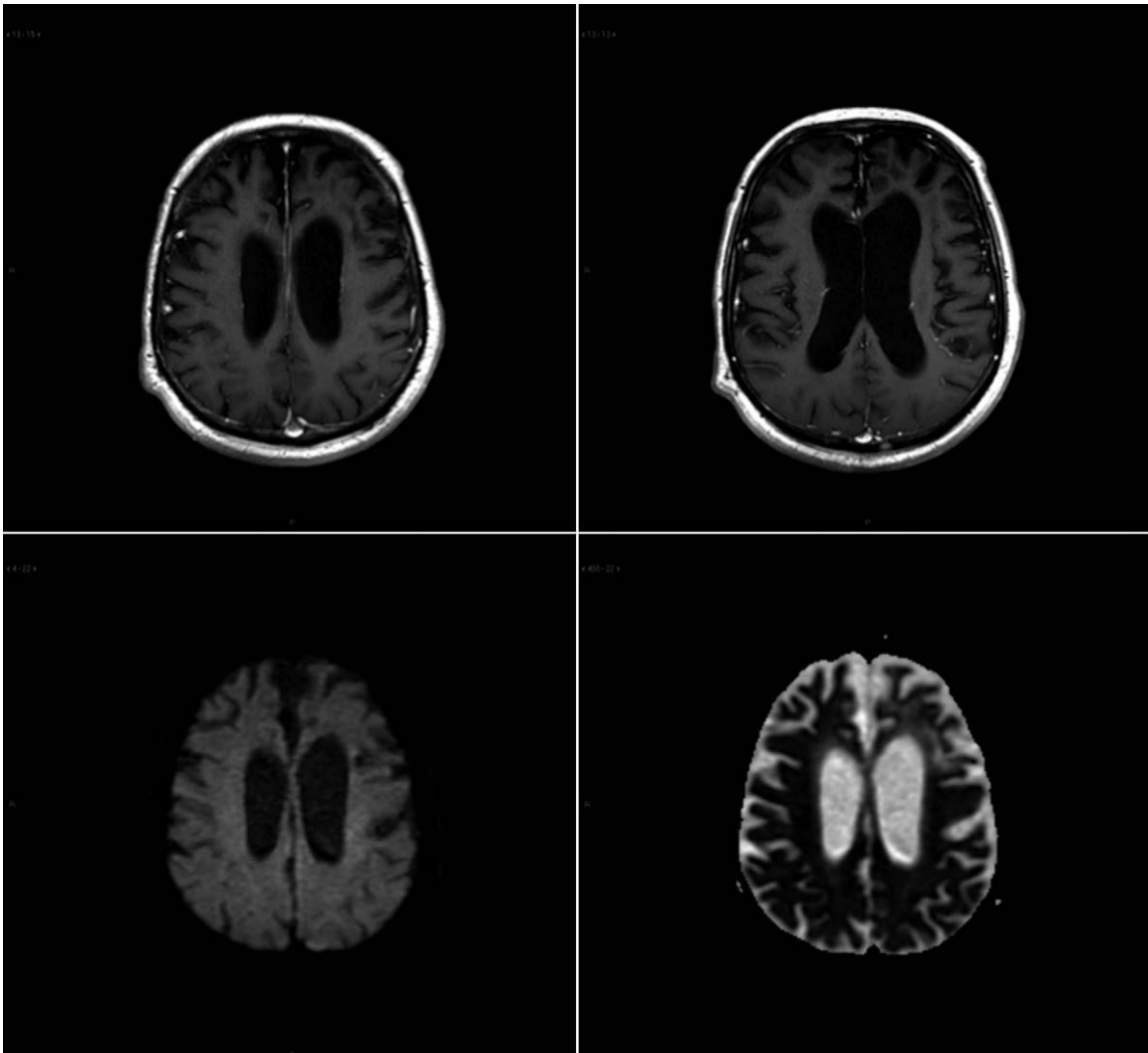


Figure 6. Axial T1 post gadolinium images (above) and diffusion and apparent diffusion coefficient (ADC) map magnetic resonance images (below) show resolution of areas of abnormal enhancement and diffusion restriction.

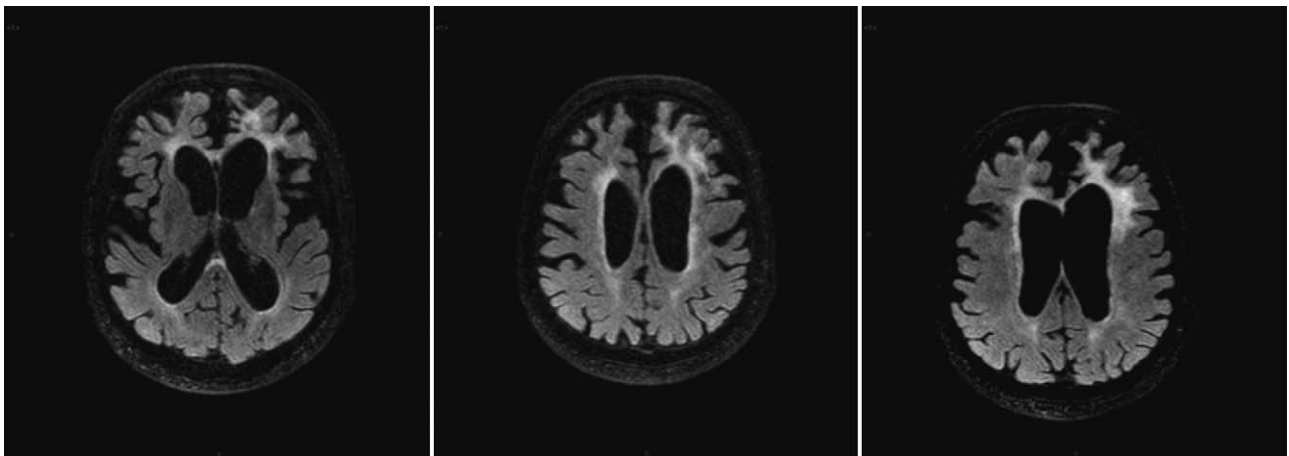


Figure 7. Axial magnetic resonance FLAIR images show persistent areas of abnormal signal in frontal lobes.

dementia, patients with *lymphomatosis cerebri* more commonly presented impaired memory, apathy, abnormal speech and gait disturbances, without headaches, seizures, or myoclonus. Some of the described autopsied cases of *lymphomatosis cerebri* underwent neuropathological evaluation.^[3,5,19,34,41] In these cases, lymphoma was present in several brain regions, indicating that *lymphomatosis cerebri* is a diffuse brain disease, even if image studies do not suggest it. In about half of the described cases, CSF analysis showed only mild pleocytosis, and protein levels were elevated in 76% of patients.^[7] Importantly, CSF malignant lymphoma cells were absent in the majority of the patients (94%), as is the present case. Flow cytometry was rarely performed in the CSF, but it was described as positive for clonal B lymphocytes in 2 of 3 cases.^[7]

The majority of CNS primary lymphomas are high-grade non-Hodgkin diffuse large B cell lymphomas, affecting both immunocompetent or immunodeficient patients. Microscopically, the CNS lymphoma is similar to systemic DLBCL: a high proliferation of large lymphoid cells with perivascular infiltration and high mitotic index. Tumor cells are permeated by reactive small T and B lymphocytes, macrophages, activated microglial cells and reactive astrocytes.^[52] Phenotypically, the neoplastic cells express B cell markers, which lack the Ig class switch (IgM and IgD, but not IgG), and often show a pattern of late stage of germinal center (demonstrated by gene expression profiling and by the expression of Bcl6 and IRF4/MUM1 in the majority of the cases).^[52,53,54]

In contrast, *lymphomatosis cerebri* affects immunocompetent patients in the great majority of the cases. Only three cases of lymphomas with non-enhancing lesions have been described in immunodeficient patients.^[12,44,46] Microscopically *lymphomatosis cerebri* is composed of large atypical lymphoid cells, sparsely distributed within a background of activated microglia and macrophages as well as small reactive lymphoid cells. Perivascular neoplastic infiltration may be present. In the current case, there was an occasional perivascular distribution of tumor cells. The majority of the described *lymphomatosis cerebri* cases were B-cell lymphomas (89%). According to the Hans Algorithm,^[55] the putative origin of lymphoma cells in the present case was activated B cells (ABC), similarly to other reports in the literature.^[7,22,23] Interestingly, in the current case, lymphoma cells co-expressed Bcl6 and IRF4/MUM1. This co-expression has also been demonstrated in DLBCL of CNS, and some authors suggested that these lymphomas are instead derived from B cells of late germinal center.^[53,54]

Indeed, cases of *lymphomatosis cerebri* were described in association with the usual form of DLBCL of CNS, either with concomitant diffuse infiltration and contrast-enhanced cohesive mass,^[37,42] or with *lymphomatosis cerebri* preceding a usual DLBCL.^[38] Brecher et al^[16] described a case of PCNSL with mass formation associated with a diffuse pattern of infiltration accompanied with demyelination. Four cases of *lymphomatosis cerebri* showed a T-phenotype,^[25,33,6,7] one of which was described as anaplastic large cell lymphoma.^[33] Fuseya et al^[56] reported a patient with systemic peripheral T-cell lymphoma who had CNS infiltration mimicking *lymphomatosis cerebri*.

An uncommon form of lymphoma that involves the brain is intravascular large B-cell lymphoma. It is a rare form of lymphoma characterized by proliferation of B-cell lymphoma in the lumen of small blood vessels that may involve virtually any organ.^[57,58] Hishikawa et al^[32] described a case of intravascular large B cell lymphoma involving multiple visceral organs, associated with lymphoma of the CNS with a *lymphomatosis cerebri*-like pattern. Cerebral cortex, white matter, brainstem and

spinal cord were infiltrated by scattered large B-cells with perivascular distribution. Atypical lymphoid cells also infiltrated the lumen of small vessels of lungs, myocardium, gastrointestinal tract, liver, spleen, genitourinary tract, endocrine organs, skeletal muscle and bone marrow. Another unusual pattern of CNS infiltration was reported by Chang et al,^[20] who described a patient with neurolymphomatosis (lymphoma infiltrating cranial nerves), which evolved to *lymphomatosis cerebri*.

In comparison with primary DLBCL of CNS, the prognosis of *lymphomatosis cerebri* is poorer, and most patients die within six months after the diagnosis.^[22] In a systematic review of the literature, Izquierdo et al^[7] showed that younger age (< 56 years), higher KPS, therapy with methotrexate and B cell histology are independent prognostic factors of a better outcome. The authors reported that patients with early-diagnosed *lymphomatosis cerebri* who were treated with high doses of methotrexate showed better overall survival (OS): 13.8 months (range: 0.7–56 months) versus OS of 2.95 months (range: 0.33–56 months), when methotrexate was not prescribed.^[7]

Histopathological examination of brain tissue is the “gold standard” for the diagnosis of *lymphomatosis cerebri* because the clinical, radiological and laboratory findings are nonspecific. However, the diagnosis of this entity is also a challenge for pathologists, due to the rarity of this histological form of presentation of CNS lymphoma and the paucity of malignant cells in the tissue. In the current case, the lymphoid cells permeated the brain parenchyma in a sparse distribution, without mass formation, and showed only discreet and focal tendency for perivascular distribution.^[19] Since there were more reactive small lymphocytes and macrophages when compared to the amount of large neoplastic cells, our initial histological differential diagnoses were vasculitis and viral encephalitis. Indeed, perivascular cuffing is not always present in *lymphomatosis cerebri*, but there is a tendency for tumor cell angiocentricity, what may mimic viral encephalitis.^[36] Only after the immunohistochemical evaluation highlighted the malignant lymphoid cells, we were able to make the proper diagnosis.

The current case illustrates how important brain biopsy can be in cases of rapidly progressive dementia of unknown causes and also the necessity for a workgroup approach.^[18,24] In a review of 53 cases where brain biopsies were performed,^[24] the procedure was diagnostic in 60% of them, with PCNSL being the most frequent diagnosis (14 of 53 patients, 26% of total), followed by infarct in 7.5% (4 patients). Of the 14 cases diagnosed with lymphoma, 2 showed *lymphomatosis cerebri*. In one of these, the proper diagnosis was only achieved in the *postmortem* examination, since a diagnosis of encephalitis was the result of the biopsy.

Albeit brain biopsies have its known risks, such as CNS hemorrhage infarction and/or infection, early diagnosis, and appropriate treatment with high doses of methotrexate are the most important prognostic factors.^[7] But even with open brain biopsies, *lymphomatosis cerebri* is not an easy diagnosis. In a series of cases from the literature including patients with rapidly progressive dementia and lymphoma,^[51] 6 of the 20 original cases (30%) died before the definitive diagnosis was made and 4 out of these 6 patients had *lymphomatosis cerebri*. Furthermore, since many patients received steroids before the biopsy, the cytotoxic effect delayed the proper diagnosis even further due to massive cell apoptosis.

4. Conclusions

Lymphomatosis cerebri is a commonly misdiagnosed entity, associated with poor prognosis and unspecific clinical presenta-

tion. Herein, we described the diagnostic dilemma we faced with an elderly man with rapid cognitive impairment and a myriad of differential diagnoses, including organic dementia and infectious diseases, before we could properly reach the diagnosis of primary CNS diffuse large B-cell lymphoma with a *lymphomatosis cerebri*-like pattern. Clinicians, neurologists, pathologists, radiologists, oncologists, and geriatrics should be aware of this unusual clinical and pathological presentation of primary B-cell CNS lymphoma, and hence, enable an early therapeutic approach and better patient outcome.

Author contributions

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References

- [1] Bathla G, Hegde A. Lymphomatous involvement of the central nervous system. *Clin Radiol* 2016;71:602–9.
- [2] Swerdlow SH, Campo E, Harris NL, Bosman FT, Jaffe ES, Lakhani SR, Ohgaki H, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. World Health Organization Classification of Tumours Lyon, France: IARC; 2008.
- [3] Bakshi R, Mazziotta JC, Mischel PS, et al. Lymphomatosis cerebri presenting as a rapidly progressive dementia: clinical, neuroimaging and pathologic findings. *Dement Geriatr Cogn Disord* 1999;10:152–7.
- [4] Hatanpaa KJ, Fuda F, Koduru P, et al. Lymphomatosis cerebri: a diagnostic challenge. *JAMA Neurol* 2015;72:1066–7.
- [5] Kitai R, Hashimoto N, Yamate K, et al. Lymphomatosis cerebri: clinical characteristics, neuroimaging, and pathological findings. *Brain Tumor Pathol* 2012;29:47–53.
- [6] Rivero SE, Torralba CMA, Sanjuan PF, et al. Lymphomatosis cerebri mimicking iatrogenic Creutzfeldt-Jakob disease. *BMJ Case Rep* 2014; bcr2013201246.
- [7] Izquierdo C, Velasco R, Vidal N, et al. Lymphomatosis cerebri: a rare form of primary central nervous system lymphoma. Analysis of 7 cases and systematic review of the literature. *Neuro-oncology* 2016;18:707–15.
- [8] Omuro AM, Taillandier L, Chinot O, et al. Temozolomide and methotrexate for primary central nervous system lymphoma in the elderly. *J Neurooncol* 2007;85:207–11.
- [9] Cellerier P, Chiras J, Gray F, et al. Computed tomography in primary lymphoma of the brain. *Neuroradiology* 1984;26:485–92.
- [10] Provinciali L, Signorino M, Ceravolo G, et al. Onset of primary brain T-lymphoma simulating a progressive leukoencephalopathy. *Ital J Neurol Sci* 1988;9:377–81.
- [11] Kazahaya Y, Doi A, Hamaya K. An autopsy case of primary central nervous system lymphoma with diffuse intracerebral lesion. *No To Shinkei* 1992;44:65–70.
- [12] DeAngelis LM. Cerebral lymphoma presenting as a non-enhancing lesion on computed tomographic/magnetic resonance scan. *Ann Neurol* 1993;33:308–11.
- [13] Matsumoto K, Kohmura E, Fujita T, et al. Recurrent primary central nervous system lymphoma mimicking neurodegenerative disease—an autopsy case report. *Neurol Med Chir (Tokyo)* 1995;35:360–3.
- [14] Terae S, Ogata A. Nonenhancing primary central nervous system lymphoma. *Neuroradiology* 1996;38:34–7.
- [15] Carlson BA. Rapidly progressive dementia caused by nonenhancing primary lymphoma of the central nervous system. *AJNR Am J Neuroradiol* 1966;17:1695–7.
- [16] Brecher K, Hochberg FH, Louis DN, et al. Case report of unusual leukoencephalopathy preceding primary CNS lymphoma. *J Neurol Neurosurg Psychiatry* 1998;65:917–20.
- [17] Furusawa T, Okamoto K, Ito J, et al. Primary central nervous system lymphoma presenting as diffuse cerebral infiltration. *Radiat Med* 1988;16:137–40.
- [18] Samani A, Davagnanam I, Cockerell OC, et al. Lymphomatosis cerebri: a treatable cause of rapidly progressive dementia. *J Neurol Neurosurg Psychiatr* 2015;86:238–40.
- [19] Rollins KE, Kleinschmidt-DeMasters BK, Corboy JR, et al. Lymphomatosis cerebri as a cause of white matter dementia. *Hum Pathol* 2005;36:282–90.
- [20] Chang GY. Evolution of neurolymphomatosis to lymphomatosis cerebri. *J Clin Neurol* 2017;13:203–4.
- [21] Lee PJ, Berrios I, Ionete C, et al. Lymphomatosis cerebri: diagnostic challenges and review of the literature. *BMJ Case Rep* 2016; bcr2016216591.
- [22] Murakami , et al. A case of lymphomatosis cerebri mimicking inflammatory diseases. *BMC Neurology* 2016;16:128.
- [23] Hashiguchi S, Momoo T, Murohashi Y, et al. Interleukin 10 level in the cerebrospinal fluid as a possible biomarker for lymphomatosis cerebri. *Intern Med* 2015;54:1547–52.
- [24] Magaki S, Gardner T, Khanlou N, et al. Brain biopsy in neurologic decline of unknown etiology. *Hum Pathol* 2015;46:499–506.
- [25] Weaver JD, Vinters HV, Koretz B, et al. Lymphomatosis cerebri presenting as rapidly progressive dementia. *Neurologist* 2007;13:150–3.
- [26] Imperiale D, Taraglio S, Atzori C, et al. Diffuse leukoencephalopathy due to lymphomatosis cerebri: a clinicopathological report. *Neurol Sci* 2015;36:1071–3.
- [27] Choi CY, Lee CH, Joo M. Lymphomatosis cerebri. *J Korean Neurosurg Soc* 2013;54:420–2.
- [28] Sato H, Takahashi Y, Wada M, et al. Lymphomatosis cerebri with intramedullary spinal cord involvement. *Intern Med* 2013;52:2561–5.
- [29] Courtios F, Gille M, Haven F, et al. Lymphomatosis cerebri presenting as a recurrent leukoencephalopathy. *Case Rep Neurol* 2012;4:181–6.
- [30] Watanabe M, Satoh H, Takahashi Y, et al. Remission of lymphomatosis cerebri induced by corticosteroid and high-doses intravenous methotrexate. *Resho Shinkeigaku* 2012;52:486–90.
- [31] Keswani A, Bigio E, Grimm S. Lymphomatosis cerebri presenting with orthostatic hypotension, anorexia, and paraparesis. *J Neurooncol* 2012;109:581–6.
- [32] Hishikawa N, Niwa H, Hara T, et al. An autopsy case of lymphomatosis cerebri showing pathological changes of intravascular large B-cell lymphoma in visceral organs. *Neuropathology* 2011;31:612–9.
- [33] Sugino T, Mikami T, Akiyama Y. Primary central nervous system anaplastic large-cell lymphoma mimicking lymphomatosis cerebri. *Brain Tumor Pathol* 2013;30:61–5.
- [34] Leschziner G, Rudge P, Lucas S, et al. Lymphomatosis cerebri presenting as a rapidly progressive dementia with a high methylmalonic acid. *J Neurol* 2011;258:1489–93.
- [35] Raz E, Tinelli E, Antonelli M, et al. MRI findings in lymphomatosis cerebri: description of a case and revision of the literature. *J Neuroimaging* 2011;21:e183–6.
- [36] Pandit L, Chickabasaviah Y, Raghothaman A, et al. Lymphomatosis cerebri - a rare cause of leukoencephalopathy. *J Neurol Sci* 2010;293:122–4.
- [37] Sugie M, Ishihara K, Kato H, et al. Primary central nervous system lymphoma initially mimicking lymphomatosis cerebri: an autopsy case report. *Neuropathology* 2009;29:704–7.
- [38] Lewerenz J, Ding XQ, Matschke J, et al. Dementia and leukoencephalopathy due to lymphomatosis cerebri. *BMJ Case Rep* 2009; pii: bcr08.2008.0752.
- [39] de Toledo M, López-Valdés E, Ferreiro M, et al. Lymphomatosis cerebri as the cause of leukoencephalopathy. *Rev Neurol* 2008;46:667–70.
- [40] Kanai R, Shibuya M, Hata T, et al. A case of lymphomatosis cerebri' diagnosed in an early phase and treated by whole brain radiation: case report and literature review. *J Neurooncol* 2008;86:83–8.
- [41] Vital A, Sibon I. A 64-year-old woman with progressive dementia and leukoencephalopathy. *Brain Pathol* 2007;17:117–8.

- [42] Jain TK, Sharma P, Suman SK, et al. Primary central nervous system lymphoma with lymphomatosis cerebri in an immunocompetent child: MRI and 18F-FDG PET-CT findings. *Rev Esp Med Nucl Imagen Mol* 2013;32:394–6.
- [43] Chen H, Dong H. A rare case of nonenhancing primary central nervous system lymphoma mimic multiple sclerosis. *Neurosciences* 2015;20:380–4.
- [44] Thurnher MM, Rieger A, Kleibl-Popov C, et al. Primary central nervous system lymphoma in AIDS: a wider spectrum of CT and MRI findings. *Neuroradiology* 2001;43:29–35.
- [45] Ayuso-Peralta L, Orti-Pareja M, Zurdo-Hernandez M, et al. Cerebral lymphoma presenting as a leukoencephalopathy. *J Neurol Neurosurg Psychiatry* 2001;71:243–6.
- [46] Moulignier A, Galicier L, Mikol J, et al. Primary cerebral lymphoma presenting as diffuse leukoencephalopathy. *AIDS* 2003;17:1111–3.
- [47] Yamamoto T, Kojima K, Koibuchi K, et al. A case of primary central nervous system lymphoma presenting diffuse infiltrative leukoencephalopathy. *Intern Med* 2012;51:1103–6.
- [48] Miki Y, Tomiyama M, Kurotaki H, et al. Primary central nervous system lymphoma mimicking Bickerstaff's encephalitis. *Neurol Sci* 2014;35:139–41.
- [49] Faro SPS, Vinholi A, da Silva TR, et al. Linfomatose cerebral: um raro diagnóstico para demência rapidamente progressiva. Relato de caso e revisão de literatura. *J Bras Neurocirurg* 2015;26:315–9.
- [50] Lachenmayer ML, Blasius E, Niehusmann P, et al. Non-enhancing primary CNS lymphoma. *J Neurooncol* 2011;101:343–4.
- [51] Mariel B, Deutsch MF, Mendez . Neurocognitive features distinguishing primary central nervous system lymphoma from other possible causes of rapidly progressive dementia. *Cogn Behav Neurol* 2015;28:1–0.
- [52] Deckert M, Brunn A, Montesinos-Rongen M, et al. Primary lymphoma of the central nervous system—a diagnostic challenge. *Hematol Oncol* 2014;32:57–67.
- [53] Montesinos-Rongen M, Brunn A, Bentink S, et al. Gene expression profiling suggests primary central nervous system lymphomas to be derived from a late germinal center B cell. *Leukemia* 2008;22:400–5.
- [54] Montesinos-Rongen M, Siebert R, Deckert M. Primary lymphoma of the central nervous system: just DLBCL or not? *Blood* 2009;113:7–10.
- [55] Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood* 2004;103:275–82.
- [56] Fuseya H, Nakao T, Hashimura M, et al. Peripheral T-cell lymphoma, not otherwise specified accompanied by central nervous system involvement with features of lymphomatosis cerebri. *Rinsho Ketsueki* 2017;58:760–5.
- [57] Mizutani S, Mizutani T. Malignant lymphoma of the brain, and dementia. *Brain Nerve* 2016;68:383–90.
- [58] Giannini C, Dogan A, Salomão DR. CNS lymphoma: a practical diagnostic approach. *J Neuropathol Exp Neurol* 2014;73:478–94.