

Multiple central nervous system lesions on chronic corticosteroid therapy – a diagnostic challenge

Lesões múltiplas do sistema nervoso central sob corticoterapia crónica - um desafio diagnóstico

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Abstract

Diagnostic challenges often arise when multiple central nervous system (CNS) lesions not accessible to biopsy are present on Magnetic Resonance Imaging (MRI). The differential diagnosis is broad, particularly in the context of exposure to steroids and/or in the setting of immunosuppression. Benign lesions to be considered are demyelinating diseases, sarcoidosis and other granulomatous diseases, and infectious diseases such as toxoplasmosis in immunocompromised patients and tuberculosis. Malignant lesions include CNS lymphoma, glioblastoma multiforme and brain metastases. The authors describe the clinical case of a 75-year-old woman with systemic lupus erythematosus (SLE), chronically medicated with Hydroxychloroquine 400 mg, Deflazacort 9 mg and Azathioprine 25 mg daily, who presented to the hospital with a 5-month history of progressive neurological deficits. It was particularly challenging, because the patient was immunocompromised, had multiple CNS lesions that were not accessible to biopsy and chronic therapy with corticosteroids altered the radiological pattern on brain MRI, masquerading the diagnosis. By writing up this case and review of the literature, further evidence is provided for loss of distinctive histological and radiographic findings of CNS lesions on steroid therapy, with a potential delay in diagnosis and subsequent worse prognosis.

Key Words: Primary central nervous system neoplasms; central nervous system infections; Epstein-Barr virus infections; corticoids.

Introduction

Diagnostic challenges may arise when multiple CNS lesions not accessible to biopsy are present on brain MRI. The differential diagnosis is broad, particularly in the context of exposure to steroids and/or in the setting of immunosuppression. Benign lesions to be considered are demyelinating diseases; sarcoidosis or other granulomatous diseases; and infectious diseases, especially toxoplasmosis in immunocompromised patients, tuberculosis and other space-occupying lesions caused by infectious pathogens. Malignant lesions include CNS lymphoma, glioma (more commonly higher grade lesions, such as glioblastoma multiforme), and metastases. The clinical setting in which the lesions occur and the presence of extra-CNS symptoms are important for differential diagnosis considerations. Etiological investigation needs to be carefully planned in order to be diagnosis-specific and cost effective¹. One of the most common diagnostic challenges is the ability to reach a definitive diagnosis when corticosteroids have already been administered. These drugs are the empirical treatment given in most settings, but response to steroids does not necessarily confirm the diagnosis, sin-

Resumo

Desafios diagnósticos surgem frequentemente quando lesões múltiplas do sistema nervoso central (SNC) não acessíveis a biópsia estão presentes na Ressonância Magnética (RM). O diagnóstico diferencial é vasto, particularmente no contexto de exposição a corticóides e/ou estado de imunodepressão. As lesões benignas a considerar são as doenças desmielinizantes, sarcoidose e outras doenças granulomatosas, e doenças infecciosas como a toxoplasmose nos pacientes imunodeprimidos e tuberculose. As lesões malignas incluem o linfoma do SNC, glioblastoma multiforme e metástases cerebrais. Os autores descrevem o caso clínico de uma mulher de 75 anos com lúpus eritematoso sistémico, medicada cronicamente com Hidroxicloroquina 400 mg, Deflazacorte 9 mg e Azatioprina 25 mg diariamente, que foi admitida no hospital com um quadro com cinco meses de evolução de défices neurológicos progressivos. Este foi particularmente desafiante, uma vez que a doente era imunodeprimida, tinha lesões múltiplas do SNC que não eram acessíveis a biópsia e a corticoterapia crónica alterou o padrão radiológico na RM cerebral, mascarando o diagnóstico. O relato deste caso e revisão da literatura fornece mais evidência sobre a perda das características histológicas e radiológicas das lesões do SNC sob corticoterapia, com um potencial atraso no diagnóstico e subsequente pior prognóstico.

Palavras-chave: Neoplasias primárias do sistema nervoso central; infecções do sistema nervoso central; infecções pelo vírus Epstein-Barr; corticóides.

ce several conditions including CNS demyelinating disease, sarcoidosis, lymphoma, metastatic carcinoma and glioma, all show a positive response^{2,3}. By writing up this clinical case and review of the literature, further evidence is provided for the loss of distinctive histological and radiographic findings of CNS lesions on steroid therapy, with a potential delay in diagnosis and subsequent worse prognosis.

Case report

A 75-year-old Caucasian woman presented to the Emergency Room with a 5-month clinical history of progressive neurological symptoms, including sudden changes of mood and behaviour, confusion, impaired long-term memory, personality changes, slurred speech, left facial palsy, decreased muscle strength and sensitivity on the right limbs and unbalanced gait. Two months after symptom onset, the patient had performed a brain MRI, which was completely normal.

Relevant medical background included systemic lupus erythematosus (SLE), diagnosed at the age of 63 and with a benign course (SLEDAI:0/SLICC:1); stage 2 chronic kidney disease; essential systemic arterial hypertension; pulmonary silicosis and pulmonary

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tuberculosis at the age of 56. She was chronically medicated with Hydroxychloroquine 400 mg, Deflazacort 9 mg and Azathioprine 25 mg daily.

The patient was initially admitted to another institution and at presentation the physical examination revealed fever, mental confusion, dysarthria, anisocoria (left>right), left peripheral facial palsy, right hemiparesis (grade 3/5), right hypoesthesia and dysmetria, ataxia and hypoactive deep tendon reflexes.

Blood tests (table 1, day 1) revealed raised inflammatory markers, thrombocytopenia and normal immunological study. Cerebrospinal fluid (CSF) examination performed on day 1 showed lymphocytic pleocytosis. Chest computed tomography (CT) scan was sugges-

tive of silicosis with massive fibrosis. Brain MRI (figure 1) depicted multiple hyperintense lesions on T2-weighted sequences located bilaterally in the frontal and occipital white matter, the posterolateral aspects of the fourth ventricle, the splenium of the corpus callosum, the right middle cerebellar peduncle and the cisternal portion of the right trigeminal nerve. All these lesions showed enhancement on post-contrast axial T1 spin-echo images. There was also evidence of bilateral medial thalamic enhancing lesions. No diffusion-weighted imaging (DWI) sequence was performed on this study. These findings were not specific of any diagnosis but raised suspicion for one of three major groups of pathologies: lymphomas, non-infectious granulomatous diseases and infectious diseases.

Table 1. Main laboratory results for diagnostic workup

Day 1 (on Deflazacort 9 mg daily)					
Blood	Cerebrospinal fluid				
	Cell count and biochemical	Culture	PCR techniques	Serology	Others
Relative neutrophilia: 76% ESR: 38mm/1st hr CRP: 30mg/L Immunological studies (complement, RF, ANA, anti-dsDNA, anti-Scl-70): all normal Immunophenotyping study: normal	WBC: 61/μL (N 42.5%, L 46.5%, LP 11%) Proteins: 0.85g/L Glucose: normal ADA: normal	Bacteria, Fungi and Mycobacteria: all negative	Mtc, HSV 1&2, Listeria monocytogenes, Borrelia burgdorferi, HTLV 1&2: all negative	VDRL, FTA-ABS, Cryptococcus neoformans antigen: all negative	India ink stain: negative Immunophenotyping study: normal
Day 12 (on Dexamethasone 24 mg daily)					
Blood	Cerebrospinal fluid				
	Cell count and biochemical	Culture	PCR techniques	Serology	Others
Relative neutrophilia: 90% Thrombocytopenia: 92000/μL CRP: 41.1 mg/L Electrophoresis and immunoglobulins: normal β2-microglobulin: 4103 μg/L ACE: normal HIV, HBV and HCV: all negative Bacteria, Fungi and Mycobacteria culture: all negative Immunological studies (complement, ANA, anti-dsDNA, anti-nucleosome, anti-ENA, anti-phospholipid, anti-thyroid, anti-neuronal antibodies): all normal Immunophenotyping study: normal	WBC: 5/μL Proteins: 1.12 g/L Glucose: normal ADA: normal OCB: negative IgG index: normal ACE: normal	Bacteria, Fungi and Mycobacteria: all negative	Mtc, HSV 1&2, H-6, VZV, CMV, Toxoplasma gondii, Enterovirus, Listeria monocytogenes, Mycoplasma pneumoniae, Tropheryma whipplei: all negative JC virus: <600 copies/mL EBV: 600 copies/mL	VDRL, Wright reaction, Borrelia, Cryptococcus neoformans antigen: all negative	Immunophenotyping study: normal
Day 38 (on Prednisolone 5 mg daily)					
Blood	Cerebrospinal fluid				
	Cell count and biochemical	Culture	PCR techniques	Serology	Others
ESR: 60mm/1st hr CRP: 112 mg/L Anti-dsDNA antibodies: normal Immunophenotyping study: normal	WBC: 340/μL (L 53%) Proteins: 2.11 g/L Glucose: 11 mg/dL ACE: normal IgG index: normal	Bacteria, Fungi and Mycobacteria: all negative	JC virus, Mycoplasma pneumoniae, West Nile virus: all negative EBV: 1200 copies/mL	–	Immunophenotyping study: CD5-, CD10+ monoclonal kappa B-cell population, both suggestive of DLBCL

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor; ANA: anti-nuclear antibodies; WBC: white blood cells; N: neutrophils; L: lymphocytes; LP: lymphoplasmacytic cells; ADA: adenosine deaminase; Mtc: *Mycobacterium tuberculosis complex*; HSV: *Herpes simplex virus*; HTLV: Human T lymphotropic virus; ACE: angiotensin converting enzyme; HIV: human immunodeficiency virus; HBV/HCV: hepatitis B/C virus; OCB: oligoclonal bands; H-6: herpes 6 virus; VZV: *varicella-zoster virus*; CMV: *cytomegalovirus*; EBV: Epstein-Barr virus; PCR: polymerase chain reaction

Because of the immunosuppression status of the patient, the previous history of pulmonary tuberculosis, the development of progressive focal neurological deficits, the presence of CSF mononuclear pleocytosis and hyperproteinorraquia and the MRI lesions described above, the possibility of tuberculous meningitis was considered. Quadruple tuberculostatic therapy plus dexamethasone 24 mg/day was started empirically, along with bacterial meningitis empirical treatment with Ceftriaxone, Ampicillin and Acyclovir. The last two were suspended within two days, as the results for *Listeria monocytogenes* and *Herpes simplex* viruses 1 and 2 DNA in the CSF were negative. More CSF analysis results were then available (table 1, day 1), and they were all negative (bacteria and fungi cultures, PCR techniques and serology), with mycobacteria culture ongoing. Peripheral blood and CSF immunophenotyping studies were not suggestive of lymphoproliferative disease. She completed seven days of Ceftriaxone 4 g daily and eleven days of Isoniazide 300 mg, Rifampin 600 mg, Pyrazinamide 1500 mg, Ethambutol 1200 mg, Pyridoxine 50 mg and Dexamethasone 24 mg daily, without clinical improvement.

The patient's family requested her admission to our hospital on day 12. Lumbar puncture was repeated (table 1, day 12) while corticosteroid therapy was still ongoing (dexamethasone 24 mg daily). CSF had less pleocytosis but was not diagnostic. Complete blood tests were also performed (table 1, day 12) and revealed overlapping values of the inflammatory markers; positive $\beta 2$ -microglobulin (4103 $\mu\text{g/L}$); normal immunophenotyping study, immunological study and ACE levels; and negative virologic markers.

A follow-up MRI performed on day 25 (figure 2) showed decreased size of the previously detected lesions. DWI sequence showed hyperintense lesions with low ADC (DWI-derived apparent diffusion coefficient), indicating restricted diffusion. This aspect pointed lymphoma as the most probable etiology of the previously stated hypotheses.

The corticosteroid therapy was progressively decreased to Prednisolone 5 mg daily (day 38), because lesions were not accessible to biopsy and CSF flow cytometry was not suspicious for lymphoma, probably because of the lymphocytolytic effect of corticosteroids. There was progressive clinical worsening and raising blood inflammatory markers. CSF cytology (table 1, day 38) revealed pleomorphic large lymphocytes with irregular nuclear contours and CSF flow cytometry a CD5-, CD10+, CD20+, monoclonal κ B-cell population, both suggestive of diffuse large B-cell lymphoma (DLBCL). Immunohistochemistry was inconclusive. Systemic lymphoma was excluded. All mycobacteria smears and cultures were negative (CSF, blood, gastric acid, sputum and urine). Anti-tuberculous therapy was stopped. Because of age and worsening clinical course, radiotherapy and corticosteroid palliative therapies were proposed. There was no clinical improvement and the patient died on the 51st day of hospitalisation.

Discussion

Primary central nervous system lymphomas (PCNSLs) are extranodal non-Hodgkin's lymphomas (NHLs) that affect primarily the CNS^{2,4}. PCNSL presents with single or multiple brain parenchyma supratentorial lesions, with involvement of the posterior fossa being much less frequent (13%) and diffuse leptomeningeal involvement occurring only in a small minority of patients. Age appears to be a significant risk factor, as the incidence of the disease increases in the elderly population. The large majority of PCNSLs are CD20+, highly malignant B-cell NHLs (diffuse large B-cell lymphoma – DLBCL), with T-cell and low-grade lymphomas representing only 1-4% of all cases in western countries^{3,4,11}.

Figure 1. Magnetic resonance imaging (MRI): a and b - axial T2 FLAIR showing bilateral hyperintense lesions in the frontal and occipital white matter, in the splenium of the corpus callosum and in a more caudal level bilateral hyperintense lesions also posterolateral to the IVth ventricle and involving the cisternal portion of the right trigeminal nerve; c and d - postcontrast axial T1 spin-echo images showing contrast enhancement on the frontal white matter lesions and the posterior aspects of the IVth ventricle bilaterally; there is also evidence of bilateral medial thalamic lesions; e and f - postcontrast coronal T1 spin-echo sequence showing enlargement and enhancement of the right trigeminal nerve (black arrowhead in e) and at the splenium of the corpus callosum (f)

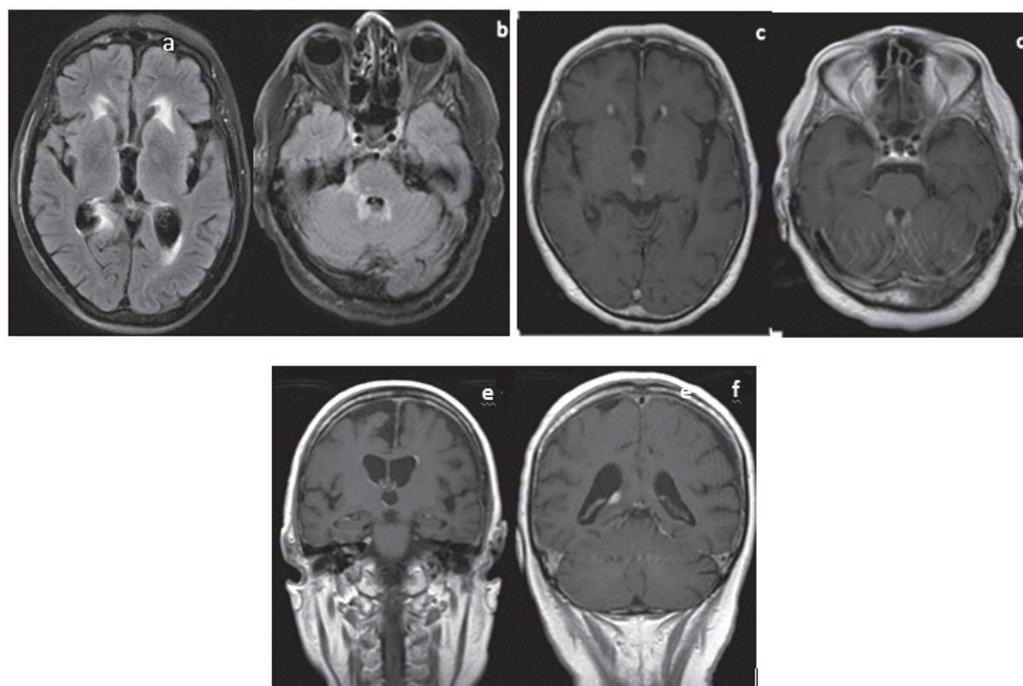
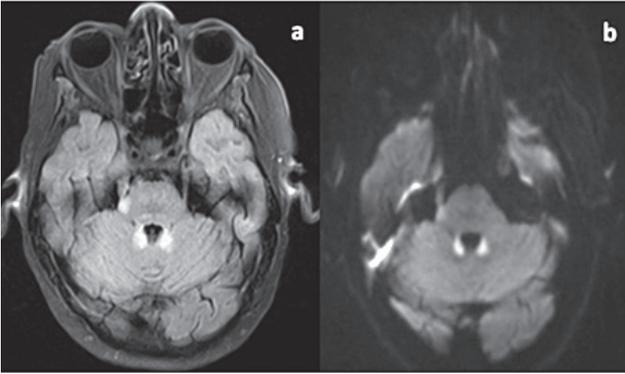


Figure 2. Second magnetic resonance imaging: axial T2 FLAIR – decreased size of the bilateral hyperintense lesions posterolateral to the IVth ventricle involving the cisternal portion of the right trigeminal nerve (a) which showed to be hyperintense on axial DWI (Diffusion-Weighted Imaging) (b) with low ADC indicating restricted diffusion on these lesions.



PCNSLs are highly proliferative tumours, with a proliferation index of more than 50% in most cases, which can lead rapidly to death if diagnosis and/or the start of treatment is delayed^{4,6}. Risk factors in immunocompetent patients are unknown, but long term immunosuppressive therapy or an underlying disease with associated immunosuppression are significant risk factors⁷. Lymphomagenesis is thought to be promoted by sustained antigenic stimulation by autoimmune diseases (such as SLE, Sjögren's syndrome or rheumatoid arthritis) and/or by direct transforming properties of infectious agents^{2,8,9}. CNS lymphomas developing in immunocompromised individuals are typically B-cell neoplasms, mostly DLBCL, and are EBV-positive (>95% vs 0%-20% in immunocompetent patients)^{3,9}. As in most CNS lymphomas developing in immunocompromised individuals, this patient was diagnosed with a DLBCL, and was EBV-positive.

PCNSL presents with progressive encephalopathy or focal neurologic deficits that reflect the location of the lesions. The vitreous, retina, and optic nerves may be involved in 10–20% of patients at presentation, with visual complaints such as 'floaters' or blurred vision occurring in about half of patients. Lymphomatous infiltration of the leptomeninges or ependymal surfaces and radicular or plexus invasion may also occur^{2,3,4,8}.

The diagnosis of CNS lymphoma can be a particular challenge because of lesional response to corticosteroids and MRI features that are shared with other pathologies. A dilated fundoscopic exam should be performed to exclude ocular involvement. Serum tests should include lactate dehydrogenase (an elevated level has prognostic implications), a complete blood count, hepatic and renal function (in anticipation of treatment with cytotoxic drugs), and HIV testing, as there is an increased risk of PCNSL in this population and HIV status may have an impact on choice of therapy. A complete staging to exclude occult systemic disease includes a CT scan of the chest, abdomen and pelvis and a bone marrow

biopsy with aspirate, because extraneural disease has been reported in 3.9% to 12.5% of patients with PCNSL^{2,3,10,11}.

The standard for initial diagnosis and detection of recurrence of PCNSL is non-enhanced [i.e. T1-weighted, T2-weighted, FLAIR, diffusion weighted imaging (DWI)] and contrast-enhanced with Gadolinium-DTPA cranial MRI. Contrast-enhanced CT scanning can be performed in patients who cannot undergo MRI^{10,11,12}. The majority (80–90%) of PCNSL lesions are located supratentorially; in 60% of the cases, they are primarily located in the periventricular white matter of the frontal and parietal lobes and the corpus callosum, and in the deep brain structures, including the thalamus and basal ganglia. On pre-contrast MRI images, the lesions are homogeneously isointense or hypointense on T1-weighted images, and hyperintense on T2-weighted images. They may be either circumscribed or have irregular borders, and show variable extent of surrounding oedema (90% of lesions are accompanied by oedema). After contrast administration, single lesions with homogenous enhancement are typical findings in immunocompetent patients^{3,4,13}. Diffuse enhancing supra- and/or infratentorial pachymeninges and extension along the ependymal surfaces can be detected with contrast-enhanced MRI in a subset of patients (3–5%), indicating leptomeningeal infiltration by tumour cells. Diffusion-weighted imaging and DWI-derived apparent diffusion coefficient (ADC) provide additional diagnostic information. Due to the hypercellularity of PCNSL the diffusion rate of unbound extracellular water molecules is restricted. Therefore, untreated PCNSLs are frequently hyperintense on DWI and hypointense on ADC maps. PCNSL in immunocompromised patients presents with greater radiological variability. These patients frequently have multiple lesions at diagnosis. Additionally, non-enhancing lesions and irregular or ring enhancement patterns, in addition to haemorrhage and necrosis, often occur in these patients^{2,4,8}. Although there is no pathognomonic brain MRI pattern of PCNSL, these non-specific radiological features allow the differentiation of PCNSL from other brain tumours, such as metastases or glioblastoma multiforme, and inflammatory CNS diseases, including demyelinating lesions, neurosarcoidosis, and infectious conditions, particularly toxoplasmosis¹. In conclusion, conventional and contrast-enhanced MRI, including DWI and ADC-maps, remain the imaging procedures of choice in PCNSL, despite promising advanced imaging techniques, i.e. MR-spectroscopy, perfusion imaging, diffusion tensor imaging and fludeoxyglucose-PET, that may serve as adjunct diagnostic tools^{1,8,13,14}.

A lumbar puncture should be performed unless contraindicated and CSF examined for cell count, glucose, protein, cytology, flow cytometry, and immunoglobulin heavy-chain (IgH) and T-cell receptor (TCR) gene rearrangement analysis by polymerase chain reaction (PCR)^{10,11,12}. Despite significant advances in cellular analyses and cytopathological examination of the CSF being regarded as gold standard for the diagnosis, CSF evaluation is diagnostic in only a minority of patients with suspected CNS lymphomas. Indeed, the

sensitivity and specificity of cytopathology are low, mainly because of the paucity of tumour cells in CSF, the morphological similarity of lymphoma cells with reactive lymphocytes, which may also be significantly enlarged with blast-like nuclei, and by the upfront use of corticosteroids. However, the diagnostic yields may be improved by repeated lumbar punctures. In addition, modern technologies, including cellular immunophenotyping by flow cytometry and molecular genetic analyses of CSF, have successfully been advanced to facilitate the diagnosis of leptomeningeal disease in lymphoma. In most cases, additional immunocytochemistry is needed (using pan-B cell markers, e.g. CD20, CD10, BCL6, MUM1 and MIB1). Flow cytometry has the major advantage of reliably detecting small cell populations. Based on size, granularity, and antigen expression pattern, flow cytometry permits distinguishing between lymphoma cells and reactive lymphocytes. In a recent study, CSF specimens from 30 PCNSL patients were analysed by both cytopathology and multiparameter flow cytometry, demonstrating an increase in sensitivity from 13.3% to 23.3% for cytopathology and flow cytometry, respectively¹⁵. PCNSL carries rearranged and somatically mutated immunoglobulin genes with evidence for ongoing mutation. Thus, PCR analysis of immunoglobulin heavy and light chain genes may be extremely useful when morphology does not provide a conclusive diagnosis, particularly for those patients with corticoid mitigated lymphoma. In these cases, PCR may still detect a monoclonal B-cell population with somatically mutated immunoglobulin genes. This technique would have been useful in our particular clinical case. The establishment of novel CSF markers, including lymphoma associated proteins and molecular genetic markers, such as microRNAs (the expression of which is deregulated in various malignancies, including lymphoma), will improve the clinical relevance of lumbar puncture and CSF analysis further^{2,3,8,12}.

Currently, histological diagnosis of PCNSL remains mandatory to plan adequate treatment, with stereotactic biopsy of a brain parenchymal lesion or vitrectomy in patients with intraocular involvement. Patients in poor clinical condition and with space occupying CNS lesions resulting in intracranial hypertension are an exception and have to be treated without prior histopathological diagnosis. However, it is necessary to stress that the most important factor reducing the rate of a conclusive histological diagnosis is corticosteroid administration prior to biopsy^{4,3,11}.

Corticosteroid therapy is the first line of treatment for PCNSL, although it should not be initiated before a definitive diagnosis in clinically stable patients is established. Steroids cause a rapid decrease in tumour size and peritumoral edema through a direct lymphocytolytic effect that may disrupt cellular morphology and lead to diagnostic inaccuracy at the time of microscopic analysis. Also, steroids may complicate the interpretation of gadolinium-enhanced MRI, because the abnormal contrast enhancement typically observed can decrease or even disappear. Clinical improvement and reduced

MRI lesion enhancement under corticosteroid treatment are highly suggestive of CNS lymphoma, although these can also be observed in demyelinating disorders, vasculitis, sarcoidosis or, more rarely, in metastatic carcinoma or glioma^{2,4,3,12,16}. This clinical case was particularly challenging, because the patient was immunocompromised, had multiple lesions not accessible to biopsy, and corticosteroid therapy had reduced lesion contrast enhancement on brain MRI, via the profound apoptotic effect of corticosteroids on lymphoma cells ("vanishing lymphoma" phenomenon), masquerading and delaying the diagnosis of PCNSL. Most patients initially respond to steroids, but relapses are frequent and additional chemotherapy should be promptly initiated in most patients, after histological diagnosis is achieved. Age is a prominent prognostic factor and older patients (>65 years of age) have a low rate of long-term survival, which must be taken into consideration when establishing a therapeutic plan. Median survival in this age group with best supportive care is only approximately 9 months^{3,4,6}. As reported in literature, the clinical course of our patient was aggressive, and she died 7 months after the first symptoms.

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