CASO CLÍNICO/CASE REPORT

Primary Central Nervous System Lymphoma Mimicking Neuro-Behcet Disease

Linfoma do Sistema Nervosa Central Mimetizando NeuroBehcet

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Abstract

Neuro-Behcet's disease (NBD) and primary central nervous system lymphoma (PCNSL) are rare conditions that can present with overlapping features, often delaying diagnosis. We report a female patient with recurrent oral aphthae and arthralgia who developed visual disturbances, behavioral changes, and hemiparesis. Brain magnetic resonance imaging (MRI) showed multiple contrast-enhancing lesions, and cerebrospinal fluid (CSF) analysis revealed elevated mononuclear cells. Extensive malignancy screening and autoimmune workup, including HLA-B51, were unremarkable. A presumptive diagnosis of NBD was made, and treatment with corticosteroids followed by infliximab led to initial improvement. Four months later, symptom recurrence with new MRI lesions and elevated CSF protein raised concerns. Lack of sustained response prompted a brain biopsy, confirming primary CNS large B-cell lymphoma. The patient was started on methylprednisolone and methotrexate, which were discontinued due to complications. Despite this, clinical improvement was observed, and the patient remains stable with mild cognitive deficits at follow-up four months later.

Resumo

Neuro-Behcet (NB) e linfoma primário do sistema nervoso central (LPSNC) são doenças raras com características sobreponíveis, frequentemente condicionando atrasos diagnósticos. Relatamos o caso de uma mulher com aftas orais recorrentes e artralgias, que desenvolveu alterações visuais, do comportamento e hemiparesia. A ressonância magnética cerebral (RM-CE) revelou múltiplas lesões com realce por contraste e o líquido cefalorraquidiano mostrou elevação de células mononucleares. O rastreio oncológico e estudo autoimune, incluindo HLA-B51, foram negativos. Assumiu-se um diagnóstico de NB, com início de terapêutica com corticoterapia, seguida de infliximab, com melhoria clínica inicial. Quatro meses depois, verificou-se recorrência sintomática com evidência de novas lesões na RM-CE e aumento da proteinorraquia. A ausência de resposta terapêutica motivou a realização de biópsia cerebral, que confirmou um LPSNC. A doente foi tratada inicialmente com metilprednisolona e metotrexato, posteriormente suspensos por complicações médicas. Apesar da suspensão terapêutica, observou-se melhoria clínica, com défice cognitivo ligeiro na reavaliação aos quatro meses.

Introduction

Neuro-Behcet (NB) represents a rare and severe neurological manifestation of Behcet's disease (BD). Diagnosis requires clinical evidence of a neurological syndrome, supported by neuroimaging, and/or cerebrospinal fluid (CSF) abnormalities, in patients meeting the International Study Group (ISG) 1990 criteria for BD, and after excluding other causes.[1] Neurological involvement includes parenchymal manifestations (brainstem or supratentorial), including focal deficits, cognitive dysfunction, altered mental status, and non-parenchymal manifestations like cerebral venous thrombosis or intracranial hypertension.[1] Acute episodes are treated with corticosteroids, but about one-third of patients experience relapses or a progressive course, necessitating disease-modifying therapies, such as azathioprine, commonly used as a first-line treatment given its safety profile and low adverse effects, or infliximab, particularly when ocular involvement is present, as recurrent episodes of hypopyon uveitis, vitritis, retinal infiltrates, and occlusive vasculitis.[1]

Primary central nervous system lymphoma (PCNSL), a rare non-Hodgkin lymphoma in the brain and/or spinal cord, has been shown an increased incidence.[2] The main manifestations include focal neurologic deficits, mental status and behavioral changes, increased intracranial pressure, and seizures. Ocular involvement is found in about 10% of cases.[2] The diagnosis is often delayed, given the nonspecific symptoms.

Case Report

A 56-year-old right-handed woman with recurrent oral aphthae and undiagnosed arthralgias, presented to the emergency department with a two-week history of decreased visual acuity with myodesopias, followed by confusion, disorientation, apathy, behavioral changes, right hemiparesis, hypoesthesia, and speech disturbances. These symptoms emerged one week after a mild flu-like syndrome. Neurological examination revealed psychomotor slowing, mild dysarthria, right hemiparesis (grade 4/5), and globally brisk reflexes. Ophthalmological evaluation identified dispersed white lesions, suggestive of bilateral panuveitis. Brain magnetic resonance imaging (MRI) demonstrated multiple T2 and T2/FLAIR hyperintensities, corresponding T1 hyposignal, diffuse contrast enhancement, and restricted diffusion in the supratentorial white matter, with subcortical predominance, and involvement of juxtacortical areas and the corona radiata (**Fig. 1**).

Cerebrospinal fluid (CSF) analysis revealed 17 mononuclear cells, normal protein (0.36 g/L), and glucose levels (0.61 g/L). Microbiological tests, oligoclonal bands, and antineuronal antibodies in the CSF were negative. A thorough workup, including thoracic-abdominal-pelvic computed tomography (CT) and vaginal ultrasound, ruled out a tumor. A comprehensive workup, including systemic (blood count, erythrocyte sedimentation rate, renal, liver, and thyroid function, angiotensin-converting enzyme, and C-reactive protein), serologic (hepatitis B and C, syphilis, borreliosis, and HIV), and autoimmune (rheumatoid factor, anti-cardiolipin antibodies, anti-nuclear antibodies, anti-dsDNA, antineutrophil cytoplasmic antibodies [ANCA], anti-Ro, anti-Sa, anti-thyroid antibodies, immunoglobulins including IgG4, complement, antineuronal antibodies, anti-myelin oligodendrocyte glycoprotein, and anti-aquaporin-4 antibodies) studies, was unremarkable. HLA-B51 was not detected. The patient met ISG criteria for BD [score ≥4: ocular lesions (2 points); oral aphthous (2 points); neurological manifestations (1 point)]. Intravenous methylprednisolone for 5 days was followed by a tapering course of oral prednisolone and prednisolone eye drops. There was a slight clinical improvement (the patient became more alert, while maintaining a grade 4 hemiparesis with py-

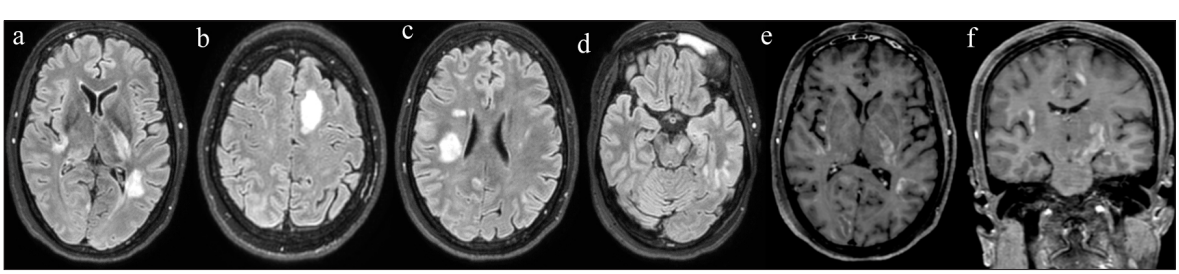

Figure 1. Initial brain MRI (**a-d:** axial T2-weighted-fluid-attenuated inversion recovery (FLAIR) images; **e-f:** axial and coronal post-contrast T1-weighted images) demonstrating multifocal T2 hyperintensities involving the bilateral and supratentorial white matter **(a-d)**, heterogeneously enhancing **(e-f)**. The affected left amygdala and hippocampus head, as well as the thalamic-mesencephalic transition can also be seen **(d)**.

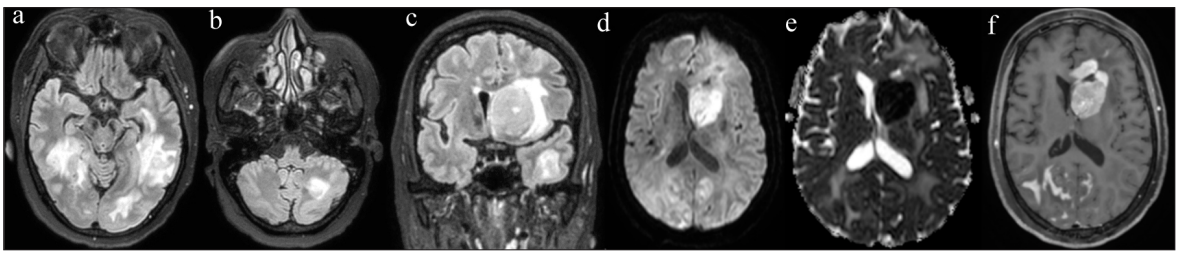

Figure 2. Brain MRI at the relapse (**a-c:** axial and coronal T2-weighted-fluid-attenuated inversion recovery (FLAIR) images; **d-e:** diffusion-weighted image and ADC map; f: axial post-contrast T1-weighted image) revealing new multiple lesions affecting the supra- and infratentorial cerebral parenchyma **(a-c)**, the largest centered in the left anterior striatum-capsular region **(c)**, with regular margins and diffuse/compact contrast enhancement **(f)**, as well as marked restricted diffusion **(d-e)**.

ramidal signs), accompanied by a significant radiological reduction in lesion size. After a multidisciplinary discussion, monthly infliximab was initiated, with initial clinical stabilization and without side effects. However, four months later, the patient was readmitted with altered mental state, visual acuity deficits, and non-positional pressure-like headaches. Neurological examination revealed psychomotor slowing, grade 3 right crural paresis, and right-sided hypoesthesia. A repeat brain MRI showed new lesions affecting supra- and infratentorial regions, with multifocal involvement of the white and grey matter, and the cortex (**Fig. 2**). A large lesion was identified in the left anterior striatum-capsular region, with ill-defined but regular boundaries, diffuse contrast enhancement, and marked restricted diffusion.

CSF analysis revealed 9 mononuclear cells, elevated protein levels (1.04 g/L), and normal glucose (0.88 g/L). Given the infliximab refractoriness and the emergence of new cerebral lesions, a diagnostic reconsideration was warranted. Stereotactic brain biopsy with histological and immunohistochemical study confirmed a diffuse large B-cell lymphoma (**Fig. 3**).

Intravenous methylprednisolone was administered, followed by methotrexate, but treatment was discontinued due to clinical deterioration (mRankin scale 5) and severe systemic complications (Stevens-Johnson syndrome, febrile neutropenia, cholestasis, grade III mucositis, multiple infections - urinary, cellulitis, and gastrointestinal). The patient was transitioned to exclusive symptomatic care. Four months later, physical rehabilitation led to clinical improvement, with the patient walking independently (mRankin scale 2), but experiencing moderate cognitive complaints.

Discussion

This case highlights the diagnostic complexities of NB and the potential for misdiagnosis with PCNSL. While the patient fulfilled BD criteria, treatment refractoriness prompted reevaluation, leading to a delayed PCNSL diagnosis. NB's diagnosis relies on meeting specific criteria, including subacute neurological symptoms, increased CSF pleocytosis, and cerebral MRI lesions suggestive of inflammation. However, these features are not pathognomonic. The ophthalmological signs were

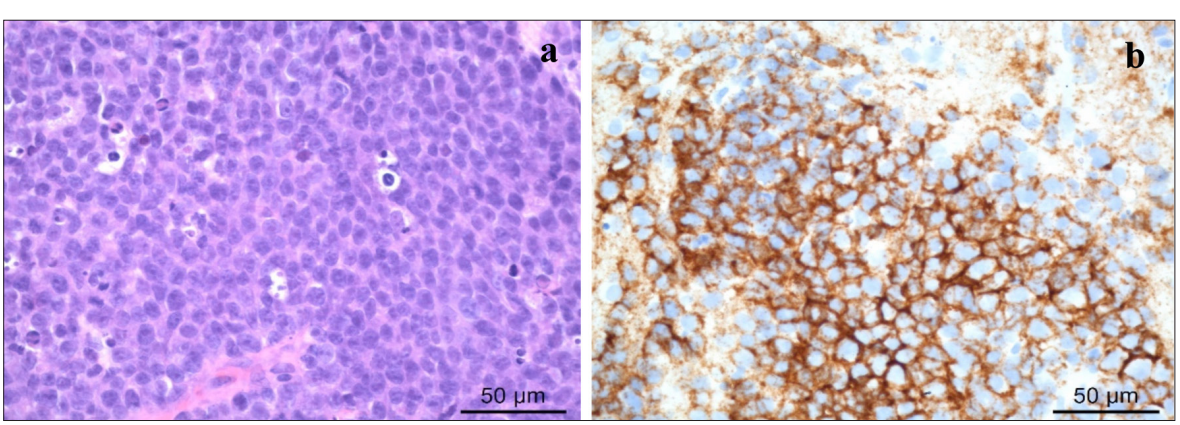

Figure 3. Brain biopsy histology. **(a)** Hematoxylin and eosin stain - diffuse infiltrate of large atypical lymphoid cells with round to oval nuclei, prominent nucleoli, and scant cytoplasm, typical of diffuse large B-cell lymphoma; **(b)** CD20 marker - Strong membranous CD20 positivity in neoplastic cells, confirming B-cell lineage.

also consistent with Behcet's ocular involvement.[3] MRI findings, such as multifocal T2 hyperintensities with diffuse contrast enhancement, are commonly seen in NB, particularly in the brainstem or hemispheres.[1] Yet, similar findings can occur in PCNSL. The international consensus criteria for NB diagnosis stipulate that those three criteria must be met, with the final criteria emphasizing the requirement of ruling out alternative explanations for the neurological signs. Although the patient met the main criteria, differential diagnosis was not ruled out in this context.[1] Once the cerebral lesions were subsequently attributed to PCNSL, and given that the oral aphthae were never observed on examination together with a negative HLA-B51, the diagnostic criteria for BD were no longer convincingly met. Therefore, the final diagnosis corresponds to PCNSL mimicking neuro-Behcet's disease.

This diagnosis may present with clinical features overlapping those of NB, including focal deficits, behavioral changes, and, in some cases, ocular involvement, such as uveitis.[3] Neuroimaging in PCNSL typically shows homogenous, contrast-enhancing mass lesions with diffusion restriction, unlike the more widespread lesions seen in NB. In this case, the appearance of new lesions, particularly the large striatal lesion, was a key clue prompting further investigation, including CSF cytology and brain biopsy. Differentiating NB from PCNSL is crucial but challenging. Features favoring PCNSL include lesions outside typical NB regions (e.g. deep cerebral structures) and transient improvement following high-dose corticosteroids. This case aligns with previous reports of misdiagnoses between NB and PCNSL.[4,5] Both conditions share overlapping clinical and radiological features, and their coexistence further complicates diagnosis. Early brain biopsy and advanced CSF studies, such as cytology and flow cytometry, are pivotal for differentiating these conditions when clinical or radiological findings are ambiguous. Delayed diagnosis can result in significant morbidity and mortality.

Several large-scale epidemiological studies and meta-analyses have shown that patients with BD have an increased risk of malignancy, particularly hematological neoplasms.[6] This association has been attributed to chronic immune dysregulation, persistent inflammation, and the use of long-term immunosuppressive therapy. Although in the present case the available evidence supports PCNSL as the sole diagnosis rather than a comorbid or secondary manifestation of BD, this potential link between BD and hematological malignancies remains an important consideration when evaluating atypical or treatment-refractory presentations. ■

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Contributorship Statement / Declaração de Contribuição

LS: Research, conception, organization and elaboration of the manuscript.
SC: Clinical evaluation of patient, drafting of the manuscript.
LI, RT and JAC: Research and revision of the manuscript.
ES: Clinical evaluation of patient, conception, organization and revision of the manuscript.
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LS: Pesquisa, conceção, organização e elaboração do manuscrito.
SC: Avaliação clínica da doente, revisão do manuscrito.
LI, RT e JAC: Pesquisa e revisão do manuscrito.
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Todos os autores aprovaram a versão final a ser publicada.

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