CASO CLÍNICO/CASE REPORT

Intravascular Lymphoma: The Great Imitator – A Case Report

Linfoma Intravascular: O Grande Mimetizador – Um Caso Clínico

Raimundo R[1,*]; Matas A[2]; Pinto M[3]; Taipa R[3]; Gabriel JP[2]
1-0000-0002-4659-425X / Departamento de Neurologia / Centro Hospitalar Trás-os-Montes e Alto Douro, Portugal.
2-Departamento de Neurologia / Centro Hospitalar Trás-os-Montes e Alto Douro,Vila Real, Portugal.
3-Departamento de Neuropatologia / Centro Hospitalar Universitário do Porto, Porto, Portugal.

Abstract

Introduction: Intravascular large B-cell lymphoma (IVLBCL) is an uncommon and aggressive lymphoma, presented typically with diverse and progressive neurological manifestations associated with constitutional symptoms. However, the lack of specific features makes its diagnosis challenging.

Case Report: A 58-year-old man presented with progressive focal deficits, behavioral alterations, consciousness fluctuation and fever of unknown cause. Neuroimaging showed multiple ischemic infarctions, despite the absence of embolic source, and CSF analysis showed pleocytosis with elevated proteins, with no evidence of neoplastic cells. Brain biopsy revealed intravascular proliferation of neoplastic lymphoid cells, CD20 positive, confirming the diagnosis of IVLBCL.

Discussion: Although the IVLBCL demonstrates a central nervous system predilection, it is uncommon to exclusively involve it. This case highlights the difficulty of achieving this diagnosis, suggesting that lesion biopsy should be planned as soon as possible.

Resumo

Introdução: O linfoma intravascular de grandes células B (IVLBCL) é um linfoma raro e agressivo, cuja apresentação consiste tipicamente em manifestações neurológicas progressivas associadas a sintomas constitucionais. Contudo, a ausência de achados específicos torna o seu diagnóstico desafiante.

Caso Clínico: Senhor de 58 anos apresentou uma clínica de défices neurológicos focais progressivos, alteração de comportamento, flutuação da consciência e febre de etiologia indeterminada. O estudo imagiológico cerebral revelou múltiplas lesões isquémicas recorrentes, na ausência de foco embólico, e o estudo de líquor revelou uma pleocitose com proteinorráquia, com estudo anatomopatológico negativo. A biópsia lesional revelou proliferação intravascular de células linfoides neoplásicas, CD20 positivas, confirmando o diagnóstico de IVBCL.

Discussão: Apesar do IVLBCL apresentar uma predileção pelo sistema nervoso central, o seu envolvimento exclusivo é raro e acarreta dificuldades diagnósticas. Este caso exemplifica a necessidade de realização precoce de biópsia lesional.

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***Autor Correspondente / Corresponding Author:**
Ana Rita Marcos Raimundo
Centro Hospitalar Trás-os-Montes e Alto Douro, EPE, Unidade Hospitalar de Vila Real, Av. Noruega, Lordelo, 5000-508 Vila Real, Portugal
ritaraimundo15@gmail.com

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Introduction

Intravascular large B-cell lymphoma (IVLBCL) is an uncommon and aggressive variant of diffuse large B-cell lymphomas, defined by a lymphoid cell proliferation in small to medium vessels, with the absence of extravascular tumor mass or cells in the circulating blood.[1] The annual estimated incidence is around 0.5/1 000 000, with a mean age of diagnosis between the sixth and seventh decade and a discrete male predominance.[2]

This neoplasm can virtually affect every organ, usually resulting from small vessels occlusion by neoplastic cells, providing an enormous variety of presenting symptoms and consequently frequent misdiagnosis or post-mortem diagnosis.[3] The pathophysiological aspects of this entity remain not fully understood, as it is still unclear whether IVLBCL represents embolization of neoplastic lymphocytes into the vascular lumina or clonal evolution of nodal lymphoma with loss of expression of chemokine receptors critical for migration across vascular walls.[3]

Herein, we present a case with a rare feature that posed as a diagnostic challenge: the exclusive involvement of the central nervous system (CNS).

Case Report

A 58-year-old Caucasian man, with a past medical history of minor depression and no regular medication, was admitted to the emergency room (ER) with a sudden onset of right sensory deficit. The neurologic examination exclusively showed a right thermoalgic hypoesthesia and the general examination was normal. Brain magnetic resonance (MRI) revealed a left frontoparietal lesion (**Fig. 1a**) and he was discharged with the diagnosis of acute lacunar ischemic infarction, medicated with an antiplatelet agent.

Two months later, he returned to the ER complaining of slurred speech, dizziness and right motor deficit. His wife had been noticing behavioral changes, such as apathy. A new brain MRI disclosed bilateral lesions, predominantly located in the left middle cerebral artery territory, with no diffusion restriction or contrast enhancement, interpreted as subacute bilateral ischemic infarctions (**Fig. 1b**). The extensive work-up revealed a normal 24 hours electrocardiography monitoring, carotid and vertebral doppler ultrasound, echocardiogram and thoraco abdominopelvic computerized tomography. Blood work showed a slight increase in the erythrocyte sedimentation rate (ESR 28 mm/h) and cerebrospinal fluid (CSF) analysis revealed pleocytosis (25 lymphocytes, 90% mononuclear) with raised proteins (2.38 g/dL), however no infectious agent or autoimmune status were identified. Flow cytometry immunophenotyping and CSF anatomopathology were also negative.

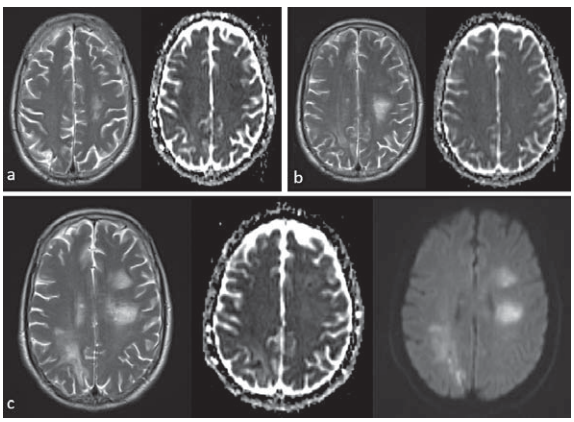

Figure 1. Brain MRI images; **a.** At presentation with a left cortico-subcortical frontoparietal T2 hyperintensity with diffusion restriction (T2 weighted image and ADC map); **b.** T2 hyperintensities in the left centrum semiovale and in the right peritrigonal region, with no diffusion restriction (T2 weighted image and ADC map); **c.** Lesion progression with bilateral areas of diffusion restriction and mass effect, one month later (T2-weighted image, ADC map and diffusion-weighted image).

A month later, sustained fever occurred without an obvious infectious focus, and although the meropenem course performed, his condition continued to worsen, with consciousness fluctuations and bilateral frontal release signs. There was evidence of imagiological progression (**Fig. 1c**), cortico-subcortical dysfunction and focal epileptiform activity in the electroencephalogram and increased pleocytosis in the CSF. A lesion biopsy revealed proliferation of large atypical lymphoid cells within the vessels, producing luminal obstruction (**Fig. 2a, 2b and 2c**), confirming the diagnosis of IVLBCL.

The patient was submitted to a course of dexamethasone with no benefit. The clinical condition continued to worsen and he died about 4 month after initial manifestation.

Discussion

The diagnosis of this neoplasm is challenging due to the absence of specific symptoms, laboratory or imagiological findings. A histological analysis is frequently required as a skin, brain or other organs biopsy.[1-3] The rapid progression of the lymphoma is demonstrated in this case, as the definitive diagnosis was made shortly before the patient's death, when the therapeutic op-

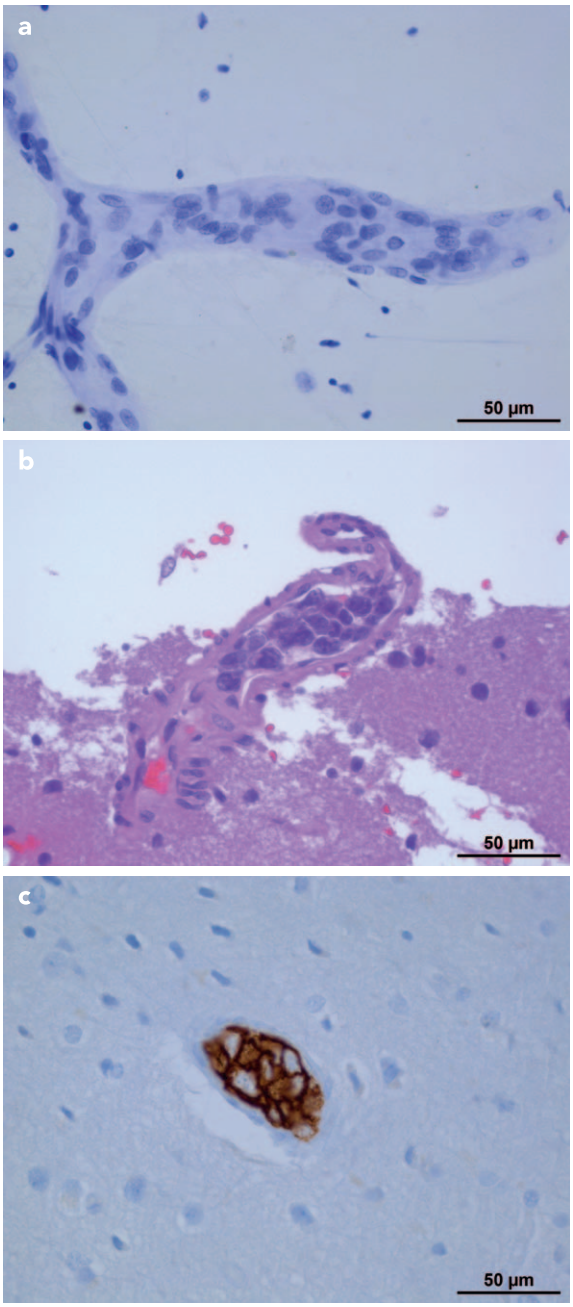

Figure 2. Histopathological findings of brain biopsy revealing proliferation of large atypical lymphoid cells in the vessels, producing luminal obstruction (**2.a** Intra-operative smear, toluidine blue; **2.b** H&E). Immunohistochemistry study revealed that neoplastic cells were CD20 positive (**2.c**).

tions were being taken into account.

Considering the clinical features, the IVLBCL is extremely heterogeneous in its clinical presentation and its presence has been described in small vessels of nearly every organ, although it demonstrates a CNS predilection.[1,2,4]

CNS manifestations are common and diverse, from cognitive impairment/dementia to encephalopathy, stroke-like events or seizures. The rapid progression of neurological signs with no other explanation should always lead to the suspicion of IVLBCL.[2,5] The peripheral nervous system can also be involved, as neuropathy, myopathy or neurogenic bladder.[2,3]

Our case presented with predominant and progressive neurological manifestations, however other diagnostic entities were considered before the correct diagnosis. For instance, the diagnosis of acute lacunar stroke was made in the first admission. Nonetheless, the behavioral changes and right hemiparesis two months later, with new lesions in the MRI and no evidence of traditional vascular risk factors or embolic source, questioned the ischemic etiology. Inflammatory and prothrombotic etiologies were also considered, although the lack of specific findings in the extensive study made these hypotheses less likely. The posterior evolution with fever of unknown cause and altered mental status, with the concomitant work up performed, pointed to an IVLBCL.

As seen in this case, fever is a prominent sign in IVLBCL, as well as other constitutional symptoms.[1,6] Our case presented fever during the progression of neurological features, and was submitted to a course of antibiotherapy with little improvement. An exhaustive search for an infectious etiology often contributes to the diagnosis delay reported by many authors.

A skin predilection has also been reported,[3,6] as well as a "cutaneous variant" with the unique affection of the skin, a female predominance and a better prognosis.[6] However, recent studies have fail to show a relevant skin involvement,[1,2] concordantly with the reported case that did not disclose skin lesions.

Other organs are usually involved by this neoplasm, namely the bone marrow, spleen or liver, and so far this lymphoma has been reported in almost every vascular bed in the organism.[2,7] However, the reported case did not disclose involvement of any other organ besides the CNS, which is rarely reported on the literature.

Although there are no specific laboratory characteristics for IVLBCL, it is common to find elevated LDH, ESR and β2 microglobulin, as well as anemia. Less frequently, thrombocytopenia, leucopenia and hypoalbuminemia can also be present.[3,6,8] Our case revealed an elevated ESR, however this single finding is very unspecific and was interpreted as an acute phase alteration.

CSF changes are also heterogeneous, being the protein elevation the commonest[6] (seen in the presented

case). Immunophenotyping of peripheral or CSF leucocytes does not appear to be a helpful technique in the diagnosis of this neoplasm, as it turns out negative in the majority of cases[3] (as disclosed in this case), due to the lack of circulating lymphoma cells.[9]

There are no pathognomonic imagiological features in IVLBCL. Previous studies reported no brain lesions on MRI in half of patients with neurological manifestations,[5] however a recent study reported otherwise: the presence of brain lesions in MRI in patients without neurological symptoms.[10] This study has also divided the MRI features in 4 categories: hyperintense lesion in the pons on T2WI, nonspecific white matter changes, infarct-like lesions and meningeal thickening and/or enhancement. The authors state that the hyperintense lesion in the pons on T2WI was present in the majority of the patients with high specificity, suggesting that this pattern may be valuable for appropriate diagnosis of IVLBCL.[10] Intraparenchymal mass-like lesions can also be observed, however the main imagiological feature of this entity is rapid lesion progression.[11]

The case presented as infarct-like lesions (with diffusion restriction), that pointed to an ischemic vascular etiology. However, additional features helped in achieving the correct diagnosis: the evolution as multifocal infarctions without the evidence of an embolic, inflammatory or prothrombotic process.

In summary, IVLBCL is a rare and aggressive neoplasm, with a high mortality rate. We presented a case showing a rare manifestation of this disease: an IVLBCL restricted to the central nervous system. ■

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