

# Rapidly Progressive Dementia as a Manifestation of Relapse in Mantle Cell Lymphoma: Experience in Diagnosis and Treatment

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## Abstract

Rapidly progressive dementia is an entity that has a multiple and heterogeneous etiology. It is characterized by the alteration of two or more cognitive domains in a period of less than 1 to 2 years. The involvement of the central nervous system attributed to mantle cell lymphoma is rare with a poor prognosis in the short term and mainly debuts in the late stages of the disease as a relapse. A 61-year-old male with a history of mantle cell lymphoma who presents a relapse of the central nervous system, given by a clinical course compatible with a rapidly progressive dementia and which is confirmed by flow cytometry studies in cerebrospinal fluid, which show a 53, 8% of mature lymphoid population: CD45, CD19, CD20, HLA-DR, BCL2. It presents an adequate response to management with a tyrosine kinase inhibitor (Ibrutinib), resolving clinical symptoms and imaging findings.

**Keywords:** Dementia • Mantle cell lymphoma • Magnetic resonance imaging • B-lymphocytes

## Introduction

Rapidly progressive dementia is a multifactorial and heterogeneous entity [1], which is defined as an alteration in two or more cognitive domains in a period less than 1 to 2 years, but it can from weeks to months [2,3]. Within the neoplastic causes, infiltration of the central nervous system (CNS) by lymphomas is not frequent and its treatment will be specific for each of these [2]. The mantle cell lymphoma is a non-Hodgkin lymphoma that is characterized by the involvement of lymph nodes, spleen and bone marrow, however, extranodal involvement has been described in skin, lacrimal glands and in the CNS [4]. The incidence of CNS involvement varies between 4% and 26% according to the different case reports found in the literature and are associated with a poor prognosis due to their low response to treatment [5,6]. Finally, in this article we present the case of a patient with meningeal infiltration secondary to mantle cell lymphoma, with an unusual progression and management response indicated with Ibrutinib.

## Case Report

A 61-year-old male patient diagnosed with mantle cell lymphoma in 2008 with a cervical lymph node involvement with a high risk mantle-cell lymphoma international prognostic index (MIPI), who received 4 cycles of R-CHOP chemotherapy (Rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate and prednisone) achieving a state of remission until 2011. In August of that year, he presents a relapse due to ocular compromise given by an intraocular mass in the left eye associated with cervical, mediastinal, retroperitoneum involvement and it was managed with R-ESHAP rescue

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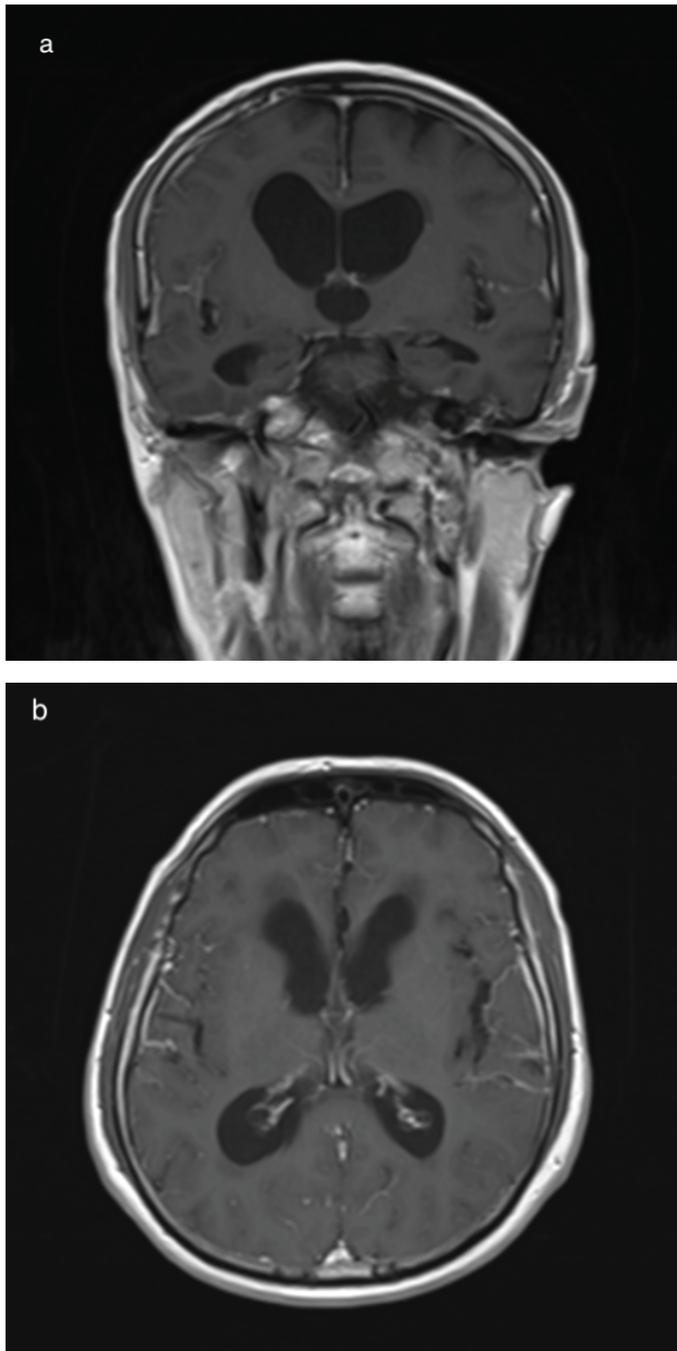
therapy (Rituximab, etoposide, methylprednisolone, cytarabine and cisplatin), receiving 4 cycles and achieved remission. In 2012 he received an autologous progenitor cell transplantation. In 2014, he presented a new relapse in the left eyeball and a biopsy of this lesion was performed, in which, through Immunohistochemistry, cyclin reactivity was identified, with a population of B lymphocytes reactive with co-expression of CD 43 and focal BCL6, confirming lymphoma infiltration. He received at that time 4 cycles of BORID therapy (Bortezomib, rituximab, dexamethasone), achieving the disappearance of the solid ocular lesion.

In 2017, he is hospitalized by the hematology service who request assessment by the department of neurology for a history of 8 months consistent in low asymmetric amplitude tremor in upper limbs associated with altered gait by short steps and abasia. With a progression of the clinical course in the last 3 months due to temporal-spatial disorientation and multi-domain cognitive commitment that generates dependence for their daily activities, so it is suspected a relapse with compromise of the CNS. MRI is performed in which dilatation of the third and lateral ventricles is evidenced with an increase in the intensity of the peri-ventricular white matter, transependymal migration suggestive of active supratentorial hydrocephalus in the T2/FLAIR sequence and abnormal leptomeningeal and dural gadolinium enhancement of the frontal interhemispheric falx and in the temporal fossa (Figure 1).

A cognitive evaluation of Montreal (MoCA) is performed with a result of 12/30 prior to lumbar puncture that shows a hyperproteinorrachia (176 mg/dl) associated with lymphocyte pleocytosis (400 cells × mm<sup>3</sup>), with slight cognitive improvement given by a MoCA with a result of 17/30 and with negative infectious studies. Flow cytometry study presents with a 53.8% of mature lymphoid population: CD45, CD19, CD20, HLA-DR, BCL2 so it is considered a relapse due to meningeal infiltrative process secondary to the mantle cell lymphoma. The Hematology service concluded a new relapse so it started treatment with a tyrosine kinase inhibitor (Ibrutinib) at a dose of 560 mg/day receiving 10 cycles until October 2018, presenting a neurological recovery and functional independence for daily activities, with a control MoCA of 25/30. Finally the patient had a full resolution of the abnormal leptomeningeal and dural enhancement.

## Discussion

In the course of mantle cell lymphoma, CNS involvement is considered an unusual site of extra nodal alteration but with a devastating prognosis [6,7].



**Figure 1.** MRI series of one T1-Coronal and one T1-Axial with gadolinium. Abnormal leptomeningeal and dural gadolinium enhancement of the (a). Frontal interhemispheric falx and (b). In the temporal fossa

The first reports of this complication date from 20 years ago, but given its low incidence it is not part of the initial approach of this pathology [8]. It has been described that relapses at the CNS occur both at the parenchymal and leptomeningeal levels, presenting clinical manifestations such as behavioural changes, headache and cranial nerve paralysis [7].

The diagnosis of CNS involvement is due to the demonstration of cellular positivity in the cerebrospinal fluid analysis of IgM/IgD, CD5, Cyclin D1 and recognition of monoclonal antibodies (CD20, CD19, CD22) [9,10]. Among the new medications to treat patients who have recurrent relapses, a tyrosine kinase inhibitor (Ibrutinib) has been studied as a single agent, providing a rapid response by blocking B-cell antigen receptor signalling, thus reducing malignant proliferation of B cells and inducing apoptosis [11]. Associated with this it has presented a response in 68% of patients with refractory characteristics and persistent relapses [12]. In this patient, there is a dramatic improvement in the condition compatible with a rapidly progressive dementia

associated with a normal pressure hydrocephalus after management with Ibrutinib and an increase in survival greater than 3.7 months, which is the average rate of survival that has been published in the literature after SNC involvement [11,13].

## Conclusion

In conclusion, CNS involvement secondary to mantle cell lymphoma is a rare complication that is associated with poor short-term prognosis and this can be explained by subtle changes in the neurological clinic of patients. The fact that it is reported in the late course of the disease makes us think that symptoms or signs suggestive of neurological compromise should be assessed as soon as possible with a strict monitoring. Finally, Ibrutinib therapy seems to indicate a good alternative in patients with refractory symptoms and persistence of relapses but more evidence is still required regarding the CNS involvement, but the case reports that have been published are promising as a unique therapy in this neurological complication.

## Conflict of Interest

None of the authors received any remuneration or financial assistance to develop the work. There is no conflict of interest on the part of any of the authors.

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