Case Report **IJCR (2018) 2:16**

International Journal of Case Reports
(ISSN:2572-8776)

Primary cerebral lymphoma in immuno-competent patient: report of 2 cases and literature review

Fatima zahra Farhane, Touria Bouhafa, Abderrahmane Elmazghi, Khalid Hassouni

Department of radiotherapy, HASSAN II university hospital, Fez, Morocco

ABSTRACT

Primary cerebral lymphoma is a form of non-Hodgkin lymphoma with a solitary localization in the brain, excepting other localizations involving the central nervous system. This is a rare cancer but with increasing incidence, it was predominantly observed in immunodepressed HIV-positive patients but since the advent of effective antiretroviral treatments, it has essentially been observed in immunocompetent patients.

We report two cases of primary cerebral lymphoma observed in immunocompetent patients.

Keywords: Primary cerebral lymphoma, immuno-competent patient, case report.

***Correspondence to Author:**
FATIMA ZAHRA FARHANE
Department of Radiotherapy, HASSAN II university hospital, Fez, Morocco.

How to cite this article:
Fatima zahra Farhane, Touria Bouhafa, Abderrahmane Elmazghi, Khalid Hassouni. Primary cerebral lymphoma in immuno-competent patient: report of 2 cases and literature review. International Journal of Case Reports, 2018 2:16.

eSciPub LLC, Houston, TX USA.
Website: http://escipub.com/

INTRODUCTION:

Primary central nervous system lymphoma (PCNSL) is a rare form of non-Hodgkin lymphoma (NHL) comprising 2.2 % of all central nervous system (CNS) tumours [1]. It encompasses lymphoma exclusively involving the brain, spinal cord, eyes, meninges, and cranial nerves. Primary cerebral lymphoma (PCL) is a form of non-Hodgkin lymphoma with a solitary localization in the brain, excepting other localizations involving the central nervous system. This is a rare cancer but with increasing incidence [2]. We report 2 cases of PCL with a literature review

PATIENTS AND OBSERVATIONS:

OBSERVATION 1:

A 38-year-old male was transferred to our institution after a 3-month history of incomplete intracranial hypertension syndrome. CT cerebral showed heterogeneous process level with parietal cerebral edema. Cerebral magnetic resonance imaging (MRI) demonstrated Left parietal expansive process, deep, periventricular, hypointense on T1 and T2 Flair, with contrast enhancement, surrounded by a large swelling. The cerebral excision biopsy with histological and immunohistochemical study revealed a non-Hodgkin lymphoma primary large B-cell. Chemotherapy was administered including intravenous methotrexate at high doses. Then the patient received a whole brain radiotherapy at total dose of 46 Gy. A complete response was observed with a decline of 11 months.

OBSERVATION 2:

A 46-year-old woman was transferred to our institution after a 6-month history of intracranial hypertension syndrome aggravated 1 month later by a left hemiparesis. CT cerebral showed a right temporo parietal process causing a mass effect on the median structures with precommitment under falcoriel. Cerebral magnetic resonance imaging (MRI) showed isointense on T1 and T2 Flair, with intense and homogenous contrast enhancement (Figure 1). The patient underwent a partial resection of the tumor. Histological and immunohistochemical study revealed a non-Hodgkin lymphoma primary large B-cell. The patient died before any further management.

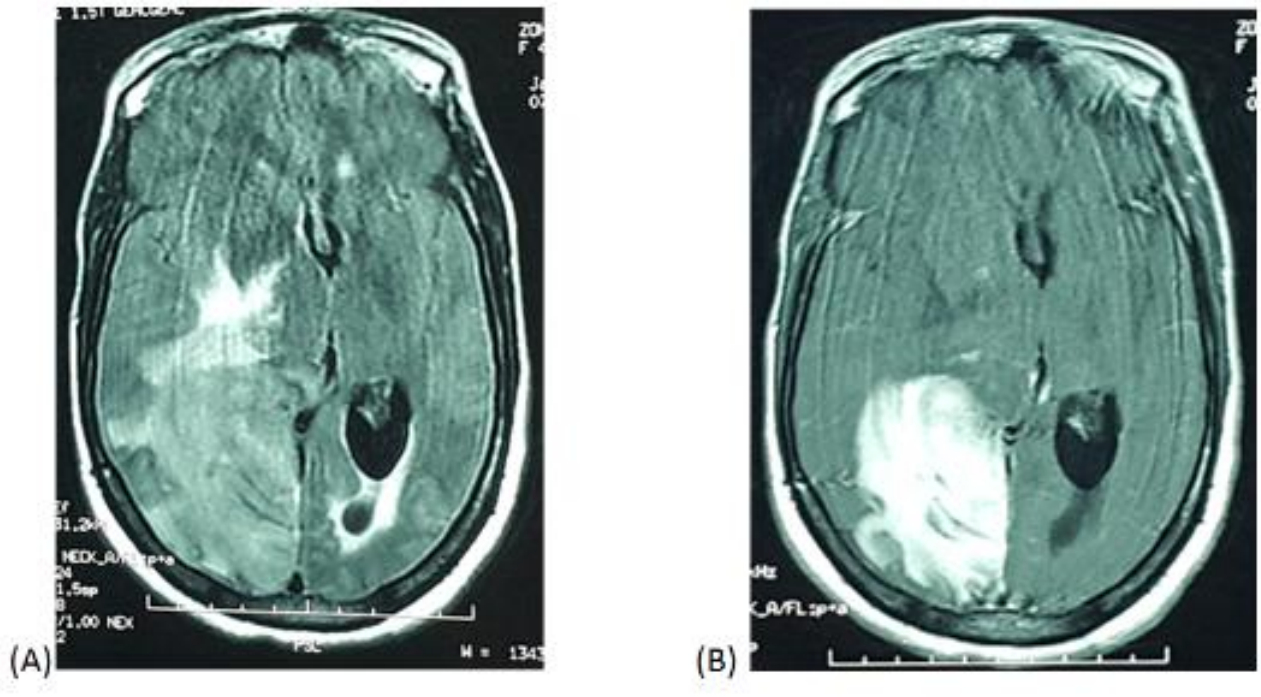

Figure 1 : Cerebral magnetic resonance imaging (MRI) showed isointense on T1(A), with intense and homogenous contrast enhancement (B).

DISCUSSION:

Central nervous system lymphoma (PCNSL) represents approximately 3% of all brain tumors and 2-3% of all cases of non-Hodgkin's lymphomas (NHL), the overall incidence of this neoplasm may be increasing, particularly among person age sixty-five years and older [3]. The majority of PCNSL are sporadic and the incidence increases with age. A minority are attributable to immunosuppressed states, including HIV infection or iatrogenic immunosuppression following organ transplantation. In the era of effective combined antiretroviral therapy (cART), the frequency of HIV-associated PCNSL has diminished [4].

Clinically, the presentation of cerebral lymphoma is nonspecific, with symptoms such as intracranial hypertension syndrome, focal deficits, cognitive impairment or rarely epileptic seizures [5]. Generally, disorders are rapidly progressive over several days to several weeks and patients can quickly develop a significant neurological handicap. There are usually no systemic symptoms [2].

Radiologically, contrast-enhanced cranial MRI is the optimal imaging modality for assessing patients with PCNSL. In patients who have a contraindication to MRI, contrast-enhanced cranial CT scans are recommended. PCNSL is often isodense to hyperdense on CT images and isointense to hypointense on T2-weighted MRI images, a finding that is attributed to its high cell density and scant cytoplasm. On postcontrast CT or MR images, there typically is a homogeneous pattern of enhancement [6].

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 [4]

Glucocorticoids typically induce a rapid improvement in symptoms, and radiographic responses in at least 40% of patients, steroid-induced responses also increase the risk of a non-diagnostic brain biopsy [7].

The majority of PCNSL are diagnosed via stereotactic biopsy or, less commonly, by flow cytometric analysis of cerebrospinal fluid (CSF) lymphocytes [4].

Approximately 95% of PCNSL are large B-cell lymphoma; other histologies that present as PCNSL include T-cell (2%) [8], lymphoblastic, Burkitt, and marginal zone lymphomas.

The DLBCL type of PCNSL is composed of immunoblasts or centroblasts that have a predilection for blood vessels, resulting in lymphoid clustering around small cerebral vessels. Reactive T-cell infiltrates can also be present in varying degrees, making it difficult for a pathologist to discriminate between PCNSL and a reactive process [6].

Between 50% to 80% of PCNSL tumors express BCL6 by immunohistochemistry [9] and at least 95% stain positive for MUM-1[10]. Immunohistochemical analysis of tumors evaluated in CALGB 50202 provided evidence that high BCL6 expression by PCNSL tumors may correlate with refractory disease and shorter progression-free and overall survival [11], thus representing a potentially useful molecular prognostic biomarker. Between 56-93% of PCNSL express BCL2 [9,10]. Transcriptional profile studies of PCNSL identified high *MYC* expression [12]. Increased MYC in PCNSL was later confirmed in the recent CALGB 50202 study [11].

The staging must contain at least systematically complete clinical ophthalmologic examination with slit lamp and fundus. The rest of the staging, in search of locations of systemic lymphoma is controversial because few profitable (<10%). It includes a throraco-abdominopelvic CT, a bone marrow biopsy, testicular ultrasonography in men and possibly a PET Scan [13]. In case of threatening lesion, the complementary assessment should not delay treatment.

The prognostic significance of the Ann Arbor staging system does not apply to PCNSL. In a review of a large historical patient database, the

International Extranodal Lymphoma Study Group reported that the following parameters were associated with poor prognosis: age older than 60 years; performance status greater than 1 on the Eastern Cooperative Oncology Group performance status scale; elevated serum LDH; high CSF protein concentration; and tumor location within the deep regions of the brain (periventricular regions, basal ganglia, brainstem, and/or cerebellum) [6]. Patients with 0 or 1, 2 or 3, or 4 or 5 of these adverse risk factors had 2-year overall survival (OS) rates of 80%, 48%, or 15%, respectively [14].

Although the prognosis of primary CNS lymphoma remains poor, it has substantially improved in the past two decades as a result of better treatment strategies with a curative aim. However, treatment of this disease remains challenging because, despite high chemosensitivity and radiosensitivity, remissions are frequently of short duration [15].

Although few data are available in the scientific literature, surgery has traditionally been deemed to have no role in the treatment of primary CNS lymphoma [15].

Until recently, most authorities have recommended against neurosurgical resection of PCNSL, based upon the scant evidence that surgical cytoreduction provides no survival benefit compared to biopsy and increases the risk of post-operative neurologic deficit [16,17]. Analysis of the results of the German PCNSL SG-1 trial provided the first evidence that aggressive resection of PCNSL at diagnosis correlated with improved progression-free survival (PFS) [18]. The absence of surgical effectiveness might be attributable to the microscopic, multifocal, and infiltrative nature of primary CNS lymphoma that can extend beyond the visible border of the lesion [19].The high radiosensitivity and chemosensitivity of primary CNS lymphoma, and the risk of postoperative morbidity in this patient population, have likewise helped discourage surgery. However, the recommendation to restrict surgical interventions to biopsies is not based on randomised data and, more importantly, not on contemporary data based on modern neurosurgical techniques [15]

The impact of Whole brain irradiation (WBRT) in the treatment of PCNSL is compromised by at least three important problems: (I) inadequate local control of lymphoma; (II) dissemination of radiographically-occult lymphoma cells outside of the radiation port; (III) long-term deleterious effects of radiation on normal brain function [3].

Following introduction of HD-MTX-based chemotherapy, WBRT (36-45Gy) has continued to be employed to consolidate responses and provide more durable disease control [4].

A recent systematic review, which assessed outcomes of chemotherapy versus combined modality treatment using a decision-analytic model, has suggested improvements in both survival and quality-adjusted life years with consolidation WBRT for those <60 years only [20]. Given the rising incidence in PCNSL in older patients, these results substantiate the need for innovative strategies that defer or eliminate WBRT as therapy in PCNSL [3]. In order to ameliorate the long-term neurocognitive sequelae of WBRT at standard doses, the value of reduced dose WBRT (rdWBRT) was assessed. Inferior outcomes have been described with a reduced consolidation WBRT dose (30.6Gy) following CHOD/BVAM induction therapy in a non-randomised comparison. Morris et al. recently reported encouraging rates of disease control using 23.4Gy radiotherapy as consolidation therapy following the R-MPV protocol, with a PFS of 7.7 years for the selected subgroup achieving complete response with immunochemotherapy. Prospective neuropsychological evaluation demonstrated no overall cognitive decline, in 12 patients assessed 48 months after rdWBRT.

The feasibility and efficacy of Systemic chemotherapy, based on methotrexate given intravenously as a high dose (HD-MTX), in CNS lymphomas was established in the 1970’s

and led to its incorporation more broadly in induction and salvage regimens. Remarkably, use of HD-MTX has been identified in multivariate analysis as the most important treatment-related prognostic variable related to survival in CNS lymphomas .Nevertheless, the optimal dose of methotrexate has not been defined. Important studies indicate that high-dose intravenous methotrexate, administered every two weeks for a minimum of six cycles, can be used to treat large cell lymphoma within brain and leptomeningeal compartments, without intrathecal therapy. Among the many therapeutic issues in PCNSL yet to be resolved is the question of what is the optimal number of cycles of HD-MTX administered during induction [3].

Regarding Intrathecal chemotherapy**,** Chemotherapeutic drugs given intrathecally have not been prospectively studied. Therefore, their clinical effectiveness in primary CNS lymphoma is controversial. Results of three retrospective studies showed that patients given high-dose methotrexate did not benefit from the additional treatment with methotrexate and cytarabine given intrathecally. By contrast, results from two consecutive single-arm trials using the same systemic polychemotherapy regimen suggested additional benefit when intraventricular chemotherapy was added.

Combined modality therapy for PCNSL was pioneered by DeAngelis and colleagues at MSK Cancer Center and consisted of HD-MTX plus procarbazine and vincristine, followed by WBRT and high-dose cytarabine. Evaluation of this approach in a multicenter RTOG trial demonstrated a median PFS of 24 months. Because of this encouraging efficacy, combined-modality therapy became a widely adopted approach for PCNSL. In a multicenter randomized phase II study, Ferreri and colleagues evaluated HD-MTX-based induction, minus or plus high-dose cytarabine followed by consolidative WBRT: the median failure-free survival in patients receiving HD-Ara-C in combination with HD-MTX was eight months; in contrast, the median failure-free survival of patients treated with HD-MTX without cytarabine, was only four months. In the SG-1 randomized trial involving 551 PCNSL patients in which half the subjects received WBRT as first-line consolidation, Thiel and colleagues provided strong evidence that omission of WBRT from first-line chemotherapy did not impact survival. While the investigators could demonstrate a modestly favorable effect of WBRT on PFS after methotrexate-based induction, this did not translate into improved overall survival, likely to a significant degree, attributable to the severe neurotoxicity detected in nearly half of patients in the radiotherapy arm.

Conclusion:

Primary cerebral lymphoma is a rare form of non-Hodgkin lymphoma. Although PCNSL in the immunocompetent host is a potentially curable primary brain tumor, current treatment regimens are achieving long-term remissions in only a small fraction of patients, and more effective treatment regimens are needed desperately

Competing interests:

The authors declare no competing interests.

Authors' contributions:

All authors read and approved the final version of the manuscript.

REFERENCES

1. Dolecek TA, Propp JM, Stroup NE, Kruchko C. CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2005–2009. Neuro Oncol. 2012;14.
2. Lymphome cérébral primitif chez un sujet immunocompétent Pratique Neurologique – FMC 2012;3:40–44.
3. Fraser E, Gruenberg K, Rubenstein JL. New approaches in primary central nervous system lymphoma. Chin Clin Oncol. 2015 Mar;4(1):11.
4. Phillips EH1, Fox CP, Cwynarski K. Primary CNS lymphoma. Curr Hematol Malig Rep. 2014 Sep;9(3):243-53. doi: 10.1007/s11899-014-0217-2.

5. Bauchet L, Rigau V, Mathieu-Daudé H, Figarella-Branger D, Hugues D, Palusseau L, et al. French brain tumor data bank: methodology and first results on 10,000 cases. J Neurooncol 2007;84:189–99.
6. Batchelor T1, Loeffler JS.Primary CNS lymphoma. J Clin Oncol. 2006 Mar 10;24(8):1281-8.
7. Porter AB, Giannini C, Kaufmann T, et al. Primary central nervous system lymphoma can be histologically diagnosed after previous corticosteroid use: a pilot study to determine whether corticosteroids prevent the diagnosis of primary central nervous system lymphoma. Ann Neurol 2008;63:662-7.
8. Shenkier TN, Blay JY, O'Neill BP, et al. Primary CNS lymphoma of T-cell origin: a descriptive analysis from the international primary CNS lymphoma collaborative group. J Clin Oncol 2005;23:2233-9.
9. Braaten KM, Betensky RA, de Leval L, et al. BCL-6 expression predicts improved survival in patients with primary central nervous system lymphoma. Clin Cancer Res 2003;9:1063-9.
10. Camilleri-Broët S, Crinière E, Broët P, et al. A uniform activated B-cell-like immunophenotype might explain the poor prognosis of primary central nervous system lymphomas: analysis of 83 cases. Blood 2006;107:190-6.
11. Rubenstein JL, Hsi ED, Johnson JL, et al. Intensive chemotherapy and immunotherapy in patients with newly diagnosed primary CNS lymphoma: CALGB 50202 (Alliance 50202). J Clin Oncol 2013;31:3061-8.
12. Rubenstein JL, Fridlyand J, Shen A, et al. Gene expression and angiotropism in primary CNS lymphoma. Blood 2006;107:3716-23.
13. Abrey LE, Batchelor TT, Ferreri AJ, Gospodarowicz M, Pulczynski EJ, Zucca E, et al. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. J Clin Oncol 2005;23:5034–43.
14. Ferreri AJ, Blay J-Y, Reni M, et al: Prognostic scoring system for primary CNS lymphomas: The International Extranodal Lymphoma Study Group experience. J Clin Oncol 21:266-272, 2003.
15. Hoang-Xuan et al. Diagnosis and treatment of primary CNS lymphoma in immunoc ompetent patients: guidelines fromthe European Association for Neuro-Oncology. Lancet Oncol. 2015 Jul;16(7):e322-32.
16. DeAngelis LM, Yahalom J, Heinemann MH, et al. Primary CNS lymphoma: combined treatment with chemotherapy and radiotherapy. Neurology 1990;40:80-6.
17. Jürgens A, Pels H, Rogowski S, et al. Long-term survival with favorable cognitive outcome after chemotherapy in primary central nervous system lymphoma. Ann Neurol 2010; 67: 182–89.
18. Sandor V, Stark-Vancs V, Pearson D, et al. Phase II trial of chemotherapy alone for primary CNS and intraocular lymphoma. J Clin Oncol 1998; 16: 3000–06.
19. Lai R, Rosenblum MK, DeAngelis LM. Primary CNS lymphoma: a whole-brain disease? Neurology 2002; 59: 1557–62.
20. Prica A, Chan K, Cheung MC. Combined modality therapy versus chemotherapy alone as an induction regimen for primary central nervous system lymphoma: a decision analysis. Br J Haematol. 2012;158:600–7.