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Case Report

Neuromeningeal Infiltration in Diffuse Large B-Cell Lymphoma: A Case Report

S El Bou[1,2]*, O Skalante[1,2], J Chougred[1,2], S Echcherif El Kettani[1,2], Y Moutmir[3], I Orchi[1], K Essahli[1], Z Jeroundi[1], S Kahouli[1,2], H Ammar[1,4], H Elmaaroufi[2,3] and H Zahid[1,2]

[1]Hematology Laboratory - HMIMV, Rabat, Morocco

[2]Faculty of Medicine and Pharmacy, Rabat, Morocco

[3]Clinical Hematology Department - HMIMV, Rabat, Morocco

[4]Faculty of Medicine and Pharmacy, Errachidia, Morocco

***Corresponding Author:** S El Bou, Hematology Laboratory - HMIMV and Faculty of Medicine and Pharmacy, Rabat, Morocco.

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Abstract

Introduction: Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma (NHL) with a male-predominant incidence. Several techniques have been implemented to ensure an appropriate diagnosis of the pathology, including biological, histological, radiological, and molecular analyses. Neuromeningeal infiltration of DLBCL is a rare presentation of the pathology with a poor prognosis limiting patient survival. We report a case of neuromeningeal dissemination of DLBCL with a review of the literature.

Case Presentation: H.M., a 54-year-old patient with no particular history, followed for high-grade diffuse large B-cell lymphoma, CG stage IV A, IPI at 3 and CNS IPI at 4 with renal involvement. In partial remission after 4 R-CHOP courses and in progression after C4 RDHAOX (Rituximab-Dexamethasone-Cytarabine-Oxaliplatin), admitted to the clinical hematology department for his 2nd RICE course (Rituximab-Ifosfamide-Carboplatin-Etoposide). Clinically, hemodynamically and the rest of the clinical examination was without any particularities. Biologically, there were no notable particularities apart from an increased LDH of 523.

During his hospitalization, the patient presented neurological signs such as: lower limb pain of the sciatic type, tingling and paresthesia with peripheral facial paralysis. The neurographic examination was in favor of a length-dependent sensory-motor axonal polyneuropathy, predominantly sensory. A brain CT scan was performed showing neurological involvement.

The cytological study of the CSF showed lymphomatous hypercellularity estimated at 58%, very often large in size with an irregular nucleus related to his lymphoma, which confirm the diagnosis of neuromeningeal dissemination of DLBCL.

After chemotherapy, the patient presented respiratory distress with a left basal opacity on chest X-ray, which badly progressed, leading to the patient's death.

Conclusion: Neuromeningeal infiltration of DLBCL is a rare complication of this pathology characterized by its aggressiveness and rapid progression. A precise diagnosis can be made using various available techniques. A comprehensive CSF examination is crucial, including conventional cytology, flow cytometry, and cytokine assays.

Collaboration between biologists, pathologists, hematologists, and radiologists effectively contributes to early detection, reducing diagnostic errors, and developing specific and individualized management plans.

Keywords: *Neuromeningeal Infiltration; Diffuse Large B-Cell Lymphoma; Flow Cytometry*

Introduction

Lymphoma is a malignant tumor of lymphocytes originating from the lymphoid system. Diffuse large B-cell lymphoma (DLBCL) is one of the most frequent non-Hodgkin lymphomas. It is a disease with highly aggressive malignant potential. It represents a heterogeneous lymphoid malignancy, regardless of morphology, genetics, and clinical characteristics, and may arise from fully developed B lymphocytes at different stages of differentiation [1]. According to the 2022 World Health Organization (WHO) classification, DLBCL is defined by a mature B-cell phenotype with large-cell morphology, comprising a heterogeneous group of clinicopathological entities with variable morphological and molecular features [2]. The neoplastic cells must have nuclei larger than those of benign histiocytes, or at least twice the size of normal lymphocyte nuclei [3].

According to the WHO, DLBCL is the most common subtype of lymphoid neoplasms, accounting for approximately 40% of all non-Hodgkin lymphomas worldwide, with an estimated 150,000 new cases annually [1,3].

Although DLBCL is the most common lymphoma in adults, neuromeningeal involvement remains rare and is associated with a poor prognosis [4]. We report a case of DLBCL with neuromeningeal dissemination.

Case Report

H.M. is a 54-year-old male patient with no significant past medical history, followed for a high-grade diffuse large B-cell lymphoma of germinal center (GC) subtype, stage IV A, with an International Prognostic Index (IPI) score of 3 and a CNS-IPI score of 4, associated with renal involvement. The diagnosis was established by biopsy of a left abdominal mass.

The patient achieved partial remission after four cycles of R-CHOP and showed disease progression after the fourth cycle of RDHAOX (Rituximab-Dexamethasone-Cytarabine-Oxaliplatin). He was admitted to the clinical hematology department for the second cycle of RICE (Rituximab-Ifosfamide-Carboplatin-Etoposide), with the aim of proceeding to autologous hematopoietic stem cell transplantation in case of complete remission.

At admission, the patient was conscious, well oriented in time and space, hemodynamically and respiratory stable, with no signs of infection. The remainder of the clinical examination was unremarkable. Laboratory investigations revealed no significant abnormalities except for an elevated lactate dehydrogenase (LDH) level of 523 U/L.

Three days after hospitalization, the patient developed lower limb pain suggestive of lumbosciatica, associated with tingling and paresthesia, as well as a peripheral facial palsy initially left-sided, grade 3, which progressed to bilateral involvement within one week, with almost complete eye closure. Neurophysiological studies were consistent with a length-dependent axonal sensorimotor polyneuropathy, predominantly sensory.

A brain CT scan showed punctate enhancement of both facial nerves at the intracanalicular segment, suggestive of bilateral facial nerve neuritis. Thoracolumbar and spinal MRI showed no abnormalities. An ^{18}F-FDG PET scan was performed and did not reveal any new hypermetabolic lesions explaining the neurological symptoms. The examination was consistent with an incomplete metabolic response compared with the initial staging PET scan. Lumbar puncture revealed marked hyperproteinorachia (5.17 g/L) and hypoglycorrhachia (0.39 g/L). GeneXpert MTB/RIF and multiplex PCR testing were negative. Interleukin-6 (IL-6) level was 10 pg/mL. Cerebrospinal fluid (CSF) immunophenotyping showed CD19 expression in 52% of cells, CD3 in 43%, and CD56 in 3%. Cytological examination of the CSF demonstrated lymphomatous hypercellularity estimated at 58%, composed predominantly of large cells with irregular nuclei, consistent with lymphoma involvement. These findings confirmed the diagnosis of neuromeningeal dissemination of DLBCL.

During hospitalization, the patient developed neutropenia treated with G-CSF, as well as thrombocytopenia and anemia requiring repeated transfusions of packed red blood cells and platelet concentrates. Neuromeningeal involvement was monitored with serial lumbar punctures and treated with chemotherapy, including MATRIX (Methotrexate-Cytarabine-Thiotepa-Rituximab) alternating with RICE.

Unfortunately, the patient's clinical course was unfavorable. Seven weeks after admission, he developed acute respiratory distress with oxygen saturation of 70%, requiring high-flow oxygen therapy at 15 L/min, and chest X-ray revealed a left basal opacity. Despite intensive care management, the patient died.

Results of the histopathological analysis of the patient's abdominal mass at the time of diagnosis

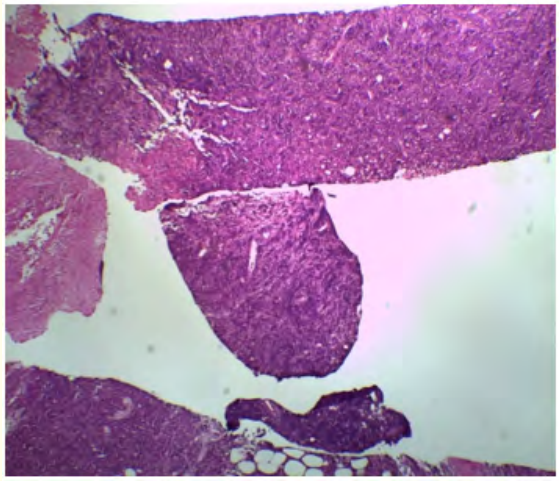

Figure 1: *Abdominal mass showing a diffuse lymphoid tumor proliferation (H&E, ×4).*

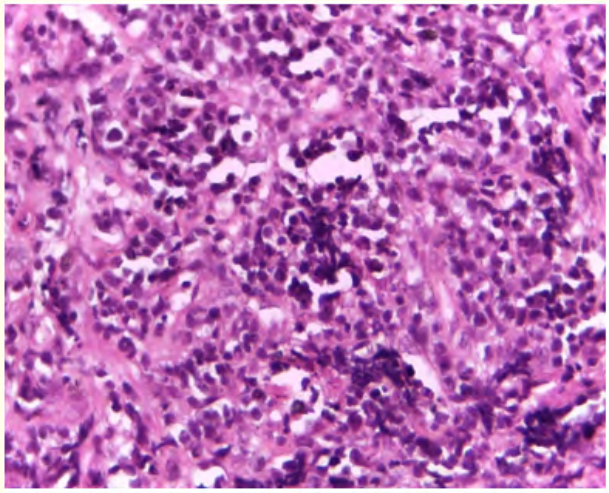

Figure 2: *Abdominal mass showing a diffuse lymphoid tumor proliferation (H&E, ×40).*

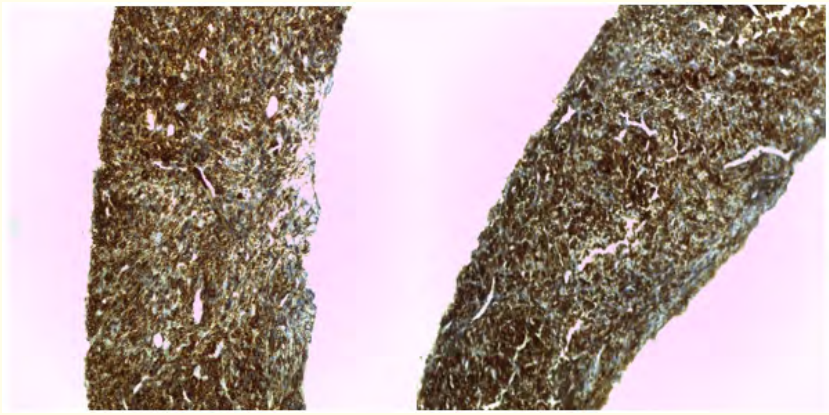

Figure 3: *Diffuse positive staining of tumor cells for CD20 and BCL2 (×10).*

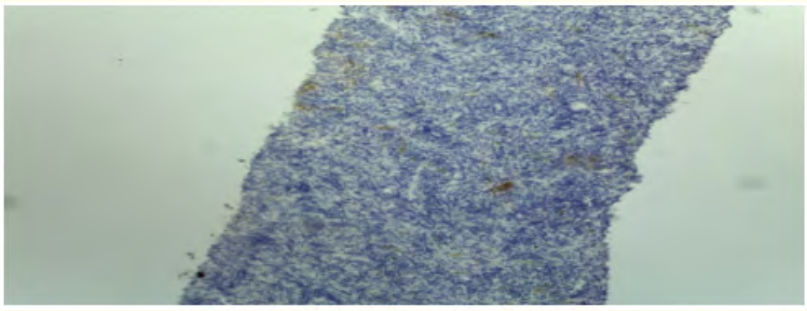

Figure 4: *Absence of tumor cell staining for CD10 (×10).*

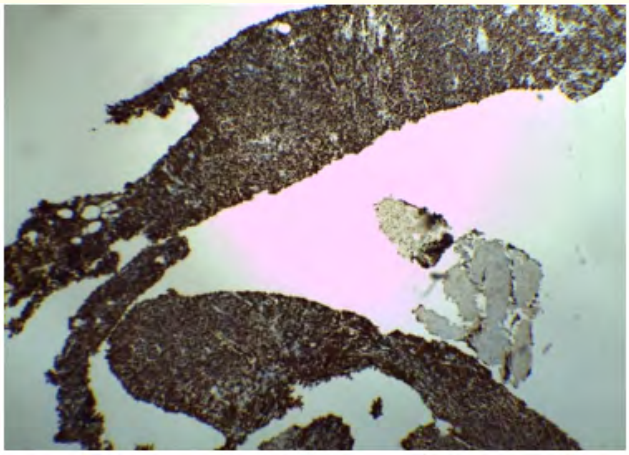

Figure 5: *Proliferation index estimated at 85% (Ki-67, ×4).*

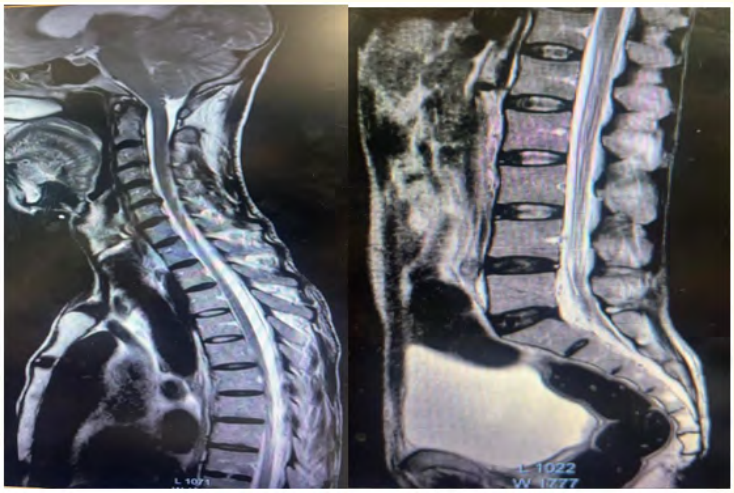

Figure 6: *Spinal MRI of the patient.*

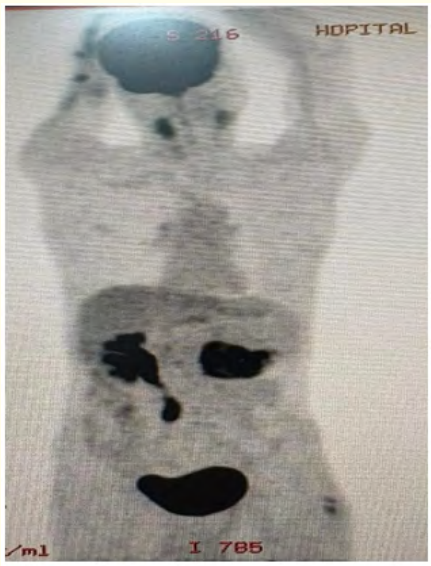

Figure 7: *Patient's PET scan.*

Discussion

Diffuse large B-cell lymphoma (DLBCL) accounts for approximately 80% of all aggressive lymphomas [1]. According to a retrospective study by Kanas G., *et al*. the incidence of DLBCL is increasing, with projections of 29,108 to 32,443 cases in the United States and 26,078 to 27,981 in the European Union from 2020 to 2025, representing a total increase of 11% in the U.S. and 7% in the EU [5].

In Morocco, DLBCL is the most frequent type of non-Hodgkin lymphoma (NHL). However, precise epidemiological data on its prevalence remain limited [6]. Although DLBCL can occur at any age, the median age at diagnosis is approximately 66 years, most commonly affecting

individuals aged 65 - 74 years. About 30% of patients are over 75 years old [7]. In contrast to Western statistics, a study conducted in southern Pakistan reported a lower median age (47.2 years) among newly diagnosed NHL patients [8]. Some studies in Morocco indicate a median age around 60 years, similar to most countries, with a male predominance [9], consistent with our case of a 54-year-old male patient.

Neuromeningeal involvement is rare in DLBCL patients, unlike other high-grade lymphomas such as Burkitt lymphoma and lymphoblastic lymphoma [4,10]. The incidence of CNS involvement has further decreased (< 5%) since the introduction of rituximab-based first-line therapies [11].

We report a rare case of neuromeningeal infiltration in a DLBCL patient. Clinical manifestations vary depending on the site of involvement. DLBCL can originate in a lymph node or affect extranodal sites. Common clinical features include lymphadenopathy, fatigue, bone pain, or pain in enlarged lymph nodes or organs. B symptoms (fever >38°C, night sweats, and unexplained weight loss) occur in approximately one-third of patients [12]. Neurological manifestations depend on the site of CNS involvement and can include cranial nerve lesions, headaches, altered mental status, and seizures [13,14]. Studies in the rituximab era report a median interval of approximately nine months between lymphoma diagnosis and CNS involvement in DLBCL patients, with 80% occurring after first-line treatment during the initial relapse period, and the remainder during first-line therapy. Fifty to sixty percent of patients present with isolated parenchymal involvement [15]. In our case, neurological signs appeared after admission for second-line therapy, including painful peripheral neuropathy (76%), mixed sensory-motor neuropathy, and cranial neuropathy-consistent with the patient's presentation of lower limb pain, paresthesia, and progressive bilateral peripheral facial palsy.

DLBCL diagnosis relies on a combination of laboratory tests including complete blood count, LDH, β2-microglobulin, electrolytes, and renal and hepatic function evaluation. Our patient had no notable laboratory abnormalities aside from elevated LDH, reflecting tumor burden. LDH is a prognostic factor indicating disease severity, treatment response, and relapse risk.

Neuromeningeal infiltration is suspected in DLBCL patients presenting with neurological symptoms. Diagnosis can be confirmed through radiological abnormalities, suggestive CSF cytology, and flow cytometry [16].

The initial DLBCL diagnosis was established via psoas muscle biopsy with immunohistochemistry confirming a germinal center-type DLBCL. CNS involvement required further investigation. Spinal MRI was unremarkable, while brain CT showed punctate enhancement of both facial nerves at the intracanalicular segment, suggesting bilateral cranial nerve VII neuritis. PET/CT with ^{18}F-FDG revealed no new hypermetabolic lesions explaining the neurological symptoms. Although ^{18}F-FDG PET is the imaging modality of choice for DLBCL, other imaging techniques such as X-ray, ultrasound, CT, and MRI are used at different stages of patient management, with MRI remaining the reference standard for neurological assessment [17].

However, imaging alone cannot reliably diagnose neuromeningeal involvement, highlighting the need for more precise diagnostic approaches to confirm the neoplastic nature of lesions [16]. CSF cytology and flow cytometry are therefore crucial.

In our patient, lumbar puncture revealed hyperproteinorachia (5.17 g/L) and CSF cytology demonstrated lymphomatous hypercellularity (58%) with large irregular nuclei, confirming CNS dissemination. Studies have shown that elevated CSF protein supports the diagnosis of CNS DLBCL; in one study, 9 out of 10 patients with CNS DLBCL had hyperproteinorachia, whereas only 3 out of 10 had positive cytology [18].

CSF cytology is highly specific for CNS dissemination in DLBCL but has limited sensitivity, with 20 - 60% false-negative rates, especially with small or delayed-sample analyses [16]. Moreover, morphological overlap between inflammatory lymphocytes and neoplastic lymphoid cells may occasionally result in false positives [16].

Despite its limitations, CSF cytology remains valuable due to its rapidity, simplicity, and accessibility. Detailed evaluation of quantitative, morphological, and proportional changes in CSF cellular components, integrated with clinical findings, neuroimaging, and laboratory data, allows accurate diagnosis, therapeutic monitoring, and prognostic assessment. Experienced personnel are essential to improve diagnostic yield and reduce errors [19]. Cytokine measurement can aid in diagnosing CNS involvement in DLBCL [20]. IL-6 and IL-10 levels in CSF have been associated with secondary CNS involvement and relapse risk [21,22]. Our patient had IL-6 of 10 pg/mL, consistent with literature reporting a median of 8 pg/mL in CNS lymphoma patients [23]. However, simultaneous IL-10 measurement is recommended for higher diagnostic significance.

Recent approaches combine conventional cytology with morphologic, immunophenotypic, molecular, and cytogenetic analyses. Flow cytometry (FC) has emerged as more sensitive than conventional cytology for detecting neoplastic cells in CSF [24-26]. The combination of conventional cytology and FC significantly improves CSF diagnostic yield in newly diagnosed, relapsed, or treated hematologic malignancies [26-28].

Flow cytometry enables qualitative and quantitative identification of cell populations, detection of surface and intracellular markers, and functional analysis, providing an objective complement to morphologic assessment. It is a cornerstone of mature lymphoid tumor diagnostics, allowing disease-specific phenotyping and sensitive detection of tumor cells [29,30]. In our patient, CSF immunophenotyping showed CD19 52%, CD3 43%, and CD56 3%, confirming B-cell infiltration. Combined with clinical signs, cytology and flow cytometry established a definitive diagnosis of neuromeningeal involvement, highlighting the importance of these complementary methods.

This case underscores the essential role of CSF cytology, the importance of trained laboratory personnel, and the necessity of combining diagnostic approaches for rapid and accurate identification of CNS involvement. Given the poor prognosis associated with neuromeningeal infiltration, timely diagnosis is crucial for individualized patient management.

Conclusion

Neuromeningeal involvement in DLBCL is a rare but aggressive complication with rapid progression. Current diagnostic techniques, combined with clinical evaluation, allow accurate diagnosis. Comprehensive CSF analysis-including cytology, flow cytometry, and cytokine measurement-is essential. CSF cytology is accessible, rapid, and easy to perform, and its combination with flow cytometry increases sensitivity and specificity.

Collaboration between laboratory biologists, pathologists, hematologists, and radiologists is critical to enable early detection, reduce diagnostic errors, and guide individualized management plans.

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