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About a Case: Orbital Plasmablastic Lymphoma in an Immunocompetent Patient

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Abstract **Case Report**

Plasmablastic lymphoma (PBL) is considered as an aggressive rare variant of diffuse large B-cell lymphoma (DLBCL) that has a predilection to develop in immunodeficient patients, particularly HIV-positive individuals. It is a rare CD20-negative aggressive lymphoma with a poor prognosis and a therapeutic challenge for pathologists. This report highlights the development of orbital PBL in a 45-year-old immunocompetent male. It includes the clinical presentation, radiological characteristics, histological appearances, immuno-histochemical particularities, and therapeutic response criteria of plasmablastic lymphoma.

Keywords: Plasmoblastic lymphoma, sphenoidal process, tumor biopsy, V-DA-EPOCH, lenalidomide.

INTRODUCTION

Plasmablastic lymphoma a previously known variant of diffuse large B-cell lymphoma (DLBCL), is classified by WHO as an independent subtype of large B-cell lymphoma in 2016. Orbital involvement by PBL is extremely rare and very few cases have been reported in the literature. PBL is often associated with HIV infection and Epstein-Barr virus (EBV). However, it has been reported to occur in immunocompetent individuals, particularly the elderly. Because of its distinct clinical and pathological features, PBL is characterised by early relapse and resistance to chemotherapy. Given its rarity, no standard of care has been established.

OBSERVATION

A 45-year-old patient, with no previous pathological history, had a headache and neck pain two months prior to admission, unresponsive to symptomatic treatment. Complications were marked by the appearance of electric discharge pain in the left eye, with the onset of palpebral oedema and chemosis prompting consultation with an ophthalmologist. The patient also suffered from weight loss that was not quantified and night sweats, with no fever noted (Figure 1). A brain MRI was performed, revealing a tumour-like lesion in the base of the skull, followed by a biopsy in favour of lymphoma.

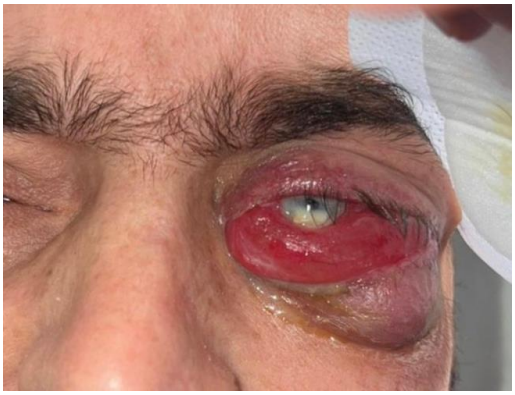

Figure 1: The clinical image at the time of diagnosis highlights the ophthalmological lesion

Physical examination revealed paralysis of nerves III and IV in the left eye, with diplopia and reduced visual acuity in a context of hypermetropia. The rest of the somatic examination was normal. Cerebral MRI showed an extra-axial tissue mass centred on the body of the sphenoid, with T1 hyposignal, T2 hypersignal, intense and homogeneous enhancement, measuring 23mm x 29mm x 32mm, and encompassing the left internal carotid artery. Orbital-cranial MRI showed a lesional process of the sphenoidal body measuring 29mm x 30mm x 33mm, predominantly on the left, encasing the carotid artery and affecting the left abducens and oculomotor nerves. A biopsy of the tumour was performed and the histological appearance was that

of a high density cell proliferation, composed of rounded cells with non-nucleated nuclei, fine chromatin, arranged in diffuse sheets and richly vascularised, with numerous mitoses observed. CD 45 and CD 138 diffusely positive. CD20, CD3, and CD56 were negative. Nuclei strongly labelled by Mum1. Ki67 estimated at almost 90%. The diagnosis of highly malignant plasmablastic non-Hodgkin's lymphoma (NHL) was accepted (Figure 2).

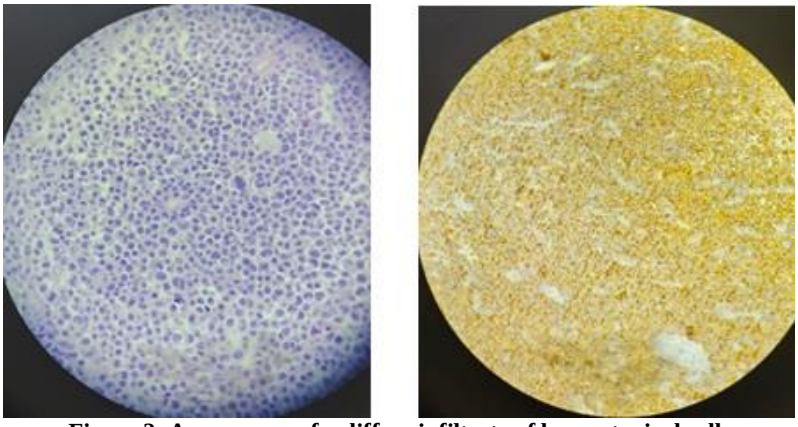

Figure 2: Appearance of a diffuse infiltrate of large atypical cells

HIV serology was negative. A complete blood count showed no lymphocytosis or cytopenia. Lactate dehydrogenase (LDH) levels were normal. EBV polymerase chain reaction (PCR) was not performed. A lumbar puncture revealed no CNS involvement. Protein electrophoresis showed monoclonal hypergammaglobulinaemia estimated at 10.1 g/L.

A positron emission tomography (CT-PET) scan, carried out as part of the extension work-up, showed discrete heterogeneous osteomedullary hypermetabolism, with no lymphomatous progression of lymph node or visceral hypermetabolism.

The plasmablastic lymphoma was stage IV according to the Ann Arbor classification, and high-risk according to histological type and skull base location.

The patient received six courses of V-DA-EPOCH (Bortezomib-Dose Adapted Etoposide-Prednisone-vincristine-Cyclophosphamid-Hydroxydaunorubicin), with a complete response after the fourth course.

He then received 18 sessions of fractionated local radiotherapy. Re-evaluation by PET-CT showed a favourable response to treatment (Figure 3).

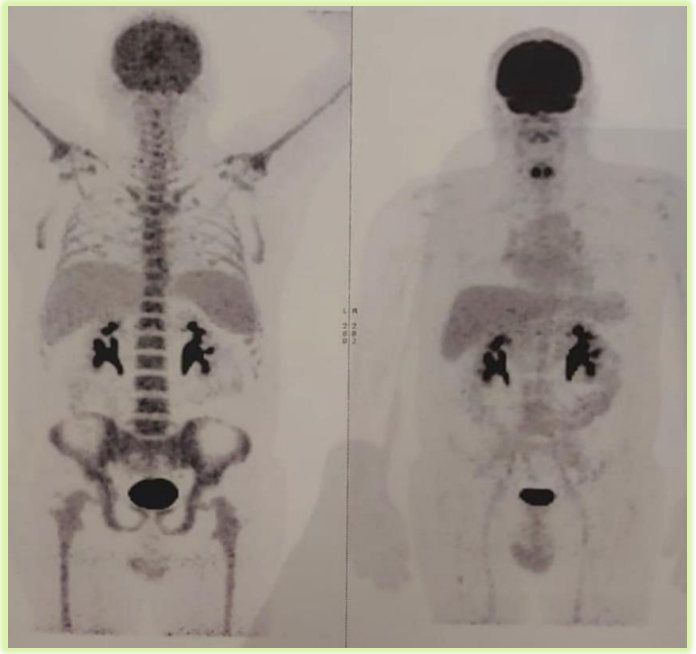

Figure 3: PET/CT scan reevaluation showing significant morphological and metabolic regression of the sphenoidal body from 17 mm to 37 mm, with morphological regression of the associated bone lysis

The extension study confirmed an early tumour relapse at the same site two months after the end of treatment, with a rapid worsening of the clinical condition. A cerebro-orbital MRI was performed (Figure 4).

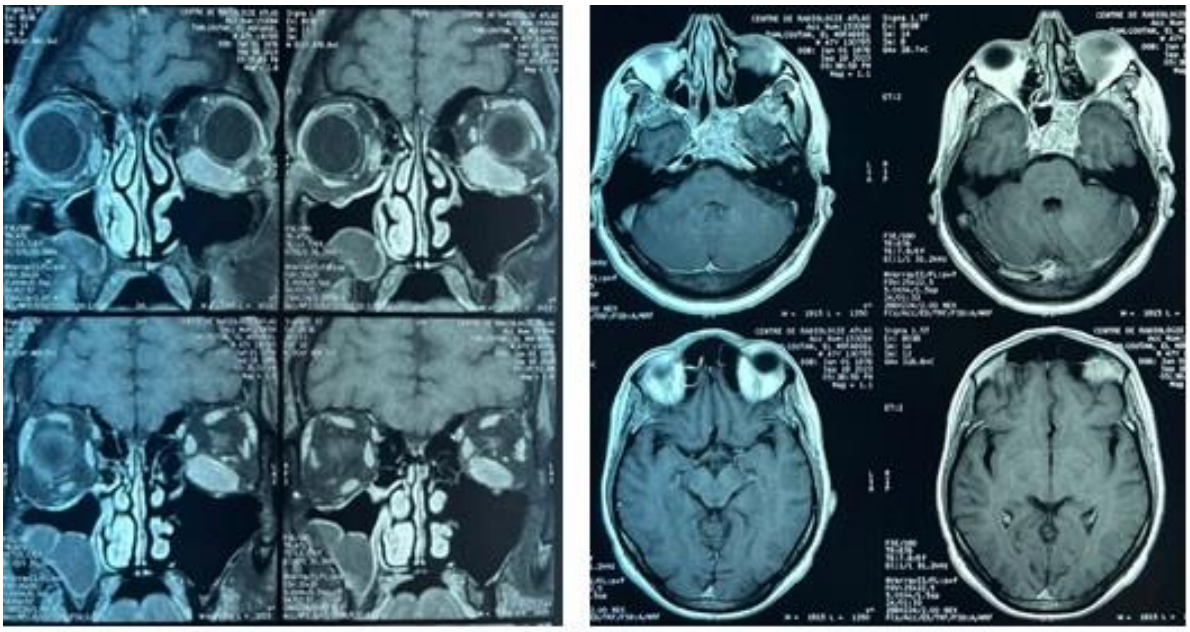

Figure 4: Cerebro-orbital MRI showing a tissue mass on the orbital floor encompassing the inferior rectus muscle, T2 hypersignal, T1 hyposignal, measuring 15mm x 27mm x 41mm

Given the severity and rapid progression of the exophthalmos, it was decided to put the patient on salvage chemotherapy consisting of alternative cycles of Hyper CVAD / Aracytin-Methotrexate high dose (CVAD: Cyclophosphamide, Vincristine, Cytarabine, Doxorubicin) with therapeutic lumbar punctures, without significant improvement. The treatment team decided to start lenalidomide-dexamethasone, with a clear regression of the exophthalmos. Autologous transplantation (ASCT) was then proposed to improve the prognosis. Failure of stem cell mobilisation has been reported.

After three courses of lenalidomide-dexamethasone, a disease progression was suspected due to the reappearance of exophthalmos. Daratumumab-based immunotherapy with ifosfamide-carboplatin-based chemotherapy and etoposide was administered. The plasmablastic lymphoma was refractory after the first course of treatment and the patient died following septic shock. The patient's overall survival was 14 months.

DISCUSSION

Plasmablastic lymphoma (PBL) is an uncommon lymphoma whose clinical and pathological appearance varies between ethnic and geographical groups. Ocular involvement by PBL is even rarer. It is an aggressive variant of large B-cell lymphoma with immunoblastic and plasmablastic morphology and a plasma cell immunophenotype. Most cases of PBL are co-infected with Epstein-Barr virus (EBV), an additional feature that differentiates them from plasmablastic myeloma. Most patients are adults with a male predominance. PBL occurs at a younger median age (55 years) than DLBCL (68 years). It occurs very rarely in children. Furthermore, six of the seven (85.7%) PBL patients with orbital presentation described in the literature were HIV-positive. PBL is diagnosed at a younger median age (42 years) in HIV-positive individuals than in HIV-negative individuals (55-62 years).

Plasmablastic lymphoma usually presents as a mass in one or more extra-nodal sites, usually the gastrointestinal tract and/or oral cavity. The majority of PBL patients present with proptosis and/or decreased vision of the affected eye. Clinical examination also reveals ptosis, conjunctival chemosis, eyelid swelling, and loss of sensation along the trigeminal nerve. The rate of extranodal disease is higher with PBL (53%) than with LBDGC (35%), although the proportion of patients at an advanced clinical stage is similar (57% and 55%, respectively). It should be noted that the patient presents an orbital mass with sphenoidal bone involvement, the thing that raises the possibility of a different spectrum of organ involvement in plasmablastic lymphomas in immunocompetent patients.

When PBL is suspected, the best diagnostic approach is to remove tissue for pathological evaluation. The immunophenotype of plasmablastic lymphoma is similar to that of plasma cell neoplasms, with positive immunohistochemical (IHC) staining for CD79a, IRF-4/MUM-1, CD38 and CD138. PBL is generally negative

for CD19, CD20 and PAX-5, but may be weakly positive for CD45. Therefore, immunophenotyping can also contribute to the diagnostic of PBL. In a few cases, it may also express CD2 or CD4 T-cell markers. MYC overexpression is observed in about half of cases. The Ki-67 proliferation index is invariably high, often exceeding 90%. Cells may also be positive for CD30, which has implications for the use of brentuximab vedotin. Most HIV-positive individuals are positive for Epstein-Barr virus. Overexpression of BCL2 and BCL6 is not seen in PBL, distinguishing it from triple hit lymphoma and Burkitt's lymphoma respectively.

In PBL, a complex karyotype, often including translocations involving the MYC locus at 8q24, can be detected by conventional cytogenetics. MYC aberrations, due to translocations or amplifications, can be detected using specific fluorescent in situ hybridisation (FISH) analysis probes. These genetic aberrations of MYC lead to overexpression of the MYC protein, which is usually detected by IHC on histological sections, with a threshold of positivity of ≥ 40% of tumour cells.

Therefore, other mechanisms must play a role in the pathogenesis of plasmablastic lymphomas: signaling pathways RAS-RAF, JAK-STAT, MCL1, IRF4, MAPK-ERK, PI3K-AKT, Wnt and NOTCH.

As with other common aggressive lymphomas, staging should be performed using positron emission tomography/computed tomography (PET/CT). Clinical staging should follow the Lugano modification of the Ann Arbor staging system.

According to published literature, age ≥ 60 years, advanced stage and high/intermediate IPI scores are associated with worse outcomes in PBL, while the prognostic role of HIV status, EBV positivity and MYC gene rearrangements is unclear. Of all the cases of orbital PBL described in the literature, only two patients survived more than 10 months after diagnosis.

Treatment approaches for PBL depend on a number of factors, including association with HIV infection, localization, tumour extension and the goals of therapy. There is no standard treatment for this type of lymphoma. CHOP (cyclophsphamides- adriamycin-vincristine-prednisone) remains a commonly used treatment, particularly in areas where resources are limited. However, the National Comprehensive Cancer Network (NCCN) guidelines on AIDS-related B-cell lymphoma (version 5.2021) recommend more intensive treatment regimens for PBL and suggest the DA-EPOCH regimen (adapted doses of etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone) as the preferred alternative. This is why the National Comprehensive Cancer Network (NCCN) recommends treating PBL with more intensive regimens than CHOP. Other new drugs and therapeutic approaches for PBL are currently in phase II clinical trials.

PD-1 and PD-L1 expression on PBL cells and the microenvironment is an attractive target for checkpoint inhibitors, particularly in relapsed and refractory cases. Other immunomodulatory drugs, such as lenalidomide, have played a key role in the treatment of myeloma and have therefore been used in PBL patients with reasonable results. Other agents with activity against DLBCLs or myeloma, including polatuzumab vedotin, selinexor, isatuximab, CELMODS, anti-PGRCD5 bispecific antibodies and CAR-Ts, are of interest in PBL. However, many patients have died within a very short follow-up period. The five-year survival rate is only 33.5%.

CONCLUSION

Orbital plasmablastic lymphoma is a rare and specific type of non-Hodgkin's lymphoma due to its biological, histological and cytogenetic aspects. Orbital location underlines the importance of urgent treatment because of the direct impact on functional prognosis. The standard of treatment has not yet been codified because of the rarity and complexity of the disease. However, a better understanding of PBL's biology offers hope for improved outcomes. The aim is to develop more effective targeted therapeutic agents for PBL patients.

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