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Case Report
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A Case Report of Primary CNS Lymphoma of Choroid Plexus

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Abstract

Primary CNS Lymphoma (PCNSL) of the choroid plexus is a very rare tumor. Its clinical and radiological manifestations are not entirely clear due to the rarity of the disease; and hence diagnosis of this condition can be delayed due lack of knowledge associated with the disease. We present a case of a 63-year-old man who presented with a few weeks of cognitive deficits with dysphasia and marked impairments in short term memory. His MRI brain showed subtle FLAIR and T1 contrast abnormalities near the lateral ventricles abutting the temporal lobe at the choroid plexus. On brain biopsy he was noted to have perivascular atypical B lymphocytes consistent with PCNSL. High-dose methotrexate, teniposide, BCNU, prednisolone and Rituximab, followed by 5 months of consolidative chemotherapy with cytarabine resulted in clinical and radiological improvement. He subsequently relapsed twice and salvage chemotherapy with consolidative radiotherapy was delivered. Unfortunately, 6 months later his condition worsened and he was referred to palliative care, and then deceased. PCNSL of the choroid plexus is very rare and cases of relapsed disease generally have poor outcome despite a variety of chemo and radiotherapy options. Targeted therapies with optimal penetration of the blood brain barrier are warranted.

Keywords: Primary CNS lymphoma; Choroid plexus; Brain malignancy

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Introduction

Approximately 4% of all intracranial tumors are primary CNS lymphomas [1], of which intraventricular neoplasms are rare representing 1% to 10% of primary CNS malignancy [2]. There is an increased incidence of primary CNS lymphoma in individuals with acquired or inherent immunodeficiency [1]. Involvement of the choroid plexus by lymphoma is rare with only less than 10 individual case reports in the literature. The aim of this report is to present a case of a 63-year-old man who presented with cognitive deficits and after a myriad of investigations on brain biopsy was found to have primary CNS lymphoma of the choroid plexus. The case highlights the challenges in diagnosis, the rarity of such cancer affecting the choroid plexus and the response to treatment where treatment efficacy might be reduced due to location of the lesion.

Case Presentation

A 63-year-old man was brought into the ED by his partner, due to a 1-week history of "confusion", short-term memory loss and inability to recall directions. There was no history of recent headaches, photophobia, neck stiffness, or seizures. He did not have fevers or night sweats but according to his partner, had lost 3 kg in weight in the past 3 months. His past medical history included a lumbar spine laminectomy 10 years ago and he was a current smoker (30 pack-year history) but had recently quit. He worked as a farmer and had horses, cattle, dogs, and sheep in the farm. He sailed regularly and his most recent travel was to Japan 3 months prior to his presentation.

On examination he was afebrile with a blood pressure of 122/74 mmHg. There was no palpable lymphadenopathy no hepatosplenomegaly. Visual acuity was normal with pinhole correction.

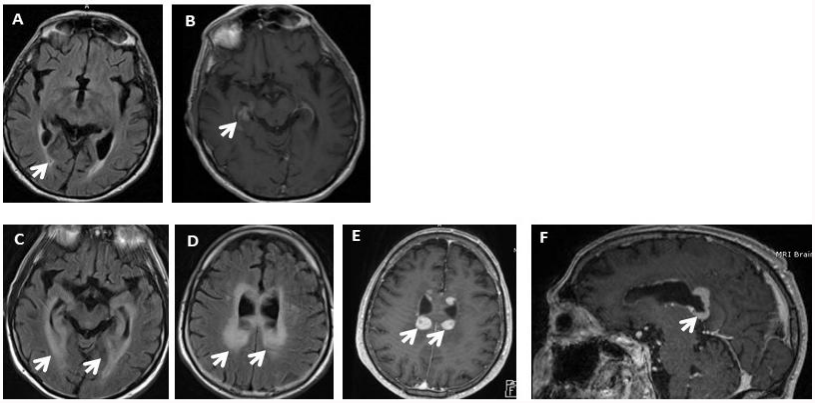

Figure 1: MRI images showing (A) FLAIR signal changes and (B) T1 with contrast abnormality during the patient's initial admission to hospital. Images C-F are when the disease relapsed with C and D showing FLAIR sequences and E and F showing T1 post contrast. White arrows indicate site of abnormality.

Cranial nerve, gait and neurological limb examination, and fundoscopy were normal.

There were no abnormalities on examination of higher centers, frontal, parietal or occipital lobe functions, however marked deficits in recall with retrograde amnesia extending for at least one week with inability to form new memories. He scored 17/30 (0/3 recall) on Mini Mental State Examination (MMSE) and NUCOG of 71/100 with deficits in short-term memory. Formal neuropsychological testing confirmed specific deficits in recall of recent events.

Full blood examination, renal and liver function, inflammatory markers, Vitamin B12, folate, TSH, ANA, dsDNA, rheumatoid factor, pANCA and cANCA were all normal. Anti-GAD, anti-NMDAR and VGKC antibodies were negative. HIV serology was negative. Immunoglobulin levels were normal. Serum protein electrophoresis detected a paraprotein band of IgM lambda 4 g/L. CT chest/abdomen/pelvis revealed no evidence of malignancy with no enlarged lymph nodes seen.

Lumbar puncture showed an opening pressure of 4 cm, H_2O with 48 × 10^6/L polymorphs, 177 × 10^6/L lymphocytes and 0 × 10^6/L red blood cells. Glucose was 1.5 mmol/L and protein was 3.93 g/L. Cytology showed chronic inflammation with no evidence of malignancy. There was no clonal B- or T-cell populations identified by flow cytometry. Cryptococcal antigen, Herpes virus multiplex PCR and syphilis screen were negative. Electrophoresis was normal. NMDA receptor and neuronal antibodies were not detected in CSF.

MRI brain with gadolinium revealed thickening of the choroid plexus at the level of the atria of the lateral ventricle (extending to the temporal horns), more pronounced on the right side associated with marked enhancement of the choroid plexus (Figure 1A, 1B). There was no pathological contrast enhancement within the brain parenchyma outside the ventricular system, and the brain parenchyma was of normal volume with no volume loss of the hippocampal formation. The differential diagnosis from the MRI findings included malignancy, sarcoid or infection. A diagnostic biopsy of the choroid plexus lesion confirmed diffuse large B-cell lymphoma consistent with PCNSL on histology and immunohistochemistry (Figure 2) showing presence perivascular atypical CD20 positive B cells, which were MUM1 positive and a Ki-67 index of approximately 80%. A bone marrow biopsy for staging showed no evidence of lymphoma involvement. On slit lamp examination, there was no ocular lymphoma involvement.

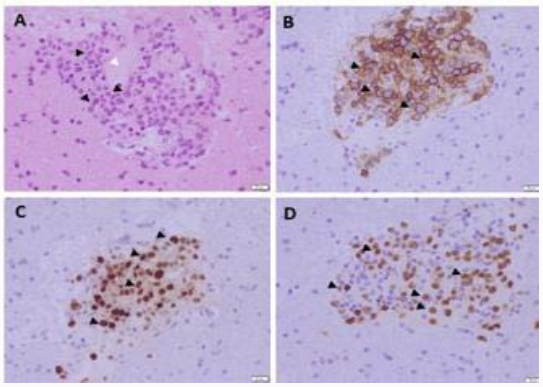

Figure 2: Histological images of brain biopsy (choroid plexus) results showing: (A) H and E stain showing large atypical cells (black arrowheads) with a perivascular distribution. White arrowhead indicates lumen of blood vessel. (B) Immunohistochemistry staining (black arrow heads) for CD20 - a marker of B lymphocytes. (C) Staining for MUM1 (as indicated by arrowheads), whose expression is seen in diffuse large B cell lymphoma. (D) Staining for Ki67 (indicated by arrowheads); where the Ki67 index was found to be approximately 80%. Scale bar 20 µm.

He was subsequently referred to Hematology and commenced treatment with multi-agent chemotherapy with high-dose methotrexate, teniposide, BCNU, prednisolone and Rituximab (monoclonal anti-CD20 antibody). He received 2 cycles, following which a MRI scan showed near complete resolution of his CNS lymphoma. He then received consolidation with high-dose cytarabine. Five months later, he presented with deterioration in gait and MRI brain scan showed recurrence of periventricular/choroidal enhancement. He received 8 cycles of salvage chemotherapy with high dose methotrexate and rituximab with the addition of temozolomide on odd-numbered cycles. Restaging MRI showed resolution of the CNS lymphoma consistent with improvement in clinical symptoms. He preceded with 30 Gy of consolidative whole brain radiotherapy delivered in 20 fractions. Unfortunately, six months later, patient exhibited worsening cognition and short-term memory loss and MRI scan confirmed relapsed disease in the ependymal surface of all ventricles, most pronounced in the lateral ventricles of both hemispheres. There was increased T2 signal extending into the white matter and this pattern of disease was in similar distribution to his original scan in June 2014 (Figures 1C-1F). Due to his poor prognosis, palliative treatment was discussed with him and his partner and he died within a month of his second relapse.

Discussion and Conclusions

PCNSL is an uncommon variant of extra nodal Non-Hodgkin Lymphoma (NHL) that involves the brain, leptomeninges, eyes, or spinal cord without evidence of systemic disease [1,2]. The CNS normally lacks lymphoid aggregates and it remains speculative whether malignant transformation develops locally within normally trafficking CNS lymphocytes, or from within a sub-population of lymphocytes with specific tropism for the CNS [3]. Such tropism may be facilitated through the expression of specific cell-surface adhesion molecules, such as CD44 and CD18, and various chemokine receptors [4]. Spreading of malignant lymphoid cells within the CNS is believed to involve a complex interaction of selection and cadherin molecules, such as adhesion molecule CD44 and transmembrane protein receptor Fas (CD95) [5].

Intraventricular neoplasms consist of two categories: those that originate from the ventricular wall, and those that originate from structures within the ventricular system such as choroid plexus [6]. The choroid plexus is a leaf-like structure with a granular surface attached to the ependyma by a thin stalk in the lateral, third and fourth ventricles. It produces CSF and is crucial in maintenance of ionic balance [7]. Tumors' arising from the choroid plexus are extremely rare, and include choroid plexus papilloma, choroid plexus carcinoma and non-neoplastic lesions. Of these, lymphoma is an extremely rare form of choroid plexus tumor. A PubMed search revealed only less than 8 cases of primary CNS lymphoma of choroid plexus, highlighting the rarity of the disease.

The risk factors for PCNSL include: iatrogenic immunosuppression, congenital immunodeficiency including ataxia-telangiectasia, Wiskott-Aldrich syndrome and severe combined variable immunodeficiencies [5]. PCNSL can also arise from EBV-mediated clonal expansion and malignant transformation of B-lymphocytes, a process that is likely regulated by immune mechanisms [5].

High-dose methotrexate-based induction chemotherapy is currently the first-line of treatment. As monotherapy, high-dose methotrexate achieves a 35% to 74% response rate [8] and combination chemotherapy regimens have increased response rates to 77% to 85% [9,10]. However, 35% to 65% of patients still relapse and radiation therapy is utilized as salvage treatment for relapsed or refractory disease with neurocognitive long-term toxicity a major concern [10]. In a recent study Yang and colleagues reported the outcomes of 11 cases of intraventricular primary CNS lymphoma showing that the majority (70%) relapsed and in the majority of cases salvage therapy (high does methotrexate and radiotherapy were required) [11]. The overall prognosis for relapsed PCNSL is poor with salvage radiation treatment increasing median overall survival by approximately 11 months in radiotherapy-naïve patients [12]. Another multi centre study used induction therapy with rituximab, high dose methotrexate and temozolomide followed by high dose consolidation with etoposide in addition to cytarabine (without whole brain radiotherapy). A complete response to rituximab, methotrexate and temozolomide of 66% and progression free survival at 2 years of 57% were seen [13]. Other studies have reported high dose chemotherapy-autologous stem cell transplantation as a first line treatment for primary CNS lymphoma; and in a phase 2 trial of 30 patients, 5 year probability of relapse-related death was 21% for all patients (n=30) and 8.7% for patients treated with high dose chemotherapy plus autologous stem cell transplantation [9].

The case that we presented died from relapsed disease where salvage chemotherapy was ultimately ineffective in controlling the underlying illness. Age and premorbid function are thought to be independent risk factors for future prognosis in PCNSL [14]. A complete response on neuroimaging after two courses of chemotherapy is also reported to be predictive of progression-free survival [15]. The case presented did not have complete resolution of radiological changes after the course of chemotherapy. One reason could have been that the location of the neoplasia being within the choroid plexus was presumably hard to access for the therapeutic agents. Future studies are required to decipher PCNSL location and its association with future outcome.

PCNSL of the choroid plexus is a very rare tumor. We present a case of diffuse large B-cell lymphoma of the choroid plexus with extension into the temporal horns of the lateral ventricle. Radiological and clinical improvement were achieved with high-dose methotrexate combination treatment with Rituximab but the patient experienced 2 relapses within 5 to 6 months of completion of treatment, heralding a poor prognosis. This is consistent with the literature where recurrent or relapsed PCNL has been reported to have poor outcome despite the many varieties of therapies that have been trialed. Targeted therapies that could penetrate the blood brain barrier are required to deal with this highly invasive brain cancer. Recent efforts on the use of agents such as ibrutinib, lenalidomide and immune checkpoint inhibitors for treatment of PCNL is underway.

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