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Case Report

Diagnosis of a secondary central nervous system Lymphoma (SCNSL) in a patient with low proliferative Mantle cell lymphoma

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Abstract

Mantle cell lymphoma (MCL) represents a rare subtype of non-Hodgkin lymphoma, with approximately 4% of patients experiencing central nervous system (CNS) involvement. There is a higher likelihood of CNS Infiltration in patients who have elevated Ki-67 Levels, a marker associated with prognosis and CNS involvement. Herein, we present the case of a 72-year-old individual of British ancestry, known to have stage 4A MCL, exhibiting a Ki-67 index of 10%. He had just completed six cycles of Rituximab and Bendamustine with a good radiological response. The patient presented with episodic vacant states accompanied by confusion, recurrent dysphasia, and frontotemporal headaches followed by visual and auditory hallucinations upon hospital admission. Initial imaging studies failed to reveal compelling evidence of secondary central nervous system lymphoma (SCNSL), leading to a presumptive diagnosis of transient ischemic attack (TIA) given the patient's recurrent visits to the emergency department. However, subsequent evaluation by cerebrospinal fluid (CSF) analysis showed lymphocytic infiltrates with a negative bioFire test. Additional testing with the haematological malignancy diagnostic service (HMDS) unveiled findings consistent with CNS involvement secondary to known MCL. Our case report underscores the imperative for thorough CSF analysis in patients with MCL, irrespective of a seemingly low proliferation index such as Ki-67. This will promptly identify and manage potential CNS involvement.

Keywords: Mantle Cell Lymphoma; Secondary Central Nervous System Lymphoma; Ki-67; Proliferation Index.

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Introduction

Mantle cell lymphoma (MCL) is a rare form of non-Hodgkin lymphoma, which is more frequent in males than females (3:1) with an average age of diagnosis between 60 to 70 years. [1] The risk of CNS involvement in patients with MCL is approximately 4%. [2] The Ki-67 expression, a proliferative index, is the most significant prognosticative index of overall survival rate in five years. [3] Higher Ki-67 indicates poor outcomes. A low Ki-67 means less probability of developing into a secondary CNS lymphoma, [4] however, responds poorly to chemotherapy. [5] It is pertinent to note that the Ki-67 holds a superior prognostic value compared to cytology and growth patterns in MCL. [3]

Case Presentation

We present the case of a 72-year-old male of British descent, who was diagnosed in 2021 with Mantle cell lymphoma stage 4A following a left axillary lymph node biopsy, revealing a Ki-67 score of 10% and a Mantle Cell Lymphoma International Prognostic Index (MIPI) score indicating intermediate risk. Following his initial diagnosis in 2021, the patient was monitored until October 2023, when he was noted to have progressive disease and was treated with six cycles of chemotherapy utilizing Rituximab/Bendamustine. The final cycle is completed approximately one month prior to the current admission. Despite Chemotherapy, the patient reported a worsening of symptoms in the interim period since concluding chemotherapy.

The patient presented with a constellation of symptoms notably intermittent vacant episodes accompanied by confusion, recurrent dysphasia, and frontotemporal headaches. Additionally, upon admission, he manifested visual and auditory hallucinations. Preceding the current admission, the patient was admitted for similar symptoms. During that admission, investigations were conducted, and the patient was presumed to have a Transient Ischaemic attack (TIA). Imaging studies conducted during the admission demonstrated unremarkable findings on both CT and MRI scans of the head, while carotid Doppler assessment revealed mild to moderate stenosis, with less than 50% stenosis in the left internal carotid artery and 60-69% stenosis in the right internal carotid artery.

Investigation

Magnetic resonance imaging (MRI) of the head with contrast showed no acute intracranial abnormality or convincing evidence of CNS or meningeal involvement. Routine blood tests as part of the delirium screen such as mid-stream urine culture, electrolytes, liver function tests, serum folate, and Serum B12 levels were normal.

CT neck, thorax, abdomen, and pelvis with contrast was done on the 25th of April 2024 to assess for chemotherapy response. In comparison to the CT scan done on the 11th of November 2023, the scan showed a reduction in the size of previous enlarged lymph nodes (intra-abdominal para-aortic lymph node). No other significant lymphadenopathy in the neck, thorax, abdomen, or pelvis. No suspicious bone lesion in the visualised skeleton. Spleen had reduced in size measuring approximately 13.9 cm (cranio-caudal) compared to 16.2 cm previously. Possible 11 mm left kidney upper pole angiomyolipoma, which was not clearly visible on the previous CT scan. There was a change in the size of some previously seen renal cysts and some new small renal cysts without any obvious suspicious features.

Lumbar puncture with CSF results showed white cell count (WCC) of 900/uL, red cells 1/uL, lymphocytes 95%, polymorphs 5%, CSF Lactate 13.5mmol/L (0.8-2.2mmol/L), glucose 0.7mmol/L (2.5-4.5mmol/L), and protein 2.68g/L(0.15-0.45g/L).CSF Culture did not grow any microbes and a Bio-Fire was negative as well.

CSF samples sent for further testing to the haematological malignancy diagnostic service (HMDS) showed the morphology of marked excess small lymphocytes, with irregular nuclear outline and smear cells. Flow cytometry showed neoplastic B-cells= 92% of leucocytes, kappa-lambda+ CD19+CD20+ CD5++CD10+(wk) CD23-ROR-1+ CD43++CD79b+CD81++. Differential cell counts showed CD3+ T-cells + 0.67% of leucocytes of which 33% are CD4+ helper T-cells and 10% are CD8+ cytotoxic T-cells. NK-cells = 0.05% of leucocytes. This is shown in Figures A, B, C, and D.

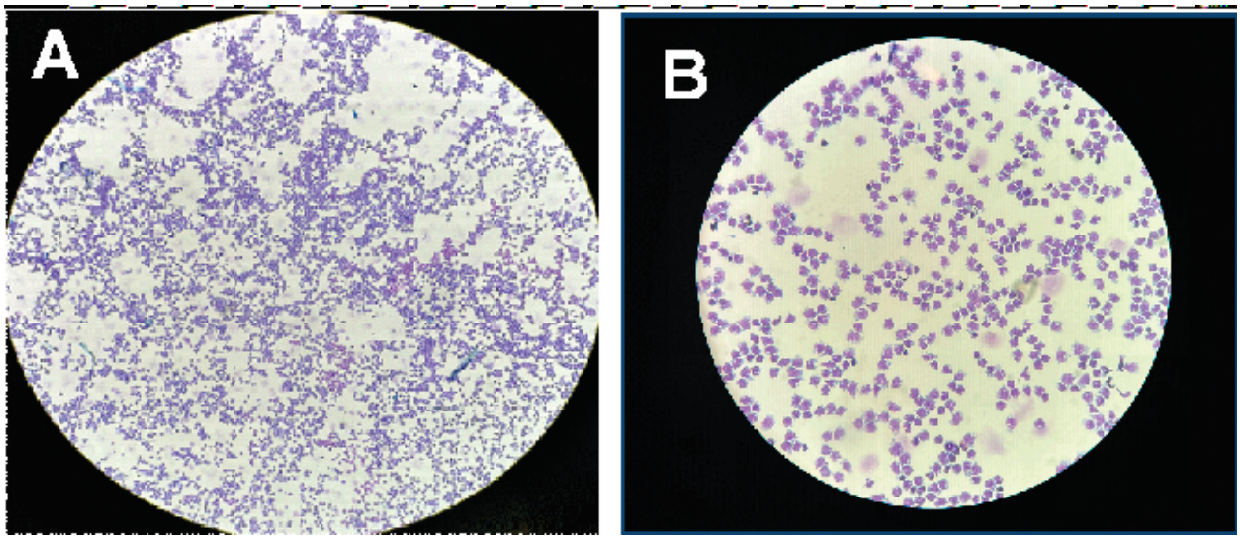

Figure A and B showed Cerebrospinal fluid (CSF) cytology illustrating marked excess of small lymphocytes, many have an irregular nuclear outline.

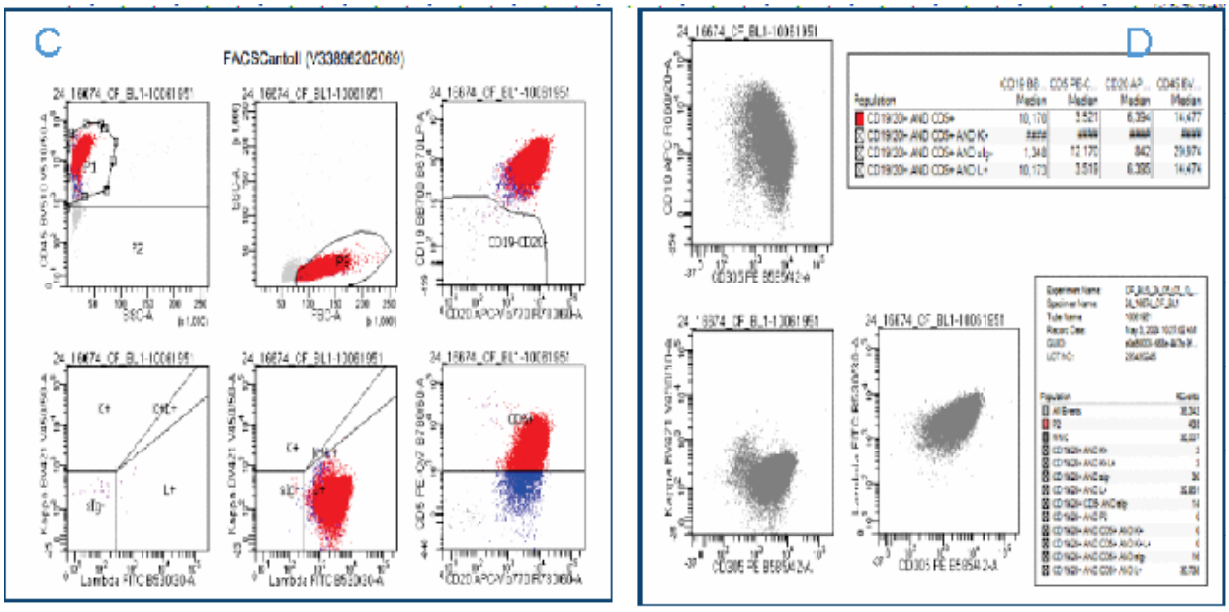

Figure C and D showed a flow cytometry plots showing neoplastic B cell with phenotype consistent with Mantle cell lymphoma.

Treatment

Supportive interventions were implemented to address episodes of agitation or aggressive behaviour presenting a risk to the patient or others. Low-dose lorazepam was administered as an anxiolytic agent to mitigate such behaviours, with due consideration given to the increased risk of falls associated with its usage. Following a comprehensive multidisciplinary evaluation, it was determined that the patient was

not suitable for intensive chemotherapy and would benefit from Ibrutinib 560mg daily, an oral bruton tyrosine kinase (BTK) inhibitor with good CNS penetration. [6, 7] The patient showed a dramatic improvement after 8 months of Ibrutinib. A repeat LP for CSF showed dramatic improvement with sparse lymphocyte morphology (See Figures E and F). The patient showed considerable cognitive improvement during outpatient follow-up. It is pertinent to acknowledge that patients diagnosed with secondary central nervous system lymphoma (SCNSL) typically exhibit a dismal prognosis, with a median survival period of 8.3 months, as reported in the literature[4].

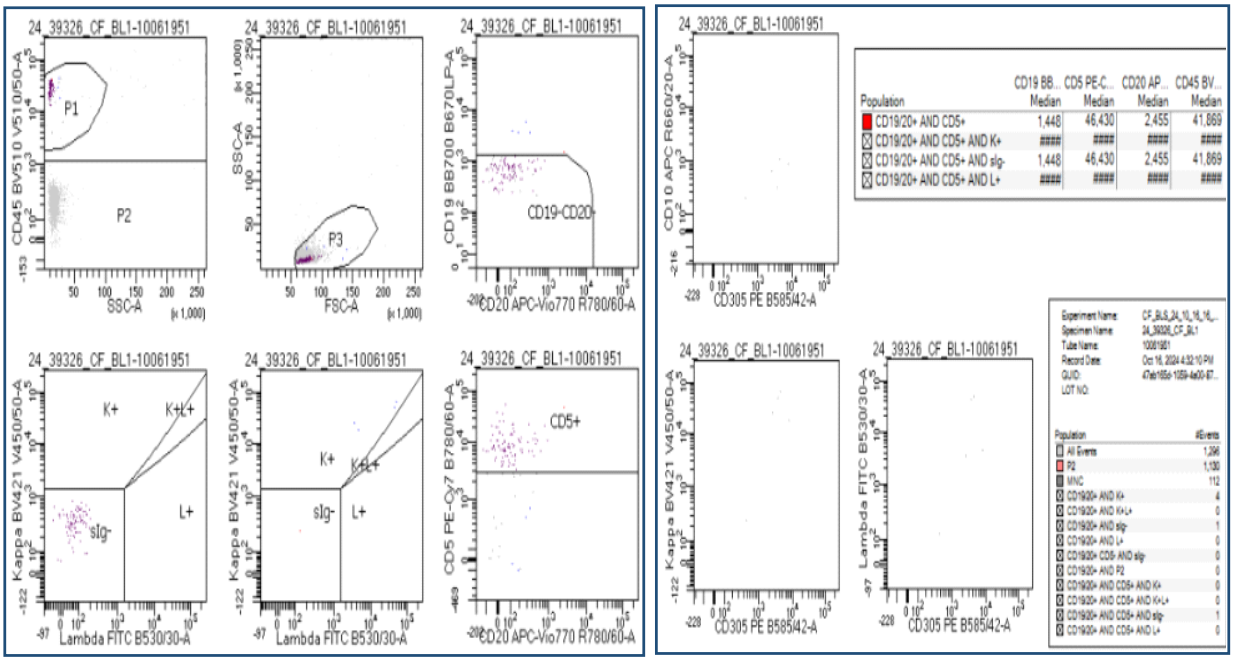

Figure E and F is a repeat flow cytometry plots (8 months with Ibrutinib) showing no evidence of lymphoma (B cells not detected). CD3$^+$ T-cells = 54% of leucocytes, of which 51% are CD4$^+$ helper T-cells and 38% are CD8$^+$ cytotoxic T-cells. NK-cells = 1.8% of leucocytes.

Discussion

The case report underscores a rare instance of CNS involvement in a patient with mantle cell lymphoma (MCL) exhibiting a low proliferation index, as reflected by a Ki-67 score of 10%. While CNS involvement in MCL is uncommon, especially in cases with low proliferative activity, the mechanisms driving MCL's spread to the CNS remain poorly understood. The potential for histological transformation of MCL into a more aggressive form, such as blastoid or pleomorphic variants, has been documented in certain cases. [8] These variants are typically associated with a higher Ki-67 proliferation index and a more aggressive clinical course. [4, 8] However, our case did not demonstrate such transformation, instead consistent with previous observations noted in some of the reported cases by Ferrer *et al.,* [9] where CNS involvement occurred without histological progression to forms that are more aggressive.

Another significant mechanism is the role of Cellular adhesion molecules (CAM) represents another well-established concept that plays a role in the growth and spread of lymphoproliferative disorders. [10, 11] CAMs, such as integrins and selectins, have been implicated not only in the extravasation and homing of malignant cells into the CNS but also in promoting anti-apoptotic signalling that interferes with the body's cellular defense mechanisms. [12] CNS involvement typically emerges later in the disease progression, often after a relapse or when it becomes refractory to initial treatment. [2, 9]

This observation aligns with the broader understanding that MCL is associated with a relatively increased risk of CNS involvement compared to other non-Hodgkin lymphomas, particularly when certain risk factors are present, such as elevated Ki-67, blastoid morphology, or high-risk cytogenetic abnormalities. [9] Despite the recognized risk, CNS prophylaxis remains controversial in MCL. Current guidelines suggest its consideration in patients at high risk for CNS disease, but the overall benefit remains unclear, and there is no robust clinical trial data to definitively support its routine use. [13]

In our case, the patient exhibited a low Ki-67 index, which is generally considered a favourable prognostic marker in MCL, reflecting a less aggressive disease course. [4] As a result, CNS prophylaxis was not deemed necessary at the time of diagnosis. However, this case highlights the potential for CNS involvement even in MCL with a low proliferative index, suggesting that risk stratification and management strategies may need to be revisited to better capture these rare but serious occurrences. Further research is required to determine the most effective preventive and therapeutic strategies for CNS involvement in MCL, particularly in cases where conventional risk factors are absent.

Conclusion

Notwithstanding the absence of detectable abnormalities on imaging studies and a Ki-67 score indicative of a less aggressive disease course, our case report accentuates the necessity for maintaining a low threshold for suspicion of CNS involvement in patients with MCL. Additionally, it emphasizes the importance of conducting thorough CSF analysis in this patient population, irrespective of a seemingly low proliferation index such as Ki-67 and absent radiological evidence, to promptly identify and manage potential CNS complications.

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