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**Primary mucosa-associated lymphoid tissue lymphoma in the midbrain: A case report**

Zhao YR *et al*. MALT lymphoma in the midbrain

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**Abstract**

BACKGROUND

Primary non-dural central nervous system mucosa-associated lymphoid tissue (MALT) lymphoma is a rare indolent B-cell lymphoma, with only a few reported cases worldwide.

CASE SUMMARY

A 33-year-old man presented with a 5-mo history of left blepharoptosis and a 4-mo history of right limb numbness and weakness. Magnetic resonance imaging showed a significantly enhanced mass in the left midbrain. Subsequent positron emission tomography revealed that the lesion had increased glucose uptake. A stereotactic robotic biopsy supported a diagnosis of MALT lymphoma. Then he was treated with radiation therapy (30Gy/15F), which resulted in complete remission. We also review the literature on brain parenchymal-based MALT lymphoma, including the clinical presentation, treatment options, and outcomes.

CONCLUSION

Although there is no consensus on the optimal treatment for this rare disease, patients can respond well when treated with radiotherapy alone.

**Key Words:** Mucosa-associated lymphoid tissue lymphoma; B-cell lymphoma; Central nervous system; Brain parenchyma; Radiotherapy; Case report

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**Core Tip:** Primary central nervous system mucosa-associated lymphoid tissue (MALT) lymphoma is a rare disease, especially in the brain parenchyma. A clear diagnosis is important because it can be cured. This report presents the treatment of MALT lymphoma developing in the midbrain. The patient received local radiotherapy and was in complete remission without apparent adverse effects.

**INTRODUCTION**

Primary central nervous system lymphoma (PCNSL) is an extranodal non-Hodgkin lymphoma (NHL). Approximately 90% of PCNSL cases are diffuse large B-cell lymphomas, defined as aggressive neoplasms[1]. The incidence of primary central nervous system (CNS) indolent lymphoma is much lower, and marginal zone lymphoma (MZL) is comparatively the most common type. Mucosa-associated lymphoid tissue (MALT) lymphoma, also known as extranodal MZL, is one subtype of MZL. It is a B-cell lymphoma originating from mucosal-associated lymphoid tissue, originally described as a low-grade lymphoma in the gastrointestinal tract by Isaacson and Wright[2]. The stomach is the most common primary site of MALT lymphoma; the salivary glands, thyroid, ocular adnexa, lungs, and breasts are other common sites[3]. Primary CNS MALT lymphoma is rare. Most previous case reports and case series have reported primary CNS MALT lymphoma arising in the dura mimicking meningioma or subdural haematoma[4-6]. Rare cases involving the brain parenchyma have been reported, and some patients are clinically misdiagnosed with glioma[7,8]. There are also case reports that describe spinal or both brain and spinal involvement[9,10].

Herein, we present a case of primary CNS MALT lymphoma occurring in the midbrain. To the best of our knowledge, this is the first report of midbrain MALT lymphoma. We also present a review of MALT lymphoma arising in the brain parenchyma, including the clinical presentation, treatment options, and outcomes.

**CASE PRESENTATION**

***Chief complaints***

A 33-year-old human immunodeficiency virus-negative man visited our hospital in April 2020 with left blepharoptosis and right limb numbness and weakness.

***History of present illness***

The patient’s symptoms started 5 mo ago with left blepharoptosis and were not taken seriously. Four months earlier, the patient began to experience right limb numbness and weakness.

***History of past illness***

The patient had a 1-year history of non-insulin-dependent type 2 diabetes mellitus and tuberculosis (TB). TB lesions were confined to the lung. Computed tomography (CT) of the chest showed multiple nodular infiltrations on both sides of the lung, and the main lesion was located in the right upper lobe. He was receiving anti-TB treatment with rifampicin, isoniazid, ethambutol, and moxifloxacin.

***Personal and family history***

There was no special history or personal history. The patient had no known family history of cancer.

***Physical examination***

Neurologic examination revealed right-sided limb numbness at the distal end, the muscle strength of the right limb was weakened (grade 4), and the superficial sensation in the right limb was hypoesthesia, without any other pathological signs.

***Laboratory examinations***

Laboratory evaluations revealed that the level of C-reactive protein was 21.6 mg/L, the erythrocyte sedimentation rate was 33 mm/h, the blood glucose level was 6.8 mmol/L, and the T-SPOT-TB test was positive.

***Imaging examinations***

A CT scan, as well as a magnetic resonance imaging (MRI) scan, revealed a significantly enhanced mass of 1.9 cm × 1.8 cm in size in the left midbrain (Figure 1A-C). Flaky edema could be seen around the lesion, and no signal abnormalities were noted elsewhere in the brain. Due to the relatively homogeneous enhancement of the lesion, the clinical impression was that the lesion most likely represented a lymphoma. Fluorodeoxyglucose positron emission tomography (PET) showed that the maximum standardized uptake volume (SUV) was 7.48, which matched with an enhanced lesion of the brain (Figure 1D). At the same time, a lesion in the right third fore rib was identified, and the maximum SUV was 5.70.

***Further diagnostic work-up***

A stereotactic robotic biopsy of the brain was performed by the left frontal-lateral paraventricular approach on June 4, 2020. The patient was in a supine position under general anesthesia. The biopsy needle was implanted into the center of the lesion according to the preoperative plan, and the pathological tissue was cut out. The histopathological evaluation of the midbrain lesion supported a diagnosis of indolent B-cell lymphoma. The morphology indicated infiltration of low-grade B-cell lymphoma with a perivascular growth pattern (Figure 2). Immunohistochemical detection showed CD20+, CD79a+, and CD38+/- results but negativity for CD3 and CD5. The Ki-67 proliferation rate was 10%-20% (Figure 3), and the other results were LCA (+), CD138 (-), CD21 (-), CD68 (scattered +), PAX-5 (+), and TdT (-). Polymerase chain reaction (PCR) analysis detected clonal rearrangement of the immunoglobulin heavy chain gene (*IgH*) (Figure 4). DNA sequencing indicted no mutations in the B-cell lymphoma genes, including *Bcl-2*.

Routine biochemical examination of cerebrospinal fluid (CSF) from lumbar puncture showed a cell count of 132 × 106/L, leucocyte count of 32 × 106/L, glucose level of 3.94 mmol/L, protein level of 54 mg/dL, and chlorine level of 124 mmol/L. The pathology of CSF was scattered lymphocytes, erythrocytes, and mononuclear cells. Bone marrow aspiration and biopsy with flow cytometry were normal, and ophthalmologic evaluations revealed no abnormalities. However, the rapid urease test for *Helicobacter pylori* was positive. Then, a rib lesion biopsy was performed on August 10, 2020.

**FINAL DIAGNOSIS**

The final pathological result was MALT lymphoma. The pathology of the rib was callus formation.

**TREATMENT**

The patient received local external beam radiotherapy without chemotherapy, and target delineation was based on the fusion image obtained from simulated CT and MRI. The gross target volume (GTV) was defined on MRI and PET, excluding the edema zone. The planning GTV (PGTV) was the GTV plus 3 mm of setup margin. Initially, we intended to administer a radiotherapy dose of 24 Gy, but re-examination by MRI showed residual lesion during the treatment course after 20 Gy was administered (Figure 5). We added 6 Gy to the total dose of 30 Gy. Radiotherapy was administered in the period from September 7, 2020 to September 25, 2020.

**OUTCOME AND FOLLOW-UP**

One month after radiotherapy, follow-up MRI showed no abnormal enhancement, and perfusion-weighted imaging showed no hyperperfusion (Figure 6). After 6 mo of follow-up, the patient's clinical symptoms significantly improved. The patient’s muscle strength recovered to grade 5-, and the superficial sensation was normal. He could walk normally, but he could not hold heavy things in his right hand and sometimes felt numbness in the right limb at the distal end. The follow-up data showed no recurrence.

**DISCUSSION**

MZL is an NHL arising from post-germinal center marginal zone B cells. According to the 2016 World Health Organization classification, MZL is subdivided into three types: Extranodal MZL or MALT lymphoma, nodal MZL, and splenic MZL[11]. MALT lymphoma is the most typical type, but primary CNS MALT lymphoma is an extremely rare entity, especially in the brain parenchyma. Initial studies showed that the most common location was the dura[12]. Only seven cases with brain parenchyma involvement have been reported, including our patient. The site of origin was the midbrain in our patient. The lesion location and clinical characteristics of the other six patients are shown in Table 1. Clinical symptoms are not specific, depending on the site of the lesion.

The CNS has no mucosa or MALT tissue, and dural-based MALT lymphoma can be explained by the embryological analogy that meningothelial cells of the arachnoid membrane could be analogous to epithelial cells, where MALT lymphomas arise[13-16]. However, non-dural-based MALT lymphoma is questionably explained by this theory. It is currently believed that the etiology of MALT lymphoma is related to chronic immune stimulation caused by infection or inflammation. For instance, gastric MALT lymphoma is associated with *Helicobacter pylori*, Sjögren syndrome, or Hashimoto thyroiditis and carries a significant risk for the development of MZL[17]. Interestingly, our patient had a 1-year history of TB and received standardized anti-TB treatment. After admission, the *Helicobacter pylori* examination was positive, and the patient also underwent *Helicobacter pylori* eradication therapy. The pathogenesis may be explained by the inflammation-based theory. However, we have no direct evidence that primary CNS MALT lymphoma is associated with *Mycobacterium tuberculosis* or *Helicobacter pylori* infection.

The diagnosis of MALT lymphoma should be confirmed by histopathological and immunohistochemical features. Differential diagnoses include lymphoplasmacytic lymphoma (LPL) and follicular lymphoma. The immunohistochemistry results of follicular lymphoma usually indicate positivity for CD10 and Bcl-2[18]. LPL and MALT lymphoma have similar morphological and immunohistochemical profiles, but relative to MALT lymphoma, LPL typically involves the bone marrow and is associated with Waldenstrom’s macroglobulinemia[19]. Our patient’s immunohistochemical findings indicated CD20+ and CD79a+ results, the Ki-67 index was 10%-20%, and there was no bone marrow involvement and no clinical history of Waldenstrom’s macroglobulinemia. At the same time, clonal rearrangement of *IgH* was detected by PCR. According to these findings, the diagnosis was most consistent with MALT lymphoma.

There is no standard treatment for CNS MALT lymphoma. The treatment modalities reported in the existing literature include surgery, radiotherapy, and chemotherapy. As shown in Table 1, among patients with lesions arising from the brain parenchyma, three of the six patients received chemotherapy: Two patients had stable disease, one showed tumor remission, and the other three received radiotherapy and had a complete response. In other words, radiotherapy may provide superior outcomes in parenchymal-based cases[20].

MALT lymphoma tends to be indolent and radiosensitive. In 2011, a randomized phase III trial reported that there was no difference in clinical efficacy between radiotherapy doses of 24 Gy and 40-45 Gy for indolent NHL[21]. Currently, reduced-dose (24-30 Gy) radiotherapy is preferred for indolent lymphoma. Unlike high-grade CNS lymphoma, the role of intrathecal chemotherapy or systemic chemotherapy in low-grade CNS lymphoma currently remains unclear[22]. Because of the particularity of the lesion location, the lesion in our patient could not be totally resected by surgery and he achieved complete remission by radiotherapy alone. Involved-site radiation therapy is an effective initial treatment for extranodal MZL[23]. The radiation field in our case included only the primary lesion demonstrated on MRI and PET, not as reported in the prior literature[7,8,13]. Reexamination during treatment showed residual disease, so we believe that 1 mo after the end of radiotherapy might be the best timing to evaluate the effect.

Considering the low biological and clinical aggressiveness of MALT lymphoma, it is curable in cases of localized disease. The data showed that there was no recurrence during the follow-up of up to 22 mo in primary left basal ganglia MALT lymphoma with radiation therapy[8]. The follow-up of our patient was short (6 mo), and we will continue to pay attention to any changes in the patient's condition.

**CONCLUSION**

In conclusion, primary non-dural CNS MALT lymphoma is a rare disease. The exact mechanism is still unclear. Diagnosis is based on morphological and immunohistochemical findings. It is radiosensitive and can be cured with radiotherapy. Chemotherapy alone cannot achieve good treatment outcomes. Due to the small number of cases, it is difficult to draw conclusions regarding the use of radiotherapy as the primary treatment for brain parenchymal-based MALT lymphoma. More clinical data are needed to confirm this opinion.

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**Footnotes**

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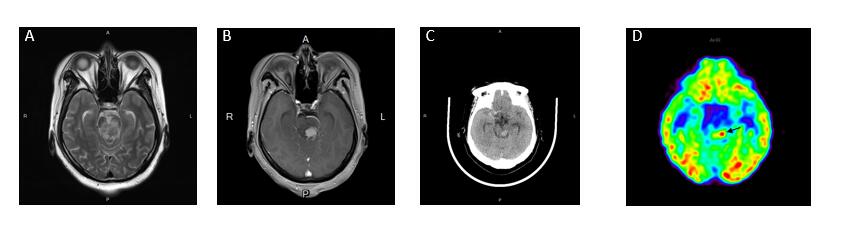
Grade C (Good): C, C

Grade D (Fair): D

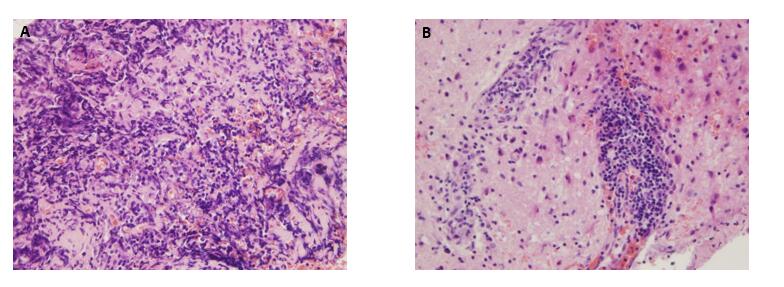
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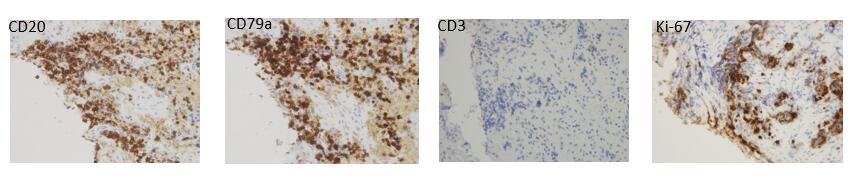
**Figure Legends**



**Figure 1 Imaging before treatment.** A: Axial T2-weighted image shows heterogeneous intensity in the midbrain, and the midbrain aqueduct was compressed; B: Contrast-enhanced magnetic resonance imaging showing a significantly enhanced 1.9 cm × 1.8 cm-sized mass in the left midbrain; C: The lesion had high density on computed tomography; D: Fluorodeoxyglucose positron emission tomography showing that the lesion had increased glucose uptake (arrow). The maximum standardized uptake volume was 7.48.

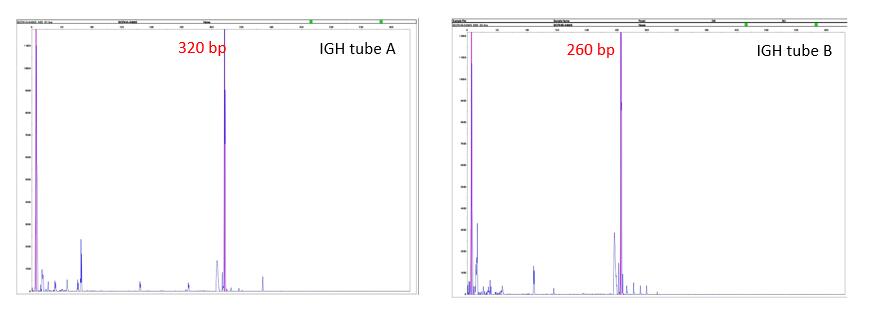


**Figure 2 Histologic features.** A biopsy showed perivascular infiltrates of small-sized lymphocytes. A: Hematoxylin and eosin staining, 20 ×; B: Hematoxylin and eosin staining, 40 ×.

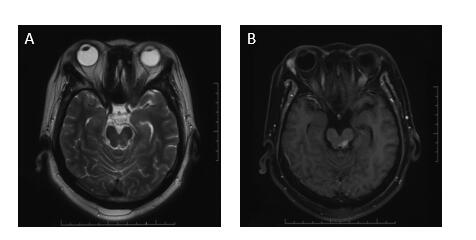


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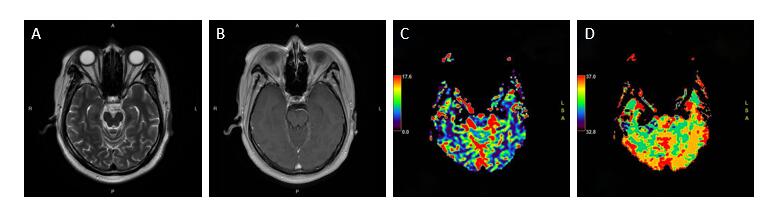
**Figure 3 Immunohistochemical features.** The tumor cells were positive for B-lymphocyte marker CD20/CD79a and negative for T-lymphocyte marker CD3. 10%-20% of the cells were positive for Ki-67. A: CD20; B: CD79a; C: CD3; D: Ki-67.



**Figure 4 IdentiClone IGH+IGK B-cell clonality polymerase chain reaction test.** The detection of clonal immunoglobulin heavy chain gene rearrangement was positive.



**Figure 5 Magnetic resonance imaging reexamination after 20 Gy radiotherapy.** A: T2-weighted image showing mixed signal in the left midbrain; B: Contrast-enhanced magnetic resonance imaging showing residual lesion.



**Figure 6 Follow-up magnetic resonance imaging.** A:T2-weighted image showing no mass effect; B: Contrast-enhanced magnetic resonance imaging showing no abnormal enhancement; C and D: Perfusion-weighted imaging showing no abnormal perfusion.

**Table 1** **Clinical summary of patients with primary non-dural central nervous system mucosa-associated lymphoid tissue lymphoma**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Ref. | Age (yr) | Sex | Location | Presentation | Treatment | Outcome |
| Tu *et al*[13] | 66 | M | R, frontal | Seizures | Radiation (WBRT, dose NA) | CR |
| Park *et al*[8] | 18 | M | L, basal ganglia | Right-sided central facial nerve palsy, right-sided weakness, dizziness, dysarthria | Radiation (CTV = GTV + 15 mm, PTV = CTV + 5 mm; 30.6 Gy/17F) | CR |
| Papanicolau-Sengos *et al*[14] | 70 | M | L, posterior  putamen | Right extremity numbness, dysarthria, blurry vision | Chemotherapy (dexamethasone, temozolamide, rituximab) | SD |
| Schiefer *et al*[15] | 39 | F | R, frontal | Seizures | Chemotherapy (intrathecal: Methotrexate, cytarabin, dexamethasone; Intravenous: High-dose methotrexate) | SD |
| Aqil *et al*[7] | 48 | M | L, frontal | Seizures, memory loss | Radiation (WBRT, 24 Gy; GTV boosted 6 Gy) | CR |
| Ueba *et al*[10] | 53 | M | R, temporal; L, occipital; spinal cord | Recent memory disturbance, gait disturbance, urinary incontinence | Chemotherapy (high-dose methotrexate, cytoarabine) | PR |

WBRT: Whole brain radiation therapy; CTV: Clinical target volume; GTV: Gross target volume; PTV: Planning target volume; CR: Complete remission; PR: Partial remission; SD: Stable disease; NA: Not available; M: Male; F: Female.



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