

Long-term Survival of Diffuse Large B Cell Lymphoma of the Trigeminal Region Extending to the Meckel's Cave Treated by CHASER Therapy: Case Report

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Abstract

A 52-year-old man with a history of malignant lymphoma of the cecum presented with lancinating facial pain in the left. Magnetic resonance imaging (MRI) revealed a tumor in the Meckel's cave extending along the trigeminal nerve. The tumor was partially removed via left retrosigmoid lateral suboccipital craniotomy. Histological examination showed findings consistent with diffuse large B cell lymphoma, which was later confirmed to be metastatic lesion from the cecal lesion. Postoperative chemotherapy with cyclophosphamide, high dose, cytarabine, steroid (dexamethasone), etoposide, and rituximab (CHASER) followed by whole brain irradiation (30 Gy) resulted in complete remission. Although facial pain persisted, the patient's general condition remained favorable and he did not experience recurrence over the 51 month follow-up period. Histological confirmation and awareness of malignant lymphoma are very important to determine the therapeutic strategy and to avoid misdiagnosis or delayed diagnosis. Long-term survival of patients with metastatic malignant lymphoma in the Meckel's cave extending along the trigeminal nerve was very rare. In addition, metastatic malignant lymphoma in the extra-axial and peripheral nervous tissue might be different from primary central nervous system lymphoma in the white matter, since the efficacy of chemotherapeutic agents against malignant lymphomas in the extra-axial regions is not attenuated by the blood brain barrier.

Key words: malignant lymphoma, trigeminal neuralgia, Meckel's cave, cyclophosphamide/high dose cytarabine/steroid (dexamethasone)/etoposide/rituximab (CHASER) therapy

Introduction

Primary central nervous system lymphoma (PCNSL) usually arises in the white matter of the brain. Most of the lesions are supratentorial in a central location near an ependymal surface, but cases can sometimes occur in extra-axial regions.^{1–6)} Despite the use of high-dose methotrexate and radiation therapy over the past decade, the prognosis for patients with PCNSL remains dismal with a mean overall survival of 15 to 45 months, even after extensive chemotherapy and radiation.⁷⁾ Long-term survival is extremely rare in such patients.^{2,4)}

The present report describes a rare case of metastatic lymphoma in the Meckel's cave with perineural extension along the trigeminal nerve. Cyclophosphamide, high

dose cytarabine, steroid (dexamethasone), etoposide, and rituximab (CHASER) therapy followed by whole brain irradiation resulted in long-term survival without adverse effect.

Case Report

A 52-year-old man presented with a left facial pain in May 2009. His medical history was notable for malignant lymphoma of the cecum that was treated by rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) therapy for eight cycles resulting in complete remission 1 year prior to his current presentation. Magnetic resonance imaging (MRI) showed a tumor in the left Meckel's cave with extension along the trigeminal nerve. The tumor was isointense on T₁- and T₂-weighted imaging with homogenous enhancement with gadolinium (Fig. 1A–D). To confirm the diagnosis, retrosigmoid lateral

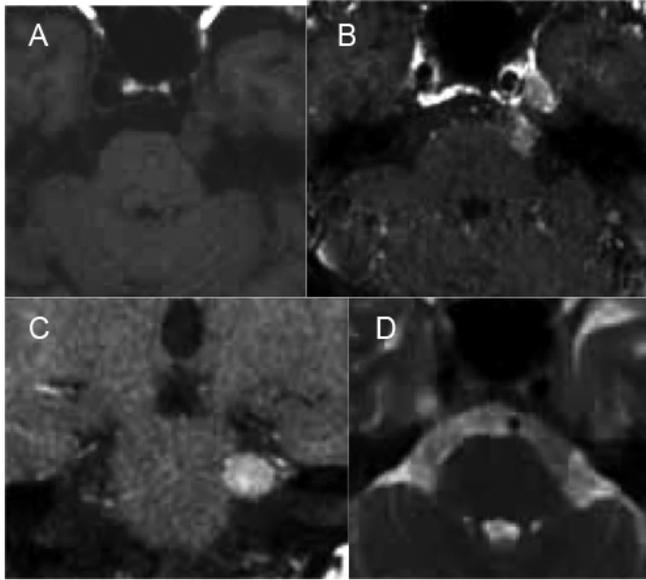


Fig. 1 Preoperative T₁-weighted magnetic resonance (MR) imaging showing an isointense (A) and large heterogeneously enhanced large tumor in response to gadolinium on axial (B) and coronal imaging (C) along the left trigeminal nerve. T₂-weighted MR image (D) shows an isointense mass.

suboccipital craniotomy was performed. The tumor was pinkish and encased the trigeminal nerve, and extended into the Meckel's cave. The tumor was easily detached from the trigeminal nerve fiber and was partially removed (Fig. 2A,B). Histological findings revealed the bizarre and large tumor cells were arranged in solid areas and predominant of nuclei with atypia and mitoses (Fig. 3A). Many of tumor cells were positive for CD79 α (Fig. 3B), which was compatible with a diagnosis of diffuse large B cell lymphoma (DLBCL) that had metastasized to the Meckel's cave and the trigeminal nerve. Postoperatively, the patient's facial pain persisted but his postoperative course was uneventful. The patient received further CHASER therapy for three additional cycles resulting in complete remission. Since the regrowth of the tumor in the Meckel's cave was detected by MRI, whole brain irradiation (30 Gy) was administered, and the patient obtained complete remission again. Four years after biopsy, he remains alive with persistent left facial numbness. No recurrent tumor was found on MRI (Fig. 4A–D).

Discussion

The present report describes a case of metastatic malignant

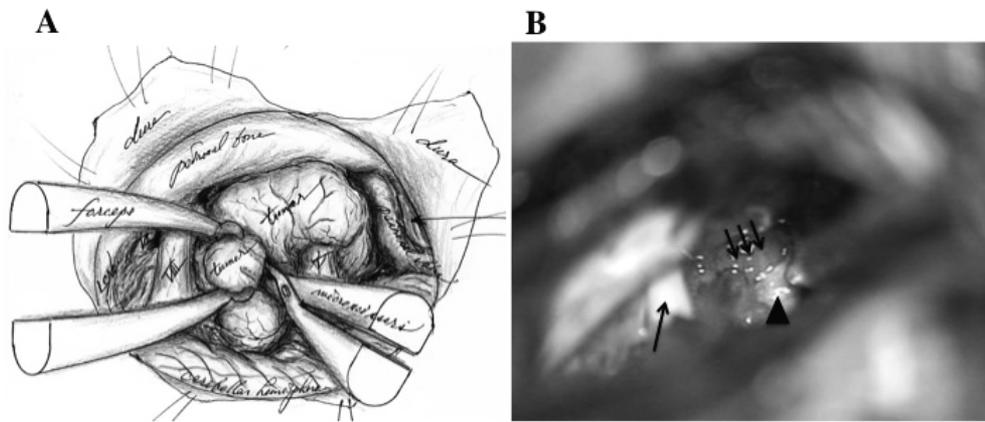


Fig. 2 Operative schema (A) and photograph (B). The trigeminal nerve (*arrowhead*) was encased by the pinkish tumor (*triple small arrow*). The tumor was easily detached from the nerve fiber. Facial-auditory nerve complex (*long arrow*) coursed into the internal auditory meatus.

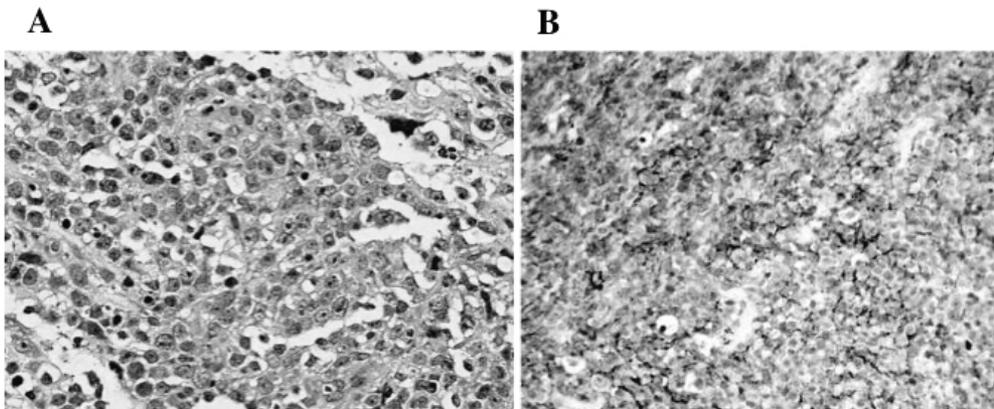


Fig. 3 Histological findings revealed bizarre and large tumor cells were arranged in solid areas. A: Nuclei with atypia and mitoses are present. B: Many of tumor cells were positive for CD79 α antibody.

lymphoma along the peripheral nerve and in the extra-axial skull base. Many kinds of tumors can occur in the cerebellopontine angle in Meckel's cave including meningioma, trigeminal neurinoma, and epidermoid and metastatic carcinoma. These tumors are very difficult to obtain early diagnosis based only on preoperative neuroimaging. The clinical symptom and MR (magnetic resonance) images associated with the present tumor were similar to those of a trigeminal neurinoma. Previous reports have described misdiagnosis of malignant lymphoma as schwannoma or skull base meningioma.^{4,5)} Therefore, histological confirmation of tumors in this region is required to determine the appropriate treatment strategy, which might include any combination of surgery, radiosurgery, conventional radiation, or chemotherapy. Several reports have described primary and metastatic lymphomas at the skull base.⁸⁻¹¹⁾ Occasionally, malignant lymphoma

can produce perineural infiltration from the trigeminal nerve via the foramen ovale or transorbitally via the superior and inferior orbital. Malignant lymphoma in the trigeminal region or cerebellopontine angle can present in three patterns: (1) an extra-axial tumor, (2) an intra-axial tumor extending into the cerebellopontine angle, or (3) as leptomeningeal dissemination.¹²⁾ In the present case based on operative finding, the tumor was an extra-axial mass, and no tumor cells were detected in cerebrospinal fluid (CSF) cytology.

In the present case, primary malignant lymphoma was originated in the cecum and was completely cured in response to R-CHOP therapy. Since metastatic intracranial lymphoma is rare, we selected direct surgery to obtain definitive histological diagnosis. The present tumor was confirmed to be recurrent metastatic malignant lymphoma invading the middle cranial fossa via the trigeminal nerve. Based on histological diagnosis and clinical course of the present case, we selected CHASER therapy along with whole brain irradiation, as the tumor recurred following R-CHOP therapy. The patient experienced remission in response to treatment, but recurrence of the tumor in the Meckel's cave was subsequently detected by MRI, and whole brain irradiation was administered, resulting in complete remission. As shown in Table 1, additional whole brain irradiation obtained long-term survival of patients with intracranial malignant lymphoma.

According to the standard treatment guidelines,¹³⁾ PCNSL should be treated with high dose methotrexate combined with radiation therapy. Kinoshita et al. described a similar case of primary lymphoma located in the trigeminal region that experienced complete remission in response to high-dose methotrexate therapy and radiation,⁵⁾ but the patient died 14 months after treatment probably due to multiple organ failure. Quality of life for patients who survive PCNSL is not always good, because treatments can have adverse effects on the white matter, and thereby cause neurological deficits and mental disorders.

Fortunately, the lymphoma in the present case was very sensitive to treatment with CHASER therapy followed

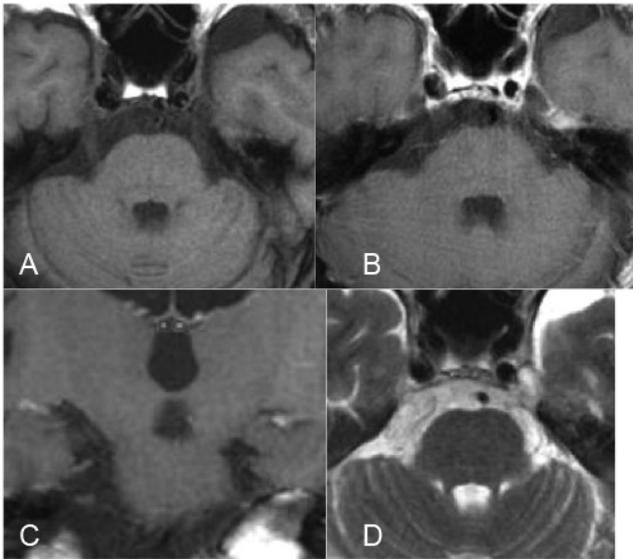


Fig. 4 Four years after operation, no recurrent tumors were present observed on T₁-weighted (A, B) or T₂-weighted (C) magnetic resonance (MR) imaging with gadolinium enhancement.

Table 1 List of malignant lymphoma in the trigeminal region

Age/Sex	Location	Treatment	Follow-up period	Clinical outcome	References
77/M	Lt. prepontine cistern-cavernous sinus	RT, MTX, PSL	31 months	Dead	Nakatomi (1996) ⁶⁾
40/F	Lt. Meckel's cave-cavernous sinus	RT, CHOP	N.D.	N.D.	Abdel Aziz (1999) ¹⁾
55/M	Lt. Meckel's cave-infratentorial	RT, high-dose MTX	14 months	Dead	Kinoshita (2003) ⁵⁾
52/F	Lt. Meckel's cave-foramen rotundum	mass reduction	N.D.	N.D.	Bulsara (2005) ¹²⁾
50/M	Rt. prepontine cistern-cavernous sinus	RT, high-dose MTX, AraC	C.R.	C.R.	Iplikcioglu (2006) ³⁾
60/M	Lt. prepontine Cistern-Meckel's cave	RT, high-dose MTX	43 months	C.R.	Akaza (2009) ²⁾
52/M	Lt. prepontine Cistern-Meckel's cave	RT, CHASER	51 months	C.R.	Present case

AraC: cytarabine, CHASER: cyclophosphamide/high dose cytarabine/steroid (dexamethasone)/etoposide/rituximab, CHOP: cyclophosphamide/doxorubicin/vincristine/prednisolone, C.R.: complete remission, F: female, GKS: gamma knife surgery, M: male, MTX: methotrexate, N.D.: not described, PSL: prednisolone, WBRT: whole brain radiation therapy.

by whole brain irradiation. The adverse effects of this regimen were mild and included nausea and grade 4 of thrombocytopenia and leukocytopenia, which was not lethal. In addition, the tumor was located in the extra-axial skull base along the peripheral nerve. Since the tumor was located outside the central nervous system, the blood brain barrier did not interfere with the efficacy of chemotherapy regimen. Therapeutic agents are more effective when the metastatic intracranial lymphoma is located in the peripheral nervous tissue rather than in the white matter of the brain. In addition, metastases to other organs were not detected. These factors might have contributed to the favorable survival seen in the present case. However, the fact that there was a tumor in the Meckel's cave and cerebellopontine cistern should be carefully monitored to detect CSF dissemination is important. Patients with disease within the CSF should receive intrathecal chemotherapy.

In conclusion, malignant lymphoma in the trigeminal region is very rare, but it should be included with the differential diagnosis of tumors in the Meckel's cave. Histological examination of a needle biopsy or surgical specimen should be obtained in patients with new lesions and a past history of systemic lymphoma in order to avoid misdiagnosis or delayed diagnosis.

Conflicts of Interest Disclosure

All authors have no conflicts of interest.

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