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Biopsy-proven Primary CNS Lymphoma in the Medulla Oblongata Presenting as Anorexia

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Abstract

Eating disorders caused by brain tumors are infrequently seen. Recent studies revealed that a neurocircuit from the nucleus tractus solitarius of the medulla oblongata to the hypothalamus participates in the control of appetite. Among brain tumors, those located in the brain stem, especially a solitary one in the medulla oblongata, are rare. Tumors in the brainstem are generally considered gliomas, and with the difficulty in reaching the lesion, treatment without histological confirmation is often performed. However, there are a few reported cases of medulla oblongata tumors other than gliomas. We describe a case of a 56-year-old man who presented with persistent anorexia. Magnetic resonance images revealed a solitary tumor in the medulla oblongata. After several examinations, craniotomy for the biopsy of the tumor using the cerebellomedullary fissure approach was carried out and primary central nervous system lymphoma (PCNSL) was histologically proven. The patient was treated with effective adjuvant therapy and was discharged home after he recovered from the symptoms. No tumor recurrence was recognized 24 months after surgery. A PCNSL arising only from the medulla oblongata is very rare, and anorexia can be an initial symptom of a tumor in the medulla oblongata. Surgical intervention is safely achieved and is a key to a better clinical outcome.

Keywords: primary central nervous system lymphoma, medulla oblongata, anorexia, nucleus tractus solitarius, open biopsy

Introduction

Anorexia, a type of eating disorder, results from mental disorders such as fear of fatness or body image disturbance in most of the cases. However, there exist cases of anorexia caused by intracranial tumors, traumatic injuries, or epileptic foci. It has long been considered that the hypothalamus is responsible for that disorder. However, recent findings reveal that a neurocircuit from the nucleus tractus solitarius (NTS) of the medulla oblongata to the right frontal cortex through the hypothalamus participates in the control of appetite.[1)] Brainstem tumors are infrequently found, and those located exclusively in the medulla oblongata are even rarer. Most common brainstem tumors are diffuse gliomas,[2)] and chemotherapy and radiotherapy for gliomas are often started without histological confirmation because of the high frequency of gliomas and the difficulty in performing safe and accurate biopsies.[3)] However, not all brainstem tumors are gliomas, and different treatments should be employed for other disorders. Primary central nervous system lymphoma (PCNSL), a relatively rare brain tumor, is an aggressive disease of which the median survival time from diagnosis is less than 60 months.[4)] On some occasions, PCNSL is detected with multiple brain lesions, and although not usually, it involves the medulla oblongata as one of them. However, a single PCNSL lesion in the medulla oblongata is exceedingly rare. Here, we present a case of a PCNSL arising solely from the medulla oblongata, which had anorexia as its initial symptom, which was diagnosed by surgical intervention, and which was successfully treated with chemotherapy, followed by radiotherapy.

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Case Report

A 56-year-old man visited a local hospital complaining of anorexia for over 6 months. He recognized gradual worsening of anorexia and had been examined by a primary-care physician, but no abnormality was found in the hematological, radiological, and gastroenterological studies. As his mental condition was well, anorexia nervosa was deemed unlikely. During that period, he lost weight from 75 to 65 kg but did not experience nausea or vomiting, and anorexia was the only symptom until 1 month before his visit to that hospital when he experienced bilateral sensory disturbance and heat sensation in the occipital and neck region. A few days before, he found slight difficulty in swallowing. Therefore, head magnetic resonance (MR) imaging study was conducted. Plain MR images revealed a tumor in the dorsal medulla oblongata, and then, he was transferred to our institution. On admission, he was alert and there was no motor laterality, but decreased sensations of warmth, pain, touch, and vibration were observed predominantly in the lower limbs. The MR images showed a homogenously enhancing tumor in the dorsal medulla oblongata (Fig. 1). No other intracranial lesions were detected. Routine blood tests, including lactate dehydrogenase (LDH), showed no abnormalities, and serum tumor markers such as CA19-9, progastrin-releasing peptide, soluble interleukin-2 receptor (sIL-2R), and β-2 microglobulin (B2MG), and autoantibodies were in normal range. Cerebrospinal fluid (CSF) collected with lumbar puncture showed a cell count of 55 cells/μL, protein of 0.05 g/dL, and glucose of 51 mg/dL. CSF cytology examination revealed scattered lymphocytosis with enlarged and irregular nuclei, and was class III. On hospital day 2, the patient began to have repeated orthostatic hypotension and syncope while standing, urinating, and bathing. On the fifth day, sleep apnea also appeared. Aiming at improving those symptoms, 8 mg/day of betamethasone administration began, but no obvious improvement was observed. From the results above, malignant glioma was suspected.

To confirm the diagnosis, a midline suboccipital craniotomy for the biopsy of the lesion was performed on day 13. By the exposure of the dorsal surface of the medulla after removing the tela choroidea and lifting up bilateral cerebellar tonsils, a bulging of the tumor covered with a thin ependymal layer in grayish-red was observed (Fig. 2A). Then, some tumor specimens were carefully resected. There were no surgical and postoperative complications. Histopathologic examination showed an accumulation of large atypical cells with large round to oval nuclei with mitotic figures, and cellularity was high, but apparent necrosis or apoptosis was not observed (Fig. 2B). Immunohistochemistry for CD20, Bcl-6, and MUM-1 was positive, and that for CD10 was negative (Fig. 2C-F). The MIB-1 labeling index was greater than 90% (Fig. 2G). From those findings, a diagnosis of a non-GCB-type diffuse large B-cell lymphoma (DLBCL) was made. Following the negative lymph node involvement shown by chest and abdominal scan and unremarkable bone marrow biopsy, a definitive diagnosis of PCNSL was achieved.

Then, the patient received chemotherapy using rituximab, methotrexate, procarbazine, and vincristine (R-MPV) for five cycles and whole brain radiotherapy (23.4 Gy/13 fr), followed by high-dose cytosine arabinoside (AraC) as a consolidation therapy. Gradually, his appetite was restored, and symptoms of orthostatic hypotension and syncope improved. The patient was discharged home 6 months after surgery and then returned to work. MR images showed the disappearance of the enhancing tumor mass (Fig. 3A-D). Twenty-four months after the surgery, there was no evidence of the disease.

Discussion

To sustain life, food intake is essential. Loss of appetite, anorexia, occurs when there is enough nutrition. Several mechanisms of appetite control are advocated. Among them, recent research proved that the NTS in the medulla oblongata plays a key role.[5] It is now revealed that a molecule called cholecystokinin (CCK), produced by the small intestine, activates NTS, followed by signal transduction to the hypothalamus,[6] resulting in loss of appetite. Anorexia due to brain tumors has already been reported, and in most cases, those tumors are located in the hypothalamus.[1,7] There are also a few case reports of anorexia caused by tumors in the medulla oblongata such as glioblastoma[8] and germinoma,[9] and in the latter case, as in ours, the patient's appetite was restored after treatment (Table 1). Generally, the reported symptoms of medulla oblongata tumors are as follows: headache, nausea/vomiting, gait disturbance, nystagmus, lower cranial nerve palsy, and dysesthesia.[10-13] Orthostatic hypotension[14] or sleep apnea[8] caused by medulla oblongata tumors are also reported so far. This patient experienced other symptoms that are commonly acknowledged in medulla oblongata lesions during the disease course.

Brainstem tumors account for less than 2% of all brain tumors.[2,15] Among them, tumors arising from the medulla oblongata constitute only 0.8%, and most of them are gliomas. Other than diffuse gliomas or glioblastomas, so far, more than 65 cases of gangliogliomas,[10] 15 cases of germinomas,[12] 5 cases of teratomas,[13] and 5 cases of neurosarcoidosis[16] in the medulla oblongata have been reported. A PCNSL arising solely from the medulla oblongata is extremely infrequent, and by our thorough literature search, only two cases of biopsy-confirmed[17] and a case of suspected (diagnosed by MR imaging findings only)[18] PCNSLs in the dorsal medulla oblongata were found.

PCNSL is an aggressive malignancy arising exclusively in the CNS, that is, the brain parenchyma, spinal cord, eyes, cranial nerves, and/or meninges. PCNSLs represent 4% of

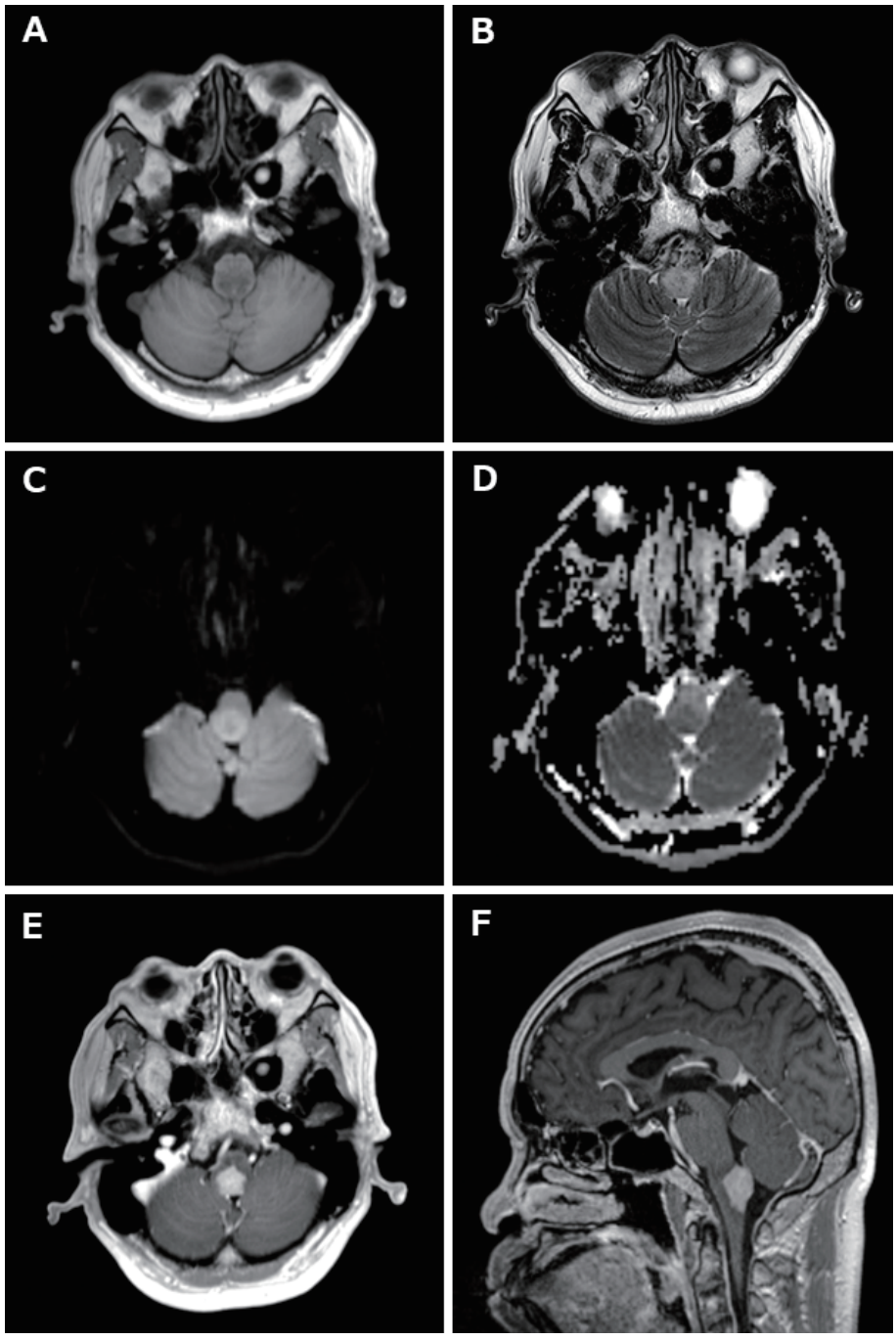

Fig. 1 Initial brain magnetic resonance (MR) images showing a space-occupying lesion in the medulla oblongata. It was observed in hypointensity on the T1 weighted image (T1WI) (A) and hyperintensity on T2WI (B) but only a minor elevation of signal intensity on the diffusion-weighted image (DWI) (C) and with poor apparent diffusion coefficient reduction (D). It was homogenously enhanced with gadolinium, and axial (E) and sagittal (F) images are shown.

intracranial neoplasms and 4%-6% of all extra nodal lymphomas. Ninety-five percent of PCNSLs are DLBCL.[19] Typical neuroimaging shows homogenous Gd enhancement and strong diffusion restriction.[20] Serum levels of sIL-2R and B2MG are useful for the diagnosis.[21] For the treatment, a recent strategy using R-MPV dramatically improved patient survival, and corticosteroid has a cytotoxic effect on lymphoma cells. Here, tumor location and biological characteristics such as nonspecific serum markers and steroid-refractory nature caused a smaller possibility of PCNSL prior to biopsy. In addition, despite homogeneous enhancement, no strong diffusion restriction supported this notion. Diffuse gliomas represent 56% to 86% of brainstem tumors.[3] Considering the frequency of

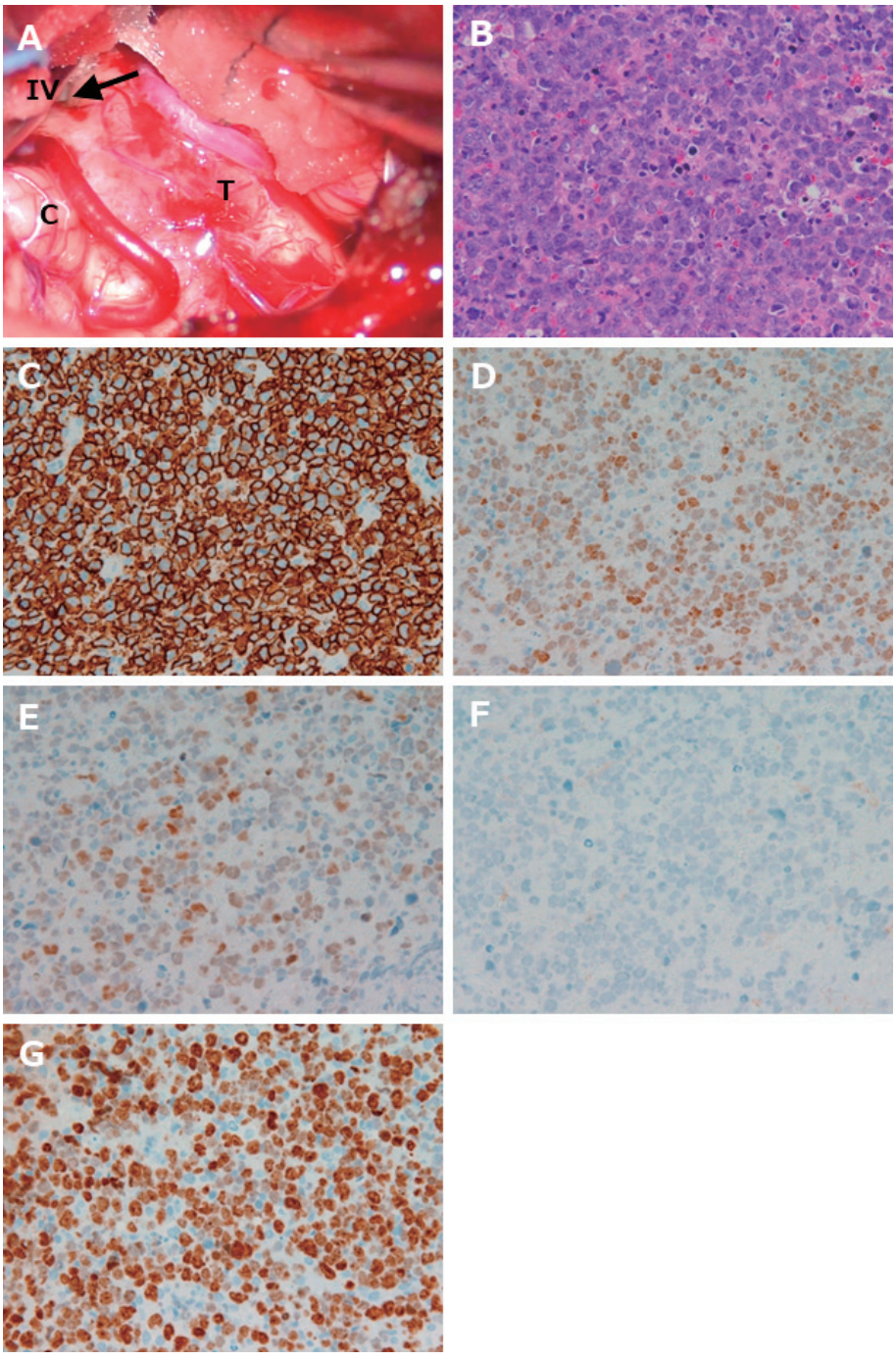

Fig. 2 A: Intraoperative view of the tumor and the surrounding structure. Note that the tumor (T) is seen at the bottom of the floor of the fourth ventricle (IV) in grayish-red whereas the cerebellar hemisphere (C) is in normal brain color. Arrowhead indicates the obex. B-G: Histopathology of the tumor specimen. Tumor cells with well-defined nuclear atypia and large round to oval nuclei grow densely. Numerous mitotic figures (more than 10 cells/HPF) are observed (B). Immunohistochemical staining is positive for CD20 (C), Bcl-6 (D), and MUM-1 (E) and negative for CD10 (F), indicating a non-GCB-type diffuse large B-cell-type lymphoma. MIB-1 labeling index is more than 90% (G).

gliomas in brainstem tumors, it was possible to initiate chemotherapy and radiotherapy for malignant gliomas without histological diagnosis. Owing to the recent advancement of the understanding of microneuroanatomy and surgical techniques like the widespread use of the cerebellomedullary fissure approach,[22] it was evaluated that biopsy by craniotomy could be safely performed. As a result, the correct diagnosis of PCNSL, but not glioma, was

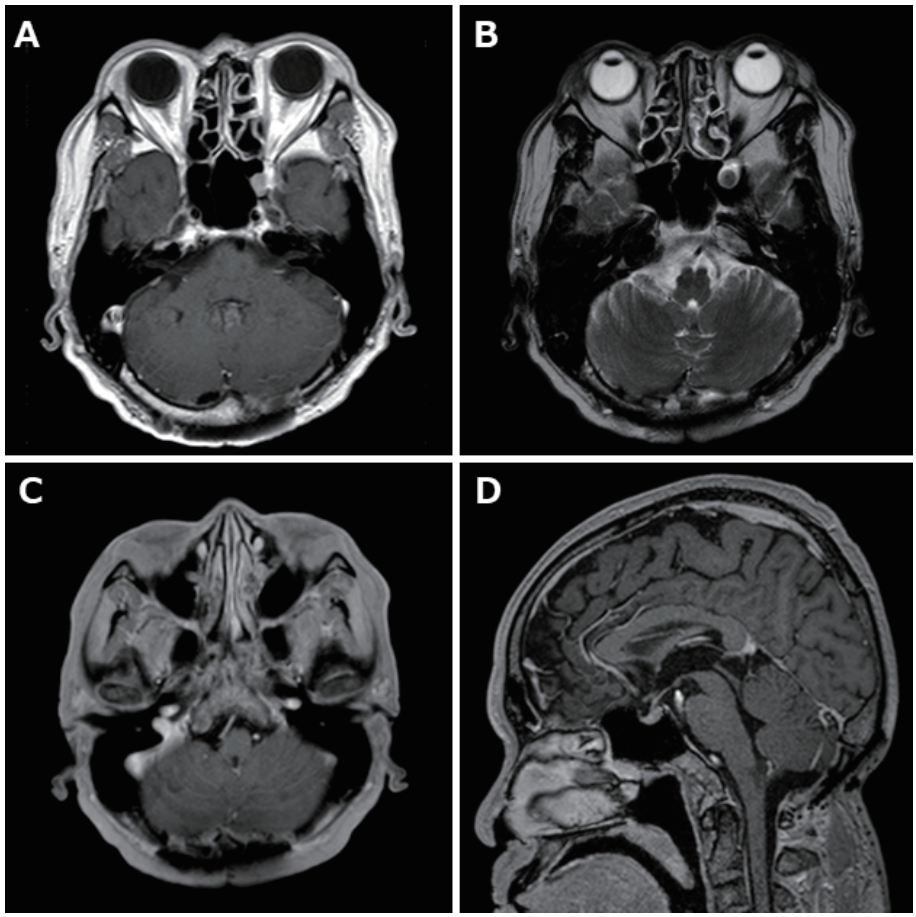

Fig. 3 MR images 5 months after the biopsy when chemotherapy was finished. By axial T1WI (A), T2WI (B), Gd-T1WI (C), and a sagittal Gd-T1WI (D), no apparent residual tumor can be detected.

Table 1 Reported cases of tumors of the medulla oblongata with anorexia

Author/ Year	Age (years old)	Gender	Treatment	Symptoms	Histology	Outcome	Appetite regain
Yang et al. 2009	12	Male	Subtotal resection and chemoradiotherapy	Cough, lethargy, reduced appetite and weight loss, postural drop in blood pressure, unable to swallow water, nystagmus on lateral and upward gaze	Germinoma	Alive at 6 months	Yes
Yoshikawa et al. 2013	63	Female	Chemoradiotherapy	Dizziness, gait disturbance, loss of appetite	Glioblastoma	Died after 9 weeks	No
Present case	56	Male	Biopsy and chemoradiotherapy	Anorexia, bilateral sensory disturbance and heat sensation in the occipital and neck region, difficulty in swallowing	PCNSL	Alive at 24 months	Yes

made, and the patient was treated according to the diagnosis and achieved a complete response. The diagnosis of PCNSL with cell-free DNA in the CSF is a promising method and can avoid craniotomy. It could be a diagnostic modality of choice in the future,[12] but still, it is not yet in routine clinical use. In this case, CSF cytology revealed lymphocytes with an irregular morphology but was class III. Although repeated CSF cytology could have yielded a conclusive diagnosis, the patient's symptoms, including orthostatic hypotension and syncope, had advanced subse-

quent to hospitalization and there was an imperative need for immediate action. We also considered it important to secure tumor specimens for molecular diagnosis. Thus, it is important to obtain tissue samples through surgical manipulations, even in the time of advanced diagnostic imaging technology.

Conclusion

We reported a case of histologically proven PCNSL that originated alone from the medulla oblongata with the initial symptom of anorexia. The initial symptom, anorexia, was related to NTS and was relieved by the treatment. Therefore, when a patient has uncontrolled appetite without any psychological or digestive organ disorders, a lesion in the medulla oblongata shall be considered. In addition, even though clinical findings did not suggest any specific tumor, it is important to obtain a tumor sample for a correct histopathological diagnosis. Making a clear strategy for a safe operation is a clue to a better outcome.

Author Contributions

All authors attest that they meet the current International Committee of Medical Journal Editors criteria for authorship.

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Informed Consent and Patient Details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient.

Conflicts of Interest Disclosure

The authors declare that they have no competing interest. Authors who are members of the Japan Neurosurgical Society have registered online Self-reported COI Disclosure Statement Forms.

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