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Case Report

Primary midbrain germinoma relapse-free for 5 years: A case report

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ABSTRACT

Background: The biology and clinical course of intracranial germinomas differ as per their location of occurrence. Germinoma of the primary midbrain is particularly rare, and its clinical features, treatment strategies, and long-term prognosis remain uncertain.

Case Description: A 39-year-old man who had been diagnosed with midbrain germinoma by open biopsy through the occipital transtentorial approach had undergone chemoradiotherapy and achieved 5 years with no recurrence.

Conclusion: Germinomas should be considered as a differential diagnosis for adolescents and young adult men with mesencephalic tumors, and reliable sampling followed by chemoradiotherapy must be performed.

Keywords: Intracranial germinoma, Midbrain tumor, Occipital transtentorial approach, Radiotherapy

INTRODUCTION

Intracranial germinoma is a rare disease with a favorable prognosis whose 5-year survival rate exceeds 90% with chemotherapy and radiation therapy.[1,10] In recent years, emerging evidence has revealed varying clinical characteristics, prognosis, and genomic backgrounds of germinomas by the tumor location.[14,15] Therefore, reports of germinomas at rare sites of origin are crucial. Intracranial germinomas originate mainly from the pineal region, suprasellar area, or basal ganglia. Only 3.2% of germinomas occur at other sites.[18] The primary midbrain is an extremely rare tumor location, with only seven reported cases thus far.[2,6-8,11,12,17] Therefore, information on clinical characteristics, treatment strategies, and prognosis are limited. Herein, we report the case of a patient with midbrain germinoma who achieved remission with chemoradiotherapy followed by 5 years with no recurrence.

CASE PRESENTATION

A 39-year-old man presented to our hospital with the complaints of double vision and memory impairment. He had suffered from anorexia and weight loss in the preceding 6 months, and diplopia and memory impairment in the preceding 3 months. Magnetic resonance imaging (MRI) revealed a 22 mm large homogeneous contrast-enhanced lesion located mainly in the

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dorsal midbrain, including the bilateral superior colliculi. A 6 mm contrast-enhancing lesion was also identified in the right medial thalamus approximating the lesion. These lesions exhibited low signal intensity on diffusion-weighted images (DWI); fluid-attenuated inversion recovery (FLAIR) images revealed extensive high signal intensity around the lesions, while the lesion itself was isointense. In the midbrain lesion, ^{18}F-fluorodeoxyglucose (^{18}FDG) accumulation was also observed on ^{18}F-FDG-positron emission tomography [Figures 1a-e]. Cerebral angiography revealed no tumor staining, and chest and abdominal computed tomography revealed no neoplastic lesions. We suspected glioma or malignant lymphoma of the central nervous system as a preoperative differential diagnosis and performed an open biopsy using the right occipital transtentorial approach (OTA). We reached the quadrigeminal cistern and confirmed the location of the lesion through navigation. The superior colliculus was mildly enlarged, and the surface was discolored, appearing pale pink [Figure 2]. A 4 mm specimen was resected from the right superior colliculus. The pineal gland was normal in size and appearance. Postoperatively, the patient recovered without neurological deterioration. As the rapid pathological diagnosis suggested lymphoproliferative disease, steroids were initiated 1 day postoperatively, and the lesion shrank transiently. Pathological examination revealed undifferentiated cells with a large round nucleus and prominent nucleoli associated with small lymphocytic infiltration, suggesting a germ cell tumor [Figures 3a and b]. Immunohistochemically, the atypical cells were positive for C-kit and placental alkaline phosphatase [Figures 3c and d]. Based on these results, germinoma was diagnosed. Blood tests performed after diagnosis revealed HCG-β ≤0.10 ng/mL and AFP 0.6 ng/mL, which were within normal limits.

The patient was treated with three courses of carboplatin 450 mg/m^2 + etoposide 150 mg/m^2, followed by whole-ventricle irradiation (WVI) at 24 Gy in 16 fractions [Figure 4a].

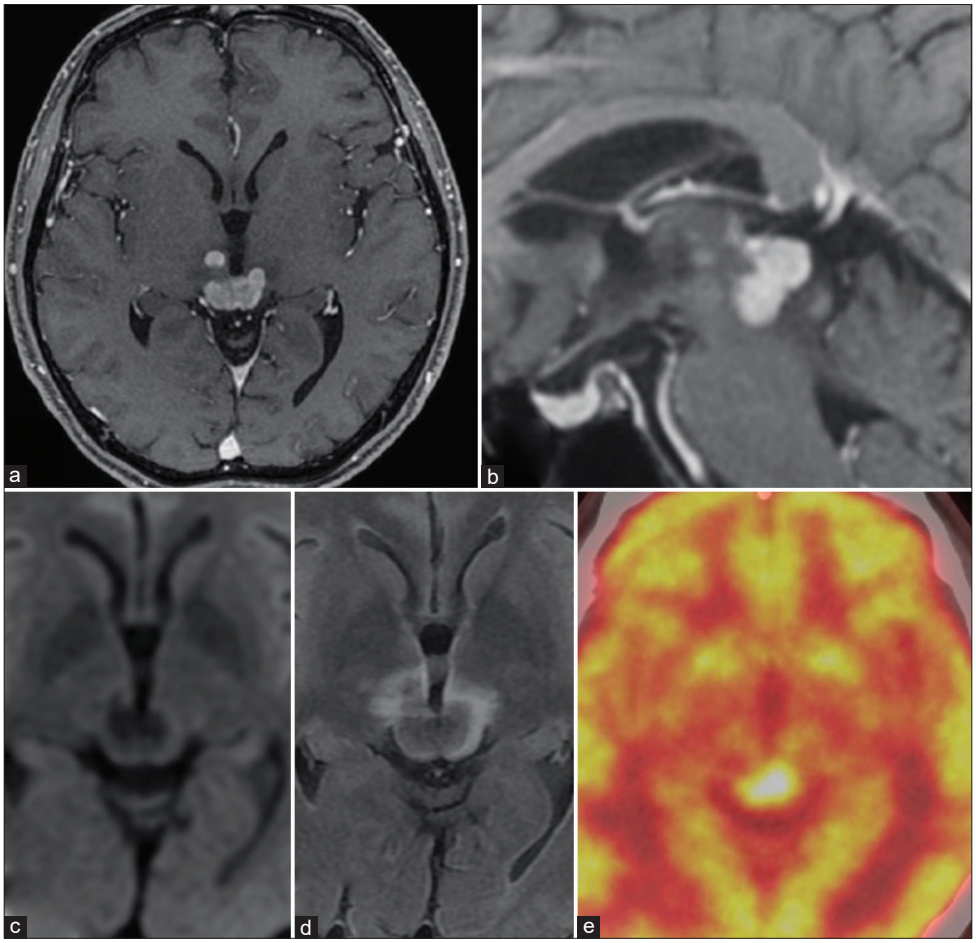

Figure 1: Axial (a) and sagittal (b) views of enhanced T1-weighted magnetic resonance imaging demonstrating a homogenous enhanced lesion in the dorsal midbrain and a skipped lesion in the right thalamus. The lesion exhibits low intensity on the diffusion-weighted image (c). In the fluid-attenuated inversion recovery image, the lesion is isointense and is accompanied by perifocal edema (d). Positron emission tomography reveals ^{18}F-FDG uptake in the lesion (e).

Immediately after completing the entire course, MRI confirmed the disappearance of the contrast-enhancing lesions [Figures 4b and c]. Outpatient follow-up was continued, and no recurrence or decline in performance status was observed until 5 years postoperatively. No late radiation morbidity such as leukoencephalopathy was observed [Figure 4d].

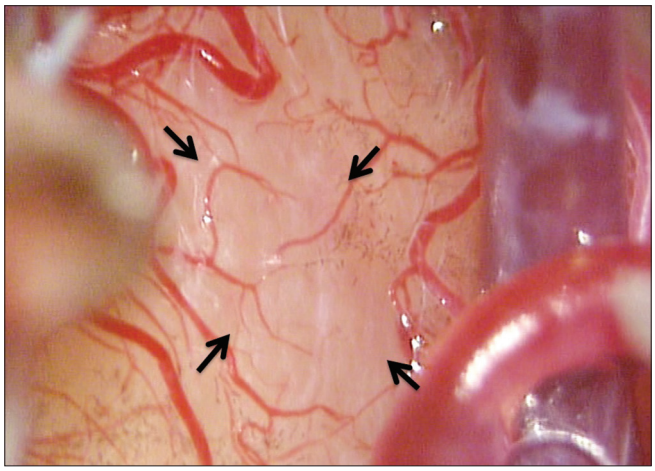

Figure 2: Microscopic intraoperative view of the tumor. The surface of the right upper colliculi is partially swollen and pinkish, and recognizable as a lesion (area surrounded by four arrows). The fourth segment of the posterior cerebral artery (P4) and the basal vein of the Rosenthal are also seen.

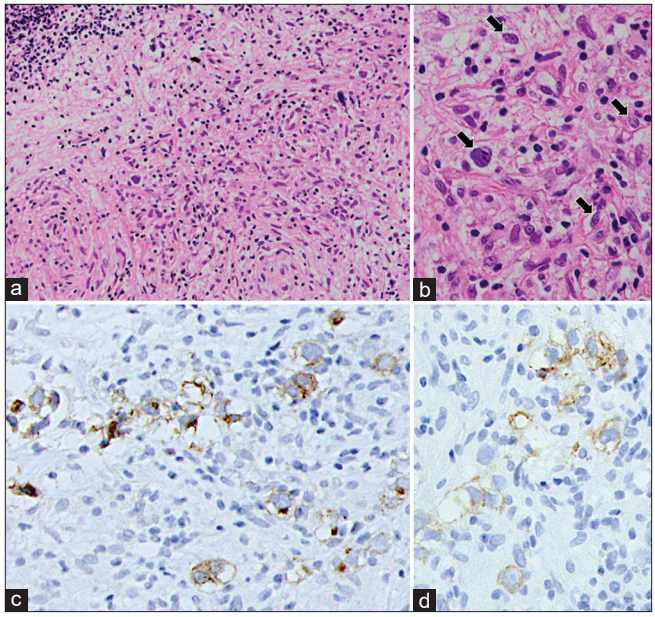

Figure 3: Histopathological findings showed large undifferentiated tumor cells with prominent nucleoli (b, arrow) and small lymphocytes by hematoxylin and eosin staining, presenting a so-called "two-cell pattern" (a and b). Immunohistochemical staining showed that the cell membrane and cytoplasm were positive for C-kit staining (c), and the cell membrane was positive for placental alkaline phosphatase immunostaining (d).

DISCUSSION

Intracranial germinoma has heterogeneous pathogenesis, and its clinical features, prognosis, and even genetic background vary with race, sex, or tumor location.[14-16] To date, only eight cases of primary midbrain germinoma have been reported, including the present case [Table 1]. All eight cases involved men, in contrast to germinomas of the medulla oblongata, 68% of which have been reported in women and 9% in men with Klinefelter's syndrome.[13] The age of onset of primary midbrain germinoma is 25.6 years, particularly in the adolescent and young adult (AYA) generation, and therefore, its onset occurred at a slightly older age than the average for all intracranial germinomas (16.1 years).[10] Five of the eight cases have been reported in Japan, which indicates a racial predisposition in its incidence.

For differentiating germinomas, solely preoperative imaging findings have proven to be insufficient.[7,17] In three previously reported cases of midbrain germinoma, the use of preoperative steroids for controlling cerebral edema[6,11,12] caused a temporary reduction in tumor volume and lymphocyte effacement, making proper sampling and pathological diagnosis difficult. Therefore, germinoma should be considered a preoperative differential diagnosis for midbrain tumors in young men, and preoperative steroid usage must be avoided.

In the present case, the origin of the tumor being either the midbrain or the thalamus remains unanswered. Both lesions appeared to be skipped on contrast T1-weighted imaging, but

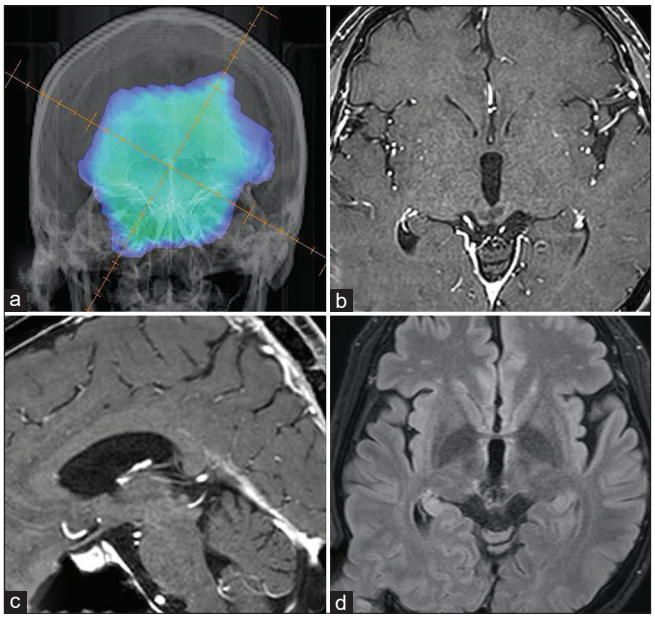

Figure 4: Dose distribution of whole-ventricle irradiation (a). Axial (b) and sagittal (c) views of enhanced T1-weighted following completion of chemoradiation therapy. The enhanced lesion disappears. The FLAIR image after 5 years of treatment reveals no recurrence or late radiation morbidity (d).

Table 1: Literature review of reported cases of midbrain germinomas.

Author	Age/sex	Localization	Symptom	Biopsy	Chemotherapy	Radiotherapy	Outcome
Matsumoto *et al.*	27/M	Left midbrain	Diplopia	MRI-guided stereotactic	Not used	WBRT 30 Gy+local 20 Gy	Alive at 1 month
Amor *et al.*	15/M	Whole midbrain - thalamus	Diplopia, headache, personality change	Stereotactic	CDDP+ETP	Local 45 Gy	Alive at 1 year
Uchino *et al.*	22/M	Left midbrain - thalamus	Diplopia, headache	Neuroendoscopic	CBDCA+ETP	36 Gy	Alive at 6 months
Koizumi *et al.*	29/M	Left midbrain - pons	Diplopia, difficulty maintaining a standing posture	MRI-guided stereotactic	CDDP+ETP	Local 40 Gy	Alive at 7 months
Maruya *et al.*	29/M	Left midbrain - thalamus	Diplopia	Open biopsy through OTA	CBDCA+ETP	WVI 24 Gy	Alive at 5 years
Strowd *et al.*	26/M	Left midbrain - thalamus	Diplopia, appendicular ataxia	MRI-guided stereotactic	Not used	60 Gy	N/A
Purkart *et al.*	18/M	Whole midbrain - thalamus	Headache, vomiting	MRI-guided stereotactic	Not used	WVI 24 Gy+local 16 Gy	Alive at 4 years
Present case	39/M	Dorsal midbrain - right thalamus	Diplopia, memory disturbance	Open biopsy through OTA	CBDCA+ETP	WVI 24 Gy	Alive at 5 years

MRI: magnetic resonance imaging, OTA: occipital transtentorial approach, CBDCA: carboplatin, ETP: etoposide, CDDP: cisplatin, WBRT: whole-brain radiotherapy, WVI: whole-ventricular irradiation

they were continuous with similar signal intensities on DWI and FLAIR, indicating that they were contiguous lesions resulting from tumor invasion. A strong accumulation of ^{18}F-FDG in the midbrain lesion reflects a high tumor growth potential, indicating it as the main lesion. However, no accumulation is observed in thalamic lesions. Thus, it is reasonable to speculate that the midbrain is the main and originating lesion and that the thalamic lesion corresponds to the invasive edge.

Appropriate surgical approaches for midbrain lesions must be individually tailored. A stereotactic biopsy may be indicated in the absence of exposed lesions in the ventricles or cisterns. In cases where the lesion extends from the midbrain to the thalamus and is exposed to the third ventricle, the transventricular approach using a neuroendoscope may be preferable in terms of minimal invasiveness.[17] Conversely, when the lesion is exposed on the dorsal surface of the midbrain, open biopsy by an OTA may be preferable. In the present case, discoloration of the lesion was directly visible, leading to an accurate diagnosis despite the minimal requirement of sampling. The pineal and trochlear nerves provide good landmarks if the quadrigeminal body is difficult to identify due to a bulging lesion.

Regarding postoperative treatment, parameters such as the field and dose of radiotherapy, with or without adjuvant chemotherapy, vary among reports. In general, intracranial germinomas are well-controlled with whole-brain radiation therapy (WBRT) or craniospinal irradiation (CSI), but they simultaneously increase the risk of higher brain or endocrine dysfunction. Chemotherapy is recognized as essential for avoiding the long-term complications of high-dose radiation therapy.[3,4,9] Importantly, the SIOP CNS GCT-96 trial revealed that local irradiation was insufficient;[5] thus, the current regimen requires chemotherapy with WVI. WBRT or CSI has historically been performed for atypically located germinomas because of their rarity and poor prognoses. However, it has recently been reported that even atypical site germinomas can be well-controlled for approximately 7.8 years by chemotherapy with or without a reduced dose/volume of irradiation.[19]

The present case involved an extremely rare site for germinoma, which, with chemotherapy followed by 24 Gy fractionated WVI, exhibited no recurrence for over 5 years. Most reported midbrain germinomas have only been followed up for short periods; thus, the long-term prognosis is unclear. Although this case requires follow-up over the next 10 years, no late radiation morbidity, including leukoencephalopathy or decreased performance status, was observed at this time. More cases are needed to determine the long-term prognosis of midbrain germinoma using a treatment strategy similar to that used for the germinoma of a typical site.

CONCLUSION

Germinoma of the midbrain should be included in the preoperative differential diagnosis for male patients with AYA. Appropriate sampling and postoperative chemoradiotherapy are essential for achieving favorable control.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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