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Malignant transformation of central neurocytoma with dissemination 17 years after initial treatment: illustrative case

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BACKGROUND Central neurocytomas usually have a favorable clinical course, and gross total resection (GTR) results in long-term survival. Recurrences of central neurocytomas are usually local, and dissemination is extremely rare.

OBSERVATIONS A 24-year-old man who presented with vomiting was found to have a mass in the right lateral ventricle. After GTR, he received whole-brain irradiation and chemotherapy and had remained disease-free on follow-up for years. The review of the initial tumor revealed central neurocytoma. Seventeen years later, he presented with deterioration of memory, and magnetic resonance imaging showed an enhanced lesion in the left hippocampus. The enhanced lesion was resected, and the histological examination revealed that the tumor was a disseminated atypical central neurocytoma with frequent mitoses. Although he was treated with chemotherapy, the disseminated tumor slowly grew and invaded the brain. Massive brain invasion occurred without enhanced lesions, and he died 27 months after the tumor recurrence.

LESSONS In this patient, a central neurocytoma disseminated after an extremely long period of time. Once neurocytomas disseminate and show aggressive behavior, patients usually follow a poor course. Patients with central neurocytomas should be followed up for a long time.

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KEYWORDS central neurocytoma; atypical neurocytoma; dissemination; brain invasion; recurrence

Central neurocytomas, which are tumors with neuron-like ultrastructure, were first reported by Hassoun et al. in 1982.[1] Central neurocytomas are relatively rare neuronal tumors that account for approximately 0.1–0.5% of all brain tumors, mostly affecting young adults. They are usually located in the lateral ventricles and are attached to the septum pellucidum near the foramen of Monro, although some tumors have been found in the third and fourth ventricles.[2] Central neurocytomas correspond to grade II according to the classification by the World Health Organization in 2016.[3] They are usually benign, and gross total resection (GTR) usually results in long-term survival.[2,4] Although atypical central neurocytoma is defined by a high MIB1 proliferation index and/or histological features of malignancy, the prognostic significance of atypical histological features remains controversial.[5]

Here, we report an adult man with malignant transformation of a central neurocytoma with dissemination and invasion 17 years after the initial GTR.

Illustrative Case

Initial Clinical Course

A 24-year-old man experienced a history of vomiting and was admitted to a local hospital. The patient had an unremarkable past medical history and no family history of malignancies. Computed tomography (CT) revealed a tumor 5 cm in diameter in the right lateral ventricle with hydrocephalus (data not shown because they were lost). The patient underwent placement of a ventriculoperitoneal (VP) shunt for hydrocephalus and partial resection of the tumor. Subsequently, an additional VP shunt was placed because

ABBREVIATIONS CT = computed tomography; FLAIR = fluid-attenuated inversion recovery; Gd-T1WI = gadolinium-enhanced T1-weighted imaging; GTR = gross total resection; ICE = ifosfamide, carboplatin, and etoposide; MRI = magnetic resonance imaging; RT = radiation therapy; STR = subtotal resection; VP = ventriculoperitoneal.

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of shunt dysfunction. The patient was referred to our hospital, and the residual tumor was totally resected via an anterior interhemispheric transcallosal approach. The patient received whole-brain radiation therapy (RT) of 59 Gy and chemotherapy with cisplatin and ranimustine on the wrong diagnosis of ependymoma.

The review of the initial tumor revealed growth of monotonous round cells with ill-defined cytoplasm and oval nuclei (Fig. 1A). No mitotic figures, tumor necrosis, or microvascular proliferations were observed. Immunohistochemically, the tumor cells were positive for synaptophysin, and the Ki-67 labeling index was $<$1% (Fig. 1B). The patient was diagnosed with central neurocytoma. The patient was followed up with magnetic resonance imaging (MRI). MRI performed 16 years after the initial treatment showed no recurrent tumor on gadolinium-enhanced T1-weighted imaging (Gd-T1WI) (Fig. 1C and D) or a fluid-attenuated inversion recovery (FLAIR) image (Fig. 1E).

Clinical Course After Tumor Recurrence

The patient presented with memory disturbance 17 years after initial treatment. MRI detected an enhanced lesion in the left hippocampus on Gd-T1WI (Fig. 2A and B) and hyperintense lesions in the left hippocampus and the right temporal lobe on FLAIR images (Fig. 2C). Cerebrospinal fluid cytology detected disseminated tumor cells (Fig. 2D).

The tumor in the left hippocampus was partially removed via a left subtemporal approach. Histopathological examinations of the resected tumor revealed growth of monotonous round cells with frequent mitoses (seven per 10 high-power fields) (Fig. 2E). Immunohistochemically, the tumor cells were positive for synaptophysin (Fig. 2F) and negative for glial fibrillary acidic protein and neurofilament, and the Ki-67 labeling index was $\sim$34% (Fig. 2G). Based on these findings, the lesion was diagnosed as a disseminated atypical central neurocytoma.

The patient was treated with temozolomide 150–200 mg/m^2 for 5 days during each 28-day cycle. Two months after the third resection surgery, an enhanced lesion on Gd-T1WI was detected in the right temporal lobe, and the hyperintense lesions on the FLAIR image were enlarged in the right temporal lobe (Fig. 3A and B). Although the patient was treated with seven cycles of temozolomide, the enhanced lesion on Gd-T1WI grew in the right temporal lobe, and the hyperintense lesions on the FLAIR image enlarged in the left hippocampus and the right temporal lobe 8 months after the third surgery (Fig. 3C and D). The patient received chemotherapy with ifosfamide (750 mg/m^2/day on days 1, 2, and 3), carboplatin (75 mg/m^2/day on days 1, 2, and 3), and etoposide (75 mg/m^2/day on days 1, 2, and 3) (ICE) every 4 to 6 weeks.

The cognitive dysfunction of the patient gradually worsened. Subsequent MRI showed slow enlargement of hyperintense lesions on FLAIR images in both temporal lobes. After the patient received nine courses of ICE chemotherapy 18 months after the third surgery, MRI showed massive brain invasion of the tumor without enhanced lesions on Gd-T1WI (Fig. 3E and F). As activities of daily

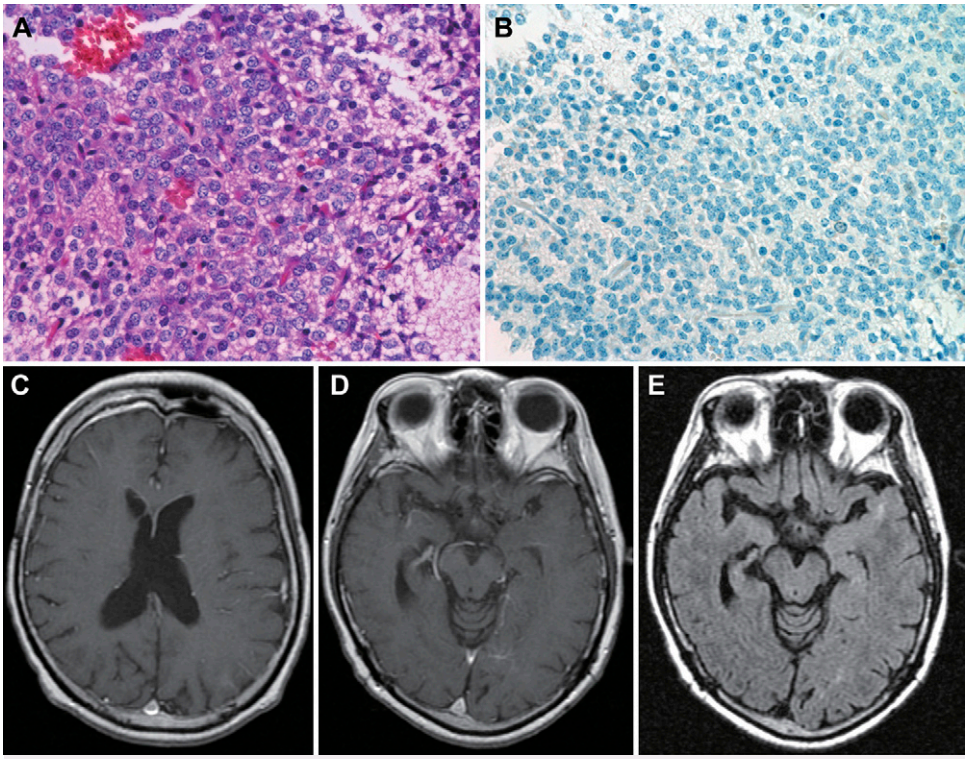

FIG. 1. Histopathological examination of the primary tumor and MRI taken 16 years after the initial treatment. **A:** The tumor was composed of monotonous growth of round cells with ill-defined cytoplasm and oval nuclei. No mitosis was observed (hematoxylin and eosin stain, original magnification $\times$40). **B:** The Ki-67 labeling index was $<$1% (Ki-67 stain, original magnification $\times$40). Gd-T1WI (**C and D**) and FLAIR image (**E**) detected no recurrent tumor 16 years after the initial treatment.

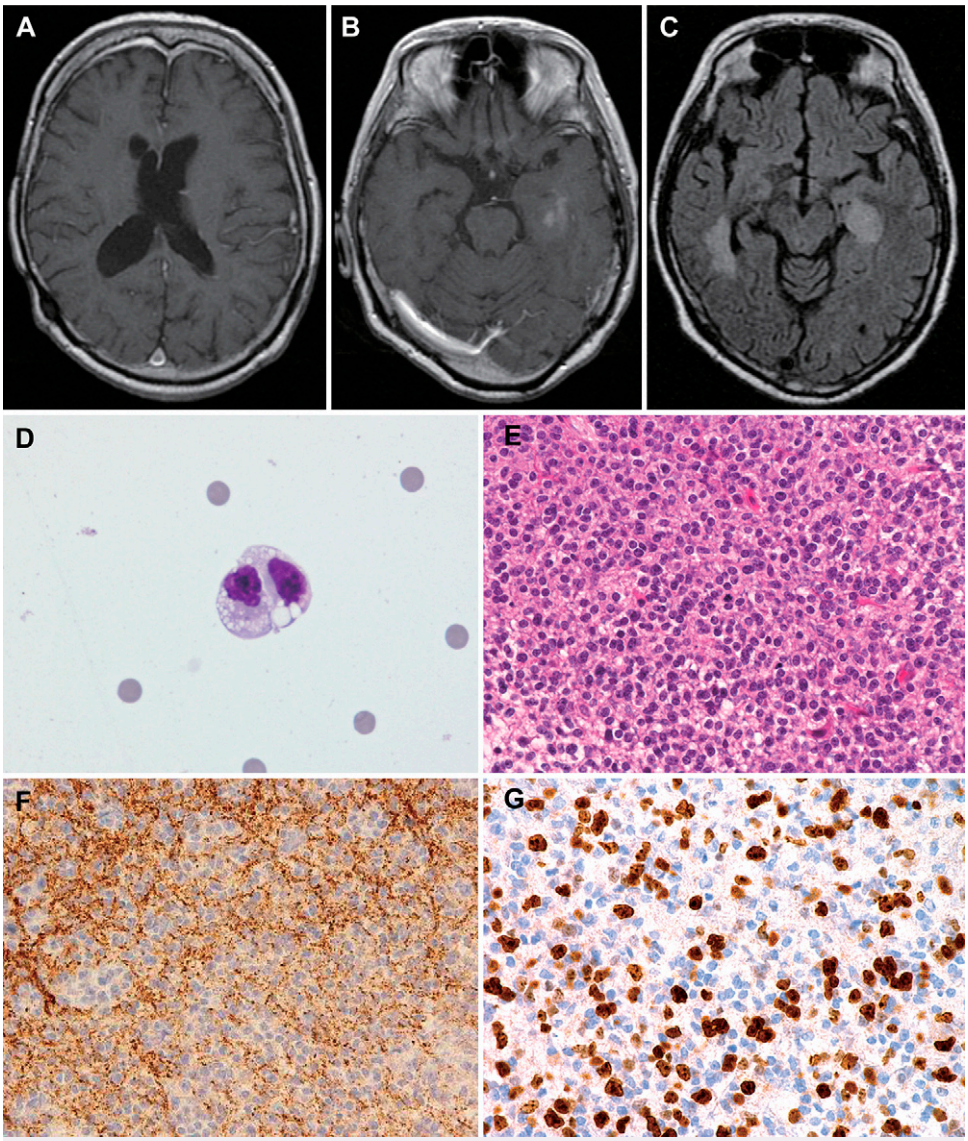

FIG. 2. MRI obtained 17 years after the initial treatment and histopathological examinations of the recurrent tumor. Gd-T1WI (**A and B**) showed the enhanced lesion in the left hippocampus 17 years after the initial treatment. FLAIR image (**C**) showed hyperintense lesions in the left hippocampus and the right temporal lobe. **D:** Cerebrospinal fluid cytology detected disseminated tumor cells. **E:** The tumor was composed of monotonous growth of round cells (hematoxylin and eosin stain, original magnification $\times$40). Mitotic figures were frequently observed (seven per 10 high-power fields). **F:** Most of the tumor cells were immunoreactive for synaptophysin (synaptophysin stain, original magnification $\times$40). **G:** The Ki-67 labeling index was 34% (Ki-67 stain, original magnification $\times$40).

living deteriorated, the patient selected hospice care and passed away 27 months after the tumor recurrence.

Discussion

Observations

Although central neurocytomas may cause symptoms associated with increased intracranial pressure, the clinical courses are usually benign.[2] The 10-year survival exceeds 90%, and the recurrence rate is relatively low ($\sim$30%).[4] The Ki-67 labeling index is used as an important predictive marker of prognosis and relapse for central neurocytoma. Söylemezoglu et al. observed that patients with a Ki-67 labeling index of $>$2% had a recurrence rate of 63%, whereas patients with a Ki-67 labeling index of $<$2% had a recurrence rate of only 22% over a 150-month period. These authors concluded that a Ki-67 labeling index of $>$2% may be related to a more malignant course.[6] Similarly, Rades et al. compared patients with a Ki-67 labeling index of $\leq$3% (n = 87) with those with a Ki-67 labeling index of $>$3% (n = 36),[7] and they concluded that a Ki-67 labeling index of $>$3% correlates with a worse prognosis for local control (5-year local control: $\leq$3%, 87%; $>$3%, 38%) and survival (5-year over survival: $\leq$3%, 95%; $>$3%, 66%). Thus, neurocytomas

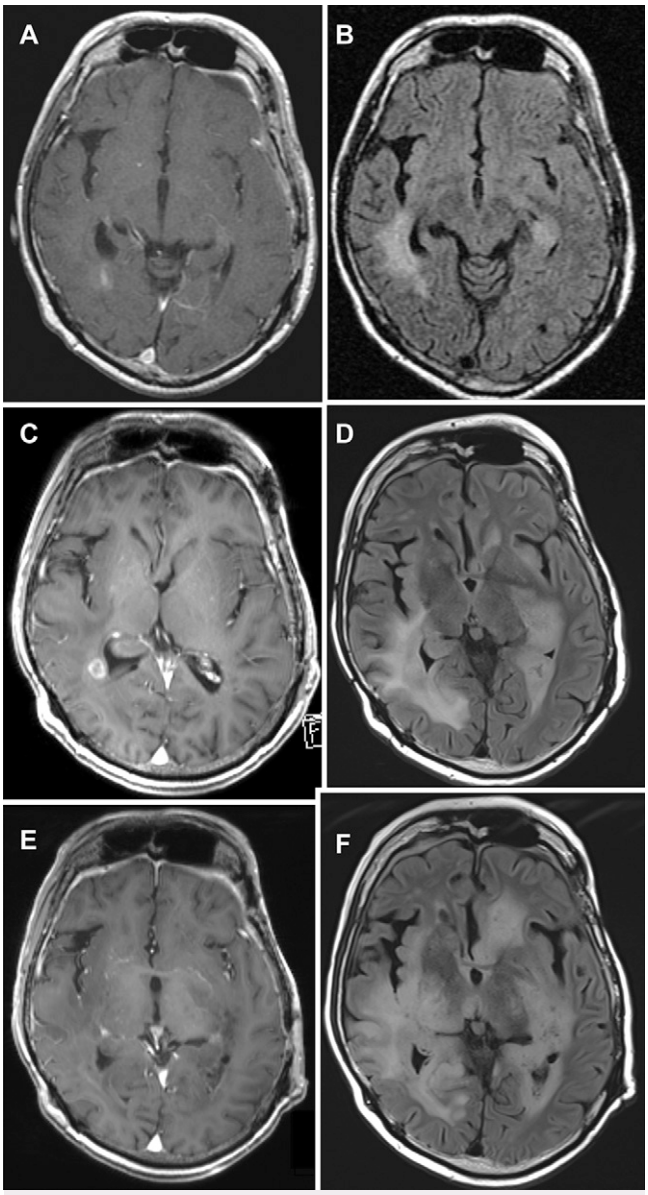

FIG. 3. MRI obtained 2, 8, and 18 months after the third resective surgery for tumor recurrence. The enhanced lesion on Gd-T1WI (**A**) was detected in the right temporal lobe 2 months after the third surgery. The hyperintense lesions on the FLAIR image (**B**) were enlarged in the right temporal lobe. The enhanced lesion on Gd-T1WI (**C**) grew in the right temporal lobe during temozolomide treatment 8 months after the third surgery. The hyperintense lesions on the FLAIR image (**D**) were enlarged in the left hippocampus and the right temporal lobe. No enhanced lesion on Gd-T1WI (**F**) was detected during ICE treatments 18 months after the third surgery. The hyperintense lesions on the FLAIR image (**G**) were enlarged in both cerebral hemispheres, which showed massive tumor invasion.

with a Ki-67 labeling index of >2–3% and/or histological atypia such as necrosis, increased mitoses, or vascular proliferation are termed atypical.[4,6–8] Furthermore, Imber et al. found that a Ki-67 labeling index of >4% is associated with a significantly higher risk of tumor progression compared to a Ki-67 labeling index of ≤4% (2-year progression free survival: >4%, 48%; ≤4%, 90%), and they proposed the use of a Ki-67 labeling index of 4% as a cut-off for atypical tumors.[9] However, the prognostic significance of atypical features remains controversial. Vasiljevic et al. showed that the histological atypical features and the high MIB1 index were not predictors of a higher risk of recurrence in 71 patients with central neurocytoma.

Treatments for central neurocytomas are mainly resection and RT. Rades et al. reviewed and analyzed 438 reports of neurocytomas, including 73 children and 365 adults. The authors defined atypical lesions as tumors that showed atypical histological features or a Ki-67 labeling index of >3% and provided treatment recommendations for typical neurocytomas, atypical neurocytomas, and neurocytomas in children, as described below.[4] GTR yields the best prognosis for both survival and local control, with 99% 5-year survival and 85% 5-year local control rate. After subtotal resection (STR), adjuvant RT significantly improves survival (5-year overall survival: no RT, 82%; adjuvant RT, 89%) and local control (5-year local control: no RT, 41%; adjuvant RT, 83%). As for the radiation dose, the authors recommended 50–54 Gy for typical lesions, 56–60 Gy for atypical lesions, and 50 Gy for lesions in children. Some studies reported that stereotactic radiosurgery has favorable local control in small lesions.[10,11]

Recurrences of central neurocytomas are usually local. We reviewed 16 patients with central neurocytomas that recurred with dissemination (Table 1).[10,12–24] The mean age of onset was 30.6 years (range 3–56 years). Of the 16 cases, 10 were men and 6 were women. The primary tumors arose from the subarachnoid space (n = 1), septum pellucidum (n = 3), fornix, or walls of the ventricles (lateral ventricles: n = 10; third ventricles: n = 2). The initial Ki-67 labeling index was available in 11 cases, and the average was 15.4% (range 0–37.3%). Five patients received GTR, one received GTR+RT, five received STR, and five received STR+RT for the primary lesions. The mean period between the primary surgery and dissemination was 26.2 months (range 0 to 117 months). In analysis according to treatment, the mean period was 49.4 months (range 17 to 117 months) after GTR, 37.0 months after GTR+RT, 14.6 months (range 0 to 45 months) after STR, and 11.4 months (range 2 to 24 months) after STR+RT.

A total of 22 treatments were carried out after dissemination. Only seven resections were performed (GTR: n = 1; STR: n = 3; STR+RT: n = 3), and the tumors were removed from the spinal cord (n = 3) and cerebral ventricle (n = 4). Ki-67 labeling indexes were examined in six cases; in four of six cases, the Ki-67 index was elevated compared to the initial index. The mean Ki-67 labeling index was 16.2% (range 4.1–40%). Ki-67 labeling indexes were elevated by an average of 9.9% (range 2.3–15%) in the elevated cases. RT or chemotherapy was carried out in all but four cases. A variety of RT techniques, doses, and cytotoxic agents was used. Mozes et al. reviewed 19 cases with malignant clinical courses and concluded that adjuvant neuroaxis irradiation should be considered in cases with histologically atypical findings and/or high Ki-67 labeling indexes because of the high possibility of spread via the cerebrospinal fluid.[13] The role of chemotherapy is still uncertain in the treatment of central neurocytomas. In disseminated cases, some response was reported with regimens including temozolomide, cyclophosphamide, cisplatin, topotecan, carboplatin, ifosfamide, and etoposide.[13,15,23] There is a case report that chemotherapy alone resulted in complete tumor remission with topotecan, ifosfamide, and carboplatin.[23] Our patient was treated with temozolomide for the

TABLE 1. Sixteen patients with central neurocytomas that recurred with dissemination

Authors & Year	Age (yrs)/Sex	Location of Primary Tumor	Ki-67 Labeling Index (primary, recurrence) (%)	Chronology of Recurrence/ Dissemination	Treatment	Follow-Up After Diagnosis
Juratli et al., 2013[12]	56/M	L1-3 spinal segments	<5, 5	STR, 8 mos later R in L5-S1 STR, 168 mos later R in C7-T1, T8-9 GTR	None	245 mos SD
Mozes et al., 2014[13]	40/M	3rd v	25–30, >40	GTR, 37 mos later R in spinal cord STR, 8 mos later P in cervical cord 12 mos later R in left frontal lobe, occipital lobes, left cerebellum	RT: 60 Gy to tumor bed R1/RT: spinal cord 36 Gy + 10 Gy to T4-6 P/TMZ, RT: 22.5 Gy to cervical cord R2/RT: brain 27 Gy + 8 Gy to cerebral, cerebellar lesions	62 mos D
Amagasa et al., 2008[14]	42/M	Left lateral v	0, >15	GTR, 46 mos later R in septum pellucidum, dis in 4th v STR, 12 mo later R in v	R1/RT: brain 50 Gy	62 mos D
Brandes et al., 2000[15]	22/F	Septum pellucidum, 3rd v, lateral v	NA	GTR, 36 mos later R in 3rd, dis in 4th, lateral v, T8, 4 mos later P	P/CTX, ETO, CDDP, RT: craniospinal 39.6 Gy + 14.4 Gy to T8	76 mos CR
Ando et al., 2002[16]	31/F	Right lateral v, right thalamus	15	STR, 24 mos later LR, dis in cerebrospinal axis	IFO, CDDP, ETO, RT: 50 Gy	37 mos D
Coelho Neto et al., 2003[17]	3/M	3rd v, left thalamus	NA	STR, 24 mos later LR STR, 19 mos later LR, peritoneal dissemination	R2/ETO, CPT, DOXO, CTX	43 mos D
Goyal et al., 2020[18]	33/M	Right lateral v, thalamus, corpus callosum	8–10	STR, 10 days later LR, spread to right thalamus, leptomeningeal spread 10 mos later R in 4th v, C2	R1/RT: craniospinal 36 Gy + 20 Gy to tumor bed R2/CDDP, ETO	15 mos P
Tomura et al., 1997[19]	43/M	Septum pellucidum, lateral vs	NA	STR, 2 mos later LR, dis in v	RT: 60.6 Gy	17 mos D
Tomura et al., 1997[19]	46/M	Lateral vs, thalamuses, velum interpositum	NA	STR, 5 mos later R in 3rd, lateral v 2 mos later dis	RT: 60 Gy R1/RT: 56 Gy	7 mos dis

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Authors & Year	Age (yrs)/Sex	Location of Primary Tumor	Ki-67 Labeling Index (primary, recurrence) (%)	Chronology of Recurrence/ Dissemination	Treatment	Follow-Up After Diagnosis
Choi et al., 2004[20]	6/M	Right thalamus, basal ganglia, 3rd v, lateral v	>30	STR, 2 mos later R in right lateral v	None	3 mos D
Vemavarapu et al., 2014[21]	44/F	Left lateral v, atrium	15, 5	STR, 14 mos later R in left occipital lobe, left posterior lobe, cerebellar vermis, left cerebellar hemisphere	Proton radiation, TMZ, Bmab, ADM, IFO, TMZ	14 mos P
Matsunaga et al., 2010[10]	41/F	Left lateral v	NA	GTR, 98 mos later LR 19 mos later R STR, 25 mos later R in left lateral v 19 mos later P STR, 17 mos later LR	R1/RT: 25 Gy R2/SRS: 12 Gy R3/SRS: 12 Gy	192 mos D
Eng et al., 1997[22]	22/F	Septum pellucidum, 3rd v, lateral v	3.3	GTR, 36 mos later LR, dis in lateral & 4th v, T8, 4 mos later P	P/ETO, CDDP, CTX	40 mos
Eng et al., 1997[22]	22/F	Right lateral v, 3rd v	1.8, 4.1	STR, 20 mos later R in lateral vs STR, 14 mos later LR, dis in spinal leptomeninges	R2/ETO, CDDP, CTX	34 mos
Amini et al., 2008[23]	5/M	Right lateral v, right frontal lobe	37.3, 23.8	GTR, 12 mos later LR GTR, 5 mos later R in left lateral v 9 mos later R in 4th v 2 mos later L3-4 drop metastasis 10 mos later multiple R	VCR, CDDP, CTX R2/local RT: 50 Gy, TMZ R3/intrathecal Ara-C, SRS: 16 Gy, TMZ M1/intrathecal Ara-C, TOPO, CPT, IFO, TEPA, CPT, TOPO + autologous blood stem cell transplant, RT: 36 Gy + 6 Gy to L3-4 R4/RT, ETO	46 mos CR
Ogawa et al., 2006[24]	34/M	Corpus callosum	25	STR, 12 mos later LR, dis around CSF	SRS: 25 Gy R1/RT: 60 Gy, CDDP, ETO, CTX	23 mos D

ADM = Adriamycin; Ara-C = cytarabine; Bmab = bevacizumab; CDDP = cisplatin; CPT = carboplatin; CR = complete remission; CSF = cerebrospinal fluid; CTX = cyclophosphamide; D = died; dis = dissemination; DOXO = doxorubicin; ETO = etoposide; IFO = ifosfamide; LR = local recurrence; NA = no assessment; P = progression; R = recurrence; SD = stable disease; TEPA = thiotepa; TMZ = temozolomide; TOPO = topotecan; v = ventricle; VCR = vincristine.

first relapse and ICE for the second relapse. Chemotherapy with temozolomide and ICE may result in slow progression for a long period.

Clinical outcomes were reported in 14 of 16 disseminated cases that we reviewed. Eight patients died because of disease progression. The mean survival after dissemination was 21.0 months (range 0 to 87 months). At the time of the last follow-up, two patients were in complete remission, three had progressive disease, and one had stable disease. The mean follow-up period was 59.3 months (range 7 to 245 months). Additionally, the mean recurrence-free survival after dissemination was 12.1 months (range 2 to 168 months). In our case, central neurocytoma with a Ki-67 labeling index of $<1\%$ recurred and disseminated 17 years after GTR, and the patient died 27 months after the recurrence. Compared with other cases, the tumor had a low initial Ki-67 labeling index and disseminated after an extremely long period of time. In terms of the clinical course after dissemination, in many disseminated cases, including this case, patients followed an aggressive course, and the prognosis was relatively unfavorable. Based on the above results, we recommend long-term follow-up for all patients with central neurocytomas.

Lessons

We reported a patient with malignant transformation of central neurocytoma with dissemination after a long period of 17 years. Compared with other cases, the tumor in our patient's case disseminated after an extremely long period of time. Once neurocytomas disseminate, patients usually follow an aggressive course. Therefore, patients with central neurocytomas should be followed up for a long time even if the tumors have a low Ki-67 labeling index or lack atypical features on histopathological examination.

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Author Contributions

Conception and design: Arakawa, Kojima. Acquisition of data: Arakawa, Kojima, Takeuchi, Haga. Analysis and interpretation of data: Kojima, Takeuchi. Drafting the article: Arakawa, Kojima, Takeuchi. Critically revising the article: Arakawa, Takeuchi, Terada, Tanji, Mineharu, Miyamoto. Reviewed submitted version of manuscript: Arakawa, Kojima, Miyamoto. Approved the final version of the manuscript on behalf of all authors: Arakawa. Administrative/technical/material support: Arakawa, Miyamoto. Study supervision: Miyamoto.

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