Epilepsy in Five Long-term Survivors of Pineal Region Tumors

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Abstract

Cognitive decline is a well-known chronic side effect of multidisciplinary treatment of pineal region tumors, whereas epilepsy is an under-reported chronic consequence caused by multiple potential factors including radiotherapy, surgery, or chemotherapy. Some long-term survivors have suffered drug-resistant epilepsy after treatment, which impaired the quality of life. We report five consecutive patients with drug-resistant epilepsy after combined treatment of pineal region tumor (5 men, aged 21–42 years) among 1201 epilepsy patients who underwent comprehensive evaluation in our tertiary epilepsy center from 2011 to 2018. The comprehensive epilepsy evaluation included medical interview, long-term video electroencephalography (EEG) monitoring (VEM), and magnetic resonance (MR) imaging. The patients started to have seizures at 2–22 years after initial treatment for the tumor. Four of the five patients had focal impaired awareness seizures, whereas one patient had only visual aura. All patients had EEG seizures during VEM, which confirmed the diagnosis of focal epilepsy, but three patients had no interictal epileptiform discharges (IEDs). Two patients had diagnoses of focal epilepsy arising from the left occipital region based on ictal EEG findings. Both patients had MR imaging lesion in the left occipital lobe, radiation-induced cavernoma, or surgical injury. The remaining three patients showed poor localization of epileptogenic foci based on VEM and MR imaging. Drug-resistant epilepsy after multidisciplinary treatment of pineal region tumor is characterized by focal impaired awareness seizures with poorly localized EEG onset or rare interictal spikes.

Keywords: epilepsy, pineal region tumor, long-term video electroencephalography monitoring, multidisciplinary treatment

Introduction

Pineal region tumors account for 2.5–8.5% of pediatric intracranial tumors, and are more common in Asian populations.1,2 Pineal germ-cell tumor and pineoblastoma used to be refractory to treatment, but multidisciplinary regimens including combined chemo-radiotherapy have recently achieved longer survival for patients with these tumors.3–6 Cognitive decline is a well-known chronic side effect of multidisciplinary treatment,7 whereas epilepsy is an under-reported chronic consequence. The prevalence of epilepsy in these patients remains unknown, but some long-term survivors have suffered drug-resistant epilepsy after treatment, which impaired the quality of life. However, little is known about the characteristics of drug-resistant epilepsy occurring after treatment for pineal region tumors.

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Case Report

We report five consecutive patients with drug-resistant epilepsy which only developed after multidisciplinary treatment for pineal region tumor among 1201 epilepsy patients who underwent comprehensive evaluation in our tertiary epilepsy center from 2011 to 2018. All five patients received appropriate treatments resulting in favorable tumor control. The patients started to have seizures 2–22 years (median 9 years) after the initial treatment. The evaluation included medical interview, long-term video electroencephalography (EEG) monitoring (VEM), and magnetic resonance (MR) imaging. Age, sex, histopathological diagnosis, tumor treatment, epilepsy evaluation, and epilepsy diagnosis are summarized in Table 1.

EEG recordings with 21 channels according to the international 10–20 system and subtemporal electrodes (T1/T2) were performed using a long-term video EEG system (Neurofax EEG-1200; Nihon Kohden, Tokyo, Japan). All patients underwent VEM for 3–5 days. Board-certified EEG technologists reviewed all data and identified interictal epileptiform discharges (IEDs) and EEG seizures, and then board-certified clinical neurophysiologists/epileptologists (KJ and YK) finalized the findings.

All patients underwent epilepsy protocol MR imaging using two 3 T scanners (MAGNETOM Trio, A Tim System; Siemens Healthcare GmbH, Erlangen, Germany, and Intera Achieva Quasar Dual; Philips Healthcare, Best, The Netherlands). The epilepsy protocol included the following sequences: axial T2-weighted imaging (6 mm thick, 1 mm gap) and fluid-attenuated inversion recovery (FLAIR) imaging (6 mm thick, 1 mm gap) parallel to the anterior-posterior commissure axis, axial magnetization prepared rapid gradient echo (three-dimensional T1-weighted) imaging (0.9 or 1.0 mm thick, no gap) parallel to the long axis of the hippocampus, and coronal short T1 inversion recovery imaging (3.5 mm thick, 0.3 mm gap) and FLAIR imaging (3.5 mm thick, 0.3 mm gap) perpendicular to the long axis of the hippocampus. Susceptibility-weighted imaging was also performed when necessary.

The study was approved by the ethical committee of Tohoku University Graduate School of Medicine. Written informed consent was obtained from all patients in accordance with the requirements of the ethical committee.

Case 1

A young man underwent resective surgery for pineal tumor with the occipital transtentorial approach (OTA) at age 13 years. The histopathological diagnosis was germinoma. He received booster local irradiation 14.4 Gy with whole ventricle irradiation 30.6 Gy, combined chemotherapy including two courses of carboplatin and etoposide (CARE) and three courses of ifosfamide, cisplatin, and etoposide (ICE), and peripheral blood stem-cell transplantation. However, recurrence of the tumor was observed after the initial radiotherapy. Stereotactic radiotherapy (SRT) was performed twice (LINAC, 40 Gy/8 fr). The detailed irradiation areas of SRT are shown in Fig. 1. He started to have visual auras at age 19 years, which were uncontrolled by antiepileptic drug (AED) treatment with a combination of carbamazepine, clobazam, lamotrigine, levetiracetam, and zonisamide. He underwent comprehensive evaluation for epilepsy at age 21 years. Three-day VEM did not show any IEDs. Habitual seizures with visual auras were recorded as ictal EEG changes arising from the left occipital region during VEM. MR imaging showed a cavernoma in the left occipital lobe (Fig. 2). The diagnosis was left occipital lobe epilepsy associated with left occipital radiation-induced cavernoma. Finally, he underwent resection of the cavernoma and was seizure-free for 2 years.

Case 2

A man underwent resective surgery for pineal tumor with OTA at age 29 years. Ventriculoperitoneal shunt was also placed to improve hydrocephalus at the same time. The histopathological diagnosis was pineoblastoma. He received craniospinal irradiation 30 Gy to the brain and 30 Gy to the spine and ICE chemotherapy. He additionally received SRT (gamma knife, 23 Gy) and salvage chemotherapy due to tumor recurrences at ages 32 and 37 years. The detailed irradiation areas of SRT are shown in Fig. 1. He started to have focal aware non-motor seizures consisting of sudden visual field deficit followed by dysphasia at age 38 years, and then started to have focal impaired awareness seizures at age 40 years. The seizures were uncontrolled despite AED polytherapy with a combination of carbamazepine, lacosamide, levetiracetam, and zonisamide. He underwent comprehensive evaluation for epilepsy at age 42 years. Five-day VEM did not show any IEDs. Habitual seizures were not recorded, but a subclinical seizure was recorded as ictal EEG change arising from the left occipital region during VEM. MR imaging showed left occipital brain injury along the surgical tract (Fig. 2). The diagnosis was left occipital lobe epilepsy. He continued to have yearly seizures after adjustment of AEDs.
| Case No. | Age, yrs | Sex | Histopathological diagnosis | Tumor treatment | Epilepsy evaluation | Seizure type (seizure frequency*) | VEM | Ictal EEG | MR imaging | Epilepsy diagnosis |
|---------|----------|-----|-----------------------------|----------------|---------------------|----------------------------------|-----|---------|------------|------------------|
| 1       | 13       | M   | Germinoma                   | OTA            | CARE                | FAS, visual (2/year)              |     |         |            | Lt occipital lobe epilepsy |
|         | 19       |     |                              | L (14.4)† + WV (30.6)/1st SRT (40)/2nd SRT (40) | ICE PBSCT        | Lt O                             | IED | Lt O     |            | Cavernoma (Lt O) |
| 2       | 29       | M   | Pineoblastoma               | OTA            | ICE                 | FIAS (1 or 2/year)                |     |         |            | Lt occipital lobe epilepsy |
|         | 42       |     |                              | WB (30)/1st SRT (23)/2nd SRT (23) | ICE               | Lt O (subclinical)               |     |         |            | Surgical injury (Lt O) |
| 3       | 14       | M   | Germinoma                   | None           | FIAS                | Blt T                             |     |         |            | Non-localizable focal epilepsy |
|         | 23       |     |                              | WB (unknown)   |                    | Diffuse brain atrophy             |     |         |            | Non-localizable focal epilepsy |
| 4       | 6        | M   | Mature teratoma             | OTA            | Done§               | Generalized, Lt TPO, Rt F         |     |         |            | Non-localizable focal epilepsy |
|         | 8        |     |                              | L (20)†        | FIAS, automatism (2–4/week) | Non-localizable                |     |         |            | Surgical injury (Lt O) |
| 5       | 15       | M   | Embryonal carcinoma         | OTA            | Done§               | FIAS, automatism (2/month)        |     |         |            | Microbleeds (multiple) |
|         | 37       |     |                              | L (12)†/WB (30) + WS (26) + L (20)‡ |                    | Non-localizable                  |     |         |            | Non-localizable focal epilepsy |

*Seizure frequency at the time of epilepsy evaluation. †Local irradiation for the pineal lesion was performed as an initial radiotherapy in Cases 1, 4, and 5. ‡Local irradiation for recurrent left frontal lesion was performed in Case 5. §Details of the chemotherapy regimen were unavailable in Cases 4 and 5. Blt: bilateral, CARE: carboplatin and etoposide, EEG: electroencephalography, F: frontal, FAS: focal aware seizure, FIAS: focal impaired awareness seizure, ICE: ifosfamide, cisplatin, and etoposide, IED: interictal epileptiform discharge, L: local, Lt: left, M: male, MR: magnetic resonance, O: occipital, OTA: occipital transtentorial approach, PBSCT: peripheral blood stem-cell transplantation, Rt: right, SRT: stereotactic radiotherapy, T: temporal, TPO: temporo-parieto-occipital, VEM: video electroencephalography monitoring, WB: whole brain, WS: whole spine, WV: whole ventricle.
Case 3
A young man had pineal and L3-4 spinal tumors, and underwent resective surgery for only the spinal tumor at age 14 years. Dissemination from the pineal tumor was suspected based on the histopathological diagnosis of germinoma. He received whole brain irradiation without brain surgery or chemotherapy. He started to have focal impaired awareness seizures with preceding unclassified aura at age 23 years. He had depersonalized feeling, and then showed left head turning and right face tonic convulsion with impaired awareness during habitual seizures. The seizures were uncontrolled despite AED polytherapy with a combination of carbamazepine, clobazam, lamotrigine, levetiracetam, perampanel, phenytoin, and valproic acid. He underwent comprehensive evaluation for epilepsy at age 29 years. Four-day VEM showed frequent spikes in the bilateral temporal regions independently during the interictal periods. Habitual seizures were recorded as non-localizable EEG changes during VEM. MR imaging showed diffuse brain atrophy (Fig. 2). The diagnosis was non-localizable focal epilepsy. He continued to have weekly seizures after adjustment of AEDs.

Case 4
A boy underwent resective surgery with OTA for pineal tumor at age 6 years. The histopathological diagnosis was mature teratoma. He underwent two additional resective surgeries for repetitive recurrences within 1 year of the initial surgery. He received local irradiation 20 Gy and chemotherapy. Details of the chemotherapy regimen were unavailable. He started to have focal impaired awareness automatism seizures at age 8 years. The seizures were uncontrolled despite AED polytherapy with a combination of carbamazepine, clobazam, clonazepam, lamotrigine, levetiracetam, perampanel, phenytoin, and valproic acid. He underwent comprehensive evaluation for epilepsy at age 29 years. Four-day VEM showed frequent generalized, left temporo-parieto-occipital, and right frontal spikes during the interictal periods. Habitual seizures were recorded as non-localizable EEG changes during VEM. MR imaging showed left occipital brain injury along the surgical trajectory (Fig. 2). The diagnosis was non-localizable focal epilepsy. He continued to have yearly seizures after adjustment of AEDs.

Case 5
A young man underwent resective surgery with OTA for pineal tumor at age 15 years. A disseminated lesion in the left frontal lobe was also resected at the same time. The histopathological diagnosis was embryonal carcinoma. He received local irradiation 12 Gy and chemotherapy. Details of the chemotherapy regimen were unavailable. However, recurrence of the tumor was observed after the initial radiotherapy. He additionally received craniospinal irradiation 30 Gy to the brain and 26 Gy to the spine with booster local irradiation 20 Gy for recurrent left frontal lesion. He started to have focal impaired awareness automatism seizures at age 37 years. The seizures continued to occur approximately twice a month despite AED polytherapy with a combination of lamotrigine, levetiracetam, and phenytoin. He underwent comprehensive evaluation for epilepsy at age 39 years. Habitual seizures were recorded with non-localizable EEG changes, although IEDs were not detected during 5-day VEM. Susceptibility-weighted MR imaging showed multiple microbleeds in the bilateral hemispheres (Fig. 2). The diagnosis was non-localizable focal epilepsy. He finally remained seizure-free for 2 years after increasing the dose of lamotrigine.

Discussion
Four of the five patients (Cases 2–5) had focal impaired awareness seizures, whereas one patient...
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(Case 1) had only visual aura. Two patients (Cases 1 and 2) were diagnosed with focal epilepsy arising from the left occipital region based on the ictal EEG findings. However, the remaining three patients (Cases 3–5) showed non-localizable ictal EEG changes. Only two of the five patients (Cases 3 and 4) had IEDs, neither with a single focus.

Localized structural abnormality was seen in three patients (Cases 1, 2, and 4). Case 1 had a cavernoma in the left occipital lobe, which was consistent with the irradiation area of the second SRT. Cases 2 and 4 had left occipital brain injury along the surgical trajectory. None of the five patients showed hippocampal abnormalities on MR images.

Deep-targeted radiotherapy for pineal region tumor may affect a diffuse neural network including the limbic system, which can cause focal impaired awareness seizures. Radiation achieves the therapeutic effect by causing breakage of DNA strands during cell division. The hippocampal neurons which continue to show neurogenesis throughout life are exceptionally sensitive to radiation damage compared to other neurons which do not replicate.8) Therefore, if the hippocampus is directly exposed to whole-brain or whole-ventricle irradiation, the limbic network may be affected. In addition, if radiation causes structural or necrotic changes in the areas adjacent to the pineal region, such as the occipital lobe, posterior cingulate gyrus, or fornix, epileptic activity arising from these areas may easily propagate to the mesial temporal structures. The OTA may also affect the occipital lobe during resective surgery,9–11) and seizures arising from the occipital lobe often propagate to the mesial temporal lobe,12–14) which can cause focal impaired awareness seizures.

All five patients had EEG seizures with or without clinical signs detected during VEM, although only two of the five patients (Cases 3 and 4) had IEDs. Therefore, ictal findings are probably more useful than interictal findings for epilepsy diagnosis and classification in patients with drug-resistant epilepsy after multidisciplinary treatment for pineal region tumor. Recently, we reported that 60% of patients without IEDs had epileptic seizures during 4- or 5-day VEM.15) Three of five patients (Cases 1, 2, and 5) corresponded to this category in the present study. Two of the five patients (Cases 1 and 2) showed ictal

Fig. 2  MR imaging findings of each patient. Axial T2-weighted image of Case 1 showing a radiation-induced cavernoma in the left occipital lobe (arrow). Axial T2-weighted images of Cases 2 and 4 showing left occipital cortical abnormalities, which implied the damage was caused by brain surgery for pineal tumor. Axial T2-weighted image of Case 3 showing diffuse brain atrophy probably due to radiotherapy. Susceptibility-weighted images of Case 5 (Case 5a and 5b) showing multiple microbleeds (arrowheads). MR: magnetic resonance.
EEG changes arising from the left occipital region, although no patient showed a single focus interictally. Consequently, ictal findings are useful to reveal localization of the epileptogenic focus in some patients, but interictal findings are not. Inpatient VEM is quite useful for epilepsy diagnosis, classification, and sometimes for localization, but outpatient routine EEG is inadequate because of the lower chance to detect ictal findings, which is not specific for drug-resistant epilepsy after multidisciplinary treatment for pineal region tumor.\(^{16,17}\)

The prevalence of epilepsy occurring after treatment of pineal region tumor remains unclear, but several points about the potential mechanism of developing drug-resistant epilepsy in such patients can be discussed. Patients with pineal region tumor have multiple factors which may cause drug-resistant epilepsy after multidisciplinary treatment. First, the tumor itself can cause focal epilepsy. Pineal cells or germ cells within the tumor are not known to acquire epileptogenicity, but peritumoral edema or remote dissemination to the cortices has the potential to cause epilepsy. The present case series contained no such patients because MR imaging showed no peritumoral edema or disseminated lesions at the onset of epilepsy and the patients started to have seizures after the tumors had been well controlled for 2–22 years after the treatment.

Therefore, the epilepsy in our five patients seems to be associated with the multidisciplinary treatment for pineal region tumor. Two patients (Cases 1 and 2) had epileptogenic lesion on MR imaging, concordant with the results of focal ictal EEG findings during VEM. The most likely cause of epilepsy in Cases 1 and 2 was radiation-induced cavernoma\(^ {16–23}\) and brain injury caused by tumor resection, respectively. One patient (Case 3) showed diffuse brain atrophy on MR imaging, which may have been caused by radiotherapy,\(^ {24–26}\) because the patient received neither cranial surgery nor chemotherapy. The other two patients (Cases 4 and 5) had multiple potential factors to cause epilepsy, so radiotherapy, surgery, and chemotherapy are all conceivable causes of the epilepsy.

Radiotherapy including SRT improved the long-term seizure control in some patients with epilepsy associated with brain tumors, but radiation-induced edema or necrosis worsened seizure control in other patients.\(^ {27,28}\) Radiotherapy is considered to be one of the main causes of epilepsy in patients, who start to have seizures several years after receiving multidisciplinary treatment under a diagnosis of intracranial and extracranial tumors or have focal impaired awareness seizures.\(^ {29}\)

No well-designed studies have been reported to clarify the incidence and clinical features of epilepsy after multidisciplinary treatment for tumors. However, a few case series have included patients with epilepsy after radiation therapy for tumors other than pineal region tumors, such as one case series of intracranial tumors.\(^ {30}\) Three case reports of radiation-induced cavernoma included a case of epilepsy associated with cavernoma after radiation therapy for right frontal lobe ependymoma, which was similar to Case 1 in the present study. Two more case series reported extracranial tumors. Three case reports described epilepsy after radiation therapy for scalp strawberry hemangioma.\(^ {31}\) The concordance between the irradiated area shown by localized alopecia, semiology of focal seizures, and EEG abnormalities suggested the diagnosis of radiation-induced epilepsy. Another case series included 11 patients with epilepsy after radiotherapy for nasopharyngeal carcinoma.\(^ {32}\) CT of all 11 patients showed abnormal low-density areas in one or both temporal lobes, which were consistent with radiation necrosis. Eight of the 11 patients had seizures after radiotherapy. Seven of the eight patients had focal impaired awareness seizures.

The small sample size is a limitation of the present study, which did not include the entire population of patients with pineal region tumors after multidisciplinary treatment, only patients with drug-resistant epilepsy. Therefore, statistical discussion of the results was difficult. This case series could not clarify the incidence of all epilepsy types after multidisciplinary treatment for pineal region tumors and the risk factors of drug-resistant epilepsy in this population. Further studies are needed to clarify the epidemiological and clinical features of such epilepsy.

**Conclusions**

Patients with pineal region tumor have multiple factors which may cause epilepsy after multidisciplinary treatment. The epilepsy is characterized by focal impaired awareness seizures with poorly localized EEG onset or rare interictal spikes. Comprehensive epilepsy evaluation including VEM and MR imaging is useful for epilepsy diagnosis and classification, and sometimes for epilepsy localization, which is essential for selecting the optimal treatment strategy including surgery.

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Conflicts of Interest Disclosure

KJ has received speaker's fees from Otsuka Pharmaceutical, Daiichi-Sankyo, UCB Japan, and Eisai Co., Ltd.; NN is a Chair of the Collaborative Laboratory with RICOH Japan Corp. and has received research funds and speaker's fees from Otsuka Pharmaceutical, Daiichi-Sankyo, UCB Japan, Fukuda Denshi, Pfizer Japan, and Eisai Co., Ltd. The remaining authors report no disclosures.

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