



Case Report

Late recurrence of primary cerebellar germinoma at unusual site after complete response to radiotherapy

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ABSTRACT

Background: The primary cerebellar germinoma is exceptional and difficult to diagnose preoperatively. Its recurrence at the middle cranial fossa after complete response to radiotherapy is unique and associated with a poor prognosis. This article aims to report the successful management of the late recurrence of primary cerebellar germinoma at an unusual site after 4 years of complete response to radiotherapy.

Case Description: A 22-year-old male was admitted to our hospital with complaints of severe headache and loss of balance. Brain magnetic resonance imaging (MRI) showed a triventricular hydrocephalus due to a 45x50mm cerebellar mass. Our preliminary diagnosis was medulloblastoma. First, we placed a ventriculoperitoneal shunt with the medium-pressure valve, and then we used midline suboccipital craniotomy to remove the tumor completely. The histopathology was germinoma. The patient received 24 Gy craniospinal irradiation (CSI) with a 16 Gy boost to the primary site and had an MRI follow-up every six months. After a 4-year follow-up, he complained of recurrent severe headaches. The brain MRI illustrated a 62 × 61 mm temporal mass. We extirpated this tumor, and histopathology again revealed germinoma. After that, the patient received induction radiotherapy. The 1-year postoperative MRI showed no tumor remnant. At the time of writing, the patient had no headache and no neurological deficits.

Conclusion: Regular follow-ups with routine neuroaxis MRI should be recommended to detect recurrence early for all patients with intracranial germinomas. Surgical resection, if possible, and subsequent CSI are the most effective salvage treatment for recurrent germinoma.

Keywords: Craniospinal irradiation, Late recurrence, Primary cerebellar germinoma, Radiotherapy

INTRODUCTION

Intracranial pure germinoma is the most common neoplasm (70-80%) of germ cell tumors derived from germ cells.^[1] The overwhelming majority (>90%) of cases occur before 20 years of age, with incident peaks occurring just after birth and in early adolescence. These tumors often affect males.^[8] Intracranial pure germinomas are usually found in the pineal and suprasellar regions. Other sites may include basal ganglia and thalamus. The primary cerebellar germinoma of the posterior fossa is an exceptional case.

Pure germinoma is radiosensitive; thus, radiotherapy is recommended as the first-line therapy with 5-year progression-free survival and overall survival rates of more than 90%.^[2] Despite not improving survival outcomes, surgery plays a vital role in treating hydrocephalus due to

germinoma and histopathological biopsy. Platinum-based chemotherapy is recommended for “induction” therapy before radiotherapy to decrease radiation dose, reducing the long-term morbidity of radiation therapy while maintaining excellent survival rates.

Despite high radiosensitivity, the proportion of recurrent germinoma after complete response to radiotherapy is estimated to be 6–17%.^[10,11] Recurrence of germinoma is likely to be associated with a poor prognosis. The median time to recurrence was 30.3 months (range, 3.8–134.9 months). More than half of failures were isolated “out-field” of radiotherapy. In 2012, Hu *et al.* showed that salvage radiotherapy and chemotherapy (58.8%) are the preferred treatment for recurrent germinoma.^[6] In which, craniospinal irradiation (CSI) (45.1%) was the most commonly used type of salvage radiotherapy for recurrent germinoma.^[6] Concurrently, the survival rates for those with salvage CSI, non-CSI radiotherapy, and no radiotherapy were 92.9%, 60.0%, and 35.8%, respectively.^[6]

This article aims to report the successful management of the late recurrence of primary cerebellar germinoma at an unusual site after four years of complete response to radiotherapy.

PRESENTATION OF CASE

A 22-year-old male was admitted to our hospital with complaints of severe headache and loss of balance. On examination, he was alert and oriented. He had cerebellar ataxia and imbalance. The motor and sensory functions of the extremities were normal. He denied cranial nerve palsies. Brain magnetic resonance imaging (MRI) showed a cerebellar mass measuring 45x50 millimeters [Figure 1]. The mass was hypointense on the T1W sequence, hyper- and iso-intense on the T2W sequence, and was enhanced heterogeneously on T1W post-gadolinium. The triventricular hydrocephalus occurred because the mass compressed the fourth ventricle and aqueduct of Sylvius. Our preliminary diagnosis was medulloblastoma. First, we placed a ventriculoperitoneal shunt with the medium-pressure valve to gradually reduce intracranial pressure. And then, we used midline suboccipital craniotomy to remove the tumor. The intraoperative frozen section showed germinoma, which is radiosensitive. This germinoma was located at a favorable site for total resection, so we completely removed the tumor. The histopathological examination confirmed germinoma. Cerebrospinal fluid β -hCG and AFP tests were negative. The patient was received 24 Gy CSI with a 16 Gy boost to the primary site and had an MRI follow-up every 6 months. The postoperative MRI of the brain and spine showed no tumor remnant and metastasis [Figure 2].

After a 4-year follow-up, when he was 26 years old, he was admitted again to our hospital with complaints of recurrent

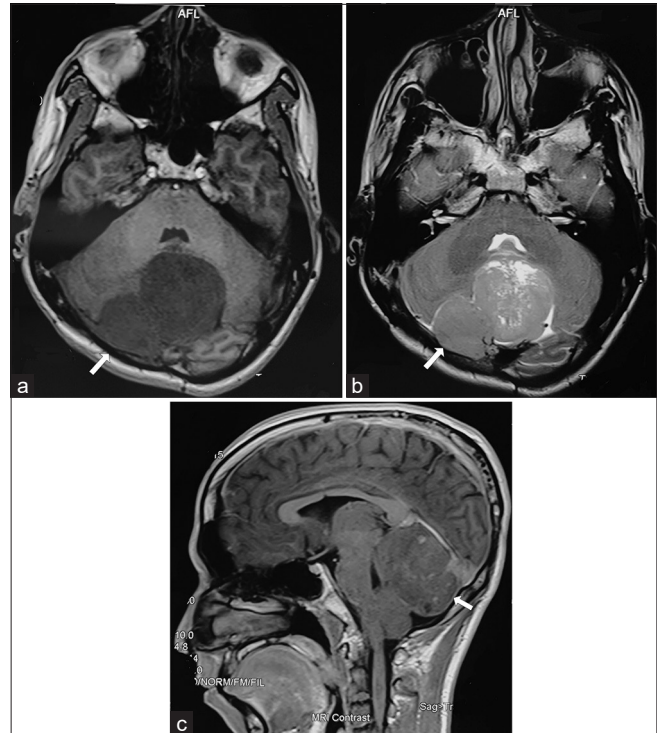


Figure 1: Brain magnetic resonance imaging (MRI) showed a cerebellar mass measuring 45 × 50 mm. The mass was hypointense on T1W sequence (a), hyper- and iso-intense on T2W sequence (b), and was heterogeneously enhanced on T1W postgadolinium (c).

severe headache. The physical examination revealed no neurological deficits. The brain MRI illustrated a temporal mass measuring 62 × 61 mm. The temporal mass was hyperdense on computed tomography, isointense on T1W sequence, hyperintense on T2W sequence, and enhanced heterogeneously on T1W postgadolinium [Figure 3]. The spine MRI showed no metastasis lesion. We used pterional craniotomy to extirpate the temporal tumor. The histopathological examination revealed germinoma again. The immunohistochemistry staining was CD117 (+), PLAP (+), Ki67 (+), β -hCG (-), AFP (-), LCA (-), S100 (-), Synaph (-), GFAP (-), and CK (-) [Figure 4]. After that, the patient received 24 Gy CSI with a 16 Gy boost to the temporal region. The 1-year postoperative MRI showed no tumor remnant [Figure 5]. At the time of writing, the patient had no headache and no neurological deficits. He was happy to return to work and daily activities.

DISCUSSION

The primary cerebellar germinoma of the posterior fossa is unique. Only six cases were reported in previous studies, in which only three patients had isolated cerebellar germinoma, as was the case of our patient.^[9] Maiuri suggested some criteria for the diagnosis of primary cerebellar germinoma,

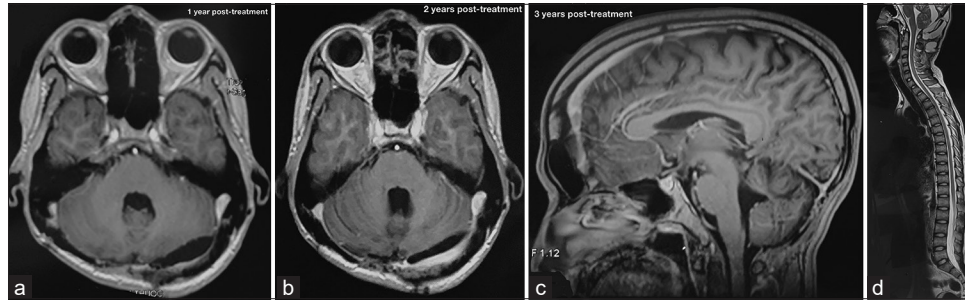


Figure 2: The brain and spine MRI follow-ups showed no tumor remnant and metastasis at 1-year, 2-year, 3-year posttreatment.

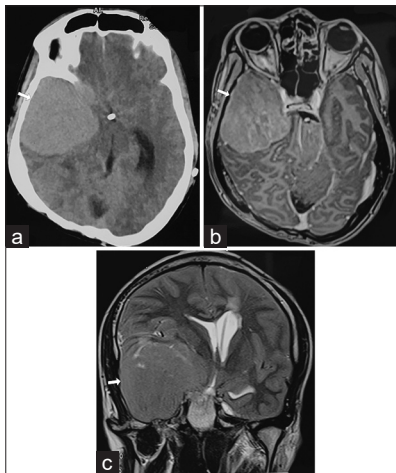


Figure 3: After a 4-year follow-up, brain computed tomography (a) illustrated a temporal mass, which was hyperdense on computed tomography. On MRI, it enhanced heterogeneously on T1W postgadolinium (b) and hyperintense on T2W sequence (c).

which include: (1) absence of germ cell tumors outside the nervous system; (2) absence of pineal, suprasellar, and other intracranial or spinal localization; (3) presence of single or multiple cerebellar lesions without CSF spread at the diagnosis. Of note, the diagnosis of primary cerebellar germinoma may not be suspected preoperatively.^[9] Therefore, surgery is usually indicated in primary cerebellar germinomas because of its favorable site for total resection and histopathological examination.

Furthermore, the common sites of recurrence are the ventricle and spine, whereas our case had a late recurrence at the middle cranial fossa, an unusual location. Thus, the preoperative diagnosis of recurrent germinoma at the middle cranial fossa was more challenging. In this case, surgery and histopathological assessment were essential for a definitive diagnosis. Besides, immunohistochemical staining may be helpful to rule out differential diagnoses in patients with unusual localizations and untypical histological features.^[9] For example, pineal parenchymal neoplasms, oligodendrogliomas, central neurocytomas, malignant lymphomas, melanomas, and metastatic carcinomas do

not express PLAP, whereas they show positive staining for GFAP or S-100 or both. Additionally, AFP and cytokeratin are merely two striking examples. This staining plays a vital role in validating the diagnosis of pure germinomas, thus excluding other germ-cell tumors or the presence of different germ-cell components within the tumor mass.

Despite high radiosensitivity, the proportion of recurrent germinoma after complete response to radiotherapy is estimated to be 6–17%.^[10,11] The median time to recurrence was 30.3 months.^[6] According to previous literature, the majority (>80%) of recurrent germinoma developed within the first 5 years.^[7,12] The most prolonged period of recurrence ever reported is 17 years.^[12] The literature also illustrated that recurrence rates were roughly 25% and 6% after 5 and 10 years, respectively. Despite the fact that recurrent germinoma was associated with poor prognosis, asymptomatic patients may have a better survival rate. Therefore, regular surveillance follow-ups with routine neuroaxis MRI should be recommended to detect recurrence early for all patients with intracranial germinomas.^[6]

Salvage treatments for recurrent intracranial germinoma vary among previous studies. More than half (58.8%) of patients received salvage radiotherapy and chemotherapy for recurrent germinoma. In which CSI was the most preferred choice of radiotherapy.^[6] The survival rates for those with salvage CSI, non-CSI radiotherapy, and no radiotherapy were 92.9%, 60.0%, and 35.8%, respectively.^[6]

Regarding chemotherapy for germinoma, chemotherapy alone cannot be used due to its due to dismal survival rates (5-year PFS <50%).^[4] However, the alternative approach has become more and more prevalent, which is “induction” chemotherapy followed by a reduction radiotherapy dose. This approach aims to decline the neurocognitive and endocrine toxicities associated with radiation therapy. Wang *et al.* demonstrated the comparative 5-year overall survival of radiotherapy alone and chemotherapy + radiotherapy in pediatric and adult patients.^[13] Concurrently, he also admitted that for localized disease radiotherapy alone (CSI) group had significantly better 5-year progression-free survival than the chemotherapy + radiotherapy group (97% vs. 88%,

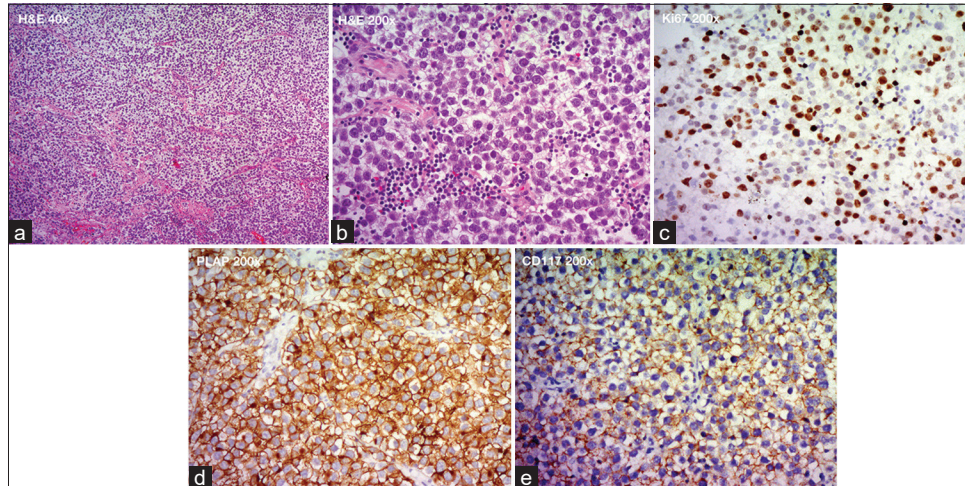


Figure 4: The histopathological examination revealed germinoma. The immunohistochemistry staining was CD117 (+), PLAP (+), Ki67 (+), β -hCG (-), AFP (-), LCA (-), S100 (-), Synaph (-), GFAP (-), and CK (-).

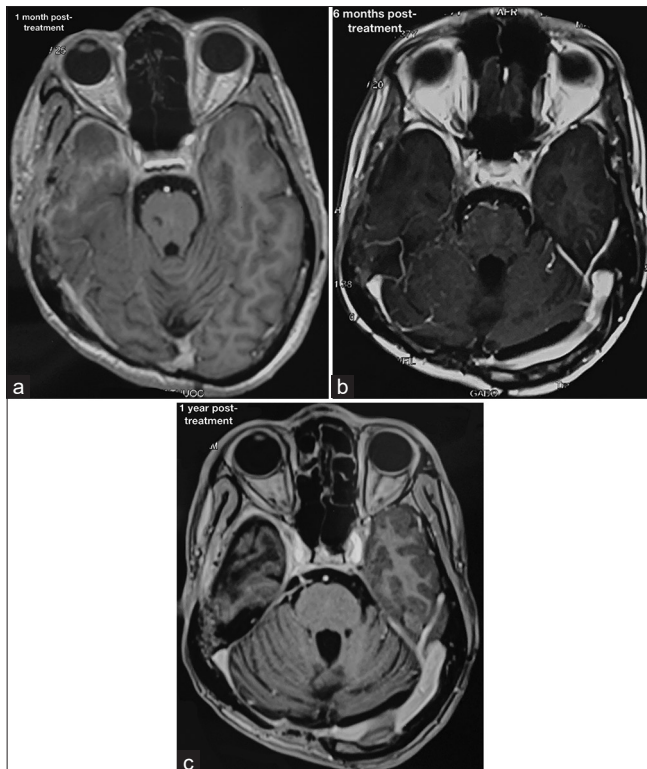


Figure 5: The 1-month (a), 6-month (b), and 1-year (c) postoperative MRI showed no tumor remnant.

$P = 0.04$). This had been shown in SIOP CNS GCT 96 trial (the largest multicenter trial).^[3] This result was also proved in a Korean study later.^[5] Therefore, our patient did not receive “induction” chemotherapy before the first radiotherapy. In the case of recurrent germinoma, as our common sense, salvage chemotherapy and subsequent radiotherapy is the most effective treatment. However, in univariate and multivariate

analysis, salvage chemotherapy and high-dose chemotherapy were not significant predictors of survival after recurrence.^[6] Thus, our patient did not receive induction chemotherapy before the second radiotherapy.

Regarding prognostic factors, age at diagnosis, gender, primary site, time to recurrence, site of recurrence, and patterns of failure were not statistically significant on univariate analysis. On multivariate analysis, Hu *et al.* demonstrated that salvage radiotherapy and initial radiotherapy doses were significant predictors of better survival time after recurrence. Interestingly, patients who received initial radiotherapy with intermediate doses had better outcomes than those with high doses ($P = 0.049$).^[6]

CONCLUSION

The primary cerebellar germinoma is exceptional and difficult to diagnose preoperatively. Its recurrence after a complete response to radiotherapy is unique. Surgical resection, if possible, and adjuvant CSI are the most effective salvage treatment for recurrent germinoma. Regular surveillance follow-ups with routine neuroaxis MRI should be recommended to detect recurrence early for all patients with intracranial germinomas.

Ethical approval

The study was approved by the Research Ethics Committee of Hanoi Medical University. The procedures used in this study adhere to the tenets of the Declarations of Helsinki.

Research registry

Not applicable – this is a single case report, not a systematic review or meta-analysis. Moreover, we attest that it is not a ‘first in man’ study, either.

Declaration of patient consent

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

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Nil.

Conflicts of interest

There are no conflicts of interest.

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