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CASE REPORT

Remarkable efficacy of temozolomide for relapsed spinal myxopapillary ependymoma with multiple recurrence and cerebrospinal dissemination: a case report and literature review

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Abstract

Purpose Myxopapillary ependymomas are intradural tumors which grow from the terminal filum of the spinal cord. Although they are classified as WHO grade I, they sometimes cause cerebrospinal fluid dissemination or local recurrence. In this report, we describe a case in that temozolomide (TMZ) showed remarkable efficacy on a recurrent spinal myxopapillary ependymoma.

Case report A 26-year-old female underwent resection of an intradural myxopapillary ependymoma at L5 initially. Although an en bloc total resection, including the capsule, could be achieved, she needed two additional tumor resection surgeries with postoperative radiotherapy at L4 and at L3 (2 and 6 years after the initial surgery, respectively). Moreover, 4 years after the initial surgery, a disseminated metastatic tumor occurred at T11/12 and local radiotherapy was not effective. After the third surgery, an aggressive adjuvant therapy was necessary because there was a high risk of another recurrence. Therefore, TMZ was administered for 1 year. After 6 months of TMZ treatment, remarkably, the disseminated metastatic tumor at T11/12 had disappeared completely. Presently, 6 years after finishing the TMZ treatment, the follow-up MRI has shown no recurrence in the brain and whole spine.

Conclusions TMZ is usually used in the treatment of glioblastoma and, recently, it has been reported to be effective for the lower grade spinal gliomas including spinal intramedullary ependymomas. However, for myxopapillary ependymomas, there has been no report that TMZ is effective. According to our results, TMZ could be one of the possible candidates for adjuvant therapy in multiple recurrent myxopapillary ependymomas.

Keywords Spinal cord tumor · Microscopic surgery · Chemotherapy

Introduction

The World Health Organization classification (WHO) classified ependymomas into the following four categories: subependymomas (WHO grade 1), myxopapillary ependymomas (WHO grade 1), ependymomas (WHO grade 2) and anaplastic ependymomas (WHO grade 3).

Among them, myxopapillary ependymomas usually occur in the terminal filum of the spinal cord. Myxopapillary ependymomas are classified at grade I according to the World Health Organization classification due to their slow growing nature.

However, it is known that some myxopapillary ependymomas result in poor prognoses [1–3], because of cerebrospinal fluid (CSF) dissemination or local recurrence of the tumor near the surgical site. Klekamp reported that the

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overall recurrence rates were 6.6, 19.0, and 37.0% after 1, 10, and 20 years, respectively [4].

Therefore, adjuvant therapy is important. Nakamura et al. recommend radiotherapy on the brain and whole spine when a piece meal resection is performed due to the rupture of the tumor capsule during surgery to prevent the local recurrence and CSF dissemination [5].

Chemotherapy has been suggested as a potential treatment to prevent recurrence, but its efficacy has not been established in Myxopapillary ependymomas. In this report, we describe a case in that temozolomide (TMZ) showed remarkable efficacy on a recurrent spinal myxopapillary ependymoma.

Case report

Initial surgery at L5

A 26-year-old female presented back pain and muscle weakness of the bilateral lower extremities. The MRI showed an intradural tumor at the L5 level (Fig. 1a). Resection surgery was performed (Fig. 1b), and an en bloc total resection including its capsule could be achieved during the first surgery (Fig. 1c). A pathological diagnosis showed the myxopapillary ependymoma. As shown in Fig. 1d, we also removed about a 1-cm length of the filum terminale together with the tumor mass. Pathologically, the MIB-1 proliferation index was 8.3% in the tumor mass, but there was no evidence of the tumor remaining in the margin of the filum terminale (Fig. 1e). After the surgery, her symptoms almost completely disappeared.

Second surgery at L4

However, 2 years after the initial surgery, back pain and leg pain re-occurred and the MRI showed that the tumor re-occurred at the L4 level (Fig. 1f). Then, a resection of the tumor was achieved again with a gross total resection. Pathologically, the MIB-1 index was 9.3%. The patient's symptoms almost completely disappeared except for a slight numbness. Conventional local radiation therapy at L4–5 was performed with a total of 50 Gy in 25 consecutive daily fractions. A follow-up MRI was taken every following year after surgery.

Disseminated tumor at T11/12

4 years after the initial surgery, she did not have any clinical symptoms. However, the follow-up MRI showed a new

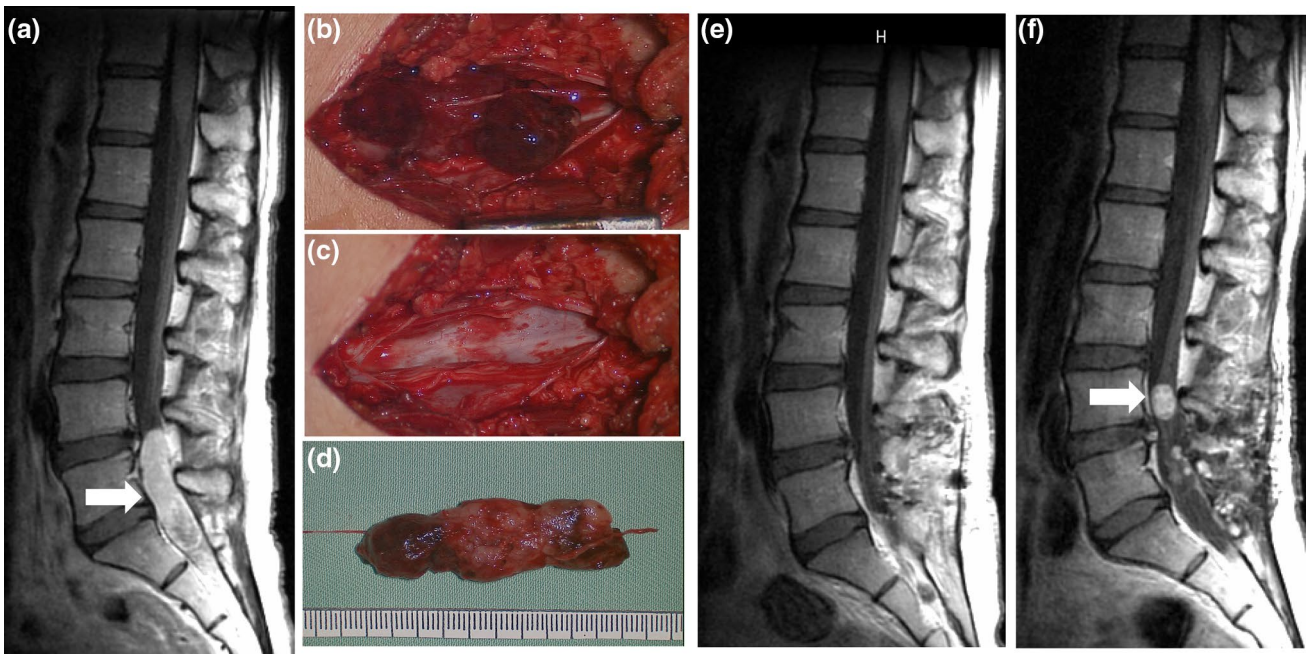

Fig. 1 **a** Prior to the initial surgery when the patient was 26 years old. Gadolinium (Gd)-enhanced MRI showed an intradural spinal lesion at L5–S. **b–d** Intraoperative microscopic photographs. Tumor was resected en bloc with preserving capsule. **e** Gd-enhanced MRI immediately after initial operation showed that the tumor was completely resected. **f** 28 years old Gd-enhanced MRI at 2 years after initial surgery showed that recurrence at L4 occurred. At second surgery, the tumor was resected completely and local radiation therapy was performed at L4–S1

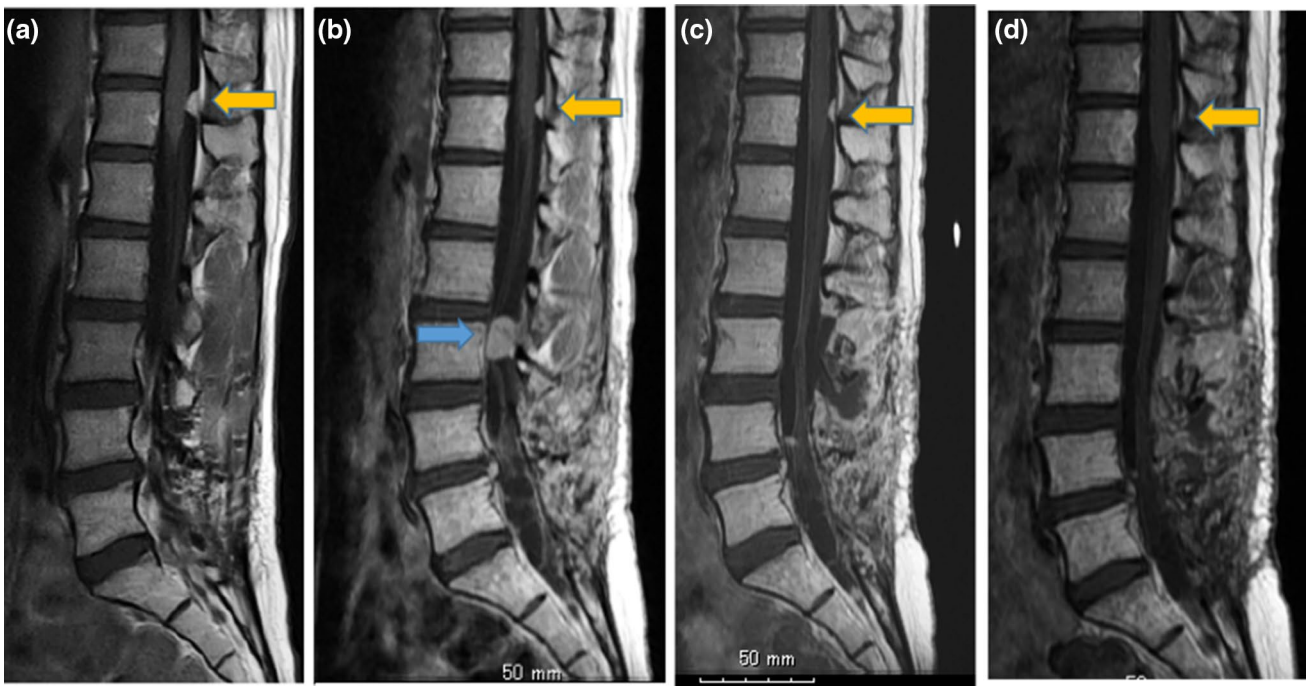

Fig. 2 **a** 4 years after the initial surgery (when she was 30 years old), the follow-up MRI showed a new tumor located on the inner surface of the dorsal dura at T11/12. It was diagnosed as a disseminated metastatic tumor via CSF flow, and local radiotherapy was performed, but the tumor size did not change after radiotherapy. **b** 6 years after the initial surgery (when she was 32 years old), a new tumor re-occurred at the L3 level. **c** Gross total resection was achieved without any paresis. However, there was the residual disseminated metastatic tumor at T11/12. Therefore, TMZ with local radiotherapy was performed. After TMZ treatment, the disseminated metastatic tumor at T11/12 disappeared completely. **d** 7 years after third surgery (when she was 39 years old). The follow-up MRI showed no recurrence in the brain and whole spine. Moreover, the patient had no complaints of any symptoms other than mild numbness

tumor located on the inner surface of the dorsal dura at T11/12 (Fig. 2a), even though there was no tumor on the MRI 1 year previously. It was diagnosed as a disseminated metastatic tumor via CSF flow. Therefore, local radiotherapy was performed with a total of 50 Gy in 25 consecutive daily fractions, but the tumor size did not change after radiotherapy. Because it was asymptomatic, the patient had follow-ups without any other treatments; an MRI was taken every 6 months.

Third surgery at L3

Although the size of the disseminated metastatic tumor at T11/12 did not change, 6 years after the initial surgery, a new tumor re-occurred at the L3 level (Fig. 2b). The patient complained of mild leg pain without paresis, but the tumor size grew rapidly within 3 months. Therefore, resection surgery was performed again. A gross total resection could be achieved without any paresis. The pathological diagnosis showed a myxopapillary ependymoma. Pathological findings showed that there were no obvious malignant findings. The MIB-1 proliferation index was 10%.

Adjuvant therapy after the third operation

Because, to this point, three operations were necessary due to the multiple local tumor recurrences, and there was the residual disseminated metastatic tumor at T11/12, an aggressive adjuvant therapy was necessary (Fig. 2c).

Therefore, temozolomide (TMZ) was administered in addition to the local radiotherapy at L3 with a total of 40 Gy in 20 consecutive daily fractions. First, a 42-day TMZ treatment, with local radiotherapy at L3, was performed every day at a dose of 75 mg per square meter of body-surface area per day. After a 4-week break, we planned to initiate 6 cycles of adjuvant 5-day TMZ treatments every 28 days at regular cycles at a dose of 150 mg per square meter per day.

During the first 42-day TMZ treatment and the first cycle of 5-day adjuvant treatment, no side effects occurred. However, after the second cycle, a blood examination showed a white blood cell decrease. The neutrophil count was around 1500 per cubic millimeter. Although there were no clinical symptoms, we waited for the recovery of white blood cells and delayed the third cycle until the fifth month after starting the first 5-day cycles of adjuvant chemotherapy.

After the third cycle, a follow-up MRI showed that there was no tumor recurrence at the lumbar lesion. Furthermore,

remarkably, the disseminated metastatic tumor at T11/12 disappeared completely. At this point, we discussed with the patient whether to continue chemotherapy or not and decided to perform a fourth adjuvant 5-day TMZ cycle at the eighth month after starting the 5-day cycles. At 1 year after starting TMZ, a follow-up MRI showed that there was no tumor in the brain and whole spine. Therefore, we decided to stop the treatment.

After finishing the TMZ treatment, follow-up MRIs of the brain and whole spine have been taken every year. Presently, 6 years after finishing the TMZ treatment (13 years after the initial surgery) the follow-up MRI has shown no recurrence in the brain and whole spine (Fig. 2d). Moreover, the patient has had no complaints of any symptoms other than mild numbness.

Discussion

Our results demonstrated that TMZ was effective for the recurrent myxopapillary ependymoma. Before the usage of TMZ, the patient required three surgeries due to the local recurrences during an 8-year period, and the disseminated metastasis on the surface of dura at T11/12 remained despite the previous radiotherapy.

According to the previous papers, there is a low risk of recurrence after en bloc total resection of myxopapillary ependymomas [5]. However, in the current case, recurrences occurred despite the gross total resection in the first surgery. Although Awaya et al. [6] reported a case with anaplastic-like myxopapillary ependymoma in their pathological findings, our case did not show such anaplastic pathological characteristics. The MIB-1 proliferation index showed higher values than the average value in myxopapillary ependymomas, reported by Prayson [7] but they also reported that MIB-1 labeling indices are unreliable predictors of tumor recurrence in cases with myxopapillary ependymomas. Therefore, we could not clarify the reason for multiple recurrences after a total en bloc resection while preserving the capsule in the current case, and we can only recommend performing a follow-up with the patient even after a total en bloc resection.

Due to the multiple local recurrence of the tumor and disseminated metastatic tumor at T11–12, we believed that there was a high risk of another local recurrence and dissemination after the third surgery. Therefore, a more aggressive adjuvant therapy was indispensable in her treatment after the third surgery.

TMZ is an oral chemotherapy drug which alkylates DNA by delivering a methyl group to the purine bases of DNA at O6-guanine, N7-guanine, and N3-adenine. The primary cytotoxic event of TMZ is O6-methylguanine induction, which leads to the insertion of thymine instead of cytosine during cellular replication. This causes double-strand breaks, failure of DNA replication, and finally cell death [8]. It has been reported to be effective in the treatment of glioblastoma, particularly in combination with radiotherapy, although the long-term effectiveness was limited because a glioblastoma tumor is such an aggressive malignant tumor [9].

Recently, Chamberlain et al. [10] reported that TMZ was also effective for the lower grade spinal gliomas in adults including grade II astrocytomas which had recurrence in spite of surgery and radiotherapy. They demonstrated that tumors became smaller after TMZ usage in 4 cases, no change in 12 cases, and grew in 6 cases.

Moreover, there were several reports of the application of TMZ for intramedullary spinal ependymomas. Kim et al. [11] used TMZ for two cases with spinal ependymomas: one case with the malignantly transformed type being stable until 21 months, and one case with the anaplastic type being non-affected. Ruda et al. [12] used TMZ for intracranial ependymomas including ten cases with grade III and eight cases with grade II, and there were complete responses in 5%, partial responses in 17%, stable in 39%, and progression in 39%. Moreover, Meco et al. [13] reported a study in that ependymoma stem cells were highly sensitive to TMZ in vitro and in orthotopic models.

For myxopapillary ependymoma, there has been only one case report in that Fegerl and Marosi [14] used TMZ to treat large intrathoracic masses which were diagnosed as delayed metastases of a coccygeal myxopapillary ependymoma that had been resected 20 years before. Although TMZ was administered for 4 months, the metastases had progressed and TMZ was not effective unfortunately.

When disseminated metastases occur in the spinal cord after surgery and radiotherapy, there are few available options except for the usage of TMZ. Among previous reports, TMZ was also reported to be useful for treating various disseminated metastases, for example, from paraganglioma [15], glioblastoma [16], etc.

In the current case, therefore, although the effectiveness of TMZ had not been clarified for recurrent myxopapillary ependymoma, TMZ with radiotherapy was administered after discussing the merits and demerits of TMZ usage with the patients and her family.

After TMZ usage, the disseminated metastatic tumor at T11/12 disappeared and no local recurrence occurred with no evidence of new disseminated metastasis in the brain and whole spine in the follow-up MRI, 6 years since finishing TMZ usage. Therefore, this is the first report demonstrating the effectiveness of TMZ for myxopapillary ependymoma.

On the other hand, when chemotherapy is performed, the toxicity risk is one of the most important factors. In the current case, the decrease in the number of white blood cells occurred. The neutrophil count was around 1500 per

cubic millimeter and was classified as a grade-1 side effect in Common Terminology Criteria for Adverse Events (CTCAE). Grade-1 is classified as a mild adverse event; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Therefore, we delayed our TMZ treatment protocol and, fortunately, the white blood cell count recovered immediately after the secession of TMZ. There has been no other side effects 6 years after TMZ usage.

Bae et al. reported that among 300 malignant glioma patients treated with TMZ, a total of 209 patients (69.7%) reported 618 toxicities. In their study, 255 toxicities (36.4%) were CTCAE grade 1, 299 (48.4%) were grade 2, 81 (13.1%) were grade 3, and 13 (2.1%) were grade 4. There was no mortality due to TMZ. Therefore, the reported severe toxicity risk is not so high.

Nevertheless, we would like to emphasize a potential risk of delayed toxicity due to DNA damage caused by TMZ. More attention should be paid to the delayed toxicity risks in cases with myxopapillary ependymomas than in cases with glioblastomas because patients with myxopapillary ependymomas have a longer expected life time. Furthermore, significant caution is necessary when TMZ is administered to women of childbearing age, like our patient, because TMZ has the risk of teratogenicity, fetotoxicity, infertility, etc.

Recently, the O(6)-methylguanine-DNA methyltransferase (MGMT) has been recognized as a useful predictor for the effectiveness of TMZ. If we could have predicted the effectiveness of TMZ before treatment, we would have been able to avoid unnecessary toxicity risks. Therefore, we now recommend performing MGMT prior to TMZ usage for such cases, although MGMT was not checked in the current case because it was not a common test, at the time, when we decided to start TMZ treatment.

It is still controversial whether TMZ is effective for myxopapillary ependymomas because this is the only case report. Therefore, we cannot clarify the best treatment for recurrent myxopapillary ependymomas, but there are very few options for such patients. We recommend considering the administration of TMZ in cases with recurrent myxopapillary ependymoma, especially when surgery and radiotherapy have been ineffective, although further examination will be necessary.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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