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Longest survival with primary intracranial malignant melanoma: a case report and literature review

Longest survival with PIMM

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Abstract

BACKGROUND

Primary intracranial malignant melanoma (PIMM) is rare, and its prognosis is very poor. It is not clear what systematic treatment plan can achieve long-term survival. This case study attempted to identify the optimal strategy for long-term survival outcomes by reviewing the PIMM patient with the longest survival following comprehensive treatment and by reviewing the related literature.

CASE SUMMARY

The patient is a 47-year-old Chinese male who suffered from dizziness and gait disturbance. He underwent surgery for right cerebellum melanoma and was subsequently diagnosed by pathology methods in June 2000. After the surgery, the patient received 3 cycles of chemotherapy but relapsed locally within four months. Following the second surgery for total tumor resection, the patient received an injection of NDV-modified tumor vaccine, interferon and β-elemene treatment. The patient was tumor-free with a normal life for 21 years before the onset of the recurrence of melanoma without any symptoms in July 2021. A third gross-total resection with adjuvant radiotherapy and temozolomide therapy was performed. The brain MRI showed no residual tumor or recurrence 3 mo after the 3rd operation, and the patient recovered well without neurological dysfunction until the last follow-up in June 2022, which was 22 years following the initial treatment.

CONCLUSION

It is important for patients with PIMM to receive comprehensive treatment to enable the application of the most appropriate treatment strategies. Long-term survival is not impossible in patients with these malignancies.
Key Words: Primary intracranial malignant melanoma; Immunotherapy; Newcastle disease virus-modified tumor vaccine; β-elmene; Long-term survival; Case report

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Core Tip: PIMM is quite rare, and its prognosis is poor. Comprehensive treatment, including the surgical resection and the maintenance of postoperative adjuvant treatments by NDV-modified tumor vaccine, Interferon and β-Elemene may prolong patient survival. We hope that the PIMM case reported in this paper, which describes a patient whose life was extended by 22 years, can provide useful information for the reference of medical practitioners and patients alike, thereby boosting their confidence in adopting the treatment reported herein.

INTRODUCTION
Malignant melanoma (MM) is the most dangerous type of skin cancer. Melanoma accounts for approximately 10% of all patients who develop brain metastases. Approximately one-third of patients with newly diagnosed metastatic melanoma are estimated to have brain metastases [1]. Primary central nervous system (CNS) melanoma accounts for approximately 1% of all melanomas [2, 3]. The diagnosis is very challenging. Three criterions to diagnosis of primary CNS melanoma: (1) no melanoma is found on the skin or eyeball, (2) no surgery history of skin or eyeball melanoma is applied, and (3) no metastatic melanoma is found in internal organs, Willis et al. Currently, it is believed that the source of primary CNS malignant melanoma may be the
melanocytes of the pia mater. From a molecular point of view, the collision of the key structures of these cells leads to focal neurological symptoms, which in turn leads to the formation of malignant melanoma. This disease usually occurs in people under the age of 50, and there is no obvious sex difference. Generally, the disease course is short, and the survival period is usually several months to several years. The survival period is not significantly related to a patient's age. The diagnosis is usually confirmed by pathological biopsy of specimens obtained by surgery. The histopathology has the following characteristics: tumor cells are different sizes, most of which are larger than normal cells; the cells are polygonal in shape; the nuclei are round; the nucleoli are obvious; and most of them have obvious nuclear divisions. The cells are consistent with the appearance of malignant melanoma in other parts. In terms of immunohistochemistry, immunohistochemical markers specific to malignant melanoma include HMB45, S100, SOX10. The positive rate is usually greater than 90% [10], which is a reliable basis for diagnosis. In terms of treatment, surgical resection is the main treatment for CNS malignant melanoma. Removal of the tumor can prolong survival to a certain extent, but the overall prognosis is very poor. Due to the presence of the blood-brain barrier, chemotherapy usually does not take effect. Radiotherapy can delay tumor recurrence, but it does not significantly help prolong the survival of patients. Therefore, it can be used but with little significance. Immunotherapy is only effective for metastatic malignant melanoma [5]. It has been reported recently that bevacizumab has a certain effect on patients with malignant melanoma brain metastases [6]. However, more treatment methods for primary central nervous system malignant melanoma still need to be developed.

CASE PRESENTATION

Chief complaints

A 47-year-old man visited our hospital for regular brain MRI follow-up after
surgery to treat PIIM 21 years ago.

**History of present illness**

All symptoms were denied, and clinical examination findings were negative. The regular brain MRI in July 2021 showed a mixed iso-/hyperdensity mass in the right cerebellopontine angle (CPA) measuring $34 \times 21$ mm with a clear margin (Figure 2), so the likelihood of recurrence of the melanoma was regarded as highly possible again. No melanoma was found on the skin or eyeball. Surgical treatment with gross-total resection (GTR) was arranged on 12th August 2021, which was the third operation.

**History of past illness**

In June 2000, the patient suffered from dizziness and gait disturbance. Brain MRI revealed a lesion in the right cerebellum, and surgical treatment was applied. Melanoma was considered by histopathology examination. The patient received 3 cycles of adjuvant chemotherapy by dacarbazine (DTIC) $400$ mg (d1-5), vindesine (VDS) $4$ mg (d1, d5), cisplatin (DDP) $30$ mg (d1-5) and interferon 3 MIU subcutaneously 3 times a week. However, the tumor relapsed locally 4 mo after the operation (Figure 1). The patient received a second surgical treatment in October 2000. Histopathology examination revealed melanoma (Figure 1). After the two operations, it was considered that melanoma was not sensitive to radiotherapy and chemotherapy. To prolong his survival period and improve his quality of life, our team used the experimental treatment of Newcastle disease virus (NDV)-modified tumor vaccine through subcutaneous injection 2 times [6]. Additionally, the patient received interferon (3 MIU subcutaneously 2 times a week) and $\beta$-elemene ($500$ mg QD x 14 days each month) for the first 6 mo, followed by maintenance treatment of interferon and $\beta$-elemene every 3 to 4 mo, resulting in a total treatment court for 43 mo up to November 2004. He had undergone
regular follow-up, and his condition had been healthy, including tumor-free survival during these 21 years.

*Personal and family history*

The patient had no specific personal or family history.

*Physical examination*

The patient had no neurological symptoms. No melanoma was found on the skin or eyeball.

*Laboratory examinations*

No specific findings of routine blood tests, blood biochemistry or immune indices were noted.

*Imaging examinations*

The regular brain MRI in July 2021 showed a mixed iso-/hyperdensity mass in the right cerebellopontine angle (CPA) measuring 34 × 21 mm with a clear margin (Figure 2), so the likelihood of recurrence of the melanoma was regarded as highly possible again.

**REVIEW OF CASES AND LITERATURE**

We searched through the primary intracranial malignant melanoma (PIMM) in English and Chinese language papers by the search engine of PubMed and Medline-based with keywords of primary intracranial melanoma or primary cerebral melanoma and surgery or radiotherapy or chemotherapy or immunotherapy. All studies published during the period from 1993 to 2021 were collected. Metastases of CNS melanocytic neoplasm and intracranial meningeal melanocytoma were ruled out. In addition, metastatic melanoma without a known primary tumor was also ruled out, as patients who did not
undergo workup with PET or whole-body CT were not enrolled in this study. Sampson et al.\cite{1} reported that the overall median survival of patients without treatment for MM was 3 to 4 mo, the one-year survival rate was 9% to 19%, and only rare patients had prolonged survival. MM treated with SRS followed by either immunotherapy or targeted therapy. The median overall survival (OS) was 11 mo, and the one- and two-year OS rates were 49.5% and 27.4%, respectively, according to Gaudy-Marqueste et al.\cite{7}, which dramatically improved survival in MM. Baena et al.\cite{8} and Arai et al.\cite{9} summarized 130 patients with PIMM over the past 30 years. They reported that the PIMM mean age was 45.8 years. No significant sex difference was found. Intracranial hypertension and focal neurologic deficits were commonly observed. The mean OS of gross total resection (>22 mo) was significantly better than that of surgeries leaving behind residual tumor (12 mo). While there was no significant difference in the survival period between patients with and without adjuvant therapies, leptomeningeal enhancement diagnosed in the initial MRI was the worst prognostic factor. Nakagawa et al.\cite{10} reported a patient with PIMM who survived for 9 years and 6 mo after 3 surgeries to remove the tumor and after receiving adjuvant chemoradiation therapy in 1989. Onal et al.\cite{11} reported a long-term OS of 17 years in a patient who underwent gross total resection of PIMM and received adjuvant chemotherapy with methyl-CCNU in 2006. Li et al.\cite{12} established an OS rate of 62.8% at 6 mo and over 5 years at 17.2%, with an estimated median survival time (EMST) of 12 mo. The EMST was better in patients with a solitary-type lesion for 13 mo than in those with a diffuse-type lesion for 5 mo. In their review of all patients, those receiving gross total resection with adjuvant radiation therapy and/or chemotherapy had significantly higher one- and five-year OS rates, which were 73% and 40.1%, respectively, and a longer EMST (53 mo) than patients who underwent gross total resection alone (20.5 mo) or radiation and/or chemotherapy without resection (13.0 mo). In our
case, a 47-year-old male patient was initially diagnosed with PIMM and survived for 22 years after comprehensive treatment, including surgical removal of the tumor three times, adjuvant chemoinmunoradiotherapy, and β-elemene, an extract from the natural plant turmeric with antitumor activity. This is the longest OS case ever reported in the English and Chinese literature according to a search of the PubMed and MEDLINE databases.

MULTIDISCIPLINARY EXPERT CONSULTATION

Not applicable.

FINAL DIAGNOSIS

The patient was diagnosed with recurrent right CPA PIMM.

TREATMENT

During the third operation, it was observed that the tentorial margin had obviously turned black, and a dark black mass was seen under the petrosal vein. The tumor was solid, soft, tender, black and rich blood supplied to attach to the dura mater, sparing the parenchyma of the cortex. The facial nerve was pushed outward and upward, and the trochlear and trigeminal nerves were pressed forward and downward. The tumor had a complete and smooth capsule, with a dark coal-like appearance and a black sesame paste-like content (Figure 3). The histopathology examination revealed melanoma (Figures 4A-C) positive for HMB45, MelanA, S-100, SOX-10, and p16. The Ki-67 was 8% (+) (Figure 4D). Chromosomal locations of positive genes were detected by FISH in MM: RREB1-6p25/6p11.1-q11.1. Chromosomal locations of negative genes were detected by FISH in MM: CCND1-6q23, MYB-6p25, MYB-6q23/6p11.1-q11.1, PCR method: BRAF gene V600E mutation detection (+), BRAF gene V600K mutation detection (-), Sanger sequencing method: NRAS gene exons 2, 3, and 4 are wild-type,
MGMT gene promoter methylation status (-). Genes variant high-throughput sequencing: loss of heterozygosity in BCL2L11, loss of heterozygosity in HLA-I tumor cells, detection results of immune checkpoint inhibitory molecular markers TMB-L, MSS. Further examination included CT scans of the chest, abdomen, and pelvic region as well as PET scans of the whole brain and body, which were all negative. The patient was discharged from the hospital 10 days after GTR with no complications and went on for adjuvant radiotherapy (IMRT, GTV 45 Gy/9 f, CTV 27 Gy/9 f) and chemotherapy by temozolomide as a 5-day oral schedule every 4 wk (administered at 150 mg/m²/day for the first cycle, then 200 mg/m²/day forward cycles).

OUTCOME AND FOLLOW-UP
Brain MRI showed that no residual tumor or recurrence was found in the right CPA 3 mo after the 3rd operation (Figure 5). Up to the last follow-up on June 17, 2022, the patient recovered well with no recurrence or related sequelae. His condition was fine without neurological dysfunction, and he resumed his normal life.

DISCUSSION
The incidence is 0.005/100,000 for melanoma. There is a slight female predisposition, F:M = 1.5:1. The age range of the primary nodular melanoma is 15 to 71 years, averaging 43 years. Intracranial melanoma is classified as primary or metastatic, and PIMM accounts for 1% of all melanomas [13]. Primary melanoma derives from leptomeningeal melanocytes. Pedersen et al. [14] established the first model of melanoma driven by the oncogenic NRAS gene and reported two cases of children with melanoma of the CNS that presented mutations in the NRAS gene [14]. The CNS melanoma is associated with mutations in the GNAQ and GNA11 genes, however mutations in the NRAS gene are rare in adults [15].
The symptoms and signs are secondary to either the local effects on the CNS parenchyma or hydrocephalus. The rapid progression with increasing ICP may suggest malignant transformation, which results in irritability, vomiting, lethargy, seizures, and so on. The diagnosis of melanocytic lesions relies on histopathological examination. Most benign and malignant melanocytic lesions display melanin pigment distributed within tumor cells, tumor stroma, and the cytoplasm of tumoral macrophages. Rare melanocytomas and fortuitous primary melanomas will not show melanin pigment, consistent with amelanotic melanoma. Histopathological and immunohistochemical examinations are highly sensitive to amelanotic melanoma.

Isiklar et al.\textsuperscript{[16]} classified the MRI performance into four groups: A) the melanotic group, with hyperintensity on T1 and hypointensity on T2; B) the amelanotic group, with iso-/hypointensity on T1 and iso-/hyperintensity on T2; C) the mixed group, suiting neither of the two criteria; and D) the hemorrhagic group, with characteristics of intra/peritumoral hemorrhage. There is hematopoietic neoplasms, cystic changes and necrosis. One of them was suspected to be amelanotic melanoma. In our present case, MRI performance T1-weighted hyperintense and T2-weighted isointensity signals in the melanotic group were noted (Figure 3). The immunohistochemical analysis showed positive staining for HMB-45, S100 and VIM. These results are important in the differential diagnosis of melanoma, particularly the positive staining for HMB-45 which is a specific biomarker for melanoma. Actually, the case in the present study also echoes such findings. These new findings reveal that RREB1 functions as both a transcriptional repressor and transcriptional activator for the transcriptional regulation of target genes. RREB1 is believed to function as a diagnostic biomarker or new drug target for melanoma detection.
Three criterions to diagnosis of primary CNS melanoma: a) the skin or eyeballs are negative for melanoma; b) the skin or eyeballs have no history of melanoma resection; and c) the internal organs are negative for melanoma metastasis. Our presented case with histopathology confirmed MM in CPA. Whole-body examination ruled out the existence of melanoma outside of the CNS, and PIMM was in accordance.

MM, which is highly aggressive and chemoradioresistant, has a poor prognosis and easily metastasizes. The prognosis of PIMM lesions appears to be better than that of metastatic examples. It is clear that total resection of tumors should be the key point for treatment [9,10]. For our case of PIMM, gross total resection was achieved; furthermore, excessive removal of invaded adjacent meninges in the 2nd surgery could be one of the important factors resulting in his long-term survival. Immunotherapy has developed rapidly for MM treatment [17]. The prognosis for patients with melanoma brain metastasis (MBM) has also improved, coinciding with the approval of PD-1 immune checkpoint blockade and combined BRAF/MEK targeting therapy [18]. However, controversy remains for MM in the CNS; at least, there is little clinical evidence showing efficacy for PIMM [19]. With respect to the experience of our case, the patient survived for more than 21 years after the comprehensive treatment. Although this patient suffered a relapse after the first surgery, he continued to survive in the following 21 years or more after the second surgery in conjunction with ensuing adjuvant treatment. It remains questionable which of the following could yield effects apart from surgery: radiotherapy, chemotherapy and immunotherapy. Based on our analysis, gross total resection should be the key leading to curative effects, while postoperative adjuvant treatments are also important, as used in this case. Franak et al. [20] reported in 1998 that the survival rate of AJCC (American Joint Committee on Cancer) stage III malignant melanoma patients was 59%
15 years after NDV oncolysate therapy. NDV has been evaluated as an anticancer agent because this virus has been shown to have direct toxic effects on tumor cells as well as indirect effects that appear to be mediated through stimulation of the host immune system [21,22]. In the case of our patient, we applied NDV-modified tumor vaccine combined with interferon treatments, which could make some contribution; however, this patient received comparatively long-term β-elemene treatment. β-Elemene is a sesquiterpene compound extracted from the herb Curcuma Rhizoma and is used to treat several types of cancer including brain cancers such as gliomas [23]. Studies have shown that β-elemene can inhibit cell proliferation, arrest the cell cycle, and induce cell apoptosis. β-Elemene also regulates the expression of several key molecules that are involved in tumor angiogenesis and metastasis [24]. Furthermore, β-elemene has been shown to have regulatory effects on the immune response; for example, β-elemene transforms the polarization of macrophages from M2 to M1, which is considered to be an antitumor phenotype to kill tumor cells directly and stimulate antitumor T cells [25]. Therefore, it is reasonable to speculate that β-elemene treatment should also have helped this patient in combination with NDV-modified tumor vaccine immunotherapy.

CONCLUSION

PIMM is quite rare, and its prognosis is poor. However, comprehensive treatment, including surgical resection followed by appropriate adjuvant treatment strategies, may prolong patient survival. We hope that the PIMM case reported in this paper, which described a patient whose life was extended by 22 years, can provide useful information for the reference of medical practitioners and patients alike, thereby boosting their confidence in adopting the treatment reported therein.
ACKNOWLEDGEMENTS

All authors contributed substantially to the diagnosis, treatment planning and retrospective analysis of this case. TW, XZ and ZC drafted the manuscript. YC, WH, YL, DH and MD critically revised of the manuscript for important intellectual content. All authors read and approved the final manuscript.
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