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Long-term control of melanoma brain metastases with co-occurring intracranial infection and involuntary drug reduction during COVID-19 pandemic: A case report

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Abstract

BACKGROUND

Melanoma brain metastasis is a common cause of death in melanoma patients and is associated with a poor prognosis. There are relatively few reports on intracranial infections after brain metastasis resection.

CASE SUMMARY

Here we report a case of melanoma brain metastases in a patient harboring a *BRAF* V600E mutation, who experienced intracranial tumor progression despite previous combined treatment with a programmed death (PD)-1 inhibitor, axitinib, and vemurafenib. She repeatedly underwent local therapy, including stereotactic radiosurgery and intracranial surgery, and developed central nervous system infection. Treatment with vemurafenib combined with cobimetinib resulted in an intracranial progression-free survival of 10 mo. During the coronavirus disease 2019 (COVID-19) pandemic, the patient did not visit the hospital for regular vemurafenib treatment, and experienced intracranial progression after involuntary drug reduction for 1 mo. The patient subsequently received various systemic treatments including vemurafenib, PD-1 inhibitor, and chemotherapy, with an overall survival of 29 mo as of September 2020.

CONCLUSION

We report the first case of melanoma brain metastases with co-occurring intracranial infection and unintended drug reduction during the COVID-19 outbreak. Long-term control of the intracranial lesions was achieved with systemic and local therapies.

Key Words: Melanoma; Intracranial infection; Brain metastases; COVID-19; Local therapy; Case report

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Core Tip: We report a melanoma patient with brain metastases who had long-term control of intracranial lesions with the combination of local therapy and BRAF/MEK inhibitor. During the treatment course, the patient experienced intracranial infection and unwanted drug reduction during the coronavirus disease 2019 outbreak.

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INTRODUCTION

Melanoma is a rare, aggressive tumor and the brain is a common metastatic site. Melanoma brain metastasis is associated with a poor prognosis, with a median overall survival (OS) of 3-5 mo^[1,2]. In patients harboring *BRAF* mutations, *BRAF* and *MEK* inhibitors significantly increase the intracranial control rate and OS for brain metastases^[3]. However, compared to extracranial lesions, the duration of response is short; progression of intracranial lesions is the main reason for treatment failure^[4]. Here we report a case of melanoma brain metastases in a patient harboring a *BRAF* V600E mutation; although the patient experienced unexpected intracranial infection and dose reduction, long-term control of intracranial metastases was achieved with a combination of *BRAF*/*MEK* inhibitor and local therapies.

CASE PRESENTATION

Chief complaints

A 46-year-old Asian woman presented with a fever and headache.

History of present illness

The patient had a seizure and the convulsion localized to the right limbs. Magnetic resonance imaging (MRI) of the brain revealed lesions in the left frontal and temporal regions. Surgical removal of the suspected brain metastases was performed on May 20, 2019, but the postoperative pathologic assessment showed only necrotic tissue without tumor cells. On postoperative day 7, the patient presented with a fever and headache.

History of past illness

The patient was diagnosed with acral melanoma with a Breslow depth of 10 mm in 2016 (Figure 1). Metastasis to inguinal lymph nodes was suspected based on Positron emission tomography/computed tomography examination. The patient later underwent extended resection of the primary lesion and inguinal lymph node dissection, with one nodal metastasis in six dissected lymph nodes. Genetic testing revealed the presence of the *BRAF* V600E mutation. Her initial pathologic stage was pT4bN1bM0 (American Joint Committee on Cancer/Union for International Cancer Control, 8th Edition).

The patient received adjuvant high-dose interferon therapy and during a comprehensive review 3 mo later, pulmonary metastasis was detected. She was started on toripalimab [a programmed death (PD)-1 inhibitor that has been approved for the treatment of melanoma in China] combined with axitinib [an oral inhibitor of vascular endothelial growth factor (VEGF) receptors 1, 2, and 3] and had a progression-free survival (PFS) of 4 mo, at which point she experienced pulmonary progression. The treatment was switched to vemurafenib and after 9 mo, brain MRI revealed left frontal lobe metastasis. The patient underwent stereotactic radiosurgery (SRS) for the metastasis (24 Gy in 3 fractions) and continued on vemurafenib. Thereafter, she was examined every 6 wk for 10 mo.

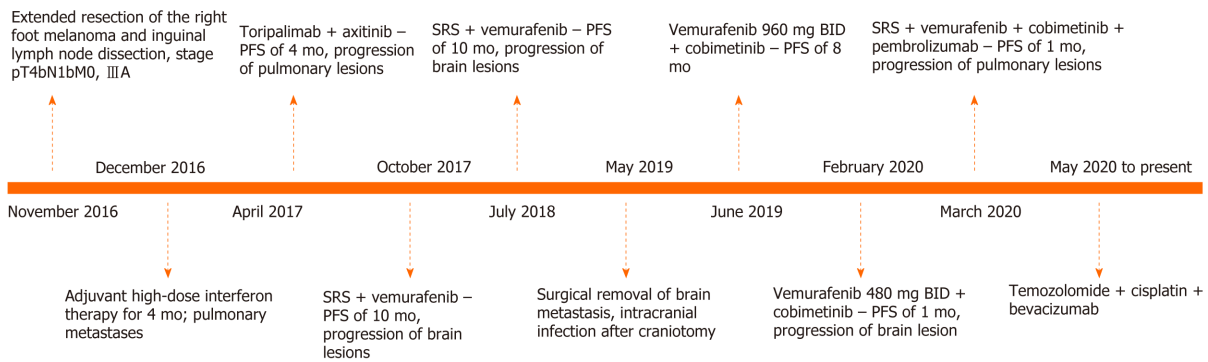


Figure 1 Timeline of the treatment course of the patient. PFS: Progression-free survival; SRS: Stereotactic radiosurgery.

Physical examination

Physical examination revealed signs of meningeal irritation. Vital signs were stable.

Laboratory examinations

A lumbar puncture was performed and the cerebrospinal fluid (CSF) had a white blood cell count of 842/ μ L, with an elevated lactate level (2.5 mmol/L) and reduced sugar level (2.4 mmol/L).

Imaging examinations

Brain MRI demonstrated left frontotemporal alterations following craniotomy (Figure 2).

FINAL DIAGNOSIS

Intracranial infection.

TREATMENT

The patient was treated with meropenem. In the re-examination 3 d later, the CSF test results were normal. A week later, the patient discontinued the antibiotic and was discharged. A combined treatment regimen of vemurafenib + cobimetinib was initiated on the 20th postoperative day.

OUTCOME AND FOLLOW-UP

The patient continued the treatment of vemurafenib + cobimetinib with monthly follow-up. During the coronavirus disease 2019 (COVID-19) pandemic period in February 2020, the patient was unable to visit specialized hospitals that were not in her city of residence to receive vemurafenib treatment because of travel restrictions, and she self-administered a reduced dose of vemurafenib (from 960 to 480 mg, BID) for 1 mo. In March 2020, the patient was re-examined by brain MRI and a new intracranial metastatic lesion was detected. The patient again underwent SRS with sequential vemurafenib, cobimetinib, and pembrolizumab treatments. After one cycle of combined therapy, imaging examination showed the progression of pulmonary metastases; the patient also presented with thrombocytopenia. The treatment was switched to chemotherapy with temozolomide + cisplatin + bevacizumab. As of September 2020, the patient had completed five cycles of combined chemotherapy and had stable disease.

DISCUSSION

Melanoma is highly malignant and often has a poor prognosis. In recent years,

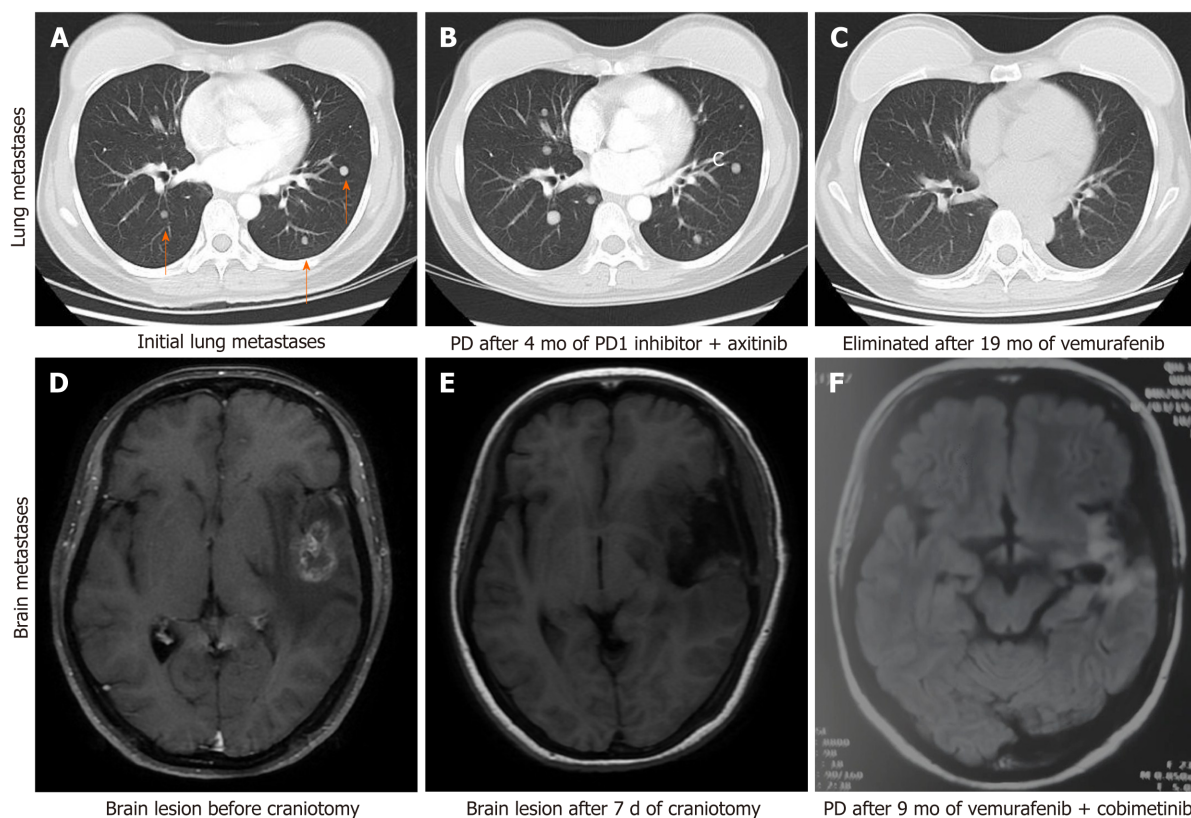


Figure 2 Representative images of lung and brain metastases in our patient at different stages of treatment. A: Initial lung metastases; B: Progression of lung metastases after 4 mo of progressive disease-1 inhibitor + axitinib treatment; C: Lung metastases eliminated after 19 mo of vemurafenib treatment; D: Metastatic brain lesions before craniotomy; E: Metastatic brain lesions 7 d after craniotomy; F: Progression of brain metastases after 9 mo of vemurafenib + cobimetinib treatment. PD: Progressive disease.

advances in immunotherapy and targeted therapy have significantly improved the survival rate^[3,5-7]. For patients harboring *BRAF* mutations, the combination of *BRAF* and MEK inhibitors yields a high response rate with a median survival of 1 year^[5]; immunotherapies such as PD-1, programmed death ligand (PD-L) 1, or cytotoxic T lymphocyte antigen (CTLA) 4 inhibitors have a lower initial response rate but longer response duration. Although in preclinical models *BRAF* and MEK inhibitors enhanced the antitumor efficacy of immunotherapy^[8,9], clinical studies^[10,11] have shown that combining *BRAF* and MEK inhibitors with PD-1 or PD-L1 inhibitor was associated with a higher risk of grade 3/4 treatment-related adverse events necessitating dose reduction or treatment discontinuation in a large number of cases. The optimal treatment regimen for patients with advanced melanoma with *BRAF* mutations has yet to be established.

Our patient preferred the PD-1 inhibitor toripalimab combined with the VEGF inhibitor axitinib as the initial systemic treatment. Axitinib combined with PD-1 blockade has shown promising antitumor activity in patients with metastatic mucosal melanoma, with a median PFS of 7.5 mo^[12]. PFS in our patient was only 4 mo on this treatment, indicating that it was not very effective. Although the patient experienced intracranial progression several times after switching to *BRAF* inhibitor and the combination of *BRAF* and MEK inhibitors, on the latter regimen the disease has been controlled for nearly 30 mo until treatment failure occurred when the patient undertook dose reduction on her own.

This case also illustrates that the combination of local therapy and *BRAF*/MEK inhibitor offers a survival benefit for melanoma patients with brain metastasis. It was previously reported that SRS combined with *BRAF*/MEK inhibitor treatment had a 1-year local intracranial control rate of 72%^[13], and concurrent or post-SRS *BRAF*/MEK inhibitors increased intracranial tumor control and improved OS in patients^[14]. SRS may affect blood-brain barrier permeability and increase the intracranial delivery of *BRAF*/MEK inhibitors^[15]. The strategy of combining local and *BRAF*/MEK inhibitor therapies warrants more detailed investigation in order to determine the optimal modality and sequence of local and *BRAF*/MEK inhibitor therapies, along with the associated risks.

Our patient had an intracranial infection after craniotomy for tumor resection. Intracranial infection is among the most common perioperative complications of craniotomy, with a reported incidence of 1.4%-9.5%^[16-19] and high rates of long-term complications and mortality. There are relatively few reports on intracranial infections after brain metastasis resection, which has an estimated incidence of 4%^[20]. To our knowledge, secondary intracranial infection after resection of melanoma brain metastasis has not been previously reported. Longer operation time, external drainage, and contamination of surgical wounds increase the risk of post-craniotomy intracranial infection^[20-22]. None of these risk factors were present in our case, except for a long operation time (4 h). The infection was quickly controlled after antibiotic treatment, allowing the systematic antitumor treatment to proceed. Our experience with this case also demonstrates that when selecting the local treatment modality for patients with melanoma brain metastasis, severe complications such as intracranial infection should be considered.

Antitumor treatments can be lifesaving and improve patients' prognosis. However, in the context of COVID-19, physicians have become more cautious when administering antitumor therapy. At the same time, because of travel restrictions and lockdown, many patients from small cities or the countryside are unable to visit cancer specialists in major cities for treatment. In this type of public emergency situation, diagnosis and treatment as well as drug distribution *via* the internet are an option. In fact, since the COVID-19 pandemic, our hospital and many others in China and worldwide have established efficient telemedicine and remote counseling systems^[23-25] for the convenience of patients to diminish the possibility of adverse events or disease progression as a result of involuntary dose reduction or treatment discontinuation.

CONCLUSION

Melanoma brain metastasis is a major challenge in the treatment of melanoma. Intracranial infection after craniotomy for resection of melanoma brain metastasis is a very rare event and has not been specifically reported in the literature. Based on our case, patients with melanoma brain metastases can achieve long-term control of intracranial lesions with a combination of BRAF/MEK inhibitors. Our experience also highlights the importance of considering severe complications of local therapy and establishing internet-based diagnosis and treatment procedures.

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