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A Unique Case of Intracranial Amelanotic Melanoma with BRAF V600E Mutation Successfully Treated via Molecular-targeted Therapy

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Abstract

Melanoma carries a high risk of brain metastasis. A small subset of metastatic melanomas, known as amelanotic melanomas, does not present black coloration, reflecting a lack of melanin pigmentation. Here, we report a case of B-Raf proto-oncogene (BRAF) V600E mutation associated with a metastatic brain tumor caused by the amelanotic melanoma. A 60-year-old man was transferred to our department following acute onsets of left upper limb paralysis and convulsion. In the brain imaging, multiple lesions in the right frontal lobe and left basal ganglia were detected, and the presence of an enlarged left axillary lymph node was revealed. Consequently, we removed the right frontal lesion and performed a biopsy of the left axillary lymph node. Histological analysis of both specimens indicated an amelanotic melanoma, and genetic testing revealed a BRAF V600E mutation. The residual intracranial lesions were treated with stereotactic radiotherapy and molecular-targeted therapy, with dabrafenib and trametinib as the systemic treatment. Based on the Response Evaluation Criteria in Solid Tumors, we determined that the patient achieved complete remission (CR) under uninterrupted molecular-targeted therapy over a period of 10 months. After the temporary withdrawal of dabrafenib and trametinib to avoid hepatic dysfunction, a new intracranial lesion appeared. CR of this lesion was achieved following reinstatement of the two drugs. These results suggest that, under limited conditions, molecular-targeted therapy can produce a sustained response against the intracranial metastasis of melanoma, and the therapy with reduced dose is still effective against a recurrent case after cessation of the therapy due to the toxicity.

Keywords: amelanotic melanoma, BRAF V600E mutation, molecular-targeted therapy

Introduction

In Japan, melanoma represents a relatively rare primary site for metastatic brain tumor.[1)] However, melanoma carries a high risk of brain metastasis. After developing brain metastasis, the prognosis remains poor, but several effective treatments have been reported.[2)] Sperduto et al. reported that the median survival time of a newly diagnosed brain metastasis caused by melanoma is 9.8 months.[3)] Thus, there is a need for the development of better treatments for the improvement of outcomes in patients with brain metastasis caused by melanoma.[4)]

Although both primary and metastatic melanoma generally display black coloration, reflecting the presence of melanin pigment, lack of pigmentation as a primary morphological feature cannot be exploited to completely rule

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out the presence of melanoma.[5] Amelanotic melanoma, a small subset of melanomas that do not present pigmentation, is less common than clinically pigmented melanoma, representing approximately 2%-8% of cases.[5] Although melanotic and amelanotic melanoma are visibly different, they share the same somatic gene mutation, known as B-Raf proto-oncogene (BRAF) V600E. Previous research has shown that half of metastatic melanotic melanoma and 70% of amelanotic melanoma present this mutation.[6] Thus, molecular-targeted therapy with BRAF inhibitors is expected to produce significant therapeutic effects for both melanotic and amelanotic melanomas.

When used exclusively, BRAF inhibitors can have undesirable side effects. In particular, they can cause paradoxical activation of the Mitogen-Activated Protein Kinase pathway, which is downstream of BRAF.[7] To avoid this side effect, several clinical trials have led to the recommendation that BARF inhibitors be used in combination with MEK inhibitors when treating melanoma associated with the BRAF V600E mutation. When assessing the efficacy of dabrafenib and trametinib for treating 125 cases of BRAF-mutant melanoma, results from the phase-2 COMBI-MB trial revealed a shorter median progression-free survival (4.2-7.2 months) and duration of clinical response (4.5-8.3 months) for patients with brain metastasis as opposed to those in patients without brain metastasis.[4,8] However, this trial did not report the potential differences between melanotic and amelanotic melanomas. Furthermore, the correct interpretation of results from this trial was complicated by the occurrence of toxic side effects, which led to the interruption of treatment in 50% of the patients and discontinuation in 10% of the patients. There are no previous reports focusing on metastatic brain tumors caused by amelanotic melanoma associated with the BRAF V600E mutation. In addition, there are no reports on the effectiveness of resuming treatment after discontinuing therapy because of toxic side effects.

In this article, we report a unique case of intracranial amelanotic melanoma with BRAF V600E mutation, which was successfully treated with molecular-targeted therapy.

Case Report

The authors obtained written informed consent from the patient. No approval from the institutional review board was sought, as this article is a case report.

A 60-year-old male was admitted into his local hospital due to complaints of left upper limb paralysis and dysarthria. During examination, he had a series of seizures with tremor of the mandible. Then, he was transferred to our department because a head computed tomography (CT) scan had revealed an intraparenchymal lesion. He had undergone excision of seborrheic keratosis near the right scapula at a local dermatology clinic one year prior to admission; however, pathological examination was not performed. There was no notable family history.

On admission, he appeared comfortable, and his vital signs were within normal range. He was alert and oriented, with no apparent neurological impairment, except for a positive Barre's sign in the left upper extremity. Plain CT scan of the head showed a 20-mm high-density lesion in the left basal ganglia (Fig. 1A), a 25-mm mass mainly located in the right inferior frontal gyrus (Fig. 1B), and a 5-mm mass in the right frontal lobe facing the cerebral falx (Fig. 1C). When inspected via magnetic resonance imaging (MRI), the lesion within the left basal ganglia showed heterogeneous intensity in both T1-weighted images (T1WI) and T2-weighted images (T2WI), whereas the right frontal lesions appeared isointense in T1WI and hyperintense in T 2WI (Fig. 1D-I). The T1WI of all the lesions were enhanced by gadolinium (Fig. 1J-L). All lesions were associated with strong edematous changes. Edema was especially pronounced for the right frontal lobe lesion (Fig. 1G-I), which extended to the precentral gyrus and could have therefore caused the observed upper left limb paralysis. Suspecting a metastatic brain tumor, we conducted a whole-body contrast-enhanced CT scan. There was no obvious neoplastic lesion, except for a 30-mm enlargement of the left axillary lymph node and features suggesting rectal mucosal thickening. Blood tests were normal. To alleviate the neurological symptoms and to determine subsequent treatment strategy, we carried out resection of the right frontal lobe lesion.

Using an optical navigation system (StealthStation S8, Medtronic, USA), we performed a right frontotemporal craniotomy to remove the lesion in the right inferior frontal gyrus on hospital day 15. We recorded the motor evoked potentials (MEPs) using the Neuromaster (Nihon Kohden, Tokyo, Japan). The lesion was grayish, soft neoplastic, and not hemorrhagic (Fig. 2A). We were able to achieve gross total resection for this lesion, as it was relatively well demarcated from the surrounding area. The pathological examination of the frozen section was consistent with metastatic brain tumor, while in the histopathological examination, we found tumor cells with well-defined cell borders and a morphology suggestive of epithelial origin (Fig. 2B). Immunohistochemistry (IHC) was negative for the epithelial markers keratin AE1/3, CAM5.2, and p40 + CK14 (Fig. 2C) and positive for S-100, HMB-45, and Melan-A (Fig. 2D-F); these markers are characteristic of melanocytes, however, no melanin pigments were found in the hematoxylin & eosin staining. A whole-body positron emission tomography-CT (PET-CT) scan with the glucose analog 18-F-fluorodeoxyglucose (FDG) showed high accumulation (SUVmax 21.9) in the left axillary lymph node (Fig. 3A). Additional biopsy of the left axillary lymph node showed similar epithelial-like tumor cells without melanin pigment (Fig. 3B), and the IHC suggested metastasis of the melanoma (Fig. 3C and D). Real-time polymerase chain reaction (PCR) applied to the specimen from the intracranial lesion

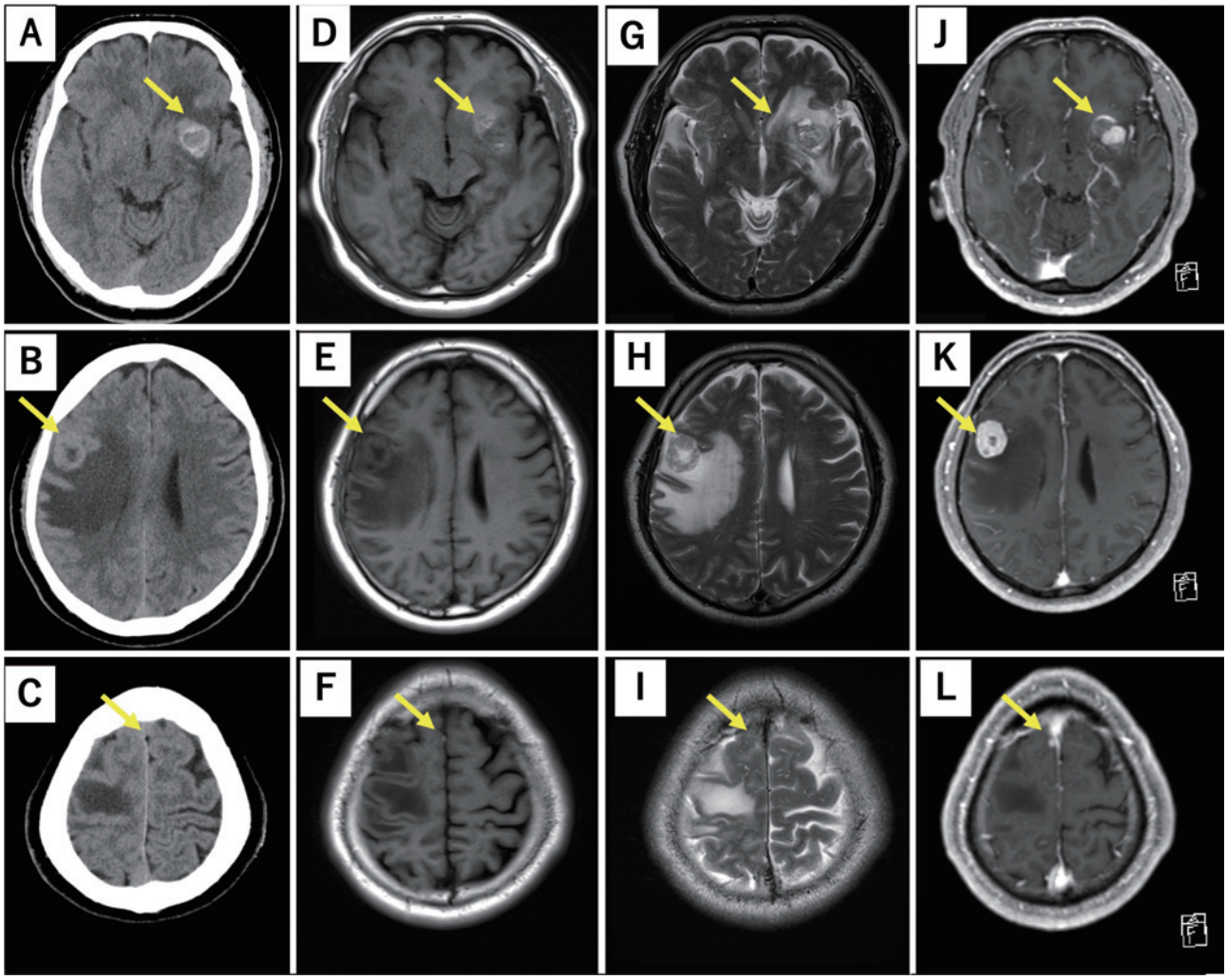

Fig. 1 Preoperative brain imaging. A plain computed tomography (CT) scan showed a 20-mm high-density lesion in the left basal ganglia (A), a 25-mm mass located primarily within the right inferior frontal gyrus (B), and a 5-mm mass in the right frontal lobe facing the cerebral falx (C). In the magnetic resonance imaging (MRI), all lesions showed isointense on a T1-weighted image (T1WI) that was enhanced by gadolinium and hyperintense on a T2-weighted image (T2WI) (D–L). All lesions were associated with strong edematous alterations, especially in the right frontal lobe lesion (G–I).

revealed BRAF V600E mutation, one of the activating oncogenic mutations. There were no malignant findings on any part of the body surface, including the existing scar from the excision surgery for seborrheic keratosis near the right scapula. Due to the difficulties associated with distinguishing between seborrheic keratosis and malignant melanoma, we suspected that the previously excised seborrheic keratosis was the primary lesion. The patient was diagnosed with BRAF V600E-mutant metastatic amelanotic melanoma in the right frontal lobe, the left basal ganglia, and the left axillary lymph node. According to the graded prognostic assessment for melanoma using molecular markers,[3] his score was 2.5, with an expected median survival of 16 months (aged <70 years old; Karnofsky Performance Status, 90-100; extracranial malignancy, present; number of brain metastases, 2-4; BRAF gene status, positive).

Starting one month after surgery, we performed postoperative radiotherapy (30 Gy of stereotactic irradiation in 6 fractions) for the intracranial lesions in the left basal ganglia and in the right frontal lobe facing the cerebral falx. After radiotherapy, the patient complained of aphasia, which was likely caused by cerebral edema, for which he took oral glucocorticoids (betamethasone 4 mg/d) over a period of 6 months. Two months after surgery, we started molecular-targeted therapy with a combination of BRAF inhibitor (300 mg/d of dabrafenib) and MEK inhibitor (2 mg/d of trametinib). Given that the patient was free of local recurrence when investigated with gadolinium-enhanced MRI at one year after surgery, we evaluated the antitumor effect as complete remission (CR) (Fig. 4A-C). Ten months after oral administration, the patient developed grade 3 hepatic dysfunction. We therefore discontin-

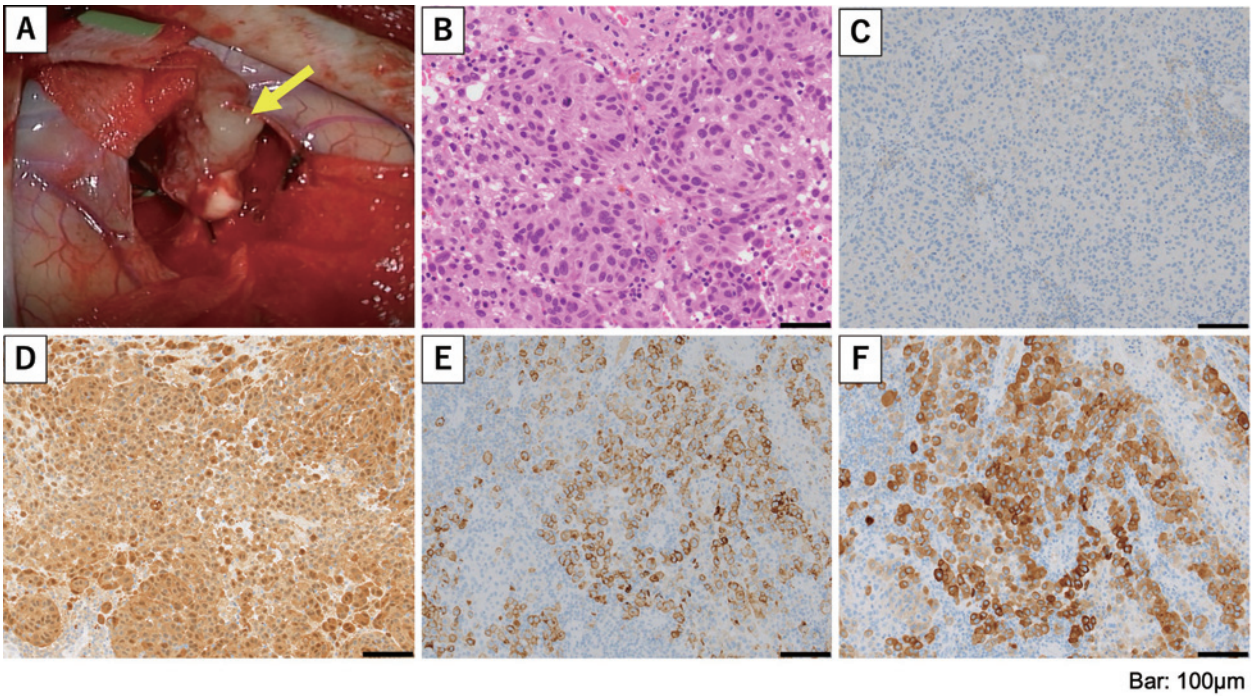

Fig. 2 Macroscopic and microscopic findings from right frontal lesion. (A) Intraoperative photo shows a grayish, soft neoplastic, non-hemorrhagic lesion (arrow). Additional pathological results are visible in (B–F). (B) Hematoxylin-eosin stain, original magnification ×400. We found tumor cells with well-defined cell borders and a morphology indicating epithelial origin. There is no melanin pigment. (C) p40 + CK14, original magnification ×200, showing negative results. (D) S-100, original magnification ×200, showing positive results. (E) HMB-45, original magnification ×200, showing positive results. (F) Melan-A, original magnification ×200, showing positive results.

ued the medication, in compliance with the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0, γGTP: upper limit of normal×5.27). Although the hepatic dysfunction improved within a month, the MRI revealed new lesions in the right parietal lobe and left cingulate gyrus (Fig. 4D) after 3 months of drug withdrawal. In the concomitant whole-body PET-CT with FDG, no new lesions were detected, indicating that the accumulation in the left axillary lymph node had disappeared (Fig. 4E). After resuming the molecular-targeted therapy at reduced doses (200 mg/d of dabrafenib and 1.5 mg/d of trametinib), those lesions disappeared within 3 months, and the therapy was therefore evaluated as CR. At 20 months postoperatively, the patient is still undergoing molecular therapy and is free of any additional recurrence.

Discussion

For the case reported here, we decided to adopt a molecular-targeted therapy with dabrafenib and trametinib. Using this therapy, we successfully treated both the intracranial and axillary lymph node lesions caused by amelanotic melanoma. These lesions possibly originated from a skin lesion presenting as seborrheic keratosis. Therapy was discontinued because of its toxicity, however resuming therapy at a reduced dose remained effective even after the recurrence of the disease.

On the pathological examination of this case, we diagnosed amelanotic melanoma based on the absence of a melanin pigment, the positive IHC results (S-100, HMB-45 and Melan-A), and the positive PCR results for BRAF V600 E mutation. In general, melanoma presents as black coloration, reflecting the presence of melanin pigment. However, melanoma without pigmentation has been reported in the past and is known as amelanotic melanoma, which is difficult to distinguish from inflammatory or benign lesions, even by dermoscopy.[5] Notwithstanding these difficulties, diagnosis based on IHC (S-100, Melan-A, HMB-45, MITF-1, tyrosinase, SOX10, PRAME) remains useful.[9,10] In cases of suspected melanoma, IHC tests should be carried out regardless of the presence or absence of melanin pigmentation. The evaluation of potential BRAF gene mutation is important for the clinical treatment of melanoma. Mutational activation of BRAF is observed in approximately 50% of all melanomas; of these, over 90% involve the V600E mutation.[11] However, approximately 70% of amelanotic melanoma present the BRAF V600E mutation,[12] suggesting that amelanotic melanoma might be more frequently associated with BRAF mutations than other melanomas.

MRI is a useful tool for the diagnosis of metastatic brain tumors, including intracranial melanoma. It is well known

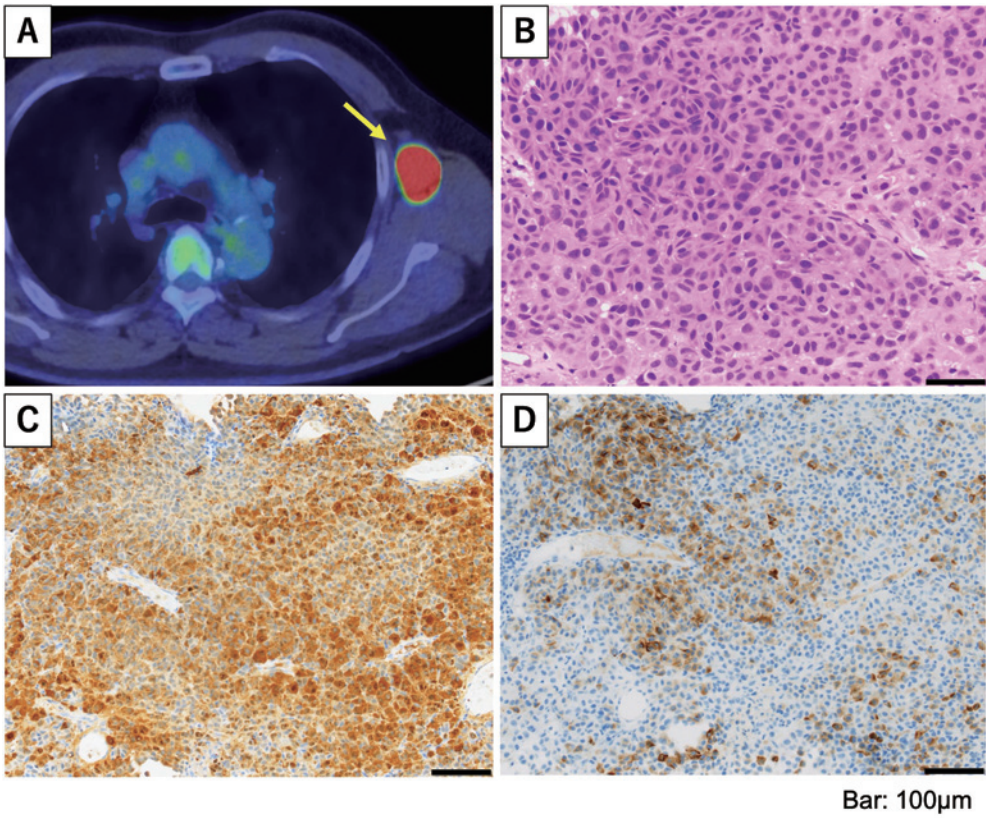

Fig. 3 Radiographic and microscopic findings from the left lymph node lesion. (A) The 18-F-fluorodeoxyglucose (FDG) positron emission tomography (PET)-CT (SUVmax 21.9) shows a 3-cm enlargement and high accumulation within the left axillary lymph node (arrow). (B–D) show pathological examination of the left lymph node lesion from fine-needle biopsy. (B) Hematoxylin-eosin stain, original magnification ×400, showing epithelial-like tumor cells without melanin pigment. (C) S-100, original magnification ×200, showing positive results. (D) HMB-45, original magnification ×200, showing positive results.

that the melanin pigment causes T1 and T2 shortening effects: melanin-rich typical melanoma shows a high T1W1 signal and a low T2WI signal.[13] In contrast, the expected signal pattern for amelanotic melanoma is similar to that for other brain tumors: low T1WI signal and high T2WI signal.[14] In the case examined here, the right frontal lesion showed normal intensity for T1WI and high intensity for T 2WI on preoperative MRI, which was comparable to previous reports. However, the left basal ganglia lesion showed heterogeneous intensity for both T1WI and T2WI. A plausible explanation for this finding is provided by the likely presence of hemorrhage in the left basal ganglia lesion. Isiklar et al. retrospectively evaluated MRI findings from 30 patients with histologically proven intracerebral melanoma. In their report, 30% of pure amelanotic lesions presented hemorrhage, while radiographically identified cases of amelanotic lesions comprising less than 10% of melanin-containing cells on histology presented hemorrhage, central necrosis, and cystic formation.[15] Furthermore, a few case reports have described cyst formations in association with brain metastasis of amelanotic melanoma.[14,16] Given that cyst formation may occur as a result of hematoma involution,[15] our MRI finding may reflect the beginning of cyst formation. Our case serves as a useful reminder of how difficult it is to secure successful diagnosis of amelanotic melanoma on the basis of MRI.

In the case examined here, we conducted systemic treatment following the diagnosis of amelanotic melanoma. The seborrheic keratosis that was previously resected without any pathological examination might be the primary lesion of amelanotic melanoma, given that a subset of melanoma can mimic seborrheic keratosis.[17] Because the left axillary lymph node lesion presented pathological features similar to those of the intracranial lesion, the two lesions may be distant metastases that are both derived from the skin lesion that resembles seborrheic keratosis. Fortunately, both lesions responded well to treatment. These results indicate that it is important to apply systemic therapy even in the presence of intracranial lesions.

According to the graded prognostic assessment for melanoma using molecular markers,[3] our case scored 2.5 with the inclusion of the BRAF V600E mutation, which corresponds to an expected median survival of 16 months. This tool assigns better clinical outcome to BRAF V600E mutations because BRAF-targeted therapy and immunotherapy generally improve outcomes for melanoma.[3] In the

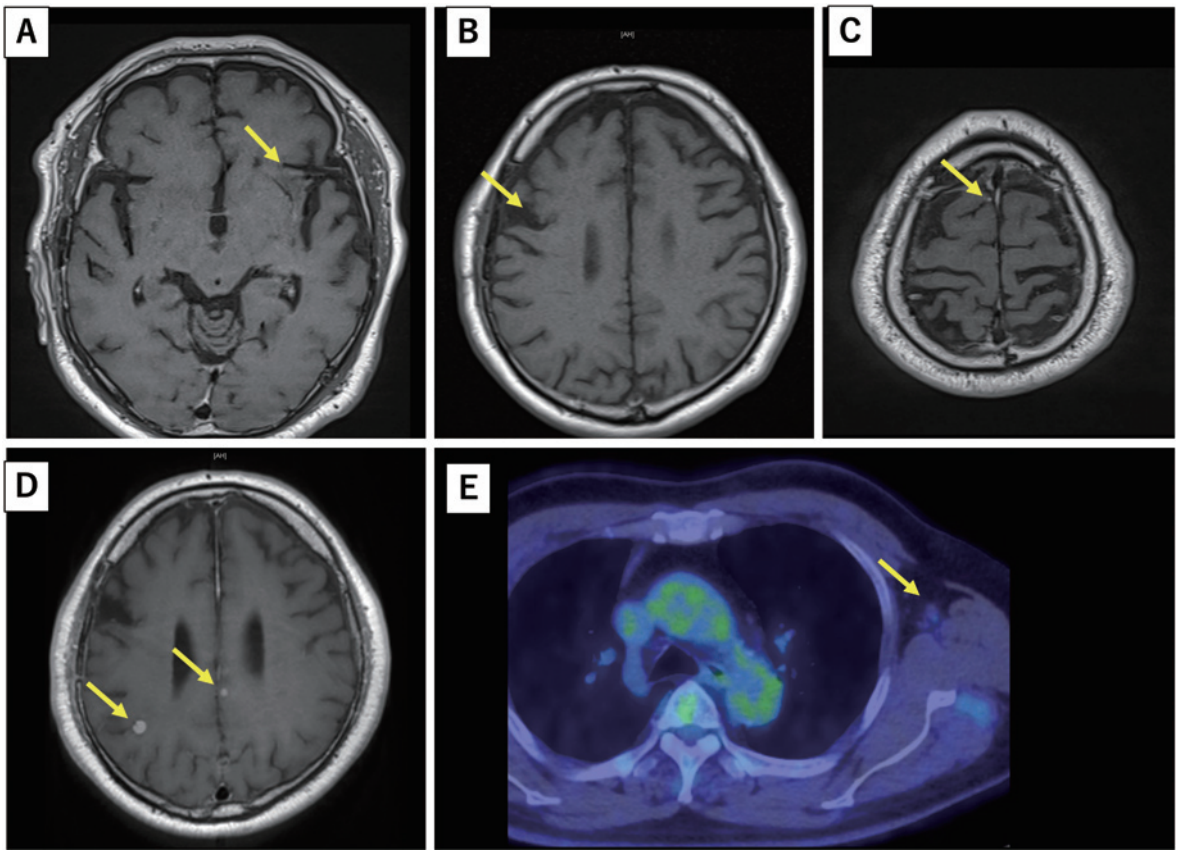

Fig. 4 Postoperative images. One year after surgery, we did not observe any recurrence of locally treated lesions in the left basal ganglia and in the right frontal lobe investigated via MRI (T1WI enhanced by gadolinium) (A–C). After temporary interruption of systemic treatment, two lesions appeared in similar MRI images of the right parietal lobe and left cingulate gyrus (D). FDG PET-CT at 1 year after the start of molecular-targeted therapy shows that the high accumulation in the left axillary lymph node has disappeared (E).

phase 2 trial COMBI-MB, the combination of dabrafenib and trametinib was effective in patients with BRAF V600E mutant melanoma characterized by untreated or progressing brain metastasis. Intracranial response rate was reported to be around 59% for symptomatic melanoma brain metastasis, and this therapy presented a manageable safety profile in those patients.[8] In line with these prior findings, we performed molecular-targeted therapy with a combination of BRAF and MEK inhibitors for this patient, who achieved CR during treatment. Although the clinical significance of BRAF V600E mutations in brain metastasis from amelanotic melanoma has not been documented, the BRAF V600E mutation might be predictive of better treatment results in amelanotic melanoma. Recent clinical trial is aiming to evaluate the effectiveness of combined dabrafenib/trametinib treatment in association with stereotactic radiation (NCT02974803). Results from this trial will improve our understanding of the mechanisms that make combination therapy with BRAF and MEK inhibitors more effective.

In the present case, these agents were also effective in treating recurrent lesions after temporary interruption of therapy. In the COMBI trial, it was necessary to discontinue treatment in 10% of the patients,[8] which is a sizable percentage of the patient population. In case of toxicity, the CTCAE grade guides the decision to reduce treatment, interrupt it, or discontinue it altogether. However, there are currently no guidelines or relevant studies on the appropriate way to restart treatment after interruption caused by drug toxicity. Our case demonstrates the viability of restarting molecular-targeted therapy with the same combination of drugs, albeit at a reduced dose. Thus, this approach should be considered as a reasonable option by practitioners, once efficacy of the therapy has been confirmed at the standard dose.

Conclusion

Here, we presented a case of intracranial amelanotic melanomas, a rare clinical event with atypical features. Treatment with molecular-targeted drugs should be considered even after recurrence, given that this pathology presents a higher frequency of BRAF V600E mutations. Once molecular-targeted therapy shows positive therapeu-

tic effects against metastatic brain tumor from amelanotic melanoma associated with BRAF V600E mutations, practitioners should consider resuming therapy at a reduced dose for the treatment of the recurrent lesion, even after interrupting treatment because of toxic side effects.

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Abbreviations

CT, computed tomography; CR, complete remission; CTCAE, Common Terminology Criteria for Adverse Events; FDG, glucose analog 18-F-fluorodeoxyglucose; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; MEP, motor evoked potential; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PET, positron emission tomography; T1WI, T1-weighted image; T2WI, T2-weighted image

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Conflicts of Interest Disclosure

The authors have no conflict of interest to declare.

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