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Case Report

Neurooncological Challenges in Relapsing Intracranial Melanoma Metastases: A Case Report

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ABSTRACT

Introduction: Treatment of melanoma brain metastases (MBM) is a complex interdisciplinary challenge. Relapsing MBMs pose an extra challenge due to limited therapeutic options and higher complication rate. Multiple surgical interventions and radiation can be indicated in the case of intracranial relapse with extracranial disease control under oncological therapy e.g., immunotherapy.

Case Presentation: Here, we report on a 37-year-old female patient with stage IV metastatic melanoma, who underwent six neurosurgical procedures, including five tumor resections, and three courses of different irradiation protocols in 26 months, all while receiving multiple regimens of immunotherapy. Throughout the different therapies, the patient showed varying neurological deficits, including facial nerve palsy, hemiparesis and reduction of cognitive function. The patient died due to symptoms related to leptomeningeal spread of the tumor.

Conclusion: With this case, we want to share our experience with multiple neurosurgical interventions and repeated brain irradiation procedures in a patient with relapsing MBM. Neurosurgical interventions contributed to symptom relief, saved steroids and potentially prolonged survival. Therefore, based on the events of this case, repeated surgery could be considered for progressive brain metastases.

Introduction

Along with lung and breast cancer, metastatic melanoma is considered as one of the main causes of brain metastases in adults, accounting for 6-11% of all brain metastases [1]. Forty percent of melanoma patients are diagnosed with symptomatic melanoma brain metastases (MBM) and up to 70% are showing MBM postmortem [2]. MBM account for up to 54% of deaths related to melanoma [2]. The median overall survival (OS) of patients with MBM is 12.8 months [3]. Besides neurosurgical resection, stereotactic radiosurgery (SRS) has been proven successful in controlling MBM with a lesion control rate of 70-80% [2, 4, 5]. The role of whole brain radiation therapy (WBRT) is controversial. Due to potential neurocognitive side effects of WBRT, SRS is preferred in patients with a limited number of MBM [6]. Since 2011, targeted

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therapies and immunotherapies (IT) are gaining importance in the therapy of MBM. Cerebral response rates in MBM to IT such as cytotoxic T-lymphocyte-associated protein 4 (CTLA4) antibody ipilimumab (IPI) and Programmed cell death protein 1 (PD-1) inhibitor nivolumab (NIVO) are up to 55% [7, 8]. Therapy with MAP (mitogen-activated protein)/MEK kinase inhibitor dabrafenib and trametinib (DABRA + TRA) reaches cerebral response rates in up to 59% [9-13].

However, the combination IPI + NIVO proved to be the better regimen in advanced stage melanoma [14, 15]. Yet despite these positive developments in the field of melanoma treatment, cases that do not respond well to the treatment options demand individual concepts. Such heterogenic therapy concepts demand closer monitoring to detect interactions between involved therapies. While radio-plus immunotherapy may have an additive positive effect on MBMs, steroids for neurologic symptom relief can have a negative impact on the efficacy of immunotherapy [12, 16, 17]. With this case, we want to share our experience with multiple neurosurgical inventions and repeated brain irradiation procedures in a young patient with relapsing MBM under immunotherapy.

Case Presentation

We report on a case of a young female, who was diagnosed with malignant melanoma at the age of 37 years. The melanoma was located on the right shoulder and was removed completely. Histopathology revealed stage IA melanoma (Clark Level III, tumor thickness: 0.6mm) [18]. No further adjuvant treatment was deemed necessary by the tumor board according to Sladden *et al.* [19, 20]. The patient then received standard follow-up for melanoma patients. 34 months after initial diagnosis, the patient presented herself with lymphadenopathy of the groin. The patient received surgical extirpation. Pathological evaluation confirmed lymph node metastasis of *BRAF*-mutated melanoma. Whole-body staging was completed showing metastases in the brain (n=4), in the left lobe of the lung (n=1), in the spleen (n=1) and in the inguinal lymph nodes (n=1, (Figure 1), radiological images: CT scan with green rectangles). On the cMRI scan, MBM were located in the left frontobasal (lFB) left parietal (lP), right frontolateral (rFL)and right insular (rI) region ((Figure 1), radiological images: MRI scans with red rectangles). The disease was now classified as a stage IV melanoma [18]. A combination therapy of NIVO and IPI for four cycles was initiated, followed by NIVO monotherapy according to current guidelines [21].

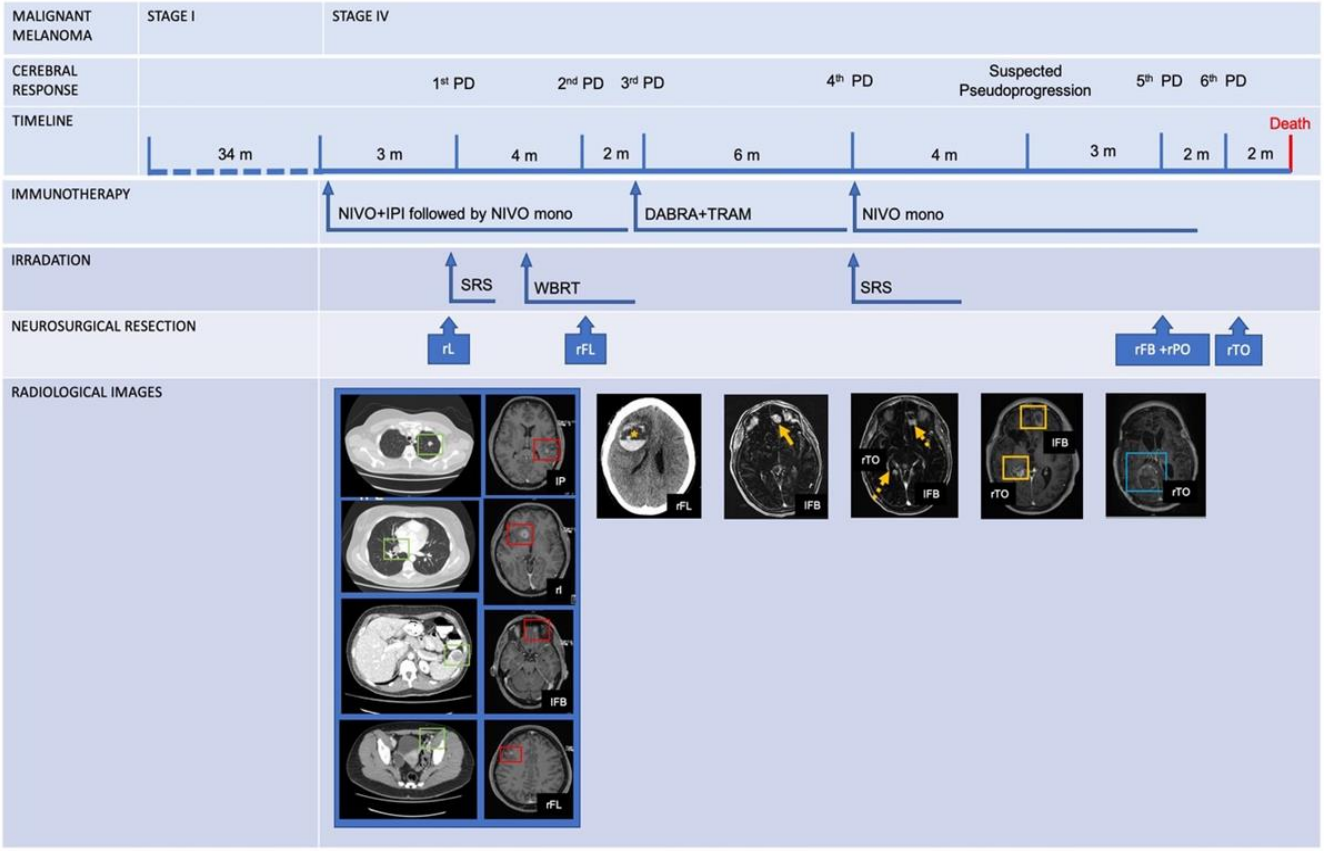

Figure 1: Timeline of the course of the disease and interventions over time with corresponding scans.
CT: Computed Tomography; DABRA: Dabrafenib; IPI: Ipililumab; lFB: left Frontabasal; lP: left Parietal; M: Months; MBM: Melanoma Brain Metastasis; Mono: Monotherapy; MRI: Magnetic Resonance Imaging; NIVO: Nivolumab; PD: Progressive Diseases; rFL: right Frontolateral; rI: right Insular; rTO: right Temporooccipital; SRS: Stereotactic Radiosurgery; TRAM: Tramatenib; WBRT: Whole Brain Radiation Therapy.

Three months later, progressive disease (PD) of MBM was diagnosed. After an interdisciplinary tumor board consensus, 3/4 MBM (lFB, lP and rFL) were treated with SRS (single dose of 21 Gy, iso-dose 70% and Dmax 30 Gy, (Figures 2A-2C), while the fourth MBM (rI) was surgically removed due to a size > 2cm and perifocal edema (1st MBM surgery). By that time, the patient had not developed any neurological symptoms. Due to suspected leptomeningeal spread on the MRI, WBRT was initiated 2 month later (Figure 2D). Due to immunotherapy-induced

pneumonitis, immunotherapy was temporarily suspended, and steroid therapy was initiated (CTCAE I) [15]. In addition, the patient developed bilateral pulmonary embolism (CTCAE III), which was treated with therapeutic anticoagulation [15]. In the following, for the first time the patient presented with acute neurologic symptoms with facial nerve palsy, left hemiparesis and comatose condition. CT-scans showed hemorrhage of the SRS- treated rFL MBM ((Figure 1), radiological images: CT scan with yellow star), which was surgically evacuated. The MBM was resected (2nd MBM surgery). Post-operatively the paresis improved. During follow-up, the patient presented herself with persistent mild left facial palsy and dysarthria. Neuropathological evaluation revealed vital tumor cells within the hemorrhage. By that time, CT-staging showed stable disease (SD) of the extracranial lesions. Consequently, NIVO monotherapy was continued.

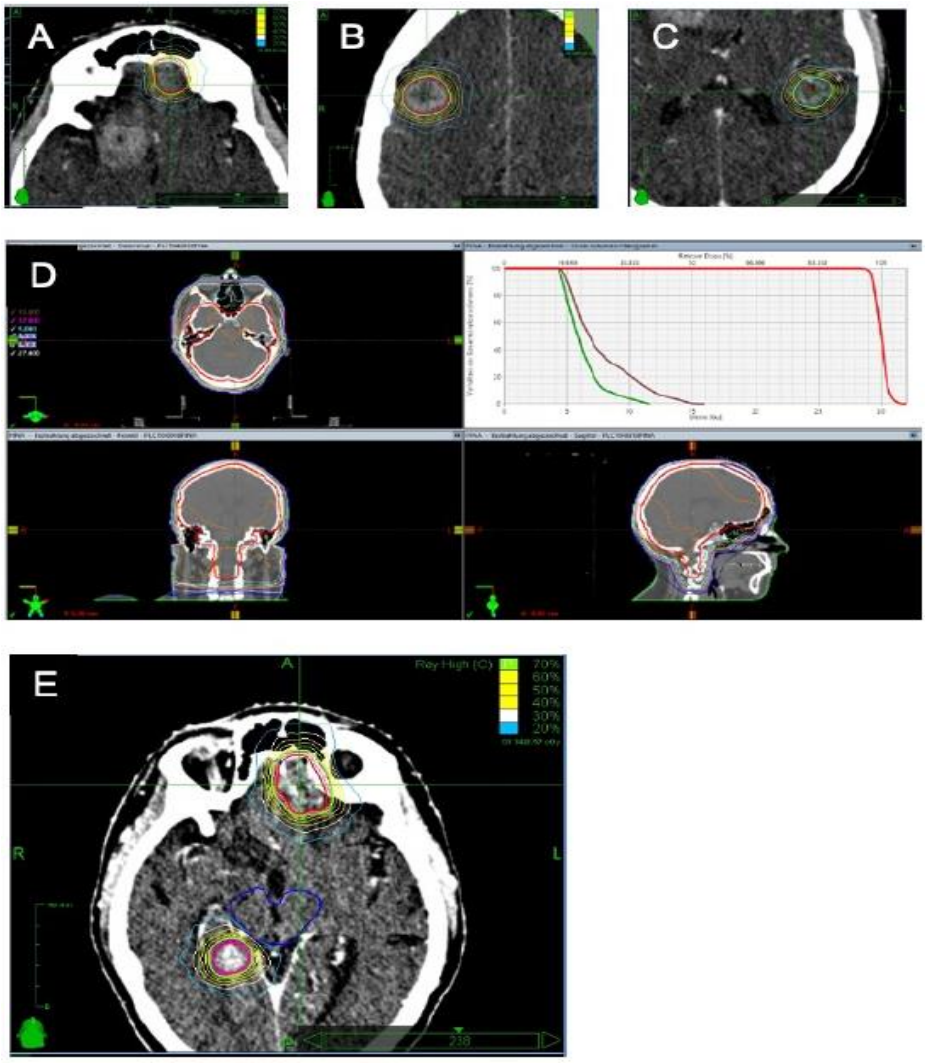

Figure 2: Overview of radiation protocols. **A-C)** SRS protocols of three MBM lesions located **A)** lFB, **B)** rFL, **C)** lP, three months after initial diagnosis of MBM. **D)** WBRT 9 months after initial diagnosis of MBM diagnosis. **E)** SRS of recurrent lFB and new lesion rTO 15 months after initial diagnosis of MBM.
lFB: left Frontobasal; lP: left Parietal; MBM: Melanoma Brain Metastasis; rFL: right Frontolateral; rI: right Insular; rTO: right Temporooccipital; SRS: Stereotactic Radiosurgery; WBRT: Whole Brain Radiation Therapy.

Nine months after initial MBM diagnosis, local recurrence of the lFB MBM was diagnosed on the cMRI ((Figure 1), radiological images: cMRI with yellow arrow). The IT was afterwards switched to a targeted therapy with DABRA + TRA. This decision was based on the results of the COMBI-MB trial [22]. Despite an episode of mild fever (CTCAE II), the IT has been well-tolerated and was given for another six months. Routine cMRI scan showed focal ischaemia in the territory of left middle cerebral artery (MCA) and right superior cerebellar artery (SCA), which remained clinically asymptomatic. Fifteen months after initial diagnosis of MBM, cMRI revealed a new right temporo-occipital lesion (rTO) and PD of the lFB MBM ((Figure 1), radiological images: cMRI with yellow arrow and dotted line). After interdisciplinary discussion, DABRA + TRA regimen was stopped and a re-challenge with NIVO initiated. SRS was applied to the rTO and lFB MBM (Figure 2E). Two months later cMRI showed further progression of the lFB and rTO MBM with relevant perifocal edema ((Figure 1), radiological images: cMRI with yellow rectangle). The patient presented herself with mild hemiparesis of the lower limb, coordination problems, vertigo and headaches. Due to suspected pseudoprogression dexamethasone dose was elevated for symptom control and subsequent cMRI scans were conducted.

After interdisciplinary case discussion, the two lesions causing relevant edema were resected in two subsequent sessions (rTO MBM and the lFB MBM, 3rd and 4th MBM surgery, 22 months after initial diagnosis of MBM). Neuropathological evaluation confirmed vital melanoma metastasis. Afterwards a re-challenge with NIVO was applied. Two weeks later, the patient presented herself with a subcutaneous surgical site infection requiring surgical revision. During follow-up the patient showed signs of subacute liver failure related to autoimmune hepatitis (differential diagnosis: toxic hepatitis due to antibiotic treatment) (CTCAE III), which has been treated with steroids and temporarily suspension of NIVO therapy. Later the re-challenge of NIVO was continued. Systemic tumor burden remained stable. Two months later, the patient was admitted to the hospital with grand-mal seizure. PD of the rTO lesion was seen on the cMRI ((Figure 1), radiological images: cMRI with blue rectangle) with increasing dimensions up to 5 cm x 4 cm and suggested leptomeningeal spread. The patient was in reduced general conditions (Karnofsky performance score. 50%). The palliative situation was discussed with the patient and her family. They repeatedly expressed their wish for further life-prolonging interventions being aware of the limited recovery potential and general risks of the procedure.

After interdisciplinary discussion, we decided to offer resection of the rTO MBM to control intracranial pressure. The resection of the rTO MBM went uneventful (5th MBM surgery). Postoperative cMRI revealed complete resection of the mass (Figure 2D). The patient showed stable neurological condition with decreasing seizure frequency and was referred to the dermatological ward 2 days later.

Follow-up and Clinical Outcome

Within one week after surgery, the patient presented herself with varying cranial nerve palsies like anisocoria, dysphagia and comatose condition. Lumbar puncture confirmed suspected leptomeningeal spread of the melanoma. Due to further deterioration of the patient's condition, a palliative concept was initiated. The patient received best supportive care for another 2 months. The patient died 60 months after initial diagnosis of malignant melanoma and 26 months after first diagnosis of MBM. The patient had been hospitalized 154 days throughout the initial diagnosis of MBM and experienced several severe side effects due to treatments (Table 1).

Table 1: Common Terminology Criteria for Adverse Events during the course of disease.

Treatment related side effects	**CTCAE, Version 4.0**
Autoimmune hepatitis	III
Autoimmune hyperthyroidism	III
Chronic pneumonitis	I
Secondary hypopituitarism	III
Empty-*Sella* syndrome	III
Secondary *Cushing* syndrome	III
Surgical site infection	III
Bilateral pulmonary embolism	III
Gastrointestinal bleeding	III
Fever	II
Stroke of left MCA and right SCA territory	I
Hospitalization due to neurosurgical interventions and medical complications since initial MBM diagnosis	154 days

CTCAE: Common Terminology Criteria for Adverse Events; MBM: Melanoma Brain Metastasis; MCA: Middle Cerebral Artery; SCA: Superior Cerebellar Artery.

Discussion

With this case we show, that repeated neurosurgical interventions in relapsing MBM might prolong the patient's survival despite the lack of durable intracranial response to irradiation and immunotherapy. The indication for the last surgery (5th MBM surgery) is controversial since clinical signs of leptomeningeal spread of the melanoma have been apparent by that time and the benefit of surgery was questionable due to reduced patient's condition. On the other hand, the patient's wish for maximum therapy needed to be considered in the therapeutic decision-making. In the present case it was considered very helpful to have an open and critical discussion on the expectations and risks of such interventions with the team of clinicians and with the patient and her family. Each neurosurgical intervention was performed with the goal to control intracranial pressure, reduce neurological symptoms and preserve patient's independence in daily life. In our patient, these goals have been reached with the first four neurosurgical procedures. In consequence to the neurosurgical interventions, steroid dosages were decreasing which otherwise might have counteracted the IT effect. In summary, neurosurgical interventions contributed to symptom relief, saved steroids and potentially prolonged survival despite poor cerebral response to the oncological treatment. Based on the surgical results of the presented case and the relatively low complication rates, we would consider repeated neurosurgical interventions in patients with progressive brain metastasis.

Funding

None.

Competing Interests

None.

Consent

After admission, patients are required to approve or disapprove consent to usage of their anonymous data/ radiological scans for scientific purposes. In this case, the patient gave her written informed consent.

Author Contributions

JO, PV and AE: Involved in the Neurosurgical Treatment of the Patient; CS and DK: Provided the Scans for Radiation Planning; JR: Provided Pathology Work Up; KM and NK: Involved in Dermatological Treatment and Provided Therapy Timeline; JO and AE: Formulated the Manuscript; All authors reviewed the manuscript.

Abbreviation

CT: Computed Tomography
CTCAE: Common Terminology Criteria for Adverse Events
CTLA-4: Cytotoxic T-Lymphocyte-Associated Protein 4
DABRA: Dabrafenib
IT: Immunotherapy
IPI: Ipilimumab
lFB: left Frontobasal
lP: left Parietal
MAP: Mitogen Activated Protein
MCA: Middle Cerebral Artery
MRI: Magnetic Resonance Tomography
NIVO: Nivolumab
PD: Progressive Disease
rFL: right Frontolateral
rI: right Insular
rTO: right Temporooccipital
SD: Stable Disease
SRS: Stereotactic Radiosurgery
TRA: Trametinib

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