



CASUISTIC PAPER

Management challenges and therapeutic strategies for metastatic melanoma – a case report

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ABSTRACT

Introduction and aim. This case report focuses on a 26-year-old female with metastatic melanoma. It highlights the diagnostic process, initial immunotherapy, disease progression, and successful response to second-line therapy. Emphasizing the importance of early detection, personalized treatment, and adaptive strategies, it provides valuable insights into managing this aggressive form of skin cancer.

Description of the case. A 26-year-old Caucasian female presented with a suspicious pigmented lesion on her thigh in 2013. The lesion was confirmed as superficial skin melanoma. No lymph node biopsy was performed. In 2021, she had abdominal pain and imaging revealed melanoma metastasis in the peritoneum, lungs and brain. Genetic testing showed BRAF V600E mutation and PD-L1 expression in tumor cells. She received immunotherapy and radiation for a central nervous system metastases but developed a brain hematoma. Follow-up imaging showed disease progression. She started second-line therapy with iBRAF/IMEK, and her condition rapidly improved with regression of metastatic lesions. Follow-up imaging confirmed significant positive changes and almost complete regression of neoplastic lesions. She continues to receive the targeted therapy and shows a positive response.

Conclusion. Early diagnosis improves outcomes in metastatic melanoma. Peritoneal metastases should be considered in patients with abdominal symptoms. The combination of gamma knife radiosurgery with immunotherapy or targeted therapy shows promise for managing brain metastases, but careful patient selection and monitoring are vital due to potential risks. Treatment responses in advanced melanoma vary, with this case highlighting a favorable response to BRAF/MEK inhibitor therapy in a patient with a BRAF gene mutation. Further research and clinical trials are needed to refine treatment approaches and improve outcomes in metastatic melanoma.

Keywords. immunotherapy, metastatic melanoma, peritoneal metastases

The list of abbreviations:

CNS – central nervous system, CT – computed tomography, GKRS – gamma-knife radiosurgery, ICI – immune checkpoint inhibitor, IT – immune therapy, MMM – metastatic malignant melanoma, MM – metastatic melanoma, MRI – magnetic resonance imaging, PET – positron emission tomography, PM – peritone-

al metastases/metastasis, SRS – stereotactic radiosurgery, SSM – superficial skin melanoma, TT – targeted therapy

Introduction

Metastatic melanoma (MM) is an aggressive form of skin cancer associated with a high mortality rate.¹ Early de-

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tection and prompt intervention play a crucial role in improving patient outcomes. However, the progression of melanoma to metastatic disease poses significant challenges in treatment and management.² In this case report, we present the case of a 26-year-old Caucasian female patient who initially presented with superficial skin melanoma and subsequently developed metastatic nodules in the peritoneal cavity, lungs, and central nervous system (CNS). We discuss the diagnostic findings, first-line immunotherapy with Nivolumab and Ipilimumab, subsequent disease progression, and the successful response to therapy with Encorafenib and Binimetinib.

Aim

The aim of this case report is to highlight the diagnosis and management of MM in a young female patient. The report focuses on the initial diagnosis of superficial skin melanoma, followed by the detection of metastatic nodules in the peritoneal cavity and CNS, eight years after the initial excision. The report also describes the patient's treatment journey, including first-line treatment with Nivolumab and Ipilimumab, which was ineffective in controlling the disease, and the subsequent successful use of second-line therapy with BRAF/MEK inhibitors Encorafenib and Binimetinib. This case report aims to provide insight into the use of various treatment options for MM and to emphasize the importance of early diagnosis and timely treatment for this aggressive form of cancer.

Description of the case

A 26-year-old Caucasian female patient initially presented with a suspicious pigmented lesion on the medial portion of her right thigh in 2013. The lesion measured approximately 8 mm, and an excisional biopsy was performed. The biopsy results confirmed the presence of superficial skin melanoma (SSM) with a Breslow thickness of 2 mm and no ulceration. The staging of the melanoma was classified as pT2a, according to the 7th Edition of the TNM classification. Following the biopsy result wide excision was performed. At that time, no sentinel lymph node biopsy was performed. Previously described steps took place in a hospital different than the current.

In July 2021, the patient was admitted to the surgical ward due to pain in the right iliac fossa, initially suggestive of acute appendicitis. An ultrasound of the abdominal cavity was conducted, revealing a hypoechoic area along the ascending colon and a hypoechoic lymph node measuring 18x10 mm. During the surgical procedure, soft tissue nodules associated with the peritoneal lymphatic network were discovered, while the appendix appeared normal. Histopathological examination of the peritoneal nodules confirmed melanoma metastasis.

Further diagnostic investigations were carried out to assess the extent of the disease. CT, PET-CT, and MRI of

the head were performed, revealing multiple metastatic nodules ranging in size from 2 to 8 mm in the lungs' parenchyma. Additionally, neoplastic implants measuring up to 24 mm in diameter were observed in the peritoneal cavity. A metastatic focus in the left temporal lobe of the CNS, measuring 10 mm, was also confirmed. Genetic testing of the histopathological sample revealed the presence of BRAF V600E mutation, indicating sensitivity to BRAF kinase inhibitors. The testing also identified PD-L1 antigen expression in approximately 1-49% of tumor cells (TPS about 5%).

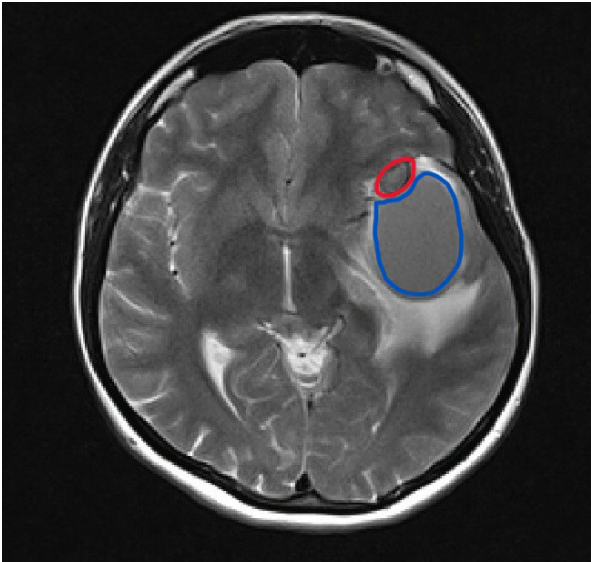


Fig. 1. Hematoma (blue circle) and metastatic lesion (red circle) following GKRS

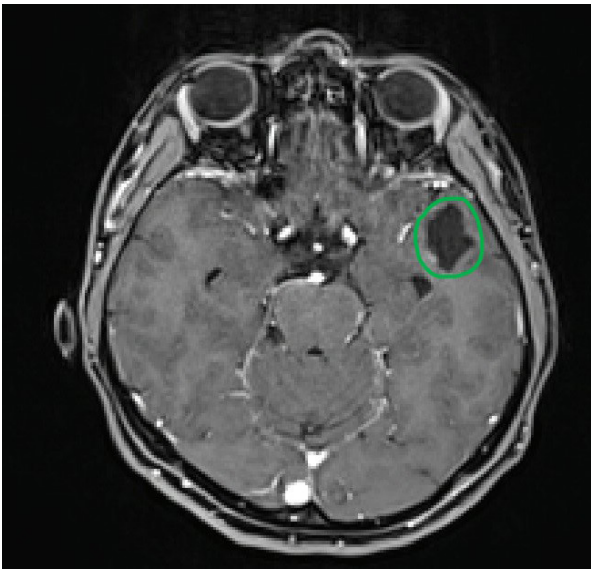


Fig. 2. Shrunken hematoma (green circle)

First-line treatment with Nivolumab (1 mg/kg) and Ipilimumab (3 mg/kg) immunotherapy was initiated on September 10th, 2021. In addition to immunotherapy, Gamma Knife stereotactic radiotherapy was adminis-

tered to the metastatic lesion in the left temporal lobe, delivering a radiation dose of 20 Gy in a single fraction. Following CNS irradiation, the patient experienced headaches accompanied by nausea and vomiting. An MRI of the head revealed a 46 x 33 mm hematoma at the site of the irradiated metastatic focus (Fig. 1). Conservative treatment, including a 2-week course of steroid therapy with Dexamethasone (6 mg/die for week 1, and 1 mg/die for week 2), was initiated, leading to the resolution of neurological symptoms and shrinkage of the hematoma (Fig. 2).

After completing four courses of immunotherapy, follow-up imaging showed disease progression according to RECIST 1.1 criteria, correlated with a rapid deterioration of the patient's clinical condition. Notably, the ineffectiveness of immunotherapy was evident in the abdominal cavity, with the presence of larger and more numerous metastatic nodules in the peritoneum (Fig. 3). The presacral region exhibited the largest focus measuring 90 mm. The metastatic lesions in the lungs remained similar in size and number compared to the baseline CT scan performed before the initiation of immunotherapy. Gastrointestinal symptoms, including abdominal pain, painful constipation, and intestinal transit disorders, developed due to the pressure of tumor implants on the intestines.

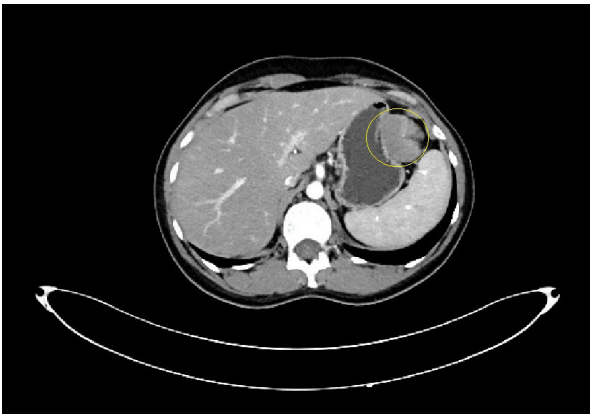


Fig. 3. Peritoneal metastases following four courses of Ipilimumab and Nivolumab

As a result of disease progression, the patient was urgently qualified for second-line therapy with BRAF/MEK inhibitors. Specifically, she started treatment with Encorafenib (450 mg) and Binimetinib (45 mg). Shortly after commencing this targeted therapy, the patient's clinical condition rapidly improved, and all gastrointestinal complaints subsided. After a month of treatment, the patient returned to a normal performance status (ECOG-0) and was able to resume her work activities.

On March 3rd, 2022, CT scans of the chest, abdomen, and pelvis, both before and after intravenous contrast administration, were performed to assess the

treatment response. The imaging findings revealed several significant positive changes. The metastatic nodules in the lungs' parenchyma had completely disappeared. The pleural cavities and mediastinal organs appeared free from any pathological findings. The pathological masses surrounding the uterus had regressed, and there was almost complete regression of the observed peritoneal tissue masses (Fig. 4). The tissue densities in the gallbladder and integuments had also regressed. Importantly, there were no signs of pathological destruction in the bones. The follow-up imaging tests conducted after three months of therapy showed almost complete regression of all neoplastic lesions, consistent with RECIST 1.1 criteria.

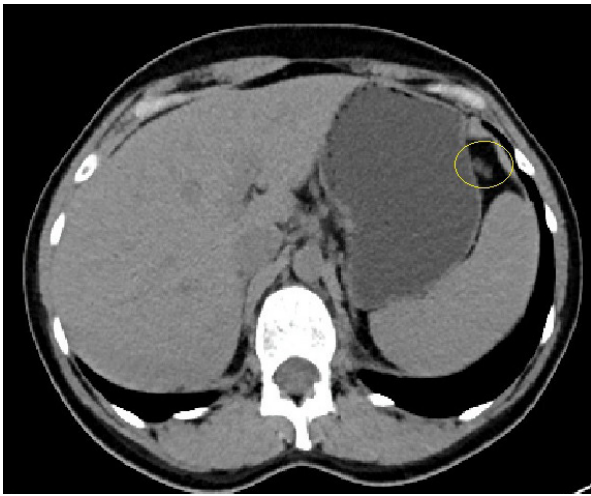


Fig. 4. Peritoneal metastases regression following three months of Encorafenib and Binimetinib therapy.

Throughout the course of treatment with Encorafenib and Binimetinib, no serious adverse events were recorded. The patient tolerated the therapy well, with the only noticeable consequence being mild alopecia

To date (May 2023), the patient continues to receive treatment with Encorafenib and Binimetinib, maintaining a highly positive therapeutic effect and experiencing minimal treatment-related toxicity.

Discussion

Metastatic malignant melanoma (MMM) is a highly aggressive form of skin cancer characterized by the spread of melanoma cells to other parts of the body beyond the skin. Historically, the prognosis for patients with metastatic cutaneous melanoma has been poor. However, recent advancements in cancer therapeutics, particularly the introduction of immune checkpoint inhibitors (ICIs) and small-molecule targeted drugs, have significantly improved patient outcomes, revolutionizing the field of melanoma therapeutic management.¹

ICIs, such as Ipilimumab and Nivolumab, have demonstrated remarkable success in various cancer types, particularly melanoma. Nevertheless, a significant proportion of patients exhibit resistance to these therapies, often due to intrinsic factors. In the case presented here, the patient's peritoneal metastases (PM) displayed high resistance to immunotherapeutic treatment, raising questions about the mechanisms of resistance specific to PM in melanoma.

While PM typically originates from abdominal primary cancers, cases of PM secondary to MMM are relatively uncommon, and the true incidence remains unknown. Despite the limited number of reported cases in the literature, it has been observed that melanoma ranks as the third most common extra-abdominal cancer to metastasize to the peritoneum. This highlights the importance of recognizing and understanding PM as a potential manifestation of MM.²

Although existing literature on resistance to ICIs in PM primarily focuses on gastric cancer and colorectal cancer, it is plausible to consider that some of the resistance mechanisms observed in those metastatic cancers may also apply to MM. A study conducted by Küçükköse et al. utilizing a humanized mice model found that peritoneal metastases derived from colorectal cancer with high microsatellite instability exhibited insensitivity to ICIs. Furthermore, the presence of elevated levels of immunosuppressive cytokines in ascitic fluid, observed in the experimental model, offers a potential explanation for the refractory nature of peritoneal metastases to ICIs.³

Further investigation into the mechanisms underlying resistance in PM secondary to MM is warranted. Understanding the unique characteristics and factors contributing to therapeutic resistance in this specific context could potentially guide the development of novel treatment strategies to overcome resistance and improve patient outcomes. Additionally, exploring the potential role of microsatellite instability in MM may provide valuable insights into immunotherapy response and the resistance mechanisms involved.⁴

Concurrent treatment with stereotactic radiosurgery (SRS) and targeted therapy (TT) or immunotherapy (IT) in the management of brain metastases has been an area with limited safety data. However, Gamma Knife radiosurgery (GKRS) has emerged as a valuable modality for delivering a high dose of radiation to the lesion while minimizing radiation exposure to the surrounding normal brain parenchyma, resulting in high tumor control rates.

In this case, although the patient developed a hemorrhage following GKRS, it is important to note that several studies have reported no significantly increased risk associated with concurrent immunotherapeutic treatments.^{5–8} The occurrence of hemorrhage or radiation reaction/necrosis after GKRS did not show any statistically significant differences in relation to IT/TT.⁹

Furthermore, patients treated with anti-PD-1, anti-CTLA-4, or a combination of anti-CTLA-4/PD-1 demonstrated a significantly longer time to new brain metastasis after GKRS compared to patients treated with other forms and combinations of oncological therapy. This finding highlights the potential synergistic effects of immunotherapeutic agents and GKRS in preventing the development of new brain metastases.⁹

The existing literature emphasizes the importance of considering GKRS as a viable treatment option in the management of brain metastases in patients receiving immunotherapy or targeted therapy for malignant melanoma.¹⁰ The combination of GKRS and immunotherapeutic agents has the potential to enhance treatment outcomes by controlling both local disease and systemic progression.

However, it is essential to recognize the potential risks associated with GKRS, such as hemorrhage, and weigh them against the potential benefits in each individual case. Close monitoring and appropriate patient selection are crucial to ensure the safety and efficacy of this treatment approach.

In the management of advanced melanoma with a mutation in the BRAF gene, two different treatment modalities exist as options: targeted therapy utilizing BRAF and MEK inhibitors, and immunotherapy, which involves checkpoint inhibition.¹¹

The combination of BRAF and MEK inhibitors has emerged as the standard of care in the first-line treatment of patients with unresectable or metastatic BRAF-mutated melanoma. This therapy has shown promising results, with response rates ranging from 68% to 76%, median progression-free survival of 11–15 months, and a 3-year overall survival rate of approximately 40%.^{12–16}

A case report by Stagno et al. highlighted the effectiveness of this combination therapy in two patients. One patient, heavily pretreated, achieved a partial response lasting 36 months with local treatment for oligoprogression disease. The second patient had a partial response lasting 10 months. However, the report also described a third patient with multisite visceral disease and high serum levels of lactate dehydrogenase, who experienced a short-lived clinical benefit followed by rapid disease progression. The fourth patient currently on treatment with BRAF/MEK inhibitors showed clinical benefit and radiological stable disease for over 3 months.¹⁷

Furthermore, the 5-year update of part 1 of the CO-LUMBUS trial further supports the use of combination treatment with BRAF and MEK inhibitors for advanced BRAF V600-mutant melanoma. This update demonstrated benefits in terms of progression-free survival and overall survival, reaffirming the role of this combination therapy as a standard of care.¹⁸

In this case, the patient demonstrated a more favorable response to BRAF/MEK inhibitors therapy compared to anti-CTLA-4 and anti-PD-1 immunotherapy. This finding is noteworthy and further shows the efficacy of such a therapy. Nevertheless, a study published by Van Breeschoten et al. reported that patients with MM treated with anti-PD-1 monotherapy as the first-line treatment exhibited a higher 2-year survival rate compared to those treated with first-line BRAF/MEK inhibitors. The median overall survival (OS) in the anti-PD-1 monotherapy cohort was 42.3 months, while patients receiving BRAF/MEK inhibitors as the first-line treatment had a median OS of 19.8 months.¹⁹

It is important to acknowledge that the selection of first-line therapy for advanced melanoma should be based on a comprehensive evaluation of available clinical evidence and, consideration of potential side effects and long-term benefits.

Conclusion

Early diagnosis plays a crucial role in improving patient outcomes for MM. As demonstrated in this case, the initial detection and excision of a superficial skin melanoma (SSM) in the patient provided an opportunity for intervention. However, despite the initial excision, the disease progressed underscoring the aggressive nature of melanoma and the importance of vigilant follow-up and surveillance.

PM as a manifestation of MM is relatively uncommon, but recognizing its potential occurrence is vital. This case report highlights the need to consider PM as a possibility in patients with MM, particularly in those presenting with abdominal symptoms. Further research is required to understand the unique characteristics and mechanisms of resistance specific to PM, as this knowledge can inform the development of effective treatment strategies tailored to this clinical context.

The combination of GKRS with immunotherapy or targeted therapy shows promise in managing brain metastases in patients with malignant melanoma. However, it is important to note that the occurrence of a hemorrhage following GKRS highlights the need for careful patient selection and monitoring.

Furthermore, this case emphasizes the diversity of treatment responses seen in advanced melanoma. Although immunotherapy using anti-CTLA-4 and anti-PD-1 agents has shown remarkable efficacy in different types of cancer, including melanoma, the standard of care for patients with BRAF V600 mutations remains the use of BRAF and MEK inhibitors. It is crucial to conduct further research and clinical trials to enhance our knowledge of treatment outcomes in this patient population.

In summary, this case report shows the multifaceted nature of MMM management, including the importance of early diagnosis, the challenges of PM, the potential

benefits and risks of combining GKRS with immunotherapy or targeted therapy for brain metastases, and the variability of treatment responses. It emphasizes the need for further research, patient-specific considerations, and ongoing clinical trials to refine treatment approaches and improve outcomes in the complex landscape of MM. By continuing to advance our understanding of this aggressive form of cancer, we can work towards personalized and effective treatment strategies that maximize patient survival and quality of life.

Declarations

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Author contributions

Conceptualization, A.M.A., S.C., G.I. and M.G.; Methodology, A.M.A., S.C. and G.I.; Software, A.M.A., S.C. and G.I.; Validation, A.M.A., S.C., G.I. and M.G.; Formal Analysis, A.M.A., S.C. and G.I.; Investigation, A.M.A., S.C. and G.I.; Resources, A.M.A., S.C. and G.I.; Data Curation, A.M.A., S.C., G.I. and M.G.; Writing – Original Draft Preparation, A.M.A., S.C. and G.I.; Writing – Review & Editing, A.M.A., S.C. and G.I.; Visualization, A.M.A., S.C. and G.I.; Supervision, A.M.A. and M.G.; Project Administration, A.M.A. and M.G.

Conflicts of interest

The authors declare no competing interests.

Data availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Ethics approval

Informed consent for publication was obtained from the patient. We complied with the policy of the journal on ethical consent.

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