CASE REPORT

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COMPLETE RESPONSE IN A PATIENT WITH BRAF-MUTANT METASTATIC MELANOMA ACHIEVED WITH THE MULTIDISCIPLINARY APPROACH: A CASE REPORT

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Summary

Melanoma is the most aggressive type of skin cancer and is often associated with extensive disease and poor outcome. We present a case of a 63-year-old man with no prior health issues who presented with high fever and malaise. After clinical and histopathological examination, multiple sites of metastatic disease were diagnosed with no site of primary melanoma. The patient started treatment with palliative radiotherapy to relieve bone pain, and immunotherapy with pembrolizumab was initiated, resulting in a complete response after ten applications of therapy. Over the next two years, control scans revealed two new metastases in the adrenal gland and small intestine, which were subsequently surgically removed. After 4.5 years, the follow-up scan still shows complete response to therapy.

KEYWORDS: *metastatic melanoma; pembrolizumab; BRAF mutation*

INTRODUCTION

Melanoma is known as the deadliest type of skin cancer, accounting for 90% of skin cancer-related deaths. Over the last decade, new insights into immunobiology and oncogenic signaling have led to a revolution in melanoma treatment(1). However, for patients with BRAF-mutant metastatic melanoma, it has not yet been established what should be the first-line therapy, targeted therapy or immunotherapy(2). We present a patient with a complete response to pembrolizumab in BRAF-mutant metastatic melanoma.

CASE REPORT

A 63 year-old male with no relevant past medical history presented to the Emergency Department in July 2018, complaining of high fever and malaise. His skin was described as tan with multiple sun-associated marks. The Computer Tomography (CT) scan revealed multiple suspicious lesions in the axilla and numerous other lymphatic nodes, the liver, spleen, lung, left adrenal gland, and multiple bones. An axillary lymph node was punctured and a diagnosis of metastatic melanoma was obtained, which was confirmed by pathological analysis of the dissected axillary lymph node. The dermatologist found suspicious cutaneous lesions on the upper arm. The biopsy confirmed a BRAF V600E (p.Val600Glu) mutated skin metastasis of melanoma. Positron Emission Tomography and Computed Tomography (PET-CT) scan showed abnormal fluorodeoxyglucose-avid activity identified in the left cervical lymph node

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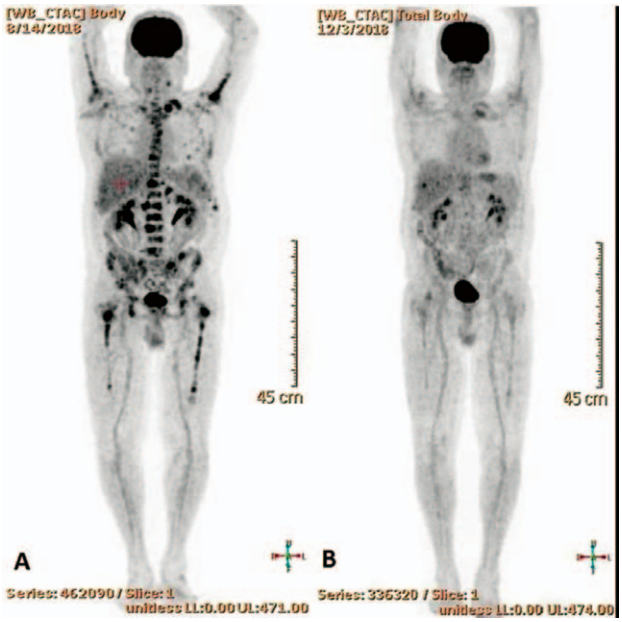

Figure 1. Results of the PET-CT scan before starting the therapy (A); complete response to pembrolizumab after 10 applications (B).

of level II, the left adrenal gland, multiple nodular formations in the lungs, liver, spleen and numerous osteolytic lesions, all suspicious for metastatic spread of the disease (*Fig.1A*). Blood and biochemical tests were performed and the patient's lactate dehydrogenase (LDH) level was 967 U/L (normal range < 240).Treatment started with palliative radiotherapy to target the most painful osteolytic lesions of the thoracic and lumbar spine. Radiotherapy was delivered in one fraction of 800 cGy per site. The multidisciplinary team (MDT) decision was to initiate immunotherapy (pembrolizumab). The administration started in August 2018, with a dose of 200 mg pembrolizumab delivered every three weeks. Blood tests were performed before each administration of the immunotherapy and after two applications LDH level was normalized (LDH level was 200 U/L), and continued to be in normal ranges continuously. of pembrolizumab treatment, a reassessment via PET-CT scan revealed a complete response Following the completion of ten cycles of pembrolizumab, reassessment PET-CT scan revealed complete response (*Fig. 1B*).

Immunotherapy continued, and the control PET-CT scan after 20 pembrolizumab applications in December 2019 revealed a satisfactory response to treatment, except for a new suspicious lesion in the left adrenal gland. The counseling endocrinologist excluded hypocorticism. In January 2020, a left adrenalectomy was performed, revealing metastatic melanoma without BRAF V600E/K mutations (wild-type) upon molecular analysis. Immunotherapy was continued. A control PET-CT scan in September 2020 revealed a complete response to treatment. After the multidisciplinary team reviewed the great outcome, the immunotherapy was paused after two years of continuous treatment. The patient underwent control scans and clinical exams every three months. The control PET-CT scan in April 2021 revealed a new metastasis in the small intestine, which was surgically removed in May 2021. The pathological analysis of the removed tissue confirmed metastatic melanoma with a BRAF wild-type phenotype. The MDT decided to continue monitoring the course of the disease. The last control PET-CT scan in July 2023 confirmed no signs of malignancy.

DISCUSSION

Melanoma is the third most frequent malignant tumor of the skin. Melanoma originates from melanocytes, primarily in the skin, but it can also develop in other sites including the eye, mucosa and meninges(1). In Croatia in 2020, melanoma had an incidence of 3% in men and women, with 412 men and 341 women who were diagnosed during that year. That makes melanoma the 9th most frequent malignancy diagnosed in the Republic of Croatia(3). In recent years, the discovery of BRAF mutations in melanoma has revolutionized the treatment of this disease(1). BRAF is proto-oncogene, a serine/threonine protein kinase, encoded with the gene BRAF, located on the long arm of chromosome 7 (7q34), that plays an important role in the MAP kinase/ERK signaling pathway(4). BRAF is mutated in about 8% of cancers with the highest incidence in melanoma (about 50%)(5). While more than 45 mutations have been identified in BRAF, one specific mutation, V600E (p.Val600Glu) accounts for over 90% of BRAF mutations found in human cancer(6). Most patients have a homogenous BRAF mutation status. However, a problem arises when we take into consideration the heterogeneity of primary melanoma, which contains multiple cell clones. Several of these clones may metas-

tasize leading to the development of multiple, genetically independent tumors within the same patient, as seen in our case(7).

The presence of BRAF mutations predict the response to BRAF and MEK inhibitors(8). Patients with BRAF mutations have 1.7 times increases risk of mortality compared to their BRAF wild-type counterparts(9,10). BRAF mutation in primary melanoma is also associated with particular clinical and histopathological characteristics, such as young age, trunk localisation, non-chronically sun-damaged skin, superficial spreading melanoma, and advanced stage of tumor(11). In addition to the BRAF mutation, other characteristics such as LDH level may influence disease progression and prognosis. Studies have shown that high LDH levels could be a poor prognostic factor for melanoma patients(12). Current strategies for the treatment of BRAF-mutant metastatic melanoma include targeted therapies in the form of BRAF/MEK inhibitors (BRAF/MEKi) and immune checkpoint inhibitors (CPI), including antibodies to programmed death-1 (anti-PD-1), programmed death ligand-1 (anti-PD-L1) and cytotoxic T-lymphocyte antigen (anti-CTLA-4)(13). Programmed death-1 (PD-1) is a cell surface receptor that functions as a T-cell checkpoint and plays a central role in regulating T-cell exhaustion. Programmed death ligand-1, a glycoprotein belonging to the protein B7 family, is expressed on antigen-presenting cells and some types of tumor cells. Interaction between PD-1 and PD-L1 activates downstream signaling pathways and results in T-cell exhaustion and apoptosis(14). Two anti-PD-1 antibodies, pembrolizumab and nivolumab, have been used in melanoma treatment(15). Clinical trials have shown that patients treated with BRAF/MEK inhibitors usually have a longer median progression-free survival and a higher response rate. In contrast, patients treated with immunotherapy such as pembrolizumab have a longer median response duration(16). According to the latest guidelines of the European Society for Medical Oncology (ESMO) from 2020, treatment decisions should be tailored to each patient and should be based on treatment goals (whether the focus is on short-term or long-term benefits), and various clinical characteristics. Important factors to consider include lactate dehydrogenase (LDH), organs involved, performance status (PS), tumor burden, and disease progression kinetics, comorbidities and patient preferences. Patients for whom immunotherapy can be delivered for the first several months should be considered for immunotherapy first, as it may provide long-term disease control(2).

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Sažetak

POTPUNI ODGOVOR U BOLESNIKA S BRAF MUTIRANIM METASTATSKIM MELANOMOM POSTIGNUT MULTIDISCIPLINARNIM PRISTUPOM: PRIKAZ SLUČAJA

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Melanom je najagresivniji tumor kože i često je povezan s opsežnom bolešću i lošim ishodom. Predstavljamo slučaj 63-godišnjaka bez prethodnih zdravstvenih problema koji se prezentirao s visokom temperaturom i malaksalošću. Nakon kliničkog i histopatološkog pregleda, pronađena su višestruka mjesta metastatske bolesti bez vidljivog primarnog melanoma. Bolesnik je započeo liječenje palijativnom radioterapijom radi ublažavanja koštane boli, započeta je imunoterapija pembrolizumabom te je postignut potpuni odgovor nakon 10 primjena terapije. Tijekom sljedeće 2 godine kontrolne snimke otkrile su dvije nove metastaze, u nadbubrežnoj žlijezdi i tankom crijevu, koje su potom kirurški odstranjene. Kontrolna snimka nakon 4,5 godina još uvijek pokazuje potpuni odgovor na terapiju.

KLJUČNE RIJEČI: *metastatski melanom; pembrolizumab; BRAF mutacija*