VIA MEDICA

CASE REPORT

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Melanoma of unknown origin with central nervous system metastases

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ABSTRACT

Melanoma is a tumor with high affinity for metastasis within the central nervous system (CNS). Brain metastases indicate a poor prognosis for the patient, often causing deterioration of neurological functions, and thus the patient's quality of life. We present a case of a 72-year-old patient with diagnosed melanoma of unknown origin in clinical stage IV with metastases to the brain, liver and lymph nodes with the current BRAF *V600E* mutation. The patient underwent stereotactic radiotherapy to the area of changes within the central nervous system and combined therapy involving encorafenib with binimetinib under the drug program of the National Health Fund with a very good response. Despite the initial poor prognosis and the appearance of skin toxicities, the patient is still undergoing oncological therapy, is in good general condition and has obtained a clear therapeutic benefit from the use of anti-BRAF/MEK therapy.

Keywords: melanoma, CNS metastasis, focus primarus ignotus

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Introduction

Therapeutic decisions regarding the treatment of melanoma patients are currently made based on the eighth edition of the American Joint Committee on Cancer (AJCC) staging system. According to this classification, location of distant metastases has the greatest prognostic impact in patients with stage IV disease. Patients with metastases to subcutaneous tissue and skin or nonregional lymph nodes (stage M1a), or metastases to the lungs (stage M1b) have a better prognosis compared to patients with metastases to other organs outside the central nervous system (stage M1c). However, dissemination to the central nervous system (CNS) (stage M1d) is associated with the worst prognosis [1]. Melanoma is the third most common cause of brain metastases after lung and breast cancer. It is estimated that approximately 7% of melanoma patients have lesions in the central nervous system at diagnosis, and 40–50% of patients with advanced melanoma will develop brain metastases during the course of disease [2].

Case report

The 72-year-old female patient, a farmer by profession, with a history of frequent exposure to ultraviolet radiation (UVR) due to the nature of her work, was admitted to the Emergency Department of the Voivodeship Multi-Specialist Center for Oncology and Traumatology in Lodz due to abdominal pain for several days, feeling unwell and chronic fatigue for the last 2 months. Laboratory tests revealed a reduced hemoglobin concentration (Hb 6.3 g/dL) and low ferritin concentration < 8 ng/mL, which corresponds to iron deficiency anemia. A year before the patient had been diagnosed by a general practitioner due to reduced complete blood count (CBC) parameters and a positive fecal occult blood test. No significant abnormalities were found in

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colonoscopy and gastroscopy performed at that time. The test for *Helicobacter pylori* was negative. A contrast-enhanced computed tomography (CT) of the chest, abdomen and pelvis performed urgently revealed a mass occluding duodenal lumen, measuring 13 × 10.6 × 6.9 cm, with several slightly enlarged mesenteric lymph nodes, the largest of which measured 18 mm in the short axis. The patient received 3 units of irradiated leukocyte-depleted red cell concentrate compatible with patient's blood group with good tolerance, and after that patient was qualified for urgent esophagogastroduodenoscopy. Intraoperatively, a friable 12 cm tumor was found in the duodenum narrowing its lumen without signs of active bleeding.

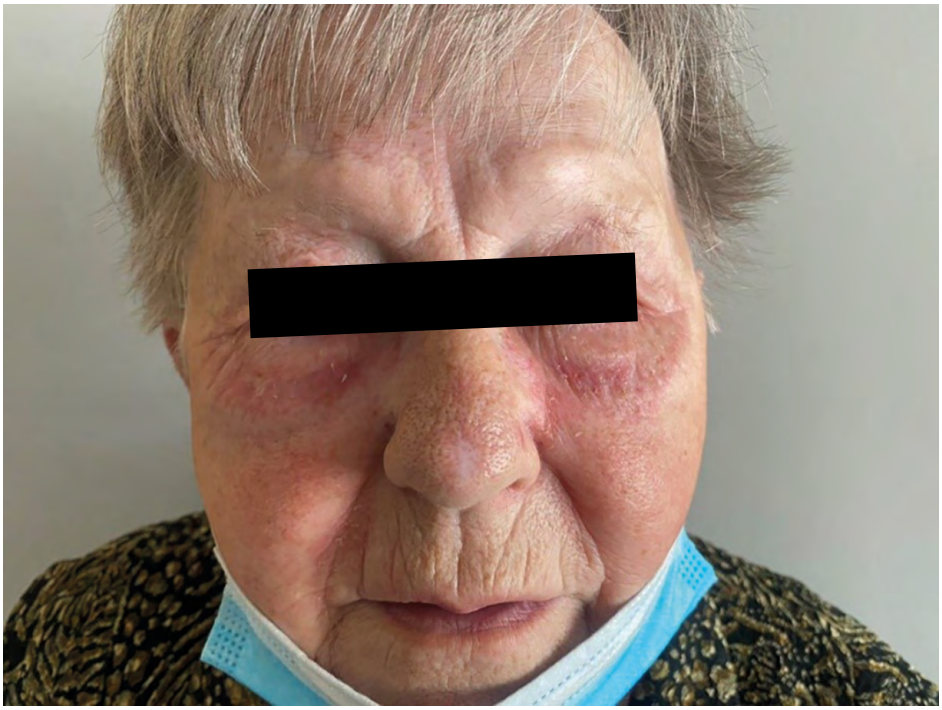
Postoperative histopathological examination showed the presence of poorly differentiated neoplastic cells with immunohistochemically positive staining for HMB-45, S100, Melan-A and SOX10, suggesting metastasis of melanoma.

Skin and mucous membranes dermatoscopy did not reveal any atypic pigmented lesions, which could correspond to a primary melanoma. The patient had never had any skin lesions removed before.

Molecular analysis revealed the presence of a valine-glutamic acid substitution in codon *600* of the *BRAF* gene (*BRAF V600*E mutation). After surgery, the patient reported weakness, periodic headaches, and loss of appetite. Positron emission tomography revealed three metastatic intracerebral lesions, several minor liver lesions, and significantly enlarged mesenteric lymph nodes. Magnetic resonance imaging (MRI) of the brain confirmed the presence of intracerebral metastases in the right parietal lobe and right occipital lobe measuring up to 8 mm. The patient was qualified for stereotactic radiotherapy of both lesions. One fraction of stereotactic radiotherapy was administered at a dose of 22.5 Gy to both brain lesions with a good clinical response. Laboratory tests showed elevated lactate dehydrogenase (LDH) level, i.e. 404 U/L (normal value below 250 U/L).

After ophthalmological consultation and performing an echocardiography, the patient was qualified for first-line treatment with encorafenib and binimetinib in standard doses as part of the drug program, which began in October 2022. During the treatment, the patient observed an improvement in well-being, a reduction in pain and better appetite. In follow-up imaging performed in January 2023, a partial response of hepatic and nodal lesions was obtained.

After more than half a year of therapy, in May 2023, the patient reported to the attending physician due to redness around the eyes (Fig. 1). The patient admitted that she had not followed the recommendations for photoprotection and had spent the last few days in the sun planting vegetables. Due to characteristic clinical picture, current treatment with BRAF and MEK inhibitors and intensive exposure to UVR, the patient was diagnosed with a grade 1 phototoxic reaction according to the Common Terminology Criteria for Adverse Events (CTCAE). Local treatment with weak-potency steroids



Rycina 1. Grade 1 phototoxicity during treatment with encorafenib and binimetinib

and antihistamines was used with a good response. The patient is still undergoing oncological therapy, is in good general condition and has obtained a clear therapeutic benefit from the use of BRAFi/MEKi therapy without other side effects.

Discussion

Melanoma is an aggressive cancer with rapidly increasing incidence worldwide. In the vast majority of patients, the primary lesion is known, located mainly on the skin. In rare cases disseminated disease is diagnosed without a visible primary lesion. These are melanomas of unknown origin (FPI, focus primarius ignotus). It is estimated that they account for 2 to 6% of all melanomas [3].

We consider and treat such patients as diagnosed with skin melanoma, assuming one of the hypotheses that the primary lesion has undergone spontaneous regression, which is why it cannot be detected at diagnosis [4].

Melanoma shows a high predisposition to metastasize to the CNS. Brain metastases are associated with a poor prognosis, and often cause deterioration of neurological functions and quality of life. In asymptomatic patients, they are often detected accidentally during observational radiological studies or during qualification for systemic treatment. It happens that, as in presented patient, the first symptoms of brain metastases are frequent periodic headaches. As in presented case, in patients with single or few mainly asymptomatic brain metastases, stereotactic radiotherapy is recommended. However, depending on the clinical situation, management of melanoma patients with brain metastases includes local and/or systemic treatment, as well as supportive care. The treatment of melanoma patients with brain metastases is currently one of the greatest challenges in the care of patients with advanced melanoma, and therapeutic decisions should be made in teams or specially created units, which should include a clinical oncologist, neurosurgeon, radiotherapist. In patients diagnosed with stage IV melanoma with a *BRAF* mutation, both immunotherapy and three combinations of anti-BRAF and anti-MEK targeted therapies approved for this indication can be used: vemurafenib with cobimetinib, dabrafenib with trametinib, and encorafenib with binimetinib, which have similar efficacy but slightly different toxicity profiles.

Phototoxic reactions are common side effects of anticancer drugs. Indeed, the first BRAF inhibitor introduced into the clinical practice, vemurafenib, was associated with significantly more skin toxicities, and their frequency was reduced by adding the MEK inhibitor, cobimetinib. Phototoxicities observed in patients receiving therapy with other anti-BRAF and anti-MEK drugs: dabrafenib with trametinib or encorafenib with binimetinib are much less frequent. Phototoxic reactions in COLUMBUS pivotal study for combination of encorafenib with binimetinib concerned only 5% of patients in the group receiving the studied combination, while the same skin adverse effect occurred in as many as 30% of patients treated with vemurafenib monotherapy [5]. Although these dermatoses have a very diverse clinical manifestation and can present as polymorphic rashes, erythematous lesions, discolorations or edema, the management patterns of these toxicities have been well known and described. It is essential to inform the patient before starting the therapy about the need for photoprotection throughout the treatment period.

Conclusions

Based on available clinical and laboratory factors, the presented patient could be classified in group with poor prognosis due to the location of metastatic lesions (brain, liver — unfavorable locations), initially elevated LDH level and the observed sign and symptoms of the disease. Despite this, the patient achieved a good therapeutic effect in the form of partial remission (according to RECIST 1.1) of metastatic lesions, which was accompanied by a reduction in pain and improvement in performance status.

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