Multiple Endocrine Toxicities in a Metastatic Cutaneous Melanoma Patient Treated with Checkpoint Inhibitors

Teodora-Elena Hanea¹, Dragoș Goada², Kiss Anamaria², Seres Remus², Claudia Cristina Burz¹,²

¹ "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania
² Department of Medical Oncology, Institute of Oncology "Prof Dr. Ion Chiricuță" Cluj-Napoca, Romania

Corresponding author: Teodora-Elena Hanea; Email: hanea_teodora@yahoo.com

Abstract

Metastatic cutaneous melanomas are typically treated with first-line checkpoint inhibitors, such as the anti-PD-1 antibody nivolumab and the anti-CTLA-4 antibody ipilimumab. Common immune-related adverse events (irAEs) from these therapies include dermatological, gastrointestinal, and endocrine toxicities.

We present a case involving a 51-year-old woman with a prior medical history of Basedow’s disease and multinodular goiter, who was diagnosed with metastatic cutaneous melanoma in 2019. Post-surgical intervention addressed most metastatic sites, leaving behind an inoperable axillary adenopathy. Initial treatment consisted of nivolumab (1 mg/kg) combined with ipilimumab (3 mg/kg). During this dual checkpoint inhibitor therapy, the patient developed hepatitis and primary hypothyroidism, prompting the discontinuation of ipilimumab. Monotherapy with nivolumab was subsequently administered.

While on nivolumab, the patient developed additional irAEs, including type 1 diabetes mellitus and primary adrenal insufficiency. Despite these significant endocrinopathies, continuation of immunotherapy was permitted, ultimately resulting in a complete response.

Keywords: immunotherapy, metastatic cutaneous melanoma, endocrinopathies, hypothyroidism

1. Introduction

Metastatic melanoma, occurring in approximately 15% of cases, presents numerous treatment challenges (1,2). The standard first-line systemic therapy for metastatic or unresectable disease, irrespective of BRAF status, involves immune checkpoint inhibitors (ICIs), such as anti-PD-1 antibodies, with or without anti-CTLA-4 antibodies. Immune-related adverse events (irAEs) are common and dose-dependent, affecting 80%-90% of patients undergoing ICI therapy. Combining these inhibitors increases the risk of significant irAEs, particularly impacting the endocrine, gastrointestinal, hepatic, and dermatologic systems. About 40% of patients experience endocrine toxicities, with the thyroid gland being the most commonly affected organ (3).
While the onset of these adverse effects is unpredictable, they generally appear within six months of starting treatment. The severity of these endocrinopathies varies, and they are rarely fatal. Due to their substantial impact on quality of life and the potential for irreversible effects, early recognition and timely initiation of hormone replacement therapy are essential (4).

2. Case Report

We present the case of a 51-year-old woman with no significant family history and a medical history of multinodular goiter (diagnosed in 2004) and Basedow’s disease (diagnosed in 2018). In 2019, the patient sought medical attention for two suspicious skin lesions, one on the left thigh and the other on the anterior abdominal wall. Both lesions were surgically excised, and the pathological report confirmed cutaneous melanoma, Clark level V, with lymphovascular invasion and a mitotic rate <6/mm², and negative for the BRAF V600E mutation. No adjuvant therapy was recommended. A whole-body 18-FDG PET/CT scan in January 2020 showed no suspicious lesions.

However, a follow-up 18F-FDG PET/CT scan in January 2021 revealed two lesions: one on the right posterior-inferior thoracic wall (9x20 mm, SUVmax=3.8) and another between the left trapezius and supraspinatus muscles (20.3x21.6 mm, SUVmax=8.8). Additionally, left axillary lymphadenopathies (10.5x11.5 mm) were noted (Fig. 1). Ultrasound evaluation detected supraclavicular and axillary adenopathies. The thoracic lesions and the supraclavicular adenopathy were surgically removed, while the left axillary adenopathy was deemed inoperable, resulting in restricted mobility for the patient. Histopathological examination confirmed cutaneous melanoma metastases. The recommended treatment plan included immunotherapy with nivolumab (1 mg/kg) in combination with ipilimumab (3 mg/kg).

Fig. 1 FDG-PET-CT scan showing metastatic lesions, coronal and transversal sections.

One lesion is situated at posterior-inferior thoracic wall (9/20 mm), and the other one is located between the left trapezius and supraspinatus muscle (20.3/21.6 mm).

Before initiating treatment with checkpoint inhibitors, hepatic, renal, thyroid, and pancreatic functions were assessed. Baseline laboratory tests revealed normal AST, ALT, TSH (1.42 μU/mL), and FT4 (17.87 pmol/L). In July 2021, the patient began immunotherapy with 59 mg of nivolumab and 177 mg of ipilimumab every three weeks. After the first administration, TSH levels dropped from 1.42 μU/mL to 0.2 μU/mL, necessitating corticotherapy. Following the second cycle, the patient developed grade 4 hepatitis (ALT: 744.8 U/L, AST: 184.9 U/L) and autoimmune hypothyroidism (FT4: 2.77 pmol/L, TSH: 5.65 μU/mL). Due to these
severe autoimmune reactions, immunotherapy was paused, and the patient was treated with methylprednisolone (2 mg/kg/day), hepatoprotective drugs, and levothyroxine (75 μg daily).

Given the high incidence of adverse events from the ipilimumab/nivolumab combination, we decided to discontinue the dual blockade and continue with nivolumab monotherapy at 240 mg every two weeks starting in August 2021. Hepatic cytolysis persisted but decreased to grade 1, and FT4 levels normalized with substitution therapy.

Over the subsequent months, the patient developed hyperglycemia, with a peak blood glucose level of 500 mg/dL. Diagnosed with diabetes mellitus, she was treated with gliclazide (60 mg three times a day) and long-acting insulin (10 UI daily) starting in January 2022. Despite treatment, she continued to experience fatigue, asthenia, loss of appetite, significant weight loss (22 kg over six months), and uncontrolled diabetes. In June 2022, she was admitted to the Endocrinology Department at the County Clinical Emergency Hospital of Sibiu, where chronic primary adrenal insufficiency was diagnosed, with serum cortisol levels at 08:00 A.M. <0.4 μg/dL. The presumed etiology was iatrogenic adrenal insufficiency as an immune-related adverse effect of immunotherapy. The therapeutic management included prednisone (2.5 mg for two months) and fludrocortisone (0.1 mg for one month).

Additionally, the patient experienced dermatologic adverse events, including poliosis of the eyelashes and eyebrows, commonly associated with nivolumab treatment and observed frequently in patients undergoing checkpoint inhibitor therapy.

Despite multiple endocrine immune-related adverse reactions, the patient continued nivolumab therapy every two weeks and currently presents no acute symptoms or additional adverse reactions to immunotherapy.

3. Discussion

The patient experienced numerous immune-related toxicities, including dermatologic, hepatic, and notably, multiple endocrinopathies. The incidence of adverse events is higher with the combination of immune checkpoint inhibitors (anti-PD1/anti-CTLA4) than with anti-PD1 monotherapy (5). Some of these immune-related adverse reactions can be life-threatening and require immediate and thoro-ough management.

Moderate to severe immune-related toxicities often necessitate the interruption and withholding of immunotherapy, coupled with the administration of glucocorticoids (1 mg/kg/day of prednisone) until toxicity is reduced to grade 1. Once the acute reaction resolves, immunotherapy may be resumed. Interestingly, immune-related adverse events are in general associated with a better prognosis, indicating that the immune system is effectively activated and capable of targeting cancer cells.

3.1. Cutaneous toxicity

The most common adverse reaction in patients receiving checkpoint inhibitors is cutaneous toxicity, typically presenting as inflammatory skin reactions (6). Although the patient experienced eyelash depigmentation, this side effect did not necessitate any adjustments to her treatment.

3.2. Endocrine toxicity

The incidence of clinically significant endocrine-related adverse reactions in patients treated with checkpoint inhibitors is 10% (6). Up to 15%-20% of patients receiving PD-1/CTLA-4 blockade develop thyroid toxicity, with hypothyroidism being the most common. A lower incidence is observed in patients treated with PD-1 inhibitors alone. Typically, patients initially experience transient hyperthyroidism followed by hypothyroidism. Management includes hormone replacement with levothyroxine and monitoring TSH and free T4 levels every 4-6 weeks and before each infusion (7).

The patient also developed primary adrenal insufficiency, a rare complication occurring in only 0.7% of patients treated with checkpoint inhibitors (6). Early initiation of glucocorticoid and mineralocorticoid therapy is crucial to minimize life-threatening effects.

Type 1 diabetes mellitus occurs in approximately 0.2% to 0.9% of patients receiving checkpoint inhibitors (6, 7). The patient exhibited persistent hyperglycemia due to the
complete destruction of pancreatic beta cells, necessitating insulin therapy for glycemic control.

3.3. Hepatic toxicity
The patient also experienced grade 4 hepatitis, necessitating the discontinuation of immunotherapy until the hepatitis grade decreased to one and treatment with methylprednisolone at 2 mg/kg/day. Hepatotoxicity is observed in 25%-30% of patients treated with the combination of anti-PD(L)1 and anti-CTLA-4 therapy, with 15% experiencing grade 3 hepatitis (9).

4. Conclusion

The adverse effects of immunotherapy, though typically non-lethal, wield substantial influence over a patient’s quality of life (10). The challenge lies in discerning these symptoms from those attributed to cancer itself, complicating diagnosis. Particularly noteworthy is the infrequent occurrence of multiple endocrine immune-related adverse effects, potentially leading to enduring endocrine dysfunction and obstructing the course of immunotherapy. In our case, strategic adjustments to the immunotherapy regimen were pivotal in mitigating adverse effects. Supplementing with substitutive endocrine therapy, including insulin, cortisone, and levothyroxine, facilitated the patient’s continuation of the treatment plan.

Abbreviations
18-FDG – Positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with computed tomography
ALT – Alanine Aminotransferase
AST – Aspartate Aminotransferase
BRAF – v-raf murine sarcoma viral oncogene homolog B1
CNS – central nervous system
CTLA-4 – Cytotoxic T-lymphocyte-associated protein 4
FT4 – Free Thyroxine
ICIs – immune checkpoint inhibitors
PD-1 – programmed cell death protein 1
TSH – Thyroid Stimulating Hormone

Statements
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References


