Case Report
Olgu Sunumu

DOI: 10.4274/turkderm.galenos.2022.47527
Turkderm-Turk Arch Dermatol Venereol 2022;56:135-7

Vitiligo in a patient with metastatic melanoma receiving human immunoglobulin G4 monoclonal antibody-nivolumab treatment

İnsan immünoglobulin G4 monoklonal antikor-nivolumab tedavisi alan metastatik melanomlu hastada vitiligo

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Abstract

Nivolumab is an immunotherapy drug developed to increase the ability of the immune system to target and kill cancer cells and is a human immunoglobulin G4 monoclonal antibody blocking programmed cell death-1. Nivolumab is a checkpoint inhibitor that stops a signal that hinders stimulation of the tumor cell-attacking T-cells. It is a relatively new drug used in melanoma treatment. A 67-year-old male patient was operated on for acral lentiginous melanoma and admitted to our outpatient clinic with white spots on his face, head, and back of both hands while receiving nivolumab treatment. New-onset vitiligo during melanoma treatment is associated with more favorable clinical outcomes. Improved survival was demonstrated in this type of patient. Therefore, nivolumab treatment was continued because of new-onset vitiligo in our patient. This patient was living for 4 years without any clinical progression since receiving nivolumab treatment. Hence, this case is reported.
Keywords: Vitiligo, melanoma, brain metastasis, monoclonal antibody, nivolumab, prognosis, indicator

Öz

Nivolumab, bağışıklık sisteminin kanser hücrelerini hedefleme ve öldürme yeteneğini geliştirmek için tasarlanmış bir immünoterapi ilacıdır ve programlanmış hücre ölümü-1'i bloke eden bir insan immünoglobulin G4 monoklonal antikorudur. T-hücrelerinin kanser hücrelerine saldırmasını önleyen bir sinyali bloke eden bir kontrol noktası inhibitörü olarak çalışır. Melanom tedavisinde kullanılan nispeten yeni bir ilaçtır. Akral lentiginöz melanom nedeniyle opere edilen 67 yaşında erkek hasta, nivolumab tedavisi alırken yüzünde, başında ve iki elinin arkasında beyaz lekeler ile polikliniğimize başvurdu. Melanom tedavisi sırasında yeni başlayan vitiligo, daha olumlu klinik sonuçlarla ilişkilidir. Bu tip hastalarda artmış sağkalım gösterilmiştir. Bu nedenle hastamızda yeni başlayan vitiligo, nivolumab tedavisinde kalmamıza neden oldu. Hasta nivolumab tedavisi aldığından beri 4 yıldır herhangi bir klinik progresyon göstermeden yaşıyor. Bu nedenle bu olguyu bildirmek istiyoruz.
Anahtar Kelimeler: Vitiligo, melanom, beyin metastazı, monoklonal antikor, nivolumab, prognoz, belirteç

Introduction

Nivolumab is an immunotherapy drug that improves the immune system's capability to destroy cancer cells. It was initially developed by Professor Tasuku Honjo at Kyoto University in 1992, and this discovery was awarded the Nobel Prize in 2018.

Nivolumab is a human immunoglobulin G4 monoclonal antibody that blocks programmed cell death-1 (PD-1). Nivolumab is a checkpoint inhibitor (CPI) that stops a signal that hinders the stimulation of tumor cell-destroying T-cells[1].

PD-1 is a protein localized over the activated T-cells surface. The binding of PD1-ligand-1 (PD1-L1) or PD1-L2 to PD1 inactivates the T-cell. Many cancer cells produce PD1-L1. Nivolumab prevents the binding of PD1-L1 to PD1, thereby reactivating the T-cell[2]. PD1-L1 is present in approximately half of the patients with melanoma (40-50%)[3].

Nivolumab plus ipilimumab is used as a first-line treatment in patients with metastatic or inoperable melanoma if the

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Cite this article as: Gökşin Ş, Değirmencioğlu S. Vitiligo in a patient with metastatic melanoma receiving human immunoglobulin G4 monoclonal antibody-nivolumab treatment. Turkderm-Turk Arch Dermatol Venereol 2022;56:135-7

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Turkderm - Turk Arch Dermatol Venereol
2022;56:135-7

cancer does not have BRAF mutation. Nivolumab following treatment of ipilimumab is used as second-line treatment in patients with metastatic or inoperable melanoma if the tumor has BRAF mutation or inhibitor[4].
Clinical studies revealed that nivolumab is a good option for monotherapy in metastatic melanoma[4].
The use of nivolumab as a monotherapy for metastatic melanoma was approved by the European Medicines Agency in April 2015.
Caponetto et al.[5] reported the effectiveness of nivolumab in patients with melanoma with brain metastases.
The incidence of vitiligo in the community varies between 0.5% and 1%[6]. Melanoma-related vitiligo is seen to be 7-10-fold more frequent compared to the normal population[7].
The literature reported the development of vitiligo or hypopigmentation during nivolumab treatment in patients with melanoma in recent years[7-9]. Newly emerging vitiligo during nivolumab treatment in patients with melanoma comes with better clinical results and improved survival in these patients[8,10].

Case Report

In December 2012, a 67-year-old male patient was diagnosed with acral lentiginous melanoma from a left foot sole biopsy. The mass was surgically excised (24x18x22 mm, excision margins of 10 mm). Clinical, pathological, or radiological examinations were performed by oncology. The tumor was only limited to the foot sole and was not ulcerated (T3N0M0, stage II).
The clinical course and treatment details of the patient are summarized in Table 1.
This patient was readmitted to the outpatient clinic in September 2016 because of white spots on his skin while receiving nivolumab treatment.



Figure 1. Vitiligo lesions on the back of both hands and the cavity of the acral lentiginous malignant melanoma surgically excised in the foot sole



Figure 2. Appearance of vitiligo on the top of the head in the patient

Table 1. The clinical course and treatment characteristics of the patient

Date	TNM classification	Clinical stage	Clinical features and decision	Treatment
December 2012	T3N0M0	Stage II	Biopsy from the left foot sole. The first diagnosis of malign melanoma.	Follow-up
December 2013	T3N1M0		Biopsy from the inguinal lymph node. Metastasis to inguinal lymph node (1 node).	Interferon
December 2014	T3N2aM0		Biopsy from the inguinal lymph node. Metastasis to inguinal lymph nodes (2 nodes).	
January 2015	T3N3bM0		1 clinically + left inguinal lymphadenopathy. Biopsy from the inguinal lymph node. Metastasis to inguinal lymph nodes (3 nodes).	Cisplatin, temozolomide
May 2015			PET/CT normal, no metastasis.	Temozolomide
May-November 2015			Maintenance therapy with a single agent orally.	Temozolomide
November 2015	T3N3bM1a	Stage III	PET/CT + lymph nodes, nonregional lymph nodes metastasis, no visceral organ involvement. Starting new treatment with ipilimumab.	Ipilimumab
December 2015-February 2016	T3N3bM1c		PET/CT + lymph nodes, nonregional lymph nodes metastasis, visceral solid organ (liver) involvement. Continuing treatment with ipilimumab.	Ipilimumab
April 2016	T3N3cM1d	Stage IV	PET/CT + lymph nodes, central nervous system plus visceral solid organ involvement. Starting new treatment with nivolumab.	Nivolumab
April 2016-April 2018			Continuing treatment with nivolumab.	Nivolumab

TNM classification and clinical staging of malign melanoma according to the eighth version of the American Joint Committee on Cancer was done. PET/CT: Positron emission tomography/computed tomography

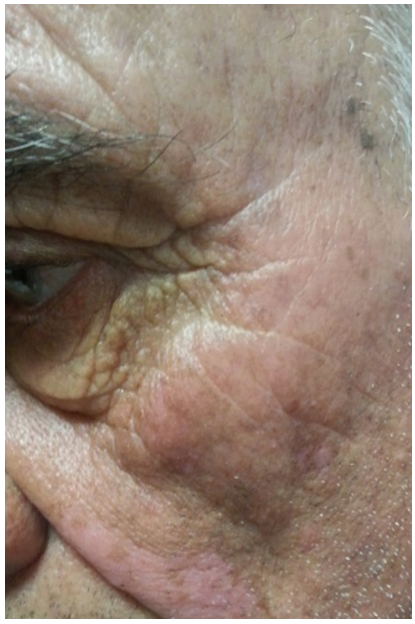


Figure 3. Appearance of vitiligo on the face of the patient

Depigmented patches were observed on his face, head, and back of both hands (Figure 1-3). The diagnosis of vitiligo was established. Vitiligo lesions were present for 4 months. The patient has had brain lesions compatible with metastasis and had wild-type BRAF mutation. He had been receiving nivolumab since April 2016. Our patient is living without any clinical deterioration after 4 years of nivolumab therapy. Hence, this case is reported. Informed consent was obtained.

Discussion

Vitiligo is one of the most frequently seen cutaneous immune-related adverse events in patients with melanoma during nivolumab treatment[7].

Hypopigmentation or depigmentation secondary to CPI drug usage in patients with melanoma is seen 10-times more according to the normal population, accounting for 2.0-8.3% of patients with melanoma in the literature. Patients with melanoma with new-onset vitiligo have a 2-4-fold prolonged survival[8].

Median overall survival in patients with metastatic melanoma receiving nivolumab is 16.8 months, and with 62%, 44%, and 40% of patients survival in 1-3 years, respectively[7]. Our patient, who received nivolumab treatment, was alive for 48 months without any clinical progression.

The literature reported that CPI-associated vitiligo has a different clinical character with multiple mottled depigmentation macules that transform into large plaques on light-exposed skin[9]. However, vitiligo lesions became coalescent over time in nearly all cases. CPI-associated vitiligo occurs on light-exposed skin areas, such as the face, head, and back of both hands, as seen in our patient[9].

The average duration to the onset of vitiligo is 5.4 weeks following nivolumab initiation[7]. This period was 8 weeks for our patient.

Newly emerging vitiligo in patients with melanoma is an indicator of strong immunity against melanoma and is associated with increased survival[10].

Vitiligo is protective against melanoma[11]. Development of melanoma in patients with vitiligo is quite low (0.24%), which supports this idea[12]. A genome-wide association study of patients with vitiligo has reported significant associations between vitiligo and several genes that regulate immunity. Vitiligo was reported to be associated with polymorphism in the TYR gene encoding tyrosinase which is the main enzyme of melanin synthesis. This study suggests that strong antityrosinase activity protects patients with vitiligo against melanoma[12].

Therefore, newly emerging vitiligo in patients with metastatic melanoma receiving nivolumab is evidence of treatment effectiveness and good prognosis.

Ethics

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ş.G., Concept: Ş.G., Design: Ş.G., Data Collection or Processing: Ş.G., S.D., Analysis or Interpretation: Ş.G., S.D., Literature Search: Ş.G., Writing: Ş.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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