*Case Report / Olgu Sunumu*

# Rare Side Effect of Immune Checkpoint Inhibitors: Adrenal Insufficiency

## İmmün Checkpoint İnhibitörlerinin Nadir Yan Etkisi: Adrenal Yetmezlik

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**Abstract**

**Background:** Immune checkpoint inhibitors are cell membrane proteins that regulate the immune response. They are used in the treatment of non-small cell lung cancer, renal cell carcinoma, melanoma, and other tumor types. They affect dermatological, gastrointestinal, hepatic, endocrine and other systems. We present a case of adrenal insufficiency caused by nivolumab in a patient who presented with fatigue, weakness, nausea, and vomiting.

**Keywords:** Adrenal insufficiency, Immune checkpoint inhibitors, Nivolumab

**Öz**

**Amaç**: İmmün kontrol noktası inhibitörleri immun yanıtı düzenleyen hücre zar proteinleridir. Küçük hücreli dışı akciğer kanseri, renal hücreli karsinom, melanom ve diğer bazı tümör tiplerinin tedavisinde kullanılmaktadır. Dermatolojik, gastrointestinal, hepatik, endokrin ve diğer sistemleri etkilerler. Halsizlik, yorgunluk, bulantı ve kusma şikâyetleri ile başvuran bir hastada nivolumabın neden olduğu adrenal yetmezlik olgusunu sunuyoruz.

**Anahtar Kelimeler:** Adrenal yetmezlik, İmmün kontrol noktası inhibitörleri, Nivolumab

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## Introduction

Immune checkpoints inhibit co-stimulatory signaling, thereby suppressing the immune response of T cells against tumour cells, functioning as an immune evasion mechanism for the tumour cells. To overcome this immune suppression, monoclonal antibodies targeting programmed cell death-1 (PD-1), programmed cell death ligand-1 (PD-L1), and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) are used in clinical practice. These immune-modulating monoclonal antibodies enhance immune system activity, thus improving the prognosis in patients with advanced malignancies (1,2). Ipilimumab, by blocking CTLA-4, is used in malignant melanoma, while cemiplimab, which blocks PD-1, is used in cutaneous squamous cell carcinoma. Pembrolizumab and nivolumab are utilized in malignancies such as melanoma, non-small cell lung cancer, renal cell carcinoma, Hodgkin lymphoma, head and neck squamous cell carcinoma, colorectal cancer, and urothelial carcinoma. Atezolizumab, durvalumab, and avelumab, which block PD-L1, are employed in urothelial carcinoma (3-5). With the introduction of immune checkpoint inhibitors (ICIs) in clinical practice, immune-related side effects, as opposed to conventional chemotherapy agents, have been reported. These side effects are often associated with better cancer survival. The most common adverse effects are dermatological, gastrointestinal, and endocrine, while neurological, cardiac, and rheumatological side effects are rarer (6-8). Management of these side effects includes strategies such as dose reduction, interruption of the drug, and steroid treatment. In severe cases, infliximab, mycophenolate mofetil, anti-thymocyte globulin, methotrexate, calcineurin inhibitors, intravenous immunoglobulin, and plasmapheresis can be used (9).

## Case

A 70-year-old female patient, followed by the department of medical oncology for malignant melanoma, was admitted to our clinic with complaints of fatigue, weakness, nausea, and vomiting for the past two months. Additionally, she had a history of hypertension and had experienced a weight loss of 15 kg over the past 2 months. The patient had received a total of 14 cycles of nivolumab therapy for her malignant melanoma. The first 12 cycles were administered biweekly, and the last two cycles were given monthly due to her current symptoms. Her family history was unremarkable. She had no history of smoking or alcohol consumption. Physical examination revealed only pallor. Laboratory investigations revealed normal complete blood counts, but her biochemistry showed a glucose level of 58 mg/dL (normal range: 74-106 mg/dL), while other biochemical tests were normal. The patient's biochemical data at diagnosis and during follow-up are presented in Table 1.Serum levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), growth hormone (GH) and
prolactin were within normal limits. Serum cortisol was <0.5 µg/dL (normal range: 4.3-22.4 µg/dL), and adrenocorticotropic hormone (ACTH) was <5 pg/mL (normal range: 5-46 pg/mL).

Thyroid-stimulating hormone (TSH) was 9.67 mIU/L (normal range: 0.35-5.5), free triiodothyronine (FT3) was 3.76 pmol/L (normal range: 2.3-4.2), and free thyroxine (FT4) was 0.81 ng/dL (normal range: 0.89-1.76). An upper gastrointestinal endoscopy performed due to her nausea and vomiting symptoms was unremarkable. A dynamic abdominal tomography scan revealed normal bilateral adrenal glands. A pituitary magnetic resonance imaging (MRI) was also normal. The patient was not using steroids for her condition or any other reason. Given the low levels of ACTH and cortisol, the normal pituitary MRI, and the absence of exogenous steroid use, secondary adrenal insufficiency induced by nivolumab was diagnosed. Nivolumab was discontinued, and intravenous methylprednisolone 40 mg/day was administered for 2 days. The patient's symptoms improved, and she was discharged on the third day with oral prednisolone.

**Table 1. Patient's Biochemical Data**

| | At diagnosis | One month after treatment |
|---|---|---|
| **ACTH** | <5 pg/mL | 6,99 pg/mL |
| **Cortisol** | < 0,5 µg/dL | 9,25 µg/dL |
| **Glucose** | 58 mg/dL | 83 mg/dL |
| **Urea** | 15 mg/dL | 27 mg/dL |
| **Creatinine** | 0,32 mg/dL | 0,52 mg/dL |
| **Albumin** | 3,19 g/dL | 3,86 g/dL |
| **ALT** | 19 U/L | 14 U/L |
| **AST** | 43 U/L | 21 U/L |
| **Sodium** | 136 mmol/L | 138 mmol/L |
| **Potassium** | 3,75 mmol/L | 3,75 mmol/L |
| **Calcium** | 10,5 mg/dL | 9 mg/dL |
| **TSH** | 9,67 µIU/mL | 8,77 µIU/mL |
| **fT4** | 0,81 ng/dL | 1,08 ng/dL |
| **fT3** | 3,76 pg/mL | 3,03 pg/mL |

*ACTH: Adrenocorticotropic hormone (normal value 1,3-16,7 pmol/L ), AST: Aspartate aminotransferase (normal value 10-35 U / L), ALT: Alanine aminotransferase (normal value 10-40 U / L), TSH: Thyroid-stimulating hormone (normal value 0,27–4,2 µIU/mL) T4:Thyroxine (normal value 0.8-1.8 ng/dL), T3: Triiodothyronine (normal value 2.3-4.1 pg/mL))*

## Discussion

Immune checkpoint inhibitors (ICIs) are among the most successful immunotherapies used extensively in recent years. These agents enhance T cells' ability to kill tumor cells and exhibit antitumor activity, resulting in significant improvements across multiple cancer types (10). However, ICIs, unlike traditional chemotherapy, radiation, and other cancer treatments, can cause a variety of autoimmune adverse events. Among these, endocrinopathies are the most frequently reported autoimmune adverse events associated with the use of these agents. While thyroiditis and hypophysitis are the most commonly reported endocrinopathies, type 1 diabetes mellitus and adrenal insufficiency are reported less frequently (11). The incidence of endocrinopathies varies depending on the type of ICIs used. Symptoms generally emerge within six months of initiating ICIs, although the onset time remains unpredictable. Endocrinopathies may develop at any point after treatment initiation or even a few months after discontinuation (12). The nonspecific nature of the symptoms, the unpredictable timing of onset, and the potential for mortality—albeit rarely—highlight the critical importance of early detection and effective management of endocrinopathies, as these factors significantly impact patients' quality of life.

Nivolumab is a novel ICI that exerts its effect by enhancing T cell-mediated immune responses against tumor cells in the treatment of various cancers (10). The T cell activation caused by the blockade of the PD-1 pathway by nivolumab increases antitumor immunity while potentially triggering dysregulated immune responses against normal endocrine tissues. Adrenal insufficiency associated with ICIs is believed to result from autoimmune-mediated damage to the hypothalamic-pituitary-adrenal (HPA) axis. This autoimmune attack can lead to hypophysitis, resulting in impaired ACTH secretion and subsequent secondary adrenal insufficiency, as observed in our patient (13). Adrenal insufficiency is a rare side effect of ICIs, occurring in less than 1% of treated patients. This adverse effect typically emerges about two months after treatment initiation (14).

The diagnosis of adrenal insufficiency requires an integrated assessment of clinical findings, laboratory tests, and imaging studies. A low morning cortisol level (<5 µg/dL) is a strong indicator of adrenal insufficiency. While elevated ACTH levels suggest primary adrenal insufficiency, low or normal ACTH levels indicate secondary adrenal insufficiency (15). Our patient presented with common clinical features of adrenal insufficiency, including fatigue, weakness, nausea, and vomiting. The patient's low morning cortisol level (<0.5 µg/dL) and ACTH level (<5 pg/mL) were indicative of secondary adrenal insufficiency, obviating the need for confirmatory cosyntropin stimulation testing. The absence of electrolyte imbalances, such as hyponatremia and hyperkalemia, commonly observed in primary adrenal insufficiency, and a normal pituitary MRI, along with no history of exogenous steroid use or recent radiation therapy, led us to attribute the findings to nivolumab use.

Adrenal insufficiency may be overlooked due to its low incidence and nonspecific symptoms. Furthermore, the absence of routine endocrine screening contributes to delays in diagnosis, which can lead to severe consequences. Endocrine dysfunction should be considered in patients undergoing immunotherapy, and these patients should be frequently monitored for endocrine complications. Clinicians must remain vigilant about the potential for adrenal insufficiency as a possible side effect of ICIs in cancer patients receiving immunotherapy. In cases of suspected adrenal insufficiency, serum cortisol and ACTH levels should be promptly evaluated.

In conclusion, adrenal insufficiency, as a side effect of nivolumab, can have serious consequences if not identified and treated early. As ICIs are increasingly used across various conditions, patients are presenting more frequently to emergency departments and outpatient clinics with adverse effects associated with these new drugs. Therefore, the side effects of these medications must be well-understood, and all physicians—not just oncologists—should be knowledgeable about how to manage these complications effectively.

***Ethical Approval:*** *There is an informed consent form for the patient.*

***Author Contributions:***
*Concept: R.Y.*
*Literature Review: R.Y., B.K.*
*Design : R.Y., M.K.*
*Data acquisition : B.K., A.Ü., Ü.K.*
*Analysis and interpretation: F.U., M.K.*
*Writing manuscript: R.Y., B.K.*
*Critical revision of manuscript: M.K., F.U.*

***Conflict of Interest:*** *The authors have no conflicts of interest to declare.*

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