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## Case Report

# Nivolumab, a new immunomodulatory drug, a new adverse effect; adrenal crisis



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## ABSTRACT

Owing to the advancements in medicine, new information is obtained regarding cancer, new antineoplastic agents are developed. Frequent use of these new pharmacological agents emergency physicians to be vigilant about their side effects. We present a case of adrenal crisis in a patient with non-small cell lung cancer (NSCLC), caused by an immunomodulatory drug; nivolumab. While adverse events are related to other immunomodulatory drugs have been reported in literature, our case is the first nivolumab-related adrenal failure to be reported. A patient with lung cancer presented to the emergency room (ER) with nausea and vomiting. Hyponatremia, hyperkalemia, persistent hypoglycemia led to the diagnosis of adrenal crisis. Having direct effect on the immune system, these drugs were claimed to be highly reliable. However, there is no reliable data on the side effect profile of these agents. It should be kept in mind that life-threatening auto-immune reactions may occur.

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## 1. Introduction

Treatment of advanced stage NSCLC has changed in the last decade. Even with the development of goal-directed therapy models, mortality rates following the year after diagnosis are still high.<sup>1</sup> For this reason, with molecular targeting agents having limited effect on treatment, studies have evolved towards tumor and blood biochemistry.<sup>1</sup> As the role of the immune system in tumor surveillance is being uncovered, there emerge developments in the treatment of advanced stage NSCLC. The discovery of antigens on cancer cells which activate and inhibit immune system cells has led to the development of immunomodulatory drugs. Normally, a mutated cell is destroyed by the immune system (cytotoxic T cell). However, cancer cells express antigens termed as checkpoint molecules, which prevent the activation of T cells. Thus, the cancer cell survives.<sup>2</sup> In the mechanism of cancer formation, after the recognition of a tumor cell, the tumor antigen is presented to the T cells and the tumor cell is killed by the activation of the T

cell. The T-cell related immune response is managed by multiple step activating and inhibiting signals. Therefore different immune-related event can develop. In literature, there was some adverse event shown; hypophysitis, pneumonitis, colitis, pruritis, adrenal insufficiency and etc. We aimed to inform the emergency physicians about the new generation cancer drugs and side effects with this case report.

## 2. Case report

A 52-years-old male who presented to the ER with nausea and vomiting revealed that the patient has received chemotherapy with Nivolumab, an anti-tumor immunomodulatory antibody 2 weeks ago, the diagnosis of NSCLC on his medical history. Physical examination revealed a cachectic patient, with dehydration and a poor general condition. Vital signs were stable. The patient was started on IV hydration with isotonic saline. Nausea receded following the administration of metoclopramide. Serum electrolyte, transaminase levels, and CBC were ordered. Hyperkalemia ( $K^+$ :6,7 mEq/L), hyponatremia ( $Na^+$ : 124 mEq/L) and high plasma creatinine (Cr:2,1 mg/dl) levels were observed. ECG did not show any signs of hyperkalemia. Blood gas analysis showed metabolic acidosis. Urinary output was normal. For hyperkalemia, the insulin-dextrose infusion was administered. Hyponatremia was predicted to be a result of hypovolemia and acute renal failure was considered

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to be prerenal azotemia. IV hydration was continued as the patient was further evaluated for the paraneoplastic syndrome. As the studies were carried out, the patient developed a general tonic-clonic seizure, and stick glucose levels were found too low to be measured. 50 mL of 20% dx IV bolus was followed by 10% dx 500 mL. However, hypoglycemia was persistent. Hyponatremia, hyperkalemia and persistent hypoglycemia raised a suspicion for adrenal failure, so blood cortisol and ACTH levels were ordered. Cortisol levels were low; 0.96 µg/dL (reference values 6.7–22.6) and ACTH levels were high; 1234 (reference values 10–46). The patient was diagnosed with a primary adrenal failure, and IV prednisolone 100 mg was added to the treatment. Although the patient had a history of malignancy to explain the reason for adrenal failure, an abdominal computerized tomography (CT) was ordered to exclude metastatic lesions and infectious pathologies. Abdominal CT showed abnormalities except for a few lymphadenopathies, his urine stick test was normal and a laboratory was denied infection so the adrenal failure was thought to be related to drug side effect. The patient was admitted to internal medicine intensive care unit. Two weeks later, the patient was extubated with oral prescriptions.

### 3. Discussion

The T-cell related immune response includes antigen-specific cell clone selection, secondary lymphoid tissue activation, management of antigen and inflammation, a trigger of direct effector function and promoting the aid of effector immune cells. Normal physiological defense against autoimmunity and inflammation is similar to this mechanism. The receptors and ligands that form T cell effector function are expressed more than usual in the tumor cell or in the microenvironment of tumors.<sup>3</sup> Research has shown that these antigens, namely the checkpoint antigens, become dysfunctional in solid tumors (such as melanoma, renal cell cancer or NSCLC) enabling the tumor to escape from the immune system.<sup>2</sup>

In literature there are six checkpoint modulators reported, most researches propose Cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death-1 (PD-1) in cancer treatment. Both carry inhibitor properties, but they regulate immune response at different levels, with different mechanisms.<sup>3</sup> The antibodies formed against CTLA-4 and PD-1 receptors hinder immune system inhibition. The discovery of these two checkpoint inhibitors has enabled new and promising advancements.<sup>4</sup>

CTLA-4 is the first described checkpoint molecule.<sup>2</sup> Mostly, it is expressed on T cells and determines the amplitude of T-cell activation in the early stages.<sup>3</sup> The monoclonal antibody developed against this is Ig G1 (ipilimumab) and has a wide spectrum of effect.<sup>2</sup> Not being CTLA-4 ligand specific, the CTLA-4 blockage may cause lethal autoimmune and hyperimmune phenomena. Immune-related toxicity affecting different tissues has been spotted at 10%, and 25–30% of patients developed colitis. Attempts to reduce mortality and morbidity were made by developing algorithms to reduce immunotoxicity (steroid, TNF).<sup>3</sup>

As the immune system and checkpoint pathways were further discovered, other molecules with different effects and toxicities, such as PD-1 and its ligand PD-L1 were developed.<sup>5</sup> PD-1 is defined as a molecule that can potentially induce an antitumor immune response by the patient's own immune system. PD-1 is an immune checkpoint protein expressed by the T-cells.<sup>1,3</sup> It is expressed more than CTLA-4 and it inhibits the lytic activities of B-cells, activated T lymphocytes and natural killer cells.<sup>3</sup> After being chronically predisposed to antigens in situations such as chronic viral infections or cancer, PD-1 is expressed by T-cells.<sup>2</sup>

Solid tumors such as NSCLC have 2 ligands of PD-1: PD-L1 and PD-L2.<sup>2–4</sup> The blockage of PD-1 and PD-L1 by monoclonal

antibodies causes tumoral regression.<sup>6</sup> Most melanomas, ovarian and lung malignancies have found to show increased expression of PD-L1.<sup>3</sup> The monoclonal antibody developed against this Ig G4 analog nivolumab, and it specifically targets peripheral tissue. Many other agents targeting PD-1 have also been developed: nivolumab (BMS936558, Opdivo®), pembrolizumab (MK-3475), lambrolizumab, (Keytruda®), and pidilizumab (CT-011).<sup>2</sup>

Nivolumab is the first PD-1 inhibitor and it is developed against unresectable melanoma.<sup>2</sup> It is a real human monoclonal PD-1 antibody that is genetically designed. Most clonal antibodies used in therapeutically in oncology are Ig G1 subtype and cause antibody-related cell cytotoxicity (ADCC). In phase 1 human studies, 0.3–1.3 and 10 mg/kg doses of treatment were administered and nivolumab was well tolerated, however, maximum tolerable dosage was not determined.<sup>2</sup>

In phase 1 studies, human analog monoclonal antibodies were given, and skin (20%), gastrointestinal (15%), and pulmonary (9%) toxicities were observed. Although widespread cohort studies are needed to define toxicity profile, it is emphasized that pneumonitis is a frequent side-effect.<sup>5</sup> Because PD-1/PD1-L1 is located peripherally, the tumoral response seems to be better, with lesser immune-related side-effects.<sup>4</sup>

In phase 2 studies, 31% skin toxicity, 12% rash, 9% pruritus, and 3% vitiligo was reported. Gastrointestinal toxicity (colitis) and pneumonitis were reported as 11% 3% respectively. These different side effects may be the result of the different mechanisms used by PD-1 and PD-L1 molecules.<sup>2</sup> In the case, we presented, the mentioned side effect may be related to the disruption of the inhibition of autoimmunity.

In literature, hypophysitis, and thyroiditis were reported as side effects of ipilimumab which is a CTLA-4 antibody. Although the etiology was thought to be the disruption of the inhibition of autoimmunity as an immune-related endocrine side effect, no clear conclusions were reached.<sup>7</sup> Two cases was reported adrenal crisis due to Nivolumab. In this cases, primary adrenal insufficiency was detected with a low level of cortisol.<sup>8,9</sup> ACTH was normal due to ACTH stimulation test was performed for diagnosis.<sup>9</sup> In our patient, high level of plasma ACTH was suggested primary adrenal insufficiency. There is no specific test to determine the cause of adrenal insufficiency. As well as in the case in literature, the diagnosis was determined with the other possible causes excluded.

Management of primary adrenal insufficiency due to immunomodulatory drugs are the same as other causes. Treatment differentiated with the severity of suppression. For the severe disease such as our case high dose corticosteroid is recommended.<sup>9,10</sup>

Being accepted as safe due to their peripheral mechanisms in cancer patients, these increasingly used immunomodulatory drugs should be well known by emergency physicians, since they may pose life-threatening risks.

New therapeutic agents are being developed for cancer treatments, and their promising profiles increase their popularity day by day. Complications caused by antineoplastic agents are increasing among emergency room presentations. Just as with any new medication, the emergency physician should be alert about possible side-effects.

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### Conflicts of interest

None declared.

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