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# Pembrolizumab induced hyponatremia. A case report

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## Abstract

Hyponatremia is the most common electrolyte abnormality inpatient. Medications are a common cause of this. Cancer treatment has evolved with immune check point inhibitors replacing conventional chemotherapy agents. Pembrolizumab, which is a program cell death receptor-1 ligand has been shown to cause endocrinopathies. We describe a case of hyponatremia due to pembrolizumab

## Keywords

adrenal insufficiency, hypophysitis, hyponatremia, pembrolizumab



## Conflict of Interest Statement

No conflicts of interest

## Cover Page Footnote

revisions made to the reviewed manuscript

CASE REPORT

# Pembrolizumab Induced Hyponatremia. A Case Report

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## 1. Introduction

Hyponatremia is the most common electrolyte disorder encountered in the hospital. It is associated with worse morbidity.[1] Many medications like thiazide diuretics, SSRIs can cause it apart from several pathological states like fluid overload, liver cirrhosis. Rarely, endocrinopathies can be associated with hyponatremia and require specific workup. We describe a case of endocrinopathy induced hyponatremia due to pembrolizumab which is a programmed cell death receptor 1(PD-1) inhibitor.

## 2. Case

A 63-year-old female presented to the Emergency Department with nausea, vomiting and poor oral intake for 2 weeks. These symptoms had intensified 3 days prior to presentation.

She was on active treatment for ovarian cancer and had completed 4 cycles of pembrolizumab and bevacizumab. Admission laboratory values were notable for serum sodium of 113 mmol/L (normal 136–145) with a baseline of 135 mmol/L one month earlier, chloride 76 mmol/L (normal 98–107), potassium 3.7 mmol/L (normal 3.5–5.1), glucose level 78 mg/dL, and creatinine 0.6 mg/dl (normal 0.5–1.0). Serum osmolality was 238 mOsm/kg (normal 275–295). Home medications included Vitamin B12, Vitamin D and mirvetuximab-soravtansine injections, of which the last one had been 6 weeks prior. She denied alcohol intake but admitted to drinking water without eating much food.

Urine Osmolarity was inappropriately high at 542 on admission. She was started on hypertonic 3% saline at 30 ml/hours and desmopressin 2 mcg intravenous every 8 hours. TSH was normal at 2.02 uIU/mL, but the next morning's AM cortisol was 0.6 mcg/dl (Normal range is 5–23). ACTH stimulation test showed insufficient rise of cortisol level (2.4 at 30 minutes and 3.8 at 60 minutes) post ACTH administration. ACTH level was low normal at 6.5 pg/ml (expected level is 10–16). Brain MRI was performed and was negative for any pituitary abnormalities.

36 hours later serum sodium was 120 mmol/L. Hydrocortisone was initiated for adrenal insufficiency and patient was transitioned to oral sodium chloride tablets 1 g thrice a day at this point. 4 days later sodium was 130 mmol/L. History revealed that pembrolizumab had been stopped 4 months prior to presentation due to hypothyroidism thought to be from thyroiditis. She was continued on levothyroxine and hydrocortisone for secondary adrenal insufficiency from hypophysitis due to pembrolizumab. 2 weeks later, sodium was 138 mmol/L and was maintained at that level after stopping salt tablets but continued prednisone for ovarian cancer. The plan was to switch to a carboplatin-based regimen.

Sodium trend during the hospitalization is shown in Fig. 1.

## 3. Discussion

In the past decade, immunotherapy has become an important pillar in cancer treatment. It is an effective therapeutic alternative whether used alone

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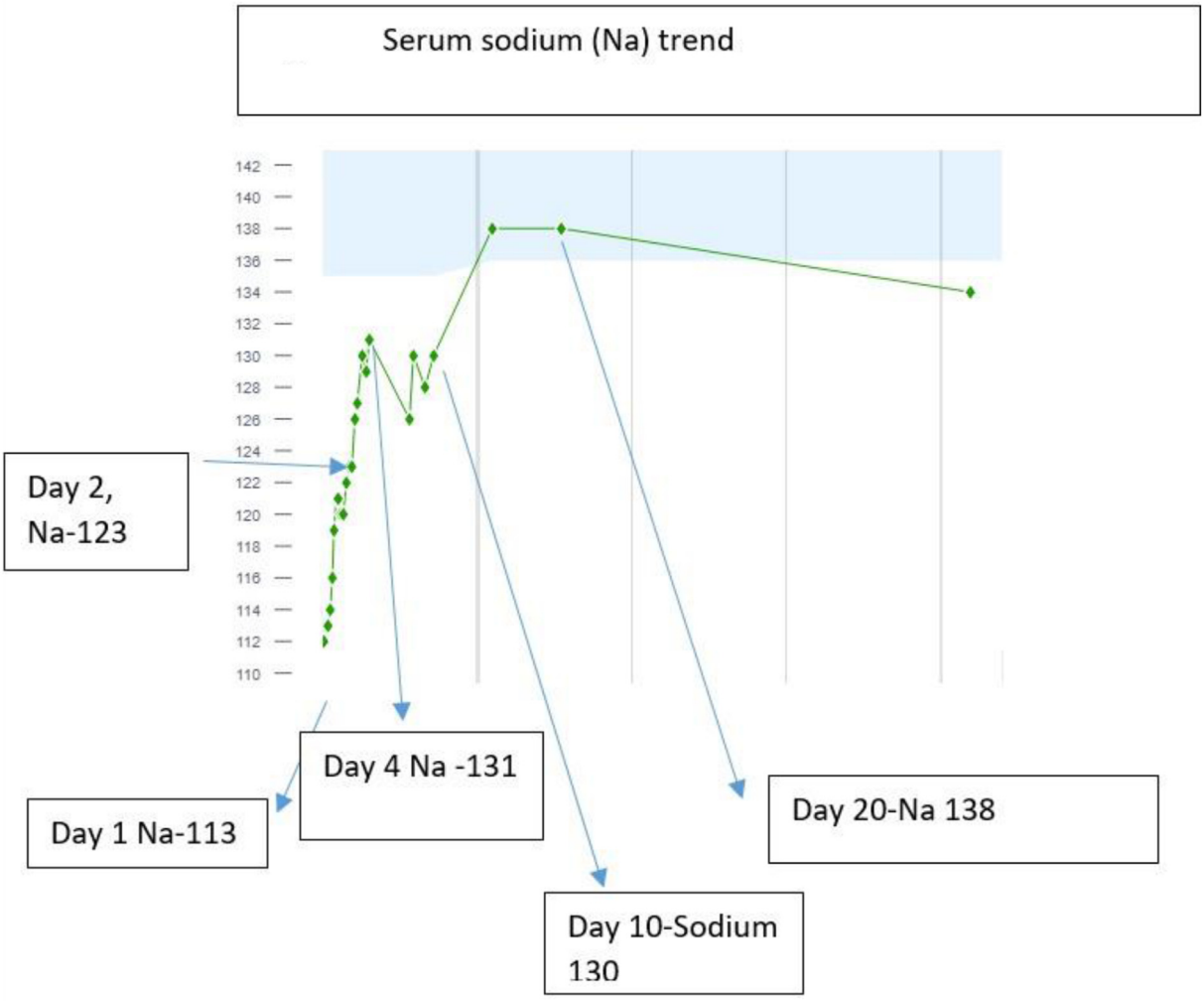


*Fig. 1. Serum sodium (Na) trend.*

or in conjunction with traditional chemotherapy regimens.[2] It has also increased survival in a wide variety of malignant tumors including but not limited to melanoma, renal carcinoma, non-small cell lung cancer, head and neck cancer, urothelial carcinoma, and Hodgkin lymphoma, whether used in advanced, recurrent or metastatic cancer.[3]

Immune checkpoint inhibitors (ICI) drugs enhance self-immunity against cancer cells. They act by blocking negative regulators expressed on immune or tumor cells. These regulators include cytotoxic T lymphocytes associated antigen 4 (CTLA-4), programmed cell death 1 (PD-1), and programmed cell death ligand (PD-L1). Normally, these regulators play a checkpoint role for the immune system by preventing its over activation and maintaining an immunological homeostatic state.[2]

Although ICI including monoclonal antibodies against programmed cell death 1 (nivolumab and pembrolizumab), provide anti-tumor activity against multiple solid tumors by activating the immune system, they also have associated adverse events, known as immune-related adverse events (irEAs).[4] Any organ system could be involved including skin, gastrointestinal, pulmonary, hepatic, and endocrine. The probability of their incidence ranges from 54% to 76% according to a 2018 systematic review by Cheng Zu et al.[2]

Adrenal insufficiency (AI), one of the endocrine irAE, is characterized by a deficient production of glucocorticoid by the adrenal glands, or impaired hypothalamic/pituitary axis regulation of adrenal function, it is classified as primary (adrenal) or secondary (central).

Clinical manifestations of secondary AI are less severe than those of adrenal crisis; however, they are nonspecific and include fatigue, fever, malaise, myalgia, weakness, and GI disturbances. Their extent depends on the degree of cortisol

deficiency, its chronicity, as well as the extent of the stress.

Lab findings of AI are also nonspecific and include hyponatremia (like our patient), hypoglycemia, or eosinophilia, which further contributes to the difficulty of establishing a diagnosis.[5]

Previously, adrenal insufficiency was thought to be more frequent with CTLA-4 inhibitors or a combination of CTLA-4 and PD-1 inhibitors, than with PD-1 or PD-L1 inhibitors alone.

However, a retrospective study by Kurokawa et al. found that it is more prevalent with PD-1/PD-L1 inhibitors than previously reported.[5] In this study, clinical data of 186 patients with non-small cell lung cancer (NSCLC) treated with pembrolizumab monotherapy or in combination with chemotherapy was reviewed.[5] Of these patients, 59 were suspected of having AI and underwent further testing, of these patients, 10 were diagnosed with AI (based on their cortisol and ACTH stimulation testing).

Most of these patients presented with fatigue and loss of appetite, and all of them had secondary AI. Isolated ACTH deficiency was the most common finding, and most patients received pembrolizumab as first line treatment.[5] These findings mirror previous reports.[6]

However, the rate of AI in patients treated with pembrolizumab in this study was 5.3%, which is higher than previous reports were AI rate was reported to be 0.2−0.7%.[5]

The precise molecular mechanisms of irAE including AI, especially those induced by PD-1/PD-L1, have not been fully elucidated. Some mechanisms have been reported, including the presence of antigens in both tumors and healthy tissue, presence of specific endocrine tissue antigens that are regulated by peripheral tolerance that can be easily overturned, as well as increasing levels of preexisting autoantibodies and inflammatory cytokines.[5,7]

In a 2021 systematic review of isolated ACTH deficiency induced by ICI, Iglesias et al. found that the number of secondary adrenal insufficiency due to isolated adrenocorticotropin deficiency has rapidly increased since his first description in 2016. They found that ICI-induced adrenal insufficiency is commonly diagnosed in the seventh decade of life. Its onset is variable, usually beginning at 6 months after starting immunotherapy, but it can develop even several months after stopping ICI therapy (up to 15 months). It was observed in 10 different types of cancers, and the main symptoms were fatigue and anorexia, with common laboratory findings being hyponatremia and eosinophilia.[3]

For these reasons, adrenal insufficiency should be considered in cancer patients who are receiving immunotherapy, who present with nonspecific symptoms and lab abnormalities like hyponatremia and/or eosinophilia after several cycles of ICI. They should undergo prompt testing for basal cortisol and plasma ACTH level, ACTH stimulation tests, as well as LH/FSH, TSH to diagnose concomitant endocrine autoimmune reactions. AI treatment requires glucocorticoid replacement, on the other hand, mineralocorticoid replacement is not warranted as its secretion by the adrenal glands is maintained.[3] However, if an adrenal crisis is suspected, intravenous glucocorticoids and immediate hospitalization is warranted.

In terms of prognosis, the occurrence of irAEs, especially dermatological, endocrine, and gastrointestinal irAEs, could predict the enhanced efficacy of immunotherapy in lung cancer and melanoma.[2,8] However, there is no consensus on the prognosis of patients with adrenal insufficiency, although in the previously mentioned study, Kurokawa et al. found favorable progression free survival (PFS) rates in patients with AI than in those without AI.

More so, larger sample sizes with longer follow up are needed to examine the correlation between incidence of AI and prognosis.[5]

## 4. Conclusion

Immunotherapy with immune checkpoint inhibitors has led to unprecedented improvements in the life expectancy of cancer patients, however its immune related adverse effect are becoming more frequent and clinically relevant given expansion of their use in recent years. AI, which is a well-established endocrine irAEs, is becoming more frequent, however remains treatable, and should be suspected in patients who are currently receiving or have received immunotherapy, who present with nonspecific symptoms with suggestive lab abnormalities.

## Conflict of interest

No conflicts of interest to report.

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