


Hyponatremia and Fever in a Patient on Ipilimumab and Nivolumab (Immune Checkpoint Inhibitors): A Case Report

Journal of Investigative Medicine High Impact Case Reports
Volume 9: 1–5
© 2021 American Federation for Medical Research
DOI: 10.1177/23247096211045249
journals.sagepub.com/home/hic


Sumit S. Patel, MD¹, Sasmit Roy, MD⁵ , Mytri Pokal, MD², Vijay Gayam, MD³, Sreedhar Adapa, MD⁴ , and Eesha S. Patel, MD¹

Abstract

Immune checkpoint inhibitors (ICIs) are novel anticancer therapy approved in multiple tumors and their use is rapidly increasing. They are associated with various systemic side effects that are immune-mediated and clinically coined as “immune-related adverse effects” (irAE). Hyponatremia is a possible side effect in patients receiving ICIs. Fever is another side effect that is mostly non-infectious. There are different mechanisms leading to hyponatremia in patients on ICIs, which could be (1) hypovolemic hyponatremia due to hemodynamic disturbance secondary to volume depletion (eg, from irAE like colitis and enteritis) or hypervolemia due to congestive heart failure, cirrhosis, or nephrosis; (2) syndrome of inappropriate antidiuretic hormone (SIADH) secretion (especially from underlying lung cancer or neurological irAE like encephalitis and meningitis) with elevated urine sodium and urine osmolality; and (3) irAE-related endocrinopathies such as hypophysitis, adrenal insufficiency, and hypothyroidism leading to euvolemic hyponatremia. We describe an interesting case of hyponatremia and fever in a patient receiving Ipilimumab and Nivolumab. The possible etiology of hyponatremia, in this case, was hypovolemia and volume depletion secondary to fever.

Keywords

hyponatremia, Ipilimumab, Nivolumab, fever, immune checkpoint inhibitors

Introduction

We present a case of hyponatremia and fever in a patient with metastatic melanoma currently receiving Ipilimumab and Nivolumab. Melanoma is the fifth most common cancer in adults, with estimated 100 350 cases in 2020, representing 5.6% of all new cancers.¹ One of the survival mechanisms of tumor cells is the ability to regulate T cells via signaling alterations. T cell receptor (TCR)–mediated stimulatory signaling is tuned down by tumor cells through downregulation of surface membrane histocompatibility complex–1 level (which are involved in binding pathogenic peptides and displaying on cell surface for recognition of specific T cells in immunological response) while programmed cell death protein (PD-1)–mediated inhibitory signaling (which regulates T cell effector functions during various physiological responses like cancer and autoimmunity) is tuned up through upregulation of surface Programmed death Ligand 1 (PD-L1) level.² Cytotoxic T-lymphocyte-associated antigen-4 (also known as CTLA-4), PD-1, and so on are some of the inhibitory immunoreceptors, and they are named immune checkpoints because they are gatekeepers of the immune response.²

Nivolumab and Ipilimumab are monoclonal antibodies targeting PD-1 and CTLA-4, respectively. They were approved

by the Food and Drug Administration (FDA) for several cancers, such as metastatic melanoma, metastatic renal cell cancer, metastatic lung cancer, unresectable malignant pleural mesothelioma, hepatocellular carcinoma, and metastatic colorectal cancer (microsatellite instability—high or mismatch repair deficient).^{3,4} They are also termed immune checkpoint inhibitors (ICIs). For most patients with metastatic melanoma, immunotherapy with PD-1 and/or CTLA-4 blockade is the preferred first-line regimen given the improved overall survival, response rate, and durability of response, which may allow patients to discontinue treatment.^{5,6} In

¹Adventist Health, Hanford, CA, USA

²Navient Health, Macon, GA, USA

³Interfaith Medical Center, Brooklyn, NY, USA

⁴Kaweah Delta Medical Center, Visalia, CA, USA

⁵University of Virginia, Charlottesville, USA

Received June 7, 2021. Revised August 9, 2021. Accepted August 22, 2021.

Corresponding Author:

Sasmit Roy, Departments of Internal Medicine and Nephrology, University of Virginia, Charlottesville, VA 22903, USA.

Email: docsasmit@gmail.com



patients diagnosed with advanced melanoma, combination therapy with Ipilimumab and Nivolumab has shown significantly longer overall survival than individual treatment.⁷ Despite prolonging survival, tumor regression is not universally achieved with ICIs, thereby contributing to a significant dent in its widespread use/success.⁸

There are several side effects of ICI which physicians need to be aware of. These immune-mediated side effects are coined as “immune-related adverse effects” (irAE).⁹ In a single-center study, among patients receiving ICI, hyponatremia was found to be a common side effect occurring in 62% of patients with sodium level <134 mEq/dL.¹⁰ The authors of this cited study also found that among the different ICI classes, being on anti-CTLA-4 monotherapy was associated with a higher risk of severe hyponatremia (serum sodium <124 mEq/dL), and hyponatremia was overall significantly more common in patients receiving combination therapy of a PD-1 inhibitor and a CTLA-4 inhibitor compared with patients receiving either one of those.¹⁰

This case report aims to describe confounding clinical presentations of patients with hyponatremia receiving ICI, which could make it difficult to distinguish clinically from adrenal insufficiency, the most likely cause with these patients. Our effort is to provide clinicians a helpful guide to approach a patient with hyponatremia who has been receiving ICI. Hyponatremia in patients receiving ICI can be secondary to causes other than endocrinopathies and syndrome of inappropriate antidiuretic hormone (SIADH) secretion like volume depletion. At the same time, it is essential to rule out endocrinopathies in a timely manner. Physicians should familiarize themselves with different side effects of immunotherapy, considering the increasing use of these agents in the last decade.⁹

Case Description

A 62-year-old Caucasian male presented to the hospital with subjective fever, nausea, extreme fatigue, decreased appetite, and insomnia for the last few days. He also reported loose stool but with only 1 bowel movement daily. Patient reported no myalgia, skin rash, and joint pains. The patient has a past medical history of metastatic melanoma, with BRAFV600 mutation negative status, and is currently on immunotherapy. The patient had completed his second cycle of immunotherapy with Ipilimumab and Nivolumab 1 week before the presentation. He was not on medications like thiazide diuretics or antipsychotic meds.

Rest of the review of system was negative. Especially, he did not have any neurological symptoms like headache, dizziness, and light headedness, nor did he have any gastrointestinal (GI) symptoms like diarrhea, vomiting, and abdominal pain. Social history was unremarkable except for drinking 2 beers on weekends. His vital signs on presentation were temperature 98.3 degrees Fahrenheit, heart rate of 85 beats per minute (bpm), sitting blood pressure of

127/84 mm of Hg, respiratory rate of 20 breaths per minute, and oxygen saturation of 98% on room air. Blood pressure checked while standing was 117/68 mm Hg with pulse of 95 bpm, which was not very suggestive of positive orthostatic sign. The physical exam showed dry mucosa and decreased skin turgor with no telling signs of volume overload. Labs during admission were remarkable for serum sodium of 118 mmol/dL (normal 135-145 mmol/dL), elevated C-reactive protein (CRP) 7.5 (normal <3 mg/L), low urine sodium and potassium, and low serum osmolality as mentioned in Table 1.

This patient was admitted to the hospital for severe hyponatremia and subjective fever. Considering the patient was on immunotherapy with Ipilimumab and Nivolumab, possible endocrinopathy was considered a differential diagnosis of hyponatremia in this patient. Hyponatremia secondary to endocrinopathies such as adrenal insufficiency, hypothyroidism, and hypophysitis has been associated with ICIs.⁸ The patient was not hypervolemic on presentation; brain natriuretic peptide (BNP) and other systemic labs were normal, which ruled out congestive heart failure/cirrhosis/nephrosis. The patient underwent AM cortisol check, which was within normal range; random cortisol checked twice during hospital stay was also within the normal range. Adrenocorticotropic hormone (ACTH) was within normal limits. Blood pressure remained stable and normal during the hospital stay. Even thyroid-stimulating hormone (TSH) level was within normal limits. Blood glucose levels remained mostly normal during the hospital stay. Urine studies revealed low random urine sodium and potassium, which was suggestive of volume depletion. The nephrology service consulted also believed the likely cause of hyponatremia was volume depletion. Notably, blood urea nitrogen/creatinine (BUN/Cr) ratio was elevated at 26 on presentation, which was also suggestive of prerenal azotemia from volume depletion.¹¹ The patient received intravenous (IV) isotonic normal saline with close monitoring of serum sodium level. With IV normal saline, serum sodium level gradually improved within tolerable limits. His IV fluids were stopped at day 5, on the morning before discharge, because he started feeling much better and was tolerating po intake with no difficulties.

The patient reported subjective fever on presentation and spiked fever intermittently during the first 2 days in the hospital with T_{max} of 103 degrees Fahrenheit. Aerobic and anaerobic blood cultures showed no growth after 5 days sent on presentation; urine analysis showed no signs of urinary tract infection, and chest X-ray (Figure 1) was unremarkable for any lung pathology/infection. Respiratory BioFire nasopharyngeal swab for viral pathogens (Table 2) and influenza polymerase chain reaction (PCR) tests were negative. Procalcitonin was <0.15ng/ml, and lactate level was 1.4mmol/L. Supportive treatment was given for fever, considering no other signs of infection. There were no known cases of COVID-19 in the United States when this case was presented in the hospital.

Table 1. Labs From Presentation to Day 6.

	Reference range	On presentation	Day 2	Day 3	Day 4	Day 5	Day 6
Sodium (mmol/L)	135-145	118 (L)	121	122	125	127	129
Potassium (mmol/L)	3.5-5.1	4.2					
Chloride (mmol/L)	98-106	87 (L)					
CO ₂ (mmol/L)	23-29	21 (L)					
Anion gap (mmol/L)	8-14	10					
BUN (mg/dL)	8-24	18					
Cr (mg/dL)	0.7-1.3	0.7					
BUN/Cr	6-20	26 (H)					
Osmolality Cal. (mOsm/L)		242 (L)					
Measured osmolality (mOsm/L)	275-290	246 (L)					
Calcium (mg/dL)	8.8-10.2	8.3					
Glucose (mg/dL)	70-105	102					
ALP (IntUnit/L)	45-115	56					
AST (IntUnit/L)	8-48	22					
ALT (IntUnit/L)	7-55	24					
CK (IntUnit/L)	40-310		49				
BNP (pg/mL)	<100	66					
ESR (mm/h)	<20		8				
CRP (mg/L)	<3		7.5				
Procalcitonin (ng/mL)	<0.15		<0.15				
Lactic acid (mmol/L)	0.5-2	1.4					
Cortisol AM (mcg/dL)	5-23			14.3			
Cortisol random (mcg/dL)	NA	15.44	11.76				
ACTH, plasma (pg/mL)	10-60	23.4					
TSH (Int Unit/mL)	0.5-4.5	1.46					
T4 (ng/dL)	0.8-1.7	1.24					
Urine, Na random (mmol/L)	NA	<10		41			
Urine, K random (mmol/L)	NA	25		58			
Urine, osmolality (mOsm/kg)	100-900	338					
White blood cells (K/mm ³)	4-10	7.7	5.9	5.0			5.6
Hemoglobin (gm/dL)	14-16	15.7	14.3	13.6			13.1
Hematocrit (%)	42-51	43.9	40.8	38.8			37.7
Platelets (K/mm ³)	150-450	206	194	209			234

Abbreviations: BUN, blood urea nitrogen; Cr, creatinine; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CK, creatinine kinase; BNP, brain natriuretic peptide; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; NA, not applicable; ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone; T4, levothyroxine, L, low; H, high; Cal, calculated, Int; International.

The patient improved clinically with improvement in serum sodium, and he was discharged with follow-up appointment in 2 weeks with his primary care physician. His serum sodium level at his primary care physician office visit in 2 weeks follow-up was at 134 mEq/dL, with him having no symptoms. Three months into his outpatient follow-up visit, the patient is asymptomatic with normal serum sodium level of 139 mEq/dL.

Discussion

Hyponatremia in patients receiving ICIs can be secondary to causes other than endocrinopathies and SIADH, but it is essential to rule out endocrinopathies in a timely manner. Fever in patients receiving ICIs can be secondary to drug-related, but it is important to rule out other infections.

Immune checkpoint inhibitor can cause various systemic side effects, notably coined “immune-related adverse effects.”⁷ A study done on 300 patients on ICI presented to the hospital showed 38 different presenting complaints of which dyspnea (19.7%), diarrhea (15.7%), fever (12.3%), fatigue (12.0%), and nausea/vomiting (5.3%) were most common.¹² In the same cohort, 32.7% diagnosed with immune-mediated toxicity, of which colitis (12.7%), hepatitis (6.3%), pneumonitis (4.7%), nephritis (2.3%), and hypophysitis (2.0%) were most common.¹²

A pooled analysis of 448 patients receiving Ipilimumab and Nivolumab showed that 94.9% of patients experienced treatment-related adverse events. Most common treatment-related adverse events were diarrhea (44%), fatigue (36.6%), pruritus (35.3%), rash (34.6%), nausea (24.8%), fever (19%), and decreased appetite (15.2%).¹³ In the same cohort, the

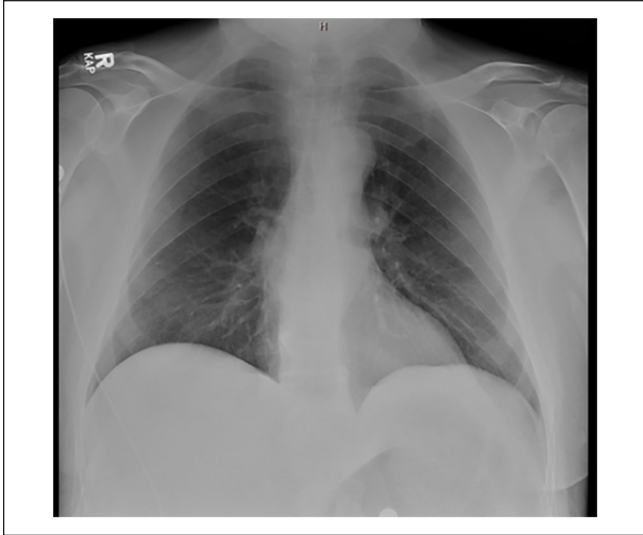


Figure 1. Normal chest X-ray findings.

Table 2. Respiratory Viral Panel.

Respiratory Virus tested	
BioFire Resp Adenovirus	Not detected
BioFire Resp Bordetella parapertussis	Not detected
BioFire Resp Bordetella pertussis	Not detected
BioFire Resp Chlamydia pneumoniae	Not detected
BioFire Resp Coronavirus 229E	Not detected
BioFire Resp Coronavirus HKU1	Not detected
BioFire Resp Coronavirus NL63	Not detected
BioFire Resp Coronavirus OC43	Not detected
BioFire Resp Human metapneumovirus	Not detected
BioFire Resp Human rhino/entero	Not detected
BioFire Resp Influenza A	Not detected
BioFire Resp Influenza B	Not detected
BioFire Resp Mycoplasma pneumoniae	Not detected
BioFire Resp Parainfluenza virus 1	Not detected
BioFire Resp Parainfluenza virus 2	Not detected
BioFire Resp Parainfluenza virus 3	Not detected
BioFire Resp Parainfluenza virus 4	Not detected
BioFire Resp Respiratory syncytial virus	Not detected

most common treatment-related select adverse events were cutaneous (64.3%), hepatic (28.8%), colitis (12.7%), hypothyroidism (15.4%), hypophysitis (8.5%), hyperthyroidism (8.3%), pneumonitis (6.9%), and renal (4.5%).¹³

Hyponatremia is the most frequent electrolyte disturbances reported with ICIs. As per meta-analysis involving more than 45 clinical trials of PD-1 inhibitor therapy in multiple cancer types, it was reported 1.2% overall incidence of hyponatremia. It also accounted for more than 50% of grade 3-5 reported electrolyte abnormalities. Also another meta-analysis of 6 randomized clinical trials involving advanced

non-small cell lung cancer patients treated with ICIs reported an incidence of 8.7%. The risk of hyponatremia is higher with anti-CTLA-4 therapy compared with PD-1 or PD-L1 inhibitors.¹⁴

In a retrospective observational study done on approximately 2500 patients with different cancers receiving ICIs, it was found that hyponatremia is the most common side effect occurring in 62% of patients with sodium level <134 mEq/dL, and out of those, 6% developed severe hyponatremia with sodium level <124 mEq/dL.⁸ Another study shows that hypophysitis has an incidence of 10% to 17% from the anti-CTLA-4 Ipilimumab, whereas a combination of Ipilimumab and Nivolumab induced hypophysitis in 13% of patients.¹⁵

Some of these side effects of ICI, similar to symptoms of adrenal insufficiency, are difficult to distinguish. Adrenal insufficiency can present with fatigue, loss of appetite, GI symptoms, hypovolemia, and hyponatremia.¹⁵

Considering hyponatremia is commonly seen in patients with ICI, it is crucial to do extensive lab work to rule out endocrinopathy like adrenal insufficiency promptly. There are different mechanisms leading to hyponatremia in patients on ICIs, including hyponatremia due to volume depletion, hypervolemia due to congestive heart failure/liver cirrhosis, euvolemic SIADH with elevated urine sodium and urine osmolarity, and endocrinopathies such as hypophysitis, adrenal insufficiency, and hypothyroidism.¹⁰

In our case, volume depletion was the likely cause of hyponatremia considering low urinary sodium and potassium, favorable response to IV fluids, and improvement in urinary sodium and potassium subsequently. Normal AM cortisol level of 14.3 was also suggestive of less likely adrenal insufficiency. One noticeable finding was our patient spiked a fever of 103 degrees Fahrenheit, but he was not tachycardic (heart rate: 73 bpm). No tachycardia was ever reported with any fever spike during the hospital stay in this patient (see Table 3). Possibly high-grade fever led to volume depletion and hypovolemia in this patient. His episodes of loose stool from colitis can also be a possible etiology here.

Conclusion

To the best of our knowledge, this could be the first reported case report of hyponatremia associated with high-grade fever and volume depletion in a patient receiving Ipilimumab and Nivolumab. It can be challenging to differentiate whether clinical symptoms of fatigue, weakness are from adrenal insufficiency or they are secondary to side effects of ICIs. Our case report can provide clinicians reference and guidance regarding the approach to the patient presenting with hyponatremia receiving ICIs. Further larger studies need to be done to find out other causes of hyponatremia in these patients.

Table 3. Vital Signs From Presentation to Day 6.

Vital signs	On presentation	Day 2	Day 3	Day 4	Day 5	Day 6
Temperature maximum in 24 hours (degrees Fahrenheit)	98.3	103	101	99.8	98.8	98.4
Blood pressure (mm Hg)	127/84 (sitting)	131/77	120/70	134/83	127/78	133/90
Pulse (bpm)	85	73	71	68	69	74
Respiratory rate (bpm)	20	16	18	17	16	17

Acknowledgments

The authors thank Narayan M. Koduri, Vikram Sangani, Venumadhav Konala, and Mamtha Balla for their valuable contributions to this article.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics Approval


Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Written informed consent was obtained from the patient for his anonymized information to be published in this article.

ORCID iDs

Sreedhar Adapa  <https://orcid.org/0000-0001-5608-5654>

Sasmit Roy  <https://orcid.org/0000-0002-2509-3915>

References

- National Cancer Institute, National Institute of Health. Cancer stat facts: melanoma of the skin. <https://seer.cancer.gov/stat-facts/html/melan.html>. Published 2021. Accessed March 7, 2021.
- He X, Xu C. Immune checkpoint signaling and cancer immunotherapy. *Cell Res*. 2020;30(8):660-669.
- Kooshkaki O, Derakhshani A, Hosseinkhani N, et al. Combination of Ipilimumab and Nivolumab in cancers: from clinical practice to ongoing clinical trials. *Int J Mol Sci*. 2020;21(12):4427.
- US Food & Drug Administration. FDA approves Nivolumab plus Ipilimumab for first-line mNSCLC (PD-L1 tumor expression >1%). <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nivolumab-plus-ipilimumab-first-line-mnslc-pd-l1-tumor-expression-1>. Published 2020. Accessed May 23, 2021.
- American Cancer Society. Treatment of melanoma skin cancer, by stage. <https://www.cancer.org/cancer/melanoma-skin-cancer/treating/by-stage.html>. Published 2021. Accessed May 23, 2021.
- Jenkins RW, Fisher DE. Treatment of advanced melanoma in 2020 and beyond. *J Invest Dermatol*. 2021;141(1):23-31.
- Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined Nivolumab and Ipilimumab in advanced melanoma. *N Engl J Med*. 2018;379(22):2185.
- Nakamura Y. Biomarkers for immune checkpoint inhibitor-mediated tumor response and adverse events. *Front Med (Lausanne)*. 2019;6:119.
- Martins F, Sofiya L, Sykietis GP, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management, and surveillance. *Nat Rev Clin Oncol*. 2019;16(9):563-580.
- Seethapathy H, Rusibamayila N, Chute DF, et al. Hyponatremia and other electrolyte abnormalities in patients receiving immune checkpoint inhibitors. *Nephrol Dial Transplant*. Published online December 29, 2020. doi:10.1093/ndt/gfaa272.
- Riccardi A, Chiarbonello B, Minuto P, Guido G, Corti L, Lerza R. Identification of the hydration state in emergency patients: correlation between caval index and BUN/creatinine ratio. *Eur Rev Med Pharmacol Sci*. 2013;17(13):1800-1803.
- Cooksley T, Gupta A, Al-Sayed T, Lorigan P. Emergency presentations in patients treated with immune checkpoint inhibitors. *Eur J Cancer*. 2020;130:193-197.
- Sznol M, Ferrucci PF, Hogg D, et al. Pooled analysis safety profile of Nivolumab and Ipilimumab combination therapy in patients with advanced melanoma. *J Clin Oncol*. 2017;35(34):3815-3822.
- Pelletier K, Škrtić M, Kitchlu A. Cancer therapy-induced hyponatremia: a case-illustrated review. *J Onco Nephrol*. 2021;5(1):70-78.
- Martin-Grace J, Dineen R, Sherlock M, Thompson CJ. Adrenal insufficiency: physiology, clinical presentation, and diagnostic challenges. *Clin Chim Acta*. 2020;505:78-91.