It’s Not Always SIAD: Immunotherapy-Triggered Endocrinopathies Enter the Field of Cancer-Related Hyponatremia

Jenny Bischoff,1,* Charlotte Fries,1,* Alexander Heer,1 Friederike Hoffmann,2 Carsten Meyer,3 Jennifer Landsberg,2 and Wiebke K. Fenske1,*

1University Hospital Bonn, Internal Medicine I, Department of Endocrinology, Venusberg Campus 1, 53127 Bonn, Germany
2University Hospital Bonn, Department of Dermatology, Venusberg Campus 1, 53127 Bonn, Germany
3University Hospital Bonn, Department for Diagnostic and Interventional Radiology, Venusberg Campus 1, 53127 Bonn, Germany

Correspondence: Prof. Wiebke K. Fenske, Department of Medicine I, University Hospital Bonn, Venusberg Campus 1, 53127 Bonn, Germany. Email: wiebke.fenske@ukbonn.de.

*J.B. and C.F. have contributed equally to this work and share first authorship

While the syndrome of inadequate antidiuresis (SIAD) is still the most common cause of hyponatremia in cancer patients, the rise in endocrine immune-related adverse events (irAEs) owing to immune checkpoint inhibitors (ICI) considerably shaped the differential diagnosis of electrolyte disorders in cancer patients. We report here 3 cases of different endocrine irAEs, first manifesting with new-onset hyponatremia under ICI therapy for malignant melanoma: one with primary adrenal insufficiency, one with hypophysitis, and one with autoimmune type 1 diabetes. Early diagnosis of endocrine toxicities can save lives but may be challenging and essentially delayed by subtle or nonspecific clinical presentation and a lack of readily available endocrinological laboratory evaluation in the primary care setting.

This exemplary case series demonstrates the broad spectrum of endocrinopathies that physicians should be aware of under ICI therapy and emphasizes new-onset hyponatremia as a possibly early, simple, and low-cost biomarker of irAEs, which may be considered as a red flag in patients receiving checkpoint blockade. As ICI-induced endocrinopathies are still under-represented in clinical practice guidelines, we here propose an updated algorithm for diagnosis of cancer-related hyponatremia, highlighting the important diagnostic steps to be considered before making the diagnosis of SIAD.

Key Words: hyponatremia, immune checkpoint inhibitor, cancer, immune-related adverse event

Abbreviations: ACTH, adrenocorticotropic hormone; anti-Tg Ab, anti-thyroglobulin antibodies; CRH, corticotropin-releasing hormone; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; fT3, free triiodothyronine; fT4, free thyroxine; FSH, follicle-stimulating hormone; ICI, immune checkpoint inhibitors; IGF-1, insulin-like growth factor 1; irAE, immune-related adverse event; LH, luteinizing hormone; MRI, magnetic resonance imaging, PD-1, programmed cell death protein 1; RR, reference range; SIAD, syndrome of inadequate antidiuresis; TPO, thyroid peroxidase; TSH, thyrotropin (thyroid-stimulating hormone).

Hyponatremia, as defined by a serum sodium concentration < 135 mmol/L, is the most frequent electrolyte disorder encountered in clinical practice and is found in up to 47% of patients in Oncology Units [1]. Regardless of the etiology and magnitude of electrolyte imbalance, hyponatremia is associated with higher mortality risk, longer hospital stay and lower progression-free survival in patients with cancer [1, 2].

Historically, cancer-related hyponatremia has ultimately been linked to the syndrome of inadequate antidiuresis (SIAD), most frequently found in patients with small cell lung cancer [3]. Since then, dilutional hyponatremia of SIAD has been described in numerous other solid tumors and hematological malignancies [4], but has also been associated with central nervous system disorders and certain drugs that enhance arginine vasopressin release, which all can be attributed to distinct types of underlying osmoregulatory defects of arginine vasopressin regulation [5]. The criteria necessary to diagnose SIAD remain essentially the same as originally defined by Schwartz and Bartter in 1967 [3]. In the setting of hypoosmolality (plasma osmolality < 275 mOsm/kg H2O) and clinical euvoelmia (defined by the absence of signs of hypovolemia or hypervolemia), an elevated urine sodium excretion (> 20-30 mmol/L) together with a urine osmolality > 100 mOsm/kg H2O reflects inappropriate antidiuresis in the absence of adrenal, thyroid, pituitary, or renal insufficiency and diuretic use [6, 7].

Still, tumor hyponatremia is not restricted to SIAD, but can also be attributed to cancer-related complications, anticancer treatment itself, or the side effects of cancer therapy [8]. These include diarrhea, nausea, vomiting, pain, toxic renal, cardiac, and liver disease, adrenal insufficiency (due to adrenal metastases) and more [9]. Importantly, over the last decade, the traditional picture of cancer-related hyponatremia noticeably changed with the development of monoclonal antibodies targeting immune checkpoint receptors (ICI), which have caused a paradigm shift in the treatment of many types of cancer within the last few years. With ipilimumab in 2011, the first antibody blocking cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) was authorized by the FDA for malignant melanoma. This was rapidly followed by the development of monoclonal antibodies targeting programmed cell death protein 1 (PD-1, pembrolizumab and nivolumab) or its
ligand (PD-L1, atezolizumab, and durvalumab). In metastatic melanoma, ICI-based immunotherapy radically modified cancer management by demonstrating long-lasting remissions in metastatic melanoma and a significant benefit in relapse-free survival in the adjuvant setting for patients with stage III or IV resected melanoma [10, 11]. However, the flip side of the quite impressive antitumor effect is the unpredictable risk of immune-related adverse events (irAEs), which may involve almost the entire organism, with a high risk for severe endocrine irAEs especially under combination therapy [12, 13]. While hypophysitis and thyroid disorders are the most frequent endocrine irAEs, autoimmune diabetes mellitus, adrenalitis, and adrenocorticotropic hormone (ACTH) deficiency are relatively rare, but potentially life-threatening irAEs, deserving further notice [14]. Rarely, an autoimmune polyendocrine syndrome (PAS) might be triggered by ICI treatment, specifically in patients receiving PD-1 monotherapy [15]. Here we report 3 cases of ICI-provoked endocrine irAEs in melanoma patients first presenting with new-onset hyponatremia.

Case Descriptions

First Case Report

A 53-year-old female patient was started on adjuvant pembrolizumab immunotherapy (400 mg every 6 weeks) in March 2020 after surgery for stage IIIA nodular melanoma. Before starting immunotherapy, thyroid function was normal under stable replacement therapy with 88 µg levothyroxine daily. After the second cycle, the patient noticed extreme fatigue, tiredness, and shortness of breath. Laboratory tests revealed a constellation of primary hypothyroidism (thyroid-stimulating hormone [TSH]: 6.28 µU/mL [0.27-4.2 µU/mL]; free triiodothyronine [fT3]: 2.17 pg/mL [2.2-4.0 pg/mL]; free thyroxine [fT4]: 1.5 ng/dL [0.93-1.7 ng/dL]) and elevated anti-thyroglobulin antibodies (anti-Tg Ab) (327 IU/mL [<115 IU/mL]) under consistent thyroid hormone replacement therapy. After increasing the levothyroxine dose, her fatigue did not improve. Before the fourth cycle of immunotherapy, the patient was admitted to the emergency department with extreme fatigue and exhaustion, dizziness, and orthostatic hypotension. Emergency lab tests revealed hypoosmotic hyponatremia (serum-[Na+] of 126 mmol/L; serum osmolality of 266 mOsm/kgH2O), with an elevated U-[Na+] excretion (38 mmol/L) and an inappropriately increased urine concentration (298 mOsm/kgH2O), hyperkalemia (5.35 mmol/L), a serum urea at the upper reference range (46.2 mg/dL; reference range (RR), 16.6-48.5 mg/dL) and acute renal failure (creatinine 1.16 mg/dL, eGFR 52 mL/min). Due to the characteristic electrolyte constellation and distinct clinical features of extreme fatigue and orthostatic hypotension, acute adrenal crisis was suspected and treatment with intravenous hydrocortisone and later fludrocortisone was initiated, after which the patient rapidly improved. Diagnosis was confirmed by low serum cortisol (5.3 µg/dL; RR, 5 to 25 µg/dL), markedly elevated plasma ACTH (759 pg/mL; RR, 7.2 to 63.3), and unresponsiveness to 250 µg cosyntropin (stimulated cortisol 5.5 µg/dL; RR, >18 µg/dL). An 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) scan excluding metastatic disease or acute hemorrhage of the adrenal glands (Fig. 1), together with positive titers for immunofluorescence screening test (IFT) against adrenal cortex antibodies (including steroid 21-hydroxylase, side-chain cleavage enzyme-hydroxylase, and 17α-hydroxylase antibodies) and steroid 21-hydroxylase antibodies separately confirmed the diagnosis of autoimmune adrenalitis.

Second Case Report

Case 2 was a 78-year-old woman with stage IV melanoma, who started on nivolumab (240 mg every 2 weeks) as second-line therapy in February 2020. After the fifth cycle, she developed an autoimmune thyroiditis followed by primary hypothyroidism (TSH: 19.50 µU/mL [0.27-4.2 µU/mL]; T3: 1.95 pg/mL [2.2-4.0 pg/mL]; T4: 0.89 ng/dL [0.93-1.7 ng/dL]; anti-Tg Ab: 530 IU/mL [<115 IU/mL]) under consistent thyroid hormone replacement therapy. Despite normalization of thyroid function, the patient continued reporting intermittent nausea, vomiting, and orthostatic hypotension. After collapsing, routine lab tests showed mild hypoosmotic hyponatremia (130 mmol/L; serum osmolality of 272 mOsm/kgH2O), with high U-[Na+]
hypokalemia and hyperglycemia (318 mg/dL). Subsequent endocrine lab tests revealed undetectable serum cortisol levels with corresponding plasma ACTH within the normal range (34.2 pg/mL [7.2-63.3 pg/mL]). Insulin-like growth factor 1 (IGF-1) and gonadotropins were within the lower normal range [IGF-1: 39.4 ng/mL [RR, 34.7-164.8 ng/mL], luteinizing hormone [LH] 14.2 U/L [RR, 7.7-58.5 U/L], follicle-stimulating hormone [FSH] 36.3 mIU/mL [RR, 25.8-134.8 mIU/mL]). Pituitary magnetic resonance imaging (MRI) scan confirmed morphological features of hypophysitis accompanied with isolated ACTH deficiency as confirmed by corticotropin-releasing hormone (CRH) stimulation test (intravenous CRH Ferring 100 µg/mL; measurement of ACTH and cortisol at time points 0, 15, 30, 45, and 60 minutes with insufficient increase in plasma ACTH (delta < 50%) and total serum cortisol levels (peak value of 3.5 µg/dL after 60 minutes).

Under replacement therapy with hydrocortisone (15-100 mg), nivolumab treatment could be continued and patient experienced marked clinical improvement and normalization of electrolytes and blood pressure.

Third Case Report
Our third case is a 54-year-old man, first diagnosed with metastatic melanoma stage IIC in July 2017 and treated with nivolumab in an adjuvant setting without any side effects. After 1 year of progression-free survival, he developed bone and liver metastases. After 4 cycles of nivolumab monotherapy in combination with stereotactic radiosurgery, multiple brain metastases were discovered on routine surveillance MRI. A second-line therapy with nivolumab (1 mg/kg) and ipilimumab (3 mg/kg) was started in March 2020. Five weeks after initiating combination therapy, he presented at the emergency department with nausea, vomiting, diarrhea, and hypotensive blood pressure values. Physical examination revealed impaired consciousness, dry mouth, and orthostatic hypotensive measures. Routine blood analysis showed hyponatremia (125 mmol/L) with elevated serum osmolality (334 mOsm/kgH2O), hyperkalemia, and hyperglycemia (318 mg/dL). Urine was concentrated (453 mOsm/kgH2O) with low U-[Na+] output (< 20 mmol/L) in the presence of acute renal failure (serum urea 52.6 mg/dL, creatinine 1.23 mg/dL, and eGFR 61.2 mL/min).

Positive urinary ketones and metabolic acidosis confirmed the diagnosis of diabetic ketoacidosis (anion gap 16 mmol/L) with corresponding hypertonic hyponatremia due to hyperglycemia. The patient was hospitalized at our intensive care unit for rehydration, monitoring, and intravenous insulin therapy. Low C-peptide levels (0.02 ng/mL; RR, 1.1 to 4.4) and positive glutamic acid decarboxylase antibodies (GADA) confirmed an autoimmune etiology of diabetes. Simultaneous manifestation of immune-mediated colitis with massive diarrhea and abdominal malaise complicated the initial insulin regimen. Immunoablation therapy was temporarily discontinued until diabetic ketoacidosis and colitis were under control. Subsequent resting identified a mixed tumor response under discontinued immunotherapy.

A brief summary of all 3 cases, including the substance used, symptom onset, diagnostics, and treatment is given in Table 1.

**Discussion**
Here we report 3 cases of new-onset hyponatremia due to endocrine irAEs, associated with acute physical deterioration in patients with malignant melanoma during treatment with immune checkpoint inhibitors ([Fig. 2 and Table 1](#)). Firstly, a case of primary adrenal insufficiency caused by autoimmune adrenalitis under pembrolizumab monotherapy. Secondly, a case of hypophysitis with secondary adrenal insufficiency in a patient that started nivolumab. Lastly, a case of new-onset autoimmune diabetes presenting with diabetic ketoacidosis and immune-related colitis under combination therapy with nivolumab/iplimumab. All 3 patients recovered after cause-specific treatment of hyponatremia secondary to the individual development of irAEs.

These cases not only illustrate the broad spectrum of endocrinopathies that may occur under targeted checkpoint therapy, but essentially may sensitize for new-onset hyponatremia as a red flag warning for possible underlying endocrine irAEs, which demand specific further endocrine investigation and may need prompt and targeted therapeutic action. Presentation of autoimmune-induced pituitary insufficiency differs depending on the ICI used. Although ICI-related hypophysitis (ICIH) is reported to occur more frequently with CTLA-4 inhibitors, isolated ACTH insufficiencies are more frequent with PD-1 inhibitors, as was the case with our patient (case 2). In contrast to the findings in our case, ICI-related hypophysitis does not necessarily manifest on MRI, but is often revealed by hyponatremia, which highlights the importance of a thoughtful screening and interpretation of lab results ([16](#)). A recent retrospective observational study reported an overall incidence of hyponatremia in 62% of patients during the first year of ICI therapy, among them 6% with severe hyponatremia (<124 mmol/L) ([17](#)). Apart from SIAD (35%) and hemodynamic disturbances (20%), 7% of severe hyponatremia were caused by immune-related endocrinopathies, whereas cases of mild and moderate hyponatremia, as reported in our series, were not further classified. Early identification of endocrine irAEs and its distinction from other causes of cancer hyponatremia is important for the rapid choice of proper treatment, prevention of often life-threatening deterioration, and optimization of cancer outcome, since hyponatremia negatively impacts survival at all stages of cancer disease ([2, 18](#)).

The detection of isotonic or hypertonic hyponatremia, as in our last case, always indicates effective solutes other than sodium present in plasma, with hyperglycemia as the most common example of transloational hyponatremia. The osmotic activity of glucose causes a redistribution of free water into the intracellular space with a resulting decrease in plasma sodium levels without any sodium loss. Resultant diabetic ketoacidosis is a rare, but often the first manifestation of new-onset immune-related diabetes, of which healthcare professionals should be aware as a potentially lethal endocrine irAE.

These exemplary cases demonstrate that the diagnostic approach in cancer patients should be the same as for any patient with hyponatremia, with SIAD remaining a diagnosis of exclusion. Here, the awareness of hyponatremia as a possible simple and low-cost biomarker of endocrine irAE under ICI therapy may be helpful and important, as early clinical signs are often nonspecific and readily attributed to underlying cancer disease. Shi et al proposed a screening strategy for endocrine irAEs.
| Case | ICI treatment | Previous irAE or autoimmune disease | Endocrine irAE | Time to onset | Symptoms | Diagnostic approach | Treatment | ICI treatment discontinuation |
|------|---------------|-------------------------------------|----------------|--------------|----------|---------------------|-----------|-------------------------------|
| Case 1 | PD-1 inhibitor Embrolizumab | Autoimmune thyroiditis (Hashimoto) | Autoimmune thyroiditis | 12 weeks | Fatigue | • Laboratory testing (TSH ↑, fT3↓, fT4, anti-TPO Ab, anti-Tg Ab↑)  
• Ultrasound | Levothyroxine dosage increase | Yes |
|       |               | Primary adrenal insufficiency/autoimmune adrenalitis | 24 weeks | Hypotension, fatigue, dizziness | • Laboratory testing (sodium↓, potassium↑, creatinine↑, cortisol↓, ACTH↑)  
• Cosyntropin test  
• 21-Hydroxylase Ab↑  
• FDG-PET/CT | Hydrocortisone replacement | |
| Case 2 | PD-1 inhibitor Nivolumab | None | Autoimmune thyroiditis | 10 weeks | Fatigue | • Laboratory testing (TSH ↑, fT3↓, fT4 ↓↓, anti-TPO Ab↑, anti-Tg Ab↑)  
• Ultrasound | Levothyroxine replacement | No |
|       |               | Hypophysis with isolated ACTH insufficiency | 34 weeks | Hypotension, collapse, vomiting, nausea | • Laboratory testing (sodium↓, potassium↑, cortisol↓, ACTH→, IGF-1, LH, FSH ↔)  
• CRH test  
• MRI (pituitary) | Hydrocortisone replacement | |
| Case 3 | PD-1 and CTLA-4 Nivolumab and ipilimumab | Autoimmune dermatitis (nivolumab treatment) | Autoimmune diabetes mellitus | 5 weeks | Vomiting, nausea, diarrhea, thirst, confusion, hypotension | • Laboratory testing (glucose ↑, sodium↓, potassium↑, serum osmolality↑, urine ketones↑)  
• Blood gas analysis  
• GADA Ab↑  
• C-peptide ↓ | Hydration | Yes |

Abbreviations: Ab, antibody; ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; FDG-PET/CT, 18F-fluorodeoxyglucose positron emission tomography/computed tomography; FSH, follicle-stimulating hormone; fT3, free triiodothyronine; fT4, free tetraiodothyronine; GADA, glutamic acid decarboxylase antibodies, ICI, Immune checkpoint inhibitor; IGF 1, insulin-like growth factor 1; irAE, endocrine adverse events; LH, luteinizing hormone; MRI, magnetic resonance imaging; PD-1, programmed cell death protein 1; Tg Ab, anti-thyroglobulin antibody; TPO Ab, anti-thyroid peroxidase antibody; TSH, thyroid-stimulating hormone.
irAEs involving measurement of electrolytes every course for 6 months and every second course for another 6 months [15]. A possible complicating factor is that the time frame for the manifestation of endocrine irAEs is highly variable (Fig. 2) and irAEs may manifest even months after cessation of therapy [19]. It is noteworthy that those patients with...
organ-specific positive autoantibody titers for any of these autoimmune-related endocrine events or with an irAE already manifested seem to be more vulnerable for an early onset [15, 20]. Therefore, apart from raising awareness, a multidisciplinary definition of diagnostic standards for early detection and surveillance of endocrine (and other) irAEs is urgently needed [20-22]. In Fig. 3, we propose a novel diagnostic algorithm for cancer hyponatremia, analogous to the European practice guidelines for diagnosis of hyponatremia [7], implementing endocrine irAEs under ICI therapy for differential diagnosis of cancer-related hyponatremia.

Various factors may trigger new-onset hyponatremia as a frequent complication of ICI therapy in cancer patients. While SIAD is the most common cause of hyponatremia in cancer patients, ICI-induced endocrinopathies are still largely under-represented or even neglected in clinical practice guidelines and consensus statements for diagnosis of hyponatremia. Early detection and cause-specific therapy of potentially life-threatening endocrine irAEs often enables continuation of antitumor therapy, thereby influencing patient outcome. Healthcare professionals should be aware of hyponatremia as a warning sign for possible endocrine irAEs, which should be considered before diagnosing SIAD in cancer patients receiving checkpoint blockade.

Acknowledgments
We thank the nurses and the outpatient clinic team.

Financial Support
There were no grants, or any funding received.

Author Contributions
J.B., C.F., and W.K.F. wrote the first version of the manuscript and created the figures. A.H., J.B., and F.H. treated the patients and collected the data. C.M. evaluated the radiological diagnostics. W.K.F. and J.L. made final assessments and corrections to the manuscript. All authors have approved the manuscript in its current form and consent to its submission.

Disclosures
The authors declare that the manuscript was prepared in the absence of any commercial or financial relationships that could be assumed as a potential conflict of interest. J.B., C.F., A.H., C.M., F.H., and W.K.F. have nothing to declare. J.L. has received speakers’ honoraria or travel expense reimbursements from Bristol-Myers Squibb and MSD.

Patient Consent
Written informed consent was obtained from all patients.

Data Availability
Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

References
1. Marquina G, Runkle I, Manzano A, et al. Incidence, classification and diagnosis of hyponatremia in patients admitted to the oncology ward. J. Clin Oncol. 2015; 33(15_suppl). doi:10.1200/jco.2015.33.15_suppl.e20656
2. Fuca G, Mariani L, Lo Vullo S, et al. Weighing the prognostic role of hyponatremia in hospitalized patients with metastatic solid tumors: the HYPNOSIS study. Sci Rep. 2019; 9(1):12993. doi:10.1038/s41598-019-49601-3
3. Barter F, Schwartz W. The syndrome of inappropriate secretion of antidiuretic hormone. Am J Med. 1967;42(5):790-806.
4. Fenske W, Allolio B. The syndrome of inappropriate secretion of antidiuretic hormone: diagnostic and therapeutic advances. Horm Metab Res. 2010;42(10):691-702. doi:10.1055/s-0030-1253117
5. Fenske WK, Christ-Crain M, Horning A, et al. A copeptin-based classification of the osmoregulatory defects in the syndrome of inappropriate antidiuresis. J Am Soc Nephrol. 2014;25(10):2376-2383. doi:10.1681/ASN.2013080895
6. Verbalis JG, Goldsmith SR, Greenberg A, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med. 2013;126(10 Suppl 1):S1-42. doi:10.1016/j.ajmed.2013.07.006
7. Spasovski G, Vanholder R, Allolio B, et al. Clinical practice guideline on diagnosis and treatment of hyponatremia. Eur J Endocrinol. 2014;170(3):G1-47. doi:10.1530/EJE-13-1020
8. Berardi R, Santoni M, Rinaldi S, et al. Risk of hyponatremia in cancer patients treated with targeted therapies: a systematic review and meta-analysis of clinical trials. PLoS One. 2016;11(5):e0152079. doi:10.1371/journal.pone.0152079
9. Berardi R, Rinaldi S, Caramanti M, et al. Hyponatremia in cancer patients: time for a new approach. Crit Rev Oncol Hematol. 2016;102:15-25. doi:10.1016/j.critrevonc.2016.03.010
10. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med. 2017;377(19):1824-1835. doi:10.1056/NEJMoa1709030
11. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med. 2015;372(26):2521-2532. doi:10.1056/NEJMoa1503093
12. de Filette J, Andreescu CE, Cools F, Bravenboer B, Velkeniers B. A systematic review and meta-analysis of endocrine-related adverse events associated with immune checkpoint inhibitors. Horm Metab Res. 2019;51(3):145-156. doi:10.1055/a-0843-3366
13. Byun DJ, Wolchok JD, Rosenberg LM, Girotra M. Cancer immunotherapy - immune checkpoint blockade and associated endocrinopathies. Nat Rev Endocrinol. 2017;13(4):195-207. doi:10.1038/nrendo.2016.205
14. Barroso-Sousa R, Barry WT, Garrido-Castro AC, et al. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis. JAMA Oncol. 2018;4(2):173-182. doi:10.1001/jamaoncol.2017.3064
15. Shi Y, Shen M, Zheng X, et al. ICPIs-induced autoimmune polyendocrine syndrome type 2: a review of the literature and a protocol for optimal management. J Clin Endocrinol Metab. 2020;105(12):e4208-e4218. doi:10.1210/clinem/dga553
16. Gubbi S, Hannah-Shmouni F, Verbalis JG, Koch CA. Hyphophysitis: An update on the novel forms, diagnosis and management of disorders of pituitary inflammation. Best Pract Res Clin Endocrinol Metab. 2019;33(6):101371. doi:10.1016/j.beem.2019.101371.
17. Seethapathy H, Rusibamayila N, Chure DF, et al. Hyponatremia and other electrolyte abnormalities in patients receiving immune checkpoint inhibitors. Nephrol Dial Transplant. 2021;36(12):2241-2247. doi:10.1093/ndt/gfaa272
18. Castillo JJ, Vincent M, Justice E. Diagnosis and management of hyponatremia in cancer patients. Oncologist. 2012;17(6):756-765. doi:10.1634/theoncologist.2011-0400
19. Paepkeay AC, Lheure C, Ratour C, et al. Polyendocrinopathy resulting from pembrolizumab in a patient with a malignant melanoma. J Endocr Soc. 2017;1(6):646-649. doi:10.1210/jes.2017-00170
20. Stamatouli AM, Quandt Z, Perdigoto AL, et al. Collateral damage: insulin-dependent diabetes induced with checkpoint inhibitors. *Diabetes*. 2018;67(8):1471-1480. doi:10.2337/dbi18-0002

21. Bayless NL, Bluestone JA, Bucktrout S, et al. Development of preclinical and clinical models for immune-related adverse events following checkpoint immunotherapy: a perspective from SITC and AACR. *J Immunother Cancer*. 2021;9(9):e002627. doi:10.1136/jitc-2021-002627

22. Brahmer JR, Abu-Sheh H, Ascierto PA, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. *J Immunother Cancer*. 2021;9(6):e002435. doi:10.1136/jitc-2021-002435