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Case Report

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

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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

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 H_2O) and clinical euvolemia (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 H_2O 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

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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/kgH_2O), with an elevated U-[Na+] excretion (38 mmol/L) and an inappropriately increased urine concentration (298 mOsm/kgH_2O), 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 ^{18}F-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 17a-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]; fT3: 1.95 pg/mL [2.2-4.0 pg/mL]; fT4: 0.89 ng/dL [0.93-1.7 ng/dL]; anti-Tg Ab: 530 IU/mL [< 115 IU/mL]) and anti-thyroperoxidase (TPO; thyroid peroxidase) antibodies 1830 IU/mL [<34 IU/mL]), and replacement therapy with levothyroxine 50 µg was started. 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/kgH_2O), with high U-[Na+]

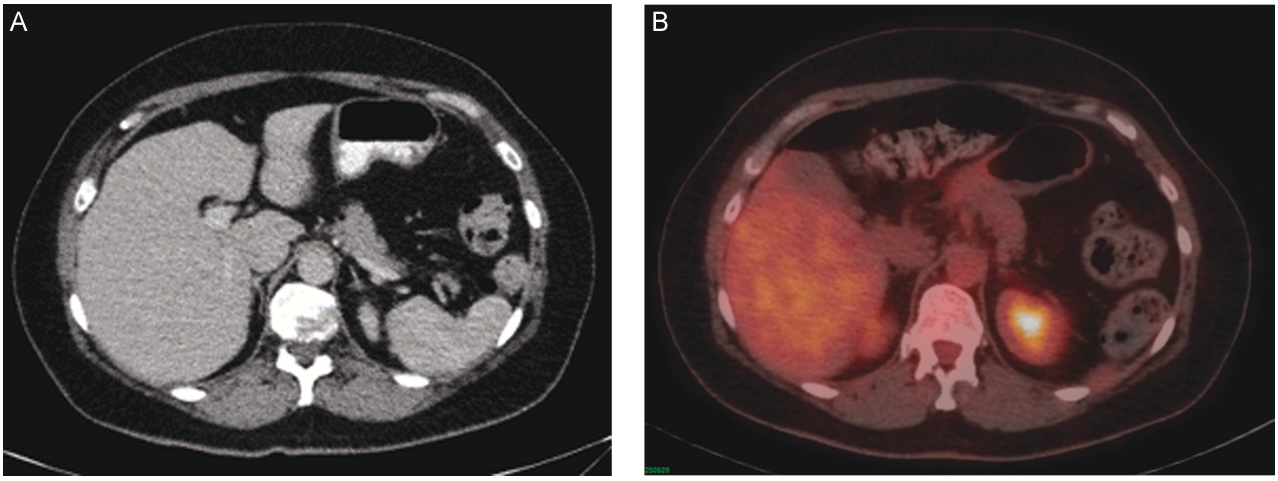

Figure 1. A and B: Case 1 PET-CT images of the adrenal glands.

excretion (56 mmol/L) under diuretic use, urine osmolality of 260 mOsm/kgH_2O and normal serum urea (29 mg/dL; RR, 16.6-48.5 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 (15-10-0 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 IIIC 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/kgH_2O), hyperkalemia, and hyperglycemia (318 mg/dL). Urine was concentrated (453 mOsm/kgH_2O) 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. Immunotherapy was temporarily discontinued until diabetic ketoacidosis and colitis were under control. Subsequent restaging 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/ipilimumab. 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 (ICIHy) 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 translocational 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

Table 1. Summary of endocrine adverse events of all 3 cases

	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 Fludrocortisone 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
			Hypophysitis 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 Insulin replacement	Yes

Abbreviations: Ab, antibody; ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; FDG-PET/CT, ^{18}F-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-thyroperoxidase antibody; TSH, thyroid-stimulating hormone.

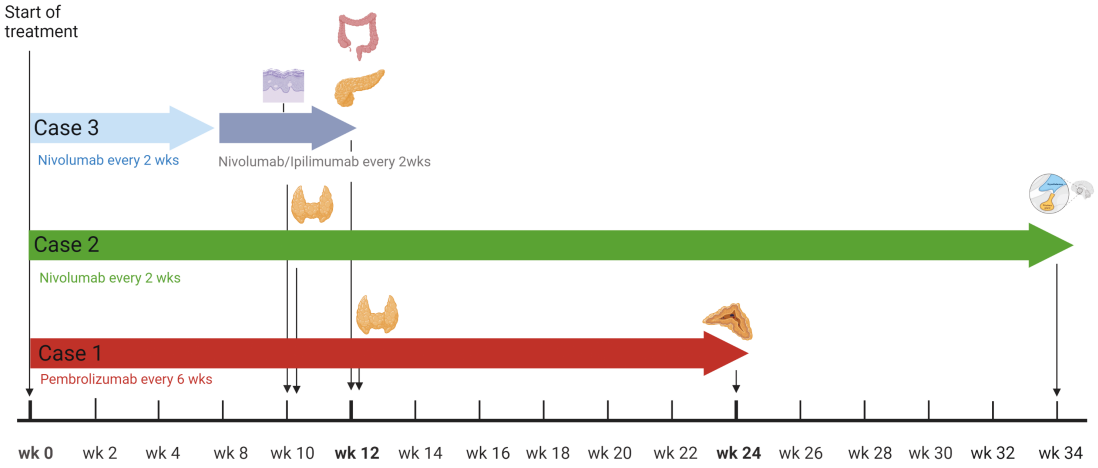

Figure 2. Timeline of immune-related adverse events for all 3 cases. Abbreviation: wk, week. Figure created with BioRender.com

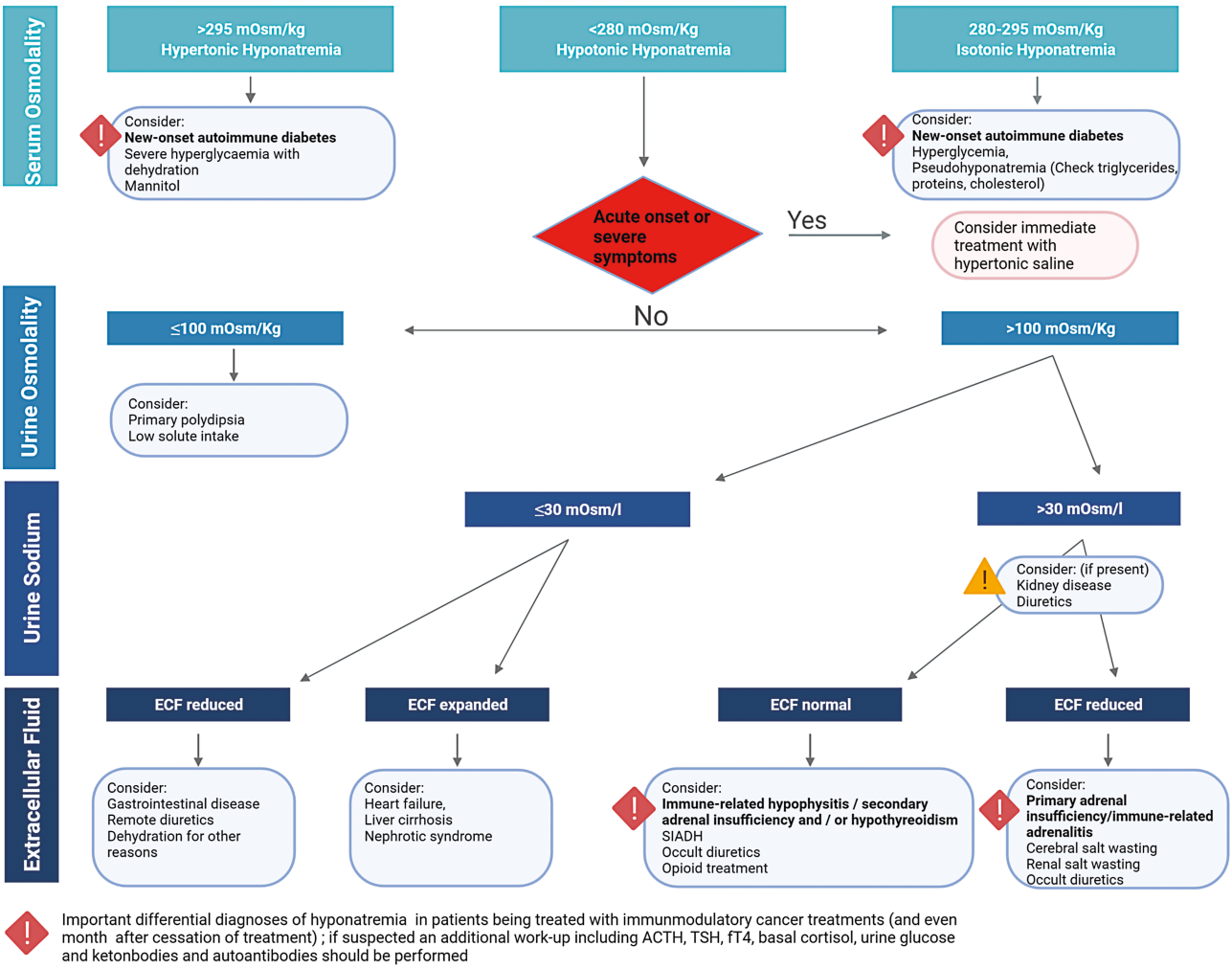

Figure 3. Diagnostic algorithm for diagnosing hyponatremia. Diagnostic algorithm for hyponatremia emphasizing important differential diagnoses of hyponatremia in patients being treated with immunomodulatory cancer treatments. Abbreviations: ECF, extracellular fluid; SIAD, syndrome of inadequate antidiuresis. Figure created with BioRender.com

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.

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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.

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