

Electrolyte and Acid-Base Disorders Associated with Cancer Immunotherapy

Nupur N. Uppal,¹ Biruh T. Workeneh,² Helbert Rondon-Berrios ,³ and Kenar D. Jhaveri ¹

Abstract

Novel immunotherapy drugs have changed the landscape of cancer medicine. Immune checkpoint inhibitors and chimeric antigen receptor T cells are being used and investigated in almost all types of cancers. Immune-related adverse events have been associated with immunotherapies. AKI has been the most commonly associated kidney adverse event. In this review, we showcase the several associated electrolyte disorders seen with immunotherapy. Immune checkpoint inhibitors can lead to hyponatremia by several mechanisms, with the syndrome of inappropriate antidiuresis being the most common. Endocrine causes of hyponatremia are rare. Hypokalemia is not uncommon and is associated with both proximal and distal renal tubular acidosis. Hypercalcemia associated with immune checkpoint inhibitors has led to some interesting observations, including immune checkpoint inhibitor-induced parathyroid hormone-related peptide production, sarcoid-like granulomas, and hyperprogression of the disease. Hypocalcemia and hyperphosphatemia may be seen with immune checkpoint inhibitor-induced tumor lysis syndrome. Chimeric antigen receptor T cell therapy-associated electrolyte disorders are also common. This is associated chiefly with hyponatremia, although other electrolyte abnormalities can occur. Early recognition and prompt diagnosis may help providers manage the mechanistically varied and novel electrolyte disorders associated with immunotherapy.

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Overview of Cancer Immunotherapy for the Nephrologist

Novel immunotherapies have become synonymous with immune checkpoint inhibitors (ICIs) and chimeric antigen receptor–T (CAR–T) cell therapy, which have revolutionized the field of oncology (1). Several cancers are able to evade destruction by attenuating activated cancer-specific T cells, which allows tumor cells to proliferate unchecked and metastasize. Immune checkpoints also regulate activated T cells at later stages by either allowing continued anticancer activity or deactivating T cells to avoid overstimulation and autoimmunity (2) (Figure 1). ICIs are now considered standard of care in the management of many advanced cancers (3). Three main classes of these agents are used in clinical practice, namely cytotoxic T lymphocyte-associated protein 4 (CTLA-4) inhibitors, programmed cell death protein 1 (PD-1), and programmed cell death ligand 1 (PD-L1) inhibitors. The immune-related adverse events are inflammatory in nature with the potential to affect multiple organ systems. Common ICI-associated immune-related adverse events include dermatitis, colitis, and endocrinopathies, and they can be life threatening. AKI after ICI was noted in early case reports with acute tubulointerstitial nephritis (AIN) as the most common pattern of injury, and AIN can frequently be accompanied by glomerular lesions (4–6). However, electrolyte disorders have been described in association with ICI use since 2017 (7).

Another novel immunotherapy agent uses genetically engineered host T cells, known as CAR–T cells, which directly bind/destroy cancer cells, thereby overcoming immune roadblocks exploited by cancer cells (8) (Figure 2). Tumor-infiltrating lymphocytes are isolated from the patient, clonally expanded, and infused into the patient. The data on various electrolyte disorders with ICI and CAR–T have been better characterized, and in this review, we will describe the known electrolyte disorders associated with immunotherapies. Figure 3 summarizes the various mechanisms associated with electrolyte disorders seen with these therapies.

Hyponatremia

Hyponatremia is the most common electrolyte disorder in patients with cancer (9), with cancer immunotherapy being a novel and important etiology causing hyponatremia by a variety of mechanisms (Table 1). The toxicities associated with ICI are distinct from cytotoxic chemotherapy because the mechanism of organ injury is inflammatory and can be diffuse or isolated. The most common kidney toxicity is the development of electrolyte disorders, of which hyponatremia is the most commonly reported (7). Manohar *et al.* (10) conducted a meta-analysis that included 39 randomized controlled trials (RCTs) for a total of approximately 4300 patients receiving PD-1 inhibitors for

¹Division of Kidney Diseases and Hypertension, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Northwell Health, Great Neck, New York
²Section of Nephrology, The University of Texas MD Anderson Cancer Center, Houston, Texas
³Renal-Electrolyte Division, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Correspondence:

Dr. Kenar D. Jhaveri, Division of Kidney Diseases and Hypertension, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, 100 Community Drive, Great Neck, NY 11021. Email: kdj200@gmail.com

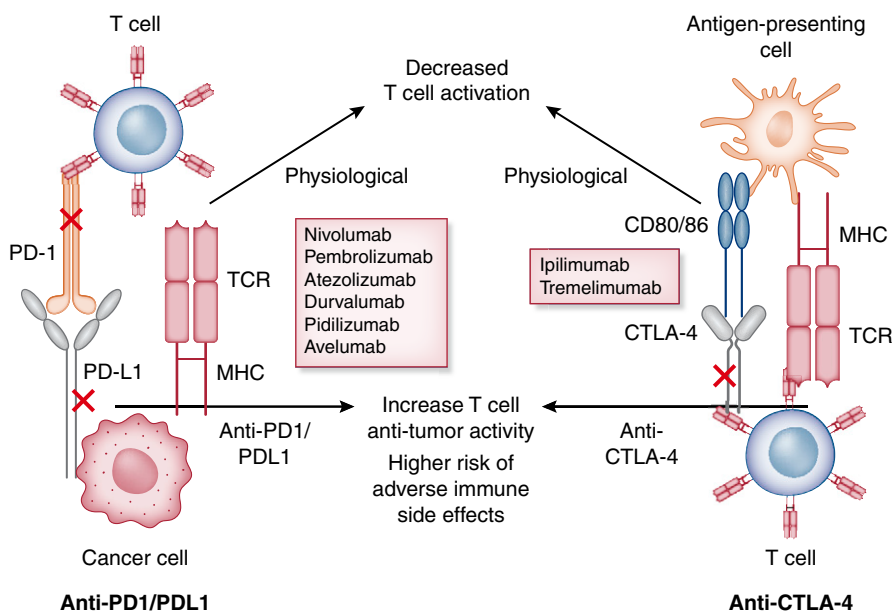


Figure 1. | Mechanism of action of immune checkpoint inhibitors. Cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) signaling networks at homeostasis. Integration of both positive and negative costimulatory signals during and after the initial T cell activation will determine the fate and intensity of the alloimmune response. For CTLA-4 (right panel), the first step in antigen recognition is the binding of the antigen to MHC molecules on the antigen-presenting cell and creating a complex with the T cell receptor (TCR) located on the T cell. This is followed by the interaction of the CD28 molecule with B7 (CD 80/86) initiating a costimulatory signal, leading to further T cell stimulation (this is in addition to other costimulatory molecules not depicted here). As a negative feedback process to prevent overstimulation, T cell activation leads to the upregulation of the CTLA-4 molecule, which competes with the B7-CD28 ligand and, in turn, leads to T cell arrest, thus providing brakes to the immune system. CTLA-4 antagonist binds to the CTLA-4 molecule and prevents it from binding to B7, leading to the sustained activation of the T cell (lifting the foot off the brakes). Similarly, binding of the PD-1 (left panel) molecule with programmed cell death ligand 1 (PD-L1) and PD-L2 leads to an inhibitory signal with decreased effector T cell function, suppressing immune surveillance and permitting neoplastic growth. PD-1 inhibitors bind to the PD-1 molecule, preventing its interaction with PD-L1/L2 and thus leading to continued T cell stimulation (pressing on the accelerator). Majority of the data support the role of increased PD-L1 expression in human tumors and serve as the biomarker to consider PD-1 inhibitors for treatment.

various malignancies, and they found that the pooled incidence rate for hyponatremia was only 1% (95% confidence interval [95% CI], 0.7% to 2.1%). Cantini *et al.* (11) performed a meta-analysis of six RCTs comparing ICI with standard chemotherapy in patients with advanced non-small cell lung cancer that revealed an incidence of hyponatremia of 9%. In contrast, Seethapathy *et al.* (12) conducted

a retrospective study that included 2459 patients from a single cancer center receiving ICI and observed an exceptionally high rate; 62% experienced hyponatremia (serum sodium ≤ 134 mEq/L), whereas 6% experienced severe hyponatremia (serum sodium ≤ 124 mEq/L). Moreover, a recent query of the Food and Drug Administration Adverse Event Reporting System (FAERS) on ICI from

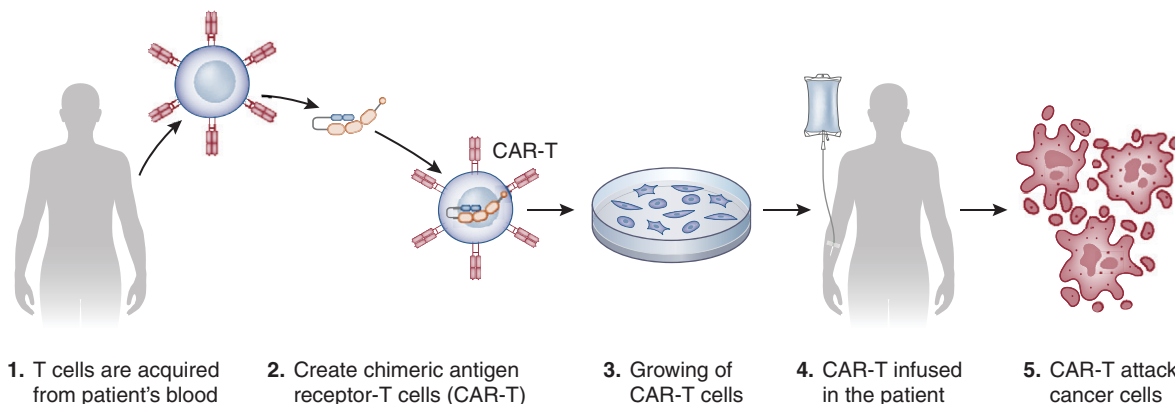


Figure 2. | Mechanism of action of chimeric antigen receptor-T (CAR-T) therapy.

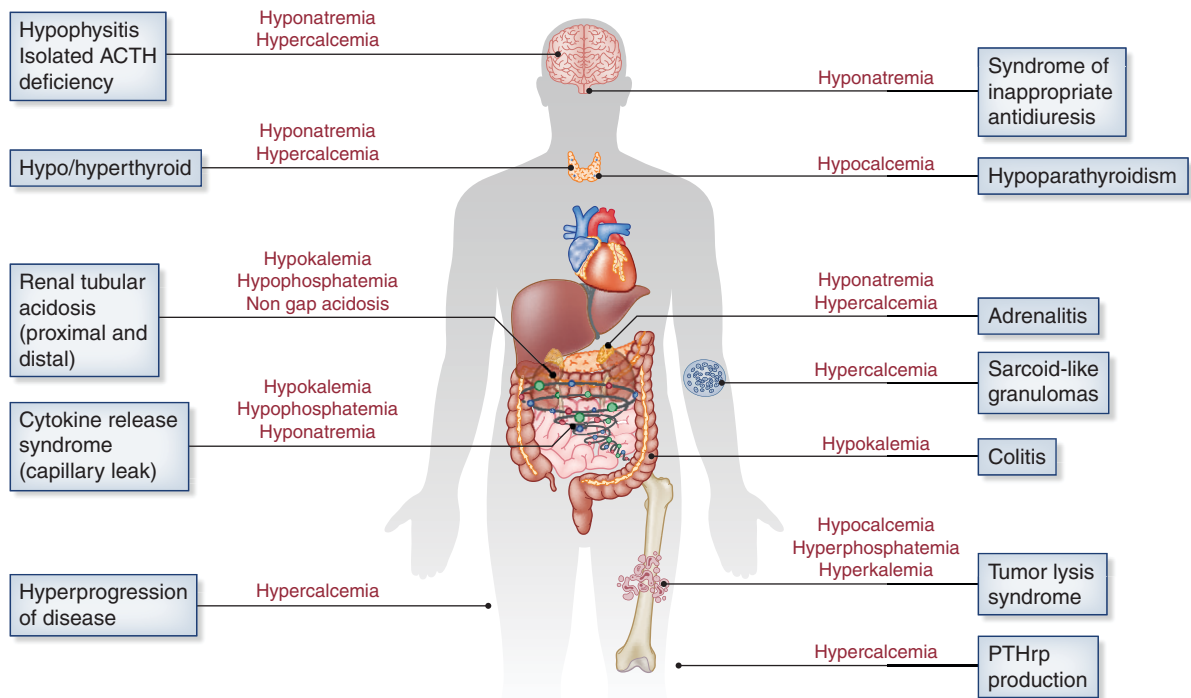


Figure 3. | Various mechanisms associated with immunotherapy-associated electrolyte disorders. ACTH, adrenocorticotropic hormone; PTHrp, parathyroid hormone-related peptide.

2011 to 2021 uncovered 2556 reported cases of electrolyte disorders, with hyponatremia being the most commonly reported electrolyte abnormality (54%) (12,13). These “real-world data” suggest that hyponatremia associated with ICI is much more common than what the RCTs suggested.

Several mechanisms by which ICI could cause hyponatremia have been proposed. Several case reports have described ICI-induced hyponatremia in association with hypophysitis, and there are reports that have described hyponatremia in association with adrenalitis (14–16). No cases of ICI-induced thyroiditis resulting in hyponatremia have been reported, but it remains a theoretical concern.

Barroso-Sousa *et al.* (17) conducted a meta-analysis of 38 clinical trials of patients with advanced solid tumors treated with ICI. The observed incidence of hypophysitis was 6% for combination therapy, 3% for anti-CTLA-4 inhibitors, 0.4% for PD-1 inhibitors, and <0.1% for PD-L1 inhibitors. The great majority of cases of hypophysitis occurred in patients with melanoma. Patients who received PD-1 inhibitors were significantly less likely to experience hypophysitis (odds ratio [OR], 0.29; 95% CI, 0.18 to 0.49; $P<0.001$); in contrast, those who received combination therapy with anti-CTLA-4 plus PD-1/PD-L1 inhibitors were significantly more likely to develop this complication (OR, 2.2; 95% CI, 1.39 to 3.60; $P=0.001$). The overall incidence of primary adrenal insufficiency was 0.7%, but among patients treated with combination therapy, the incidence was 4%. The overall incidence of hypothyroidism in this cohort was estimated to be 7%. Patients who received PD-1 inhibitors (OR, 1.89; 95% CI, 1.17 to 3.05; $P=0.03$) or

combination therapy (OR, 3.81; 95% CI, 2.10 to 6.91; $P<0.001$) were significantly more likely to develop hypothyroidism.

In the study by Seethapathy *et al.* (12), the most common etiologies of severe hyponatremia encountered were the syndrome of inappropriate antidiuresis (SIAD; 36%), terminal illness (34%), hemodynamic (20%), endocrinopathies (7%), and other (4%). Endocrinopathies were responsible for only nine patients (0.3%) of hyponatremia in the overall cohort (12). All of these cases of endocrinopathy were due to secondary adrenal insufficiency caused by hypophysitis with panhypopituitarism ($n=8$) and hypophysitis with isolated adrenocorticotropic hormone (ACTH) deficiency ($n=1$). Of these nine patients, five also developed thyroiditis. Most of these cases occurred in patients with melanoma. The use of anti-CTLA-4 agents was associated with a high risk of severe hyponatremia in this cohort (adjusted OR, 2.69; 95% CI, 1.42 to 5.09; $P=0.01$).

Overall, anti-CTLA-4 is more commonly associated with hypophysitis, less commonly associated with thyroiditis, and rarely associated with adrenalitis. Moreover, an autopsy series revealed that among six patients with cancer who received anti-CTLA-4 therapy, CTLA-4 antigen was expressed by pituitary endocrine cells in all patients but at different levels, with the highest levels encountered in the patient with clinical and pathologic evidence of more severe disease (18). PD-1/PD-L1 inhibitors have been predominantly associated with thyroiditis.

Altogether, the studies suggest that ICI-induced endocrinopathy is a relatively rare cause of hyponatremia.

Immune Checkpoint Inhibitors		T Cell Transfer Therapy			Immunomodulators		
Programmed Cell Death Protein 1/Programmed Cell Death Ligand 1 Inhibitors/Anticytotoxic T Lymphocyte–Associated Protein 4		Tumor-Infiltrating Lymphocyte Therapy	Chimeric Antigen Receptor T Cell Therapy	mAbs	IL-2	IFNα	
SIAD	Cortisol deficiency (1) Hypophysitis: panhypopituitarism, ^a isolated ACTH deficiency ^b (2) Adrenalitis, ^b primary adrenal insufficiency	Hypothyroidism, thyroiditis ^b	SIAD	Hypovolemia, capillary leak syndrome	SIAD	Hypovolemia, capillary leak syndrome	SIAD
SIAD, syndrome of inappropriate antidiuresis; ACTH, adrenocorticotrophic hormone. ^a More common with anticytotoxic T lymphocyte–associated protein 4. ^b More common with programmed cell death protein 1/programmed cell death ligand 1 inhibitors.							

^aMore common with anticytotoxic T lymphocyte-associated protein 4.

^bMore common with programmed cell death protein 1/programmed cell death ligand 1 inhibitors.

Mechanistically, endocrinopathy leading to ICI-associated hyponatremia can be explained by two mechanisms: cortisol deficiency and hypothyroidism. ICI can result in cortisol deficiency by causing hypophysitis, leading to either panhypopituitarism or ACTH-isolated deficiency. ICI can also affect the adrenal gland, causing adrenalitis, which can lead to primary adrenal insufficiency. Cortisol deficiency results in hyponatremia by loss of inhibitory effects over arginine vasopressin (AVP), leading to AVP hypersecretion. Cortisol inhibits corticotropin-releasing hormone, which, in turn, stimulates AVP release (19). Cortisol can also directly suppress AVP gene transcription in parvocellular neurons (20–22). Cortisol may also regulate vascular reactivity by increasing sensitivity of vascular smooth muscle to circulating catecholamines (23,24), with cortisol deficiency leading to reduced effective arterial blood volume, which also stimulates AVP release. In addition, in patients with primary adrenal insufficiency, aldosterone deficiency contributes to AVP hypersecretion by causing kidney salt wasting and subsequent hypovolemia (25).

ICI can also lead to hypothyroidism by causing thyroiditis. Thyroiditis can present initially as thyrotoxicosis due to the release of preformed thyroid hormone from the inflamed gland followed by a hypothyroid state from inflammatory damage to the gland. The mechanism of hyponatremia in hypothyroidism is less clear, but proposed mechanisms include decreased cardiac output with reduced effective arterial blood volume and AVP hypersecretion as well as decreased GFR (25,26). Hyponatremia seems to occur more commonly in patients with severe forms of hypothyroidism (*i.e.*, myxedema).

The treatment of ICI-induced SIAD follows the same principles as the treatment of SIAD in the general population: fluid restriction with or without oral urea or vasopressin antagonists (9). ICI-induced endocrinopathy is rarely reversible, and patients typically require long-term hormone replacement therapy (*e.g.*, glucocorticoids or thyroid hormone) (9,27,28). ICI therapy can often proceed uninterrupted after the hormonal replacement is initiated.

CAR-T cell therapy has been associated with various electrolyte disorders, including hyponatremia. Lee *et al.* (29) conducted a phase 1 trial of 19 children and young adults with acute lymphoblastic leukemia who received CD19–CAR-T cell therapy and observed an incidence of hyponatremia of 5%. In another multicenter phase 1 study, Locke *et al.* (30) enrolled seven patients with diffuse large B cell lymphoma who received CD3 ζ /CD28–CAR-T cell therapy and observed an incidence of hyponatremia of 14% (29). Gupta *et al.* (31) conducted a case series of 78 patients with diffuse large B cell lymphoma who received CAR-T cell therapy in two major cancer centers; hyponatremia (serum sodium <130 mEq/L) occurred in 15% of patients, with 1% of patients experiencing serum sodium <125 mEq/L within the first 30 days of therapy.

The mechanism of hyponatremia associated with CAR-T cell therapy is unclear, but it might be related to the occurrence of cytokine release syndrome, an inflammatory response that occurs secondary to cytokine release by infused CAR-T cells, occurring in over 40% of patients (32–36). The release of high concentrations of cytokines, predominantly IL-6, can lead to vasodilation, decreased cardiac output, and decreased effective arterial blood volume due to increased

vascular permeability and third spacing of fluids, resulting in AVP hypersecretion (37). In addition, there is mounting evidence for a key role of IL-6 in AVP secretion in various inflammatory states (38). Dixon *et al.* (39) conducted a single-center retrospective study of patients who received CD19 + CAR-T cell therapy and found an inverse correlation between IL-6 levels and lowest serum sodium in patients who developed hyponatremia ($P=0.001$). IL-2 therapy has been associated with hyponatremia as a result of capillary leak syndrome, with subsequent decreased effective arterial blood volume and AVP hypersecretion (39,40).

Hypokalemia

Hypokalemia has been reported using ICIs, but it is unknown what proportion of these reported adverse events was therapy related, and there is a nascent understanding of the specific mechanism of injury. In a recent evaluation of the FAERS database, hypokalemia was the second most common electrolyte abnormality reported (19%) after hyponatremia (13). Nevertheless, it is important to be aware that severe hypokalemia can develop with serious consequences. Several reported cases illustrate the potential for severe hypokalemia related to immunotherapy resulting from gastrointestinal or kidney losses. Immune-mediated gastritis and colitis have been described with associated hypokalemia (41,42). Hypokalemia from kidney losses can also be induced by ICIs (43–46). Mechanisms and a summary of distal and proximal renal tubular acidosis (RTA) cases are discussed later in this review under the acidosis section.

In a report examining 78 patients who received CAR-T cell therapy, no patient experienced severe hypokalemia (serum potassium <3.0 mEq/L) (31). However, 43 (54%) patients developed serum potassium <3.5 mEq/L; there was no protocol for replacement, but generally, patients were closely monitored. Electrolyte abnormalities, in general, occurred 5–6 days from the time of CAR-T administration. The authors hypothesized that hypokalemia could be related to cortisol release or a global renal tubular defect, but not much is known about more specific mechanisms.

Hypercalcemia

Parathyroid hormone-related peptide (PTHrP) from tumor cells, osteolytic lesions, and 1,25-dihydroxy vitamin D3 production are common mechanisms in hypercalcemia associated with cancer (47,48). ICI-related hypercalcemia is the third most common electrolyte abnormality noted in a recent query of FAERS (13). No specific published cases or case reports have been reported with other forms of immunotherapy.

In phase 2 and 3 trials with ICI therapy, hypercalcemia has been rarely mentioned (49–51). In the expansion cohorts of the phase 1 study of cemiplimab for patients with locally advanced or metastatic cutaneous squamous cell carcinoma, hypercalcemia occurred in 15% ($n=4$) and 8% ($n=2$), respectively (50,51). Another retrospective review of endocrine side effects related to anti–CTLA-4 therapy documented two patients with cases of incidental hypercalcemia of 256 patients (52). Additional case reports

have been published that suggest an association of hypercalcemia with ICI therapy (53,54).

Several mechanisms are thought to be responsible for the pathophysiology of ICI-associated hypercalcemia (Figure 3). Endocrinopathies reported with ICI therapy are the most likely mechanism (55). Thyroid disorders are not uncommon following ICI therapy (55,56). Hypercalcemia secondary to hyperthyroidism is nonparathyroid hormone dependent, with enhanced bone resorption and calcium mobilization. Hypothyroidism can affect calcium homeostasis by decreasing bone turnover and by increasing parathyroid hormone and 1,25-dihydroxyvitamin D3 concentrations (57). ICI-related adrenal disorders, including primary adrenal insufficiency or hypophysitis, and isolated ACTH deficiency can be associated with hypercalcemia (58,59). Although hypercalcemia is reported in 5%–6% of ICI-unrelated primary adrenal insufficiency, its incidence is unknown in ICI-related primary adrenal insufficiency and/or isolated ACTH deficiency (60). It is possible that lack of cortisol may be related to the increase in calcium reabsorption from renal tubules and release from bone. Deficient adrenal hormone and a decreased level of stanniocalcin (a paracrine hormone secreted by the adrenal gland) may affect skeletal calcium efflux into circulation and result in hypercalcemia (60). Activity of 1 α -hydroxylase may be increased in adrenal insufficiency, leading to increased intestinal absorption of calcium. Sarcoidosis-like granulomas, which are noncaseating epithelioid granulomas found in the absence of systemic sarcoidosis, have been reported following ICI therapy (61–67). They have also been reported with other immunomodulatory agents, such as IFN α (68), and B-Raf inhibitors, such as vemurafenib (69). Sarcoidosis-like granulomas are likely induced by a shift toward T helper-1 and T helper-17 immune pathway activation. Combination or sequential therapy with these ICIs may synergistically increase the risk for sarcoidosis-like granulomas as reported by Rambhia *et al.* (70). Sarcoidosis-related hypercalcemia is reported in 11% of patients (71). Prompt investigation of potential sarcoidosis-like granulomas in patients receiving ICI is necessary to distinguish these from malignancy progression (71,72). Rarely, immune-related PTHrP-mediated hypercalcemia can occur in patients receiving ICI therapy, as reported by Deligiorgi *et al.* (73) in two patients who developed hypercalcemia concurrent with immune-related adverse events following administration of nivolumab. In both patients, hypercalcemia arose while the cancer was in remission, suggesting that the cause of the hypercalcemia was ICI-related PTHrP production (73). Further studies are needed to unravel the source of PTHrP attributed to immunotherapy. A final mechanism that can lead to hypercalcemia in patients getting ICI therapy is hyperprogression of disease. This occurs when the tumor initially increases in size after ICI therapy with a subsequent decrease of the tumor burden (53,74). Kobari *et al.* (49) discuss three patients with hyperprogression of disease after nivolumab therapy in metastatic renal cell carcinoma, one of whom developed hypercalcemia 3 days after the first dose of nivolumab.

Treatment of ICI-associated hypercalcemia should be tailored to lower the serum calcium to treat the patient's symptoms and target the underlying cause. If the patient is not symptomatic, mild hypercalcemia and moderate

hypercalcemia do not require immediate therapy, and management of the underlying cause is required. Most commonly, treating endocrinopathies will help treat hypercalcemia. The initial treatment for sarcoidosis is prednisone at a dose of 20–40 mg/d for 6–12 weeks, followed by a taper over 3 months. This is a different dose and taper plan than what is normally used for immune-related adverse events management as a result of ICI therapy, which tends to utilize higher initial doses with a faster taper (4,75). Furthermore, hypercalcemia related to sarcoidosis usually responds promptly to glucocorticoid therapy (49,72). ICI-induced PTHrP-related hypercalcemia could also respond to systemic steroid therapy (49).

Hypocalcemia

Hypocalcemia, as compared with hypercalcemia, is less common with the use of cancer immunotherapy. Although the data on hypocalcemia with the use of ICIs are limited to case reports, it has been described in association with both CTLA-4 and PD-1 inhibitors as well as with their combined use for the treatment of cancer.

In the meta-analysis performed by Manohar *et al.* (10), hypocalcemia was found to be prevalent in patients on PD-1 inhibitors (pembrolizumab or nivolumab). The pooled incidence rate of hypocalcemia was reported to be 1%, with a severe degree of hypocalcemia (grade 3 or higher) seen in 13% of cases (10). However, the study performed by Seethapathy *et al.* (12) did not delineate an association between ICIs and hypocalcemia and found grade 3 or 4 hypocalcemia to be rare (incidence rate of 0.2%) in these individuals. The more recent review of the FAERS database on electrolyte disorders associated with ICIs noted hypocalcemia in 5% of the reported events (13).

Most of the cases of hypocalcemia associated with ICIs have proposed autoimmune hypoparathyroidism as the underlying mechanism for the onset of hypocalcemia (76–82). It is postulated that hypoparathyroidism can develop either due to inflammation of the parathyroid gland related to immune-mediated damage (77,80,82) or in response to calcium-sensing receptor-activating antibodies. The presence of calcium-sensing receptor antibodies has been seen in several reported cases (78,79,81). Dadu *et al.* (81) demonstrated that these antibodies were negative prior to initiation of ICI therapy, and they were later detected at multiple occasions corresponding to the patient's clinical course of hypoparathyroidism after introduction of immunotherapy. Few patients who developed autoimmune hypoparathyroidism were also noted to have other immune-related adverse events (77,82), suggesting that the presence of an immune-related adverse event may predict the development of another immune-related adverse event (82).

Hypocalcemia can occur as a manifestation of tumor lysis syndrome as well, which has been described with the use of both ICI and CAR-T cell therapies. Additionally, the use of denosumab (humanized mAb to RANK ligand) in combination with ICIs can increase the likelihood of hypocalcemia (83).

Treatment of ICI-associated hypocalcemia includes intravenous and oral calcium and vitamin D supplementation.

Table 2. Reported cases of renal tubular acidosis with use of immune checkpoint inhibitors

Reported Case	Renal Tubular Acidosis Type	AKI	Cancer	Immune Checkpoint Inhibitor	Serum pH	Serum Potassium, mEq/L	Serum Phosphate, mg/dl	Urine pH	Urine Anion Gap	Kidney Biopsy	Treatment	Outcome	Ref.
1	Proximal	No	HCC	N	7.39	1.7	1.2	7.0	NR	Not performed	Electrolyte replacement of potassium phosphate	ICI held, acidosis improved	44
2	Proximal	Yes	Lung	P	NR	2.5	1.5	NR	NR	Not performed	Electrolyte replacement of potassium, phosphate, magnesium, and iv steroids	ICI was held, resolution of electrolyte abnormalities	45
3	Proximal	Yes	Lung	N/P	7.35	4.5	2.3	NR	NR	Not performed	iv bicarbonate therapy and prednisone	ICI held, resolution of electrolyte abnormalities	46
4	Proximal	Yes	Melanoma	I/N	NR	1.7	NR	NR	NR	Not performed	iv bicarbonate, steroids and electrolyte replacement	Presented with hypokalemia and paralysis that resolved, rechallenged with P	43
5	Distal	Yes	Lung	N	7.21	2.4	NR	6.5	22	Not performed	iv bicarbonate therapy, and dexamethasone 4 mg every 8 h	ICI held	94
6	Distal	Yes	Lung	P	7.26	2.8	NR	6.5	10	Tubulointerstitial nephritis	Oral sodium bicarbonate, prednisone	AKI, acidosis improved	90
7	Distal	Yes	Melanoma	N	7.25	4.2	NR	6.3	48	Acute and chronic tubulointerstitial nephritis	iv normal saline, oral potassium citrate, prednisone	AKI, acidosis improved	90
8	Distal	Yes	RCC	N	7.23	3.9	NR	6.7	NR	Not performed	Prednisone, oral sodium bicarbonate	ICI held, AKI, acidosis improved	90
9	Distal	No	Lung	N/P	7.29	3.3	NR	6.0	36	Interstitial edema, tubulitis of DCT and collecting ducts	Initially oral bicarbonate for a week, then initiated on steroids	ICI held, acidosis improved	89
10	Distal	Yes	Melanoma	P	7.05	3.2	NR	6.0	49	Not performed	1mg/kg per d iv and oral bicarbonate supplementation, prednisone ×15 d	ICI held, acidosis improved	95
11	Distal	No	Melanoma	P	NR	3.6	2.6	6.0	8	Not performed	iv and oral steroids	Acidosis improved	96

HCC, hepatocellular carcinoma; N, nivolumab; NR, not reported; ICI, immune checkpoint inhibitor; P, pembrolizumab; iv, intravenous; RCC, renal cell cancer; I, ipilimumab; DCT, distal convoluted tubule.

Although the persistence of hypoparathyroidism despite discontinuation of ICI therapy has been recognized (81), it remains unclear whether hypocalcemia and hypoparathyroidism may resolve after the discontinuation of these agents. ICIs can be continued with close monitoring of calcium level and repletion as needed.

Hypophosphatemia

The review of the FAERS database showed that hypophosphatemia was reported in 3% of patients receiving a CTLA-4 inhibitor, 1% of patients receiving a PD-1 inhibitor, and 3% of patients receiving a PD-L1 inhibitor (13). In a meta-analysis of 27 clinical trials using nivolumab, the most frequent severe (grade ≥ 3) adverse event requiring hospitalization or invasive intervention was hypophosphatemia (13,84). Hypophosphatemia in patients receiving immunotherapy can develop by several proposed mechanisms. We describe below in the acidosis section the association of ICI with proximal tubulopathy and Fanconi syndrome. Urinary phosphate wasting can occur in association, resulting in hypophosphatemia. Also, if patients have gastrointestinal- and immune-related adverse events, hypophosphatemia can occur as a result of diarrhea or prolonged decreased nutrient intake.

In a study examining 78 patients receiving CAR-T therapy, hypophosphatemia was the most common electrolyte abnormality, with 51% of patients experiencing severe hypophosphatemia with serum phosphates < 2 mg/dl and 18% with serum phosphate < 1.5 mg/dl (31). There are no published data on the fractional excretion of phosphate and other methods to characterize mechanistically how hypophosphatemia develops. Hypotheses include intracellular shifts in phosphate or gastrointestinal or kidney losses. Interestingly, CAR-T therapy induces high levels of IL-6, which has been shown to increase fibroblast growth factor 23 levels in other settings and may contribute to the hypophosphatemia observed in AKI and CKD; therefore, elevations in IL-6 levels in cytokine release syndrome may contribute to phosphaturia and hypophosphatemia (31,85,86).

Hyperphosphatemia

Hyperphosphatemia in patients receiving ICIs is not common across all classes (13). Hyperphosphatemia can occur as a result of tumor lysis syndrome, but the syndrome is not as frequent in solid tumors, where ICIs are commonly used. However, the use of immunotherapy in solid tumors has resulted in a higher incidence of tumor lysis syndrome. Tumor lysis syndrome, marked by hyperphosphatemia and other elements in the Cairo-Bishop criteria, has been described in multiple reports with atezolizumab, nivolumab, and pembrolizumab (76,77). Shah *et al.* (87) examined several published cases of ICI-related tumor lysis syndrome. They note that the risk factors that need to be taken into consideration for tumor lysis syndrome include chemosensitivity of the tumor, the burden of the disease includes size > 10 cm, bone marrow involvement, and pretreatment hyperuricemia and hyperphosphatemia (76,77). Although infrequently

reported, hypoparathyroidism can occur as an immune-related adverse event of checkpoint inhibitors (76,77,87).

Tumor lysis syndrome can also occur after CAR-T cell therapy, resulting in hyperphosphatemia from the destruction of tumor cells, especially in patients with large tumor burden. Cellular contents from nontumor cells also occur because of on-target off-tumor toxicity (85). There is a narrow set of tumor-specific antigens that are recognized by CAR-T cells, but in addition, there are tumor-associated antigens, which are weakly expressed in normal tissues and can be damaged as a result of the therapy contributing to hyperphosphatemia (85,88).

Metabolic Acidosis

The most frequent form of acidosis noted in association with the use of ICI is distal RTA. It is a common occurrence with hypokalemia (as described above). Table 2 summarizes the several published cases of both proximal and distal RTA seen with ICIs. Over 90% of the patients required steroid and alkali therapy. Kidney biopsies described in patients exposed to ICI with distal RTA even without AKI showed mild to moderate forms of interstitial nephritis. This suggests that distal RTA may be an early sign of ICI kidney toxicity (89). Additionally, Herrmann *et al.* (90) describe a case series investigating the potential mechanism for developing distal RTA using special staining for transporters in α -intercalated cells. They found decreased expression of V-ATPase pump and anion-exchanger 1 in kidney biopsy specimens, a finding also observed in patients with Sjogren syndrome. Although phenotypically, the cases were consistent with distal RTA, they also observed a reduction in electrogenic sodium bicarbonate cotransporter 1 staining in the proximal tubule.

Proximal RTA has also been described as a result of immunotherapy in four recent cases (43–46). All cases required aggressive potassium and phosphate replacement, steroid therapy, and temporary discontinuation of ICI. Most cases also had AKI associated with the acidosis. Although AIN is a frequent feature in patients who develop RTA, to date there are no detailed examinations of kidney pathology to describe the specific lesions associated with proximal and diffuse tubulopathy. It has been shown that PD-L1 is expressed on renal epithelial cells, which may protect the kidney against ischemia-reperfusion injury, but it is unknown to what degree exposure to PD-L1 blockade may be inducing an autoimmune response (91). Interestingly, a single case of type B lactic acidosis after the first dose of nivolumab has also been reported (92). Recently, another case report has described severe diabetic ketoacidosis in the setting of acute development of autoimmune diabetes mellitus secondary to ICI therapy. This patient had no known history of diabetes; however, the patient presented with severe diabetic ketoacidosis (arterial pH 6.9, serum glucose 1123 mg/dl, serum anion gap 34 with positive serum ketones) after the second cycle of pembrolizumab. C-peptide levels were undetectable, and antigliutamic acid decarboxylase antibodies were positive, suggestive of autoimmune diabetes. The patient was successfully treated with insulin and volume expansion (93).

Summary

Several types of electrolyte disorders have been described with the use of immunotherapy. Early recognition and prompt diagnosis may help oncologists better manage the various novel electrolyte disorders associated with immunotherapy. Presently, there are no known patient-specific risk factors that may predispose a given patient to a particular ICI- or CAR-T-related electrolyte/acid-base abnormality. We have summarized what is known about these agents from descriptions in case reports and case series and have extrapolated tissue pathologic findings, but the reader should be aware that early summaries may be prone to bias and confounding factors. Further research is needed to better understand the true incidence and pathophysiology associated with various forms of electrolyte disturbances with immunotherapy and how to anticipate them.

Disclosures

K.D. Jhaveri reports consultancy agreements with Astex Pharmaceuticals, ChemoCentryx, ChinookGSK, GlaxoSmith-Kline, Natera, George Clinicals and Traver Therapeutics; reports honoraria from the American Society of Nephrology and the International Society of Nephrology; is a paid contributor to UpToDate.com and is section editor for ononephrology for *Nephrology Dialysis Transplantation*; serves on the editorial boards of *American Journal of Kidney Diseases*, *CJASN*, *Clinical Kidney Journal*, *Frontiers in Nephrology*, *Journal of Onco-Nephrology*, and *Kidney International*; serves as the Editor-in-Chief of *ASN Kidney News*; and serves as Co-President of the American Society of Onco-Nephrology. H. Rondon-Berrios reports honoraria from Memorial Sloan Kettering Cancer; serving as an associate editor for *Frontiers in Medicine/Nephrology*; and serving as an editorial board member for *CJASN*. B.T. Workeneh reports serving on speakers bureau for AstraZeneca. The remaining author has nothing to disclose.

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