Chapter 5: Electrolyte and Acid–Base Disorders in Malignancy

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INTRODUCTION

Renal complications in cancer patients include AKI, hypertension, or electrolyte and acid–base disorders. Of the latter, there are various types that share the ability to increase morbidity and mortality, delay treatment, and decrease quality of life. Understanding the etiology of electrolyte and acid–base abnormalities in cancer patients is critical to prompt recognition and appropriate treatment so that these complications may be avoided. This section of the Onco-Nephrology Curriculum will review the pathophysiology, clinical presentation, and management of electrolyte and acid–base abnormalities in patients with malignancies. Specifically, disturbances in the following will be reviewed: 1) electrolytes: disorders of sodium, potassium, calcium, magnesium, and phosphorous; and 2) acid–base: metabolic acidosis.

BACKGROUND, EPIDEMIOLOGY, AND SPECIFIC DISORDERS

Electrolyte and acid–base disturbances are common in cancer patients, either due to the malignancy or treatment of the malignancy. For example, a patient may develop metabolic acidosis from lactate produced by disseminated lymphoma or from chemotherapy-induced diarrhea. Published statistics are not robust for each type of electrolyte or acid–base disorder, but there are data on those associated with greater morbidity or mortality, such as hyponatremia. In one such analysis of cancer-related admissions, 47% of patients with mostly solid tumors had hyponatremia, and of these, 11% had moderate (sodium [Na] 120–129 mEq/L) to severe (Na < 120 mEq/L) hyponatremia (1). This is disproportionately higher than the hyponatremia prevalence rates of 15%–30% reported for general medicine admissions (2). In cancer patients with nonsolid tumors, rates of hyponatremia are less. For example, in acute leukemia, the prevalence of hyponatremia is only 10%, whereas the prevalence of hypokalemia ranges between 43% and 64% (3). This suggests that differences in pathophysiologic mechanisms may drive unique electrolyte disorders in different malignancies. In the next sections, the clinical features, pathophysiology, and treatment of the most common electrolyte and acid–base disorders in cancer patients will be considered.

Hyponatremia

Cancer is a common etiology for hyponatremia in the hospitalized patient, accounting for 14% of cases in a prospective observational cohort (4). Similar to reports on hyponatremia in the general population, lower serum sodium concentration is associated with increased hospital length of stay and 90-day mortality (1). In patients with small-cell lung cancer (SCLC), in those who had hyponatremia prior to chemotherapy initiation, failure to achieve normonatremia within the first two cycles of chemotherapy was a predictive marker for decreased survival (5).

Hyponatremia associated with cancer may have several potential etiologies (Table 1). Regardless of the etiology, patients may be asymptomatic with mild to moderate disease but may experience headache, fatigue, and mental status changes with moderate to severe hyponatremia. Examination findings such as frank or orthostatic hypotension in volume depletion or edema in the third-spacing states of cirrhosis may point to potential causes. In conjunction with examination data, urine studies are indispensable, with urine sodium <20 mEq/L reflecting the sodium avidity of volume depletion and urine sodium >40 mEq/L suggesting the syndrome of inappropriate antidiuretic

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Table 1. Common mechanisms for hyponatremia in the cancer patient

Etiology of hyponatremia	Clinical examples specific to the cancer patient
Pseudohyponatremia	Paraproteinemias
Reduced water excretion	Underlying CKD or AKI
Decreased circulating volume	Nausea, vomiting, nasogastric suctioning, and diarrhea; hematemesis or hematochezia (gastrointestinal malignancies or steroid-induced ulcer disease)
Decreased effective circulating volume	Underlying or new onset of CHF, cirrhosis, ascites, severe hypoalbuminemia, veno-occlusive disease
SIADH	Tumor release of ADH: SCLC and head and neck cancer Chemotherapy: cyclophosphamide, cisplatin/carboplatin, vincristine, vinblastine Other drugs: SSRIs, NSAIDs
Nonosmotic stimuli for ADH	Pain, nausea, vomiting
Salt wasting	Cisplatin

ADH, antidiuretic hormone; CHF, congestive heart failure; SIADH, syndrome of inappropriate ADH secretion; NSAIDs, nonsteroidal anti-inflammatory drugs; SCLC, small cell lung cancer; SSRI, selective serotonin reuptake inhibitors.

hormone secretion (SIADH) in a euvolemic patient or rarely salt wasting due to cisplatin therapy.

Although patients with cancer have hyponatremia due to many etiologies (Table 1), SIADH is the most common etiology that is directly attributable to cancer. This is because cancer patients have nonvolume and nonosmotic stimuli for antidiuretic hormone (ADH) release, such as nausea/vomiting and pain or medications such as cyclosphosphamide. An additional factor is the paraneoplastic release of ADH from tumor subtypes, notably SCLC and head and neck cancer (6). Finally, several chemotherapy drugs have been linked to hyponatremia via potentiation of ADH release or action, including vinblastine, vincristine, and cyclophosphamide (7).

Cisplatin is another antineoplastic agent linked to hyponatremia through a mechanism that involves salt wasting at the loop of Henle (8). Ten percent of patients on cisplatin therapy at a single center developed hyponatremia with a high urine sodium concentration but with profound volume depletion. Thus, these patients required volume expansion with saline to correct their hyponatremia, in contrast to patients with SIADH who are volume replete. This underscores the need for correct etiologic diagnosis of hyponatremia to provide appropriate therapy. Therapy must be tailored for the patient, the underlying diagnosis, and the severity of hyponatremia. Severe hyponatremia with serum Na concentration <110 mEq/L and neurologic symptoms may need 3% hypertonic saline for acute management. Fluid restriction is the mainstay of treatment for SIADH, with salt tablets and loop diuretics as adjunctive therapy. However, these measures can hinder quality of life in the cancer patient, and thus, aquaretics that inhibit the vasopressin type 2 receptor (V2-R) to inhibit water reabsorption in the collecting duct are suggested for management of hyponatremia secondary to SIADH in cancer patients if other therapies are not feasible or effective. However, the data on their clinical utility in cancer patients are sparse. In a small, single center safety and efficacy study, tolvaptan, a V2-R antagonist, was superior to placebo in the correction of hyponatremia but did not decrease hospital length of stay (LOS)

or improve cognitive testing (9). In addition, chronic tolvaptan use may be limited by expense and cumulative dose-dependent hepatotoxicity (10).

Hypokalemia

Similar to hyponatremia, hypokalemia is commonly encountered in cancer patients, resulting from cancer-distinct and cancer-specific causes (Table 2) and, more commonly, from a combination of the two. Proper diagnosis starts with excluding pseudohypokalemia from postphlebotomy transcellular shifts, which is seen in patients with profound leukocytosis whose blood samples are not refrigerated or immediately analyzed. Once true hypokalemia is confirmed, measurement of urine potassium and the trans-tubular potassium gradient can be helpful in analyzing renal potassium wasting (11).

In cancer-distinct causes, chemotherapy leads to hypokalemia either indirectly via side effects of decreased appetite/intake, vomiting, and diarrhea or directly via renal tubular effects. For example, ifosfamide causes renal potassium wasting, either as an isolated proximal tubulopathy or Fanconi syndrome (FS), which may persist after treatment. Fifteen percent of pediatric cancer patients who received ifosfamide therapy exhibited persistent hypokalemia months to years after the end of treatment (12).

Cancer-specific causes of hypokalemia include tumors that secrete ectopic adrenocorticotropin hormone (ACTH) such as SCLC, thymus or bronchial carcinoid, thyroid medullary carcinoma, or neuroendocrine tumors (13). Although uncommon, these tumors stimulate renal potassium wasting via excessive cortisol release that activates the mineralocorticoid pathway. Accordingly, other features of hypercortisolemia are also present including pigmented skin, diabetes, and hypertension (13). Another cancer-specific etiology for hypokalemia is evident in acute myeloid leukemia (AML), M4 and M5 subtypes, which has been long associated with hypokalemia (14,15). These malignancies increase serum lysozyme and lysozymuria, leading to the hypothesis that lysozyme-mediated tubular injury leaks potassium (and other electrolytes)

Table 2. Cancer-distinct and cancer-specific causes of hypokalemia in the patient with malignancy

Etiology of hyponatremia	Cancer distinct	Cancer specific
Pseuodohypokalemia	Phlebotomy error with tight tourniquet	Clonal leukocytosis with leukemias
Redistribution into cells	Use of GM-CSF, vitamin B_{12}	Blast crisis with leukemias
Poor intake	Anorexia, nausea, mucositis	Tumor-induced dysphagia
Extrarenal losses	Vomiting, diarrhea from chemotherapy or radiation enteritis	VIPoma, villous adenoma (rare)
Renal losses	Hypomagnesemia, Fanconi syndrome with chemotherapy	Lysozymuria, Fanconi syndrome from light chain injury (myeloma), ectopic ACTH production

ACTH, adrenocorticotropin hormone; GM-CSF, granulocyte macrophage colony stimulating factor; VIP, vasoactive intestinal peptide.

into urine. Another putative mechanism may be renin-like activity by AML blast cells stimulating the mineralocorticoid pathway (16).

The potassium losses in these cases may be profound and require aggressive replacement. The choices for replacement are the same as those utilized for hypokalemia in the noncancer patient (11), but it should be noted that given the difficulty cancer patients may have with oral intake due to nausea, mucositis, etc., intravenous dosing is often necessary. Hypokalemia treatment is also ineffective if hypomagnesemia remains uncorrected, due to unchecked potassium losses via the renal outer medullary K+ channel (ROMK) channel in distal nephron tubular cells (17).

Hypomagnesemia in cancer patients

Hypomagnesemia in the cancer patient may be due to decreased intake or from renal magnesium wasting. Renal losses of magnesium are principally due to chemotherapy-mediated injury to the distal nephron, the site of active magnesium reabsorption in the nephron. This has been noted with cisplatin, but a rising number of cases are being attributed to drugs that target the epidermal growth factor receptor (EGFR) pathway. Monoclonal antibodies against EGFR, such as cetuximab and panitumumab, display tumoricidal activity against a variety of cancers, but they also prevent the insertion of a magnesium channel, transient receptor potential M6 (TRPM6), into the apical membrane of distal tubular cells (Figure 1) (18). As a result, magnesium cannot be reabsorbed from the tubular lumen and serum magnesium levels fall, affecting 10%–36% of patients in early clinical trials of cetuximab (7). A fractional excretion of magnesium >15% in a hypomagnesemic patient indicates renal wasting. Treatment involves replacing magnesium, and intravenous dosing is usually needed because diarrhea is a dose-limiting adverse effect of oral magnesium. Fortunately, renal magnesium wasting subsides over time following discontinuation of the EGFR antagonist. However, this is not the case with the platin drugs, where renal magnesium wasting can be permanent.

Hypercalcemia

Twenty percent to 30% of cancer patients experience hypercalcemia during the course of their malignancy (19), and this is predictive of poor prognosis (20). Hypercalcemia of malignancy uses one of two mechanisms: 1) osteolytic release of local calcium from bone directly involved by cancer cells or 2) stimulation of osteoclast activity by release of the tumor-derived endocrine factors. Although these mechanisms are distinct,
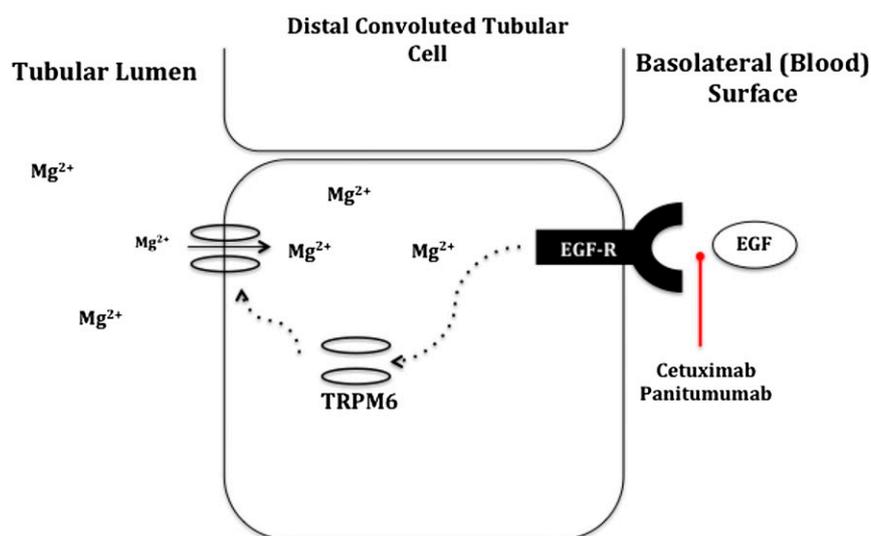

Figure 1. Absorption of magnesium from the tubular lumen is via an EGFR-dependent apical channel, TRPM6. This pathway is inhibited by use of anti-EGFR monoclonal antibodies such cetuximab. EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; TRPM6, transient receptor potential M6. Red line denotes inhibition of interaction.

the resultant hypercalcemia in either case may be mild and asymptomatic, moderate and accompanied by nausea/vomiting, constipation, bone pain, and fatigue, or severe and manifested by confusion and coma (21). It is important to correct serum calcium concentration for hypoalbuminemia so that hypercalcemia levels can be properly graded.

Among solid tumors, primary bone cancers and metastatic breast or prostate cancer stimulate osteolysis, which correlates with the overall tumor burden. Although metastases do not occur in nonsolid tumors, osteolysis may be stimulated by a variety of immune and nonimmune pathways in multiple myeloma. Both result in release of sequestered calcium from bone with the common pathway centered on the interaction between receptor activator of nuclear factor-κB (RANK), which is present on osteoclasts and their precursors, and RANK ligand (RANKL), which is present on osteoblast and bone marrow stromal cell surfaces (22). The putative mechanism involves RANKL binding to its cognate receptor RANK through the influence of parathyroid hormone (PTH) and PTH-related peptide (PTHRP), which subsequently increases osteoclastic activity and release of local calcium (21).

Tumor-derived endocrine factors are responsible for the humoral hypercalcemia of malignancy, including PTHRP and 1,25-dihydroxyvitamin D [1,25(OH)$_2$D]. More rarely, there is PTH release from primary parathyroid carcinoma (23) or ovarian cancer (24). PTHRP is most commonly secreted by squamous cell carcinoma of the lung or head and neck, but renal cell, ovarian, breast, and esophageal cancers have all been associated with hypercalcemia from PTHRP release (21). 1,25(OH)$_2$D, however, is more likely to be secreted by lymphoma cells or tumor-associated macrophages that possess inherent 1-α-hydroxylase activity that is not subject to regulation by PTH (25–27).

Treatment of hypercalcemia of malignancy is focused on increasing urinary calcium excretion and suppression of the calcium source. The first objective is achieved by volume expansion with saline to drive urinary calcium excretion. Furosemide, once routinely touted as an adjunct to saline, has no proven benefit and should only be reserved for cases of volume overload (28). The second objective may be fulfilled by suppressing osteoclast activity through use of bisphosphonates such as zoledronate or pamidronate. The former causes acute renal tubular injury, and the latter has been linked to a collapsing variant of FSGS, and high intravenous (IV) dosing should be used with caution, particularly with preexisting CKD. An emerging option that directly targets a pathway in hypercalcemia of malignancy is the use of RANKL inhibitors such as denosumab. These agents have shown to be superior to bisphosphonates in the treatment of skeletal related events in cancers with bony metastases (29,30), and early evidence suggests they are useful in the treatment of hypercalcemia of malignancy, particularly in bisphosphonate-resistant cases (31).

Hypophosphatemia in cancer patients

Cancer patients usually experience hypophosphatemia as a consequence of chemotherapy. This may be due to generalized malnutrition from anorexia or malnutrition causing poor intake, or it may be the result of renal phosphate wasting from drug-induced proximal tubulopathy and FS. As mentioned previously, FS is common with ifosfamide, but has also been associated with cisplatin and imatinib use (32,33). A fractional excretion of phosphate that is >5% in the setting of hypophosphatemia is diagnostic of renal phosphate wasting. Treatment of hypophosphatemia centers on phosphate replacement, which may approach several grams per day in cases of renal phosphate wasting.

A rare cause of hypophosphatemia is tumor-induced osteomalacia, whose mechanism is dependent on the phosphatonin, fibroblast growth factor 23 (FGF-23). The role of the FGF-23 pathway has been detailed previously (6,34). Briefly, FGF-23 is a phosphaturic agent whose expression is tightly regulated by phosphate, 1,25(OH)$_2$D, and other factors. In tumor-induced osteomalacia, constitutive release of FGF-23 without usual regulatory checkpoints leads to persistent FGF-23 activation, resulting in severe phosphaturia, hypophosphatemia, and osteomalacia. Several malignancies are associated with this syndrome including hemangiopericytomas, giant cell tumors, and osteoblastomas (34). Definitive treatment is surgical resection, as the phosphate wasting may be so profound that medical management may not be sufficient. Thus, functional imaging such as F-18 fluorodeoxyglucose positron emission tomography is suggested for diagnosis, which has high sensitivity for these tumors but may not be specific (34).

Metabolic acidosis in cancer patients

Anion gap (AG) acidosis and non–anion gap (NAG) acidosis is prevalent in cancer patients. Among the various AG acidosis disorders, lactic acidosis (LA) is the most cancer specific. Cancer patients may have type A LA due to tissue hypoxia from sepsis or cardiac failure, but they may also have type B LA with no evidence for tissue ischemia. Type B LA is well described in leukemias and lymphomas (35), but other reported cases include multiple myeloma, gastric cancer, and breast cancer (36–38). The pathophysiology of malignancy-associated LA is unclear, but speculative mechanisms include anaerobic glycolysis by tumor cells, stimulation of lactate production by tumor-derived cytokines, and thiamine deficiency (36). Treatment involves control of tumor burden. Bicarbonate infusion may be necessary for critical drops in serum pH, but paradoxically may stimulate more lactate production. Dialysis is often requested for lactic acidosis, but clearance with either intermittent or continuous dialysis modalities is insufficient to overcome ongoing production.

Non-AG acidosis in cancer patients is most likely related to infection or therapy-related diarrhea, but renal tubular acidosis (RTA) should be considered. Tubular injury from chemotherapy can cause RTA either in isolation or as part of the FS. Light chain–associated tubular injury in multiple myeloma is another cause of FS and can present with RTA. Bicarbonate supplementation is sometimes necessary in patients with RTAs, and its success depends on the degree of renal bicarbonate wasting.

Other disorders

Cancer patients may have electrolyte and acid–base abnormalities beyond those reviewed in this chapter. In particular, hyperkalemia, hyperphosphatemia, and hypocalcemia are diagnostic criteria for tumor lysis syndrome, which is detailed in Chapter 4 of the ASN Onco-Nephrology Curriculum. In acid–base disorders, metabolic alkalosis may accompany the rare renin-producing tumor but is more common with persistent vomiting or diuretic use. Respiratory alkalosis may occur with pontine tumor or infection-associated stimulation of central respiratory centers.

CONCLUSION

A myriad of cancer and chemotherapy-related electrolyte and acid-base disorders can affect cancer patients. Although most patients develop mild disease, some patients may experience significant morbidity. Diagnosing electrolyte and acid–base abnormalities and initiating treatment quickly is essential for the nephrologist seeking to improve the outcomes of cancer patients.

TAKE HOME POINTS

- Electrolyte and acid–base abnormalities occur frequently in the cancer patient and contribute to poor quality of life.
- Disturbances in electrolyte and acid–base homeostasis may occur due to the cancer itself or due to adverse effects of therapy.
- Treatment of electrolyte and acid–base disorders in cancer should be etiology specific and patient centered.

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REVIEW QUESTIONS

1. Which of the following tumors is most likely to be associated with SIADH?

   a. Non–small-cell lung cancer
   b. Acute myeloid leukemia, M4 type
   c. Small-cell lung cancer
   d. Breast cancer
   e. Bronchial carcinoid

   Answer: c is correct. Hyponatremia in cancer patients from persistent ADH stimulation or potentiation may be cancer distinct, e.g., from pain, nausea, or chemotherapy. Certain cancers, however, are known to release ectopic ADH, including small cell lung cancer and head and neck cancer. Non–small cell lung cancer and breast cancer are not associated with SIADH from ectopic ADH release. AML-M4 is associated with lysozyme-mediated renal potassium wasting, whereas bronchial carcinoid secretes ectopic adrenocorticotropin hormone.

2. Which of the following laboratory abnormalities are seen in Fanconi syndrome?

   a. Hyperkalemia
   b. Hypomagnesemia
   c. Hypophosphatemia
   d. Metabolic alkalosis
   e. Hyperglycemia

   Answer: c is correct. Fanconi syndrome is a constellation of metabolic abnormalities, which result following proximal tubule injury. As the proximal tubule is the primary site for reabsorption of bicarbonate, ammonia, amino acids, glucose, and most electrolytes including sodium, potassium, and phosphorus, this syndrome typically results in potassium, phosphorus, and bicarbonate wasting. Patients may exhibit hypokalemia, hypophosphatemia, metabolic acidosis due to renal tubular acidosis, and glucosuria. Because active magnesium reabsorption takes place at the distal tubule, magnesium levels are not affected.

3. Which of the following is true of the lactic acidosis of malignancy?

   a. Levels of lactic acid decrease with bicarbonate infusion
   b. Continuous RRT is recommended for control of lactic acid levels
   c. Measurement of the urinary anion gap can aid in diagnosis
   d. Control of tumor burden is not necessary in improving lactic acid levels
   e. It may be the result of anaerobic glycolysis and lactate production by tumor cells

   Answer: e is correct. Type B lactic acidosis is the production of lactic acid in the absence of ischemia. It is linked with certain malignancies, particularly lymphoma, and hypotheses for its pathophysiology include tumor-induced anaerobic glycolysis and lactate production. Lactic acidosis of malignancy correlates well with tumor burden, and levels improve with control of that burden. The urinary anion gap is not useful in the diagnosis of this disorder. Although acute treatment of acidosis may require bicarbonate, levels of lactic acid may rise with sustained bicarbonate infusion. Last, hemodialysis is an inefficient modality for lactic acid clearance, as production is higher than clearance rates, even in continuous RRT.