Electrolyte Disorders Associated With Cancer

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Patients with malignancies commonly experience abnormalities in serum electrolytes, including hyponatremia, hypokalemia, hyperkalemia, hypophosphatemia, and hypercalcemia. In many cases, the causes of these electolyte disturbances are due to common etiologies not unique to the underlying cancer. However, at other times, these electrolyte disorders signal the presence of paraneoplastic processes and portend a poor prognosis. Furthermore, the development of these electrolyte abnormalities may be associated with symptoms that can negatively affect quality of life and may prevent certain chemotherapeutic regimens. Thus, prompt recognition of these disorders and corrective therapy is critical in the care of the patient with cancer.

Key Words: Cancer, Hyponatremia, Hypokalemia, Hypercalcemia, Hypophosphatemia

Introduction

Electrolyte disorders are commonly encountered in the patient with cancer. In most cases, these disorders are associated with etiologies seen in all types of patients and are not specifically linked to the malignancy or its therapy (for example, diuretic-induced hyponatremia or hypokalemia). In other cases, electrolyte disorders are due to paraneoplastic syndromes or are specifically associated with chemotherapeutic regimens. When these malignancy-specific electrolyte disorders are manifest, they can lead to life-threatening complications that require emergent therapy. Thus, proper recognition and treatment of these disorders is important in the overall care of the patient with cancer. This review will discuss selected malignancy-associated electrolyte disorders.

Hyponatremia Associated With Cancer

Hyponatremia is the most common electrolyte disorder encountered in patients with malignancies. Studies have reported a prevalence that ranges from approximately 4% to as high as 47%.[1,2] Approximately 14% of hyponatremia encountered in medical inpatients is due to an underlying malignancy-related condition.[3] It is important to note that nearly half of these cases represented hospital-acquired hyponatremia, suggesting that management of these patients (most likely with intravenous fluids) significantly contributes to the development of hyponatremia.

Hyponatremia is clearly associated with significant morbidity and mortality when it occurs in the patient with cancer. For instance, hospital length of stay is nearly doubled in patients with moderate to severe hyponatremia.[1] The hazard ratio for death within 90 days after the diagnosis of hyponatremia was 4.74 in those patients with moderate hyponatremia and 3.46 in patients with more severe hyponatremia.[1] Other studies have also demonstrated a marked association with hyponatremia and mortality in patients with non-Hodgkin's lymphoma, renal cell carcinoma, gastric cancer, and small-cell lung cancer.[4-6] Hyponatremia may affect patient response to therapy, as shown in non-Hodgkin's lymphoma, in which patients with serum sodium less than 137 mEq/L had a lower rate and shorter duration of remission after chemotherapy as compared with patients with higher sodium levels.[4] Likewise, hyponatremia may limit the use of chemotherapeutic options that require extensive hydration. Symptoms attributable to hyponatremia, such as confusion, lethargy, and headache, may also further compromise quality of life in this population. It is debatable whether hyponatremia independently contributes to these poor outcomes or is simply a marker of disease severity, progression, and overall debility. A recent study would argue that the latter is the case, although correction of hyponatremia before hospital discharge does seem to improve outcomes whereas persistent hyponatremia was associated with worse outcomes.[7-10]

The differential diagnosis of hyponatremia in patients with cancer is extensive (Table 1) and requires a careful history, physical examination, and laboratory evaluation to elucidate the etiology. It should be emphasized that the symptoms related to hyponatremia may be nonspecific and attributable to the underlying disease and its therapy. Thus, clinicians should measure serum sodium values in patients with symptoms compatible with hyponatremia rather than assume that the etiology is due to the underlying disease. Understanding the etiology of hyponatremia is critical in allowing proper management. For example, intravenous 0.9% saline would be the appropriate therapy in a patient with hypovolemic hyponatremia due to vomiting but not for a patient with the syndrome of inappropriate ADH secretion (SIADH). In some cases of drug-associated hyponatremia, simply

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Conflict of interest: M.H.R has served as a consultant to Otsuka and Novartis; A.D. declares no relevant financial interests.

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1548-5595/$36.00
http://dx.doi.org/10.1053/j.ackd.2013.05.005

stopping the offending medication along with transient free water restriction will lead to correction of the hyponatremia.

The most common etiology of hyponatremia that is directly related to malignancy is SIADH. The diagnostic criteria for SIADH are listed in Table 2.[11] This syndrome can be associated with many different types of malignancy and antineoplastic therapies (Table 3), but it is most commonly seen with small-cell lung cancer, in which as many as 10% to 15% of patients are hyponatremic at presentation and as many as 70% of patients have significant elevations of plasma arginine vasopressin (AVP).[12-16] Although hyponatremia may be quite severe at presentation with small-cell lung cancer, only 25% have symptoms that can be attributable to hyponatremia, suggesting that in most instances hyponatremia develops slowly and insidiously.[15] It is controversial whether the development and severity of hyponatremia correlates with tumor burden and the extent of metastatic disease.[12-16] In 1 study, the presence of SIADH did not affect response to chemotherapy or overall survival.[15] However, other studies showed a higher mortality rate in those patients with small-cell lung cancer and a serum sodium less than 130 mEq/L, and hyponatremia in small-cell lung cancer patients is generally a poor prognostic feature.[6,17–19] An intriguing possibility regarding the association of SIADH with poor outcomes in patients with small-cell lung cancer is that AVP itself may directly stimulate tumor growth.[20]

CLINICAL SUMMARY

- Electrolyte disorders in patients with cancer are common and can be secondary to either the cancer or its therapy.
- The most common electrolyte disorder seen in cancer patients is hyponatremia; this is most commonly due to the syndrome of inappropriate ADH secretion.
- Electrolyte disorders in cancer patients are associated with a poor prognosis; appropriate treatment may improve short term outcomes and quality of life.

The next most common malignancy types associated with SIADH are head and neck tumors (occurring in 3% of these patients).[21] Outside of small-cell lung cancer and head and neck cancers, most data linking SIADH with tumor subtypes come from isolated case reports that may be confounded by abnormal kidney or adrenal function or the use of medications associated with SIADH. In fact, only small-cell lung cancer cell lines have been demonstrated to produce AVP.[6] Furthermore, serial measurements of AVP reflect the state of small-cell lung cancer, with levels falling during remission and increasing with recurrence.[13,15] It should be noted that measurement of plasma vasopressin is difficult and requires proper handling and prompt processing, and conditions such as thrombocytosis can hinder quantification.

Antineoplastic drugs are also well known to cause hyponatremia, and the mechanism of action for many of these agents may involve SIADH (Table 3). The drugs most conclusively associated with SIADH are cyclophosphamide, vinblastine, and vincristine.[22] An important contributor to the development of severe hyponatremia associated with cyclophosphamide is that aggressive hydration protocols are used to prevent hemorrhagic cystitis. Cisplatin has been demonstrated to cause SIADH and to lead to a salt-losing nephropathy that can exacerbate the development of hyponatremia.[23]

In some cases SIADH may be subclinical with patients demonstrating only mild degrees of asymptomatic hyponatremia (serum sodium values 130-135 mEq/L). However, when patients are challenged with a water load or hypotonic fluids, severe hyponatremia may result.[24] This has been specifically demonstrated with small-cell lung cancer, in which 65% of patients had abnormalities in water handling when administered a water load.[12] This is also consistent with the finding that a large percentage of hyponatremia cases encountered in patients with cancer develop in the hospital setting.[1]

In patients with SIADH, it is common to see secondary elevations of atrial natriuretic peptide (ANP).[25,26] The elevations in ANP are due to a combination of increased atrial stretch secondary to the mild volume expansion that occurs with AVP-induced water retention and the direct effect of AVP to increase ANP secretion.[27] Nonphysiological release of ANP by small-cell lung cancers has also been demonstrated, and this ANP-driven kidney sodium loss may also contribute to the development and worsening of hyponatremia in these patients.[6,28,29] Thus, the development of hyponatremia in patients with small-cell lung cancer may be multifactorial.

Therapeutic options for the treatment of hyponatremia in the patient with cancer are the same as for other causes of hyponatremia and rely on the presence of related symptoms, the duration of hyponatremia, and the volume status of the patient. If possible, correction of the underlying cause is the optimal therapy. However, for many patients with malignancy-related SIADH, the hyponatremia may be more refractory to therapy; the underlying cancer cannot be cured, or the causative medications cannot be easily stopped. In these cases, other therapeutic options must be explored. In the case of severe (serum sodium < 110 mEq/L) or symptomatic acute-onset (<48 hours from onset) hyponatremia, the use of 3% hypertonic saline (with or without a loop diuretic to prevent volume overload), which leads to a rapid increase in the serum sodium and improvement in neurological symptoms, should be considered. It is important to note that in these circumstances, the neurological symptoms typically improve with small (4-5%) increases in the serum sodium, and more

Table 1. Etiologies of Hyponatremia in Patients With Cancer

a. Syndrome of inappropriate antidiuretic hormone secretion
b. Gastrointestinal fluid losses due to vomiting, diarrhea, enteric fistulas, and nasogastric suctioning
c. Third-spacing (sequestration of fluid from the intravascular space) such as from ascites or anasarca
d. Kidney failure
e. Drugs: diuretics, cisplatin, carboplatin, selective serotonin reuptake inhibitors, nonsteroidal anti-inflammatory agents, steroid withdrawal, cyclophosphamide, vinca alkaloids, narcotics, haloperidol, carbamazepine
f. Adrenal insufficiency
g. Liver failure
h. Heart failure (such as malignant pericardial disease)
i. Central nervous system disorders (primary or metastatic disease)
j. Hypothyroidism
k. Primary polydipsia
l. Cerebral salt-wasting
m. Natriuretic-peptide-induced kidney salt-wasting
n. Pain and emotional stress
o. Nausea, vomiting
p. Inappropriate intravenous fluids

rapid correction beyond this is seldom warranted.[30] In all cases in which 3% saline is used, frequent monitoring of the serum sodium is required and a correction rate greater than 10 mEq/L over the first 24 hours of therapy should be avoided.

Fluid restriction (generally to 500 mL less than the daily urine output) is an option for mild hyponatremia that may be transient in nature. However, fluid restriction may be particularly difficult in the patient with cancer in which chemotherapy regimens require hydration protocols and the restriction of fluids may compromise nutrition and quality of life. Thus, the efficacy of fluid restriction should be carefully assessed and other therapies should be used when the burden of this maneuver outweighs its benefits. A newer, physiologically based therapy for hyponatremia is to antagonize the vasopressin type-2 receptor, the site of action for vasopressin in the distal tubule that leads to water retention. In the United States, 2 vasopressin-receptor antagonists are approved by the U.S. Food and Drug Administration (conivaptan and tolvaptan). Conivaptan is an intravenous-only preparation that can only be used up to 4 days; thus, it is not appropriate long term for patients with malignancy-associated SIADH. Tolvaptan is an oral agent that is approved for euvolemic and hypervolemic hyponatremia. Tolvaptan was studied in the pivotal Study of Ascending Levels of Tolvaptan in Hyponatremia-1 (SALT-1) and SALT-2 trials,[31] although neither trial specifically addressed hyponatremia in patients with underlying malignancy. Of note, some patients will still require some degree of fluid restriction to normalize serum sodium levels, especially in those patients with urine osmolalities greater than 600 mOsm/kg.[32] Tolvaptan is contraindicated in patients with hypovolemic hyponatremia, volume depletion, and anuria as well as in those who cannot perceive or respond appropriately to thirst, and it should not be used in patients whose serum sodium levels need to be urgently raised. Moreover, acute hepatotoxicity has been reported with tolvapatan; hence, the U.S. Food and Drug Administration has limited its use to 1 month or less.

Table 2. Diagnostic Criteria for Syndrome of Inappropriate Antidiuretic Hormone Secretion[12,13]

Essential criteria
• Decreased serum osmolality (<275 mOsm/kg)
• Urine osmolality > 100 mOsm/kg
• Clinically euvolemic
• Urine sodium > 30 mEq/L on a normal daily sodium intake
• Normal thyroid and adrenal function
• No recent use of diuretics
Supplemental criteria
• Plasma uric acid < 4 mg/dL
• Blood urea nitrogen < 10 mg/dL
• Failure to correct hyponatremia (or worsening hyponatremia) after 1-2 L of 0.9% saline
• Correction of hyponatremia with fluid restriction
• Abnormal result on test of water load (<80% excretion of 20 mL water/kg body weight over a period of 4 h) or inadequate urinary dilution (<100 mOsm/kg H_2O)
• Plasma arginine vasopressin level elevated relative to plasma osmolality

Hyperkalemia Associated With Cancer

Hyperkalemia in the patient with cancer is often attributable to acute kidney injury, rhabdomyolysis, or tumor lysis syndrome (which are discussed in other articles in this journal). Less common causes include adrenal insufficiency associated with metastatic disease or drugs such as ketoconazole, metapyrone, calcineurin inhibitors (stem cell transplant patients), nonsteroidal anti-inflammatory agents, trimethoprim, and heparin.

Of particular importance in this patient population is pseudohyperkalemia.[33] The presence of pseudohyperkalemia should be considered in any patient with marked leukocytosis or thrombocytosis (for example, patients with chronic lymphocytic leukemia acute myeloctic leukemia or essential thrombocytosis), in which elevated potassium values are obtained in the absence of corresponding clinical symptoms or changes on the electrocardiogram. It is caused by a shift of potassium out of platelets or leukocytes after a blood draw and when a blood clot has formed. If the initial sample was serum, repeat measurement using simultaneously drawn plasma and serum specimens should be performed to observe for disparate results. A serum-to-plasma potassium gradient greater than 0.4 mEq/L is diagnostic of pseudohyperkalemia.[33] Because of this issue, it is recommended that plasma samples be used in those patients with extreme leukocytosis or thrombocytosis. However, another phenomenon that can be seen in plasma samples is

Table 3. Malignancies and Therapies Associated With the Syndrome of Inappropriate Antidiuretic Hormone Secretion

Cancers	Therapies
Small-cell lung cancer	Cyclophosphamide
Head and neck	Hematopoietic stem cell transplantation*
Brain (primary and metastatic)	Bortezomib*
Hematological (lymphoma, leukemia, multiple myeloma)	Vincristine, vinblastine
Skin (melanoma)	Ifosfamide
Gastrointestinal (esophageal, gastric, pancreatic, colon)	Cisplatin, carboplatin
Gynecological	Melphalan*
Breast	Methotrexate*
Prostate	Interferon-α and γ*
Bladder	Levamisole*
Sarcomas	Pentostatin*
Thymoma	Monoclonal antibodies (alemtuzumab, bevacizumab)*
Adrenal	Interleukin-2*
	Busulfan*
	Chlorambucil*
	Cytarabine, fludarabine*
	Hydroxyurea*
	Imatinib*

*Mechanism of action is not definitive, but it may involve syndrome of inappropriate antidiuretic hormone secretion.

reverse pseudohyperkalemia.[34] Here, a falsely high potassium level is found in plasma samples (defined as a serum-to-plasma potassium gradient <0.4 mEq/L). The true mechanism of reverse pseudohyperkalemia has not yet been established, but it is likely due to minor leakage of intracellular potassium from leukemic cells due to mechanical stressors (pneumatic tube transport and specimen sampling into vacuum tubes) or heparin-induced lysis of leukocytes during laboratory processing.

Therapy of hyperkalemia in this patient population is the same as for other patient groups.

Hypokalemia Associated With Cancer

Hypokalemia is the second most common electrolyte disorder encountered in the patient with cancer.[35] In most cases, the etiology of hypokalemia is multifactorial and includes medications that can cause tubular damage (such as cisplatin, ifosfamide, amphotericin B, and aminoglycoside antibiotics) as well as gastrointestinal and kidney losses of potassium. Hypokalemia is also commonly seen in conjunction with other electrolyte disorders such as hyponatremia and hypomagnesemia and reflects the underlying etiologies such as diuretic use. Patients with hypercalcemia may also develop hypokalemia due to the kaliuretic effect of the elevated calcium level as well as due to the injudicious use of diuretics in this population.[36] Transcellular shifts can also occur postphlebotomy, leading to spurious hypokalemia.[37] This phenomenon is usually encountered in patients with marked leukocytosis ($>100{,}000/\mu L$) and with blood that is kept at room temperature for prolonged periods of time. Rapid separation of the plasma and storage at 4°C limits this issue.

Specific etiologies of hypokalemia encountered in the patient with cancer are depicted in Table 4. Ectopic adrenocorticotropin hormone (ACTH) syndrome is an uncommon cause of severe hypokalemia and typically presents with severe hypercortisolemia, increased skin pigmentation, diabetes, bone loss, hyperlipidemia, generalized infections (especially fungal), hypertension, mental status changes, and Cushingoid habitus.[38] Excess cortisol overloads cellular mechanisms to limit mineralocorticoid receptor access to glucocorticoids, thereby enhancing kidney potassium excretion. Numerous tumors can produce ectopic ACTH, with the most common etiologies including bronchial carcinoid tumors, small-cell

Table 4. Etiologies of Hypokalemia in the Patient With Cancer

Inadequate potassium intake
- Poor nutrition, anorexia

Excessive gastrointestinal losses
- Vomiting (chemotherapy-induced)
- Diarrhea (chemotherapy-induced, tumor-associated, postsurgical resection)
- Posturetosigmoid diversion

Kidney losses- Diuretics
- Hypercalcemia
- Hypomagnesemia
- Postobstructive diuresis
- Drugs
  - Amphotericin B
  - Aminoglycosides
  - Cisplatin
  - Ifosfamide
  - Glucocorticoids
- Lysozymuria with acute leukemia
- Mineralocorticoid excess
  - Primary hyperaldosteronism (adrenal adenoma or carcinoma)
  - Renin-producing tumors
  - Ectopic adenocorticotropin syndrome

Intracellular shifts
- Pseudohypokalemia
- Use of growth factors and vitamin B12 therapy

lung cancer, lung adenocarcinomas, thymic tumors, pancreatic tumors, and medullary thyroid cancer.[38] Of note, more than 50% of these tumors are found in the lung or thymus, although in 10% to 15% of cases of ectopic ACTH syndrome, the source remains unknown.[39] Diagnosis rests on biochemical/endocrine testing to document elevated ACTH levels in the presence of hypercortisolism followed by radiographic localization.[38] The optimal management of this syndrome is surgical excision, but this can only be achieved with curative intent in up to 40% of cases; thus, drugs that antagonize the synthesis of glucocorticoids such as metapyrone and ketoconazole may also be needed.[38] Patients with occult ectopic ACTH syndrome will likely need adrenalectomy to achieve a biochemical cure.[38] Prognosis in this syndrome is dependent on the etiology, and patients with small-cell lung cancer have the worst prognosis with survival generally less than 12 months after diagnosis.[38]

A prominent association between hypokalemia and acute myelogenous leukemia (specifically subtypes M4 and M5) has been noted, with 40% to 60% of these patients developing significant hypokalemia at some point in their disease course.[35,40] Of importance is that hypokalemia in these patients is usually associated with other electrolyte and acid-base disorders (hyponatremia, hypocalcemia, hypophosphatemia, hypomagnesemia and non-anion gap metabolic acidosis), suggesting a more global tubular defect in these patients.[40] The mechanism of hypokalemia is due to inappropriate kaliuresis and has been postulated to be secondary to increased serum lysozyme levels and lysozymuria-induced tubular damage.[41] The frequency of hypokalemia is so high that patients with acute myelogenous leukemia should have frequent laboratory monitoring and electrolyte supplementation as needed.

The treatment for hypokalemia in patients with malignancy is similar to that used in patients without an underlying malignancy. A thorough review is beyond the scope of this manuscript. For a more in-depth discussion, the reader is directed to an excellent review by Unwin and colleagues.[42]

Hypophosphatemia Associated With Cancer

The regulation of phosphate balance reflects the actions of an array of factors altering phosphate absorption and excretion as well as changes related to the intimate connection between phosphate and calcium levels.[43] In patients with malignancy, pathologic derangement at any of several regulatory steps can result in hyper- or hypophosphatemia. Hence, it is important for the clinician to have an understanding of phosphate homeostasis (Fig 1) as a backdrop upon which to evaluate altered phosphate levels in patients with cancer (Fig 2).

Dietary intake of phosphate usually exceeds the recommended daily allowance of 700 mg for adults,

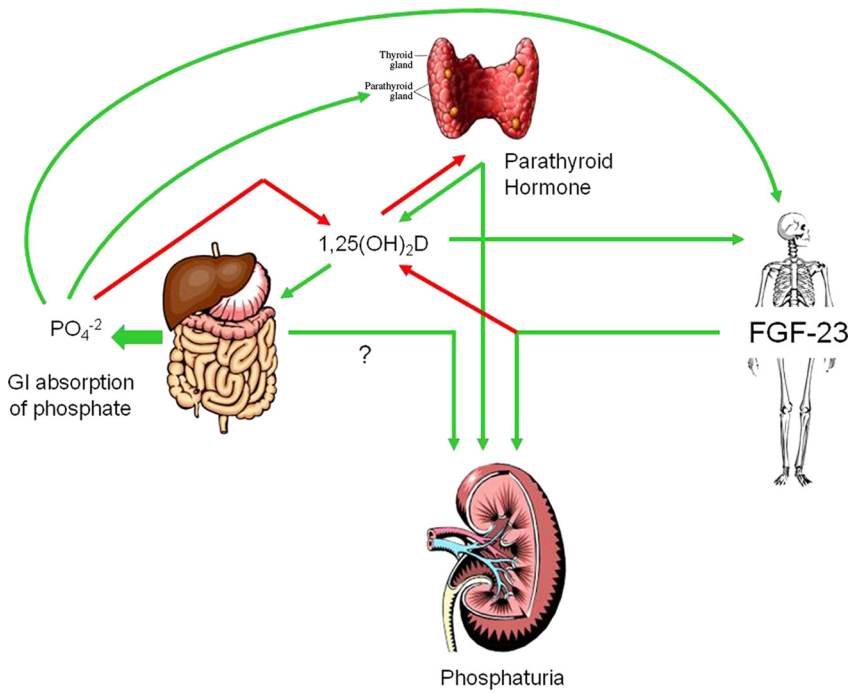

Figure 1. Regulation of phosphaturia. Kidney phosphate excretion is driven by bone-derived fibroblast growth factor-23 (FGF-23) and parathyroid hormone (PTH) along with an as-yet unidentified factor from the gastrointestinal tract. 1,25-Dihydroxy vitamin D stimulates phosphate absorption, which in turn drives phosphaturia and parathyroid hormone release. Feedback inhibition results from FGF-23 and phosphate inhibition of 1-α-hydroxylase as well as the actions of vitamin D to reduce PTH secretion.

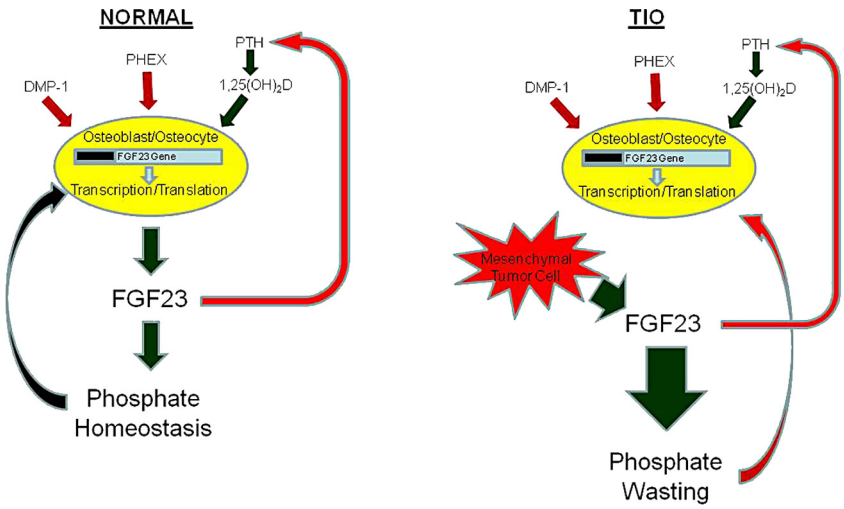

Figure 2. The role of fibroblast growth factor-23 (FGF-23) in tumor-induced osteomalacia (TIO). Production of FGF-23 from the osteoblast and osteocyte is inhibited by dentin matrix protein-1 (DMP-1) and phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX) by as-yet unclear mechanisms. 1,25-Dihydroxy vitamin D ($1,25(OH)_2D$) stimulates FGF-23, which in turn favors phosphaturia. Changes in phosphate level feedback at the osteoblast/osteocyte (hyperphosphatemia stimulates FGF-23 synthesis and secretion whereas hypophosphatemia inhibits FGF-23). FGF-23 also inhibits parathyroid hormone (PTH), which in turn lowers $1,25(OH)_2D$. In patients with TIO, tumor production of FGF-23 is unrestrained and the normal feedback inhibition to the parathyroid gland and the osteoblast/osteocyte is ineffective at lowering FGF-23.

and much of it is not absorbed. Changes in dietary phosphate intake alter the expression of the sodium-phosphate cotransporter IIB (such that a reduction in dietary intake of phosphate enhances absorption whereas excess dietary intake results in reduced intestinal absorption) by an as yet unknown mechanism(s).[44] Moreover, an undefined communication between the gastrointestinal tract and the kidney appears to exist because there is rapid appearance of phosphaturia after phosphate absorption.[45]

In contrast, 30% of gastrointestinal phosphate transport is dependent on the actions of active vitamin D—1,25-dihydroxy vitamin D ($1,25(OH)_2D$).[46] Other factors, including phosphate, calcium, insulin-like growth factor-1 and the "phosphatonins" (such as fibroblast growth factor-23 [FGF-23] and secreted frizzled-related peptide), can modify that effect.[47] The actions of vitamin D on intestinal cellular function are complex and enhance expression of the sodium-phosphate cotransporter IIB.[48]

Parathyroid hormone (PTH) is an essential hormonal regulator of kidney phosphate handling. PTH (and PTH-related peptide [PTHrP]) acts via a G-protein-coupled cell surface receptor, PTH receptor-1.[49] In terms of kidney phosphate balance, PTH acts on the proximal tubule cells to drive internalization of the sodium-phosphate cotransporters NaPi-IIa and IIc, preventing reabsorption of phosphate and enhancing phosphaturia.[50] PTH secretion is regulated by calcium (via the calcium-sensing receptor), phosphate (via an unknown mechanism), and vitamin D (via a direct action on PTH release as well as via the effects of hypercalcemia).

The final regulatory component in maintaining phosphate balance includes a group of factors referred to as phosphatonins, which directly regulate phosphate concentration.[47] The most important member of this family is FGF-23, produced primarily by osteoblasts and osteocytes, which is important in the healthy individual and several disease states.[51] FGF-23 acts via fibroblast growth factor receptor-1 and the co-receptor α Klotho to inhibit kidney expression of the sodium-phosphate transporter 2a and 2c, thereby promoting phosphaturia and hypophosphatemia.[52,53] Phosphate and $1,25(OH)_2D$ are the major stimuli for FGF-23.[54,55] Indeed, there may exist a feedback regulatory loop because FGF-23 inhibits the formation of $1,25(OH)_2D$, an action which then, in turn, would limit further production of FGF-23.[56] The relationship between FGF-23 and PTH is complex. As noted, FGF-23 inhibits the activation of vitamin D, thereby indirectly increasing PTH. On the other hand, FGF-23 can directly inhibit PTH secretion. Thus, FGF-23, like PTH and vitamin D, is involved in a complex regulatory cascade for phosphate.

Additional factors also bear upon phosphate metabolism, although their role in physiology and the mechanism(s) by which they act are unclear.[57] The phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX), which cleaves matrix extracellular phosphoglycoprotein (MEPE), another potential regulator of phosphate, can inhibit FGF-23. Dentin matrix protein plays a similar role in the inhibition of FGF-23. Excess MEPE has been associated with hypophosphatemia (see below) because of actions at the intestinal tract and the kidney.

Disordered regulation of phosphate, as a consequence of neoplasia, is relatively common. Cachexia and malnutrition, including calcium and vitamin D deficiency, can directly result from malignancy or as the result of cancer treatment. These patients present with low normal serum calcium levels, or frank hypocalcemia, hypophosphatemia, low vitamin D, and elevated PTH levels. Chemotherapy, including cisplatin, can damage renal tubules and result in phosphate wasting. In addition, multiple myeloma can directly alter kidney phosphate reabsorption and result in phosphaturia and hypophosphatemia. Certain malignancies, such as lymphoma, may contain the enzyme 1-α hydroxylase and lead to increased levels of active vitamin D metabolites and cause hypercalcemia and, to a lesser degree, hyperphosphatemia.

More complex, and more rare and indolent, is the syndrome of tumor-induced osteomalacia (TIO), also known as oncogenic osteomalacia, in which tumor production of phosphaturic factors such as FGF-23 results in phosphate wasting, hypophosphatemia, and osteomalacia.[58] A wide array of neoplasms has been described, including malignancies such as chondrosarcoma and osteoblastoma, although the most common neoplasm is a hemangiopericytoma. Ossifying fibromas, giant-cell tumors, and granulomas causing TIO have also been described. These neoplasms are generally mesenchymal in origin (phosphaturic mesenchymal tumor, mixed connective tissue variant), with a high degree of vascularity but absent or low levels of mitotic activity.[58]

The initial steps in the evaluation of a patient with acquired hypophosphatemia include a thorough evaluation of medications, nutritional status, and medical history. In the presence of hypercalcemia, causes of hyperparathyroidism should be pursued (chemistry panel including calcium, albumin, kidney function, PTH, and PTHrP). If there is coexistent hypocalcemia, vitamin D status must be ascertained. In patients with a normal calcium level and hypophosphatemia, the presence of kidney phosphate wasting should be pursued. Assessment of either the percentage tubular reabsorption of phosphate or the tubular maximum for phosphate corrected for the glomerular filtration rate can be used.[58] If phosphate wasting is confirmed, measurement of FGF-23 levels can be performed. As noted, there are multiple potential causative factors; therefore, a "normal" FGF-23 level does not eliminate the diagnosis of TIO.

Most neoplasms associated with TIO are found in the limbs or sinuses. Because of their small size and slow growth rate, it is not uncommon for the tumor to remain occult, thereby warranting more extensive imaging studies.[58,59] F-18-Fluorodeoxyglucose positron emission tomography, with computed tomography (FDG-PET/CT) is favored at our institution, but ^{111}Indium octreotide scintigraphy has also been useful. Because of the lack of specificity in these scans, especially FDG-PET/CT, follow-up imaging with standard computed tomography or magnetic resonance imaging is essential. If the neoplasm remains elusive, venous sampling for FGF-23 has been attempted with some success.[60]

The mainstay of therapy is surgical resection because removal is usually curative. Phosphate levels rapidly increase because the half-life of FGF-23 is relatively short.[61] Symptoms of hypophosphatemia may also improve quickly, although the time needed to heal from osteomalacia is longer and more variable. Metastatic disease (often in the lung), or late recurrence, has been reported in a few individuals.[62,63] For individuals in whom the tumor cannot be found, or if metastatic disease prevents surgical cure, medical therapy with vitamin D and phosphate is essential. As noted, these patients are often deficient in $1,25(OH)_2D$ because of the inhibition of the 1-α hydroxylase step by FGF-23. In that light, calcitriol is the preferred form of vitamin D used in these individuals, at doses between 1 and 3 μg/day, but it is often limited by the development of hypercalcemia. Phosphate supplements, usually 1 to 3 g/day in divided dosing, are given using any of several available sodium phosphate or potassium phosphate preparations. Dosing of phosphate is generally limited by the development of loose stools. In our practice, it has been difficult to achieve a normal phosphate level in these patients. Reaching a phosphate level between 2 and 2.5 mg/dL is usually adequate to greatly reduce symptoms and promote, to some degree, healing of osteomalacia.

For those individuals in which one is unable to identify the site of the neoplasm, regular follow-up is essential. Careful examination of the extremities as well as the head and neck are areas of focus. Sequential measurement of phosphate is helpful, especially to gauge whether replacement is adequate. In addition, we have had most patients complete a 24-hour urine for calcium, phosphorous, and creatinine once they are stable. Because oral supplementation with phosphate and vitamin D can exacerbate hyperphosphaturia, there is a substantial risk of developing calcium phosphate kidney stones; hence, thiazide diuretics may be needed to help reduce urine calcium excretion.

Hypercalcemia and Cancer

In patients with an underlying malignancy, most instances of disordered regulation of calcium generally involve the development of hypercalcemia.[64] In the evaluation of disordered calcium, one must keep in mind that circulating calcium is in part bound to albumin such that the measured calcium level must be corrected for the albumin.[65] The severity of hypercalcemia in patients with cancer will vary greatly and is dependent on the mechanistic basis for the hypercalcemia as well as the patient's overall health status and hydration. In the presence of mild hypercalcemia (10.5-11.5 mg/dL), patients may be asymptomatic or have fatigue, malaise, constipation, or

anorexia. As the degree of hypercalcemia worsens, bone pain (either related directly to the presence of malignancy or secondary to increased bone remodeling), abdominal pain (peptic ulcer disease), polyuria (nephrogenic diabetes insipidus), and weakness are common. In severe hypercalcemia with levels above 14 mg/dL, neurologic changes including altered mental status, confusion, and coma may be present, warranting immediate intervention and hospitalization.

The regulation of calcium concentrations is primarily via the actions of PTH and vitamin D. As with phosphate, PTH activates bone turnover and thereby favors the release of bone calcium stores, along with phosphate, into the circulation. Again, PTH initiates this action via the PTHR1 on the osteoblast, which in turn signals the osteoclast via the RANK/RANKL pathway.[49,50] At the collecting system, PTH drives calcium reabsorption and phosphate excretion as well as activation of vitamin D, which favors the absorption of calcium and phosphate from the gastrointestinal tract. Calcium concentration in the circulation dictates signaling via the calcium-sensing receptor to provide feedback inhibition.

Perturbations at each of these steps in the homeostasis of calcium can be detected as a potential cause of disordered calcium regulation in patients with malignancy. In general, there are 3 broad categories of hypercalcemia. Most commonly, tumors can synthesize and secrete PTH-like substances, specifically PTHrP, which increases bone turnover and the release of calcium stores. Squamous-cell carcinomas of the lung, cervix, and esophagus as well as certain lymphomas, kidney cell carcinoma, and adenocarcinoma of the breast, prostate, and ovary have been reported to cause hypercalcemia via PTHrP release.[66-68] Likewise, although considerably less common, tumors can make PTH themselves, including neoplasms of pulmonary, ovarian, thyroid, and pancreatic origin.

A second, less common mechanism for the development of hypercalcemia in patients with malignancy involves the direct actions of metastatic tumor cells to cause local osteolysis. The degree to which bone metastases cause hypercalcemia correlates directly with the bone tumor burden. Each metastasis likely releases factors such as prostaglandins or PTHrP that stimulate local osteoclast activity and the release of calcium into the circulation. This scenario is most commonly noted in patients with metastatic breast and lung cancers as well as in patients with extensive multiple myeloma.[69-71]

The third general mechanism in which patients with cancer experience hypercalcemia includes the activation of vitamin D by the tumor itself, most commonly seen in Hodgkin lymphoma and non-Hodgkin lymphoma, as well as multiple myeloma.[72] In patients with tumors directly activating vitamin D, hypercalcemia with hypoparathyroidism is generally observed due to feedback inhibition of calcium on the normal parathyroid glands.

Therefore, the evaluation of the cancer patient with hypercalcemia includes an investigation toward these potential causes. After confirmation of true hypercalemia, measurement of circulating PTH levels is the first most important step. If the PTH levels are inappropriately normal, or elevated, evaluation for a coexistent parathyroid adenoma should be sought because tumor-related production of PTH itself is rare. More likely, PTH levels will be suppressed, and other etiologies need to be sought. Generally, other laboratory results may provide a clue to aid in the investigation. A low phosphorus level, perhaps coupled with an elevated marker of bone turnover such as alkaline phosphatase, can indicate PTHrP-mediated disease. Of note, alkaline phosphatase is derived from numerous sources, including liver and bone, and hence is relatively nonspecific. Hyperphosphatemia in the presence of hypercalcemia, especially in the absence of coexisting kidney insufficiency, often indicates a vitamin D-mediated etiology. Thus, additional testing generally should include measurement of phosphorus, $1,25(OH)_2D$, PTHrP, and alkaline phosphatase along with a serum and urine protein electrophoresis looking for light-chain disease.

The therapy for hypercalcemia can be complex, involves short- and long-term interventions, and is highly dependent on the mechanism by which hypercalcemia develops.[73] The initial step, regardless of the cause, is the emergent reduction in circulating calcium concentration. The mainstay of therapy is intravenous hydration with a goal of increasing kidney clearance of calcium. Most patients with significant hypercalcemia are volume depleted at presentation, and a reduced glomerular filtration rate can exacerbate the hypercalcemia with ongoing mobilization from bone. Aggressive intravenous hydration with 0.9% saline, usually at 200 to 500 mL/hour, is the initial regimen suggested to establish a kidney urine output of more than 75 mL/hour. If hydration results in excessive fluid retention and potentially cardiac compromise, usually congestive failure, the addition of a loop diuretic is suggested. Furosemide at increasing doses can be used to facilitate the forced saline diuresis, but only after vigorous hydration has been achieved.[74]

To block mobilization of calcium from bone, antiresorptive therapy is generally mandatory. The primary class of medications with which one can accomplish this is via use of the bisphosphonates. The high-potency bisphosphonates, available for intravenous dosing, include pamidronate, zolendronic acid, and ibandronate. Pamidronate and zolendronic acid are approved by the U.S. Food and Drug Administration for the treatment of hypercalcemia. Ibandronate has been shown to have efficacy in this setting, but hypercalcemia is not an approved indication. Each of these agents targets the osteoclast to reduce resorption.[75] Tubular injury and glomerular damage have been reported. Therefore, each agent should be dose-adjusted when used in patients with kidney

insufficiency. Alternative antiresorptive agents include denosumab, a monoclonal antibody directed against RANKL. Denosumab is not cleared by the kidney; hence, kidney insufficiency does not alter dosing or efficacy. Denosumab has documented benefit in metastatic cancers and can reduce skeletal-related events.[76,77] In addition, denosumab (along with the intravenous bisphosphonates) has antiresorptive actions that can extend for weeks to months, providing a longer term effect.

For patients with tumor-induced hypercalcemia resulting from excess 1-α hydroxylase, corticosteroid therapy may be beneficial. Intravenous hydrocortisone, at doses of 200 to 300 mg/day, can inhibit the 1-α hydroxylase and reduce $1,25(OH)_2D$ levels.[78] Although the response is not rapid, limitation of dietary calcium may be helpful in expediting the effect. High doses of corticosteroids can have a direct action on the underlying malignancy (for example, certain lymphomas). After a period of 3 to 5 days of intravenous steroid administration, it is standard practice to transition the patients to oral dosing, usually prednisone at 10 to 30 mg/day.

Hypocalcemia, Hypomagnesemia, and Cancer

Although rare, and described primarily in case reports,[79,80] some malignancies are associated with hypocalcemia. The tumors are usually metastatic to bone and have osteoblastic activity. Hypomagnesemia can be associated in patients with cancer, although this disturbance is generally the result of therapy rather than being due to the underlying disease state.

Summary

Proper management of the patient with cancer is complex, and their medical treatment often includes efforts to restore electrolyte levels to or toward normal. Disordered regulation of sodium, potassium, phosphate, and calcium composes a substantial proportion of these abnormalities and are relatively commonplace in this patient population. In many instances, until they are corrected, electrolyte disturbances can affect health and may limit treatment of the underlying neoplasia. An understanding of the pathologic basis for the specific chemical imbalance is essential for the clinician to institute a proper and effective corrective measure.

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