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