Electrolyte Complications of Malignancy

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• Malignancy • Electrolytes • Hypoglycemia • Hyponatremia
• Hypercalcemia • Hyperphosphatemia

Electrolyte abnormalities are perhaps the most common laboratory finding in patients with malignancies who present to the emergency department. Although most minor abnormalities have no specific treatment, severe clinical manifestations of several notable electrolytes occur with significant frequency in the setting of malignancy. If improperly treated, abnormalities of serum sodium, glucose, calcium, magnesium, and phosphorus may have serious consequences. A review of the most serious electrolyte abnormalities associated with malignancy follows.

HYPONATREMIA

Hyponatremia is a common electrolyte disorder, reported to occur in 3.8% of emergency department patients.[1] Among the population of emergency department patients with underlying malignancy, hyponatremia occurs most commonly with small cell lung cancers. Hyponatremia has been reported with other malignancies, including primary and metastatic malignancies of the brain, pancreatic adenocarcinoma, and prostate cancer.[2] Hyponatremia has also been reported in association with treatment with chemotherapeutic agents, particularly cisplatin and carboplatin.[3] Regardless of the associated malignancy, hyponatremia can present as either an incidental finding or with life-threatening severity. Correction of hyponatremia requires an understanding

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of both the rapidity with which the hyponatremia has developed as well as the potential complications of treatment.

Pathophysiology

Syndrome of inappropriate antidiuretic hormone

Hyponatremia associated with malignancy is most commonly caused by the syndrome of inappropriate antidiuretic hormone (SIADH) secretion. Ectopic secretion of arginine vasopressin (AVP) by tumor cells appears to play a significant role in the development of hyponatremia.[4] Small cell lung cancer is particularly notorious for elevated levels of circulating AVP despite serum hypotonicity.[4] Other hormones have been implicated in the pathogenesis of hyponatremia of malignancy, including atrial natriuretic peptide, but their ultimate contribution to hyponatremia remains somewhat unclear.[5]

Elevated levels of AVP in patients with malignancy cause hyponatremia primarily due to inappropriate retention of free water at the collecting-duct level despite relative serum hypotonicity.[6] Normally in the setting of hypotonicity, the secretion of AVP is suppressed. In malignancy, the release of AVP by tumor cells does not respond to changes in serum tonicity, and, as a result, AVP remains present in the circulation and results in cyclic AMP-mediated insertion of water channels in the collecting ducts (aquaporin 2).[7] The absorption of free water at the collecting-duct level results in worsening hypotonicity and inappropriately concentrated urine.[7] Clinically, the result is hyponatremia in an apparently euvolemic patient.

Renal salt wasting

Hyponatremia of malignancy has also been reported as a complication of chemotherapy. Both cisplatin and carboplatin have been reported to cause hyponatremia.[3] The mechanism for hyponatremia associated with chemotherapeutic drugs is believed to be renal salt wasting syndrome (RSWS). In this disease process, damage to the renal tubules with subsequent inability to retain sodium is thought to result in increased sodium loss.[8] Clinically, the patient will appear hyponatremic with euvolemia; however, the treatment of RSWS is sodium supplementation rather than water restriction. An elevated spot urine sodium level may suggest RSWS. In SIADH, urinary excretion of sodium is usually normal or decreased. Definitive diagnosis of RSWS, however, can only be made after measurement of daily sodium intake and excretion. RSWS is diagnosed when daily sodium intake is less than urinary excretion.[3] In extremis, however, treatment of hyponatremia due to RSWS is identical to the treatment of hyponatremia due to SIADH.

Clinical Manifestations

The clinical presentation of hyponatremia is largely related to the acuity with which the sodium has declined and has less direct correlation with the actual measured sodium. Levels of decline greater than 0.5 mEq/L/h appear to be more likely to result in serious sequelae, but considerable variation exists between individuals.[9] Most symptomatic individuals will have serum sodium less than 120 mEq/L; however, symptoms have been reported with sodium levels of 129 mEq/L or less.[7]

The brain appears to be the organ most sensitive to changes in the serum sodium level. If the rate of sodium decline outstrips the adaptive capabilities of the brain, symptoms of hyponatremia develop. When the rate of sodium decline is slower, the brain will adapt by expelling potassium and other osmotically active substances (osmolytes) to maintain normal cell volume. These osmolytes include amino acids, myoinositol, creatine, and creatine phosphate.[7] If, however, the rate of sodium decline