Hypercalcemia of Malignancy: Part I

Hypercalcemia is a metabolic condition that occurs when the serum calcium level rises above the normal range of 9–11 mg/dl (Myers, 2001; Smith, 2000). It is a complex metabolic oncologic emergency that can be life threatening. This column is the first of a two-part series about hypercalcemia of malignancy (HCM). Part I focuses on the pathophysiologic mechanisms of hypercalcemia and includes questions about calculating the corrected serum calcium level based on the patient’s serum albumin level. Part II, which will be published in the June 2004 issue, will focus on patient assessment, management, and nursing implications of HCM.

Case Study

Mr. C is a 62-year-old male who was diagnosed with stage IV squamous cell cancer of the lung. A computed tomography scan of the spine revealed metastatic disease in the thoracic and lumbar spine at the T1 and L3 vertebrae. Based on the extent of the disease and poor pulmonary function studies, Mr. C was not a surgical candidate. His wife accompanies Mr. C to clinic visits. He is scheduled for a follow-up physician visit, laboratory work-up, and a second course of palliative chemotherapy. Mr. C also is receiving concurrent radiation for the spinal metastases.

While Mr. C is getting settled in the chemotherapy suite, his wife consults with the nursing staff. She is concerned about her husband’s increasing forgetfulness and wonders if the confusion is because of the recent change in pain medication (oxycodeone) he has been taking. Mr. C is not taking any other medications. On further discussion, she reports that in addition to the confusion, her husband has been experiencing more fatigue than usual as evidenced by his practice of taking multiple naps during the day. Review of the laboratory work reveals a white blood count of 4,500/mm³, hemoglobin 11.2 g/dl, hematocrit 35%, and a platelet count of 119,000/mm³. Significant chemistries include a serum calcium level 10.4 mg/dl, creatinine 1.1 mg/dl, blood urea nitrogen 19 mg/dl, and serum albumin 2.3 g/dl.

1. Based on the available information, what is the most likely cause of Mr. C’s hypercalcemia?
   a. HCM
   b. Primary hyperparathyroidism
   c. Medication side effects
   d. Renal dysfunction

2. What is Mr. C’s corrected serum calcium level considering his low serum albumin level?
   a. 10.6 g/dl
   b. 10.5 g/dl
   c. 11.8 g/dl
   d. 12.1 g/dl

3. Which factor(s) will not increase Mr. C’s hypercalcemic condition?
   a. Vitamin D and calcitonin
   b. Parathyroid hormone (PTH)
   c. Growth factors
   d. Dietary intake of calcium

4. The underlying mechanism(s) of Mr. C’s hypercalcemia is/are
   a. Humoral HCM (HHCM).
   b. Local osteolytic hypercalcemia.
   c. Osteoclastic hypercalcemia.
   d. Humoral and local osteolytic hypercalcemia.

Discussion

Question 1: The correct answer is choice a. HCM. Although all of the selections are potential causes of hypercalcemia, the most likely cause of Mr. C’s hypercalcemia is malignancy because of his underlying cancer and bone metastases. Hypercalcemia occurs in about 10%–40% of all patients diagnosed with cancer (Barnett, 1999; Morton & Lipton, 2000; Myers, 2001; Wickham, 2000). Hypercalcemia can occur with or without the coexistence of skeletal metastases, but more than 80% of patients have both; however, the extent of metastases does not correlate with the severity of hypercalcemia. Malignancies associated with elevated serum calcium levels include multiple myeloma, lymphomas, and solid tumors of squamous cell origin, including lung, breast, prostate gland, head and neck, esophagus, and kidney (National Cancer Institute, 2003) (see Table 1). Mr. C’s diagnosis of squamous cell carcinoma places him at risk for hypercalcemia. Choice b, primary hyperparathyroidism, is the most common differential diagnosis to consider. Primary hyperparathyroidism and malignancy together account for 90% of hypercalcemia cases. However, in HCM, the PTH level may be increased, decreased, or normal (Smith, 2000; Wickham). Choices c and d, medication side effects and renal dysfunction, are causes of hypercalcemia; however, Mr. C is not taking medications that can cause hypercalcemia (e.g., thiazides, lithium, large doses of vitamin A or D), and his renal status is borderline normal limits. Other differential diagnoses include endocrine disorders such as thyrotoxicosis, Addison’s disease, and pheochromocytoma. In addition, immobility, nutritional intervention side effects (total parenteral nutrition), and familial hypercalciuric hypercalcemia can lead to hypercalcemia (Barnett).

Question 2: The correct answer is choice c, 11.8 g/dl. For every g/dl of albumin lost, a 0.8 g/dl correction of calcium can be found. Using the formula in which corrected calcium equals measured serum calcium plus 0.8 (4.0 – serum albumin level), the correct answer is 11.8 g/dl. The corrected calcium is 10.4 plus 0.8 multiplied by 1.7, which equals 10.4 plus 1.36 and rounds to 11.8 g/dl.

Calcium is essential for several metabolic processes in the body. It is required for forming and maintaining bone and teeth, cardiac contractility, transmission of nerve impulses, and maintaining normal clotting. Ninety-nine percent of total body calcium is stored in bone (Myers, 2001). The remaining 1% is stored in the serum and body cells. About half of the circulating calcium is in the form of free

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Calcium balance and is influenced by several factors such as dietary intake of calcium, physical activity, and local factors such as cytokines, growth factors, and prostaglandin. Osteoclasts, which are bone-resorbing cells, are stimulated to resorb the area of bone that is going to be remodeled. Growth factors (e.g., macrophage–colony-stimulating factor, several interleukins) play a role in the formation of these osteoclasts (Morton & Lipton, 2000). Additionally, calcitriol, the active form of vitamin D, stimulates osteoclast precursors to differentiate. The osteoclasts release a proteolytic enzyme that dissolves the bone matrix. This results in the release of calcium into the extracellular fluid, which is followed by a repair phase where osteoblasts secrete a specialized extracellular matrix into the defect that subsequently mineralizes. This remodeling process helps to maintain the strength and integrity of bone. Bone remodeling is actually a balanced state, and very little calcium moves to the circulation during this process (Smith, 2000). The entire cycle takes about three months to complete (Wickham, 2000). Anything that increases osteoclastic activity or decreases osteoblastic bone formation, upsetting the steady state, will lead to an increase in circulating calcium.

Question 3: The correct answer is choice d, dietary intake of calcium. All other factors listed work together to regulate the serum calcium level. Choices a, b, and c, vitamin D and calcitonin, PTH, and growth factors, could exacerbate Mr. C’s hypercalcemia. Extracellular calcium homeostasis is regulated by PTH, vitamin D, and calcitonin (Barnett, 1999). When circulating calcium levels drop, several events occur. PTH enhances bone resorption (part of bone remodeling) by acting on bone osteoclasts. This leads to a breakdown of bone with subsequent release of calcium into the extracellular fluid. In the distal tubules, PTH increases the efficiency of renal tubular calcium reabsorption with a subsequent decrease in calcium excretion and indirectly increases vitamin D production through the kidney by converting the vitamin to its active form, calcitriol. Calcitriol then increases gastrointestinal absorption of calcium and phosphate. Calcitonin antagonizes the activity of PTH by lowering serum calcium and inhibiting bone reabsorption.

Bone remodeling is a dynamic process that modifies the body’s normal physiologic calcium balance and is influenced by several factors, including hormones, physical activity, and local factors such as cytokines, growth factors, and prostaglandin. Osteoclasts, which are bone-resorbing cells, are stimulated to resorb the area of bone that is going to be remodeled. Growth factors (e.g., macrophage–colony-stimulating factor, several interleukins) play a role in the formation of these osteoclasts (Morton & Lipton, 2000). Additionally, calcitriol, the active form of vitamin D, stimulates osteoclast precursors to differentiate. The osteoclasts release a proteolytic enzyme that dissolves the bone matrix. This results in the release of calcium into the extracellular fluid, which is followed by a repair phase where osteoblasts secrete a specialized extracellular matrix into the defect that subsequently mineralizes. This remodeling process helps to maintain the strength and integrity of bone. Bone remodeling is actually a balanced state, and very little calcium moves to the circulation during this process (Smith, 2000). The entire cycle takes about three months to complete (Wickham, 2000). Anything that increases osteoclastic activity or decreases osteoblastic bone formation, upsetting the steady state, will lead to an increase in circulating calcium.

Question 4: The correct answer is choice d, humoral and local osteolytic hypercalcemia. Humoral hypercalcemia and local osteolytic hypercalcemia are the two main mechanisms that cause HCM (Barnett, 1999; Morton & Lipton, 2000; Wickham, 2000). Choice c, osteoclastic hypercalcemia, is incorrect. Hypercalcemia found in patients with very little or no bone metastasis is called HHCM, choice a. In HHCM, PTH-related protein (PTHrP), produced by solid tumors, binds to and activates PTH receptors in the tissue. Like PTH, PTHrP affects calcium homeostasis and increases bone resorption and calcium reabsorption in the renal tubules. HHCM is the dominant form of hypercalcemia in patients with cancer. The kidneys attempt to control the excess serum calcium by excreting calcium in the proximal tubules. This leads to polyuria and a loss of blood volume. As the glomerular filtration rate decreases, further dehydration occurs. Normally, sodium is found in highest concentrations on the outside of the cell. With a loss of calcium lining the cellular membrane, sodium enters the cell and depolarization occurs. As calcium levels continue to rise, central nervous system symptoms and muscle weakness develop. Once dehydration and low serum sodium occur from this mechanism, the kidneys start to conserve sodium and water in an effort to improve extravascular fluid volume. This mechanism also results in calcium reabsorption because of its close relationship with sodium.

Choice b, local osteolytic hypercalcemia, is believed to be an infrequent cause of hypercalcemia because patients with bone metastases do not always develop hypercalcemia. In local osteolytic hypercalcemia, PTHrP and cytokines (tumor necrosis factor, interleukin-6, osteoclastic activating factor, and interleukin-1) are found within or adjacent to skeletal metastases. This leads to bone resorption, more destruction from metastatic disease, and formation of lytic lesions.

In HHCM, solid tumors secrete transforming growth factors (TGF-α and β, platelet-derived growth factor (which may potentiate effects of TGF), and prostaglandins (present in renal cancers) (Barnett, 1999). All of these stimulate osteoclastic activity. In local osteolytic hypercalcemia, metastatic tumor cells may directly resorb bone. The tumor cells produce PTHrP and cytokines. Along with regulating factors (such as interleukin-6, interleukin-1β, tumor necrosis factor-α, and lymphotoxin), PTHrP and cytokines induce the osteoclasts to migrate to the tumor and become active (Wickham, 2000).

HCM is a complex and dynamic process. Knowledge of the causes of hypercalcemia, its pathophysiologic mechanisms, and the exacerbating factors of the disease will enable nurses to understand this oncologic emergency in greater detail and provide better care and education for patients.

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References