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Disorders of Serum Minerals

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INTRODUCTION

In this chapter, we consider disorders that lead to increases or decreases in the circulating concentrations of calcium, phosphorus, and magnesium. Chapter 72 describes normal calcium, phosphorus, and magnesium metabolism.

The optimal approach to diagnosing and treating these disorders is to understand their underlying physiology and pathophysiology. Coherent diagnostic and successful therapeutic plans can then be developed. Years of experience suggest a persistent propensity to jump to the common items on the differential diagnosis list without fully considering the other options. In so doing, the correct and often easily treatable diagnosis is overlooked. For example, hypercalcemia in the setting of a pulmonary nodule may indicate the humoral hypercalcemia of malignancy, and many physicians jump to this diagnosis with its grim prognosis. However, this complex may represent hypercalcemia in a patient with treatable tuberculosis or primary hyperparathyroidism (HPT) in a person with a long-standing and inactive pulmonary scar. Complete differential diagnoses are provided in the tables that follow.

HYPERCALCEMIA

Symptoms and Signs

Hypercalcemia causes hyperpolarization of neuromuscular cell membranes and therefore refractoriness to stimulation (see Chapter 72). This condition manifests clinically as skeletal muscular weakness, smooth muscle hypoactivity with constipation and ileus, and the full spectrum of neurologic dysfunction, progressing from lassitude to mild confusion to deep coma. Hypercalcemia also leads to renal failure. It reduces the glomerular filtration rate (GFR) through afferent arteriolar vasoconstriction and activation of the calcium receptor in the distal nephron. It causes a form of nephrogenic diabetes insipidus that is associated with polydipsia and polyuria. These events lower the extracellular fluid (ECF) volume and lower the GFR.

Hypercalcemia may lead to interstitial calcium phosphate crystal deposition in the kidney (i.e., nephrocalcinosis or interstitial nephritis) and nephrolithiasis with obstructive uropathy. Hypercalcemia may also lead to shortening of the QTc interval on the electrocardiogram. Frequently, however, asymptomatic hypercalcemia is discovered on routine laboratory testing.

Whether a person develops symptoms depends on several factors. One is the degree of hypercalcemia. People with serum calcium values above 13 mg/dL usually are symptomatic. The duration of hypercalcemia is also important. A gradual increase in serum calcium, even into the severe 15- to 17-mg/dL range, may cause few symptoms if it occurs slowly enough. The overall health status and age of the person with hypercalcemia influence the severity of symptoms. For example, a child with severe immobilization-induced hypercalcemia in the 15-mg/dL range may be completely alert, whereas an elderly person with underlying Alzheimer's disease and narcotic use may become comatose with a serum calcium level of 11.5 mg/dL.

Pathophysiology

The physiologic black box described in Chapter 72 should be considered when attempting to diagnose or treat hypercalcemia. These disorders can be grouped into factitious disorders (e.g., abnormalities in serum proteins), renal disorders (e.g., thiazide diuretics, lithium use), gastrointestinal disorders (e.g., sarcoid, milk-alkali syndrome), skeletal disorders (e.g., hypercalcemia of malignancy, immobilization hypercalcemia), and combined disorders. Primary HPT is a good example of the latter, with important gastrointestinal (GI) and renal components. The diagnoses in Table 73-1 should be considered with regard to the underlying pathophysiologic mechanism and the clinical setting.

Differential Diagnosis

Malignancy-Associated Hypercalcemia

The most common cause of hypercalcemia among hospitalized patients is cancer. Hypercalcemia occurs late in the course of cancer and usually progresses rapidly, followed by death. About 50% of patients with cancer survive 30 days after the development of hypercalcemia.

Hypercalcemia usually is encountered only in patients with large tumor burdens. Conversely, small, occult cancers rarely cause hypercalcemia. The exceptions to this rule are small neuroendocrine tumors, such as islet cell tumors and bronchial carcinoids. Certain tumors are common causes of hypercalcemia, including breast, renal, squamous, and ovarian carcinomas and multiple myeloma and lymphoma. Other common cancers, such as colon, prostate, and gastric carcinomas, are not commonly associated with hypercalcemia.

Cancer may lead to hypercalcemia through several mechanisms, the most common of which is humoral hypercalcemia of malignancy (HHM). HHM accounts for about 80% of patients with malignancy-associated hypercalcemia (MAHC) and is the result of excessive secretion by tumors of parathyroid hormone–related protein (PTHrP). PTHrP mimics the actions of parathyroid hormone (PTH) on the kidney to prevent calcium excretion