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Hypercalcemia: etiology and management

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INTRODUCTION

Hypercalcemia (defined as a serum calcium level >10.5 mg/dL or 2.5 mmol/L) is an important clinical problem [1]. Among the causes of hypercalcemia, primary hyperparathyroidism (PHPT) and malignancy are most common, accounting for 80–90% of cases. PHPT is the major cause of hypercalcemia in the ambulatory population, comprising up to 60% of cases, while malignancy represents the leading cause in hospitalized patients (54–65%) [2]. Hypercalcemia may occur in up to 30% of patients with cancer and portends a worse prognosis [3].

The clinical presentation of hypercalcemia is influenced by the rapidity of onset as well as severity. Symptoms are nonspecific and include fatigue, weakness, nausea, vomiting, abdominal pain, bone pain, polyuria and confusion, as well as coma in severe cases. Hypercalcemia may cause cardiac arrhythmias, renal vasoconstriction, volume depletion with acute kidney injury (AKI) and nephrogenic diabetes insipidus (NDI) [1, 4].

ETIOLOGIES AND PATHOPHYSIOLOGY

Common conditions associated with hypercalcemia can be categorized into those with elevated parathyroid harmone (PTH) levels and those with PTH levels that are appropriately suppressed [4]. PTH-dependent processes include PHPT caused by parathyroid gland adenoma or hyperplasia, rare cases of PTH-producing cancers and familial hypocalciuric hypercalcemia (FHH). PTH-independent mechanisms include most cases of malignancy-associated hypercalcemia (MAH), vitamin D intoxication, granulomatous diseases, vitamin A intoxication, thyrotoxicosis, milk-alkali syndrome and immobilization [5].

Causes of MAH can be classified into four groups: (1) overproduction of parathyroid hormone-related peptide (PTHrP) by tumor cells (humoral hypercalcemia of malignancy [HHM]), (2) excess conversion of vitamin D to active 1,25-dihydroxyvitamin D by lymphomas that leads to increased intestinal calcium absorption (absorptive hypercalcemia), (3) bone dissolution by metastasis or multiple myeloma through secretion of local PTHrP and other factors (local osteolysis) and (4) (rarely) excess PTH secretion by tumor cells (parathyroid carcinoma or ectopic PTH production) [3, 4].

EVALUATION

Evaluation of hypercalcemia begins with confirming the presence of an elevated calcium level. Total serum calcium concentrations in patients with low or high serum albumin levels may not reflect the amount of physiologically active ionized calcium. Therefore it is critical to correct serum calcium for the albumin level or measure ionized calcium [1, 5].

Once hypercalcemia is confirmed, workup includes a detailed history and review of medications, calcium and vitamin D supplementation, herbal preparations, dietary intake and prior calcium values. PHPT is suggested by long-standing hypercalcemia that is asymptomatic and mild (usually <12.0 mg/dL) [2, 5]. In MAH, the underlying cancer is often advanced at the time of presentation, and history and physical examination may lead to the correct diagnosis with limited laboratory evaluation [1, 3].

Laboratory assessment begins with measurement of intact PTH (iPTH) by immunoradiometric or immunochemoluminescent assay (Figure 1). An upper normal or elevated iPTH concentration is usually caused by PHPT, however, FHH should be considered. A low or low-normal iPTH level (<20 pg/mL) is consistent with a PTH-independent process [1]. Additional workup should assess for HHM, vitamin D excess and paraproteinemia.

MANAGEMENT

The approach to the management of hypercalcemia depends on the serum calcium level and the presence or absence of clinical manifestations. Most patients with mild hypercalcemia (<12.0 mg/dL) are asymptomatic and do not require acute treatment, however, confounding factors such as volume depletion and use of thiazide diuretics should be addressed. Patients with moderate elevations in serum calcium (12.0–14.0 mg/dL) may develop symptoms when levels rise rapidly; these symptomatic patients require immediate intervention. All patients with serum calcium >14.0 mg/dL require aggressive treatment [5].

Patients with acute hypercalcemia are often profoundly volume depleted from nausea and vomiting, coupled with polyuria caused by the effects of excess calcium on the kidney (impaired

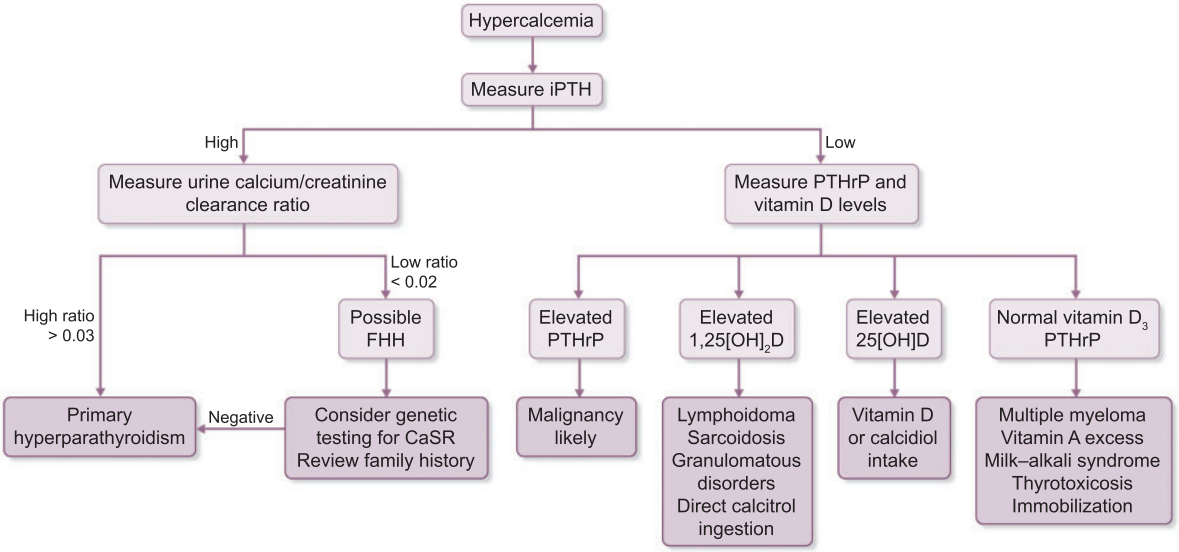

FIGURE 1: Diagnostic algorithm for the workup of hypercalcemia. The diagnostic workup for patients presenting with hypercalcemia rests on the measurement of PTH to divide patients into those with elevated versus suppressed PTH values. The urine calcium:creatinine clearance ratio (CCCR) should be derived from a 24-h urine collection. Of note, at a CCCR cutoff value of 0.0115, sensitivity for correct classification of FHH was 0.80 and specificity was 0.88, thus misclassifying 20% of patients with FHH and 12% of primary hyperparathyroid patients [6]. Further, testing and family history should be used to conclusively diagnose FHH. CaSR, calcium-sensing receptor. Adapted with permission from Reagan *et al.* [4].

urinary concentrating ability and NDI) [1]. The first step in treatment is to restore extracellular volume with intravenous fluids. A typical regimen is a 1- to 2-L bolus of 0.9% saline solution followed by 200–250 mL/h, with frequent monitoring of calcium and vigilance for volume overload. In the presence of NDI, hypernatremia may result with 0.9% saline solution infusions and hypotonic fluids may be required [4].

Loop diuretics have been employed in the treatment of hypercalcemia in an attempt to augment calciuresis, despite little evidence to support this practice. Use should be restricted to patients who develop fluid overload while receiving volume resuscitation [7].

High-potency bisphosphonates are considered first-line therapy for MAH that reduce bone resorption by inhibiting recruitment, activity, adhesion and survival of osteoclasts [3–4]. In the USA, only pamidronate and zoledronate are approved by the Food and Drug Administration for treatment of MAH. Because response typically requires 2–4 days, therapy should be initiated as soon as hypercalcemia is discovered [3].

Bisphosphonates are generally well tolerated. Their most common side effect is self-limited infusion-related fever. Hypocalcemia and hypophosphatemia have also been described. Osteonecrosis of the jaw, a rare but serious toxicity, has been reported with repeated high doses. Both pamidronate (primarily) and zoledronate (only rarely) have been associated with nephrotic-range proteinuria, and zoledronate has been linked to acute tubular necrosis [4]. American Society of Clinical Oncology guidelines recommend that zoledronate be avoided in patients with creatinine clearance <30 mL/min [8]. Kidney function and urine protein excretion should be monitored in those receiving prolonged treatment.

Calcitonin transiently reduces serum calcium levels and may serve as an adjunctive agent in the initial phase of treatment when combined with a bisphosphonate and intravenous fluids. However, the overall efficacy is modest and its duration of effect is limited due to tachyphylaxis [1].

Denosumab, a human monoclonal antibody directed against receptor activator of nuclear factor κB ligand, targets osteoclast-induced bone resorption and has been shown to be effective for MAH refractory to bisphosphonates [9]. Adverse effects include osteonecrosis of the jaw and hypocalcemia, which may be severe [10]. Denosumab does not require changes in dosing with decreased kidney function.

Corticosteroids inhibit the activity of 1α-hydroxylase and are effective in managing hypercalcemia caused by malignancies and granulomatous diseases that produce calcitriol [1].

In patients with acute hypercalcemia and significant AKI (especially in the setting of oliguria), saline-induced calciuresis may not be feasible and may produce volume overload. In these cases, hemodialysis using a very-low-calcium dialysate ($\leq$1 mmol/L) may be considered [1].

CONFLICT OF INTEREST STATEMENT

None declared. This article has not been previously published nor is it under consideration for publication with any other journal.

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