A SELF-TEST OF CLINICAL RECOGNITION

CME CREDIT

WIAM I. HUSSEIN, MD
Department of Endocrinology, Cleveland Clinic

ANGELO A. LICATA, MD, PHD
Head, Calcium and Metabolic Bone Osteoporosis Section, Department of Endocrinology, Cleveland Clinic

# Asymptomatic hypercalcemia in a 51-year-old woman

A 51-YEAR-OLD white woman has a serum calcium level of 11.6 mg/dL (normal range: 8.5–10.5) on a routine blood chemistry test; TABLE 1 shows her other laboratory values. She had normal calcium levels 2 years ago, when she suffered a kidney stone.

The patient says she experiences arthralgia, which she attributes to aging, but she denies having fractures, constipation, polyuria, or weakness. No one in her family has ever had hypercalcemia or kidney stones. She takes atenolol 50 mg daily for hypertension, cimetidine for dyspepsia, and estrogen as postmenopausal hormone replacement therapy.

A physical examination is normal. Her pulse is 78 per minute and regular, and her blood pressure is 134/70 mm Hg.

TABLE 1

**Laboratory studies on admission**

| STUDY | RESULT | NORMAL RANGE |
|---|---|---|
| Total calcium | 11.6 mg/dL | (8.5–10.5) |
| Total protein | 6.5 g/dL | (6.0–8.4) |
| Albumin | 4.3 g/dL | (3.5–5.0) |
| Phosphorus | 1.8 mg/dL | (2.5–4.5) |
| Magnesium | 1.9 mg/dL | (1.6–2.4) |
| Blood urea nitrogen | 20 mg/dL | (10–25) |
| Creatinine | 0.8 mg/dL | (0.7–1.4) |
| Chloride | 110 mmol/L | (98–110) |
| Carbon dioxide | 23 mmol/L | (24–32) |
| Intact parathyroid hormone | 95 pg/mL | (10–60) |

## CAUSES OF HYPERCALCEMIA

**1** What is the most likely cause of this patient's hypercalcemia?

- ❑ Humoral hypercalcemia of malignancy
- ❑ Familial hypocalciuric hypercalcemia
- ❑ Primary hyperparathyroidism
- ❑ Drug-induced hypercalcemia

All of these choices are well-recognized causes of hypercalcemia, but primary hyperparathyroidism is the most likely cause in this case.

**Primary hyperparathyroidism** accounts for more than 70% of cases of asymptomatic hypercalcemia in ambulatory patients. The incidence is one case per 800 persons per year. It is most common in the fifth and sixth decades, and three times more common in women than in men.

Primary hyperparathyroidism is mainly a biochemical diagnosis, because it causes no symptoms in more than 50% of cases. In the days before routine calcium determinations by automatic analyzing machines, this condition was thought to be rare, and was discovered only after it progressed to severe hypercalcemia and bone disease (osteitis fibrosa cystica). Usually, there are no findings on examination that are diagnostic.

The serum calcium level is generally mildly elevated (< 12.0 mg/dL), but can be much higher. The serum phosphorus level is low. The level of intact parathyroid hormone (PTH) is elevated in 90% of cases, but is inap-

propriately normal in the rest. (In a normal parathyroid gland, PTH secretion is suppressed and unmeasurable when calcium rises to the high end of the normal range.) Mild hyperchloremia with metabolic acidosis is common.

**Humoral hypercalcemia of malignancy** accounts for more than 50% of cases of hypercalcemia in hospitalized patients. The most common malignant diseases that cause hypercalcemia are lung cancer, breast cancer, myeloma, lymphoma, and renal cell carcinoma. Most of these tumors increase the calcium level by secreting PTH-related peptide, others secrete lymphotoxins and interleukin-1, and certain lymphomas produce an excess of 1,25 vitamin D.

Nothing in our patient's history, physical examination, or laboratory data suggests an underlying malignant condition. In most cases the malignant disease is already advanced by the time the hypercalcemia is found; hypercalcemia precedes the diagnosis of malignancy in fewer than 20% of cases. Intact PTH is usually suppressed. Of note: the new immunoradiometric assay of the entire PTH molecule is the best assay to use to measure intact PTH, since it is not affected by metabolic fragments of PTH (which may be increased in renal dysfunction) and does not cross-react with PTH-related peptide.

**PTH is high in primary hyperparathyroidism, but low in hypercalcemia of malignancy**

**Familial hypocalciuric hypercalcemia** is caused by decreased renal clearance of calcium. It is a benign autosomal dominant condition that occurs at an early age, without symptoms, signs, or complications of hypercalcemia. There may be a family history of hypercalcemia. Patients have normal or mildly elevated intact PTH levels, mild hypermagnesemia, and normal serum phosphorus levels.

One way to distinguish familial hypocalciuric hypercalcemia from primary hyperparathyroidism is to measure the concentrations of calcium and creatinine in a sample of urine and blood, and from these values calculate the fractional excretion of calcium: (urine calcium concentration x serum creatinine concentration) / (urine creatinine concentration x serum calcium concentration). In familial hypocalciuric hypercalcemia, the fractional excretion of calcium is very low (ie, < 0.01); in contrast, patients with primary hyperparathyroidism usually have a value greater than 0.02.

No treatment is required for familial hypocalciuric hypercalcemia, and parathyroidectomy does not reverse the hypercalcemia.

**Drug-induced hypercalcemia** can be asymptomatic. Several drugs and vitamins can cause hypercalcemia, including:

- Estrogen and antiestrogen (tamoxifen), in patients with bone metastases due to breast cancer. An "estrogen flare" may happen in one third of patients with breast cancer and skeletal metastases.
- Lithium
- Theophylline
- Thiazide diuretics
- Vitamin A
- Vitamin D

Some of these drugs increase serum calcium by increasing bone resorption, renal calcium reabsorption, or gut absorption; however, the exact mechanisms are not fully understood for all of them. A history of the medications and vitamins that the patient is taking should be an essential part of the evaluation.

## CAUSES OF PRIMARY HYPERPARATHYROIDISM

**2** What is the most likely cause of primary hyperparathyroidism?

- ❑ Solitary parathyroid adenoma
- ❑ Generalized hyperplasia of all parathyroid glands
- ❑ Multiple parathyroid adenomas
- ❑ Parathyroid carcinoma

**Solitary benign parathyroid adenomas** account for 80% to 85% of cases of primary hyperparathyroidism. Removing the adenoma produces a long-term remission in nearly all patients. The recurrence rate of new adenomas is 0.6% at 8 to 10 years.

**Diffuse hyperplasia of all parathyroid glands** is less common, occurring in only 15% of patients with primary hyperparathyroidism. This condition can occur sporadically or as

part of the syndrome of multiple endocrine neoplasia (MEN), either type 1 (Wermer syndrome, with tumors of the pituitary gland, parathyroid gland, and pancreas) or type 2a (Sipple syndrome, with medullary thyroid carcinoma, pheochromocytoma, and hyperparathyroidism). MEN syndrome is found in about half of cases of diffuse hyperplasia. Treatment consists of removal of all glands except for remnant parathyroid tissue left in situ or autotransplanted in the nondominant forearm.

**Multiple parathyroid adenomas** are found in only 1% to 2% of all cases of primary hyperparathyroidism. These can be sporadic or, rarely, part of familial syndromes.

**Parathyroid carcinoma** is very rare, occurring in fewer than 0.5% of patients. The average serum calcium level in patients with parathyroid carcinoma is 14 mg/dL, with marked elevations in intact PTH levels. Parathyroid carcinoma may be very difficult to diagnose histologically unless it invades the capsule or lymph nodes. The cancer may also be detected when hypercalcemia recurs after apparently successful surgery. Aggressive surgical resection of the tumor and lymph nodes is important to maximize survival.

## SURGERY FOR PRIMARY HYPERPARATHYROIDISM

**3** Which of the following is an indication for surgery in primary hyperparathyroidism?

- ❑ Urinary calcium excretion > 400 mg/day
- ❑ Osteoporosis
- ❑ Serum calcium level > 1 mg above the upper limit of normal
- ❑ Symptomatic hypercalcemia
- ❑ All of these are indications for surgery.

Surgery cures primary hyperparathyroidism, but not all patients require surgery. Patients with nephrolithiasis, nephrocalcinosis, bone disease, or neuromuscular disease should have surgery to reduce their symptoms. However, most patients with primary hyperparathyroidism have no symptoms—and there are no indices that can predict who will develop complications from the disease. To address this issue, the National Institutes of Health convened a consensus committee in 1991 to draft a set of guidelines (TABLE 2). However, the committee emphasized that these recommendations are not exact, and that clinicians should use their own judgment.

**Surgery cures hyperparathyroidism, but not all patients require surgery**

Our patient underwent surgery, and a large adenoma was found. Afterward, her serum calcium level returned to the normal range, and, as expected, her energy improved and her arthralgia decreased.

### Imaging studies of the parathyroid glands

Most experienced surgeons can find the adenoma in 90% to 95% of patients, without preoperative imaging studies to locate it. However, patients undergoing a repeat operation for recurrence or unsuccessful surgery should have imaging studies, because the previous surgery will have distorted the anatomy.

Radioisotopic scanning with thallium-technetium or technetium-sestamibi is nonin-

**TABLE 2**

**Indications for surgery for primary hyperparathyroidism**

Serum calcium level ≥ 1 mg/dL above upper limit of normal (ie, ≥ 11.5 mg/dL, depending on the laboratory)

Marked hypercalciuria (> 400 mg/day)

Any overt manifestation of primary hyperparathyroidism
- Classic neuromuscular disease
- Nephrocalcinosis
- Nephrolithiasis
- Osteitis fibrosa cystica

Cortical bone density in the distal radius < 2 standard deviations below age- and sex-matched control values (radial Z score < –2 SD)

Reduced creatinine clearance in the absence of other cause

Age < 50 years

SOURCE: ADAPTED FROM CONSENSUS DEVELOPMENT CONFERENCE PANEL. DIAGNOSIS AND MANAGEMENT OF ASYMPTOMATIC PRIMARY HYPERPARATHYROIDISM: CONSENSUS DEVELOPMENT CONFERENCE STATEMENT. ANN INTERN MED 1991; 114:593–597

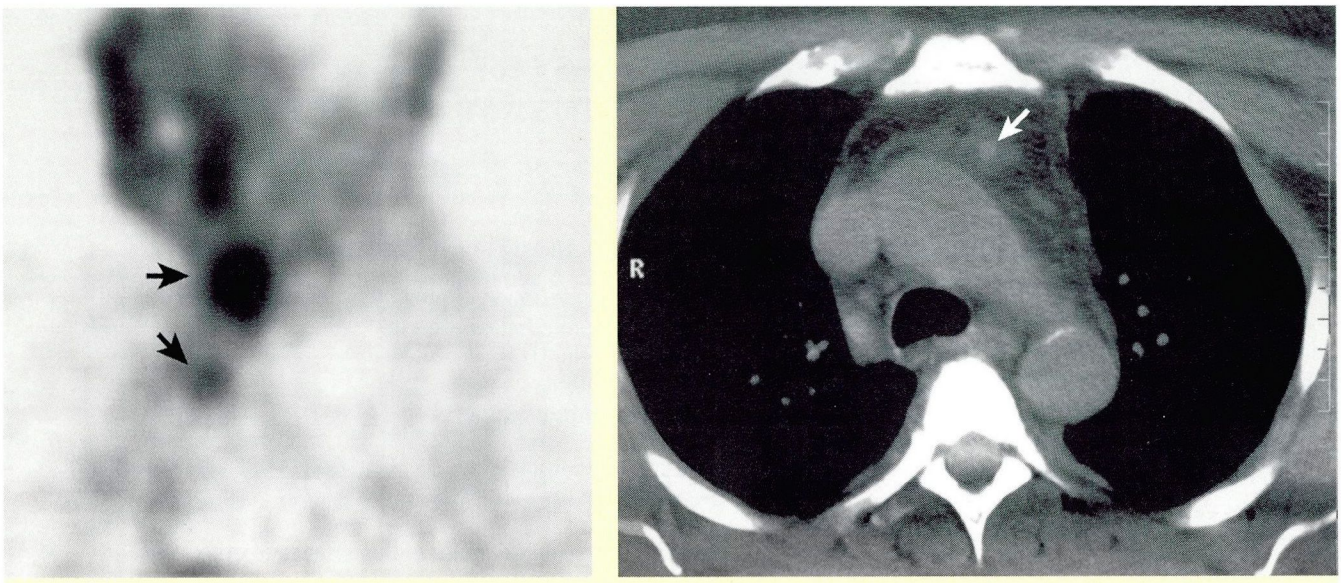


**FIGURE 1.** Left, sestamibi scan of the neck and chest, sagittal view. Top arrow points to the thyroid gland, bottom arrow points to an ectopic parathyroid adenoma behind the sternum. Right, computed tomographic scan showing the ectopic parathyroid adenoma (arrow) in the same patient.

SOURCE: SCANS COURTESY OF DONALD NEUMANN, MD.

vasive, but is available in few institutions and requires experienced personnel to perform. Ultrasonography, magnetic resonance imaging, and computed tomography can be of value, but the sensitivity of these procedures is only about 60% to 75%. Ultrasonography and radioisotopic scanning are best for parathyroid tissue located proximal to the thyroid gland, whereas computed tomography and magnetic resonance imaging are better for ectopic parathyroid glands (FIGURE 1).

### Postoperative care

After surgery, patients may experience a brief period of transient hypocalcemia, during which normal but suppressed parathyroid glands regain their sensitivity to calcium. Permanent complications of surgery are rare. Hypoparathyroidism may appear even years after the surgery. Recurrent laryngeal nerve damage may cause hoarseness and reduced voice volume.

## SUGGESTED READING

**Bilezikian JP.** Primary hyperparathyroidism. In: Favus MJ, Christakos S, editors. Primer on the metabolic bone diseases and disorders of mineral metabolism, 3rd ed. Philadelphia: Lippincott-Raven 1996:181–186.

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***ADDRESS:*** *Angelo A. Licata, MD, PhD, Department of Endocrinology, A30, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.*