Bones, Moans and Groans

Diagnosing and Treating Primary Hyperparathyroidism

By M. Usman Chaudhry, MD

Endocrine evaluation was sought for a 52-year-old married post-menopausal legal secretary, for hypercalcemia discovered in an osteoporosis clinic. She had noticed fatigue, lethargy, and malaise for a year and had been on antidepressant therapy for the same duration of time. She had a partial hysterectomy at age 42 and was maintained on estrogen replacement therapy. She never sustained an episode of nephrolithiasis or bone fracture. She was a nonsmoker.

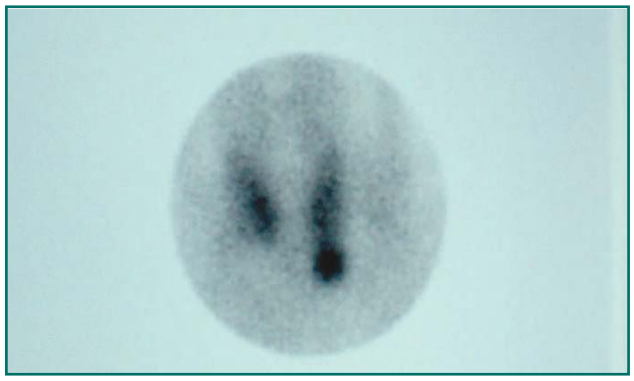

Figure 1. Anterior image of neck of the patient with primary hyperparathyroidism obtained with technetium-99m sestamibi, showing a parathyroid adenoma in near left lower pole of thyroid.

Table 1

Laboratory parameters

- Her bone density had osteopenic T-Scores of -2.3 at lumbar spine, and -1.9 at femoral neck.
- Serum total calcium (with normal albumin) was 2.71 mmol/L (normal < 2.60 mmol/L).
- Phosphate level was 0.83 mmol/L (normal 0.65-1.60 mmol/L).
- Inappropriately high parathyroid hormone (PTH) 11.4 pmol/L (normal < 7.6), normal serum creatinine, but high 24 hour urine calcium of 12.1 mmol (normal < 7.50mmol/24-hr).
- Repeat labs confirmed persistent hypercalcemia (2.66 mmol/L) with a high PTH level (12.5 pmol/L) and a low phosphate level of 0.49 mmol/L.
- She was biochemically euthyroid. 24-hour studies for fractionated catecholamines and metanephrines were insignificant for pheochromocytoma. Imaging with 99Tc-labeled Sestamibi displayed an area of increased focal uptake despite subtraction images, adjacent to lower pole of left thyroid lobe, consistent with parathyroid adenoma (Figures 1 and 2).

Figure 2. Subtraction images showing persistent sestamibi tracer after washout depicting left lower parathyroid adenoma.

A physical examination revealed supine blood pressure of 170/90 mmHg (not known to be hypertensive), and no palpable neck masses or thyromegaly. She had no kyphosis, spinal tenderness, or café au lait skin spots. The remainder of the examination was unremarkable.

Primary hyperparathyroidism is an abnormality of the parathyroid glands that causes inappropriate parathyroid hormone (PTH) secretion, with resultant hypercalcemia. Primary hyperparathyroidism is the most common cause of hypercalcemia in the outpatient population. The increase in identified cases of primary hyperparathyroidism is largely attributed to the use of automated blood testing, which detects hypercalcemia in asymptomatic patients.

Secondary hyperparathyroidism is an appropriate increase in PTH secretion in response to hypocalcemia.[1] Solitary parathyroid adenomas account for 85% of cases of primary hyperparathyroidism. Hyperfunction in multiple parathyroid glands (a broad category that includes hyperplasia, multiple adenomas, and polyclonal hyperfunction) occurs in most of the remaining casees, while a few patients (< 1%) have parathyroid carcinoma. Approximately 75% of patients with sporadic primary hyperparathyroidism are women with the average age at diagnosis being 55 years.[2] Among the minority of patients with primary hyperparathyroidism caused by hyperfunction of multiple parathyroid glands, the disorder is inherited. Parathyroid tumours may occur either sporadically, or as part of inherited syndromes, such as multiple endocrine neoplasia (MEN) type 2A and familial hypocalciuric hypercalcemia.[3]

About 75% of patients with sporadic primary hyperparathyroidism are women.

Patients with multiple endocrine neoplasia type 1 have various combinations of parathyroid, enteropancreatic, anterior pituitary, and other tumours.[4] Multiple endocrine neoplasia type 2A is characterised primarily by medullary thyroid carcinoma, pheochromocytoma and hyperparathyroidism. Familial hypocalciuric (or

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benign) hypercalcemia is characterised by long-term hypercalcemia with normal urinary calcium excretion. A very rare presentation of primary hyperparathyroidism is parathyroid carcinoma occurring in less than 0.5% of patients with hyperparathyroidism.[5,6]

The classic initial presentation of "bones, moans and groans" has evolved to an asymptomatic picture for primary hyperparathyroidism, as it is now detected early. Usual features of severe disease may vary. Skeletal involvement due to increased osteoclastic bone resorption causes hypercalcemia, subperiosteal resorption of the distal phalanges, ground glass appearance of skull, brown tumours of the long bones, and osteopenia. Renal manifestations include nephrolithiasis, nephrocalcinosis, hypercalciuria, and polyuria. Gastrointestinal symptoms are anorexia, nausea, vomiting, constipation, peptic ulceration, and abdominal pain. Patients may experience a variety of neuropsychiatric symptoms ranging from weakness, fatigue, apathy to depression and psychosis. Some patients also have hypertension.[7] In most patients, primary hyperparathyroidism progresses slowly, if at all. Among asymptomatic patients, only about 25% have progressive disease, which is usually manifested as a decrease in bone mass during a ten-year period of followup.[8]

In addition to a thorough history and physical examination during clinical assessment, additional tests include serum calcium, albumin, serum intact PTH, phosphate, 24-hour urine calcium, creatinine clearance, and bone mineral density with attention to distal radius apart from lumbar spine and hip area.

Practice Pointer

In addition to a thorough history and physical examination, additional tests include:

- serum calcium
- albumin
- serum intact PTH
- phosphate
- 24-hour urine calcium
- creatinine clearance
- bone mineral density

If indicated by history and physical examination, evaluation for other endocrine disorders associated with MEN may be necessary.

Treatment is primarily surgical. A consensus conference of the National Institutes of Health concluded in 1990 that surgery was not routinely needed in asymptomatic patients 50 years old or older who had a serum calcium concentration 0.25 mmol/L to 0.40 mmol/L above the upper limit of normal, a level of urinary calcium excretion of < 10 mmol/L per day, a creatinine clearance of at least 70% of normal, or a Z-score (not T-score) higher than –2 for bone mass.[8]

Case Resolution

Patient underwent a successful surgical resection with transient postoperative hungry bone syndrome. She eventually had resolution of her biochemical abnormalities of hypercalcemia and elevated PTH levels. She continues to do well with no hypertension or recurrence of her symptoms.

According to a new consensus conference panel, the criteria for surgery have been revised for asymptomatic patients with primary hyperparathyroidism. It includes the following revised recommendations: Total corrected serum calcium 0.25 mmol/L above the upper limits of normal bone density at the lumbar spine, hip, or distal radius that is more than 2.5 SD below peak bone mass (T-score <-2.5, instead of Z-score, as in prior recommendations). The rest of the previous recommendations remain unchanged. The Panel concurred with the previous recommendations that for asymptomatic primary hyperparathyroidism, there are no medical therapies for which data are convincing regarding either efficacy or safety. The greatest challenge in preoperative localization of the parathyroid adenoma is locating an experienced parathyroid surgeon. The standard operation for parathyroidectomy is full exploration of the neck with identification of all four parathyroid glands. The rationale for identifying all four glands is that in 15% to 20% of patients with sporadic primary hyperparathyroidism, enlargement of more than one gland will be discovered.[9] One of the most promising minimally invasive procedures is minimally invasive parathyroidectomy. It is performed with preoperative localization using 99Tc-labeled Sestamibi-SPECT (single photon emission computed tomography) imaging. The sensitivity of parathyroid scintigraphy varies 78% to 80% with specificity of 98%.[10,11] This technique is particularly helpful for accurate localization of parathyroid adenoma before attempting re-exploration neck surgery for an initial failed procedure. If surgery is not selected as the primary modality, there is no specific medical therapy. Estrogens have been shown to ameliorate bone loss. New therapies involving oral bisphosphonates show promising results in prevention of bone loss with primary hyperparathyroidism.[12] CME

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