

Hyperparathyroidism

High calcium and vitamin D₃ raise suspicions

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Presentation

History

- breast cancer at age 41, treated with mastectomy and radiation
- hypertension, dyslipidemia
- coronary artery disease with angioplasty
- medications: hydrochlorothiazide (HCTZ) 25 mg, weekly alendronate 70 mg

Physical examination

- cardiac exam: normal
- respiration: normal
- abdomen: unremarkable
- head and neck: no cervical lymphadenopathy, thyroid enlargement, or other palpable neck masses
- slight dorsal kyphosis
- thoracic and lumbar spine palpation: no tenderness

Investigations

- total serum calcium: 2.57 mmol/L (normal range 2.20-2.65)
- albumin: 44 g/L
- ionized calcium: 1.44 mmol/L (1.15-1.35 mmol/L)
- PTH: 17.1 pmol/L (1.6-6.9)
- 1,25-dihydroxyvitamin D: 119 pmol/L (30-120)

MRS. O.S., 63 YEARS OLD, is referred for assessment due to elevated levels of parathyroid hormone (PTH). She had presented with osteopenia — T-score of -2.0 at the lumbar spine and hip. She reports one fragility fracture of her clavicle at the age of 60 and has sustained a 5-cm height loss over the past several years. There's no history of nephrolithiasis. Mrs. O.S. was menopausal at age 50 and didn't take hormone replacements. She's a past smoker, with minimal alcohol intake. Her diet doesn't include much calcium.

- 25-hydroxyvitamin D: 38 nmol/L (25-100)
- serum protein electrophoresis: normal
- serum creatinine: 58 μmol/L
- 24-hour urine calcium: 3.26 mmol (2.5-8.0)
- 24-hour urine creatinine clearance: 7.0 mmol (5.2-14.1)
- calcium/creatinine ratio: 0.0105

Diagnosis and treatment

Repeat investigations after stopping HCTZ confirmed the diagnosis of primary hyperparathyroidism (PHPT). Serum creatinine indicated well-preserved kidney function, while the serum protein electrophoresis ruled out a myeloproliferative disorder as a cause of hypercalcemia. The relative vitamin D inadequacy and the HCTZ use may have contributed to the elevated PTH. The patient was referred to an experienced head and neck surgeon for a parathyroidectomy. A single parathyroid adenoma was removed.

Making the case

PHPT may present as an incidental finding on routine blood work or in the workup for osteoporosis. Serum calcium (total or ionized) is elevated, with a concomitant high or inappropriately normal PTH level. Most patients are asymptomatic. There may be fatigue, mental clouding and arthralgias with vague bony discomfort.

Symptomatic PHPT can present with serum calcium elevations 0.25 mmol/L > normal, osteoporosis, fragility fractures, nephrolithiasis or renal insufficiency. Uncommonly, PHPT may present as an acute hypercalcemic crisis, with severe hypercalcemia, volume contraction and hypotension. Nausea, vomiting, abdominal pain, decreased consciousness, neuromuscular dysfunction or cardiac arrhythmias can be present.

The routine measurement of serum calcium has led to a marked increase in the detection of primary hyperparathyroidism. There are 10-40 cases per 100,000. Most are women, found as a result of bone mineral density (BMD) assessments after menopause.

Investigations and diagnosis

Lab tests showing elevations in PTH and serum calcium should be repeated prior to confirming the diagnosis. Secondary hyperparathyroidism ought to be excluded as well — 25-hydroxyvitamin D levels should be checked, as vitamin D deficiency ($< 25 \text{ nmol/L}$) or insufficiency ($< 75 \text{ nmol/L}$) are common causes for elevated PTH.

If vitamin D and urine calcium levels are persistently low despite adequate supplementation, suspect impaired gut absorption, and consider a celiac panel. Serum creatinine can indicate underlying renal disease with impaired conversion of calcidiol to the active form of calcitriol. A 24-hr urine collection for creatinine and calcium will exclude familial hypocalciuric hypercalcemia (FHH), where the calcium/creatinine clearance ratio is < 0.01 . In such patients, parathyroidectomy should not be performed. Other lab abnormalities associated with PHPT might include hypophosphatemia and an elevated alkaline phosphatase indicating increased bone turnover.

Management

Surgical: The cure for PHPT is parathyroidectomy. The Canadian standards and guidelines of 2003 outline criteria for surgical intervention:¹

- serum calcium $> 0.25 \text{ mmol/L}$ above normal
- 24-hr urine calcium $> 10 \text{ mmol/day}$
- creatinine clearance reduced by 30%

- BMD with a T-score < -2.5 at any site (lumbar spine, hip or 1/3 radius)
- age < 50

Medical: Asymptomatic individuals with mild hypercalcemia, with relatively well-maintained skeletal and renal status, or with general contraindications to surgery, can be successfully treated with medical management alone. Long-term data has shown mild PHPT to be stable without surgery, while the fracture risk for those with mild PHPT is still unknown.² The recommended follow-up in the absence of surgery is:

- serum calcium levels — every 6 months
- 24-hour urine calcium, 24-hour creatinine clearance, serum creatinine, BMD — annually

Hormone replacement therapy maintains BMD in postmenopausal women with PHPT. Alendronate, a bisphosphonate, has been shown to effectively prevent bone loss and to decrease bone turnover in PHPT.³ The selective estrogen receptor modulator raloxifene may also preserve skeletal status and is a good choice for patients with contraindications to bisphosphonate therapy or risk factors for breast cancer.⁴ Calcimimetic agents, such as cinacalcet (not yet approved in Canada), stimulate the calcium sensing receptor in the parathyroid glands and decrease PTH synthesis and release. Dietary calcium and vitamin D intake should be moderate; as an increased intake may exacerbate hypercalcemia, while an inadequate intake may further stimulate PTH secretion. Patients should avoid thiazide diuretics and lithium carbonate, which can elevate serum calcium. Lastly, encourage physical activity and adequate hydration to maintain BMD. **PE**

References:

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4. Vestergaard P. *Drugs* 2006;66(17):2189-211.

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