APMB - Atti della Accademia Peloritana dei Pericolanti
Classe di Scienze Medico Biologiche
Vol. 107(1) 2019

ISSN 1828-6550

DOI: 10.6092 / 1828-6550 / APMB.107.1.2019.CCS5

Clinical Case Seminar CCS 5(1-6)

Primary Hyperparathyroidism: lessons from two cases.

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Abstract

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia and is characterized by hypercalcemia and levels of parathyroid hormone (PTH) that are inappropriately high for the hypercalcemic state. The clinical presentation of PHPT has evolved over the past 40 years to include three distinct clinical phenotypes: the classical symptomatic disorder, the asymptomatic disorder and the normocalcemic disorder (1).

Key-Words: Primary hyperparathyroidism;
hypercalcemia; normocalcemic hyperparathyroidism.

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Introduction

In PHPT serum calcium levels are elevated in the context of non suppressed parathyroid hormone levels. Approximately 80% of patients with PHPT have a single parathyroid adenoma, 10% have more than one adenoma, and less than 10% have hyperplasia of all four gland. Parathyroid carcinoma causes less than 1% of cases of hyperparathyroidism (1). Patients with mild hyperparathyroidism are at increased risk for renal stones, cortical bone loss, and fractures. Evaluation should include measures of serum calcium, intact parathyroid hormone, 25-hydroxyvitamin D, glomerular filtration rate, 24-hour urine calcium excretion, and bone density (including the distal third of the radius), as well as a renal ultrasound examination to detect stones (2).

Clinical Case 1

A 56-year-old woman had a fasting serum calcium level of 11.4 mg /dl (reference range 8.4 to 10.2), the serum phosphorus level is 2.0 mg/dl and the parathyroid hormone (PTH) level is 98 pg/ml (reference range 11 to 67). She presented normal renal function and BMD with vertebral T-score of –1.6. A diagnosis of Asymptomatic Primary Hyperparathyroidism was made. To localize abnormal parathyroid tissue, neck ultrasound was negative and technetium-99m sestamibi scanning shows a left paratracheal ectopic parathyroid adenoma confirmed by CT imaging. (Fig 1).

ISSN 1828-6550
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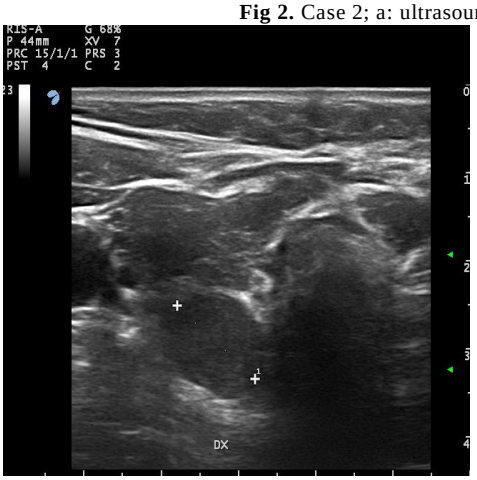
After six months the serum Ca was 11.2, P 2.0 and PTH 102, and Cinacalcet therapy, at dose of 15 mg/day, was started. After two years the serum Ca was 10.1 and PTH 65 pg/dl, but vertebral BMD worsened (T-score – 2.5) and Alendronate 70 mg/weekly was added to Cinacalcet.

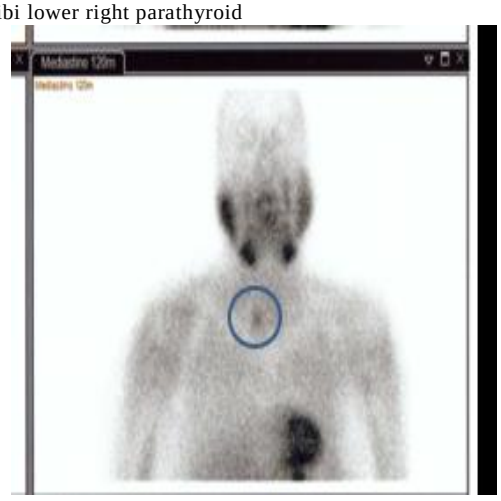
Fig 1. Case 1: Ectopic left paratracheal parathyroid

Clinical Case 2

In a 68-year-old man with serum calcium level of 14.1 mg/dl and PTH level of 132 pg/ml was made a diagnosis of Primary Hyperparathyroidism by Adenoma of parathyroid lower right confirmed at ultrasound, sestamibi-scanning and CT imaging; Fig 2. He was operated and two months after surgery his serum Ca was 10 mg/dl and PTH level 65 pg/ml. After eight months serum calcium was 12.5 mg/dl and PTH level 57 pg/ml with hypercalciuria (>400 mg/day) and a Persistent or Recurrent Primary Hyperparathyroidism was diagnosed, without any hyperplasia parathyroid imaging.

Fig 2. Case 2; a: ultrasound and b: sestamibi lower right parathyroid





Discussion

Surgery remains the only definitive treatment for hyperparathyroidism. Guidelines from the 4th International Workshop (3) recommend surgery for patients younger than 50 years of age

ISSN 1828-6550
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and for patients with clinically significant hypercalcemia (>1 mg/dl above normal), osteoporosis (T-score -2.5) or a fragility fracture, renal calculi, hypercalciuria (especially with a lithogenic urine biochemical profile), or impaired renal function (creatinine clearance <60 ml/min); Tab. 1.

In a 15-year retrospective study, patients who received a surgical cure had a 10-year absolute risk of hip fracture that was 64% lower than that among patients who had not received any treatment (4). Randomized, controlled trials have not consistently

shown alleviation of PHPT- related neurocognitive and emotional symptoms after surgical cure (5). Similarly, whether surgery reduces the cardiovascular disease risk associated with hyperparathyroidism remains unclear.

Like clinical case 1, for patients who decline or are not candidates for surgery, medical therapies have been used to address hypercalcemia, bone disease and hypercalciuria in hyperparathyroidism; Tab. 2. Deficiencies in vitamin D and dietary calcium worsen hyperparathyroidism, so patients should have a calcium-sufficient diet and maintain a serum 25-hydroxyvitamin D level in the range of 20 to 30 ng/ml (6). Cinacalcet is an activator of the of the calcium sensing receptor and in hyperparathyroidism sensitizes that receptor to serum calcium which, when activated, suppresses the secretion of PTH. In a descriptive, prospective, observational study in hospital and specialist care centers, reductions in calcium levels of >1 mg/dl was observed in 60% of patients 12 months after initiation of cinacalcet, without notable safety concerns (7), but cinacalcet had no significant effect on bone loss like in clinical case 1. The bisphosphonate, alendronate, improves the lumbar spine BMD without any changes in the serum calcium (8). Very recently, denosumab has been evaluated in women with PHPT and after 2 years showed increases in BMD at lumbar spine, total hip and femoral neck (9)

Table 1. Indications for surgery in asymptomatic primary hyperparathyroidism

age	<50 years
Serum calcium	>1 mg/dl above upper limit of normal
Skeletal manifestations	Reduced BMD to a score of -2.5 at any site
Renal manifestations	Creatinine clearance <60 ml/min Kidney stone or nephrocalcinosis Hypercalciuria >400 mg/day

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Table 2. Response to medication in patients with PHPT

Drug	Serum calcium level	Serum PTH level	Urinary calcium excretion	BMD
HCTZ	No change	No change	Decreases	No data
Oestrogen	No change	No change	No change	Increases
Raloxifene	Decreases**	No change	No change	No data
Alendronate	No change	No change	No change	Increases
Cinacalcet	Decreases	Minimal decrease	No change	No change

In the clinical case 2, the serum calcium returned high after 10 months of surgery with PTH level non suppressed and without any enlarged parathyroid imaging.

Persistent primary hyperparathyroidism is when the calcium and PTH levels do not return to normal levels after the operation or became abnormal again within 6 months of the operation. Persistent primary hyperparathyroidism usually happens because not all of the abnormal parathyroid tissue was removed at the first operation. This can happen if an inexperienced surgeon "misses" the diseased gland or if there is an ectopic gland located in a difficult to find location or if the patient has multiple abnormal glands. Recurrent primary hyperparathyroidism is when the calcium and PTH levels initially are normal but after 6 months again become abnormal. Recurrent hyperparathyroidism usually happens when one or more of the remaining glands becomes hyperactive. This is a new problem and does not reflect a "missed gland" at the first operation (10). Although parathyroid imaging is not necessary to establish a diagnosis of primary hyperparathyroidism, four preoperative imaging methods are routinely used to localize abnormal parathyroid (11-13); Fig 3 and Table 3.

Surgical treatment of hyperparathyroidism should incorporate intraoperative PTH measurements where available. After removal of a single adenoma, the intraoperative PTH should decrease by at least 50% and into the normal range. Intraoperative measurements of PTH are particularly valuable when more than one gland is abnormal (14).

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Fig. 3. Parathyroid Imaging. Panel A shows a longitudinal ultrasonographic image of the right parathyroid. Panel B shows a delayed-phase planar sestamibi scan indicating a marked uptake at the level of the right thyroid lobe. In Panel C, a delayed-phase sestamibi scan shows a marked uptake at the level of the middle mediastinum (arrow). In Panel D, a magnetic resonance imaging scan of the chest shows a lesion in the aortopulmonary window (arrow)

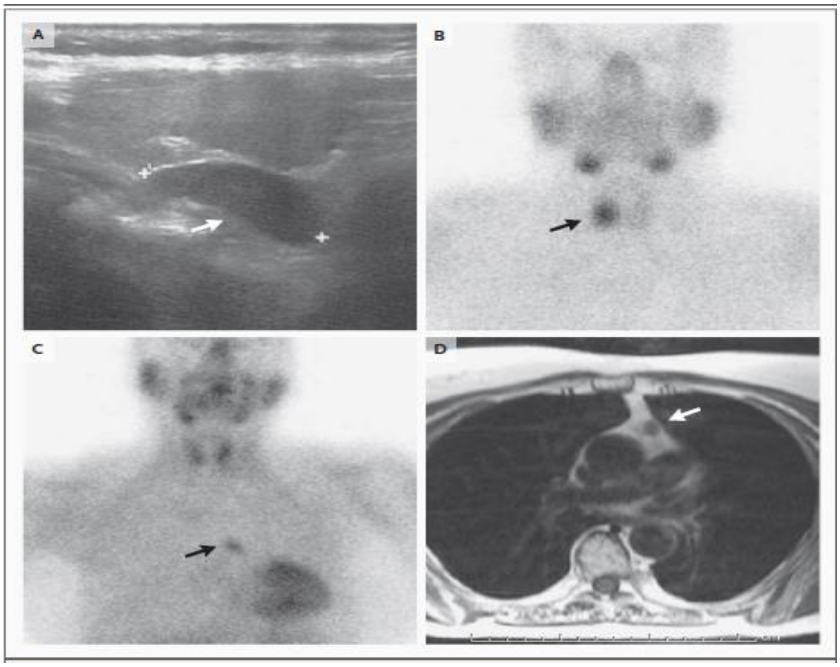

Table 3. Preoperative imaging method used to localize abnormal parathyroid

Imaging Method	sensitivity	PPV	
Ultrasonography	70.4-81.4%	90.7-95.3 %	Safe, no radiations
Technetium-99msestamibi scanning	64-90.6%	83.5-96 %	Can be used to detect ectopic parathyrid tissue
Dynamic (4D) CT imaging	89.4%	93.5%	Useful for identifying multiple adenomas
Magnetic resonance imaging	88%	90%	Same principles as CT imaging, but obviates concerns about radiation

Summary

Surgery in PHPT offers the promise of definitive cure. Surgery does not correct cardiovascular abnormalities in hyperparathyroidism, and whether it alleviates psychiatric and cognitive deficits is a subject of controversy.

Medical management includes correction of dietary calcium and vitamin D insufficiency. Cinacalcet lowers serum calcium levels but does not affect rates of bone loss. Bisphosphonates improve bone density, but whether they reduce the risk of fracture is unknow

Conflicts of Interest: There is no potential conflict of interest, and the authors have nothing to disclose. This work was not supported by any grant

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Communicated and received December 13, 2018, revised January 26, 2019, published on line April 23, 2019