



Case Report

Normocalcemic primary hyperparathyroidism associated with progressive cortical bone loss – A case report

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ABSTRACT

The existence of normocalcemic primary hyperparathyroidism (NPHP) was acknowledged at the Third and Fourth International Proceedings on primary hyperparathyroidism PHPT but data relating to its clinical presentation, natural history, and skeletal status were limited and there was no information nor guidelines as to definitive therapy. Herein are reported biochemical, hormonal, and densitometry data in a postmenopausal woman seen initially for osteoporosis who was found to have increased serum PTH levels and normal serum total and ionized calcium levels without evidence of secondary hyperparathyroidism. Over a seven year period, the patient exhibited continuing preferential cortical bone loss at the one-third site of the radius in the face of relatively stable readings at the lumbar spine and hip that led to a subtotal parathyroidectomy for parathyroid hyperplasia with resultant normalization of serum PTH.

1. Introduction

Mather (1953) was the first to report a patient with PHPT with normal serum total calcium levels, skeletal symptoms, and osteitis fibrosa cystica. Through the years a number of reports of patients with NPHPT were reported on the basis of serum total calcium levels (McGeown and Morrison, 1959; McSwiney and Prunty, 1961; Bogdonoff et al., 1956; Wills et al., 1969). McSwiney and Prunty (1961) may have reported the first patient with PHPT with normal serum total and ionized calcium levels. With the increasing availability of improved ionized calcium measurements, many patients with normal serum total calcium were found to have elevated serum ionized calcium (Monchik, 1995; Fanconi and Rose, 1958; Monchik and Gorgun, 2004; Forster et al., 1988) and therefore could no longer be considered normocalcemic.

Silverberg and Bilezikian (2003) reported 22 patients who were referred for skeletal evaluation and were found to have increased serum PTH levels and normal albumin-corrected serum total calcium levels. In eight patients serum ionized calcium levels were also normal. These data were felt to be in keeping with the earliest manifestation of PHPT or a “forme fruste” of the disease. Interestingly, these patients had no evidence of preferentially decreased cortical bone mineral density readings at the one-third site of the radius. At the Third International Workshop of PHPT in 2008, the existence of NPHPT characterized by consistently normal serum calcium concentrations in the face of

abnormal serum PTH levels in the absence of any underlying cause was acknowledged (Bilezikian et al., 2009). At the Fourth International Workshop of PHPT in 2013, there was more discussion of this disorder with mention of reports proposing that NPHPT may indeed be the first phase of a biphasic disorder that may later evidence hypercalcemia (Eastell et al., 2014). Data relating to the clinical presentation of NPHPT and its natural history were quite limited and there was no information available that would clarify surgical guidelines for this entity (Bilezikian et al., 2014).

Herein are observations in a postmenopausal woman with osteoporosis, increased serum PTH levels, and consistently normal serum total and ionized calcium levels in whom secondary hyperparathyroidism was excluded. Documentation of continuing preferential cortical bone loss led to a subtotal parathyroidectomy and normalization of serum PTH.

2. Case report

In 2003, this 65-year-old nurse at our facility was referred by her general physician for DXA studies in our unit revealing osteopenia at the lumbar spine and hip (Fig. 1). No therapy was suggested by her physician at that time. In September 2006 she was referred for further skeletal evaluation. Her skeletal risk profile included a fracture of the right arm at the age of eight years, menopause at age 48 years, hormone replacement therapy for six years, and when seen she had been off the

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DXA Results Summary: L1-L4 SPINE

Scan Date	Age	BMD (g/cm ²)	T-Score	BMD Change	
				vs Baseline	vs Previous
12/30/2015	65	0.806	-2.2	-2.6%	0.9%
12/18/2014	64	0.799	-2.3	-3.5%*	1.2%
12/12/2013	63	0.789	-2.3	-4.6%*	-2.5%
10/06/2010	59	0.810	-2.2	-2.1%	-3.6%*
09/23/2008	57	0.840	-1.9	1.5%	8.1%*
08/08/2006	55	0.777	-2.5	-6.1%*	6.1%*
02/04/2003	52	0.827	-2.0		

HIP TOTAL

Scan Date	Age	BMD (g/cm ²)	T-Score	BMD Change	
				vs Baseline	vs Previous
12/30/2015	65	0.636	-2.5	-6.8%*	-2.6%
12/18/2014	64	0.653	-2.4	-4.3%*	2.8%
12/12/2013	63	0.635	-2.5	-6.9%*	-3.3%
10/06/2010	59	0.657	-2.3	-3.8%	-0.5%
09/23/2008	57	0.660	-2.3	-3.3%	3.9%
08/08/2006	55	0.635	-2.5	-6.9%*	-6.9%*
02/04/2003	52	0.682	-2.1		

1/3 RADIUS

Scan Date	Age	BMD (g/cm ²)	T-Score	BMD Change	
				vs Baseline	vs Previous
12/30/2015	65	0.446	-4.1	-13.8%*	-2.7%
12/18/2014	64	0.458	-3.9	-11.4%*	-3.6%
12/12/2013	63	0.475	-3.6	- 8.1%*	-8.1%*
09/23/2008	57	0.517	-2.9		

*Denotes significant change at the 95% confidence level.

Fig. 1. By 2015 when compared with the readings in 2008 there was a 4% decrease in BMD at the lumbar spine, no change at the femoral neck (not shown), a 4% decrease in BMD at the femoral total site, and a 14% decrease at the one-third radial site.

medication for one and a half years. Family history was negative for osteoporosis, there was a 20-pack year smoking exposure that was discontinued at the age of 35 years, and there had been a negligible dietary intake of elemental calcium for a number of years. In recent years, she was supplemented with 500 mg of calcium and 800 units of vitamin D daily. A diagnosis of mild hypothyroidism due to Hashimoto's thyroiditis was made about six years earlier and she was clinically and chemically euthyroid on 25 mcg of levothyroxine. Physical examination was unremarkable with a blood pressure of 132/80, weight of 137 lb, and BMI of 25. A metabolic panel was normal. Serum calcium was 2.35 mmol/L, albumin was 44 g/L, and serum phosphorus 0.97 mmol/L. Serum 25-OHD was 152.5 nmol/L and serum PTH was 74 ng/L (≤ 72) (Table 1). Bone density readings revealed osteoporosis at the spine with a T-score of -2.5 with a decrease of 6.1% over a three-year period, probably related to losses which occur in the early postmenopausal years or after discontinuation of hormone replacement therapy. At the hip, she had an osteoporotic reading at the neck site

with a T-score of -2.7 , and a total T-score of -2.5 with a 6.9% decrease over that three-year period (Fig. 1). DXA vertebral assessment failed to reveal any compression fractures from T3 to L5. In October 2006, she was begun on 70 mg alendronate therapy weekly and was maintained on 2000 units of vitamin D and a total intake of 1200 mg of calcium daily. Three months later in 2007, total serum calcium was normal and an ionized calcium, though ordered, was not done and serum PTH was again increased at 94 ng/L. In 2008, there was a BMD increase of 8% at the lumbar spine, 2% at the femoral neck, and 4% at the total femoral site (Fig. 1). Because of the persistent increase in serum PTH levels, a DXA measurement was also obtained at the one-third site of the radius (Fig. 1). The T-score at this site was -2.9 which was the lowest of the BMD readings. In 2010, there was a decrease in BMD at the lumbar spine of 3% and stable readings at the hip (Fig. 1). She was not seen again until 2013 when she indicated that a year before she had discontinued taking alendronate after six years of therapy. When compared with the readings in 2010 there was a 3% decrease at

Table 1
Biochemical and hormonal data.

	Serum						2nd voided urine		
	Alb	Ca	PO4	Ca + + ^a	Cr	PTH ^b	25-OHD	NTx/Cr	Ca/Cr
	g/L	mmol/L	mmol/L	mmol/L	μmol/L	ng/L	nmol/L	nmol/mmol	mg/mg
	34–47	2.15–2.63	0.87–1.45		53–106		80–250	19–63	
2006	44	2.35	0.97		61.9	74 (≤ 72)	152.5	54	0.15 (0.05–0.25)
2007	45		1.13			94 (≤ 72)	82.5	33	0.08 (0.05–0.25)
2008		2.28	1.03			82 (≤ 72)	85.0		
2009		2.55	1.29		70.7	66 (≤ 72)	97.5		
2009		2.50			70.7				
2010		2.48			61.9		82.5		
2011		2.55			61.9		70.0		
2014	45	2.50	1.00	1.26 (≤ 1.32)		99 (≤ 88)	135.0	25	
2014	49	2.53	1.13	1.35 (≤ 1.4)	61.9	127 (≤ 66)	157.5	46	
2015									
2015	42	2.43	1.29	1.40 (≤ 1.4)		134 (≤ 66)	100.0	29	

^a Roger Williams Medical Center (1.13–1.32), East Side Laboratory (1.13–1.4).

^b Roger Williams Medical Center (14–72 and 12–88), East Side Laboratory (10–66).

the lumbar spine, a 7% decrease at the femoral neck, and a 3% decrease at the total femoral site (Fig. 1). There was an 8% decrease at the one-third radial site when compared to the BMD reading in 2008. In 2014, when compared with the readings in 2008 when there were measurements at all three skeletal sites there was a 5% decrease at the lumbar spine, no change at the femoral neck, a 1% decrease at the total femoral site, and an 11% decrease at the one-third radial site (Fig. 1). In December 2015, the T-score at the one-third site was -4.1 with a decrease of 14% versus the reading in 2008, a 4% decrease at the lumbar spine, no change at the neck site, and a 4% decrease at the total femoral site (Fig. 1).

Through the years, she remained eucalcemic with serum calcium levels ranging from 2.28 to 2.55 mmol/L (2.15–2.63) and serum albumin levels ranging from 42 to 49 g/L (34–47) (Table 1). Serum phosphate levels were also normal ranging from 0.97 to 1.29 mmol/L (0.87–1.45). Serum intact PTH levels with one exception were consistently elevated at 94 ng/L (≤ 72) in 2007, 82 ng/L (≤ 72) in 2008, 66 ng/L (≤ 72) in 2009, 99 ng/L (≤ 88) in 2014, 127 ng/L (≤ 66) in 2014, and 134 ng/L (≤ 66) in December 2015. Serum 25-OHD levels were consistently normal at 152.5 nmol/L in 2006, 82.5 nmol/L in 2007, 70 nmol/L in 2011, 135 nmol/L and 157.5 nmol/L in 2014, and 100 nmol/L in 2015. Serum creatinine levels were normal varying from 61.9 to 70.7 μmol/L (35.4–97.2) and glomerular filtration rates in 2009, 2010, and 2014 were > 1.0 mL/s/m². In January 2014, serum ionized calcium was normal at 1.26 mmol/L (1.13–1.32), in December 2014 normal at 1.35 mmol/L (1.13–1.4), and in December 2015 normal at 1.4 mmol/L (1.13–1.4). Serum 1,25-OHD was normal at 133 pmol/L (52–205).

From 2006 to 2015, second voided morning urine NTx/creatinine ratios were normal varying from 25 to 54 nmol/mmol (19–63). In January 2015, a 24 hour urine collection revealed a creatinine clearance of 1.85 mL/s/m², calcium excretion of 264 mg (100 – 300) with a calcium-creatinine ratio of 0.24 (0.05–0.25). Urine sodium was 180 meq. Phosphorus clearance was increased at 24 mL/min, tubular reabsorption of phosphorus (TRP) was 78% (78–95), and tubular maximum phosphorus (TMP) was low normal at 2.57 mg/dIGF (2.5–4.2). A calcification was noted on a CT scan obtained in May 2010 by her general physician for assessment of abdominal and pelvic pain. On the CT scan, the left kidney showed a single tiny calcification which appeared to be nonobstructing. She never knowingly passed a stone. There was no family history of urolithiasis. In January 2016, a renal ultrasound revealed no calcifications.

The chronically increased serum PTH levels and normal serum total and ionized calcium levels in the absence of secondary

hyperparathyroidism were all in keeping with NPHPT. As noted by [Sfeir and Drake \(2016\)](#) NPHPT has clinical features that differ from those with asymptomatic PHPT and individualized management of NPHPT may be more appropriate. Accordingly, because of the continuing preferential cortical bone loss at the one-third radial site, this patient was referred for evaluation of possible parathyroid surgery. A sestamibi parathyroid scan was negative. On January 21, 2016, the patient underwent neck surgery. There was evidence of Hashimoto's thyroiditis and associated lymphadenopathy. The left inferior parathyroid gland appeared enlarged. The left superior parathyroid gland was enlarged and appeared to be an adenoma. The right superior parathyroid gland was enlarged and appeared to be consistent with an adenoma. It was excised with pre-excision serum PTH level of 103 ng/L (≤ 72) and 5, 10 and 15 min after excision, levels were 124, 126, and 183 ng/L, respectively. The left superior parathyroid gland was then excised and 10 min post-excision, the serum PTH level was 69 ng/L. A gland was identified in the left central neck. It appeared slightly abnormal and was excised. The right inferior parathyroid gland was never definitively identified. Given the extensive dissection there was a small concern for its possible devascularization and several pieces of the right superior gland were implanted in the right sternocleidomastoid muscle just in case the residual right inferior gland was inadvertently devascularized. After removal of both superior glands and the left inferior gland the final serum PTH level had come down to 39 ng/L. The next day, the patient's serum total calcium level was 1.93 mmol/L (2.13–2.63), and serum PTH was 13 ng/L and she was supplemented with a gram of elemental calcium per day. Nineteen days after subtotal parathyroidectomy, serum total calcium and ionized calcium levels were normal at 2.28 mmol/L and 1.1 mmol/L (1.05–1.3), respectively, serum phosphorus was 1.2 mmol/L (0.78–1.55), and serum PTH was 72 ng/L. Five weeks postoperatively, serum total calcium was 2.38 mmol/L (2.15–2.6), serum ionized calcium 1.28 mmol/L (1.2–1.4), phosphorus 1.23 mmol/L (0.68–1.39), and PTH 44 ng/L (14–64).

3. Discussion

Many cases of NPHPT have been reported based on albumin adjusted serum calcium levels and abnormally elevated PTH levels some after exclusion of secondary causes of hyper-parathyroidism ([Mather, 1953](#); [Wills et al., 1969](#); [Lowe et al., 2007](#); [Grimelius et al., 1973](#); [Maruani et al., 2003](#)). In 2007, [Lowe et al. \(2007\)](#) reported the clinical course of 37 patients seen in a referral center who were referred for evaluation of increased serum PTH levels that had been discovered during the evaluation of low bone mass, fragility fractures,

or kidney stones. Albumin-corrected serum total calcium levels were normal. On subsequent follow-up for up to eight years, seven patients developed hypercalcemia within the first three years of observation. Although many of these patients were initially evaluated because of low bone mass, there was no evidence of preponderance of cortical bone loss as seen typically in hypercalcemic patients with PHPT. This was consistent with preliminary observations by Silverberg and Bilezikian (2003).

As in the case of other patients reported with increased serum PTH levels who were seen for skeletal evaluation, our patient was seen originally for osteoporosis. Ultimately, during her continuing assessment increased serum PTH levels and normal serum total and ionized calcium levels were in keeping with NPHPT. This is, indeed, a new variant of PHPT that is quite different from the variety of cases seen for many years. In 2006, our patient's BMD readings were consistent with osteoporosis. She continued with weekly alendronate for six years and then on her own discontinued the therapy. In 2008, because of the persistent increase in serum PTH levels, a one-third radial bone density measurement was obtained which revealed a T-score lower than those at the lumbar spine and hip. Blood chemistry profiles were consistently normal in terms of renal function and serum total calcium and albumin levels as were serum carotene and 25-OHD levels. When seen again in 2013 BMD readings were stable at the spine and reduced at the hip and at the one-third radial site. By 2015 when compared with the readings in 2008 there was a 4% decrease in BMD readings at the lumbar spine, no change at the femoral neck, a 4% decrease at the femoral total site, and a 14% decrease at the one-third radial site.

Maruani et al. (2003) reported their observations in 178 patients with PHPT that included 34 with normal serum total and ionized calcium levels. After exclusion of vitamin D and magnesium deficiency, impaired renal function, and therapy with diuretics, corticosteroids, and bisphosphonates, their data in the normocalcemic patients were felt to be consistent with skeletal and renal resistance to PTH action. The authors suggested that estrogen deficiency in the postmenopausal state might play a role in the development of hypercalcemia related to an increased sensitivity of target tissues to PTH action. Silverberg and Bilezikian (2003), however, reported that since several patients described with incipient PHPT were progressing to the second phase of the disease, resistance to PTH action or an abnormality of the calcium receptor would be unlikely explanations for their earlier findings. More recently, as noted by Cusano et al. (2013), the suggestion by Maruani et al. (2003) of an increased sensitivity to PTH in postmenopausal women would not explain the fact that NPHPT occurs more commonly in postmenopausal estrogen-deficient women. In our patient, the findings do not support the postulate of peripheral resistance to excess PTH on bone nor does the high phosphate clearance, low-normal TRP, and low-normal TM phosphate support the postulate of a diminished renal response.

4. Conclusions

It is likely that more patients particularly those being evaluated for osteopenia, osteoporosis, or calcium urolithiasis will be diagnosed with NPHPT. From a review of the literature, it appears that the case herein presented is quite unusual. The interesting feature of this case not previously described is the continuing significant decrease in cortical bone at the one-third site of the radius with the lowest readings at that site in the face of relatively stable readings at lumbar spine and hip. Her

biochemical and densitometry data do not support the postulate of peripheral resistance to excess PTH on bone nor do the renotubular phosphate values support the postulate of a diminished renal response to parathyroid hormone. A subtotal parathyroidectomy for asymmetric hyperplasia resulted in normalization of serum PTH.

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