Case Report

# Normocalcemic primary hyperparathyroidism in a patient with severe osteoporosis receiving teriparatide

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ABSTRACT

We describe here the case of an elderly female with severe osteoporosis, who presented with a worsening backache, following teriparatide treatment. She was subsequently diagnosed to have normocalcemic primary hyperparathyroidism. Before prescribing teriparatide, an appropriate endocrine evaluation must be undertaken by all healthcare physicians (serum intact parathyroid hormone (iPTH) level), despite having a normal serum calcium. Normocalcemic hyperparathyroidism should be considered as an important alternate cause for osteoporosis.

**Key words:** Forsteo, hyperparathyroidism, normocalcemic hyperparathyroidism, osteoporosis, parathyroid adenoma, teriparatide

## Introduction

Most cases of primary hyperparathyroidism (around 80-90%), are caused by an increased secretion of parathyroid hormone (PTH) from a single adenoma. Most studies have shown a higher incidence of primary hyperparathyroidism (PHPT) among women than men, with the highest incidence in postmenopausal women. Patients with normocalcemic (normal calcium <10.5 mg%) hyperparathyroidism have more substantial skeletal involvement than is typical in primary hyperparathyroidism and develop more features and complications over time. Up to 57% of the patients have osteoporosis, with significant bone loss, seen more frequently at the hip and forearm than at the spine.[1,2]

## Case Report

A 61-year-old, married lady, was referred to our Endocrine Clinic by a general practitioner, with a background of hypertension (untreated, since four years) and right hemi-thyroidectomy (performed 15 years ago for multinodular goiter), with complaints of persistent lower backache (non-radicular) and generalized severe body ache that had worsened after she was put on teriparatide (since four months). The teriparatide was started by the primary care physician for severe osteoporosis that was thought to be due to premature menopause (achieved at the age of 35 years). She was a vegetarian, non-smoker, non-ethanolic without any significant family history or drug history.

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Examination revealed a lady withdrawn in pain, weighing 61 kg, with a body mass index of 27.5 kg/m$^2$. The blood pressure was 160/92 mm of Hg supine and 170/106 mm of Hg when sitting, without any postural fall. The proximal muscle weakness was 4/5 in all four limbs. General and systemic examination was otherwise normal.

Biochemistry was unremarkable, except for mild hyponatremia (sodium 130 mmol/L) and elevated alkaline phosphatase 140 IU/L (50-136), which was associated with a corrected calcium of 9.7 mg/dl (calcium 10.1 mg/dL, albumin 4.5 gm%) and normal liver function. Although teriparatide therapy could possibly have accounted for

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these changes, we chose to look at her previous results, with a suspicion of a possible secondary cause for the elevated high alkaline phosphatase on the background of worsening symptoms.

It was noted that she had corrected calcium as high as 10.3 mg% on review of her previous results, which we thought was significantly elevated, especially as her diet was poor in calcium. Further enquiry suggested large volumes of fluid intake (free water) approximately 4-5 liters/day, which the patient put down to persistent thirst, which we considered to be secondary to polydipsia. The adrenal and thyroid screen (TSH: 1.14 mIU/ml) screen was normal

Subsequent specialized testing revealed an elevated parathormone 166 pg/mL (11-54), insufficient vitamin D3 27 ng/L (11-42), and hypercalciurea (24-hour urine calcium 624 mg% (50-300 mg%)), and thus a PTH-dependant etiology for hypercalcemia was considered.

Plain x-ray of the chest was normal. A skeletal survey revealed spondylolisthesis of L4 over L5, without any obvious fractures. Dual Energy X-Ray Absorptiometry (DEXA) densitometry showed a worsening T-score at the spine (T-scores, hip — 2.3, spine — 3.9, forearm — 4.5), compared to the previous results. The echocardiogram was consistent with evidence of systemic hypertension showing diastolic dysfunction with mild concentric left ventricular hypertrophy. A fundoscopy revealed evidence of early hypertensive changes.

Specialized imaging in the form of Doppler ultrasound of the neck suggested a mass at the inferior pole of the right lobe of the thyroid gland (most likely a parathyroid adenoma). The SESTAMIBI scan confirmed the presence of a right inferior parathyroid adenoma as localized by ultrasonography.

A minimal invasive parathyroidectomy was undertaken. A mass 1.5 × 1.0 cm was removed that was consistent with parathyroid adenoma. Microscopy showed an encapsulated lesion composed of a diffuse proliferation of chief cells with surrounding delicate capillary network [Figure 1]. The patient continued to remain well with corrected calcium of 9.3 mg%, with a plan of yearly zolendronic acid infusions for a total of five infusions

## Discussion

Osteoporosis is a systemic skeletal disorder characterized by low bone mass and micro-architectural deterioration of the bone, with a consequent increase in bone fragility and susceptibility to fracture.[3] Previous prospective studies

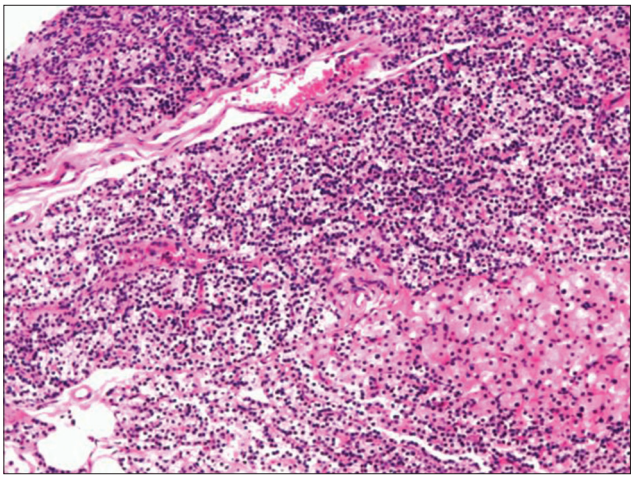

**Figure 1:** Photomicrograph showing parathyroid adenoma (H and E, ×10)

indicate that the risk of an osteoporotic fracture increases continuously as bone mineral density (BMD) declines, with a 1.5 to 3-fold increase in the risk of fracture for each standard deviation fall in the BMD[4]

Most American women under the age of 50 have normal BMD, however, as many as 70% are osteoporotic at the hip, lumbar spine, or forearm by the age of 80 years. Epidemiological studies from North America have estimated the remaining lifetime risk of common fragility fractures to be 17.5% for a hip fracture, 15.6% for a clinically diagnosed vertebral fracture, and 16% for a distal forearm fracture, among white women of age 50 years. The corresponding risks among men are 6, 5, and 2.5%, respectively.[5] A British study using the General Practice Research Database estimated the lifetime risk of any fracture to be 53.2% at the age of 50 years among women and 20.7% at the same age among men[6]

Teriparatide refers to the 1-34 N-terminal active fragment of the recombinant parathoromone, an osteoanabolic that has revolutionized the treatment of osteoporosis. It is indicated for use in postmenopausal women, men with idiopathic or hypogonadal osteoporosis, and in men or women with glucocorticoid-induced osteoporosis, with a bone mineral density lower than three standard deviations from normal. Its efficacy is seen at both the vertebral and non-vertebral sites. Kung AW[5] showed that vertebral bone mineral density values (assessed at the lumbar spine) significantly increased from baseline to a greater extent with teriparatide 20 ug/mL than with placebo, alendronate[7] or calcitonin.[8] In the Fracture Prevention Trial, the bone mineral density was increased by 9% more in recipients of teriparatide[7]

Teriparatide is licensed for use for approximately 18 months

and not longer than 24 months. Contraindications include primary, tertiary hyperparathyroidism, elevated alkaline phosphatase of uncertain cause, Paget's disease, and osteosarcoma. A study of teriparatide on the effects of calcium were studied and it was seen that following teriparatide 20 mcg/day therapy, the serum calcium levels increased from approximately two hours post-dose, reaching peak levels at 4-6 hours post-dose (median increase 0.4 mg/dL (0.1 mmol/L)). Serum calcium levels started to decline approximately six hours post-dose, reaching baseline levels at 16-24 hours after each dose.[9] After 12 months treatment with teriparatide, >98% of postmenopausal women or men with primary or hypogonadal osteoporosis had peak serum calcium levels of <11 mg/dL (2.76 mmol/L). The median peak serum levels were 9.68 mg/dL (2.42 mmol/L) in postmenopausal women with osteoporosis and 9.44 mg/dL (2.35 mmol/L) in men with primary or hypogonadal osteoporosis. Sustained hypercalcemia (calcium levels >11 mg/dL [2.76 mmol/L]) was not observed in the studies[10,11]

Although teriparatide can improve bone mass when given for the correct indication, it can be disastrous if used injudiciously as in this case. The patient had underlying primary hyperparathyroidism, which was the cause of severe osteoporosis. Teriparatide is contraindicated in patients with hyperparathyroidism. The case presented cannot emphasize enough the need to undertake a thorough endocrine evaluation and rule out all secondary causes of osteoporosis before considering a patient for teriparatide therapy. Parathyroid disease is a common cause of raised alkaline phosphatase and is associated with elevated to high normal serum calcium. Other isolated endocrine causes of raised alkaline phosphatase (bone-origin) include (severe vitamin D deficiency (osteomalacia); metastatic bone disease; severe hyperthyroidism; fluorosis, and Paget's disease).[12,13]

Baseline serum calcium in excess of 9.5 mg% with an elevated serum parathormone, with a background of a calcium-poor diet, should prompt physicians to consider 'normocalcemic primary hyperparathyroidism,' as the possible cause for osteoporosis. Moreover lack of improvement of osteoporotic symptoms while on teriparatide should be considered as a clue to look for underlying secondary cause of osteoporosis, like 'normocalcemic primary hyperparathyroidism' as the cause for failure of therapy. The case should serve as a warning to healthcare professionals who use teriparatide that appropriate metabolic evaluation including a parathormone level must be routinely undertaken before instituting teriparatide.

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