

Primary Hyperparathyroidism: An under-diagnosed endocrine disorder in Sri Lanka

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Abstract

Primary hyperparathyroidism (PHPT) has become one of the commonest endocrine disorders during past few decades. Clinical presentation varies according to the extent to which the biochemical screening is being routinely carried out in clinical evaluation. Even though data from western countries show increased incidence, PHPT is still under-diagnosed in Sri Lanka. Here we report a case of PHPT detected during the evaluation of an incidentally found hypercalcemia in a postmenopausal female patient.

Keywords: Primary hyperparathyroidism, Hypercalcemia, Familial Hypocalcaemic Hypercalcemia

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Introduction

Primary hyperparathyroidism is the third most common endocrine disorder in the world and most often identified in postmenopausal women with a female to male ratio of 3-4:1. According to data from western countries, clinical presentation of PHPT has evolved over the past few decades from symptomatic to asymptomatic hypercalcemia probably due to early detection of asymptomatic patients as the availability and accessibility of biochemical investigations in clinical practice has markedly improved(1). However, in Sri Lanka the clinical picture is still similar to what was seen in western countries decades ago probably due to lack of facilities to measure serum calcium and parathyroid hormone levels in government hospitals and the lack of awareness regarding this common endocrine disorder among the clinical practitioners(2). This case report highlights the importance of having a lower threshold to screen for hypercalcemia even with mild symptoms to detect under diagnosed, yet a curable condition of

primary hyperparathyroidism.

Case Report

A 56-year-old postmenopausal lady with hypertension, ischemic heart disease and Type II Diabetes Mellitus for 12 years complicated with stage IIIb Chronic Kidney Disease (CKD) for last three years, presented with fever and lower abdominal pain for five days duration on a background of progressive lower back pain for one month. Investigations confirmed culture positive urinary tract infection and the patient became afebrile with antibiotics prescribed according to the sensitivity pattern. However, she continued to have lower back pain with difficulty in walking. It was mild to moderate in intensity lasting throughout the day without touching the baseline and gets worse at night. She was experiencing constipation for one month. Simultaneously, her appetite had got reduced with a significant loss of weight (12 kg) over two-months. Clinically she was euthyroid and neither had features of connective tissue disorders. She was on Gliclazide,

Sitagliptin, Aspirin, Atovastatin, Losarton and Amlodipine for her preexisting medical conditions. On examination she was hemodynamically stable with a pulse rate of 80bpm and blood pressure of 120/60 mmHg. Rest of the examination findings were unremarkable except for tenderness over lower abdomen and lower back with positive straight leg raising test on right side. Her initial full blood count showed neutrophil leukocytosis (WBC – 21.7 x 10³, N- 18.0, L- 2.1) which returned back to normal with antibiotic treatment. There was persistent mild anemia with a haemoglobin of 8.2g/dl and the platelet count remained normal throughout. Blood picture and iron studies were suggestive of anaemia of chronic disease due to renal pathology and Vitamin B12 or folate deficiency. WBC changes and rouleaux formation was suggestive of infective or inflammatory process. She was investigated for the back pain once recovered from acute infection. Investigations were as follows. ESR – 25mm/1st hr, serum creatinine 200µmol/l and stable, liver enzymes were normal except for elevated alkaline phosphatase of 192 U/L. Serum electrolytes showed hypercalcemia with an albumin

corrected calcium of 3.1mmol/L (2.06 - 2.6), hypomagnesemia of 0.33 mmol/L (0.73- 1.06) and hypophosphatemia of 2.4mg/dl (2.9 – 5.0). Serum sodium and potassium was normal. X-ray lumbo-sacral spine showed generalized osteopenia with age related degenerative changes in lumbo-sacral spine. Further evaluation showed grossly elevated parathyroid hormone level of 745.3pg/ml (normal range 15-65pg/ml) with Vitamin-D deficiency (19.3ng/ml). Ultrasound Scan (USS) of the neck showed 1.6 x 1.4 x 1.4 cm hypoechoic well defined lesion inferior to the lower margin of the right lobe of thyroid gland compatible with right-side parathyroid adenoma. Contrast Enhanced CT (CECT) scan of the neck was performed and it also showed an enhancing mass posterior to right lobe of thyroid gland suggestive of parathyroid adenoma. Thyroid gland was normal in size and shape. Multiple Endocrine Neoplasia was excluded after performing necessary radiological and biochemical investigations. Tc 99m SESTAMIBI Parathyroid scan was performed for accurate localization of the adenoma to decide on definitive management.



Figure 1 : SESTAMIBI scan – A focal abnormal and persistent tracer retention in the inferior pole of the right lobe of the thyroid gland in the neck. Suggestive of parathyroid adenoma in view of rising PTH level

She was hydrated well with a fluid target of 3-4 L per day, and intravenous Zolendronic acid 4mg single dose was given for the management of hypercalcemia. Hypomagnesemia was corrected with intravenous Magnesium Sulphate followed by oral Magnesium Sulphate. Vitamin-D replacement was done with oral Vitamin-D 50000 IU weekly for eight weeks with a plan to continue it as 2000 IU daily thereafter. Anemia was managed with oral hematinic and subcutaneous Erythropoietin weekly injection. Surgical excision of parathyroid adenoma was planned as the definitive management for this patient following multi-disciplinary team discussion held with the participation of Endocrinologist, Radiologist, Surgeon and the Physician.

Discussion

Hyperparathyroidism is due to excessive production of parathyroid hormone (PTH) either due to intrinsic abnormality of the gland (primary or tertiary hyperparathyroidism) or due to extrinsic abnormality affecting calcium homeostasis stimulating PTH production. Solitary benign adenoma is the most common cause accounting for 75-85%. Multi-gland adenoma occurs in substantial proportion (two glands in 2-12% of cases, three glands in <1-2%, and four or more in <1-15%) and parathyroid carcinoma is rare (<1%). Ectopic glands can be present 4-16% cases(3).

At present, three clinical phenotypes of PHPT have been described namely, symptomatic hypercalcemia with overt target organ involvement, asymptomatic mild hypercalcemia and elevated PTH levels with normocalcemia (3). Our patient presented with symptoms of urinary tract infection on a background of chronic back pain, constitutional symptoms and constipation. On further evaluation she was found to have hypercalcemia, hypophosphatemia and frankly elevated (>10 folds) PTH level. When these biochemical abnormalities are present, further investigations are usually unnecessary to come to the diagnosis of PHPT. Usually, in PHPT the expected rise of PTH is around three fold but, Vitamin-D deficiency in PHPT leads to frank rise of PTH level with greater expression of disease activity which justify the presentation of our patient(3,4). In addition, hypercalcemia with frankly elevated PTH in CKD raise the suspicion of tertiary hyperparathyroidism. Shorter duration of CKD and low phosphate levels made it unlikely in this patient(4). Further, in the context of hypercalcemia and elevated PTH level Familial Hypocalcemic Hypercalcemia (FHH) needs to be excluded by measuring 24-hour urine calcium

excretion or by spot urine calcium to creatinine ratio. An elevated urinary calcium concentration (>200-300mg/day) excludes the diagnosis of FHH but, lower levels (<200mg/day) can be due to FHH or PHPT with Vitamin-D deficiency(5). Urine calcium measurement was not carried out in our patient due to Vitamin-D deficiency and CKD as it can cause false positivity. Further, being a female with an age of >50 years, grossly elevated PTH levels and absence of family history of hypercalcemia made the diagnosis of FHH remote in our patient(3,4).

Imaging studies were obtained only after the biochemical confirmation of PHPT and should be used only to localize the gland prior to surgery. The accuracy of USS is operator dependent and the sensitivity ranges from 72-89%. Combining Tc 99m SESTAMIBI scintigraphy with USS neck provides high sensitivity (79-95%) for parathyroid localization(5). 4D-CT is a novel imaging modality which has robust diagnostic accuracy (>90%) in lateralization of single-gland adenoma compared to traditional sonography and scintigraphy techniques. Even though this has low sensitivity (44%) in multi-gland disease, it has 100% specificity for ruling out multi-gland involvement. In addition, this facilitates detection of coexisting pathology in ultrasonically inaccessible regions like mediastinum prior to surgery(7).

Management of Hyperparathyroidism includes definitive management and management of biochemical derangement. Treatment modalities which are used to manage hypercalcemia vary according to the degree of hypercalcemia. Asymptomatic and mildly symptomatic patients with mild hypercalcemia (Albumin-corrected-calcium <3 mmol/l) can be managed with adequate hydration. Asymptomatic and mildly symptomatic patients with chronic moderate hypercalcemia (Albumin-corrected-calcium 3-3.5 mmol/l) do not need immediate treatment whereas, symptomatic patients with acute rise needs aggressive therapy as in severe hypercalcemia mainly with intravenous hydration and bisphosphonates. Severe hypercalcemia (Albumin-corrected-calcium >3.5mmol/l) requires more aggressive therapy(8). Volume expansion with intravenous isotonic saline 4-6 L for first 24 hours followed by 3-4 L per day is needed. Hydration should be done cautiously in renal impairment, heart failure and elderly patients. Bisphosphonate inhibits osteoclastic bone resorption. Zolendronic acid is contraindicated in patients with creatinine clearance <30ml/min. Dose reduction is required in renal impairment(8). Our patient's eGFR was 40 ml/min/1.73m² and Zolendronic acid was given with

Nephrologist's opinion. Other options available for hypercalcemia management are Calcimimetic agents (Cinacalcet), Denosumab, and Calcitonin(1). Haemodialysis as well as peritoneal dialysis against a low or zero calcium dialysate is an option in treatment failure and for patients already receiving haemodialysis, or severe renal insufficiency(8).

Definitive management of PHPT is parathyroidectomy by a highly experienced and skilled surgeon. Vitamin-D level should be checked and replaced if deficient (<20 ng/ml is deficiency) prior to surgery to prevent post-op hypocalcaemia(1).

Indications for parathyroidectomy includes symptomatic patients (Nephrolithiasis, fractures, symptomatic hypercalcemia) and asymptomatic

patients who meet at least one criteria of Fourth International Workshop on Asymptomatic Primary Hyperparathyroidism Guidelines 2014(1).

Patients who do not meet surgical intervention criteria may still choose parathyroidectomy as it is the only definitive therapy. If surgery is not an option disease activity should be monitored regularly while continuing medical management(1).

Conclusion

Even though PHPT has become the third most common endocrine disorder it is still under diagnosed in Sri Lanka. Therefore, raising clinical suspicion to detect asymptomatic patients is required in order to prevent long term disability from overt target organ involvement.

Table 1

Parameter	Criteria for parathyroidectomy
Age	< 50 years
Serum calcium	> 1 mg/dL above upper limit of normal
Skeletal manifestations	Reduced BMD by DXA to a T-score of < -2.5 at any site (lumbar spine, hip, or distal one-third radius) Vertebral fracture by X-ray, CT, magnetic resonance or VFA (vertebral Fracture Assessment)
Renal manifestations	Creatinine clearance < 60 mL/min Kidney stone or nephrocalcinosis by abdominal imaging Hypercalciuria (>400 mg/day) accompanied by biochemical stone risk profile placing patient at risk of kidney stones

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