Medical Practice and Review Vol. 4(1), pp. 1-4, January 2013
Available online http://www.academicjournals.org/MPR
DOI: 10.5897/ MPR12.002
ISSN 2I41-2596 ©2013 Academic Journals

Case Report

Normocalcemic primary hyperparathyroidism in type 2 diabetes with associated comorbidities: A diagnostic approach

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Accepted 15 February, 2012

We report the case of a 57 year old lady, known to be diabetic for last 4 years getting treated with oral hypoglycemic agents. She reported to the medical outpatient department (OPD) of a tertiary medical care hospital with the history of pain abdomen, nausea, and loss of appetite since 3 months. On examination, she was conscious and well oriented, afebrile, with pulse rate of 86 min^{-1}, blood pressure of 130/84 mmHg, respiratory rate of 16 min^{-1}, mild pallor, no icterus, right hypochondriac tenderness was present. Routine investigations revealed Hb of 9.6 g%, fasting blood glucose of 214 mg/dl and HbA1c of 10.6%; normal serum amylase and lipase levels, urine for ketones was negative; all other investigations were within normal limits except for elevated serum alkaline phosphates. Abdominal ultrasound showed multiple gall bladder stones. She underwent an endoscopic ultrasound which revealed a distended gall bladder containing multiple small calculi and a single large calculus; pancreas appeared bulky, parenchyma was hypoechoic with multiple hyperechoic areas with evidence of calcification, the impression was chronic pancreatitis, cholelithiasis. We further proceeded with endoscopic retrograde cholangiopancreatography (ERCP). ERCP showed common bile duct (CBD) stones with left intra hepatic biliary dilatation with chronic calcific pancreatitis. For this, she underwent endoscopic sphincterotomy and internal biliary stenting and was discharged with pancreatin tablet, H2 blockers and human mixtard injection of 30 units per day and she was asked to attend the OPD after a fortnight. After 1 week, she presented with symptoms of gastritis, insomnia, and mood disturbances. Upper gastrointestinal (GI) endoscopy showed Grade 1 distal oesophagitis, severe antral gastritis and duodenitis of D1 and D2, serum electrolytes and serum calcium were within normal range and she was managed conservatively and treated by psychiatrist for symptoms of depression with antidepressants tablet (fluoxetine) 20 mg once daily (OD). Despite this, there was no improvement. Owing to her age and symptoms, we evaluated her parathyroid status.

Key words: Diabetes, primary hyperparathyroidism, parathyroid adenoma.

INTRODUCTION

Primary hyperparathyroidism (PHPT) is usually characterized by fasting hypercalcemia associated with inappropriately high parathyroid hormone (PTH) concentration. In normal individuals, PTH maintains a normal serum calcium concentration through its action on bone (presumably by a cell-mediated bone calcium release) and kidney (in which it enhances tubular calcium reabsorption) (Sitges-Serra et al., 1988). PHPT is the most common cause of hypercalcemia and should be considered in any person with an elevated serum calcium level. In 1970s, the estimated prevalence of PHPT ranged from 1 case per 1000 persons in the United States to 4.3 cases per 1000 persons in Sweden (Cope, 1960). Several factors have been considered to explain the maintenance of normal serum calcium concentration in PHPT. It has been proposed

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that, in the patients with normocalcemic PHPT, serum total calcium concentration may not reliably reflect the expected increase in the free biologically relevant fraction of serum calcium (Geffken et al., 1998). Another commonly admitted explanation is that normocalcemic PHPT may represent an early and/or a mild variety of PHPT (Heath, 1989). Classic symptoms and signs of PHPT are rare today, but nephrolithiasis still occurs in 4 to 15% of cases. Patients may have weakness, easy fatigability, anxiety, and cognitive impairment even when the level of serum calcium is modestly increased. PHPT is associated with insulin resistance hyperglycemia and dyslipidemia. Severe hyperglycemia can worsen hypercalcemia by causing osmotic diuresis leading to dehydration and hypercalcemia, which in turn, can worsen or induce hyperglycemia by causing insulin resistance (Khan, 1997). The incidence and prevalence of frank diabetes mellitus (DM) is significantly increased in patients suffering from hypercalcemia (Lundgren et al., 1997). Despite the presence of several promising agents for medical management, the presence of DM may be an indication for parathyroidectomy, which may result in either stabilization or improvement in glycemic control and reduce the need for use of antidiabetic agents (Mendizova et al., 1976). The presentation of PHPT is asymptomatic and hence attention has been diverted to the features like hypertension, mental changes, peptic ulcer disease and gallstone disease.

A 24 h urinary report is as follows: total volume: 2200 ml; creatinine: 517 mg/day (reference range 1 to 2 g/day); calcium: 158 mg/day (reference range 80 to 200 mg/day); phosphorous: 378 mg/day (reference range up to 1 g/day); X-Rays of skull, spines were done: normal.

HISTOPATHOLOGY REPORT

Clinical history: Tumor right parathyroid gland.
Specimen: Resected right parathyroid gland.

Macroscopic examination

Measurements: 4.2 × 2.8 × 2.3 cm; weight: 8 g. External surface: greyish brown tissue, capsule abraded in one area. Surgical cut surface: tumour with fleshy appearance throughout. Number of bits: 2.

Microscopic examination

Here, an encapsulated tumour, which consists of closely packed acini with scanty stroma in between, was shown. The acini are lined by cuboidal to low columnar epithelium with round regular darkly stained nuclei with minimal variation. The cytoplasm is scanty to moderate and pale eosinophilic.

The capsule is thick, shows few trapped acini and plenty of pigment. For hemosiderin laden macrophages, there is no significant atypia or mitoses or necrosis. There is no definite capsule or vascular invasion of surrounding structures.

Diagnosis

The histological features are consistent with parathyroid adenoma.

Parathyroid scintigraphy with tracer Tc99m SESTAMIBI

Early post injection and 1 h images of anterior neck and anterior chest were obtained.

FINDINGS

Early images show tracer localized in the entire thyroid gland with large area of abnormally increased tracer uptake in the region of lower pole of right lobe of thyroid. Delayed images show good washout of tracer from the thyroid gland with abnormal retention in the focus showing hyper concentration. No other focus of abnormal tracer retention was detected elsewhere in the neck and mediastinum.

Impression

Scan findings are consistent with right parathyroid adenoma. She underwent right parathyroidectomy (Figures 2 to 4).

Histopathology report is consistent with parathyroid adenoma. She is asymptomatic after then and improved, doing well with routine day to day activity and receiving human mixtard injection of 30 units in two divided doses.

DISCUSSION

Here, we report a 57 year old diabetic female presented with chronic pancreatitis, cholelithiasis. Initially, we thought her symptoms to be attributed in the background of cholelithiasis, chronic pancreatitis and diabetes. Considering her age, psychiatric manifestations, and no improvement in her clinical status, we investigated her parathyroid status (Table 1). Finally, we arrived to the diagnosis of parathyroid adenoma and she was operated, following which she improved dramatically.

Currently, the prevalence rates of hyperparathyroidism are about 1 to 4 per 1000, with a female:male ratio of 3:1 (Heath, 1989). We further evaluated bone density using DEXA scan (Figure 1), which showed osteopenic changes. Most densitometry studies support the concept that the PTH appears to be catabolic at cortical sites and may have anabolic effects at cancellous bone sites (Khan, 1997). Hypercalcemia is considered to be a rare cause of pancreatitis, but the true cause-and-effect relationship between hyperparathyroidism and pancreatic inflammatory disease remains controversial (Sitges-Serra et al., 1988). Here, the serum calcium, ionised calcium, albumin corrected calcium and urinary calcium levels were within normal limits, as such, albumin corrected

Table 1. Investigations done for assessing parathyroid status.

Parathyroid status	Result	Reference range
Calcium total (mg/dl)	9.6	8.5-10.1
Ionised calcium (mg/dl)	5.8	4.5-5.6
PTH (intact) (pg/ml)	903.7	14- 72
Serum C-peptide (ng/ml)	0.9	0.9-4.0
Serum albumin (g/L)	3.4	4-5
Albumin corrected calcium (mmol/L) Corrected calcium = (0.8 × (Normal Albumin - Pt's Albumin)) + Serum Ca	9.6	-
Vitamin D3 levels (ng/ml)	20	30-60

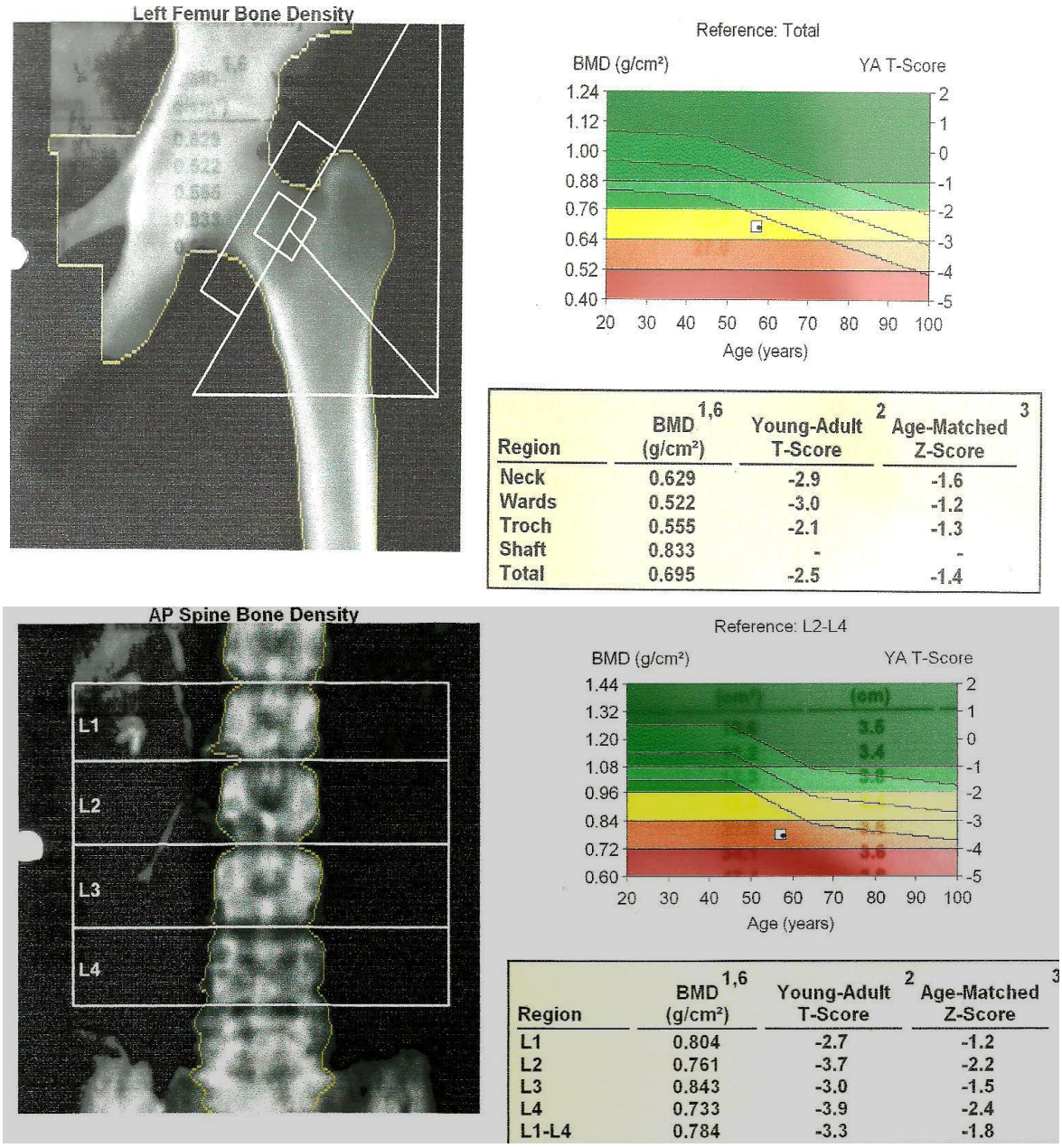

Figure 1. Bone density of Hip and Spine by DEXA. Features suggestive of osteopenia.

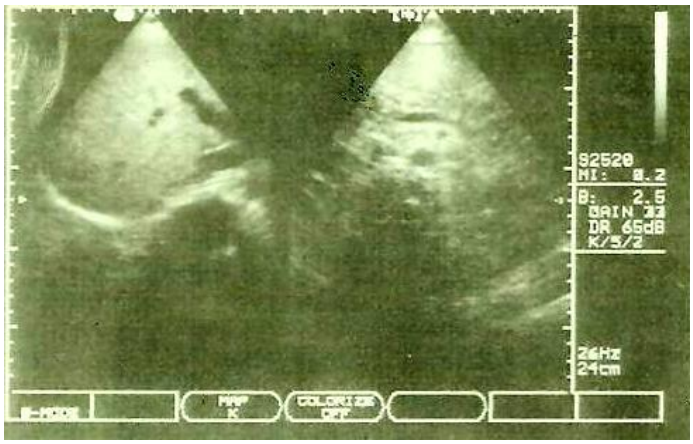

Figure 2. Ultrasound of liver and pancreas.

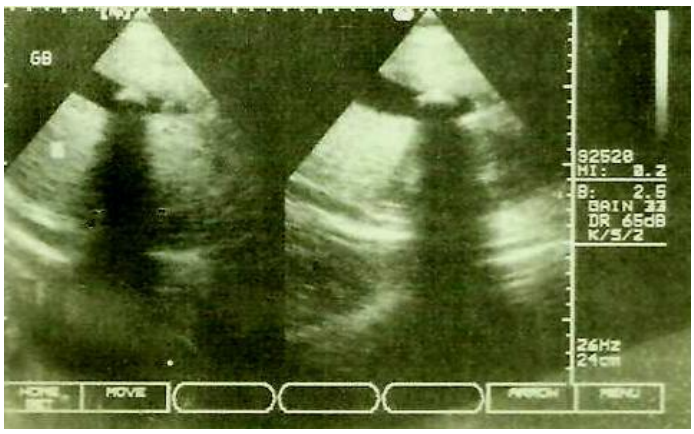

Figure 3. Ultrasound of gall bladder.

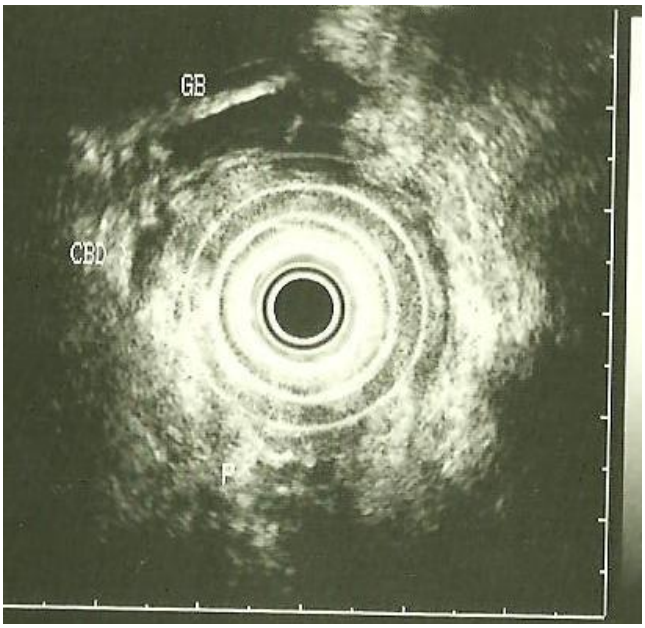

Figure 4. Endoscopic ultrasound.

calcium has significance in albuminemic patients. Calcium and PTH levels vary inversely. Cope (1960) reported that cholelithiasis is a common complication of hyperparathyroidism.

Neuropsychiatric symptoms associated with primary hyperparathyroidism span a range of affective anxiety, cognitive, and psychotic presentations. The most common neuropsychiatric manifestations of the disorder appear to be depressive symptoms with general apathy and mild cognitive disturbance (Geffken et al., 1998; Spivak et al., 1989). There is increased incidence of type 2 DM in patients with hyperparathyroidism. Monica et al. (2008) reported the crude prevalence rate of type 2 DM in patients with primary hyperparathyroidism as 15.9%. Chronic recurrent pancreatitis with erosive gastritis is seen in patients with primary hyperparathyroidism (Mendizova et al., 1976). Despite her normal serum calcium levels, her PTH levels were elevated. A Swedish study suggested the incidence of 27.5% of normocalcemic PHPT and 16% amongst post menopausal women (Lundgren et al., 1997). Earlier studies showed low levels of vitamin D3 in hypercalcemia and parathyroid tumors. In a study by Michael (2007), 67% of patients with PHPT had low levels of vitamin D3. A relationship between high levels of PTH and low levels of vitamin D3 was established.

A discrete evaluation confirmed the diagnosis of a parathyroid adenoma in patient with type 2 diabetes in association with chronic pancreatitis, cholelithiasis, and neuropsychiatric manifestations.

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