LONG-LASTING ADVANCED PRIMARY HYPERPARATHYROIDISM ASSOCIATED WITH END-STAGE RENAL FAILURE IN A DIABETIC PATIENT

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Abstract- In this report we explain a case of primary hyperparathyroidism in a 45 years old diabetic woman that was initially presented with recurrent nephrolithiasis of more than 10 years duration leading to right complete and left partial nephrectomy and complicated by end-stage renal failure. After diagnosis of primary hyperparathyroidism and parathyroid adenectomy, she developed severe hypocalcaemia due to severe and advanced osteitis fibrosa cystica. Despite starting hemodialysis and treatment by high dose calcium the general condition did not improve and the hypocalcemia was not corrected. Severe hungry bone syndrome did not get better and the patient died finally.

Key words: Primary hyperparathyroidism, Hungry bone syndrome, Osteitis fibrosa, Nephrolithiasis, Hemodialysis

INTRODUCTION

Primary hyperparathyroidism (PHPT) is a disease which has evolved from its classic presentation to a one quite different (1). It may be asymptomatic and be discovered after a routine chemistry profile or may cause symptoms of hypercalcemia and be associated with symptoms of renal stone and bone disease (2-4).

The routine measurement of serum calcium with the widespread use of multichannel biochemical screening initially led to a marked rise in the apparent incidence of PHPT. Thus PHPT evolved from a disease of “bone, stones and groan” to a disorder that is asymptomatic in most patients of western countries (5). It seems that the clinical presentations of PHPT in the eastern countries has not changed fundamentally; however, this disease has been evolved from what was initially thought to be a very rare disease to a relatively frequent endocrine disorder (6). Finding of long-lasting cases of PHPT with progressive renal damage and severe bone disease is infrequent. In this report we explain a case of long-lasting advanced PHPT in a diabetic patient that was complicated by end-stage renal disease (ESRD) and after parathyroid adenectomy (PTX) complicated by severe hungry bone syndrome and hypocalcaemia due to very progressive osteitis fibrosa cystica.

CASE REPORT

A 45 years old woman was admitted to the emergency section of our hospital because of left flank pain, intense weakness and severe illness on Feb 2001. Pain had started since 8 days before admission and was accompanied by fever and chills.

She was married, had five children, and was uneducated, living in a village far from the city. She had history of right nephrectomy 15 years ago due to multiple kidney stones and had 2 episodes of multiple
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left kidney stones and finally partial left kidney nephrectomy seven years ago due to unsuccessful medical treatments of retained stones. Ten years ago she had 3 hemodialysis sessions but since then she had no hemodialysis. Since 10 years ago she developed diabetes mellitus (DM) that was under insulin therapy, but her diabetes was not fully controlled. She had a history of car accident and right foot fracture and had history of bone cyst of the distal right foot. From 1991 to 2001 she had several hospital admissions for DM control, bladder catheterization and vomiting and diarrhea. One year before admission she developed hypertension which was treated by captopril. Her appetite had decreased since last year and since then she was on a diet composed mainly of fluids.

In examination, blood pressure was 160/100 mmHg and temperature 38˚ C. Thyroid was impalpable, with no cervical lymphadenopathy. Heart and lung examinations were normal, abdomen was normal in auscultation and palpation and she had 2+ leg edema. The results of laboratories were as follows: blood urea nitrogen (BUN), 74 mg/dl; fasting blood sugar (FBS), 360 mg/dl; phosphorus (P), 3.7mg/dl; Creatinine (Cr), 4.2 mg/dl; glomerular filtration rate (GFR), 12 cc/min; Alkaline phosphatase (ALP), 3615 IU/ml; Hemoglobin (Hgb), 10.9 g/dl; Albumin, 3 g/dl, Calcium (Ca), 8 mg/dl. Urine analysis showed 3+ albuminuria with pyuria and bacteriuria and urine culture was positive for E coli > 10^5 bacteria. Twenty four hour urine protein was 2497 mg. In sonography, right kidney was not detected, left kidney had mild hydronephrosis and had a 5 mm stone in mid calyx and also was severely hyperechoic and had a longitude of 10 cm. Kidney, ureter and bladder radiograph showed the stone and also intense pelvic vascular calcification as well as diffuse osteopenia. Parathyroid sonography revealed a hypoechoic nodule in left lower pole of thyroid gland. Neck CT scan with contrast agent confirmed this nodule and its location behind the thyroid (Fig. 3). During her hospital admission she was found to have serum calcium of 13.5 mg/dl which was treated by calcitonin nasal spray. With the diagnosis of PHPT we referred the patient to surgery ward for parathyroidectomy. On June 2002, the patient underwent surgical intervention. Nodule was found to be 2.5×2×1 cm and had a capsule with 0.1 cm thickness, without capsular invasion. On light

Due to presence of hypercalcemia and high iPTH and normal phosphorus in spite of ESRD, we suspected PHPT. Evaluation included lower extremities X-ray which showed lucency in the distal fibula and vascular calcifications (Fig. 1). CT scan of right distal fibula showed a brown tumor (Fig. 2). Hand X-ray showed cortical resorption and vascular calcifications. Chest X-ray showed an old rib fracture in one of the ribs of right hemithorax, as well as generalized osteopenia. Parathyroid sonography revealed a hypoechoic nodule in left lower pole of thyroid gland. Neck CT scan with contrast agent confirmed this nodule and its location behind the thyroid (Fig. 3). During her hospital admission she was found to have serum calcium of 13.5 mg/dl which was treated by calcitonin nasal spray. With the diagnosis of PHPT we referred the patient to surgery ward for parathyroidectomy. On June 2002, the patient underwent surgical intervention. Nodule was found to be 2.5×2×1 cm and had a capsule with 0.1 cm thickness, without capsular invasion. On light

During her admission, she was treated for urinary tract infection (UTI) with IV antibiotics and DM was controlled with 40 units of NPH subcutaneous insulin. Considering chronic renal failure (CRF) and lab results, treatment with CaCO3, 2 g q8h after meals, and calcitriol (Rocaltrol), 0.25 µg/d, were started. Three days after starting treatment we noticed new blood levels of calcium and phosphorus as Ca, 12.5 mg/dl and P, 4 mg/dl. As a result Rocaltrol was discontinued and CaCO3 dose was decreased to 1 gram q8h. Nine days after admission, the patient was discharged with this prescription and was referred to surgeon for A-V fistula insertion. We requested the lab exams consisting of Ca, P, ALP, intact parathyroid hormone (iPTH) and renal function tests one week after discharge. On May 2002, she came to hospital complaining of intense pruritus; she had also weakness, malaise and whole body pain. The results of lab exams were Ca, 9 mg/dl; ALP, 5940 IU/L, P,4 mg/dl; iPTH, 395 pg/ml (RIA) (normal 9-55).

Fig. 1. Calcification of right femoral artery
microscopy parathyroid cells with epithelial cell proliferation, predominantly of chief cells, was seen. She was treated with CaCO3 and Rocaltrol and discharged.

On July 2002, she came to hospital again and was admitted due to intense weakness and illness. In lab exams she had serum calcium level of 3.2 mg/dl (corrected by serum albumin). Figure 4 shows serial calcium and phosphorus levels. She was admitted in CCU and we treated for hypocalcaemia with 10 ampoules of calcium gluconate in 5% DW 24 h infusion daily and oral CaCO3, 2 g q8h and Rocaltrol, 4 µg/d. General condition improved. The results of exams at the end of 10 days of admission were as follows; Ca, 7.8 mg/dl; BUN, 30 mg/dl; P, 3.8 mg/dl; Cr, 4.6 mg/dl; ALP, 3950 IU/ml. The patient was discharged at this time with prescription of CaCO3, 2 gram every 8 h and Rocaltrol 2.5 µg daily.

During the follow up in November 2002, we noticed continuing of the hypocalcaemia and decided to admit the patient. Since A-V fistula was not ready, we inserted internal jugular catheter and hemodialysis was started 3 times per week. After starting dialysis our drug order changed to Rocaltrol, 5 µg (pulse therapy) after dialysis sessions, and CaCO3, 5 g/q8h between meals. During each dialysis session we added five calcium gluconate ampoules to dialysate fluid. The patient was discharged on January 24th, 2003. On January 27th 2003 she was admitted to the hospital because of fever, chills and weakness. After sepsis workup and catheter extrusion, broad spectrum antibiotics were started and because of continuing hypocalcemia, treatment with daily infusion of 6 gluconate calcium ampules diluted in 5% DW at 8 h infusion rate was started in combination with Rocaltrol, 2.5 µg daily and CaCO3, 4 g every 8 h and magnesium sulfate 20%, 2 cc in two days.

One week after antibiotic therapy the fever diminished, general condition improved and she was discharged. On February 10th 2003, the patient came to the hospital because of illusion, anxiety, restlessness, and severe psychiatric disturbances. She was admitted and because of continuing hypocalcemia, we preferred the infusion route of calcium by 10 gluconate calcium ampules in 5% DW at 24 h infusion rate daily in addition to Rocaltrol 5 tablets 3 times daily. The level of iPTH was 775 pg/ml, using ELISA test, and 803 pg/ml, using RIA. For evaluation of parathyroid glands status, sonography and CT scan of the neck were done.

Fig. 2. CT scan of right distal fibula of the patient, showing a brown tumor.

Fig. 3. Parathyroid CT scan showed adenoma behind the left lower pole of the thyroid.

Fig. 4. Serial calcium, phosphorus and GFR during the times that patient referred to or admitted in the hospital.
which showed no parathyroids enlargement. Parathyroid isotopic scintigraphy with MIBI showed no parathyroid enlargement. We decided to perform bone biopsy for evaluation of osteitis fibrosa but the patient did not accept. Finally, on February 20th 2003 due to prolongation of treatment period, fatigue of family, and distance from medical center, the patient left the hospital and went back to her village and did not refer for hemodialysis. After 15 days she died at home. Her last iPTH was done on February 11th 2003 and was 915 pg/ml, using RIA.

**DISCUSSION**

PHPT is one of the most common endocrine disorders. Its clinical presentation has dramatically changed in the last 40 years and now the disease typically affects elderly women and is characterized by mild hypercalcemia and few traditional classic (bone and kidney) manifestations (5). The change in clinical presentation was largely caused by development of automated serum calcium measurement in the early 1970s that made possible the introduction of serum calcium determination in the routine biochemical screening and the identification of a large number of “asymptomatic” patients (5-8). This led also to a 5-fold increase in the apparent incidence of PHPT (catch-up effect). In the most recent study, a 21/1000 PHPT prevalence was found in women aged 55-75 years, which is equivalent to 3/1000 prevalence in the general population (8). Epidemiological studies performed in Rochester, Minnesota, have shown an apparent decline in the annual incidence from 75 to approximately 20/100,000 in the last decade (9). Most of this apparent decline in the incidence of PHPT is explained by the decline of the “catch-up effect”, although a number of other factors that might result in changes in PHPT incidence have been identified (8).

PHPT is a disease which has evolved from its classic presentation to a one quite different (1, 5) and now most patients have few symptoms and mild hypercalcemia (8-11) but it seems that the clinical presentations of PHPT in the eastern countries has not been basically changed. We have shown previously that Iranian patients with PHPT (30 cases) had many complications at the time of diagnosis (11). Biyabani et al. from Pakistan on 37 patients with PHPT (12), Younes et al. from Jordan on 40 PHPT patients (13) and Mishra et al. from India on 31 PHPT patients (14) have insisted on bone and renal presentations rather than the asymptomatic hypercalcemia as the clinical presentation of PHPT. Recently Bilezikian in study of PHPT in women of two cities, New York and Beijing, showed that compared to patients of United States, PHPT in China presents much differently. Patients were younger, with an average age of 37, the serum calcium level was much higher, averaging about 12 mg/dL, PTH was over 20 times of the upper limits of normal and average 25-hydroxyvitamin D concentration was much lower (8.8 ng/mL). Radiological evidence for osteitis fibrosa cystica was found in 60% of patients; virtually all patients had osteoporosis. Thirty-five percent of patients suffered pathological fractures, most often of the femur or humerus. Forty-two percent demonstrated kidney stones, with half of them showing bilateral disease. Constitutional features of weakness and easy fatigability were always present (15).

PHPT can occur at any age but the great majority of cases occur in subjects over than age of 45 years and women are affected twice as often as men (8-9). Solitary parathyroid adenoma accounts for 85 percent of cases of PHPT (4, 16). The diagnosis of the disease is based on high normal calcium or hypercalcemia with lower normal limit phosphorous and high alkaline phosphatase and finally high PTH values (5, 10, 17).

The classic manifestations of hyperparathyroid bone disease are osteitis fibrosa and brown tumors (2, 16-18). The most important renal manifestation of PHPT is nephrolithiasis, chronic renal insufficiency and a variety of abnormalities in renal tubular function particularly decreased concentrating ability (9, 10, 19). About 20 percent of patients with PHPT have nephrolithiasis caused by chronic hypercalcemia (9, 16). In fact among patients with nephrolithiasis who do not have overt hypercalcemia PHPT should be suspected in those patients, especially women, who have serum calcium concentrations in the high-normal range; some of these patients might have
normocalcemic hyperparathyroidism. The cause of nephrolithiasis in PHPT is probably multifactorial; an increase in the amount of calcium filtered at the glomerulus due to the hypercalcemia of hyperparathyroidism may lead to hypercalciuria despite the physiologic actions of PTH to facilitate calcium absorption (3, 20-23). Although the incidence of nephrolithiasis is reduced from that seen in classic PHPT, kidney stones remain the most common manifestation of symptomatic PHPT (5, 8-10).

In the case of association of PHPT with CRF, disturbed renal function may play an important role in the clinicopathological presentation of PHPT. In a recent and interesting report by Yamashita et al. on 141 patients with surgically proven PHPT, he found DM was more frequent in the renal failure group of his patients (n=37), in whom the creatine clearance was <70cc/min (24). Results of this study as well as our case report raise the question of association between DM and PHPT with chronic renal failure, an association that remained to be determined.

In our patient neglecting to evaluate the etiologies of recurrent nephrolithiasis for more than one decade and absence of obvious hypercalcemia were causes of failure to diagnosis hyperparathyroidism. Persistence of hypercalcemia after 3 days of calcium and Rocaltrol therapy led us to suspect PHPT. Since she did not have hyperphosphatemia, secondary hyperparathyroidism (SHPT) was easily ruled out, albeit in some cases with SHPT complicated by malnutrition hyperphosphatemia cannot be seen; in fact it may sometimes be difficult to distinguish primary from secondary hyperparathyroidism when advanced renal failure coexists (25). It seems that the superimposed renal failure by itself can intensify the PHPT, as Mizumoto et al. in his five case report of PHPT accompanied by CRF have shown (26).

After localization of the adenoma and surgical resection, despite treatment by calcium carbonate and oral calcitriol, the patient developed severe hypocalemia. One of the factors contributing to hypocalemia following parathyroidectomy is hungry bone syndrome. In this state postoperative hypocalemia is severe and prolonged despite normal or even elevated levels of PTH and is accompanied by hypophosphatemia. This phenomenon occurs mainly in patients who have developed bone disease preoperatively due to chronic increase in bone resorption induced by high levels of PTH (osteitis fibrosa) (21-23).

In the high turnover state associated with hyperparathyroidism, the enhanced bone resorption produced by osteoclast leads to increased osteoblastic bone formation, sudden withdrawal of PTH results in disappearance of osteoclasts, however, osteoblast-mediated bone formation continues, leading to a marked increase in bone uptake of calcium and phosphate, thus the development of hypocalemia and hypophosphatemia is due both to decreased bone resorption and to persistent enhancement of bone formation (5, 19, 21). The degree of fall in the plasma calcium concentration is directly related to the preoperative rate of bone turn over and to the degree of PTH elevation (5, 18, 19, 21). Higher preoperative levels of calcium and alkaline phosphatase are markers of PTH activity and also predictive of increased risk of hungry bone syndrome (5, 20, 21). In this case, long-standing disease and severe bone involvement were causes of development of severe hungry bone syndrome. The syndrome is considered to be present if the plasma calcium concentration is below 8.5 mg/dl and plasma phosphate concentration is below 3 mg/dl on the third post operative day. In one study 13 percent of 198 PHPT patients fulfilled these criteria, with a mean plasma calcium concentration of 8.2 mg/dl and mean plasma phosphate concentration of 2 mg/dl. The hypocalemia resolved by ninth day but hypophosphatemia persisted for several months (19, 20). Laroche et al. in a study on two cases of advanced PHPT with CRF among his 19 patients operated for PTX found worsening of kidney function after surgery and concluded that a sharp decrease in serum level of PTH and parathyroid hypertensive factor playing a role via intrarenal homodynamic changes could be the factor (27).

In conclusion, more attention must be paid to patients with recurrent nephrolithiasis, vague symptoms and bone pain and such patients must be evaluated for PHPT. Also, we propose routine serum calcium measurement to find the cases of this disease in its earlier stages before the start of complications. We hope to find PHPT in its asymptomatic stages.
REFERENCES


