

Supernumerary Parathyroid Glands in A Patient with Tertiary Hyperparathyroidism (Case Report)

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Abstract

Supernumerary parathyroid glands could be affected by tertiary hyperparathyroidism after long-term phosphate therapy in an adult-onset hypophosphatemic Osteomalacia, and it may be the cause of refractory hyperparathyroidism. We Report a 63-years old Jordanian man who has been diagnosed at age of 26 years as having sporadic adult-onset hypophosphatemic Osteomalacia and developed tertiary hyperparathyroidism as a complication of prolonged oral phosphate therapy, which requires repeated surgical interventions. This patient had six parathyroid glands all ended with tertiary hyperparathyroidism, the 5th and the 6th gland were activated serially. This rare association is discussed along with a review of literature.

Keywords: Hypophosphatemic osteomalacia, Long-term phosphate therapy, Tertiary hyperparathyroidism, Supernumerary.

(J Med J 2014; Vol. 48 (3):212- 219)

Received

Oct. 13, 2013

Accepted

May 8, 2014

Introduction

Adult-onset hypophosphatemic osteomalacia is a rare acquired form of hypophosphatemia. It is attributed to reduced renal tubular reabsorption of the filtered phosphate in patients older than 15 years⁽¹⁾. Parathyroid function is generally described as normal in patients with hypophosphatemic osteomalacia before initiation of therapy with phosphate salts; however, hyperparathyroidism is an occasional complication of treatment^(1, 2). We describe a male patient in whom long-term phosphate supplementation resulted in tertiary

hyperparathyroidism associated with surgically proven adenomatous hyperplasia of the four normally located glands followed by serial activation of the 5th and 6th parathyroid glands.

Case Report

A 64 years- old Jordanian man had sought medical attention first in 1974 when he was 26 years old due to progressive skeletal pain and generalized weakness that rendered him almost crippled within one year. He was treated first in Germany at Klinikum Westend in Berlin, and found to have a high alkaline phosphatase level, low serum phosphorus concentration,

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increased phosphate clearance and phosphate excretion index. He had a normal serum calcium concentration and urinary calcium excretion. The phosphate clearance decreased after infusion of calcium. His urinary excretion of hydroxyproline was increased, but no other abnormal aminoaciduria or albuminuria was noted. The serum 25-hydroxyvitamin D was reported as normal on three different occasions, but no exact data was recorded. Similarly, the plasma parathyroid hormone (PTH) concentration, arterial blood gases, and complete hematologic and biochemical workup were reported to be normal. The x-ray films showed signs compatible with osteomalacia, especially in the thoracic vertebrae, which was confirmed by bone biopsy. Intestinal absorption of calcium was reported to be severely impaired. The patient was diagnosed as having vitamin D-resistant rickets, and treatment with 40,000 IU of vitamin D per day was initiated. His symptoms were considerably diminished; however, his biochemical findings remained unchanged.

In February 1979, he was seen at Hammersmith hospital in London, at that time he was unable to walk without aid. The laboratory workup at that time revealed a serum calcium level of 2.47 mmol/L, serum phosphorus of 0.43mmol/L, alkaline phosphatase of 360 U/L, phosphate excretion index of +0.121, and normal urinary calcium excretion. The reports of his skeletal x-ray were notable for the presence of fractures and Looser transformation zones in the scapulae, right radius, several ribs, both iliac bones, and both femoral necks. Iliac crest biopsy and quantitative histological evaluation of the decalcified bone confirmed the diagnosis of osteomalacia.

Oral treatment was initiated with phosphate (0.5 g of effervescent phosphate), one tablet three times daily for a week, and then 1 α -

hydroxycholecalciferol, 2 g three times per day, was added to the regimen. The patient's clinical condition improved dramatically, and his biochemical profile normalized within 5 weeks.

Our first contact with the patient was in February 1998 when he had progressive right hip pain that forced him to use a cane for walking; he insisted that he was compliant with the treatment. On examination the patient height was 180 cm and weight was 75 kg, he was normotensive with limited abduction in his right hip and generalized ill looking, there were no family history of similar medical problems or short stature.

At the time of our initial assessment, laboratory findings showed hypercalcaemia [serum calcium level, 2.95 mmol/L (11.8mg/dl)], normophosphatemia (serum phosphorus, 0.87 mmol/L), hypercalciuria (urine calcium, 6.7 mmol in a 24-hour urine specimen), hyperphosphaturia (urine phosphate in a 24-hour urine collection, 42.0 mmol), Creatinine clearance of 80 mL/min, high alkaline phosphatase (705 U/L), and very high PTH (360 pg/mL), which was measured by using an immunoradiometric assay for quantitative determination of biologically active intact PTH (sensitivity of 0.7 pg/mL and <0.1% cross reactivity). With use of a radioimmunoassay for quantitative determination of 25-hydroxyvitamin D and other hydroxylated metabolites (sensitivity of 1.5 ng/mL and cross-reactivity with other forms of vitamin D of 0.8%), the 25-hydroxyvitamin D value was 10.9ng/mL. A radiographic skeletal survey showed generalized osteopenia, loss of dental lamina dura, widened anterior rib ends, "codfish vertebrae," a large osteolytic lesion of the right iliac bone, and subperiosteal bone resorption of the radial end of the middle phalanges.

Magnetic resonance imaging showed

enlargement of all four parathyroid glands. the diagnoses of tertiary hyperparathyroidism was made and parathyroidectomy of the four glands performed with implantation of a piece of a gland on the Left arm, all the four glands were enlarged (the weight of the right superior gland was 0.3 g, the right inferior was 3.635 g, the left superior was 1.34 g, and the left inferior was 3.215g)⁽³⁾. Histopathological examination of these glands showed parathyroid hyperplasia. The patient condition improved gradually, he was able to walk without aid and return to his work. He was maintained on caltrate 1.2 gm daily, Oral phosphate (0.5 g of effervescent phosphate), one tablet three times daily, and 1 α -hydroxycholecalciferol, 1 g twice daily.

In June 2003; five years after the operation, the patient complained of skeletal aches and pain again with easy fatigability and inability to walk without aid. Lab work up revealed mildly elevated serum calcium of (10.6mg/dl), low serum phosphate level (0.9mg/dl) with high PTH level (238pg/ml), high alkaline phosphates of 158U/L (references range 40-129U/L). The patient was also noticed to have high Blood pressure for which he was started on calcium channel blocker. Skeletal survey was repeated and it showed osteopenia and new multiple lytic lesions in the ribs and the pelvic bone, sestamibi scan showed an area of increased activity in the mediastinal region mostly in the superior part with no other area of activity. Chest CT-scan showed 2x1.5 cm soft tissue nodule in the retrosternal area related to the thymus, for which the patient underwent thymectomy with removal of the ectopic parathyroid tissue there (Fig. 1).

The patient condition improved only for few days, and then the patient complained of skeletal aches and pain again with easy fatigability. PTH level, serum Ca start to rise up again. One month after the second surgery (thymectomy) his lab workup showed serum

Calcium of 11.5mg/dl, parathyroid hormone of 1042pg/ml. Sestamibi scan was repeated at the 20th of July 2003, which showed an area of increased activity at the region of the left lower pole of the thyroid gland. Ultrasound thyroid was consistent with multinodular goiter (MNG). The patient underwent hemithyroidectomy of the left thyroid lobe with the removal of the impeded parathyroid tissue. Histopathological report showed parathyroid hyperplasia surrounded by thyroid tissue. The PTH level drops dramatically to 100pg/ml and serum calcium was 9mg/dl while whole body sestamibi scan fail to show any parathyroid activity. The patient condition improved except from hoarseness of voice noticed after the operation. The patient was discharged on calcium, phosphate and 1 α – hydroxycholecalciferol daily beside his antihypertensive medications.

The patient parathyroid hormone level showed steady slow progressive increase and his serum calcium & phosphorus levels was fluctuating which was related to complaint issues. The patient develops lower urinary tract symptoms at 2006 with signs of prostate enlargement which was proved by ultrasound, but he was relatively well until March 2008 when he was admitted again with polyurea, polydipsia and generalized bone pain, his serum calcium was 13.7mg/dl, serum phosphate 3.4mg/dl, serum magnesium 1.91mg/dl, parathyroid hormone level was 709.8pg/ml, chest x-ray showed evidence of bilateral multiple old rib fractures, the heart was normal and no pleural effusion.

Whole body sestamibi scan was done and the only active parathyroid tissue was on the left arm, there were lateralization repeatedly in the PTH levels between right and left arm samples, the left arm samples were always high (300-400pg/ml) while the right arm was near the upper normal reference range. The

previously implanted parathyroid tissue was removed through an elliptical incision around

the previous left arm scar with excision of the gland and the surrounding muscle, (Fig 3).

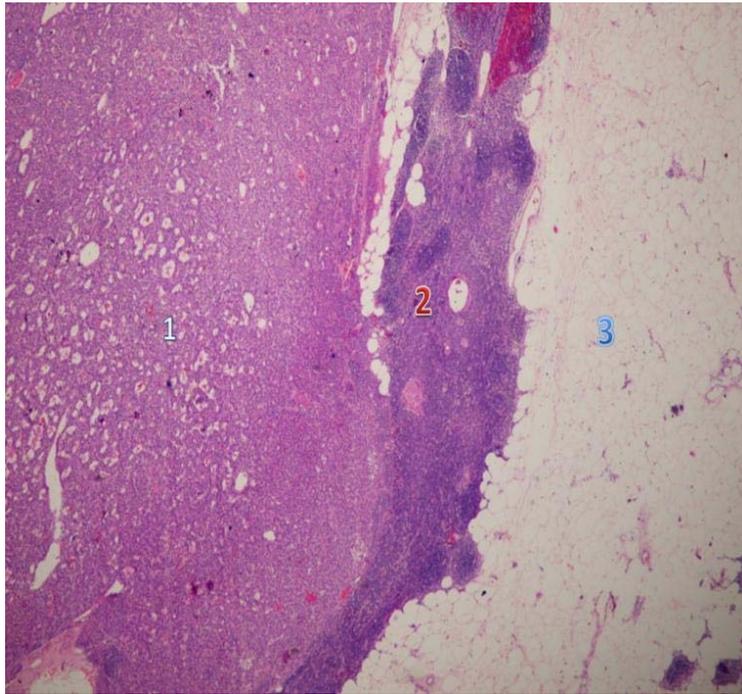


Figure 1. Showed (1) histological features of the parathyroid tissue with (2) remnants of the thymus as removed from the patient at the second operation surrounded by fat tissue (3).

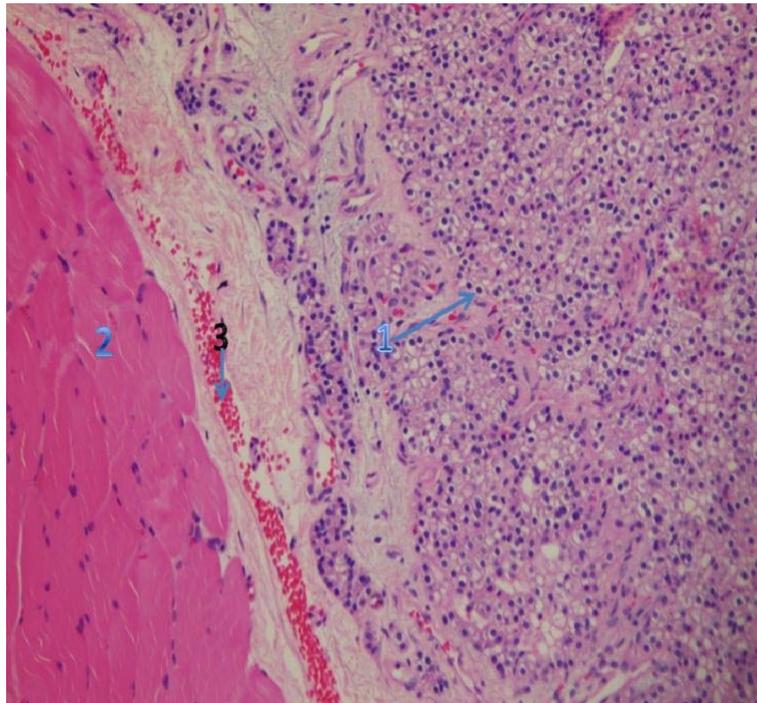


Figure 2. Showed (1) histological features of parathyroid tissue, arrow pointing to chief cell. (2) Skeletal muscle cells removed from the patient left arm at the fourth operation adjacent to parathyroid tissue. (3) Blood vessel.

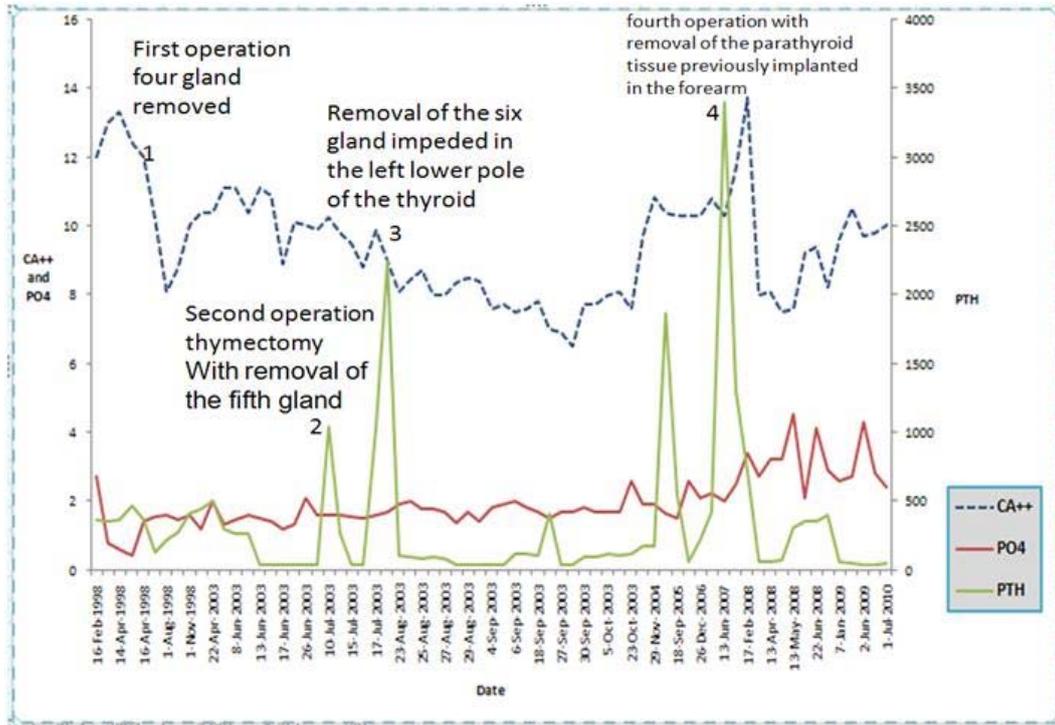


Figure 3. Calcium, phosphorus, PTH levels) for the follow up period, numbers are related to surgical interventions

In the last two years, the patient condition remains stable, his PTH, serum calcium, and phosphorus levels were within the normal ranges. Levels were between 32-48pg/ml for PTH (right arm sample), left arm samples continue to show PTH of 80-100pg/ml. His serum calcium was between 8.2-10mg/dl, and his serum phosphate was between 2.4-2.8mg/dl (Fig. 3).

Discussion

Most humans have 4 parathyroid glands. Postmortem studies reveal that 84% have 4 parathyroid glands, 13% have 5 or more (supernumerary) glands, and 3% of individuals have only 3 parathyroid glands, but numbers exceeding five glands are rare⁽⁴⁾. Wang studied a total of 645 parathyroid glands recovered from 160 postmortem subjects of whom 156 had 4, 3 had 5, and only 1 had 6 parathyroid glands⁽⁵⁾. Supernumerary glands could be

found in variable ectopic sites including retroesophageal, retropharyngeal, intrathyroid, intrathyroid, carotid sheath, submandibular, retroclavicular, and an occasional mediastinal location such as the aortopulmonary window⁽⁶⁾.

The presence of a fifth gland is well recognized cause of refractory hyperparathyroidism but finding of a sixth gland is extremely rare. Supernumerary hyper functioning parathyroid glands were previously reported patient with chronic renal failure who develops Secondary hyperparathyroidism⁽⁷⁾. In addition, Gordon HE reported a case of a patient with Secondary hyperparathyroidism who had eight parathyroid glands⁽⁸⁾ but among the spectrum of cases reported in the English literature we could not find a report of tertiary hyperparathyroidism associated with six or more parathyroid glands complicating sporadic

adult-onset hypophosphatemic osteomalacia; we describe this case as sporadic adult-onset hypophosphatemic osteomalacia because the patient had normal bone development and attained a height of 180 cm. Furthermore, the absence of a family history of any bone disease or similar conditions is supportive of the sporadic label.

Our case represents a rare complication of prolonged oral phosphate treatment, and also it was one of the rare cases where six parathyroid glands were found. Tertiary hyperparathyroidism caused originally by normally located four hyperplastic parathyroid glands and later by ectopically found two parathyroid adenomas in two different anatomical positions (one in the thymus and the other one were impeded in the thyroid gland) and lastly by the activated parathyroid tissue implanted in the left arm previously.

Orally administered phosphate supplementation is the mainstay of therapy for Hypophosphatemic osteomalacia of diverse causes; however, it is well recognized that long-term phosphate therapy may induce a decrease in serum calcium levels and trigger the release of PTH, resulting in secondary hyperparathyroidism. Sometimes, chronic parathyroid stimulation may eventually lead to adenomatous hyperplasia and become autonomous, resulting in hypercalcaemia (tertiary hyperparathyroidism)⁽⁹⁾ and this was the case of our patient.

Rivkees et al. reported three girls with familial Hypophosphatemic rickets developed sever tertiary hyperparathyroidism after prolonged treatment with oral phosphate. Profound multiglandular hyperplasia was found in each patient after surgery. They observed that even in the presence of considerable parathyroid hyperplasia and dysfunction, oral phosphate further stimulated

parathyroid activity, possibly leading to the further hyperplasia⁽²⁾. The functional characteristics of the excised parathyroid tissue were examined in vitro and revealed that higher calcium concentration is needed to suppress PTH release.

Our patient develop sever multiglandular disease first in the normally located parathyroid glands, and after the first surgery he continue to receive oral phosphate for his condition, this exposed the remaining glands to develop hyperplasia as described previously, this case is an excellent prove for the possible complication of oral phosphate therapy and suggests that in the presence of prolonged phosphate therapy, the parathyroid's proceed through stages of progressive Calcium insensitivity with the development of sever hyperparathyroidism. The serial activation of the 5th and 6th parathyroid glands is a good explanation especially the patient remains free of symptoms for five years after the first operation, and even sestamibi scanning was not done befor 1998 (was not available in Jordan) these glands was not hyper functioning before 2003.

The origin of persisting PTH after the last operation (were even the implanted gland were removed also) is not entirely clear. Missed supernumerary glands could be there or at least small nested pieces. It is also presumed that small nests of parathyroid cells left behind the last surgery undergo hyperplasia because of their continued exposure to the milieu of chronic phosphate exposure.

High success rate of parathyroid reoperation may be achieved with improved localization diagnosis, new technical possibility for diagnosis as Tc99m-MIBI-SPECT, or SPECT scan, with 3-D capability, combined with CT imaging seems very helpful, particularly in recurrent or residual

hyperparathyroidism⁽¹⁰⁾. Technetium-sestamibi scanning has been extensively studied in patients with primary hyperparathyroidism but not tertiary hyperparathyroidism. While sestamibi imaging is now the imaging procedure of choice (particularly for localization of single parathyroid tumors in the mediastinum) in patients who are not cured after initial neck exploration, it is less helpful in localizing multiple abnormal parathyroid glands or hyperplasia, and coexisting thyroid disease can decrease sensitivity⁽¹¹⁾. This explained why sestamibi scan fail to detect the six gland before the second operation especially it was imbedded in the thyroid and associated with MNG.

Finally, although multiple mediastinal parathyroid tumors have been reported in patients with carcinoma of the parathyroid gland⁽¹²⁾, no pathologic changes that could suggest malignant neoplasms were found in

any of the submitted specimens of our patient.

Conclusion

This case emphasizes that patients with refractory hyperparathyroidism could have multiple parathyroid glands especially in the extra cervical areas. These glands could become hyperplastic (either simultaneously or consecutive) if tertiary hyperparathyroidism developed. Detection of hyperparathyroidism at early stages may lead to successful treatment before it become irreversible.

Consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images

Competing interests: The authors declare that they have no competing interests. All authors read and approved the final manuscript.

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تعدد الغدد جارات الدرقية العالي عند مريض لديه فرط نشاط متكرر

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1- المركز الوطني للسكري

الملخص

في هذا البحث نقدم حالة نادرة لمريض يبلغ من العمر 63 عاما ويعاني من لين العظام المزمن الناتج عن تدني الفسفور وقد تمت معالجته بالفسفور العضوي لفترة طويلة مما أدى لزيادة نشاط الغدد جارات الدرقية لديه وبالبحث تبين أن لديه تعدداً عالياً من الغدد جارات الدرقية. وقد تم اكتشاف ست غدد جارات درقية على الأقل.

إحداها خارج الرقبة وقد تنشطت إلى الدرجة الثالثة بشكل متوالٍ مما استدعى التدخل الجراحي عدة مرات.

الكلمات الدالة: فرط نشاط متكرر، العلاج بالفسفور العضوي لفترة طويلة، الغدد جارات الدرقية.