Recurrent Persistent High Parathyroid Hormone with No Recognized Source

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ABSTRACT

The diagnosis of primary hyperparathyroidism (PHPT) is based on an elevated concentration of parathyroid hormone (PTH) in patients with hypercalcemia and hypercalciuria. A recent study showed that the prevalence of PHPT was 274 cases per 100,000 population in Bahrain, where the incidence of the disease has significantly increased in those aged of 50 years and above. A case of recurrent primary hyperparathyroidism and hypercalcemia is present. This occurred not once but twice after surgical treatment, in which the source of persistently high PTH was not identified despite thorough investigation. Parathyroidectomy is the definitive curative treatment for PHPT and is indicated for all patients with symptomatic PHPT, evidence of renal involvement, osteoporosis, or fractures; when the serum calcium level is greater than 1 mg/dL, for patients aged 50 years or younger, and when parathyroid cancer is suspected. The cause of this interesting case is still undetermined so far. One of the goals of this report was to draw attention to this common complication, the role of imaging, and the management in such cases. We strongly believe that post-surgical treatment of recurrent hyperparathyroidism needs more attention as there is a lack of studies on the mechanism, risk factors, and most importantly, the management of such cases.

INTRODUCTION

The diagnosis of primary hyperparathyroidism (PHPT) is based on an elevated concentration of parathyroid hormone (PTH) in patients with hypercalcemia and hypercalciuria[1]. It is considered the third most common endocrine disorder worldwide, but its incidence is variable in different populations. A recent study showed a prevalence of PHPT of 274 cases per 100,000 population in Bahrain, where the incidence of the disease has significantly increased in those aged 50 years and above[2].

CASE PRESENTATION

A 72-year-old male presented to the endocrine clinic with history of persistent hypercalcemia. The patient was known to have osteoporosis, diabetes, dyslipidemia, hypertension, and multiple renal stones. He also had a history of hyperparathyroidism, which began in 2004, when he presented with pain and weakness in the back and lower limbs. At the time, he was diagnosed with primary hyperparathyroidism based on a parathyroid scan, which showed a small focus of increased uptake in the left lower neck indicating a parathyroid adenoma. Laboratory investigations at the time revealed the following: serum calcium level of 3.86 mmol/L, phosphate level of 79 mmol/L, urea level of 6.8 mmol/L, creatinine level of 110 mmol/L, albumin level of 43 g/L, alkaline phosphatase level of 290-372 u/L, vitamin D level of 41 nmol/L, urinary calcium level of 13.69 mmol/day, and parathyroid hormone (PTH) level of 995.3 ng/L. A CT scan of the chest, abdomen, and pelvis yielded unremarkable results.

The patient subsequently underwent surgical removal of a left inferior parathyroid adenoma in 2004. His post-operative PTH level was 47 ng/L. There were no records of intra-operative PTH measurement. The histopathology report described a firm, tan, ovoid mass measuring 2 x 1 x 0.7 cm^3 and weighing 1.82 g, which was consistent with a parathyroid adenoma in microscopy. Upon discharge, the patient was prescribed calcium supplements at 600 mg twice daily and vitamin D (calcitriol) at 0.25 mcg daily.

The patient remained well until 14 years later, when he noticed recurrent body aches. Laboratory investigations revealed an increase in serum calcium and PTH. A parathyroid catheter (venous sampling) examination was performed, and 15 sampling sites showed significant increases in PTH. A choline PET scan was done, and the result was negative. Therefore, the patient underwent a second surgery. The procedure involved total thyroidectomy with removal of the 3 remaining parathyroid glands and implantation of a portion of the right upper parathyroid gland into the right forearm. An intra-operative rapid test did not show an adequate drop in PTH. The histopathology report of the 3 removed parathyroid glands was negative for malignancy and hypercellularity. The patient was discharged with a prescription of thyroxine and cinacalcet at 30 mg twice a day.

The patient's serum calcium and PTH remained persistently high until the time of re-evaluation 4 years later. He underwent a sestamibi scan, and the result was negative, even in the forearm where the implanted parathyroid gland was located. At the same time, he was also noted to have elevated prolactin and insulin-like growth factor-1 (IGF-1). This raised the suspicion of multiple endocrine neoplasia type 1 (MEN-1). Therefore, a pituitary MRI was done, which revealed sellar remodeling with an empty sella. An ultrasound of the abdomen showed no pancreatic lesions, making MEN-1 unlikely. The patient is currently

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taking cinacalcet at 120 mg. His latest investigations show a calcium level of 2.6 mmol/L, PTH level of 411 pg/ml, and vitamin D level of 68.9 nmol/L.

DISCUSSION

The present case is one of recurrent PHPT and hypercalcemia. This occurred not once but twice after surgical treatment, in which the source of persistently high PTH was not identified despite thorough investigation. Parathyroidectomy is the currently the treatment of choice for this condition.

The "Miami criterion" is defined as a PTH decrease > 50% from either the highest pre-incision or pre-excision hormone level in a peripheral blood sample obtained 10 minutes after complete excision of all hyper-functioning parathyroid tissues. An intra-operative reduction of PTH > 50% should then occur, and the observed hormone dynamic allows the termination of the operation without further exploration. If the 10-minute sample does not meet the criterion, a delayed sample at 20 minutes is measured, and/or further neck exploration is continued until all hyper-secreting parathyroid glands are removed. This is confirmed by another >50% decrease from the highest subsequent pre-excision sample. This protocol was developed and refined at the University of Miami and indicates a successful parathyroidectomy with a sensitivity of 98%, specificity of 97%, positive predictive value of 99%, negative predictive value of 90%, and overall accuracy of 97%[3].

Studies have shown that persistent hyperparathyroidism after total parathyroidectomy with auto transplantation is never graft dependent but is related to missed tissue in the neck or mediastinum. Other causes are failure to locate all four hyperplastic glands and overlooking supernumerary glands, which can be expected in 13% of patients with secondary hyperparathyroidism[4]. Many studies have been done to determine the risk factors for persistent or recurrence of hyperparathyroidism after surgical treatment. Most of these have noticed that the majority of patients with recurrent post-operation hyperparathyroidism where those who initially presented with musculoskeletal symptoms and patients who are Black.

Some of the studies found that the recurrence rate is somehow related to the pre-operative PTH level, with higher levels corresponding to a higher risk of recurrence. Others suggested that the recurrence is related to bone hunger, vitamin D deficiency, inadequate calcium intake or absorption, reduced peripheral sensitivity to PTH, chronic kidney disease, and renal leak of calcium. Women were also more likely to have elevated post-operative PTH levels[5,6]. For the prevention of recurrence, calcium and vitamin D supplements immediately after surgery have been suggested.

Imaging studies play a critical role for these patients. Surgeons should not perform a blind exploration in the neck pre-operatively because a positive imaging study can almost always be obtained and is a major guide during surgery. The goal of imaging is to obtain an adequate roadmap to guide the surgeon. Imaging can be divided into noninvasive methods (ultrasound, technetium 99m sestamibi scan, 4D CT scan, and occasionally MRI) and invasive methods (ultrasound-guided PTH aspiration and angiographic procedures, including arteriography and venous sampling for PTH).

However, all imaging studies are found to be less reliable in re-exploration of the neck, and false-positive and false-negative results are frequently noticed[7]. For patients who are denied, fail, or refuse re-exploration, there are medical options, such as simple observation and maintenance of adequate hydration for patients with mild disease. Pharmacological agents can be used if the disease is moderate to severe and surgery is not an option. The pharmacological options include bisphosphonates, hormonal replacement therapy, and the calcimimetic cinacalcet[8,9].

CONCLUSION

We have presented an interesting case of recurrent hyperparathyroidism with a cause that is undetermined thus far. One of the goals of this report was to draw attention to this common complication, the role of imaging, and the management in such cases. We strongly believe that more attention is warranted toward recurrent hyperparathyroidism post-surgical treatment as there is a lack of studies on the mechanism, risk factors, and most importantly, its management.

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