A case of hypercalcemic parathyroid crisis in a patient with normocalcemic hyperparathyroidism

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Summary

We present a man with normocalcemic primary hyperparathyroidism who developed hypercalcemic parathyroid crisis following years of normal blood calcium levels. The patient was a 59-year-old male with a history of recurrent nephrolithiasis. Initial PTH was 70 ng/L (13-54) with serum calcium of 2.44 mmol/L (2.1-2.5), albumin 39 g/L, and phosphate 0.70 mmol/L (0.8-1.5). Many repeat serum total calcium levels were normal. 24-hour urine calcium was within normal limits at 6.82 mmol/day. He was followed with regular monitoring of serum calcium and PTH, and remained asymptomatic and normocalcemic for 8 years until he suddenly presented feeling unwell and was found to have a serum calcium of 4.05 mmol/L and PTH of 585 ng/L. He was referred to hospital and treated with intravenous fluids and pamidronate. Sestamibi scan revealed a large MIBI-avid soft tissue nodule, highly suspicious for a parathyroid adenoma. Six weeks later, he underwent right unilateral parathyroidectomy. Pathology demonstrated a 2.2x 2.0 x2.1 cm benign parathyroid adenoma. Postoperatively he has remained normocalcemic with normal PTH.
Normocalcemic primary hyperparathyroidism is not clearly associated with adverse clinical outcomes and longitudinal studies suggest it rarely progresses to overt hypercalcemia. This is the first case of normocalcemic primary hyperparathyroidism that evolved to hypercalcemic crisis. We postulate an infarct of the large parathyroid adenoma resulting in sudden marked increase in PTH secretion. Normocalcemic hyperparathyroidism may not have a benign course if associated with a large parathyroid adenoma. Progression to severe hypercalcemia may occur suddenly in rare cases.

KEY WORDS: calcium; primary hyperparathyroidism; parathyroid hormone; hypercalcemia; parathyroidectomy; metabolic bone disease.

Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by elevated serum and ionized calcium levels and elevated or inappropriately normal parathyroid (PTH) hormone levels (1). Over the past decade, an entity of PHPT that presents with elevated PTH levels and normal calcium levels has been recognized; this has been deemed normocalcemic PHPT (2). These cases are typically identified due to PTH measurement during comprehensive biochemical screening of individuals with osteoporosis or nephrolithiasis (1). We present a man with normocalcemic primary hyperparathyroidism who developed hypercalcemic parathyroid crisis following years of normal blood calcium levels.

Case

The patient was a 59-year-old man with a history of recurrent nephrolithiasis. PTH was found to be elevated during investigation for metabolic etiologies of nephrolithiasis. Initial PTH was 70 ng/L (13-54) with serum calcium of 2.44 mmol/L (2.1-2.5), albumin 39 g/L, and phosphate 0.70 mmol/L (0.8-1.5). Many repeat serum total calcium levels were normal. Ionized calcium was normal at 1.25 mmol/L. 24-hour urine calcium was within normal limits at 6.82 mmol/day. Calcium to creatinine ratio was 0.5 mmol/mmol. The patient had normal renal function with baseline creatinine of 80-90 µmol/L and normal eGFR. Vitamin D level was initially 59.5 nmol/L. After a course of vitamin D supplementation, a follow-up vitamin D level was 76.9 nmol/L and no change to serum PTH level was observed. Initial bone mineral density (BMD) showed T scores of -2.7 at the spine, -0.4 left total hip, -1.0 left femoral neck, and -0.3 left forearm. There was no previous history of fracture and no alternate causes of low spine BMD identified.
The patient was followed with regular monitoring of serum calcium and PTH, and remained normocalcemic for 8 years without developing any further clinical sequelae of PHPT, until he suddenly presented feeling unwell and was found to have a serum calcium of 4.05 mmol/L and PTH of 585 ng/L. He was referred to hospital and treated with intravenous fluids and pamidronate. Sestamibi scan revealed a large MIBI-avid soft tissue nodule, highly suspicious for a parathyroid adenoma. Endocrine surgery was consulted and six weeks later, he underwent right unilateral parathyroidectomy. Pathology demonstrated a 2.2 x 2.0 x 2.1 cm benign parathyroid adenoma.
Postoperatively the patient has remained normocalcemic with normal PTH over three years of follow-up. Recent investigations show calcium level of 2.33 mmol/L and PTH level of 32 ng/L, and calcium to creatinine ratio of 0.2 mmol/mmol. The patient has had continued recurrence of nephrolithiasis since his parathyroidectomy. Current BMD shows T-scores

of -0.3 at the left total hip, -0.3 at the left femoral neck, and 0.5 at the forearm (BMD of the spine was not interpretable due to sclerosis from degenerative arthritis). There was a slight increase in the bone density at the total hip of 0.017 g/cm^2 compared to the baseline BMD.

Discussion

There is limited data regarding the natural history of normocalcemic PHPT. It has been suggested that PHPT has a biphasic presentation, with normocalcemic PHPT representing a subclinical phase that is followed by a hypercalcemic phase (3). Cohort studies have demonstrated a benign clinical course without development of adverse outcomes or progression to hypercalcemia over several years (4, 5). One study, which observed progression to hypercalcemia in 19% of patients over a median 3-year follow-up interval, found that older age, higher baseline serum calcium levels, and higher baseline serum calcium excretion were all factors predictive of progression to hypercalcemia (6). However, the cohort of patients in this study did not have the typical phenotype of normocalcemic PHPT, as at baseline majority had features in keeping with classic PHPT including nephrolithiasis, osteoporosis, and/or fragility fracture, so the rate of progression to hypercalcemia is likely not representative of truly asymptomatic normocalcemic PHPT. Even in this cohort, progression to severe hypercalcemia did not occur; all the patients that developed hypercalcemia maintained serum calcium within 0.25 mmol/L of normal. Taken together, these previous studies suggest that patients with normocalcemic PHPT typically maintain a subclinical course for many years. Eventual progression to mild hypercalcemia may occur in a minority of patients, but this appears to have an insidious onset and may be preceded by clinical features of PHPT (2, 6). This is the first case of normocalcemic primary hyperparathyroidism that evolved to hypercalcemic crisis. As we did not observe any clear precipitating factors, we hypothesize that this may have been due to an infarct of the large parathyroid adenoma albeit no longer seen in the pathologic specimen at surgery 6 weeks later. However, given the lack of evidence of infarction on histopathology, this is purely speculative although spontaneous infarction and subsequent functional change of hormone producing tumours have been described elsewhere (7, 8).

The observation of recurrent nephrolithiasis post parathyroidectomy is not unexpected. The recent urine calcium to creatinine ratio, though reduced compared to pre-surgery, remains consistent with hypercalciuria (9), which is a known risk factor for nephrolithiasis (10). Though both urine calcium excretion and risk of nephrolithiasis have been shown to decrease following parathyroidectomy in patients with PHPT, both remain elevated compared to the general population, and a clear benefit of parathyroidectomy over observation with respect to risk of nephrolithiasis has not been demonstrated (10). A large hospital registry study demonstrated risk of nephrolithiasis was increased from baseline for over ten years following parathyroidectomy (11). One theory is the causal relationship between PHPT and nephrolithiasis is such that renal hypercalciuria may lead to development of PHPT, which lends explanation as to why the risk of renal stones may predate diagnosis of PHPT and persist following surgery (12).

Patients with PHPT classically show more marked decreases in BMD at the distal third of the forearm compared to other sites; this finding is thought to be due to the greater effect of PHPT on cortical bone (1). We did not observe this densitometric pattern in our patient, who had osteoporosis at the lumbar spine. Previous Authors have shown that compared to a cohort of patients with hypercalcemia PHPT, patients with normocalcemic PHPT did not have a preponderance of cortical bone loss, as osteoporosis tended to be more common at the lumbar spine and hip than it was at the distal one third radius in these patients (6). A subsequent study has demonstrated that patients with normocalcemic PHPT had significantly higher BMD at the distal radius compared to patient with hypercalcemic PHPT, while BMD did not significantly differ at the lumbar spine or femoral neck between the hypercalcemic and normocalcemic patients (13). While reduction in cortical BMD is a hallmark of hypercalcemic PHPT, this does not appear to necessarily be the case for patients with normocalcemic PHPT. Nonetheless, successful parathyroidectomy has been shown to results in improvements in BMD in patients with normocalcemic PHPT that are comparable to those observed in hypercalcemic PHPT (14). Unfortunately, we cannot draw any definitive conclusions on the effect of parathyroidectomy on BMD in our patient, given the measurements at the lumbar spine post parathyroidectomy are not interpretable.

The most recent guidelines concerning PHPT recommend patients with normocalcemic PHPT should be referred for surgery if there is evidence of disease progression with nephrolithiasis, nephrocalcinosis, worsening BMD, or fracture (14). It is therefore important to highlight that our patient presented a few months prior to the publication of these guidelines. As we have discussed, existing evidence to guide the long-term management of normocalcemic PHPT is limited to a few small cohort studies (4-6). Nonetheless, we agree with the current guideline based recommendation to perform parathyroidectomy in cases such as ours with aim of preventing progression of end organ complications. We feel our case is important in further informing clinical decision making in patients with normocalcemic PHPT by illustrating a rare but potentially life-threatening consequence of untreated normocalcemic PHPT that has not previously been considered.

Conclusions

Our case illustrates that normocalcemic hyperparathyroidism may not have a benign course if associated with a large parathyroid adenoma; progression to severe hypercalcemia may occur suddenly in rare cases. Nephrolithiasis can be a clinical feature of normocalcemic PHPT which persists following surgery. Parathyroidectomy should be considered in normocalcemic PHPT when there are features of bone or renal involvement, or when an obvious or large parathyroid adenoma is detected.

Conflict of interest

K Lithgow, J Pasieka, and G Kline declare that they have no conflicts of interest to disclose.

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