CASE REPORT

Distal renal tubular acidosis in primary hyperparathyroidism

Tom Edward Ngo Lo, Iris Thiele Isip Tan

Department of Medicine—Endocrinology, University of the Philippines—Philippine General Hospital, Manila, Philippines

Correspondence to
Dr Tom Edward Ngo Lo, tomedwardlo@yahoo.com

Accepted 13 January 2015

SUMMARY

Primary hyperparathyroidism manifests biochemically as a disturbance in serum calcium homeostasis. The kidney appears to be the central organ that sets the serum calcium level. Hyperchloraemia, defective urinary acidification and renal tubular acidosis have been reported to be associated with primary hyperparathyroidism. Distal renal tubular acidosis due to primary hyperparathyroidism is rarely reported. Renal tubular dysfunction due to significant hypercalciuria appears to be one of the proposed mechanisms. This case report will highlight a case of primary hyperparathyroidism in a 26-year old Filipino man due to a solitary functioning parathyroid adenoma presenting with recurrent nephrolithiasis leading to distal renal tubular acidosis manifesting with hypokalaemia and hypomagnesaemia. The patient underwent a minimally invasive selective parathyroidectomy that resulted in full reversal of hypercalcaemia and hyperparathyroidism together with the features of distal renal tubular acidosis. He is currently on frequent follow-up for monitoring of electrolyte abnormalities and gradual resolution of nephrocalcinosis.

BACKGROUND

Primary hyperparathyroidism manifests biochemically as a disturbance in serum calcium homeostasis. The kidney appears to be the central organ that sets serum calcium level. Aside from its high rate of active calcium transport, the kidney also modulates serum calcium homeostasis via 1,25-dihydroxyvitamin D secretion. Parathyroid hormone receptors are widely expressed throughout the renal tubule, which is mainly involved in calcium reabsorption as well as endocrine function.[1]

Several observed biochemical features of primary hyperparathyroidism are induced by the kidney. These include hypercalcaemia caused by increased tubular reabsorption of calcium, hypophosphataemia caused by decreased tubular phosphate reabsorption, mild acidosis from decreased bicarbonate tubular reabsorption and increased serum 1,25-dihydroxyvitamin D leading to further increased gastrointestinal absorption of dietary calcium. Hypercalciuria is an expected feature caused by the combined effects of increased calcium reabsorption and bone resorption.[1] Hyperchloraemia, defective urinary acidification and renal tubular acidosis (RTA) have been reported to be associated with primary hyperparathyroidism.[2]

RTA is considered to be a condition where metabolic acidosis is brought about by specific defects in renal tubular hydrogen ion secretion. Three types of RTA have been identified based on the nature of the tubular defect. Nephrolithiasis is only seen in distal RTA, a condition marked by a defect in the generation and maintenance of a hydrogen ion gradient by the distal tubule.[3] The type of RTA occurring in patients with primary hyperparathyroidism has been observed to be of distal type.[2] Distal RTA due to primary hyperparathyroidism is rarely reported. Renal tubular dysfunction due to significant hypercalciuria appears to be one of the proposed mechanisms.[4]

This case report will highlight a case of primary hyperparathyroidism from a solitary functioning parathyroid adenoma presenting with recurrent nephrolithiasis leading to distal RTA manifesting with hypokalaemia and hypomagnesaemia.

CASE PRESENTATION

We present a case of a 26-year old Filipino man presenting with a 3-year history of recurrent episodes of dysuria, minimal haematuria and bilateral flank pain. He was considered to have urinary tract infection and was treated with co-amoxiclav 625 mg twice daily for 1 week, which temporarily resolved the infection. Passage of a stone during urination was noted once. He had no other associated signs or symptoms and had asymptomatic intervals. He did not take any medications or herbal supplements. He did not have any family member with renal stones. He had a history of one hospital admission for significant progressive proximal muscle weakness limiting ambulation, which was eventually attributed to significant hypokalaemic periodic paralysis based on the finding of hypokalaemia (serum potassium 2.1 mmol/L; normal value (nv) =3.5–5.0) and hyperkaluria (24 h urine potassium 156 mmol/day; nv=25–100). Owing to persistence of recurrent urinary tract infection and stone passage, the patient consulted a nephrologist.

INVESTIGATIONS

Initial biochemical and imaging work up revealed complicated urinary tract infection and bilateral medullary nephrocalcinosis. Incidental hypercalcaemia (2.94 mmol/L nv=2.23–2.58 mmol/L) was noted hence further work up for the cause of hypercalcaemia in was performed (table 1). This eventually led to the diagnosis of primary hyperparathyroidism from a hyperfunctioning parathyroid adenoma with renal complications brought about by prolonged hypercalcaemia and hypercalciuria. The patient was advised and planned for surgery at our institution.

To cite: Lo TEN, Tan ITI. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2014-208120

Table 1 Initial biochemical and imaging work ups for incidental hypercalcaemia

Biochemical tests			
Test performed	**Normal value**	**Result**	**Interpretation**
Serum calcium	2.23–2.58 mmol/L	2.94 ↑	Hypercalcaemia
Serum phosphorus	0.81–1.49 mmol/L	0.72 ↓	Hypophosphataemia
Serum creatine	57–113 μmol/L	166 ↑	Renal insufficiency
Serum albumin	35–48 g/L	42	Normal
Intact PTH	15–65 pg/mL	246.9 ↑	Hyperparathyroidism
Free T4	11–24 pmol/L	22.3	Normal
TSH	0.3–3.8 mIU/mL	0.8	Normal
Plasma renin	0.5–1.9 nmol/L	0.9	Normal
Plasma aldosterone	8–172 pg/mL	56	Normal
Serum 25(OH)-vitamin D	>30 ng/mL	35	Normal
Urine crystals	Absent	2+ (Calcium phosphate)	Kidney stones
Random urine calcium	<0.3 mmol/L	0.84 ↑	Hypercalciuria

Imaging work ups	
Imaging test performed	**Results and interpretation**
Kidney ultrasound	Bilateral medullary nephrocalcinosis; normal prostate and urinary bladder
Parathyroid scan (Sestamibi scan)	Hyperfunctioning parathyroid tissue at the inferior right thyroid bed due to parathyroid adenoma or hyperplasia
Chest X-ray	Unremarkable findings
Neck ultrasound	Parathyroid nodule (0.8 cm); normal thyroid gland; no lymphadenopathies noted
Bone densitometry	Normal bone density on femoral neck and spine

PTH, parathyroid hormone; TSH, thyroid stimulating hormone.

On admission, additional preoperative tests were carried out revealing concomitant findings of severe hypokalaemia (1.9 mmol/L nv=3.6–5.1) and hypomagnesaemia (0.63 mmol/L nv=0.7–1.0). The patient was not on any diuretics or other offending drugs. He did not have recurrence of urinary tract infection during his admission and was not on any antibiotics. To rule out other causes of hypokalaemia, he also had thyroid function tests performed revealing normal results. After correction of serum potassium to 4 nmol/L, plasma renin and aldosterone were also carried out in a supine position to rule out hyperaldosteronism (table 1).

Table 2 Further renal work ups for electrolyte abnormalities

Arterial blood gas and urine analysis			
Test performed	**Normal value**	**Result**	**Interpretation**
Blood pH	7.35–7.45	7.28 ↓	Acidic
Serum bicarbonate	22–30 mmol/L	15 ↓	Low
Plasma anion gap	8–16 mmol/L	12	Normal anion gap
Urine pH	<5.5	7.3 ↑	Alkaline urine
24 h urine potassium	25–100 mmol/day	41	Normal
24 h urine sodium	100–260 mmol/day	140	Normal
24 h urine chloride	140–250 mmol/day	155	Normal
24 h urine calcium	<7.5 mmol/day	8.1 ↑	Hypercalciuria
24 h urine phosphorus	12.9–42.0 mmol/day	22.3	Normal
24 h urine ammonia	30–50 mmol/day	22	Low
Transtubular potassium gradient	8–9	11	Slightly elevated
Random urine glucose	Negative	Negative	No glucosuria
Random urine protein	Negative	Negative	No proteinuria
Urine culture	Negative	No growth after 5 days	Normal

The patient's hypercalcaemia was only managed with intravenous hydration and increased oral fluid intake. Work ups for concomitant electrolyte abnormalities led to the consideration of a possible renal wasting syndrome as confirmed by a slightly elevated transtubular potassium gradient in this patient with hypokalaemia. Urine analysis for electrolytes revealed isolated hypercalciuria. Arterial blood gas revealed normal anion gap metabolic acidosis consistent with a RTA. Absence of proteinuria, glucosuria, alkaline urine pH and inability to acidify urine despite acidosis led to the diagnosis of concomitant distal RTA in a patient with primary hyperparathyroidism (table 2).

TREATMENT

The patient underwent minimally invasive selective parathyroidectomy. Intraoperative findings revealed a 1 cm soft tissue mass at the right inferior thyroid bed, which turned out to be parathyroid gland hyperplasia on frozen section. Final

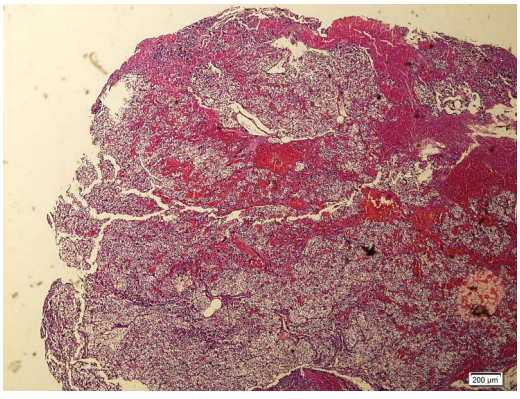

Figure 1 Final biopsy of the tumour revealing parathyroid adenoma on low power magnification.

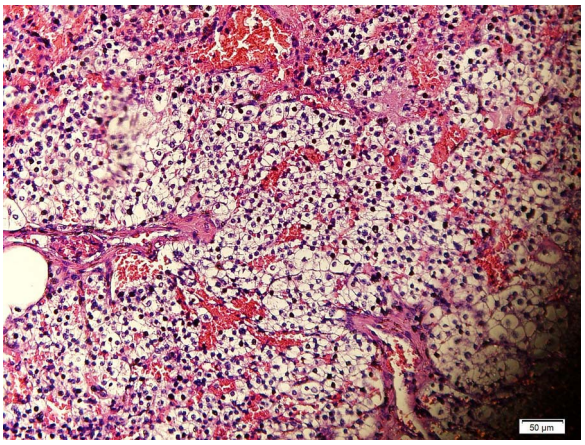

Figure 2 High power magnification of the parathyroid adenoma showing normal parathyroid tissue.

histopathological biopsy of the mass revealed parathyroid adenoma (figure 1) with normal parathyroid tissue (figure 2).

OUTCOME AND FOLLOW-UP

Removal of the parathyroid adenoma resulted in reversal of hypercalcaemia and hyperparathyroidism together with the features of distal RTA (table 3). The patient is currently on frequent follow-up for monitoring of electrolyte abnormalities and gradual resolution of nephrocalcinosis.

DISCUSSION

Nephrolithiasis is considered to be the most common clinical manifestation of primary hyperparathyroidism occurring in about 50% of cases.[5] It is the second most common cause of calcium stone formation after idiopathic stone disease. Calcium combined with phosphate is the main composition of the stone formed in primary hyperparathyroidism.[6] Hypercalciuria, mild hyperoxaluria and a more alkaline urine are considered chemical risk factors that lead to stone formation. The alkaline urine is caused by the direct action of parathyroid hormone on bicarbonate reabsorption.[7]

Table 3 Biochemical comparison before and after surgical tumour excision

Parameter	Normal values	Preoperative result	Postoperative result
Serum calcium	2.23–2.58 mmol/L	2.82 ↑	2.31
Serum phosphorus	0.81–1.49 mmol/L	0.79 ↓	0.94
Intact PTH	10–65 pg/mL	246.9 ↑ (3.8×)	36.2
Alkaline phosphatase	38–126 IU/L	208 ↑	65
Serum creatine	57–113 µmol/L	166 ↑	112
Serum potassium	3.6–5.1 mmol/L	1.6 ↓	3.8
Serum magnesium	0.7–1.0 mmol/L	0.63 ↓	0.82

PTH, parathyroid hormone.

Parathyroid hormone excess can influence proximal as well as distal renal tubular functions.[8] Hypercalciuric renal tubular damage, parathyroid hormone excess, or a combination of these mechanisms may cause changes in renal tubular epithelium. This results in damage to the ion channel integrity, which will then alter the urinary acidification process.[9] Although proximal tubular function is more commonly affected, longer disease duration can predispose to medullary nephrocalcinosis and lead to distal RTA. About 10% to 20% of cases of hypercalciuric nephrolithiasis have been associated with distal RTA, especially to kidney stone formers.[10]

Parathyroidectomy often results in rapid reversal of the risk factors for stone formation, leading to a permanent reduction of stone recurrence rates although existing stones may still be present.[6] Parathyroidectomy may also result in complete resolution of the distal RTA as shown by the case series by Muthukrishnan *et al*[4]. Complete reversal after parathyroidectomy established primary hyperparathyroidism as the cause of tubular abnormality leading to concomitant electrolyte imbalances.

Learning points

- Primary hyperparathyroidism can cause distal renal tubular acidosis accompanied by medullary nephrocalcinosis.
- Hyperparathyroidism should be considered as a differential in young patients presenting with significant electrolyte imbalance.
- Early treatment via parathyroidectomy can help cure secondary distal renal tubular acidosis before development of irreversible renal tubular changes occurs.

Contributors TENL was the primary author and physician who saw the patient. ITIT was attending consultant and editor of the manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Peacock M. Primary hyperparathyroidism and the Kidney: biochemical and clinical spectrum. *J Bone Miner Res* 2002;17:87–94.
2 Siddiqui AA, Wilson DR. Primary hyperparathyroidism and proximal renal tubular acidosis: report of two cases. *Can Med Assoc J* 1972;106:654–9.
3 Buckalew VM. Nephrolithiasis in renal tubular acidosis. *J Urology* 1989;141:731–7.
4 Muthukrishnan J, Kumar KVS, Jha R, *et al*. Distal tubular acidosis due to primary hyperparathyroidism. *Endocr Prac* 2008;14:1133–6.
5 Keating F. Diagnosis of primary hyperparathyroidism. *JAMA* 1961;178:547–55.
6 Peacock M, Robertson WG, Marshall RW. Disorders associated with recurrent calcium containing kidney stones. In: De Groot LJ, Cahill GF, Martini L, eds. *Endocrinology 2*. New York, NY, USA: Grune & Stratton, 1979:823–37.
7 Peacock M, Marshall RW, Robertson WG, *et al*. Hypercalciuria and recurrent calcium stone disease: effect of oral phosphate. In: Avioli L, Bordier PH, Fleisch H, eds. *Phosphate metabolism, kidney and bone*. Paris, France: Amour Montagu, 1976:63–78.
8 Rodriguez Soriano J. Renal tubular acidosis: the clinical entity. *J Am Soc Nephol* 2002;13:2160–70.
9 Hulter HN, Peterson JC. Acid base homeostasis during Chronic PTH excess in humans. *Kidney Int* 1985;28:187–92.
10 Arruda JA, Cowell G. Clinical disorders of acid-base physiology. *Curr Nephrol* 1989;12:39–79.