

Hyperparathyroidism in chronic kidney disease: complexities within the commonplace

Michael M Cai, Lawrence P McMahon, Edward R Smith, David S Williams and Stephen G Holt

ABSTRACT — Secondary hyperparathyroidism in patients with chronic kidney disease (CKD) is common and usually caused by associated metabolic abnormalities, in particular, hypocalcaemia and hyperphosphataemia. Nevertheless, other causes of hyperparathyroidism can exist concurrently with CKD, challenging diagnostic interpretation and therapeutic intervention. We present four cases of hyperparathyroidism in patients with CKD that highlight some of these dilemmas.

KEY WORDS: hyperparathyroidism, chronic kidney disease, parathyroidectomy, calcimimetic

Key message:

- Hyperparathyroidism in patients with chronic kidney disease (CKD) is common. While most cases are due to secondary hyperparathyroidism, other causes also need to be considered, especially when the biochemistry is incongruent.
- Imaging is of limited value in distinguishing between secondary and other forms of hyperparathyroidism.
- The use of calcimimetics has altered the therapeutic approach in most instances, but their long-term safety and efficacy, particularly in non-dialysis CKD patients, requires further evaluation.

Introduction

Secondary hyperparathyroidism (HPT) is common in chronic kidney disease (CKD) as the result of a multitude of metabolic derangements. The prevalence of secondary hyperparathyroidism (sHPT) increases as glomerular filtration rate (GFR) reduces, from <20% in patients whose GFR is over 60 ml/min/1.73 m² to >50% in patients with a GFR of less than 30 ml/min/1.73 m².¹ The high prevalence of sHPT in CKD, together with the attendant complexities of management, can obscure less frequent causes of hyperparathyroidism, particularly when the presenting clinical and biochemical parameters are similar. We present four cases of

hyperparathyroidism and renal dysfunction that highlight the diagnostic and therapeutic dilemmas that can arise.

Case 1

A 66-year-old male with a past history of gastro-oesophageal reflux disease presented to his GP having lost 10 kg in weight and feeling systemically unwell. Physical examination was unremarkable. Investigations revealed an elevated serum creatinine of 193 µmol/l (this had been recorded at 100 µmol/l two years earlier). The patient was markedly hypercalcaemic (adjusted serum calcium 4.40 mmol/l), with a normal serum phosphate 0.71 mmol/l and an elevated alkaline phosphatase 235 IU/l (reference range [RR] 30–120). Parathyroid hormone concentration (PTH) was also elevated at 168 pmol/l (RR 1.0–6.5). Serum and urine electrophoresis and urine microscopy were normal, and there was no evidence of proteinuria or urinary obstruction. The patient was admitted to hospital for intravenous fluids and intravenous bisphosphonate was given to lower his serum calcium. Subsequently, a ⁹⁹Tc-Sestamibi parathyroid scan demonstrated intense uptake in the region of the left lower pole of thyroid, but there was also a focus of less intense uptake in the right lower pole of thyroid, suggesting the possibility of multiple adenomata in association with hyperparathyroidism (Fig 1). A subtotal parathyroidectomy consisting of removal of the right and lower left parathyroid glands was performed, leaving a single gland. Histologically, adenomatous tissue was found in the left lower gland but there was no evidence of adenoma in the other resected glands. The patient's serum calcium returned to normal, but the serum creatinine continued to be elevated at approximately 180 µmol/l.



Fig 1. ⁹⁹Tc-Sestamibi scan showing an intense focus of uptake in the region of the left lower pole of the thyroid (Case 1).

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The working diagnosis was primary hyperparathyroidism, with the renal dysfunction probably related to longstanding hypercalcaemia.

Case 2

A 52-year-old female with no significant family history but with a past history of a congenital single kidney, pseudogout and chondrocalcinosis presented with moderate renal impairment (estimated GFR (eGFR) 36 ml/min/1.73 m²), Stage 3 CKD. She was persistently hypercalcaemic, with repeat serum calcium levels measuring between 2.77 and 3.12 mmol/l. Her serum phosphate was in the normal range (between 0.81 and 1.03 mmol/l) and plasma PTH was 19.1 pmol/l. A diagnosis of primary hyperparathyroidism was suggested. A ⁹⁹Tc-Sestamibi parathyroid scan demonstrated a single focus of increased

activity in the lower pole of the right lobe of the thyroid and the patient underwent a single-gland parathyroidectomy. Intraoperatively, the right lower parathyroid gland, thought to be an adenoma, was identified and removed; but histopathological examination failed to identify adenomatous elements. Postoperatively, the patient's serum calcium fell only to the high-normal range (corrected calcium 2.50–2.55 mmol/l) and her PTH remained persistently elevated (10–20 pmol/l). The patient's calcium and plasma PTH concentrations remained stable for a further 10 years, after which her serum calcium climbed again to 2.83 mmol/l, with a serum PTH of 22.7 pmol/l and a 25-hydroxy vitamin D level of 42 nmol/l. At this time, she was on no diuretic medication. Her concurrent eGFR was 17 ml/min/1.73 m². A diagnosis of familial hypocalciuric hypercalcaemia (FHH) was considered, and a urine calcium creatinine clearance ratio (UCCR, calculated as urinary calcium/plasma calcium x plasma creatinine/urinary creatinine) was determined. This showed relative hypocalciuria, with a UCCR of 0.005.

The working diagnosis was secondary hyperparathyroidism, possibly with FHH.

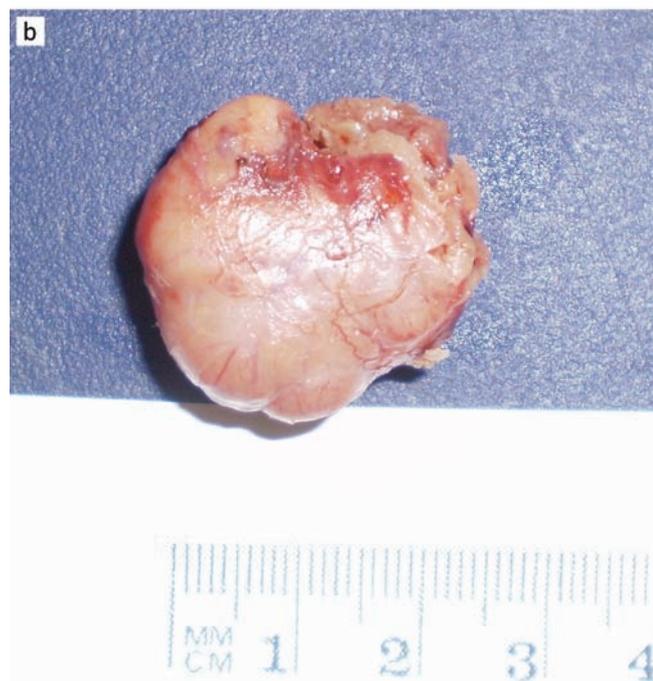
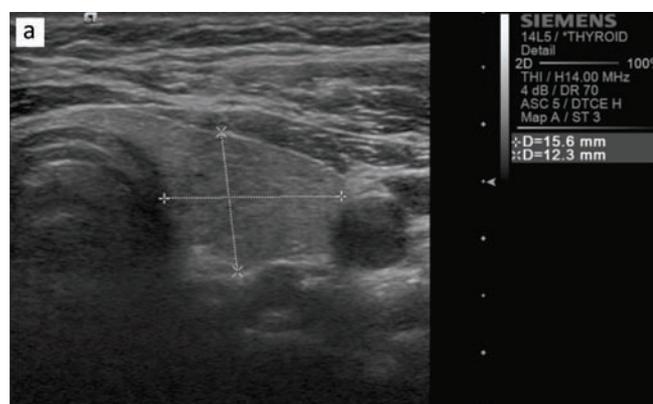


Fig 2 (a) ultrasound showing a very large parathyroid mass. (b) at parathyroidectomy, the mass was easily localized and removed.

Case 3

A 25-year-old mother of two presented to her GP with mild fatigue. She described a past history of childhood enuresis, gout and cholelithiasis. There was also a strong family history of end-stage kidney disease. After referral to the renal department, she was considered likely to have an autosomal dominant disorder, uromodulin (UMOD)-associated kidney disease (UAKD),² because a related family member was found to have a mutation in the UMOD gene. Investigation showed a serum creatinine of 120 µmol/l, with a reduced creatinine clearance of 54 ml/min, adjusted serum calcium of 2.29 mmol/l and serum phosphate of 0.51 mmol/l. This patient was lost to renal follow-up until the age of 33, by which time her renal function had deteriorated and her serum creatinine was 189 µmol/l (eGFR 28 ml/min/1.73 m²). Her adjusted serum calcium at that time was 2.37 mmol/l, her serum phosphate 1.1 mmol/l and her serum uric acid levels also elevated at 0.58 mmol/l. A renal biopsy showed nephrosclerosis with no diagnostic features. The renal dysfunction continued to progress, and four years later, the patient was dialysis-dependent. Before starting dialysis, her PTH was measured at 300 pmol/l with an adjusted serum calcium of 2.14 mmol/l and phosphate of 1.77 mmol/l. A ⁹⁹Tc-Sestamibi parathyroid scan showed a large, right-sided hyperactive gland at the base of the neck, which was also visible on ultrasound scans (as a hypoechoic structure; Fig 2a). The patient underwent a subtotal parathyroidectomy, during which the very large parathyroid gland (9.5 g) was removed (Fig 2b). The contralateral gland was also removed. Histology showed nodular parathyroid hyperplasia in both glands. The PTH measured one day post-operatively had fallen to 11 pmol/l, but within one month it had rebounded to 84 pmol/l. The patient then successfully commenced cinacalcet for medical management of secondary hyperparathyroidism.

The working diagnosis was secondary hyperparathyroidism resulting from CKD.

Case 4

A 55-year-old male was found to have hypercalcaemia two weeks after a non-related living-donor kidney transplant. The pre-transplant period had been complicated by the unexpected discovery of a donor-specific antibody six days pre-transplant. The antibody was successfully cleared by plasmapheresis and there were no other immediate postoperative complications. The patient's past history included hepatitis B and C infection from IV drug use, end-stage kidney disease resulting from hypertensive nephrosclerosis and secondary hyperparathyroidism requiring calcimimetic treatment (cinacalcet, 60 mg daily). Whilst on dialysis, the patient's adjusted serum calcium concentration ranged between 2.30 and 2.40 mmol/l and his serum PTH between 20 and 50 pmol/l. Post transplant, the cinacalcet was discontinued and four months after transplantation, the patient's adjusted serum calcium had increased to 2.92 mmol/l. His serum PTH remained elevated (20–30 pmol/l). A ⁹⁹Tc-Sestamibi parathyroid scan demonstrated no focal uptake. A biopsy performed five months post transplantation demonstrated tubulointerstitial calcium deposits with secondary inflammatory changes (Fig 3). The patient was admitted to hospital for intravenous hydration and bisphosphonate therapy, after which his adjusted serum calcium normalised to 2.40 mmol/l. He subsequently recommenced cinacalcet at 30 mg daily, which kept his serum calcium at normal levels.

The working diagnosis was tertiary (autonomous) hyperparathyroidism after renal transplantation.

Discussion

Secondary HPT as a consequence of CKD is well recognised. It usually presents with a normal or elevated serum phosphate and low or low-normal serum calcium concentration.¹ Multiple factors mediate the development of hyperparathyroidism in CKD patients. These include hypocalcaemia, decreased 1,25 dihydroxycholecalciferol synthesis and hyperphosphataemia. The differential diagnosis of a raised PTH in the setting of CKD should include primary, secondary and autonomous (tertiary) hyperparathyroidism and, more rarely, FHH and ectopic PTH secretion.

All causes of hypercalcaemia (including primary HPT (pHPT), myeloma, sarcoidosis, hypervitaminosis D and the milk-alkali syndrome) can result in marked renal dysfunction. Hypercalcaemia damages tubular epithelial cells, particularly those in the loop of Henle and in the collecting and distal tubules, eventually leading to dilatation, atrophy, and fibrosis.³ It also down-regulates aquaporin expression which, clinically, can manifest as polyuria, nocturia and reduced urinary concentrating ability.⁴ Hypercalcaemia also has haemodynamic effects, reducing both renal blood flow and glomerular filtration.⁵ Thus, common renal manifestations of pHPT include nephrolithiasis, hypercalciuria and sometimes nephrocalcinosis.⁶

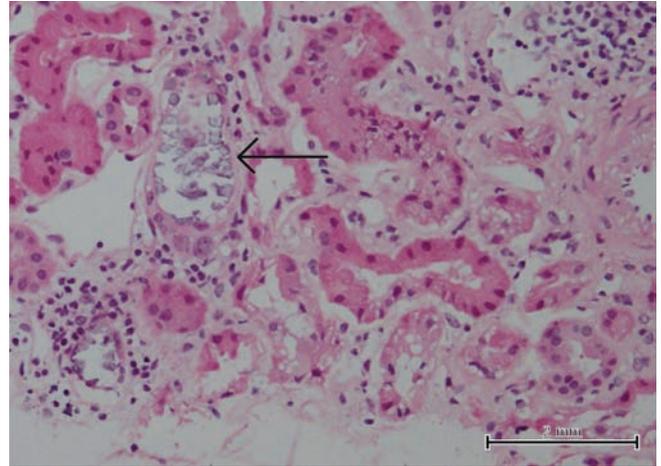


Fig 3. Renal transplant biopsy showing nephrocalcinosis with interstitial calcium deposit (arrow) and inflammatory changes.

Yamashita and co-workers found that hypercalcaemia was more severe in pHPT patients who had renal insufficiency.⁷ Current guidelines suggest that a parathyroidectomy should be considered for most patients with pHPT, specifically those with any of the following: serum calcium concentration >0.25 mmol/l above the upper limit of normal, a creatinine clearance of <60 ml/min, reduced bone density (especially if in the osteoporotic range) and age <50 years.⁸ In patients with a high surgical risk, medical management with a calcimimetic agent is usually an effective alternative.⁹

Case 1 illustrates the difficulty often encountered by clinicians in distinguishing pHPT from tertiary HPT (tHPT), as both can present with the triad of renal insufficiency, hypercalcaemia and high PTH. Patients with tHPT usually have moderately severe CKD and a prolonged history of sHPT (ie a period of normo- or hypocalcaemia with concurrent hyperparathyroidism). Serum phosphate is typically elevated in tHPT because of severe renal impairment. By contrast, patients with pHPT typically have a low serum phosphate. The reliance on parathyroid imaging to distinguish between pHPT and tHPT has pitfalls. First, multiglandular involvement occurs in up to 25% of patients with pHPT.¹⁰ Second, asymmetric proliferation of the parathyroid glands is common in patients with tHPT and often results in an apparent single focus of intense uptake in imaging studies because of differential tracer retention.¹⁰ Third, there are other local structures that can take up and retain tracer, giving false positive results.¹¹ Thus, multimodal imaging, usually scintigraphy and ultrasound, is recommended.

In Case 2, tHPT was initially considered, but the lack of a prolonged history of CKD and low-normal phosphate on initial presentation argued against this. In addition, PTH was increased only three-fold, whereas in tHPT, elevations are often at least ten-fold. The stability of PTH levels for more than decade is also very atypical of tHPT. This evidence leaves pHPT and FHH as possible diagnoses. It is interesting to note that despite her initial partial parathyroidectomy, the patient's post-operative PTH remained elevated and hypercalcaemia eventually recurred. The

failure of surgery to resolve the condition suggests either multi-glandular involvement or the presence of FHH. UCCR is often used as a screening test for FHH, but its validity in CKD patients remains uncertain. Hypocalciuria and 25-hydroxy vitamin D deficiency, both commonly seen in CKD, could potentially increase the false positivity of the test.^{12,13} The patient's serum vitamin D level was slightly reduced, but not deficient, and she was on no thiazide diuretics that may have contributed to a low UCCR. The patient's very low UCCR suggested FHH as a potential co-diagnosis,¹² but a corroborative family history was lacking.

FHH is a rare, usually autosomal dominant, condition that is associated with defects in the calcium-sensing receptor (CaSR).¹⁴ The CaSR is expressed in both parathyroid and renal tubular cells,¹⁵ where loss of function results in increased tubular calcium reabsorption, leading to hypocalciuria that persists even after parathyroidectomy. Analysis of the CaSR gene for clinical use is available in some countries. To diagnose FHH, many experts now suggest using UCCR as a screening test. If positive (UCCR <0.02), a follow-up CaSR gene analysis would provide a certain diagnosis if a mutation was detected and 98% sensitivity if no mutations were found.¹⁶

Case 3 was a severe case of sHPT. The largest gland removed was over 150 times the normal volume. The pre-operative localising ⁹⁹Tc-Sestamibi scan revealed only one hyperfunctioning gland with no other abnormal areas of uptake, suggesting an adenoma. This was consistent with the intraoperative finding of one very large gland, but interestingly, the additional gland that was removed was also enlarged, a finding not detected by scintigraphy.

Discordance between imaging and pathological findings is not uncommon in sHPT; hence there is continuing debate on the value of preoperative imaging, with some authors using it only for recurrent or persistent disease.¹⁷ Indeed, the choice of modality that is best for imaging parathyroid glands is also contentious. Imaging of the normal parathyroid gland is difficult as this tissue is not easily distinguished from surrounding tissue. As the gland expands and increases in cellularity, however, it becomes increasingly easy to detect by ultrasound. High-resolution colour Doppler ultrasound now also enables more accurate assessment of changes in parathyroid volume.¹⁸ ⁹⁹Tc-Sestamibi imaging helps to localise parathyroid tissue but provides little anatomical localisation and often must be used in combination with another imaging modality.¹⁹ Thyroid uptake of radiotracers can also be a source of error and some authors advocate a subtraction scan by imaging with ¹²³I or ⁹⁹Tc-Pertechnetate. Previous studies have demonstrated the poor sensitivity of various imaging techniques in identifying all affected glands.¹⁷ Some authors advocate a combination of ⁹⁹Tc-Sestamibi single photon emission computed tomography (SPECT) with CT to gain high sensitivity and accuracy gland localisation.¹⁹ MRI can also be helpful, especially when combined with scintigraphy.²⁰

Another noteworthy lesson from Case 3 was the fact that severe secondary hyperparathyroidism can occur early in CKD: recent guidelines suggest that PTH concentrations should be

monitored when the GFR falls below 60 ml/min/1.73 m².²¹ The ideal target for PTH is not known, but the current Kidney Disease Outcome Quality Initiative (KDOQI) guidelines suggests that the PTH should be kept at between 3.85 and 7.7 pmol/l in Stage 3 CKD, and between 7.7 and 12.1 pmol/l in Stage 4 CKD.²² The interpretation of PTH concentration is further complicated by the high intra-individual biological variation in PTH secretion in CKD patients; a single measurement rarely provides an accurate picture of parathyroid activity.²³ Indeed, PTH itself might not be the best molecule to measure in early CKD. The hormone fibroblast growth factor-23 (FGF-23) could be a more appropriate measure when assessing bone and mineral disorders. FGF-23 is a phosphaturic hormone that down-regulates the activation of vitamin D in the kidney. This hormone is elevated long before changes are seen in calcium, phosphate or PTH,²⁴ but because of its instability in plasma samples, it is not easy to measure.²⁵

In the past decade, parathyroidectomy in dialysis patients has been substantially delayed by the introduction of calcimimetic agents. Parathyroidectomy continues to be performed, but at a markedly decreased frequency. The role of calcimimetics in non-dialysis patients is less well defined. In randomised, controlled, placebo-controlled trials, cinacalcet treatment reduced PTH levels, but it did so at the cost of significant hypocalcaemia and hyperphosphataemia.²⁶ Thus, early routine use of calcimimetics in CKD is currently neither recommended nor licensed. Nevertheless, there may be individual cases in which pre-dialysis use might help to prevent severe secondary hyperparathyroidism.

The last case presents a common scenario of hypercalcaemia post renal transplantation. Secondary HPT occurs frequently in CKD patients and, although pHPT cannot be excluded completely without histology, the symmetrical uptake and excretion of tracer in the parathyroid scan in this case argues against this. Although renal transplantation eventually corrects the sHPT for many, the correction can take time and is incomplete in 50% of recipients.²⁷ As demonstrated in this patient, marked hypercalcaemia can cause graft dysfunction and nephrocalcinosis. Traditionally, hyperparathyroidism post transplantation has been managed with phosphate supplementation, bisphosphonates and, in refractory cases, parathyroidectomy. In some cases, this procedure has been shown to be deleterious to graft function.²⁸ Numerous case series have now reported the effectiveness of cinacalcet in reducing serum PTH and calcium after transplantation (see review by Copley²⁹). There are, however, at least three case reports of graft dysfunction resulting from nephrocalcinosis after the initiation of cinacalcet treatment.^{29–32} CaSR is present in both parathyroid tissues and renal tubules.³³ In addition to the suppression of PTH secretion, cinacalcet can also interact directly with the CaSR expressed in renal tubules, resulting in increased calcium excretion that is independent of PTH's action on renal tubules.¹⁴ Therefore, cinacalcet might exert hypercalciuric effects through both PTH-dependent and -independent mechanisms. With these concerns in mind, the results of a randomised placebo-controlled trial (see clinicaltrials.gov NCT 00975000, due for completion in 2013) will

hopefully provide a more definitive answer on the efficacy and safety of cinacalcet in this setting.

In conclusion, renal dysfunction and hyperparathyroidism often co-exist. Although usually caused by secondary hyperparathyroidism, incongruent biochemistry can challenge both the diagnosis and treatment of these conditions.

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