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Case Report

Iatrogenic nephrocalcinosis with acute renal failure: an underestimated complication after parathyroidectomy?

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Abstract

Hypocalcaemia often occurs in patients after parathyroidectomy (PTX) due to hypoparathyroidism and/or hungry bone syndrome. To avoid hypocalcaemia, patients are substituted with large doses of calcium and vitamin D. Here, we present four patients, who developed acute renal failure with hypercalcaemia and/or histologically confirmed nephrocalcinosis after PTX due to oversubstitution with vitamin D analogues and calcium. As a consequence, serum and urinary calcium should be closely monitored after PTX, and calcium and vitamin D substitution should be continuously adapted to avoid not only hypocalcaemia but also nephrocalcinosis and hypercalcaemic renal failure.

Keywords: acute renal failure; nephrocalcinosis; parathyroidectomy; vitamin D substitution

Background

Hypocalcaemia occurs in up to 52% of patients after parathyroidectomy (PTX) [1] due to persistent hypoparathyroidism, transient suppression of the remaining parathyroid glands by preoperative hypercalcaemia and hungry bone syndrome. The latter two causes have only a transient effect requiring adjustment of supplementation. To avoid initial hypocalcaemia, patients are frequently given large doses of calcium and vitamin D. In contrast, oversubstitution of calcium and/or active vitamin D can lead to acute hypercalcaemia with hypercalcaemic complications such as acute renal failure [2] and nephrocalcinosis [3].

Case report

We describe a series of four patients (two females, two males), who developed acute renal failure with hypercalcaemia and/or histologically confirmed nephrocalcinosis from 2 months up to 13 months after PTX, while receiving supplementation therapy with vitamin D analogues and calcium. The course of kidney function, levels of serum calcium, phosphate and intact parathormone (iPTH), kidney biopsy results and therapeutic regimens were retrospectively reviewed.

Patient characteristics, serum chemistry and kidney biopsy results and medication are summarized in Table 1. Indication for PTX in two patients was persistent hyperparathyroidism after kidney transplantation (tertiary hyperparathyroidism due to hyperplasia of the parathyroid glands). Total PTX with autotransplantation of one gland or subtotal PTX was performed in these individuals. One patient had a total PTX because of a lithium-induced hyperparathyroidism [4]. One patient without pre-existing hyperparathyroidism developed hypoparathyroidism after total thyroidectomy because of accidental removal of the parathyroid glands. No patient was parathyroidectomized for an adenoma of primary hyperparathyroidism. Postoperatively, all patients received vitamin D analogues in combination with calcium supplementation. Two months to 13 months after PTX acute renal failure (defined as loss of eGFR >25% of baseline values) occurred. In all patients, it was associated with significant hypercalcaemia (total calcium 3.23–3.5 mmol/L). All patients had very low iPTH and normal to low serum phosphate levels. Kidney biopsies were performed in two out of four patients and showed tubulointerstitial calcium deposits, accompanied by interstitial fibrosis, tubular atrophy and/or inflammation, findings consistent with the diagnosis of nephrocalcinosis. The biopsy of Patient 1, who was accidentally parathyroidectomized and therefore had no pre-existing hyperparathyroidism that could have caused nephrocalcinosis, is shown in Figure 1. The kidney biopsy revealed nine glomeruli; two of them were globally sclerotic. The other seven glomeruli appeared on histology normal without pathological findings. There was a moderate interstitial fibrosis and corresponding tubular atrophy. The main finding on histology was an extensive intratubular and interstitial calcification with distortion of the tubular epithelial cells.

Table 1. Patient characteristics, biopsy results, medication and renal function

	Patient 1	Patient 2	Patient 3	Patient 4
Sex (m/f)[a]	f	f	m	m
Age (years)	67	45	61	75
Main diagnosis	Graves' disease, hypertension, asthma bronchiale	Diabetes mellitus type 1 with ESRD, kidney and pancreas transplantation, obesity, epilepsy	Pre-existing lithium-induced nephropathy with CKD stage 3 and diabetes insipidus, schizoaffective disorder, hypothyroidism	Diabetes mellitus type 2 with ESRD, kidney transplantation, hyperthyroidism, ischaemic heart disease, hypertension
Indication for PTX	Accidental during thyroidectomy, total PTX	Persistent hyperparathyroidism post kidney-TPL, 3¾ PTX	Lithium-induced hyperparathyroidism, total PTX	Persistent hyperparathyroidism post kidney-TPL, total PTX with autotransplantation of one gland
Time from PTX to hypercalcaemic complication	5.5 months	13 months	2 months	2.5 months
Serum chemistry levels				
- Ca (N: 2.19–2.54 mmol/L)	3.5 mmol/L	3.25 mmol/L	3.35 mmol/L	3.23 mmol/L
- Ph (N: 0.87–1.45 mmol/L)	0.86 mmol/L	0.73 mmol/L	0.80 mmol/L	1.27 mmol/L
- iPTH (N: 15–65 ng/L)	8.3 ng/L	5 ng/L	3.9 ng/L	4.4 ng/L
Medication	Dihydrotachysterol 0.6 mg/d	Calcium 1000 mg/d Calcitriol 1.5 µg/d	Calcium 1000 mg/d Calcitriol 1.5 µg/d	Calcium 3000 mg/d Calcitriol 1.5 µg/d
Hypercalcaemic complications	Nephrocalcinosis with tubular calcification and interstitial fibrosis (Figure 1)	Nephrocalcinosis with intratubular calcium deposits, interstitial fibrosis and tubular atrophy	Symptomatic hypercalcaemia	Asymptomatic hypercalcaemia
Mechanism underlying renal dysfunction	Functional and structural	Functional and structural	Mainly functional	Functional
Evolution of renal function	Progressive decline of GFR (MDRD) to 31 mL/min, after resolution of hypercalcaemia partial recovery to GFR 41 mL/min	Decline of GFR (MDRD) from 62 mL/min to 12 mL/min, partial recovery to 37 mL/min	Decline of GFR (MDRD) from 33 mL/min to 20 mL/min, partial recovery to 27 mL/min	Decline of GFR (MDRD) from 33 mL/min to 17 mL/min, recovery to 32 mL/min

CKD, chronic kidney disease; ESRD, endstage renal disease; TPL, transplantation; GFR, glomerular filtration rate.
[a]m = male, f = female.

All patients were transiently treated with fluids and loop diuretics to treat hypercalcaemia, and supplementation regimens were adapted. After correction of hypercalcaemia, three patients showed partial and one complete recovery of the renal function. No patients required dialysis.

Discussion

Because of the well-known occurrence of symptomatic hypocalcaemia after PTX, patients are frequently substituted with large doses of vitamin D and calcium. However, some causes of hypocalcaemia such as hungry bone disease or suppression of remaining parathyroid glands have only a transient effect, and supplementation with calcium and vitamin D therefore needs to be adjusted over time. Oversubstitution with vitamin D analogues and calcium is well known to induce hypercalcaemia [5,6] and hypercalciuria [7,8], which can cause nephrolithiasis, nephrocalcinosis [3] and renal failure [2].

In three of our cases (Patients 2–4), nephrocalcinosis could have been caused by pre-existing hyperparathyroidism, oversubstitution with calcium and vitamin D analogues after PTX, or both. Pre-existing nephrocalcinosis due to hyperparathyroidism and its aggravation due to iatrogenic hypercalcaemia is a probable scenario in these patients. There are also case reports of nephrocalcinosis triggered by phosphate loading [5], but none of our patient had an oral phosphate substitution or received a phosphate-loaded enema. The heterogeneity of the study population and uncertainty of the presence of nephrocalcinosis before the PTX are the limitations of our study.

Patients 2 and 4 had undergone kidney transplantation before PTX for persistent hyperparathyroidism. Nephrocalcinosis after kidney transplantation occurs in 10–20%, is significantly correlated to persistent hyperparathyroidism and also represents a risk factor for a chronic allograft nephropathy, as shown in the protocol biopsy study by Schwarz *et al.* [6]. This study suggests an adverse effect of hyperparathyroidism on kidney allograft function. On the other hand, our two kidney transplant recipients, who later underwent PTX, illustrate the danger of oversubstitution of calcium and vitamin D analogues with possible aggravation of nephrocalcinosis. This may be one possible

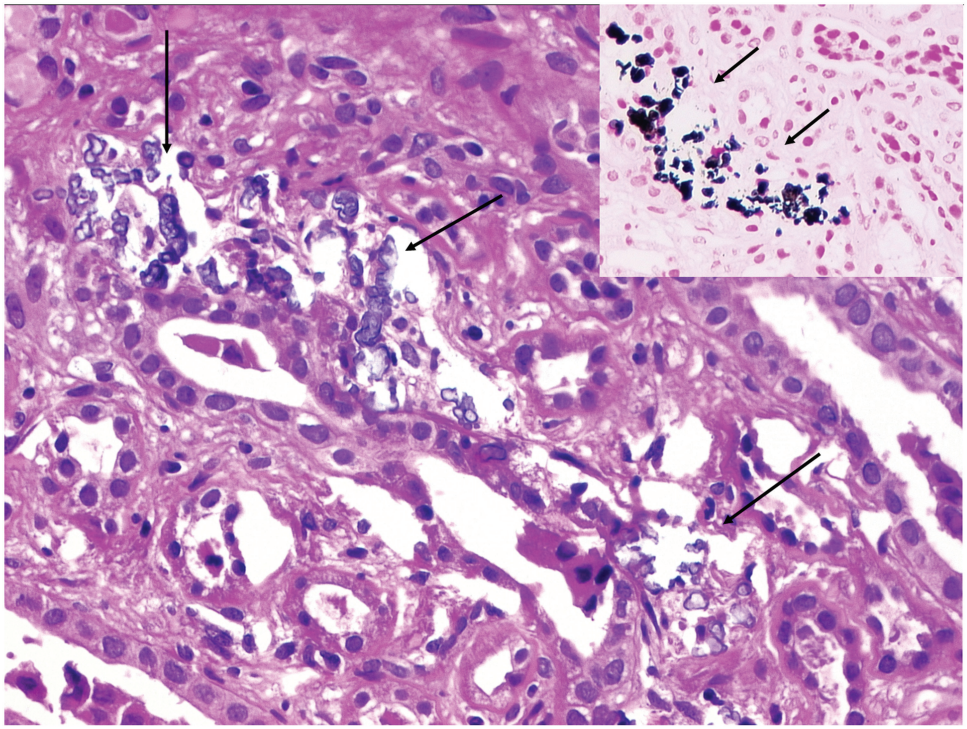

Fig. 1. HE stain (×250): intratubular and interstitial calcification with destruction and deformation of tubular epithelial cells. The calcification appears as an accumulation of an amorphous slightly crystalloid basophilic irregular mass (arrows). Inset, von Kossa stain (×250): positive black-coloured stain within the calcification (arrows).

mechanism of deterioration of renal function in kidney transplantation recipients that has been noted shortly after PTX [7].

The occurrence of de novo iatrogenic nephrocalcinosis is suggested by Patient 1, who had no pre-existing hyperparathyroidism and a normal renal function before the accidental parathyroidectomy occurred. This situation seems reminiscent to the occurrence of nephrocalcinosis in children with congenital hypoparathyroidism, who are substituted with parathyroid hormone (PTH; 1–34) or vitamin D plus calcium [3,8].

Apart from nephrocalcinosis, which can be irreversible if not adequately treated, hypercalcaemia can also cause transient decline of kidney function by vasoconstriction and induction of hypovolaemia resulting in prerenal azotaemia. This may explain the partial (3/4) or complete (1/4) recovery of GFR to baseline levels in all of our patients. A limitation of our study is the fact that hypercalciuria as a risk factor for renal calcification and serum levels of calcitriol as a marker of oversubstitution have not been measured. However, it is very likely that hypercalciuria was present in these patients given the very low iPTH levels and consecutive impairment of renal tubular calcium reabsorption [9].

The goal of therapy in patients with hypoparathyroidism is to raise and maintain the serum calcium concentration in the long term in the low to normal range (~2.0–2.1 mmol/L) to prevent the occurrence of hypercalciuria and nephrocalcinosis [10]. Furthermore, it is recommended to reduce the dose of calcium and vitamin D, if the 24-h urinary calcium excretion is elevated (≥300 mg in 24 h) [10]. We recommend to use calcitriol instead of cholecalciferol or dihydrotachysterol (which had been used in Patient 1), because the drug action of calcitriol is shorter and hypercalcaemia due to drug overdosing does not persist as long [11]. In newer studies, treatment of hypoparathyroidism with PTH (1–34) may be beneficial in order to maintain normal serum calcium levels while avoiding hypercalciuria [12].

Taken together, vitamin D and calcium oversubstitution after PTX can lead to hypercalcaemia, de novo or aggravation of pre-existing nephrocalcinosis and acute renal failure. Therefore, serum and urinary calcium should be closely monitored (in 2-week intervals initially and then every 3–6 months once a stable dose is achieved) after PTX, similarly to patients with hypoparathyroidism [13]. Oral or intravenous calcium supplements should be given only immediately after parathyroidectomy to treat hungry bone disease. For long-term therapy, no oral calcium should be used routinely, but active vitamin D derivatives should be titrated in order to ideally obtain low normal blood calcium levels.

Conflict of interest statement. None declared.

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