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CASE REPORT

Treatment of extreme hypercalcaemia: the role of haemodialysis

Anna B. Basok, Boris Rogachev, Yosef Shmuel Haviv, Marina Vorobiov

Department of Nephrology, Soroka University Medical Center, Beer Sheva, Israel

Correspondence to
Dr Anna B. Basok, basok@bgu.ac.il

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SUMMARY

A patient with extremely high calcium level of 23.9 mg/dL (5.97 mmol/L) was admitted to our department unconscious with pathological ECG recording, demonstrating shortening of QT interval. The patient was treated by fluid resuscitation, bisphosphonates, salmon calcitonin and steroids. Haemodialysis with low calcium bath had been promptly provided with improvement of consciousness and calcium level. ECG changes disappeared. Subsequent investigations revealed hyperparathyroidism and a large parathyroid adenoma was then surgically removed. Extreme and rapid calcium elevation (parathyroid crisis) is rarely seen in primary hyperparathyroidism and usually is distinctive for malignancy. In the context of acute kidney injury and refractory hypercalcaemia with life-threatening complications (coma, ECG changes with impending danger of arrhythmia), haemodialysis may effectively decrease calcium levels. It should be pointed out that dialysis is an efficient method of treatment of refractory hypercalcaemia, parathyroid crisis, but it is rarely used due to its invasive nature.

BACKGROUND

Severe hypercalcaemia is a life-threatening disorder that may cause muscle flaccidity, acute kidney injury, brain dysfunction with obtundation or coma and eventually dangerous arrhythmia and cardiac arrest. Along with conservative treatment, haemodialysis is an additional option of treatment of severe refractory hypercalcaemia poorly responsive to medical management. Haemodialysis provides rapid correction of calcium level, especially in patients with renal failure or cardiac comorbidities, in whom hydration cannot be safely performed.

CASE PRESENTATION

A 68-year-old patient of African-American origin was admitted for weakness and refusal to eat and drink. His medical history was unremarkable and he was not treated with any medications. It should be mentioned that the patient is a strict vegetarian—'vegan', not consuming eggs or dairy products and abstains from eating animal-derived substances. On admission, he was unconscious with Glasgow Coma Scale (GCS) of 8–9. Blood pressure was 132/67, heart rate 115, respiratory rate (RR) 24 per min and body mass index 16. Muscle flaccidity and decreased skin turgor were observed. Laboratory data on admission were: urea 143 mg/dL; creatinine 3.08 mg/dL (260 mmol/L); calcium 23.9 mg/dL (5.97 mmol/L), phosphate level 2.5 mg/dL, alkaline phosphatase 189, albumin 3.8 g/L, globulin 3.7 g/L (table 1).

Calcium in 24 hours urine collection was 1156 mg/24 hours (286 mmol/24 hours). ECG recording demonstrated shortening of QT (120 ms) with RBBB pattern (figure 1).

INVESTIGATIONS

Bone marrow biopsy which was performed in order to exclude multiple myeloma was normal with no evidence of myeloma cells. Prostate specific antigen (PSA), cancer embrionic antigen (CEA) and CA 19–9 were normal. PTHrP had not been measured due to inaccessibility of the test. CT revealed a hypodense lesion near the thyroid gland, 2.7×4.8×3.1 cm in size, which propagated towards sternal manubrium, oesophagus and bifurcation of trachea (figure 2A,B). Extremely high iPTH (more than 1900 pg/dL) level and findings disclosed on CT were consistent with a parathyroid tumour. Parathyroid scintigraphy was not performed, because of the obvious findings on the CT scan, demonstrating a huge parathyroid gland together with high iPTH level. Surgery including right lower parathyroidectomy was performed. The specimen was 6.5×3.0×1.5 cm in size, covered partially by a capsule and its weight was 19.5 g. Pathohistological examination disclosed parathyroid tumour with histological features of parathyroid adenoma, with no evidence of malignancy (figure 3). After surgery, iPTH level dropped from 1900 pg/mL to 3 pg/mL.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis in this patient with extreme hypercalcaemia included solid-organ malignancies with metastatic disease, plasma cell dyscrasia (multiple myeloma), primary hyperparathyroidism (pHPT), granulomatous disease (sarcoidosis) and vitamin D intoxication.

TREATMENT

Intensive therapy was provided including fluid resuscitation with normal Saline 200 cc/hour; s/c Calcitonin 300 units × 2 per day during 5 consecutive days; intravenous Aredia (Pamidronate—bisphosphonate) 60 mg; intravenous Dexamethasone 40 mg for 5 days followed by oral Prednisone 20 mg during the next 5 days. Despite adequate fluid replacement, the patient remained oliguric during first hours after admission. Six hours after admission, due to extraordinary high calcium

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Table 1 Laboratory data on admission

Complete blood count	
White blood cell	10 820/µL
Red blood cell	6×10^6/µL
Haemoglobin	17.6 g/dL
Platelet	177×10^3/µL
Blood chemistry	
Blood urea nitrogen	143 mg/dL
Creatinine	3.08 mg/dL
Uric acid	15.7 mg/dL
Sodium	143 mEq/L
Potassium	3.0 mEq/L
Chloride	107 mEq/L
Calcium	23.9 mg/dL
Phosphorus	4.6 mg/dL
Magnesium	1.9 mg/dL
Alkaline phosphatase	189 U/L
Aspartate aminotransferase	102 U/L
Alanine aminotransferase	115 U/L
Lactate dehydrogenase	681 U/L
Amylase	167 U/L
Lipase	50 U/L
Albumin	3.8 g/dL
Globulin	3.7 g/dL
Intact parathyroid hormone	>1900 pg/mL

level, stupor, oliguria and ECG changes with impending danger of arrhythmia, central venous catheter was placed and urgent haemodialysis with low calcium dialysate and high flux filter was provided. Dialysis session lasted for 4 hours and resulted in reduction of calcium level to 12.8 mg/dL (3.2 mmol/L). Few hours later, calcium level rebounded to 18.8 mg/dL (4.7 mmol/L) and another haemodialysis session was provided. All together, three consecutive daily dialysis sessions using low calcium bath had been done (figure 4).

General condition of the patient improved and he became more alert (GCS 14). ECG pattern normalised (figure 5). During the next days, his urine output increased to polyuric extent of 3000–5000 cc with urine osmolality of 140 mOsm/kg, reflecting polyuria due to nephrogenic diabetes insipidus in a patient with hypercalcaemia. Fluid replacement therapy with normal Saline solution was continued to replace urine losses. Plasma creatinine level decreased to 1.8 mg/dL (160 mmol/L). Calcium level stabilised at the level of 11–12 mg/dL (2.75–3 mmol/L). Vitamin D (25-OH) was 19 nmol/L (less than 25 nmol/L-deficiency), 1–25 Dihydroxy vitamin D 9 pg/mL. Urine samples 4 days after admission showed: calcium urine 1156 mg/dL24 hours, calcium sample 26 mg/dL, sodium urine 465 mEq/24 hours, sodium sample 108 mEq/L, creatinine urine 855 mg/24 hours, creatinine sample 19.9md/dL, urine volume 4300 mL/24 hours.

OUTCOME AND FOLLOW-UP

After correction of hypercalcaemia by fluid therapy, medication treatment and haemodialysis, creatinine level decreased to 1.5 mg/dL. Polyuria resolved after the following week of treatment. The patient had a successful parathyroidectomy with removal of a large parathyroid gland which resulted in correction of iPTH level.

'Hungry bone syndrome phenomena' were observed after surgery with maximal drop of calcium level to less than 6.5 mg/dL (1.62 mmol/L) and phosphorus level of 1.8 mg/dL (0.58 mmol/L). The patient was treated by capsules alpha D3 1 μg × 2 and drops of vitamin D 2400 units per day, calcium carbonate 600 mg × 2, oral phosphorus had been given with improvement of blood electrolytes. The patient has been feeling good since surgery and continues treatment with vitamin D (1600 units per day). At present (5 years after parathyroid surgery), his iPTH is 169 ng/dL and creatinine 1.38 mg/dL (121 mmol/L).

DISCUSSION

Several organs are involved in calcium metabolism: kidneys, bone, intestine and parathyroid gland. Calcium level is regulated by parathyroid hormone (PTH), which increases calcium resorption from the bone and from the distal part of the nephron. PTH raises intestinal calcium resorption indirectly by alpha-1-hydroxylation of 25-OH-Vit D, with increased intestinal absorption of

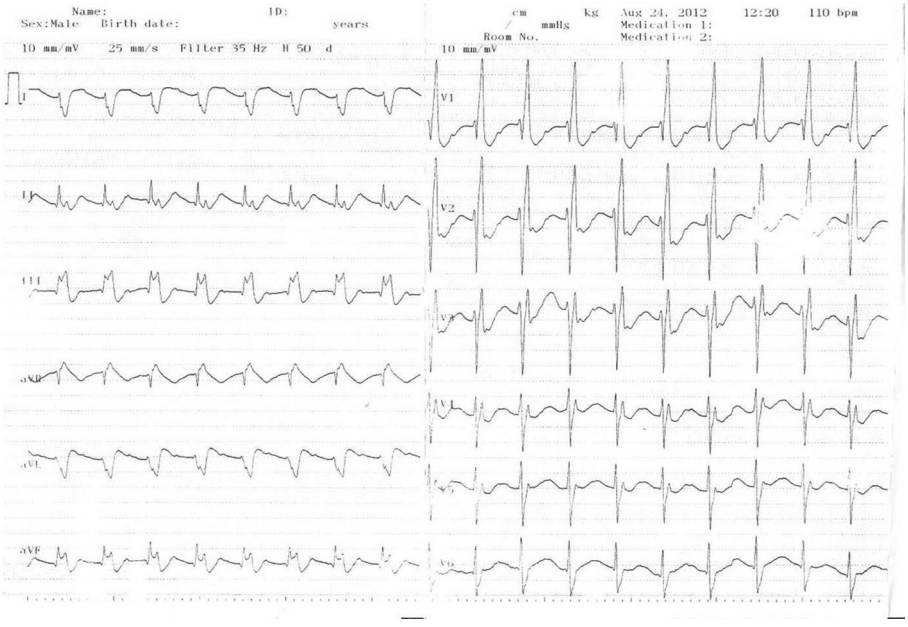

Figure 1 ECG recording at presentation, calcium 23.9 mg/dL (5.97 mmol/L), disclosed shortening of QT (120 ms) with RBBB pattern.

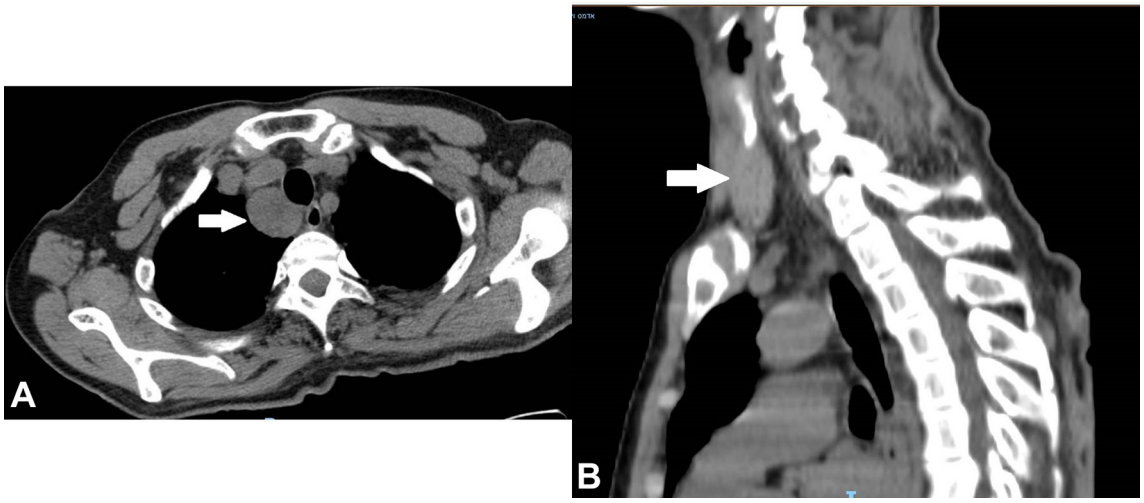

Figure 2 CT demonstrated hypodense lesion near the thyroid gland, 2.7×4.8×3.1 cm^3 in size, extending towards the sternal manubrium, oesophagus and bifurcation of trachea, consistent with parathyroid adenoma (white arrow) frontal plane (A), sagittal plane (B).

calcium through transient receptor potential vanilloid 6 (TRPV6) intestinal channels. Calcitonin released by parafollicular C cells in the thyroid counteracts PTH in response to high calcium level, thus inhibiting osteoclasts and renal tubular epithelial transport of calcium.

In the nephron, PTH activates TRPV5 channel in distal tubule and stimulates activation of vitamin D 1,25$(OH)_2D_3$ (or calcitriol) synthesis in the proximal tubule.[1] Regulation of PTH release is achieved through calcium-sensing receptor (CaSR), G-protein-coupled cell surface protein, expressed in the parathyroid gland and influenced by serum calcium level.[2] In the kidney, CaSR regulates calcium reabsorption and modulates claudin 14/16/19 complex.[3] Claudins are tight-junction membrane proteins, which determine the permeability and selectivity of different nephron segments along the renal tubule and serve as the gatekeepers of paracellular calcium transport in the thick ascending limb, thus regulating urinary calcium and magnesium reabsorption.[4] Hypercalcaemia may be linked to several mechanisms: accelerated bone resorption, calcium absorption and increased renal calcium retention. In some cases, more than one mechanism is involved. Among all causes of hypercalcaemia, hyperparathyroidism and malignancy are the most common, accounting for more than 90% of cases.

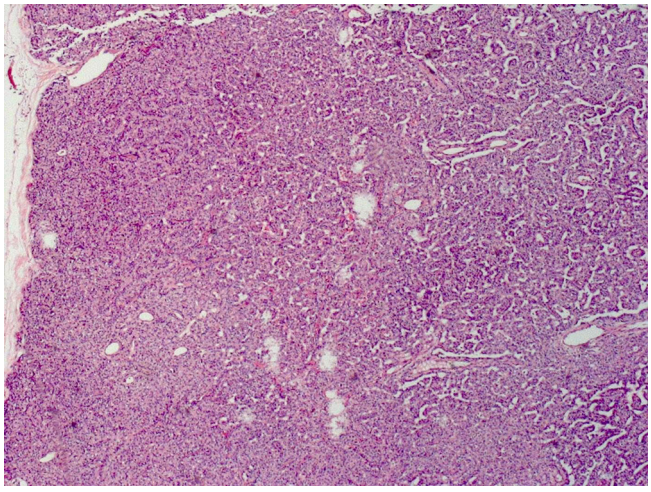

Figure 3 H&E staining disclosed parathyroid tumour with histological features of parathyroid adenoma with no evidence of malignancy.

PTH mediated hypercalcaemia includes pHPT, lithium therapy, tertiary hyperparathyroidism and familial hypocalciuric hypercalcaemia, caused by loss of function mutation of CaSR. Cross-sectional study conducted in Brazil estimated prevalence of pHPT among 4207 patients with hypercalcaemia receiving ambulatory care.[5] Prevalence was 0.78 (95% CI 0.52 to 1.04) of which 81.8% were asymptomatic and 18.2% symptomatic, most of them being postmenopausal women (mean age 61.12±15.73 years). Mean serum calcium was 10.63±1.33 mg/dL and mean serum PTH was 182.48±326.51 pg/mL. Most cases were due to parathyroid adenoma with PTH-mediated activation of osteoclasts and increased bone resorption. Calcium can be only slightly elevated (mild hypercalcaemia) and stable over a period of time and may be defined as *equilibrium hypercalcaemia*. Still, rare cases of extreme hypercalcaemia in patients with primary HPT were reported by various authors.[6] Shibata *et al* described a novel CDC73 mutation in recurrent pHPT. CDC73 mutation analysis should be performed in cases of early-onset, recurrent, pHPT with polyglandular parathyroid involvement and pHPT presenting with severe hypercalcaemia, even if there is no positive family history.[7] Other rare forms of genetic hyperparathyroidism, including hyperparathyroidism-jaw tumour syndrome (also CDC73), gain of function mutation of GCM2 and MEN (multiple endocrine neoplasia) types 1 (menin mutation), 2 (RET) and 4 (CDNK1B) had been described.

On the contrary, malignancy-associated hypercalcaemia is characterised by abrupt symptomatic calcium elevation and is defined as *disequilibrium hypercalcaemia*, complicating the course of 10%–30% of all patients with malignancies and can be a sign of very poor prognosis.[8] Several mechanisms are implicated in hypercalcaemia of malignancy including humoral hypercalcaemia, due to secretion of parathyroid-related hormone (PTHrP), osteolysis, caused by tumour cells invasion of bone with secretion of cytokines (TNF, IL-1, IL-6) and absorptive hypercalcaemia due to vitamin D produced by tumour cells.[9] Hypercalcaemia in multiple myeloma is caused by release of receptor activator of nuclear factor kappa B ligand (RANK ligand), which stimulates osteoclasts.[10]

Other causes of hypercalcaemia are: inactivating mutation of CaSR with slight elevation of PTH (familial hypocalciuric

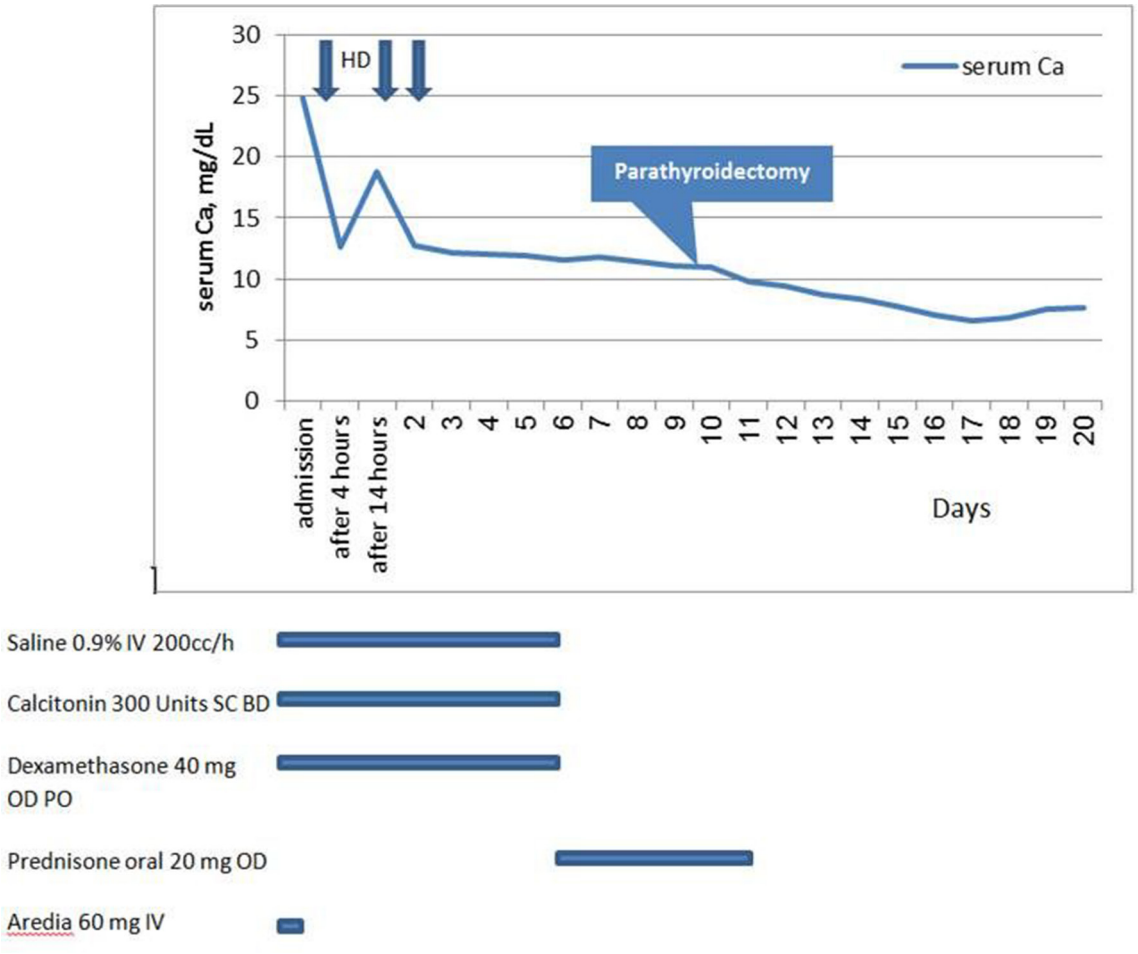

Figure 4 Clinical course of serum calcium level and medical treatment before and after parathyroidectomy. HD, haemodialysis session.

hypercalcaemia) or vitamin D mediated hypercalcaemia. The last one is typically caused by exogenous vitamin D therapy in patients with renal insufficiency, granulomatous diseases (sarcoidosis, infectious diseases) with increased production of $1,25(OH)_2$ vitamin D by macrophages of granuloma or ectopic production of vitamin D in patients with lymphoma. Other causes of hypercalcaemia include vitamin A intoxication, thyrotoxicosis, adrenal insufficiency, thiazide treatment, immobilisation, especially in Paget's disease of bone and milk-alkali syndrome.

Patients with hypercalcaemia may present with neurological signs, including CNS dysfunction, memory disturbances, obtundation or coma.[11] In addition, muscle weakness, constipation, shortening of QT segment on the ECG and band keratopathy due to corneal calcium deposits can be observed. Kidney disorders caused by hypercalcaemia include acute and chronic kidney injury, nephrolithiasis and nephrogenic diabetes insipidus.[12]

Recognition of hypercalcaemia and urgent treatment can be lifesaving. The key stones of hypercalcaemia treatment are vigorous

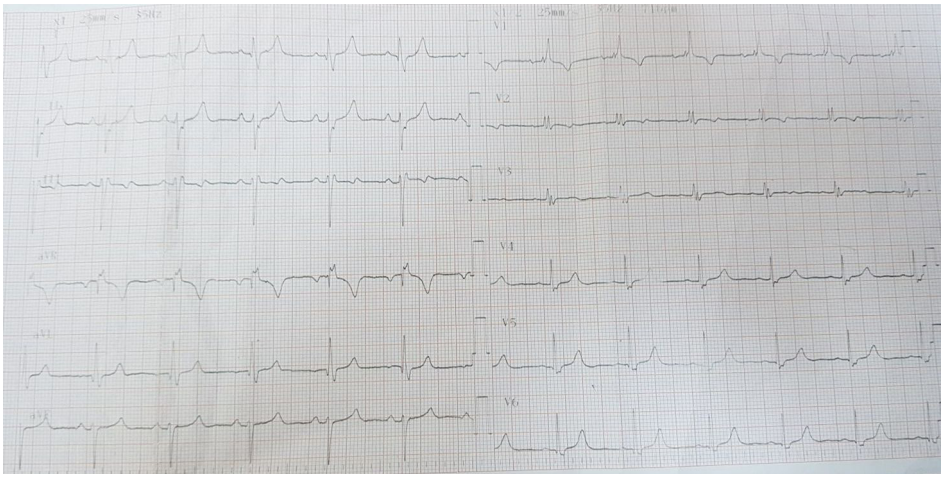

Figure 5 ECG recording after resolution of hypercalcaemia.

intravenous volume expansion with saline, bisphosphonate therapy, calcitonin, corticosteroids and loop diuretic to enhance renal excretion of calcium.[13 14] Patients with severe hypercalcaemia are usually volume depleted due to anorexia, nausea and changes in sensorium with decreased fluid intake. Polyuria and decreased urinary concentration ability due to downregulation of aquaporin may cause additional fluid loss. Intravenous fluid infusion will help to restore intravascular volume and increases urinary calcium excretion. It should be started immediately and helps to decrease calcium rapidly to relatively safe levels. The rate of fluid infusion (usually with normal saline) must take into account age of the patient, comorbidities, especially oedematous states (eg, congestive heart failure or renal failure) and is usually done at the rate of 200–300 mL/hour in relation to urine output. Glucorticoids are especially effective in absorptive hypercalcaemia and can decrease intestinal calcium absorption. They also decrease 1,25-dihydroxyvitamin D production in patients with granulomatous diseases or lymphoma.[15] RANK-L inhibitor—Denosumab (Amgen) (0.13 mg/kg) may be used for treatment of hypercalcaemia in patients with renal failure, where bisphosphonates are relatively contraindicated.

Dialysis is an efficient method of treatment of extremely high calcium level with rapid clearance of calcium and may be used in addition to other modes of therapy, especially when complicated by renal function impairment. Kaiser *et al* treated hypercalcaemic crisis of different aetiologies (breast cancer, hepatocellular carcinoma, cirrhosis of the liver and immobilisation, hydrochlorothiazide medication) by haemodialysis with low or zero calcium bath with rapid fall of serum calcium from a mean value of 3.96 mmol/L to 2.71 mmol/L. (15.8 mg/dL to 10.8 mg/dL). Calcium free acetate solution was sufficient to maintain serum calcium levels within the normal range.[16]

Dialysis may be regarded as salvage treatment of arrhythmia, associated with severe hypercalcaemia.[17] Haemodialysis with low dialysate calcium and haemodialysis with calcium free dialysate (zero calcium acetate based solution) are effective for therapy of hypercalcaemic crisis, but calcium free dialysate may cause haemodynamic instability and is unavailable in our haemodialysis unit.

Two types of dialysis solutions are currently used in dialysis practice with calcium content, 1.25, 1.5 mmol/L (5 mg/dL and 6 mg/dL, respectively). Haemodialysis with low-calcium bath was originally created to prevent vascular calcifications. Seyffart *et al* performed a 20-year survey, where 387 chronic haemodialysis patients used low calcium dialysate together with phosphate binders and observed extremely low incidence of hypercalcaemia, hypocalcaemia, extraosseous, extravascular calcification, bone pain and spontaneous bone fractures, high survival rates, low incidence of cardiovascular fatalities and secondary HPT.[18] Low calcium bath is highly effective for treatment of acute hypercalcaemia, especially in patients presenting with acute kidney injury (AKI) and may provide clearance of one-third of the initial calcium level. In other case, patient with mucosa-associated lymphoid tissue lymphoma and multiple bony metastases, admitted with coma and severe hypercalcaemia with calcium level 4.15 mmol/L (18 mg/dL) was treated by 2 hour calcium-free haemodialysis session with rapid decrease of serum calcium to 2.15 mmol/L (8.6 mg/dL) and regained consciousness shortly after haemodialysis. According to the authors, calcium- free haemodialysis is favourable for rapid correction of hypercalcaemia in the presence of severe hypercalcaemic symptoms, congestive heart failure, renal failure or other conditions that contraindicate adequate hydration.[19]

Our opinion is that calcium free haemodialysis may be dangerous and low calcium 1.25 mmol/L(2.5mEq/L) may be performed repeatedly and safely. Haemodialysis for treatment of severe hypercalcaemia with low calcium dialysate was also demonstrated by Strauch and Ball and was shown to be rapidly effective while patients are being prepared for surgery or while diagnostic studies are being performed.[20] In two other patients with severe hypercalcaemia (one with multiple myeloma and another patient with vitamin D intoxication) treated by haemodialysis using low calcium bath (0–1 mEq calcium per litre), authors demonstrated calcium clearance rate of 682 mg per hour on haemodialysis, as compared with 124 mg per hour for peritoneal dialysis and 82 mg per hour with forced saline diuresis.[21] Continuous venovenous haemodiafiltration with citrate anticoagulation may be highly efficient for acute reduction of elevated serum calcium levels along with classic modes of treatment, in this case citrate, and may have an additional benefit in hypercalcaemia setup owing to its ability to chelate calcium.[22]

Learning points

- Severe hypercalcaemia (calcium level more than 14 mg/dL or more than 3.5 mmol/L) can cause hypercalcaemic crisis with oliguria and anuria, life-threatening arrhythmia, somnolence or coma.
- Hypercalcaemia is rarely seen as complication of primary hyperparathyroidism (pHPT) since calcium is only slightly elevated and stable over time. In such cases, other causes of hypercalcaemic crises should be ruled out. Yet, severe hypercalcaemia can be found in pHPT due to parathyroid adenoma.
- Haemodialysis is rare, but efficient mode of therapy in patients with severe refractory hypercalcaemia. Along with conservative treatment, low calcium bath haemodialysis should be considered in cases of acute kidney injury and if aggressive fluid treatment is relatively contraindicated or ineffective. Even in the absence of AKI, extreme hypercalcaemia is an indication for haemodialysis.

Contributors AAB: treated the patient on admission, with case management, idea of article, writing the manuscript and review of literature. BR: participated in patient's management. YSH: participated in writing and editing of the manuscript. MV: patient management and treatment decisions, writing the manuscript and data collection.

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