Introduction

In the normal human subject, the plasma concentration of ionized calcium is tightly regulated within an extremely narrow range [1]. The kidney plays an important role in normal calcium homeostasis. It regulates the excretion of calcium and phosphorus and is the site of production of 1,25(OH)\(_2\)D\(_3\). Furthermore, it is one of the effector organs for calcium-regulating hormones, 1,25(OH)\(_2\)D\(_3\) and PTH. In uraemia, production of 1,25(OH)\(_2\)D\(_3\) and excretion of phosphate are reduced, leading to hypocalcaemia and secondary hyperparathyroidism (HPT). Thus in patients with chronic renal failure (CRF) disturbances in the stability of Ca\(^{2+}\) concentration are frequent. Hypocalcaemia used to be the condition most frequently seen. It resulted from hyperphosphataemia, low vitamin D levels, and skeletal resistance to PTH. Today, hypercalcaemia, previously less common, has become ever more frequent, mainly as a result of new treatment strategies.

We present a case with hypercalcaemia to discuss the different causes to consider in the differential diagnosis of hypercalcaemia in patients with chronic renal failure.

Case report

A 60-year-old man was admitted because of mental confusion and acute onset of advanced uraemia. He had never been hospitalized before, but had a history of alcoholism. In the past 3–4 years he had not been drinking.

During the 3–4 months preceding admission he had girdle-shaped pain across the lumbar spine and the abdomen without radiation of the pain to other areas. He had become increasingly tired, had a weight loss of approximately 5 kg/3 months and suffered from progressive dementia. He had no further symptoms, specifically no further skeletal complaints.

At the time of admission he had polyuria (3400 ml/day), normal blood pressure (150/85 mmHg), and normal heart rate. Auscultation of heart and lungs and examination of the abdomen were all normal. No abnormalities were found when examining the lumbar spine and the upper and lower extremities. He was aware of his personal data, but was disoriented with respect to time and situation.

Laboratory examination revealed serum creatinine of 0.627 mmol/l and serum urea of 17.3 mmol/l. Creatinine clearance was 10 ml/min and protein excretion 11.4 g/day. Hb was 5.0 mmol/l and Hct 0.23. Serum protein was normal (80 g/l), while plasma albumin was only slightly reduced (508 mmol/l). He had slightly elevated alkaline phosphatases (389 U/l), isoenzymes were not determined. Other liver enzymes were normal. He had normal prostate-specific antigen (PSA) concentration. Plasma sodium and plasma potassium concentrations were normal, but plasma ionized calcium was 1.72 mmol/l, while plasma phosphate was only slightly elevated (1.63 mmol/l). Plasma PTH (10 pg/ml) as well as 1,25(OH)\(_2\)D\(_3\) (18 pg/ml). A positive M-component of the kappa type was found in blood and urine.

X-ray of the skull showed multiple osteolytic changes, while only mild halisteresis was found in long bones, pelvis, hips and the spine (which also showed a past fracture at L\(_3\)). The bone marrow contained 8% plasma cells and showed signs of plasma cell dyscrasia with monoclonality of kappa light chains.

The kidneys were of normal shape and size. There was no evidence of hydronephrosis. Kidney biopsy showed normal glomeruli and normal vessels; tubules were irregularly dilated and contained an eosinophile substance which was sharply delineated with the tendency to 'fracture'. There were several foci of leukocyte and plasma cells. Staining for amyloid was negative. The diagnosis was tubulointerstitial changes consistent with myelomatosis.

The patient was treated with prednisone (80 mg/day) and later pulse cyclophosphamide (1 g). To treat hypercalcaemia, besides prednisone, haemodialysis with low-calcium dialysate (1.25 mmol/l) was used together with administration of calcitonin (Miacalcic) 400 U/day intravenously and clodronate (Bonfos 800 mg twice daily). After 1 week the patient developed hypocalcaemia (Ca\(^{2+}\) 0.95 mmol/l). GFR decreased further and plasma phosphate increased (2.62 mmol/l). The treatment with calcitonin and clodronate was stopped. Plasma ionized calcium has since remained within the normal range, i.e. between 1.2 and 1.38 mmol/l. The patient did not recover kidney function and 4 months later he is still maintained on chronic haemodialysis.
Discussion

The diagnosis of myeloma as the cause of renal failure and hypercalcaemia was easy and straight forward in this patient. Bone pain, osteolytic lesions in the skull, presence of an M-component in plasma and urine, as well as the histological findings in the bone marrow and kidney biopsy pointed to this diagnosis. Several mechanisms may account for the development of hypercalcaemia, which is seen in approximately one-third of all patients with myeloma. These include increased production of bone-resorbing cytokines by the myeloma cells, e.g. 'osteoclast activating factor', which has been identified as tumour necrosis factor (TNF), alpha, beta and interleukin 1. Furthermore prostaglandin E2 and rarely (less than 20% of cases) parathyroid hormone-related peptide (PTHrP) have been identified. One should also consider that the paraprotein in myeloma may exhibit considerable Ca2+ binding capacity, e.g. 2–4 mmol of Ca2+/mol of protein, leading to an increase of total plasma calcium despite normal levels of plasma ionized Ca2+ (pseudo-hypercalcaemia).

Several differential diagnosis have to be considered when the clinician is confronted with a patient who has CRF and high ionized calcium values (Table 1).

Today the most frequent cause of hypercalcaemia in CRF, at least in my opinion, is the use of vitamin D analogues in an attempt to improve secondary hyperparathyroidism. Undoubtedly there is a good rationale for such treatment. 1,25(OH)2D3 [2-4] binds to its nuclear receptor. Together with retinoic acid it forms a complex which regulates PTH gene expression. Vitamin D probably also has a direct effect on parathyroid cell proliferation and might be of importance for the induction of apoptosis of parathyroid cells. The net effect of vitamin D analogues on the parathyroid gland is to reduce PTH mRNA synthesis and secretion of PTH. Vitamin D analogues may be given as intravenous pulse or oral pulse therapy or as daily oral therapy. Which of these different treatment modalities is most beneficial has not been clarified. Pulse therapy has been recommended with the consideration that high peak plasma concentrations of vitamin D lead to better suppression of PTH secretion and less frequent episodes of hypercalcaemia. On the other hand, daily oral therapy is easier to administer and quite effective. The risk of developing hypercalcaemia should not discourage the clinician from using vitamin D, but I underline the importance of careful monitoring of plasma Ca. The treatment of hypercalcaemia during vitamin D therapy consists in reduction of the dose or interruption of vitamin D administration.

'Tertiary' HPT with extremely high PTH levels and hypercalcaemia may develop in patients with severe secondary HPT, especially those with complicating severe hyperphosphataemia. For unknown reasons autonomous (often monoclonal) growth of the parathyroid glands may occur. The possible association with high phosphorus levels is not quite understood. Nevertheless, a direct stimulatory effect of phosphorus on PTH secretion unrelated to calcium and vitamin D has recently been demonstrated by Almaden et al. [5] and others [6, 7]. High PTH levels are associated with the development of ostitis fibrosa. Furthermore, as shown by Massry and Smogorzewski [8], PTH may be one of the 'uremic toxins' with detrimental effects on a large number of organ systems other than skeleton and kidneys. Corresponding effects of PTH are not known in normal human physiology [9]. It is now well established that common receptors exist for PTH and PTHrP [10]. The latter is expressed in a large variety of fetal and adult tissues. It seems likely that the effects of high PTH concentrations in uraemia are mediated via these common receptors. Treatment of severe tertiary HPT will often require parathyroidectomy. Attempts to reduce ionized calcium concentrations by dialysis using a dialysate containing no calcium has been tried, with limited success. Another rationale for the approach to use low-calcium dialysate and vitamin D simultaneously was the consideration to create a 'window' where vitamin D is tolerated without aggravating hypercalcaemia. It has not however, been documented in uraemic patients whether parathyroid glands with monoclonal growth [11] will respond to vitamin D and whether PTH synthesis can be suppressed at all by vitamin D in cases of tertiary HPT. This approach is even more problematical in view of the reduction of vitamin D receptors in adenomatous parathyroid glands.

The nephrological community is still divided between those who use a dialysate with approximately 1.75 mmol/l of calcium and those who prefer a dialysate of 1.25 mmol/l as the standard dialysate concentration [12,13]. Net calcium balance during dialysis is positive when 'high calcium' dialysate is used. The benefit is some suppression of PTH levels, but often at the price of mild hypercalcaemia and calcium phosphate deposits, at least in some patients. In hypercalcaemic patients, a 'low calcium' dialysate (1.25 mmol/l)
is recommended, as in the present case. Furthermore the concentration of 1.25 mmol/l is used in many centres in order to allow treatment with vitamin D and calcium-containing phosphate binders. The level of 1.25 mmol/l corresponds to the physiological range of plasma ionized calcium. It has not been shown, however, which calcium concentration in the dialysate is optimal for the majority of renal failure patients, e.g. 1.25 or 1.35 mmol/l. Reducing the calcium concentration in the dialysate entails the risk of aggravation of secondary HPT.

High calcium intake is today mainly due to administration of calcium-containing phosphate binders such as calcium carbonate or calcium acetate. High calcium intake may also be the consequence of high intake of dairy products, which in addition result in hyperphosphataemia. This problem may be solved by dietary restriction of phosphate intake. Nevertheless, in some cases it is necessary to reduce or stop the use of calcium-containing phosphate binders. In their stead the patient must be given aluminium hydroxide. It is well known that uraemic patients on treatment with aluminium hydroxide absorb aluminium from the intestine. Accumulation of aluminium is toxic for bone and brain. Today, in uraemic patients, the most frequent bone disease is presumably low-bone-turnover disease, so-called adynamic bone disease. Initially this condition was ascribed mainly to aluminium deposition along the mineralization front in combination with a direct toxic effect of aluminium on the parathyroid gland. Aluminium deposits can be removed by treatment with desferrioxamine. Of course, if possible, treatment with aluminium hydroxide should be avoided. However, even patients on no oral aluminium may become aluminium-loaded via occasionally high aluminium concentrations in the dialysate. This may happen despite regular monitoring. Another cause is administration of aluminium-containing fluids, aluminium solutions etc. So the possibility of aluminium toxicity in a hypercalcaemic patient should not be excluded out of hand because the patient did not have any aluminium-containing oral phosphate binders.

Today the diagnosis of adynamic bone disease is made in many uraemic patients who have not been exposed to excessive amounts of aluminium. These patients are more sensitive to treatment with vitamin D analogues and may develop hypercalcaemia even at low doses of these compounds. Adynamic bone disease is especially frequent in diabetic patients. This condition is characterized by low normal or low levels of serum PTH, but the diagnosis can only be established by bone histology. Therefore patients with low PTH levels on vitamin D treatment should be carefully monitored for hypercalcaemia. The risk arises because adynamic bone is not able to incorporate and sequester calcium. Vitamin D treatment should in general be avoided, if adynamic bone disease is suspected.

Overzealous treatment of hyperphosphataemia may not only provide a high calcium load, but also result in severe hypophosphataemia, which in turn may aggravate hypercalcaemia. If patients develop hyper-
increased production of PTHrP (found in 30–50%). Today this hormone can be measured in plasma and this will help in the differential diagnosis to exclude hyperparathyroidism (in hypercalcaemia of malignancy PTH levels are normal or low). In CRF patients, the same types of malignancy may cause hypercalcaemia as in non-renal patients. It has been shown that these patients have an increased production of cytokines, such as osteoclast activating factor (interleukin 1, tumour necrosis factor alpha and beta) or interleukin 6. In some patients with tumours extrarenal production of 1,25(OH)2D3 has been documented. The diagnosis is based upon the demonstration of a tumour, high PTHrP levels in the presence of low PTH levels, and hypercalcaemia. The treatment is (1) specific treatment of the malignancy, (2) administration of steroids and/or calcitonin, bisphosphonate or mitramycin, analogous to what is recommended for treatment of hypercalcaemia of non-renal patients. Severe hypercalcaemia can be reduced temporarily by using ‘low calcium’ dialysis as in the present case.

Approximately 10–15% of cases with sarcoidosis develop hypercalcaemia. In some cases CRF is the result of sarcoidosis, which may cause granulomatous interstitial nephritis, focal glomerulosclerosis, or membranous glomerulonephritis. In sarcoidosis hypercalcaemia is the result of extrarenal production of 1,25(OH)2D3 in granulomatous tissue, primarily in the lung. The same may occur in patients with other granulomatous diseases, such as tuberculosis, histoplasmosis, silicosis.

Thus, in patients with chronic renal failure, hypercalcaemia is most frequently iatrogenic, i.e. the result of different treatment modalities; but it is wise to remember that these patients may also develop hypercalcaemia for exactly the same reason as non-uraemic patients.

References