Bone-Eating Kidney Disease

SCIENCE

Case Studies

A 31-year-old female patient reported severe pain in the left forearm, right hand, right knee, right hip, and lower back following a fall sustained three days before presentation. The patient had a history of end-stage renal disease (ESRD) and received maintenance hemodialysis. Medical records revealed that she had poor compliance with her diet, medications, and dialysis treatments. Laboratory values were significant for marked elevation in serum parathyroid hormone level (1735 pg/mL), as well as hyperphosphatemia and normal serum calcium levels.

These symptoms are most consistent with which of the following disease?

a) Renal failure
b) Hyperparathyroidism
c) Brown tumour

Introduction

In chronic kidney disease (CKD) patients, the levels of parathyroid hormone (PTH) are progressively increased. Many observational studies demonstrate the association between PTH levels at extremes and mortality in these patients.1 It is not easy to observe skeletal manifestations of secondary hyperparathyroidism with early detection and treatment of CKD.2 This is particularly notable in the current era of potent phosphate binders, calcimimetic agents, and use of high-flux dialyzers that provide excellent clearance of uremic toxins such as phosphate. In this study, the case of secondary hyperparathyroidism is presented with brittle bones and characteristic radiographic changes.

Medical History

The patient had a past medical history notable for end-stage renal disease (ESRD) for which she has been receiving maintenance hemodialysis for the past 15 years, hypertension, diabetes, and congestive heart failure. She was wheelchair bound due to disabling peripheral neuropathy and chronic leg pain. She reported that she had fractured her left wrist about three weeks before presentation. She also experienced femoral fracture about a year ago, that was managed conservatively.

Examination and Laboratory Investigations

Physical examination showed a blood pressure of 153/81 mm Hg and pulse rate of 101 bpm. There were moderate swelling and tenderness over the right distal femur with a limited range of motion of the right knee due to pain — left forearm splint due to the previous fracture. Tenderness was also noted over the tip of the right index finger. There was no distal neurovascular deficit in the extremities.

Treatment

Medications included aspirin of 81 mg per day, lisinopril of 40 mg per day, carvedilol of 25 mg twice a day, sevelamer carbonate of 800 mg thrice a day with meals, and insulin regimen. The patient reported non-compliance with medications, diet, and hemodialysis treatment.
Initial laboratory values were significant for hemoglobin of 8.5 g/dL (12–15 g/dL), white blood cell count of 6.2 thou/mm3 (4–10 thou/mm3), platelet count of 222 thou/mm3 (150–450 thou/mm3), blood urea nitrogen of 36 mg/dL (6–20 mg/dL), and creatinine of 5.72 mg/dL (0.4–0.9 mg/dL). Serum intact PTH was found to be significantly elevated at 1735 pg/mL (15–65 pg/mL (goal 150–300 pg/mL for ESRD)) with serum calcium level of 9.5 mg/dL (8.4–10.2 mg/dL) and phosphate of 5.7 mg/dL (2.7–4.5 mg/dL). Serum 25-hydroxy vitamin D level was 24 ng/mL (>20 ng/mL).
X-ray of the right lower extremity showed diffusely decreased osseous mineralisation and a comminuted distal femoral fracture. Similarly, X-ray of the left upper extremity revealed significant diffuse osteopenia. X-ray of the right hand showed findings concerning for possible fracture of the distal phalanx of the index finger. CT scan of the abdomen and pelvis showed remarkable diffuse severe demineralisation of the bones, with florid changes of renal osteodystrophy, prominent subligamentous resorption in the sacroiliac joints bilaterally, and widespread brown tumors.
Typical imaging stigmata of hyperparathyroidism including diffuse demineralisation, insufficiency fractures, and brown tumors supported the diagnosis in this young woman.
Her fractures were managed with the non-operative treatment given her poor baseline functional status and severe hyperparathyroidism. The patient refused surgical parathyroidectomy. A high-dose phosphate binder (i.e., sevelamer carbonate) and also an oral calcimimetic (i.e., cinacalcet) were started for management of hyperphosphatemia and hyperparathyroidism. We reinforced compliance with low phosphate diet, medications, and hemodialysis treatment.

Discussion

In advanced kidney disease, the phosphorus clearance significantly decreases the glomerular filtration rate (GFR). Even in patients with a GFR of greater than 30 mL/min, subclinical and postprandial hyperphosphatemia has been observed, which could be the major cause of secondary hyperparathyroidism. PTH stimulates the osteoclasts and leads to bone resorption, which, in turn, increases the serum concentration of calcium and phosphorus. Moreover, PTH indirectly increases intestinal calcium and phosphorus absorption by stimulating 1,25-dihydroxy vitamin D production.3 Calcium has a negative feedback effect on the parathyroid glands through the calcium-sensing receptor;4 activation of this receptor is the primary mechanism of action of cinacalcet.
Optimise the levels of serum phosphate and calcium are the first step in the management of hyperparathyroidism due to kidney disease. Calcitriol supplementation is effective in suppressing high PTH levels, but without physical exercise, it can increase the absorption of both calcium and phosphate from the gut and may increase calcium phosphate product. Previous data showed that 25-hydroxyvitamin D levels below 15 ng/mL are associated with higher severity of secondary hyperparathyroidism even in ESRD patients receiving dialysis.5 In patients with persistently elevated PTH levels and serum calcium is lower than 8.4 mg/dL, in spite of optimising serum phosphate and calcium levels, the addition of calcimimetic drug cinacalcet should be considered. In our patient with serum PTH levels of >1000 pg/mL, the likelihood of improvement is low with hyperphosphatemia control alone, and so we chose to add cinacalcet. In patients who have markedly elevated PTH levels and have unmanagable signs and symptoms, They should be considered surgical parathyroidectomy if they are acceptable surgical candidates.6 Parathyroidectomy has been suggested to reverse the bone resorption and result in complete regression of brown tumors.7 In this context, it is of note that cinacalcet has failed to improve all-cause or cardiovascular mortality, but could reduce the need for parathyroidectomy in patients with ESRD.8

Learning

1. Patients with CKD, especially those on dialysis, are at high risk of secondary hyperparathyroidism and consequent bone fractures.
2. The accumulation of phosphate, reduction in active vitamin D production, and the tendency to hypocalcemia; these all act as stimuli for the increased secretion of PTH.
3. The laboratory parameters need to be periodically monitored and optimised early in the course of CKD.
4. Appropriate patient education and adherence to therapy plays vital role in the management of this bone-eating disease, which can otherwise contribute to significant morbidity.

References:

1. Moorthi RN, Moe SM. CKD-mineral and bone disorder: core curriculum 2011. Am J Kidney Dis 2011; 58(6): 1022–1036.
2. Koratala A, Bhatti V. Skeletal findings in secondary hyperparathyroidism. Oxf Med Case Reports 2017; 2017(1): omw097.
3. Saliba W, El-Haddad B. Secondary hyperparathyroidism: pathophysiology and treatment. J Am Board Fam Med 2009; 22(5): 574–581.
4. Brown EM, Hebert SC. Calcium-receptor-regulated parathyroid and renal function. Bone 1997; 20: 303–309.
5. Ghazali A, Fardellone P, Pruna A, et al. Is low plasma 25-(OH)vitamin D a major risk factor for hyperparathyroidism and Looser's zones independent of calcitriol? Kidney Int 1999; 55: 2169–2177.
6. Tominaga Y, Uchida K, Haba T, et al. More than 1,000 cases of total parathyroidectomy with forearm autograft for renal hyperparathyroidism. Am J Kidney Dis 2001; 38(4 Suppl. 1): S168–S171.
7. Arabi A, Khoury N, Zahed L, et al. Regression of skeletal manifestations of hyperparathyroidism with oral vitamin D. J Clin Endocrinol Metab 2006; 91(7): 2480–2483.
8. Palmer SC, Nistor I, Craig JC, et al. Cinacalcet in patients with chronic kidney disease: a cumulative meta-analysis of randomized controlled trials. PLoS Med 2013; 10(4): e1001436.

Exploratory, Aspirin, Lisinopril, Carvedilol, Osteoporosis, Forearm, Right hand, Right knee, Right hip, Lower back, Case