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A Case Study of Renal Osteodystrophy: Challenges of Management

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ABSTRACT

The presence of chronic kidney disease (CKD) has a variety of effects on mineral and bone metabolism, hence the term Mineral Bone Disease (CKD-MBD). It encompasses interrelated pathophysiology of bone turnover, mineralization and volume. This leads to alterations in calcium, phosphate, vitamin D, parathyroid hormone and a phenotype of increased fracture risk, cardiovascular disease, and mortality in the context of ESRD.

Here we present a case vignette of fourteen years old male who had been referred for pre-transplant assessment and discovered to have severe form of high turnover bone disease (hyperparathyroid bone disease) with altered biochemical bone profile and some classical imaging findings of hyperparathyroidism. In addition, we discuss the pathophysiology and therapeutic implications and challenges of management.

Key words: ESRD, CKD-MBD, Hyperparathyroidism.

CASE VIGNETTE

A 14 year-old male with end stage renal disease (ESRD) was referred to our unit for pre-transplant assessment. He was on regular haemodialysis programme (twice per a week) for the last three years. During evaluation, the family reported that he experienced recurrent attacks of severe bone and joint aches. Clinical examination revealed growth retardation, limping, anaemia, wasting of muscles, and bowing of the legs. Bone profile and imaging studies were done. Serum calcium concentration was 7 mg/dl (reference range 8.5-10.5), and serum phosphate concentration was 6.8 mg/dl (reference range 2.7-4.6). Serum alkaline phosphatase was 1150 IU (reference range 45-150 IU). Vitamin D3 (25 hydroxy vitamin D) concentration was 10 ng/ml. His parathyroid hormone level was 1800 pg/ml. Imaging studies for the wrist, hip joints, iliac bones and the spine had been done. (Figure 1,2,3)

DISCUSSION

Abnormalities in mineral metabolism and bone structure are almost universal finding with progressive chronic kidney disease (CKD).[1] Changes in mineral metabolism and bone structure develop early in the course of chronic kidney disease (CKD) and worsen with progressive loss of kidney function. The magnitude of these changes may also be influenced by various therapeutic interventions, such as vitamin D administration.[2]

Renal osteodystrophy is an alteration of bone morphology in patients with CKD.[3] Four main types of renal bone disease can be seen in patients with CKD with many patients showing evidence of more than one defined bone lesion (called mixed uremic osteodystrophy).[4]

- Osteitis fibrosa cystica, in which bone turnover is increased due to secondary hyperparathyroidism.
- Adynamic bone disease, in which bone turnover is low. Although aluminium deposition may cause this disorder, most current cases result from excessive suppression of the parathyroid glands. This represents the major bone lesion in peritoneal dialysis and haemodialysis patients.
- Osteomalacia, in which bone turnover is also low in combination with an increased volume of unmineralised bone (osteoid). This problem, which is now uncommon, was

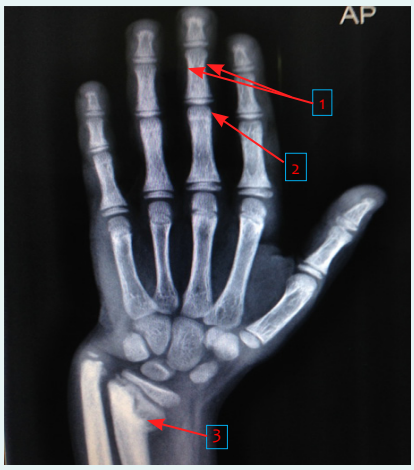

Figure 1: There is marked sub-periosteal resorption of several of the phalanges (1), erosion of the tufts (2) , and metaphyseal changes resembling rickets seen in distal radius (3).

Figure 2: Hip joints and iliac bones: Metaphyseal changes also seen resulting in rickets like changes and the so called rotting fence-post appearance along with slipped capital femoral epiphysis. Subligamentous resorption seen in the ischial tuberosity. Subchondral bone resorption found at symphysis pubis and sacroiliac joints.

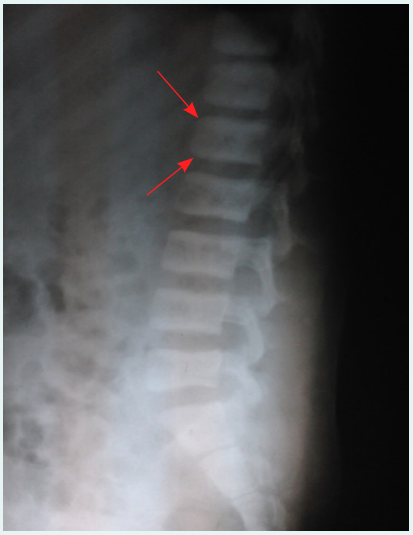

Figure 3: Spine: Osteosclerosis see in the vertebral endplates giving appearance of (`rugger-jersey' spine)

due primarily to aluminium deposition in bone at a time when aluminium-containing antacids were used as phosphate binders. The mineralization lag time is prolonged in osteomalacia: greater than 100 days, in comparison to less than 35 days in normal subjects and those with pure osteitis fibrosa.

- Mixed uremic osteodystrophy, in which elements of both high and low bone turnover may be observed. This is also characterized by marrow fibrosis and increased unmineralized osteoid.

In this vignette the picture is that of mixed uremic osteodystrophy with clear evidence of high turnover bone disease plus rachitic picture and reduced bone density. The main picture is that of hyperparathyroidism or what do we know as osteitis fibrosa cystica. Secondary hyperparathyroidism begins quite early in the course of CKD, frequently when kidney function declines to less than 60 mL/minute/1.73m2. This occurs in response to a series of abnormalities that initiate and maintain increased PTH secretion.[3]

The main abnormalities that contribute to the pathogenesis of secondary hyperparathyroidism are:

- Phosphate retention
- Decreased free calcium level
- Decreased 1,25-dihydroxyvitamin D (Calcitriol) level
- Reduced expression of vitamin D receptors, calcium-sensing receptors.

The relative importance of these abnormalities in triggering PTH production can be understood by examining the changes in their levels in relation to the increase in PTH during the course of CKD. Increased PTH levels first become evident when the estimated glomerular filtration rate (eGFR) drops below 60 mL/min/1.73m^2. At that time, serum calcium and phosphate levels are normal and remain within normal ranges until eGFR decrease to approximately 20 mL/min/1.73m^2. However, low levels of calcitriol are common at higher levels of eGFR. [5,6]

Hyperphosphatemia contributes to hyperparathyroidism independently of serum calcium and vitamin D via increasing PTH gene transcription, PTH peptide secretion and parathyroid cell proliferation.[7]

The clinical symptoms, signs and bone lesions of this 14 year-old boy are consistent with such diagnosis. Bone pain, myopathy and even muscle wasting are common features in such degree of bone disease. Bone deformities like bowing of weight bearing bones are frequent manifestation. Widening of the metaphyseal re-

gions may develop in all long bones with different degrees according to the severity of metabolic bone disease and on metaphyseal growth, which vary with age.[8,9]

Pronounced secondary hyperparathyroidism, hypocalcaemia, and severe osteitis fibrosa promote disintegration of the growth plate and increase the risk of epiphysiolysis and subsequent slipping of epiphysis. The most frequent localization is the proximal femur. This in turns leads to serious complications like osteonecrosis, severe deformities and degenerative bone diseases.[10]

There is no precise data on fracture incidence in ESRD, but it seems to be more than the incidence for healthy children which is 14 fractures per 1000 person a year. Hyperparathyroidism and reduced plasma 1,25 (OH)2D3 level result in high bone turnover which compromises bone dimension and strength, thus increasing the risk of fractures.[8]

Growth failure is a regular feature of children with CKD/ESRD is mainly due to endogenous growth hormone and Insulin like growth factor (IGF) resistance, malnutrition and metabolic acidosis. The effects of altered vitamin D and PTH metabolism on growth are not entirely clear. From the clinical observations, it is not clear which PTH levels are optimal for growth. Whatever the level is, it should be taken in the view of nutritional status and phosphate intake.[8]

Hyperparathyroidism and renal bone diseases have other non-skeletal effects. Erythropoietin resistant anaemia is a serious complication that negatively impact patient's management plan and quality of life. Excessive vascular calcification is one of the main mechanisms for increased cardiovascular mortality. More than 90% of young adults with childhood onset of CKD already have significant coronary calcification. Refractory pruritus may be a manifestation of hyperparathyroididsm.[11, 12, 13]

The critical question here is whether all these complications are preventable or not? The answer is fortunately, Yes they are potentially preventable. This can be achieved through the following steps:

- Attention for early detection of altered bone and mineral homeostasis especially in children.
- Optimal control of serum phosphate levels is probably the crucial element of preventive strategy.
- Serum calcium should be maintained in normal range.
- Optimum dialysis dose and care should be provided.

In reality these goals are not easy to achieve specially in the developing countries. In Iraq, it's difficult to have early diagnosis because of the late referral to nephrology services. Early detection needs low diagnostic threshold because patients are initially asymptomatic and may be mistaken for nonspecific symptoms. The second big challenge is how to achieve optimal phosphate control. It needs regular dietary counselling. This should balance the need to avoid phosphate rich foods (meat and dairy products) and the risk of malnutrition in a growing child with a chronic disease. In addition, the availability and provision of phosphate binder medications and different sterols are not always consistent. Conventional haemodialysis is not so efficacious for removal of excess phosphate.[8] This is augmented by the provision of inadequate dialysis time and dose in some paediatric dialysis unit in Baghdad, as well as the under use of haemodiafiltration as a standard practice in our units. The best haemodialysis approach is frequent or nocturnal haemodialysis. This is not easily achievable even in well-equipped centres. Vitamin D3 level is not regularly measured in our practice beside the non-availability of bone pathology studies.

In addition to preventive measures, therapeutic strategy should include phosphate binders, calcium and non-calcium based compounds, plus calcitriol. Our patient was already using such medications. Thus we left with two options to target the relentlessly increasing PTH levels. These are either the use of calcimimetic agents or to go for parathyroidectomy.

Calcimimetics bind to the parathyroid calcium sensing receptors, increase its sensitivity to ionized calcium and a dose dependently decrease plasma PTH level by 80%.[14] In spite of being very expensive and not available in Iraq, the patient started this treatment in a maximum dose of Cinacalcit (60 mg/day) for more than three months without measurable response. This raised the challenge and parathyroidectomy would be inevitable. The proper parathyroid imaging with sestamibi scan is not available and still parathyroid surgery needs proper training and standardization.[15]

CONCLUSION

Prevention of renal bone disease should always be the primary objective in managing children with CKD/ESRD or at least to delay its development. This should be achieved through proper dialysis dosing, regular dietary counselling, and proper use of phosphate binders and vitamin D derivatives. Early referral to nephrology and transplantation services is mandatory to avoid these serious complications of CKD/ESRD to have the best possible life quality.

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Abbreviation list: Chronic Kidney Disease (CKD), Chronic Kidney Disease/ Metabolic Bone Disease (CKD-MBD), End Stage Renal Disease (ESRD), Parathyroid Hormone (PTH), Estimated Glomerular Filtration Rate (eGFR), 1, 25 dihydroxycholecalceferol (1,25 (OH)2D3), Insulin Like Growth factor (IGF)

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