Brown Tumor Management In End Stage Renal Disease Patients On Chronic Dialysis: Case Reports And Literature Review

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Abstract: Patients with CKD are prone to developing secondary and tertiary hyperparathyroidism due to altered calcium and phosphorus metabolism. Brown tumor is an uncommon terminal stage of cystic osteitis fibrosa which is being increasingly reported in hyperparathyroidism secondary to renal failure, as a result of increased survival of these patients on dialysis. We report four cases of brown tumors in end stage renal disease patients on maintenance dialysis at Madras Medical Mission Hospital who underwent parathyroidectomy with gratifying outcomes.

Keywords: Brown tumor, CKD, Dialysis, Parathyroidectomy

Introduction:

Chronic kidney disease (CKD) related mineral bone disease (MBD) is challenging in dialysis patients and contributes to increased morbidity and mortality in them (1). CKD-MBD refers to abnormalities of calcium and phosphorous, parathyroid hormone(PTH) and vitamin D metabolism that result in alteration in bone turnover and calcification of vascular or other soft tissues(2). Patients suffering from CKD may develop secondary and tertiary hyperparathyroidism due to altered calcium and phosphorus metabolism. Brown tumor is an uncommon condition that represents the terminal stage of the cystic osteitis fibrosa and has been increasingly reported in hyperparathyroidism secondary to renal failure, due to the increased longevity of CKD patients on dialysis (3). The brown appearance result from hypervascularity, haemorrhage and haemosiderin accumulation. These contain fibrous tissue with giant cells, haemosiderin-laden macrophages and fibroblasts that fill the lytic areas. We report four cases of brown tumors in end stage renal disease patients on maintenance haemodialysis at Madras Medical Mission Hospital who underwent parathyroidectomy with gratifying outcomes.

Discussion:

Renal bone disease was renamed chronic kidney disease-mineral bone disease (CKD-MBD) in 2005 by KDIGO sequel to observation of diverse features of bone and mineral disease in CKD which included extra-skeletal manifestation (4). The current definition of CKD-MBD is systemic disorder of mineral and bone metabolism due to CKD manifested by one or a combination of the following: (i) abnormalities of calcium, phosphorus, PTH or vitamin D metabolism (ii) abnormalities of bone turnover, mineralization, volume, linear growth or strength and/or (iii) vascular or other soft tissue classification (4).

Hyperphosphataemia with accompanying hypocalcaemia from impaired renal phosphorus elimination is the primary event triggering hyperparathyroidism and bone remodeling, a process aimed at achieving a balance between the processes of osteoblastic bone formation and osteoclastic bone resorption (5). Osteitis fibrosa cystica is mineral bone disease characterized by presence of subperiosteal resorption in the digits, skull and long bones with diffuse osteopenia (6). Brown tumors are an unusual non-neoplastic bone lesion that represents a localized manifestation of osteitis fibrosa cystica.
<table>
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<th>Case 4</th>
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<tr>
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<td>F</td>
<td>M</td>
<td>M</td>
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<td>Difficulty in chewing &amp; swallowing</td>
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<td>8.4/7.2</td>
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<td>Calcification of plantar fascia &amp; achilles tendon Osteopenia Hyperplasia of parathyroid gland</td>
<td>Destructive osteodystrophy of mandible (Figure 2)</td>
<td>Hyperfunction &amp; adenoma of parathyroid gland (Figure 3)</td>
<td>Hyperfunction &amp; adenoma of parathyroid gland (Figure 3)</td>
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<td>Drugs</td>
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<td>Vitamin D Calcium carbonate</td>
<td>Calcium carbonate &amp; Sevelemar</td>
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<td>Total Parathyroidectomy</td>
<td>Sub-total Parathyroidectomy</td>
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<td>Histology</td>
<td>Brown tumor (Figure 1)</td>
<td>Brown tumor (Figure 1)</td>
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<td>Brown tumor (Figure 1)</td>
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Figure 1 - Histopathology of parathyroid adenoma showing parathyroid cells with uniform looking nucleus (black arrow) in low power and intervening adipose cells (white arrow) in high power.
Figure 2: MRI showing mandible bone destruction by Brown Tumor with isotope scan showing increase uptake by the mandible (arrows)

A study from Senegal showed that CKD-MBD is frequent in Senegalese haemodialysis patients and are dominated by high bone turn-over disease (10), in contrast to report from Nigeria that found low bone turn-over as the commonest form (11). Onyemekheihia et al found hypocalcaemia and hyperphosphataemia in 7% and 79% of their CKD patients respectively while 90% of those who had bone biopsies demonstrated histological evidence of renal bone disease (12). In the Czech Republic (13), Israel (14), and Egypt (15), the prevalence of CKD-MBD was found to be 57%, 66.7% and 33.3% among uraemic patients respectively. The disease can manifest itself at any age, but is more common among people older than 50 years, and is three times more common in women than in men (15). It develops in 3-4% of patients with primary hyperparathyroidism and in 1.5-1.7% in those with secondary hyperparathyroidism (16). About half of patients with CKD may develop osteitis fibrosa cystica making brown tumor more prevalent (17).

Clinical manifestations of CKD-MBD are often nonspecific with majority being asymptomatic. The paucity of specific clinical features make diagnosis of CKD-MBD more difficult (18,19). Symptoms associated with CKD-MBD include bone pains, pruritus, and loss of function in the limbs as a result of fracture or cord compression syndrome (3,12,20). CKD-MBD is associated with high fracture risk because of disturbances in bone quality (21). Patients in stages 3 to 4 CKD and ESRD have twofold and fourfold likelihood of experiencing hip fracture respectively (22,23).

induced by persistent hyperparathyroidism, independent of its cause (7).

Increased parathyroid hormone levels induce the proliferation and differentiation of pluripotent bone marrow cells into osteoblast which trigger the migration and differentiation of monocytes into osteoclasts; the increased number of the latter in the bone tissue causes bone resorption to predominate over the formation of new bone tissue. Brown tumor is a combination of both osteoblastic and osteoclastic activities (8). Histologically, brown tumors are made up of mononuclear stromal cells mixed with multinucleated giant cells, recent haemorrhagic infiltrates and hemosiderin deposits (9). Brown appearance is due to hypervascularity, haemorrhage and hemosiderin accumulation.
Management of brown tumor includes vitamin D supplementation which improves serum parathyroid hormone levels. The cornerstone of managing CKD-MBD is to maintain normal bone turnover by ensuring adequate parathyroid hormone and vitamin D receptor integrity with normalized phosphorus, calcium and calcitriol levels. The main thrust includes phosphate binders, vitamin D analogs and calcimimetics. Phosphate binders can be in form of calcium and non-calcium containing formulations like calcium acetate and sevelamer carbonate. Generally, calcium based products may be associated with hypercalcemia which can contribute to the development of adynamic bone disease and coronary calcification (24,25). Vitamin D exacts its effect by increasing intestinal absorption of calcium and phosphorus with increased risk of hypercalcemia. Cinacalcet hydrochloride is a calcium receptor agonist specific for the calcium receptor on the parathyroid. Cinacalcet therapy will result in reduction of PTH secretion and lower serum calcium and phosphorous levels. However, increased use of vitamin D receptor agonists may be possible when the therapy is combined with cinacalcet (26,27). Cinacalcet is well tolerated and is shown to improve biochemical control of secondary hyperparathyroidism in PD patients (28).

The definitive treatment of brown tumor is parathyroidectomy as studies have shown that 80% of brown tumors result from parathyroid adenoma while parathyroid hyperplasia and co-existence of hyperplasia and adenoma account for the rest (29-32). The available data demonstrate a tendency towards adynamic bone disease in patients undergoing PD. Diabetes and conventional dialysate solutions may directly influence and adversely affect bone metabolism by competing with the anabolic effect of PTH. Consequently, it could be hypothesized that higher PTH concentrations are required to preserve normal bone cell function and bone turnover in these patients (33).

These four cases highlight the salutary benefits of appropriate parathyroidectomy intervention in the management of brown tumor in CKD patients. The finding of a suspicious bone mass in ESRD patients on chronic dialysis should prompt a search for parathyroid disorder as timely removal of such a lesion may be rewarding. We recommend periodic evaluation and prompt management of mineral bone disorder in the early stages of CKD in a bid to prevent brown tumour formation with the attendant devastating consequences.

References


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