Facial Swelling in a child on chronic hemodialysis

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Answers:

Question 1. CT images show multiple, expansible osteolytic lesions involving the mandible and maxilla, with variability in size. The largest involving the body of the left mandible measuring 3.7 x 37.7 x 31.9 cm with cortical expansion, erosions, and multiple loculations. No peri-osteal reaction and no definite associated soft tissue masses.

Question 2. Brown tumor of the mandible due to secondary hyperparathyroidism (SHPT)

Question 3. The management of brown tumor depends on the severity of the lesion. Control of hyperparathyroidism is critical as normalization of parathyroid hormone (PTH) levels will typically lead to the regression of tumor size or even its resolution. Surgical resection might be indicated for large, disfiguring tumors which fail to regress by medical treatment. Parathyroidectomy as well as renal transplantation could resolve the tumor.

Question 4. Cinacalcet is a calcimimetic that targets the calcium sensing receptors on the parathyroid cells, thereby down regulating PTH levels and subsequently serum calcium and phosphate levels in renal failure. It significantly reduces PTH levels in patients with SHPT on dialysis and could help in regression of the tumor.

Discussion:

We present a case of Brown tumor in young child originating from the cranio-facial bones associated with refractory SHPT. Chronic kidney disease (CKD) is associated with a disturbance of mineral and bone homeostasis. This condition is termed CKD-mineral bone disorder (CKD-MBD) and represents an obstacle to optimal bone strength, final adult height, and cardiovascular health (1). Impaired renal function with progressive glomerular filtration rate (GFR) reduction stimulates a number of compensatory mechanisms, including the increase of bone fibroblast growth factor-23 (FGF-23) FGF23 binds to its receptor FGFR1 and co-receptor Klotho in the kidney, with a key consequence in CKD being reduced 1-hydroxylase activity, resulting in decreased circulating 1,25 (OH)2 D with consequent SHPT) (2). High-turnover renal osteodystrophy and osteitis fibrosa cystica are the consequences of these changes (3).

Chronic hyperparathyroidism increases bone remodeling leading to rapid osteoclastic activity, erosive bony lesions and peritrabecular fibrosis which can result in a local destructive phenomenon called Brown tumor(4). Bone pain and fractures are common complications (5, 6). Brown tumors can be located in any part of the skeleton, but are most frequently encountered in the ribs, clavicles, extremities, and pelvic girdle. Clinically significant lesions in the craniofacial or orbital bones are rare (7,8,9). Costal lesions are more frequent than spinal lesions (6). It can also be multifocal (6). It has also been reported in children on prolonged hemodialysis (10, 11). A brief review of published pediatric cases is summarized in Table 1.

The diagnosis of Brown tumor is established through medical history, clinical examination, laboratory findings and radiological imaging. Borzych et al, reported that at least one in six children on chronic dialysis show radiological and/or clinical signs of bone disease and 44% developed severe secondary HPT with PTH levels five times above the upper limit of normal, with a 10% higher likelihood of developing severe HPT for each year on dialysis (12).
This fits with our case who had been on long-term dialysis for 7 years, increasing the risk of complications associated with end stage kidney disease (ESKD), including CKD-MBD and Brown tumor. Our patient had persistent hyperphosphatemia and poor metabolic control despite his regular hemodialysis. Compliance with medications was thought to be inconsistent.

Potentially, more frequent and/or prolonged dialysis would have prevented or ameliorated the complications. Cinacalcet was added to his medications at 10-years of age, without significant reponse, again potentially reflecting poor compliance or refractory SHPT. Cincalcet is a calcimimetic that down regulates PTH levels and subsequently serum calcium and phosphate levels in patients with SHPT on dialysis (13). Treatment with cincalcet for nine months showed evidence of revision of high bone turn-over bone disease towards normal in the majority of patients, based on histomorphometry (2), However its use in children is not approved by the Food and Drug Administration (FDA). Pediatric clinical trials are on hold following the death of a 14-year-old patient in February 2013 (14).

Parathyroidectomy (PTX) is another potential treatment option in severe renal HPT refractory to medical treatment. Hypoparathyroidism is a potential complication after extended PTX. Supplementation with calcium and activated vitamin D is needed in these patients to prevent hypocalcaemia with all its clinical manifestations, such as seizures, tetany and arrhythmia. Symptomatic hypocalcaemia is most likely occur in patients with poor compliance with medications. PTX needs to be carefully considered in each individual patient. Timing and extent of parathyroidectomy require an interdisciplinary approach from both nephrologist and endocrine surgeons (15).

One potentially overlooked contributor to CKD-MBD is metabolic acidosis as it results in bone demineralization and release of sodium, potassium and calcium. Furthermore metabolic acidosis stimulates osteoclasts and suppresses osteoblasts activity leading to direct dissolution of bone (16). Graham et al concluded that correction of metabolic acidosis increases the sensitivity of parathyroid gland to the ionized calcium leading to its suppression (17).

Normalizing PTH level with medications, dialysis, parathyroidectomy, or kidney transplantation will often lead to tumor regression or resolution (4). Surgical resection of a Brown tumor should only be considered if the patient needs quick resolution if it is compromising body functions or promoting facial deformation (18).

The management of CKD-MBD remains a challenge in children with ESKD. Our case demonstrates the importance of meticulous attention to markers of CKD-MBD, their correction

with medications and/or intensified dialysis and, ideally, early renal transplantation to prevent such serious complications.

First Author	Age, years	Gender (M/F)	HD Duration, years	Location	PTH (pmol/L)	Treatment	Responce
Youssef 2016 (11)	13	-	4	mandible	602	Complete surgical excision	-
Szeverényi_ 2011 (19)	9	M	Presented late	Vertebrae (C1-T2)	188.5	Complete surgical excision	PTH level remained high
Karabekmez 2008 (20)	11	M	4	Maxilla & mandible	2,528	None	Died before surgery
Tarrass 2008 (8)	18	M	6	Mandible	1,335	Subtotal parathyroidectomy	Significant reduction in the tumor size

(Table 1): A brief review of published pediatric Brown Tumor cases

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