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BONE AND MINERAL CASE REPORT

Rebound Hypercalcemia After Denosumab Therapy in a Child With Cherubism
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Background: Cherubism, caused by autosomal dominant mutations in the SH3BP2 gene, is characterized by increased bone resorption with development of bilateral fibro-osseous lesions limited to the maxilla and mandible. The SH3BP2 gene is thought to be involved in osteoclastogenesis. Affected children, while usually asymptomatic at birth, typically present at 2–5 years of age with cheek and jaw swelling with upward tilting of eyes due to expansion of fibrous tissues. Bone resorption and proliferation of lesions continues until puberty after which spontaneous regression occurs. RANKL is a cytokine expressed on the surface of osteoclast precursors and is responsible for inducing osteoclast differentiation. Denosumab is an anti-RANKL monoclonal antibody which prevents osteoclast maturation. However, it has a short half-life, and effects on bone turnover have been found to be rapidly reversible after drug discontinuation. The rebound increased bone turnover can lead to severe hypercalcemia.

Clinical Case: A 4-year-old boy with cherubism (c.1253C>G pathogenic variant in SH3BP2), after failing a 10-month trial of tacrolimus, was placed on monthly denosumab (2 mg/kg) for a total of 10 doses. During denosumab therapy, he received calcium and vitamin D to prevent hypocalcemia; these were stopped once denosumab was discontinued. He presented to the hospital 4 months after the final denosumab dose with polyuria, polydipsia, fatigue, nausea and abdominal pain. Work-up revealed serum Ca 15.3 mg/dL (N: 8.4–10.2), PTH <3 pg/mL (N: 24–86), 25-OH vitamin D 32 ng/mL (N: >19 ng/mL), 1,25-dihydroxyvitamin D 6.7 pg/mL (N: 19.9–79.3), and urine Ca/Cr 0.48. Renal ultrasound showed normal kidneys with a small amount of layering debris in the bladder. During hospitalization, he received IV fluids, 1 dose of furosemide, 3 doses of calcitonin, 24 hours of hydrocortisone, and a single 0.5 mg/kg dose of pamidronate. He was discharged 48 hours after the bisphosphonate with serum Ca 9.5 mg/dL. He returned with serum Ca 13.5 mg/dL 9 days after the pamidronate and was readmitted. He again received 4 doses of calcitonin and 1 dose of pamidronate (0.5 mg/kg). Calcium levels improved to 9.5 mg/dL at discharge but rose to 11.6 mg/dL a week later. He received a 0.05 mg/kg dose of zoledronate outpatient, with improvement in serum Ca to 10.1 mg/dL. A week later, he twisted his ankle, resulting in transverse impacted buckle fractures of his left distal tibia and fibula; no lytic or sclerotic lesions were noted on x-ray. His leg was immobilized by Orthopedics. Calcium levels remained within range (9.9 mg/dL) 7 months after the zoledronate. Conclusion: Rebound hypercalcemia can occur months after denosumab withdrawal, indicating the need for close monitoring of calcium levels in patients who receive this drug. The hypercalcemia appears to respond best to bisphosphonates, with a more sustained response to zoledrenate compared to pamidronate.

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Rebound-Associated Vertebral Fractures Two Months After a Missed Dose of Denosumab
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Introduction: Denosumab, an anti-resorptive medication approved for treatment of osteoporosis, increases bone mineral density and reduces fracture risk. Discontinuation of treatment is associated with bone turnover rebound and reduced bone mineral density. We report a case of a woman without prior history of fragility fractures who presented with multiple spontaneous vertebral fractures two months after a missed dose of Denosumab, which is earlier than current available literature.

Clinical Case: A 54-year-old female was diagnosed with osteoporosis at the age of 50 with a DXA revealing T-scores of LS -2.9 SD, LFN -0.6 SD, TH -0.5 SD. Ten-year probability of MOF evaluated by FRAX was 6%. Work-up for secondary causes of osteoporosis during the time was unremarkable. She was started on Denosumab 60 mg every 6 months from July 2016 to July 2019, receiving a total of 5 injections. She had missed her dose of Denosumab in January 2020. Two months after the missed dose, she presented to a local hospital with complaints of chest and epigastric pain. A CTA was performed as part of evaluation which was unremarkable aside from an incidental finding of thoracic compression fractures. An MRI of the spine was subsequently done which showed a recent-appearing moderate to severe wedge compression fracture and edema of the T7 and T6 vertebral bodies, and of the upper two-thirds of the T4. A biological and radiological work-up to exclude other causes of osteoporosis to explain the patient’s vertebral fractures was performed. The patient did not have renal failure, vitamin D deficiency, hyperthyroidism, primary hyperparathyroidism, Cushing’s disease, hypophosphatemia, multiple myeloma, Celiac disease, diabetes mellitus, or prior glucocorticoid treatment. During the time of treatment and discontinuation of Denosumab, the patient was on adequate supplementation of calcium and Vitamin D. The patient’s vertebral fractures were treated with kyphoplasty. To treat osteoporosis and prevent further risk of fractures, she was started on an anabolic agent Abaloparatide.

Conclusion: This case demonstrates rebound vertebral fractures occurring very shortly after discontinuing Denosumab in a relatively young woman with low probability of major osteoporotic fracture. Further investigation must be done to determine pathophysiological process involved of vertebral fractures and treatment regimen after sudden discontinuation of Denosumab.

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Recurrent Atraumatic Pelvic Fractures in a Patient With Cushing’s Disease - Is DEXA Scan Really Useful

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Background: Cushing’s disease may present with a variety of clinical features, including osteoporosis and fracture. Due to the inhibitory effects of cortisol on osteoblastic activity and enhancing effects on osteoclastic activity, these patients are more prone to have osteoporotic fractures. We report a case of ACTH dependent Cushing’s disease presenting with recurrent atraumatic pelvic fractures in a woman despite normal bone mineral density for her age.

Clinical Case: A 56 year-old-woman was referred to the endocrinology department for suspected Cushing’s syndrome following a recent atraumatic fracture of right pubic ramus. She had a history of weight gain and easy fatigue. On examination, she had subtle changes suggestive of Cushing’s syndrome, including mild truncal obesity, minimal bruising and moon face. She had been taking hormone replacement therapy for 3 years for the post-menopausal symptoms. Her bone mineral density was normal for her age on a recent DEXA scan [femoral neck T score: -0.9, Z score: 0.1, lumbar spine (L1-L4) T score: -1.2, Z score: -0.1]. Her vitamin D, serum calcium and parathyroid hormone levels were normal. Her 24-hour urinary cortisol was 688 nmol/day (reference range: <200 nmol/day), low dose dexamethasone suppression cortisol 525 nmol/L (reference range: <50 nmol/day), ACTH 96 ng/L (reference range: <50 ng/L), indicating ACTH dependent Cushing syndrome. MRI pituitary showed 7 mm right sided hypoenhancing area suggestive of a pituitary microadenoma. CT neck, thorax, abdomen and pelvis did not show any source of ectopic ACTH secretion but did show generalised osteopenia, with old fractures of the ribs and left ilium. She was referred for transsphenoidal resection of pituitary tumour. While awaiting pituitary surgery she was treated with metyrapone: at this time she suffered a further atraumatic fracture of the left pubic ramus. Conclusion: Glucocorticoid excess predominantly affects trabecular bones (pelvis, ribs, lumbar spine) as compared to cortical bones. Due to micro-architectural changes, reduction in bone strength is disproportionately greater than would be expected from BMD measured by DEXA. Clinicians should be aware that recurrent fracture of trabecular bones may indicate Cushing’s disease even though other clinical features of cortisol excess are minimal or absent.

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Response of Severe Osteomalacia to High Dose Vitamin D3 Replacement in a Patient With Ulcerative Colitis and Liver Transplantation on Immunosuppressive Therapy

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Background: Bone disease is common in inflammatory bowel disease (IBD), more frequently in Crohn’s disease than ulcerative colitis (UC). We present the case of a patient with prior history of ulcerative colitis with severe 25 OH vitamin D deficiency and metabolic bone disease. Case: 67 year old male with h/o ulcerative colitis, colon cancer a/p proctocolectomy and ileostomy, chemo-radiation, h/o primary sclerosing cholangitis (PSC) and orthotopic liver transplantation (OLT) 20 years prior presented with presented with severe muscle aches, severe limitation in mobility and severe vitamin D deficiency. He had been on chronic prednisone and tacrolimus, mycophenolate. Three years after OLT, he had fragility fractures at different times in both hips requiring hip arthroplasty. Labs were significant for persistently elevated alkaline phosphatase (ALP) up to 1569 U/L for last 10 years, bone specific ALP at 423.6 mcg/L, Calcium 9 mg/dl, phosphorus 2 mg/dl, 25 OH vitamin D was 4 ng/ml, 25-hydroxy vitamin D (25-OHD) was 34 ng/ml, PTH was 189 pg/ml, urine calcium/creatinine ratio was 50 mg/g and urine NTX at 223 nM BCE/mM. Celiac screen was negative and tacroliumus levels were within normal range. Patient had extensive workup by gastroenterologist for elevated ALP including three liver biopsies which were unrevealing. A bone scan showed increased uptake in thoracic region and metaphyses of large joints. A diagnosis of osteomalacia and secondary hyperparathyroidism was made and he was started on high dose vitamin D gradually increased to 8000 units thrice a day. Within few weeks, he noted marked improvement in mobility, bone pain and need for pain medications. In few months, BSAP decreased to 144.9 mcg/l, NTX and PTH also improved. 25 OH has also increased slightly to 13. He continues on high dose vitamin D and 1200mg of calcium daily. Discussion: Our patient likely had severe osteomalacia due to prolonged vitamin D deficiency, caused by multiple etiologies. Firstly, poor absorption in UC might lower 25-OHD levels. Secondly CYP3A enzymes are involved in the metabolism of calcineurin inhibitor tacrolimus as well as vitamin D, this could result in enhanced vitamin D metabolism, which would explain persistently low vitamin D level despite replacement with such high doses. The significant improvement in his symptoms with supplementation resulting in increased mobility despite not having a normal vitamin D level suggest other pleiotropic effects of vitamin D on muscle and bone as well. Additionally effects of liver transplantation on vitamin D metabolism need to be explored further.

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Severe Hypercalcemia as Rare Manifestation of Acute Lymphoblastic Leukemia in Adolescent

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Background: Hypercalcemia is a rare manifestation of acute lymphoblastic leukemia (ALL). Several studies reported that severe hypercalcemia is very uncommon in pediatric ALL, but there is no report regarding ALL in adolescence and young adult (AYA) which comprises distinct entity with diverse prognosis.