Bone & Mineral Metabolism
PSAT225
Severe Hypercalcemia Following Denosumab Withdrawal in Giant Cell Tumor of Bone: A Double-edged Sword Treatment Paradigm?
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Introduction: Denosumab inhibits receptor activator of nuclear factor k-B ligand and is approved to treat giant cell tumor of bone (GCTB). Rebound hypercalcemia is a rare complication of denosumab withdrawal in pediatrics which is not reported in adults. We describe severe hypercalcemia in an adult with metastatic GCTB associated with denosumab withdrawal that was complicated by cancer treatment directed against fibroblast growth factor receptors (FGFR).

Clinical case: A 29-year-old male with metastatic GCTB was admitted for severe hypercalcemia, acute kidney injury (AKI) and fatigue, constipation and poor appetite. An extraosseous GCT of abdominal wall had been resected and monthly denosumab was started a year later for bone metastases. Molecular analysis showed FGFR-1 rearrangement and he was enrolled in a clinical trial using an FGFR inhibitor (FGFRi) against FGFR1, 2 and 3. The patient received 8 doses of denosumab before the FGFRi was started and denosumab was held for 3 months as the FGFRi dose was increased. After 80 days of the FGFRi, he had an increased serum phosphorus concentration of 7.4mg/dL (2.5-4.5mg/dL), increased 1,25 dihydroxyvitamin D at 164pg/mL (18-64pg/mL) and corrected serum calcium concentration of 8.9mg/dL (8.4-10.2mg/dL). The FGFRi was held for hyperphosphatemia; one week later he presented with severe hypercalcemia (17.0mg/dL) with suppressed parathyroid hormone 13.8pg/mL (15-65pg/mL) and 1,25dihydroxyvitamin D <8pg/mL. Phosphorus was reduced to 5.6mg/dL, but he now had evidence of AKI: serum creatinine 2.9mg/dL (0.67-1.17mg/dL), 25-hydroxyvitamin D was 25ng/mL (30-100ng/mL) and PTHrP was 0.6pmol/L (<4.2pmol/L). He was treated with intravenous fluid hydration, calcitonin, and a single dose of denosumab; hypercalcemia and AKI resolved. He now continues monthly denosumab and FGFRi. The hypercalcemia was likely due to denosumab withdrawal, as reported in 2 children with GCTB. Denosumab can result in accumulation of osteoclast fragments (osteomorphs), which fuse to form active osteoclasts when denosumab is discontinued. Since GCTB consist of osteoclasts, denosumab is highly effective to reduce tumor burden. However, it is likely that more osteoclast fragments accumulate which then reform with denosumab withdrawal to fuel hypercalcemia. This patient’s clinical course was complicated by hyperphosphatemia, due to FGFRi to also inhibit FGF23, which acts through FGFR1 to suppress 1-alpha hydroxylase activity and conversion of 25hydroxyvitamin D to 1,25dihydroxyvitamin D. Thus, FGFRi can cause hyperphosphatemia and increased 1,25dihydroxyvitamin D, observed in this patient; which was rapidly reversed when the drug was discontinued. The combination of hypercalcemia, hyperphosphatemia and presumed dehydration contributed to AKI.
**Conclusion:** This case illustrates the severe, rapid nature of hypercalcemia associated with denosumab withdrawal when used to treat an extreme osteolytic tumor: GCTB. It also illustrates potential interactions when denosumab is discontinued in the setting of other drugs which alter mineral metabolism, such as the phosphate and vitamin D pathway regulated by the FGFRs.

**Presentation:** Saturday, June 11, 2022 1:00 p.m. - 3:00 p.m.