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Bone and Mineral Metabolism
BONE AND MINERAL CASE REPORT

Calcitriol-Mediated Hypercalcemia from Hepatic Granulomatosis Following Percutaneous Cholecystostomy Tube

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Granulomatous conditions can present with calcitriol-mediated hypercalcemia via increased 1-hydroxylase activity—activity that is not inhibited by calcium or calcitriol—indicating a lack of feedback inhibition. Differential diagnosis of granulomatosis is quite broad and can require extensive workup as highlighted by this case. Our patient is a 69-year-old white female admitted to the hospital with altered mental status and hypotension. Initial evaluation was concerning for infection, due to leukopenia and thrombocytopenia. CT abdomen revealed cholecystitis, percutaneous cholecystostomy tube was placed, and the patient's mental status improved. One month after discharge, the patient presented to the hospital with a corrected calcium of 15.2 mg/dl. PTH was 22 pg/mL with normal renal function and phosphorus. The patient was treated with intravenous fluids, calcitonin, and zoledronic acid. Calcitriol was 69 pg/ml (18–75 pg/ml) and corrected calcium responded by time of discharge. During outpatient follow up, she was found to have corrected calcium 11.2 mg/dl and calcitriol 166 pg/ml with appropriately low PTH. Additional workup of apparent calcitriol-mediated hypercalcemia with whole-body CT imaging, tuberculosis screening, and flow cytometry only notable for possible right cervical lymphadenopathy on CT. Subsequent lymph node biopsy was benign. The patient completed a 30-day course of prednisone 20 mg daily followed by prednisone taper and her corrected calcium and calcitriol levels normalized. However, after discontinuation of prednisone, lab work demonstrated increase in calcium and liver enzymes. Repeat CT scan showed multiple hypoechoic areas with subsequent biopsy consistent with necrotizing hepatic granulomatosis. PAS-A, Fite, and AFB stains were negative for fungi and mycobacteria. Removal of cholecystostomy tube resulted in complete resolution of hypercalcemia and elevated calcitriol levels. Foreign body-induced granulomatosis is associated with PTH-independent hypercalcemia. Silicone has been implicated in foreign body granuloma. Hepatic granulomatosis is associated with percutaneous tube, especially with prolonged placement (approximately 11 months in this case). Removal of the foreign body is associated with improvement in hypercalcemia. Follow-up liver ultrasound demonstrated complete resolution of hepatic granulomas at three months following removal of the cholecystostomy tube.

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Calcium of 19mg/dL and Yet Asymptomatic

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Lithium is a commonly used medication for Bipolar disorder. Lithium induced hyperparathyroidism is a rare disorder but leading cause of hypercalcemia in patients receiving Lithium treatment. Lithium may lead to exacerbation of pre-existing hyperparathyroidism or it may increase set point for calcium for PTH suppression.
We present a case of 65 year old female presented with hypercalcemia of 19mg/dl. She was sent by PCP office for hypercalcemia. She did not have any complains and was completely asymptomatic. Her history includes hypertension, Bipolar disorder and Diabetes mellitus type 2. She has not been able to get her labs drawn because of COVID-19. She was only having Tele visits with Psychiatrist. Her mood and bipolar symptoms were under controlled. She denies any abdominal pain, headache, visual problems, polyuria, polydipsia, numbness or tingling. She was given IV fluids and calcium was monitored. Her PTH was 65mg/dl, CBC and metabolic panel normal otherwise. Her Sestamibi scan was negative for parathyroid adenoma. Her lithium level was 4mg/dl. Lithium was discontinued after Psychiatry consultation. Her calcium came down to 9mg/dl after aggressive fluid resuscitation. Her calcium, parathyroid and lithium levels were monitored for next 6 months. Given her asymptomatic course she was not started on any calcium lowering medication. Her lithium level normalizes after one year of abstinence.
A patient who is started on Lithium therapy should be monitored for hypercalcemia, hyperparathyroidism and nephrogenic diabetes.

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Case of Juvenile Onset Hypophosphatasia Diagnosed in an Adult Patient

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Background: Hypophosphatasia is a rare multisystem disease caused by mutations in genes encoding tissue nonspecific alkaline phosphatase, a key player in promoting bone mineralization[1]. Here we present a case of hypophosphatasia in a patient with history of recurrent fractures and dental caries since childhood. **Case Report:** Patient is a 52-year-old woman with history of multiple fractures who initially

presented for follow up of osteoporosis following an atraumatic ankle fracture. Further questioning revealed a history of 16 atraumatic fractures since the age of 4, involving ankles, toes, and fingers. Several adult teeth had never developed requiring braces to fill in gaps at age 13, dental caries and tooth fractures involving the majority of her adult teeth. DEXA scan in 2019 revealed T score of -2.4 in the left femoral neck. Suspicion for hypophosphatasia in February 2019 following an ankle fracture and patient's prior history prompted further workup, revealing low serum alkaline phosphatase levels of 29 and 32 (bone fraction 62 percent, liver fraction 38 percent), and Vitamin B6 levels elevated to 66.2. Remainder of workup, with Vitamin D, PTH, Magnesium, and Calcium was normal. A childhood history of multiple atraumatic fractures, various dental issues, with elevated Vitamin B6 and low serum alkaline phosphatase suggested Hypophosphatasia. As bisphosphonates are contraindicated in these patients due to their potential to reduce ALP, teriparatide was initiated. **Discussion:** Hypophosphatasia involves mutations in tissue nonspecific alkaline phosphatase, a key player in bone mineralization. In normal individuals, this enzyme dephosphorylates inorganic pyrophosphate (PPi), which otherwise inhibits bone mineralization. The mutated TNSALP leads to accumulation of PPi, and thereby unmineralized osteoid.[1] Although individual presentations can vary, developmental abnormalities, such as delayed growth, early loss of primary or secondary teeth, or history of multiple fractures are characteristic. Due to the rarity of the disease, and its potential to be confused for more common bone and rheumatologic diseases, diagnosis is often delayed[1]. Patients in whom suspicion for hypophosphatasia is present, should undergo further testing with bone specific Alkaline phosphatase and Vitamin B6 which would be low and elevated, respectively and may be candidates for enzyme replacement therapy with bone-targeting recombinant alkaline phosphatase[1]. Traditional treatments such as bisphosphonates potentially decrease ALP and worsen disease, making accurate diagnosis all the more crucial. **References** [1] Bishop N. Clinical management of hypophosphatasia. *Clin Cases Miner Bone Metab*. 2015;12(2):170–173.

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BONE AND MINERAL CASE REPORT

Clinical Presentation and Management Approach in a Case of Familial Hypocalciuric Hypercalcemia Type 3 Due to APS21 Gene Mutation

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Familial hypocalciuric hypercalcemia (FHH) is a genetic disorder caused by dysfunctional calcium homeostasis. Thus far, three types of FHH are known to be caused by mutations inCASR (FHH1), GNA11 (FHH2), and AP2S1 (FHH3). The patient in this case report is a 36-year old male that initially presented for a second opinion after being diagnosed with Primary Hyperparathyroidism(PHPT) with subsequent parathyroidectomy done at another institute, and developed recurrent symptomatic hypercalcemia. Prior to considering this patient for further surgical options, he underwent genetic testing, which revealed he had c.43C>T (p.Arg15Cys) mutation in the AP2S1 gene diagnostic of Familial Hypocalciuric Hypercalcemia Type 3 (FHH3). The patient's father and sister also have hypercalcemia, and have been offered genetic testing. There have been cases reported of patients with FHH3 that have symptomatic hypercalcemia and that have associated cognitive issues. Many patients with FHH can be misdiagnosed and may undergo unnecessary parathyroidectomy. This case report further elucidates the need to raise awareness of FHH.

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Coexistent CYP24A1 and PHEX Gene Mutations With Hypervitaminosis D Plus Hypercalcemia Treated With Fluconazole

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Background: *CYP24A1* and *PHEX* gene mutations are rare and can cause hypercalcemia, hypervitaminosis D and elevated FGF23 levels. Fluconazole, an antifungal medication, has shown therapeutic benefit in achieving normocalcemia plus normalisation of vitamin D levels in this case report. **Clinical Case:** A 42 year old man was referred to the endocrine clinic with a history of severe nephrocalcinosis and recurrent nephrolithiasis requiring surgical intervention and gradual decline in kidney function over 20 years. Biochemical investigations revealed hypercalcaemia with adjusted calcium levels of 2.83 mmol/L (R 2.2–2.6 nmol/L) and suppressed PTH 1.1 pmol/L(R 1.6–6.9 pmol/L). Twenty-four hour urine calcium/creatinine clearance ratio was above 0.0578 mmol/mmol indicating hypercalciuria. Vitamin D metabolites 25 OH Vitamin D was elevated at 201 nmol/L, (R 50–120 nmol/L) along with intermittently elevated 1,25 OH Vitamin D 147 pmol/L(R 55–139 pml/L). 24,25 Vitamin D was low at 2.0 nmol/L producing a 25:24,25 dihydroxyvitamin D ratio of 80 (n<25). This biochemical data was highly suggestive of a loss of function mutation in the *CYP24A1* gene that codes for the enzyme 24-hydroxylase, which is responsible for conversion of 1,25 vitamin D to 24,25 vitamin D. A pathogenic variant (heterozygous c.756G>A) was confirmed on genetic testing.
Plasma FGF23 (immutopics) was raised (with a peak of 596 RU/mL, n<100 RU/mL) but a full body octreotide scan did not reveal malignancy or other paraneoplastic syndromes such as oncogenic osteomalacia. A pathogenic variant in his *PHEX* gene (homozygous c.1874A>T) was also identified that has been associated with increased levels of FGF23 plus hypophosphataemia. Fluconazole at 50 mg once daily was initiated. Azoles inhibit cytochrome P450 enzymes and have been used in sarcoidosis to block vitamin D-synthesizing enzymes such as 25-hydroxylases and 1-α-hydroxylase that are P450 dependent. Few cases of *CYP24A1* gene defects