

of Covid-19 diagnosis. All Covid-19 symptoms subsided 14 days after onset. Repeat labs 1 and 3 months after Covid-19 infection showed persistently normal serum Ca (10.0 and 9.8 mg/dL), with low then normal PTH (13 and 43 pg/mL), compatible with spontaneous resolution of PHPT. Patient denied any neck discomfort before, during, or after Covid-19 infection. Spontaneous resolution of PHPT is rare and follows apoplexy of a large parathyroid adenoma. In our patient, imaging failed to localize a large parathyroid adenoma, making it less likely that resolution of her PHPT was caused by apoplexy. Resolution of PHPT temporally coincided with Covid-19 infection, although the link between the two conditions is unclear at this time. Hypothesized mechanisms include an imbalance in the normal PTH-Ca axis caused by SARS-CoV-2 mediated release of inflammatory cytokines (e.g. interferon, previously reported to lower serum calcium), or development of antibodies against the parathyroid or CaSR. RNA and protein expression of *ACE2*, the SARS-CoV-2 cell receptor gene, is not detected in normal parathyroid tissue. **Conclusion:** To our knowledge, this is the first reported case of spontaneous resolution of PHPT after Covid-19 infection. Further studies are needed to understand the frequency of this occurrence, and the underlying mechanism.

## Bone and Mineral Metabolism

### BONE AND MINERAL CASE REPORT

#### *Sporadic Pseudohypoparathyroidism 1B in Monozygotic Twins: Insights Into the Pathogenesis of Methylation Defects*

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**Background:** Pseudohypoparathyroidism (PHP) 1B is an imprinting disorder characterized by renal resistance to parathyroid hormone (PTH) without Albright Hereditary Osteodystrophy (AHO). PHP1B is associated with methylation defects at the *GNAS* differentially methylated regions (DMRs). In sporadic cases with PHP1B, the mechanistic basis of methylation defects remains to be solved, except in rare cases with uniparental disomy of chromosome 20. In addition, to date, monozygotic twin cases with sporadic PHP1B have not been reported.

**Clinical Case:** The patients were 26-year-old Japanese female monozygotic twins. They had been born to nonconsanguineous parents after an uneventful pregnancy. Both twins had common biochemical features, including hypocalcemia, hyperphosphatemia, elevated PTH levels, and impaired urinary excretion of phosphorus and cAMP in response to teriparatide. They showed no signs of AHO. The serum calcium levels of their parents and brother were within the normal range, and family history was unremarkable. Based on these findings, the twins were diagnosed with PHP1B. Targeted bisulfite sequencing of the *GNAS* DMRs in all family members revealed almost complete gain-of-methylation at the *NESP55* DMR, and loss-of-methylation at the *AS*, *XL*, and *A/B* DMRs in the twins, but not in other

family members. Except for the *GNAS* locus, we did not find clear methylation defects in other imprinted genome loci in the twins. Methylation defects at the *GNAS* locus were further confirmed by methylation-sensitive restriction enzyme-qPCR. Whole-genome sequencing of the twins showed no pathogenic variants in the *GNAS* exons encoding the Gs alpha subunit. No large deletions or insertions were found at the *STX16* locus or in the region from AS exon 5 to XL. Based on the SNP genotyping results, large paternal isodisomies in the *GNAS* DMRs were unlikely. Collectively, these results suggested that the twins had concordant methylation defects that are seen in the sporadic form of PHP1b. We speculate that an early developmental event before the twin splitting is responsible for the abnormal methylation of the *GNAS* DMRs.

**Conclusion:** We report, for the first time, monozygotic twins with sporadic PHP1B who were phenotypically and epigenetically concordant. Our comprehensive molecular genetic analyses have thus far ruled out the previously described genetic defects underlying PHP1B. The current findings provide new insights into the mechanistic basis of the *GNAS* methylation defects in sporadic PHP1B.

## Bone and Mineral Metabolism

### BONE AND MINERAL CASE REPORT

#### *Sternal Phosphaturic Mesenchymal Tumor-Induced Osteomalacia, Diagnosis and Management: A Case Report*

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**Background:** Tumor induced osteomalacia (TIO) is a rare paraneoplastic disorder in which overproduction of fibroblast growth factor-23 (FGF-23) by mesenchymal tumor results in decreased renal phosphorus reabsorption and low to inappropriately normal 1,25-dihydroxyvitamin D, leading to hypophosphatemia and osteomalacia. Patients often present with bone pain, fractures, muscle weakness, and progressive decline in mobility. Due to the nonspecific nature of presenting symptoms of TIO diagnosis is often delayed. **Clinical Case:** A 55-year-old male presented with complaints of chest pain, shortness of breath, and generalized weakness following a ground level fall. Patient also reported a 10-year history of osteoarthritis with chronic back pain and 1-year history of generalized weakness, resulting in significant decline in functional status. On work-up, the initial CT scan of chest revealed multiple fractures including ribs, manubrium, scapula, and pubic rami. Subsequent biochemical evaluation was remarkable for hypophosphatemia to low of 1.3 mg/dL (2.4 - 5.0 mg/dL), low of 1,25-dihydroxyvitamin D of 13.1 pg/ml (19.9 - 79.3 pg/mL), reduced tubular phosphate reabsorption rate of 28% (normal > 80%) ratifying for renal phosphate wasting, normal iPTH level, and elevated serum FGF-23 level of 460 (normal < 180). Then, localization imaging for TIO was performed. After PET/CT scan showing increased uptake at the sternal area suggestive of lytic metastasis, subsequent CT angiogram of the chest identified mottled, irregular, mildly expansile appearance of the sternal manubrium. Sternal biopsy revealed phosphaturic mesenchymal tumor with positive FGF 23 mRNA expression. Surgical resection

was delayed due to poor functional status and concurrent discovery of an EBV-positive nasopharyngeal carcinoma. Prior to surgery patient was treated with phosphorus and calcitriol supplements. Post-operatively serum phosphorus and FGF-23 levels were normalized. Patient also improved clinically. Patient's treatment course was complicated by secondary hyperparathyroidism; however, this improved following surgery. **Conclusion:** Diagnosis of TIO can be delayed due to its nonspecific symptoms. Thus, in patients with chronic bone pain, muscle weakness, and atraumatic fractures, TIO should be kept on the differential and these patients should undergo thorough biochemical and imaging evaluation. Tumor localization could be challenging. Patients should be managed with supplements of active vitamin D and phosphorus with goal to normalize phosphorus level to prevent further bone demineralization prior to surgery. However, surgical intervention remains the mainstay of management as this is curative of TIO.

## Bone and Mineral Metabolism

### BONE AND MINERAL CASE REPORT

#### *Successful Early Treatment of Severe Neonatal Hyperparathyroidism With Cinacalcet*

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**Introduction:** Neonatal severe hyperparathyroidism (NSHPT) can cause significant bone disease early in life and prompt treatment is therefore necessary. Cinacalcet is a calcimimetic primarily used in adult patients with hypercalcemia to treat secondary hyperparathyroidism, but has only been trialed in neonates with NSHPT. Successful treatment appears to be dependent on the mutation leading to hypercalcemia. We describe a neonate born with severe hypercalcemia and a suspected mutation of the calcium sensing receptor (CaSR) who received successful early treatment with cinacalcet and decrease in calcium levels.

**Case Report:** A full-term baby girl was found to have rapid breathing at 2.5 hours of life requiring CPAP. A chest x-ray demonstrated bone demineralization with rib fractures. Lab evaluation demonstrated hypercalcemia (total calcium = 12 mg/dl) with an inappropriately elevated PTH level of 386 pg/mL, hypophosphatemia (3.3 mg/dL), normal magnesium (2.0 mg/dL), a normal urine calcium to creatinine ratio of 0.26 and calcium to creatinine clearance ratio of 0.05 and a slightly low vitamin D-25 of 28.8 ng/mL.

The father had a history of asymptomatic hypercalcemia without a diagnosis. Paternal genetic testing identified a heterozygous pathogenic CASR defect: c. 554G>A (p.Arg185Gln). This has been described in patients with NSHPT.

The patient was initially treated with IV fluids and Lasix, but calcium levels did not decrease. Cinacalcet therapy was given on day of life 10. Patient had a decreased PTH to 231 pg/mL after one day. After 26 days of treatment, patient's PTH level decreased to 63 pg/mL. Patient was weaned off of CPAP and was discharged home.

**Discussion:** Cinacalcet, a calcimimetic that works at the level of the CASR, was able to successfully and significantly decrease PTH levels in a neonate patient with NSHPT. Treatment options are limited in patients with this condition and we believe prompt treatment with this therapy facilitated patient's discharge. The patient's osteopenia secondary to the NSHPT and subsequent rib fractures resulted in a prolonged requirement of CPAP. Early recognition and treatment, even prior to results of genetic testing, prevented further fractures. We demonstrate the potential benefit of calcimimetics in a case of NSHPT where conventional treatment was ineffective. More importantly, we anticipate improvement in osteopenia and any future comorbidities secondary to this condition. Continued success with this treatment is yet to be evaluated.

## Bone and Mineral Metabolism

### BONE AND MINERAL CASE REPORT

#### *Successful Medical Management of a Non-Localising Case of Tumour-Induced Osteomalacia*

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**Introduction:** TIO is a rare paraneoplastic syndrome characterised by renal phosphate wasting due to fibroblast growth factor-23 (FGF23) over-secretion from a phosphaturic mesenchymal tumour (PMT). While surgery is potentially curative, localisation is often challenging.

**Clinical Case:** A 53 year old lady presented with recurrent fragility fractures in the spine (T10-L1, L4, S1-2), right femoral neck fracture and pelvic fractures at the bilateral superior and inferior pubic rami, associated with a 2 year onset of lower limb pain and proximal myopathy. Power was 2/5 proximally, rendering her progressively chairbound. She had no family history of fragility fractures. Biochemistry revealed hypophosphatemia of 0.48 mmol/l (NR 0.86–1.45 mmol/l), normal adjusted calcium of 2.32 mmol/l (NR 2.15–2.55 mmol/l), hyperphosphaturia (TmP/GFR 0.39 mmol/l, NR 0.88–1.42 mmol/l), mildly insufficient 25(OH)<sub>2</sub>D level of 25 µg/l, inappropriately suppressed 1,25(OH)<sub>2</sub>D at 13 pg/ml (NR 18–78 pg/ml) and raised FGF23 at 484 RU/ml (NR<180 RU/ml). Localisation of the PMT was unsuccessful, despite multiple investigations including 68-Gallium-DOTANOC PET-CT, bilateral lower limb MRI for non-specific inguinal lymph nodes and various ultrasonographic evaluation of soft tissue lesions including biopsy of a benign breast tumour. Surgical removal of the breast papilloma did not affect FGF23 levels. In the absence of any suspicious lesion, selective venous sampling was not performed due to uncertain utility. She was treated medically, requiring 16mmol oral phosphate, 1000 IU cholecalciferol and 0.5mcg calcitriol daily, with a view to perform interval DOTA-peptide scan. Despite an increase in FGF23 to 760 RU/ml over 29 months, phosphate level was maintained in the low-normal range and alkaline phosphatase, as a marker of disease activity, normalised from 370 U/l to 92 U/l (NR 40-130U/l). Development of secondary hyperparathyroidism improved with up-titration of calcitriol. There was no hypercalciuria on monitoring of