## Bone and Mineral Metabolism
### BONE AND MINERAL CASE REPORT

***Osteogenesis Imperfecta With Cerebral Atherosclerosis: A Family Report***

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**Background:** Osteogenesis imperfecta (OI) is a rare hereditary connective tissue disease. It is mainly associated with pathogenic variants in COL1A1 or COL1A2. Patients with OI usually have repeated history of bone fractures. Besides, osteogenesis imperfecta is associated with some cardiovascular complications, such as aortic and mitral valve dysfunction, aneurysm and aortic dissection. But the relationship between these diseases has not been well studied.
**Case Presentation:** A 55-year-old man was admitted to our hospital mainly due to "dizziness for 2 hours". He had a 4-month history of hypertension and a history of smoking for more than 20 years. He had no history of drinking alcohol. He had hunchback and O-type legs. Besides, the patient and some of his relatives had a history of repeated brittle fractures,which was considered as "osteogenesis imperfecta". The clinical manifestation of OI in this family varies to a certain extent, from simple tooth disintegration to severe fracture deformity. The most serious patient of his family was unable to walk. CT and MRI revealed multiple systemic arteriosclerosis, including vertebral artery, posterior inferior cerebellar artery, cervical artery, and bilateral cerebellar multiple lacunar cerebral infarction. The blood sample of the patient was tested by whole exome sequencing, and the saliva samples of the patient's family members were tested by Sanger sequencing. A mutation c.3159 + 2T > A was detected in COL1A2 gene associated with OI, also found in the other affected family members, which had not been reported before. It was a segregating mutation in the family. The clinical severity of the family members was heterogeneous.
**Discussion:** This case is worth learning from the following aspects: 1. A pathogenic heterozygous mutation, c.3159 + 2T > A was detected in COL1A2 gene in the patient with OI, which is not reported in previous cases of OI. 2. The clinical manifestation of OI in this family varies to a certain extent, from simple tooth disintegration to severe fracture deformity. The most serious patient of his family was unable to walk. It presented the clinical heterogeneity of OI. Further basic researh on the mutation site of related gene of OI are needed. 3. We found the possibility of developing cerebral atherosclerosis in patients with OI. Therefore, patients with OI should give up smooking, exercise properly and keep on a low fat diet. They should pay attention to control blood pressure and blood lipid so as to reduce the risk of atherosclerosis.
**Conclusion:** A c.3159 + 2T>A mutation in COL1A2 gene detected by whole exome sequencing was the causing reason of OI, the discovery enriched the gene mutation spectrum of OI. We also found that OI may have relationship with premature atherosclerosis, and the abnormal bones of the cervical spine may lead to vertebrobasilar ischemia.

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### BONE AND MINERAL CASE REPORT

***Osteopetrosis - A Case Series Exploring Complications and Multidisciplinary Management***

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**Background:** Osteopetrosis is a group of rare inherited skeletal dysplasias, with each variant sharing the hallmark of increased bone mineral density (BMD). Abnormal osteoclast activity produces overly dense bone predisposing to fracture and skeletal deformities. Whilst no cure for these disorders exists, endocrinologists play an important role in surveillance and management of complications.
**Clinical Cases:** A 43-year-old female had findings suggestive of increased BMD on radiographic imaging performed to investigate shoulder and back pain. X-ray of lumbar spine demonstrated a 'rugger jersey' spine appearance, while shoulder X-ray revealed mixed lucency and sclerosis of the humeral head. DXA scan showed T-scores of +11 at the hip and +12.5 at the lumbar spine. MRI of head displayed bilateral narrowing and elongation of the internal acoustic meatus and narrowing of the orbital foramina. Genetic assessment confirmed autosomal dominant osteopetrosis with a *CLCN7* variant. Oral colecalciferol supplementation was commenced and multi-disciplinary management instigated with referral to ophthalmology and ENT teams. A 25-year-old male presented with a seven-year history of low back pain and prominent bony swelling around the tibial tuberosities and nape of neck. Past medical history included repeated left scaphoid fracture in 2008 and 2018. Recovery from his scaphoid fracture was complicated by non-union requiring bone grafting with open reduction and fixation. Plain X-rays of the spine again demonstrated 'rugger jersey' spine. DXA scan was notable for elevated T scores; +2.9 at hip and +5.8 lumbar spine. MRI spine showed vertebral endplate cortical thickening and sclerosis at multiple levels. The patient declined genetic testing and is under clinical review. A 62-year-old male was referred to the bone metabolism service following a DXA scan showing T scores of +11. 7 at the hip and +13 at the lumbar spine. His primary complaint was of neck pain and on MRI there was multi-level nerve root impingement secondary to facet joint hypertrophy. Past medical history was significant for a long history of widespread joint pains; previous X-ray reports described generalized bony sclerosis up to 11 years previously. Clinical and radiological monitoring continues.
**Conclusion:** Individuals with osteopetrosis require a multidisciplinary approach to management. There is no curative treatment and mainstay of therapy is supportive with active surveillance for complications.

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***Paget 's Disease: Not So Typical for Atypical Femur Fracture***

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**Introduction:** Atypical femur fractures (AFF) are reported in patients taking prolonged bisphosphonate therapy, but Paget's disease (PD) has been rarely reported as a cause of AFF. **Case:** 71-year-old female with past medical history of right hip osteoarthritis, seizure disorder, hypertension, and Hashimoto's thyroiditis presented with persistent right hip pain. There was no history of trauma or fall. She had otosclerosis with bilateral hearing loss and bilateral stapedectomies. Her medications were primidone, levothyroxine, lisinopril-hydrochlorothiazide, and vitamin D. She did not smoke tobacco or drink alcohol. She had elevated serum alkaline phosphatase of 300 U/L (35–104). The X-ray of the skull was negative for any cortical thickening. CT of right femur revealed cortical thickening and coarsening of trabeculae of the proximal right femur consistent with PD and incomplete atypical subtrochanteric proximal fracture. Urine NTx 303 BCE/mM Cr (<89). Bone scan showed uptake in the R proximal femur, L distal tibia, and L3-L4 vertebral bodies suspicious of PD. DXA showed osteopenia. She was given zoledronic acid 5 mg IV. **Discussion:** PD leads to an increased incidence of fractures particularly of the lower extremities with most fractures transverse in nature. Non-union is not uncommon[1]. Stress fractures in PD are caused by disorganized bone remodeling due to excessive breakdown and formation of bone. Our patient met the major criteria for AFF as per the ASBMR 2010 task force report but there was no exposure to bisphosphonates[2]. The ASBMR task force recommended that bisphosphonates should be discontinued in patients with bisphosphonate-associated AFF due to their severely suppressed bone turnover status. On the other hand, the AFF in patients with PD may heal in response to bisphosphonate treatment. **References:** 1. Singer FR. Bone Quality in Paget's Disease of Bone. Curr Osteoporos Rep. 2016;14(2):39–42. DOI:10.1007/s11914-016-0303-62. Shane E, Burr D, Ebeling PR, Abrahamsen B, Adler RA et.al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2010; 25:2267–2294.

# Bone and Mineral Metabolism

## BONE AND MINERAL CASE REPORT

### *Paget's Disease of Bone Affecting Site With Orthopedic Hardware*

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**Introduction:** Paget's disease of bone is a focal disorder of accelerated bone remodeling which leads to bone hypertrophy, cortical expansion and abnormal bone architecture. Either a single bone (monostotic) or multiple bones (polyostotic) can be affected. Although it has been suggested to be caused by a chronic slow viral infection of the bone, a cause and effect relationship has not been clearly established. Therefore, the etiology of Paget's disease remains an uncertain and controversial topic of discussion. **Case Description:** A 62-year-old African American male with a past medical history of a left tibial fracture presented with worsening left leg pain for the past 6 months. He denied any recent traumatic events, falls or strenuous physical activity. Since the pain started, his ambulation had been significantly affected requiring the use of a cane for gait stability. His left tibial fracture occurred over 20 years ago after landing on another person's foot while playing basketball. It was surgically treated with intramedullary nailing and metal rod insertion into the canal of the tibia. Since then, he remained an active person with no physical limitations or ailments until the recent developments that brought him to clinic. A left leg CT-Scan ordered for evaluation of the tibial hardware revealed cortical thickening, marrow expansion and coarse trabeculae throughout the majority of the tibia consistent with Paget's disease. The hardware was intact with no peri-hardware lucency to suggest loosening or infection. His laboratory workup showed a normal alkaline phosphatase level (94 U/L; normal range 40 - 115 U/L) and low 25-OH Vitamin D level of 14. A Radionuclide Bone Scan done for evaluation of location and extent of bone disease resulted in diffusely abnormal uptake present in the left tibia with no other locations of suspicious uptake. After his 25-OH Vitamin D levels were replenished, a dose of Zoledronic acid IV infusion was given with significant improvement of pain several months after. **Discussion:** Paget's disease of bone is the second most common bone disease after osteoporosis. Affected skeletal sites develop a disorganized mosaic of woven and lamellar bone more susceptible to deformities and fractures than normal bone. It is often asymptomatic, but classical features include bone pain experienced either at rest or with motion, cutaneous erythema and warmth. The goal of medical therapy is to relieve symptoms and to prevent future complications with high potency bisphosphonates. Although it is well known that Paget's disease increase the risk of fractures, this case brings up an interesting take about the possibility of fractures managed with hardware placement increasing the risk of Paget's disease in the involved site.

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## BONE AND MINERAL CASE REPORT

### *Paraneoplastic Hypercalcemia as the Initial Presenting Sign of Metastatic Renal Cell Carcinoma*

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**Introduction:** Malignant hypercalcemia can occur in patients with renal cell carcinoma as part of a paraneoplastic syndrome. The suggested mechanisms of malignant hypercalcemia include overproduction of parathyroid hormone-related peptide (PTHrP), interleukin-6 (IL-6), prostaglandins, and tumor necrosis factor-alpha (TNF-α). This report describes an unusual case of paraneoplastic hypercalcemia as the initial manifestation of metastatic renal cell carcinoma (RCC). Case presentation: A 44-year-old Caucasian male with no past medical history who presented to his PCP complaining of unintentional weight