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Commentary

# The Osseous Masonry-Osteopetrosis

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## Preface

Osteopetrosis is an infrequently discerned hereditary disorder engendered from defective osteoclasts. Initially scripted by German radiologist Heinrich Ernst Albers-Schönberg in 1904, disease terminology originates from Greek and the condition is designated as a concurrence of 'osteo' or bone and 'petrosis' or stone. Osteopetrosis is additionally denominated as Albers-Schönberg disease or marble bone disease [1].

The exceptional, hereditary disorder arising due to dysfunctional osteoclasts is accompanied by diffuse and symmetric skeletal sclerosis and elevated bone density. Incriminated bones are significantly brittle, fracture with ease and delineate a "stone-like" texture.

Plain radiography displays significantly enhanced bone density secondary to osteoclast dysfunction with consequent emergence of brittle bones. Consequently, weakened, brittle bones display an anomalous morphology and appear sclerotic and thick.

## Disease pathogenesis

The bone is a dynamic organ demonstrating a balance between osteoclast-mediated bone resorption and osteoblast-mediated bone deposition. Osteopetrosis delineates a defective development or function of osteoclasts which disrupts normal bone homeostasis. Osteoclasts with deficient proton pumps, chloride channels or carbonic anhydrase II proteins are incompetent in adequately resorbing the bone. Consequently, disorganized development of excessively dense bone ensues with a predilection for pathological fractures [2,3].

Osteopetrosis is comprised of an amalgamation of hereditary metabolic bone disorders which appear as a detriment to bone growth and remodelling. Osteoclasts are devoid of enzyme carbonic anhydrase, a feature which is implicated in pathophysiology of osteopetrosis [2,3]. Deficiency of carbonic anhydrase II engenders osteopetrosis due to failure in dissolution and resorption of bone matrix or urinary acidification. The enzyme is required by osteoclasts and renal tubular cells in order to appropriately excrete the hydrogen ion [2,3].

Additionally, on account of decimated bone marrow space anaemia and hepatosplenomegaly may ensue [2,3].

Osteoclastic dysfunction is accompanied by diverse genetic mutations. Loss of functional mutations is encountered with TCIRG1, CLCN7, OSTM1, PLEKHM1 and SNX10 genes, a feature which engenders an osteoclast predominant version of autosomal recessive osteopetrosis. The abundant osteoclasts are incompetent in resorbing bone on account of disorderly configuration of the cellular ruffled border. Loss of functional mutations within TNFSF11 and TNFRSF11A genes initiates defective development of osteoclasts and is observed with osteoclast deficient osteopetrosis [2,3].

## Disease characteristics

Osteopetrosis demonstrates distinctive disease variants denominated as

- Benign adult autosomal dominant osteopetrosis which is discerned in asymptomatic individuals with disease extension into adulthood. The condition is associated with repetitive pathological fractures, mild cranial nerve deficits and anaemia and is divided into specific subtypes. Typically, subtype I is devoid of enhanced possible occurrence of pathological fractures. Besides, singular thickening and osteosclerosis of cranial vault may be encountered [3,4]. Subtype II commonly emerges in adults and manifests anaemia, pathological fractures or preliminary arthritis. Autosomal dominant osteopetrosis emerges on account of dysfunction of chloride channel 7 occurring as a consequence to dominant-negative mutation of CLCN7 gene [3,4].

- Infantile or intermediate autosomal recessive osteopetrosis which clinically appears within the first decade. The disorder may be discerned in utero on account of pathological fractures and is associated with anaemia, hydrocephaly, cranial nerve deficits, infections and hepatosplenomegaly. Incriminated subjects may represent with pathological fractures and progressive cranial nerve compression neuropathies. Life expectancy extends into adulthood. Intermediate autosomal recessive osteopetrosis appears as a consequence of loss of functional mutation of CAII, the gene incriminated in the production of carbonic anhydrase II protein [3,4].

- Malignant autosomal recessive osteopetrosis is associated with severe disease and mortality in early childhood. Malignant, autosomal recessive form of osteopetrosis demonstrates genomic alterations of six pertinent genes [3,4].

Aforesaid categories of osteopetrosis may be congenital and associated with localized chromosomal defects. Consequently, defective function of osteoclasts is accompanied with bone overgrowth and emergence of thick, sclerotic bones. However, architectural distortion engenders weak, brittle bones [3,4].

The autosomal dominant variant of osteopetrosis is commonly discerned with a frequency of roughly 1 in 20,000 live births, in contrast to autosomal recessive form which occurs as nearly 1 in 250,000 live births [3,4].

## Clinical elucidation

Majority of subjects with weakened bones represent with predominantly transverse fractures. Consequently, generalized osteosclerosis or pathological fractures ensue. Multiple foci of callus formation and normal bone healing are observed [3,4].

Additionally, pancytopenia, cranial neuropathies and hepatosplenomegaly may be discerned with emergence of severe disease. The bone marrow is compressed thereby affecting bone marrow function with consequent occurrence of myelophthisic anaemia, focal extramedullary haematopoiesis and associated splenomegaly with ultimate appearance of acute leukaemia [3,4].

Type 1 autosomal dominant osteopetrosis is associated with a mild clinical representation. The condition arises due to erroneously enhanced configuration of bone, rather than dysfunctional osteoclasts. Consequently, augmented possible occurrence of pathological fractures is absent. Specifically, osteosclerosis of the cranial vault and cranial nerve compression neuropathies are commonly observed [3,4].

Type 2 autosomal dominant osteopetrosis is a commonly exemplified variant accompanied with a heterogeneous clinical course. Majority of subjects demonstrate a normal life expectancy. The disorder may be discovered incidentally with cogent clinical representation and upon radiographic evaluation of a pathological fracture or early onset osteoarthritis. Pathological fractures ensue in around ~80% subjects, commonly within the femur. Arthritis frequently affects the hip with around 50% subjects demonstrating antecedent hip pain although no joint is exempt from disease implication. Fatigue due to anaemia and cranial nerve neuropathies may ensue. Optic or auditory nerve damage occurs in around 5% individuals [3,4].

Intermediate autosomal recessive osteopetrosis arises due to dysfunction of carbonic anhydrase II and may be accompanied with renal tubular acidosis. Besides, the condition demonstrates variable clinical symptoms, akin to malignant autosomal recessive variant of osteopetrosis although disease onset is delayed and severity is reduced.

Malignant, autosomal recessive osteopetrosis arises in infants or within few months of birth and manifests frequent infections, pathological fractures, anomalous haemorrhage and bruising. Clinical symptoms arise as a consequence of inappropriate osteoclastic resorption of bone and encroachment upon the medullary space. Additionally, macrocephaly, hepatosplenomegaly due to extramedullary haematopoiesis, sinus malformation with nasal congestion, dental abscess or osteomyelitis of the mandible due to significantly decimated magnitude of medullary canal with disordered vascularity is observed. Defective bone may constrict cranial nerve foramina with occurrence of progressive deafness, blindness and possible facial palsies. The optic nerve, auditory nerve, trigeminal nerve and facial nerve are implicated in decreasing order of frequency [3,4].

## Histological elucidation

On gross examination, solid, weighty bones lack a medullary canal. Neural foramina are miniature and compress traversing nerves. Edges of long bones appear bulbous [4,5]. On microscopy, the incriminated bone is predominantly woven with absence of remodelling. Bone trabeculae are dense and irregular with a centric core of cartilage. Osteoclasts are abundant. The bone marrow space is decimated [4,5].

Osteoporotic bone is comprised of vacant osseous lacunae, occluded Haversian canals, foci of calcified cartilage disseminated within bony trabeculae and aggregates of defective osteoclasts devoid of a clear zone and ruffled perimeter [4,5]. Clear zone and ruffled cellular margin is pathognomonic of osteoclasts engaged in active bone resorption. Thus, absence of aforesaid morphological features in osteoclasts are concordant with dysfunctional osteoclasts exemplified in osteopetrosis.

Superficial bone surface is comprised of abundant matrix of smooth cartilaginous tissue with disseminated, roughened foci of anomalous ossification. Nevertheless, uniform lamellar Haversian system as configured in normal bone is discerned. Several, irregular fracture lines are discerned [4,5]. On ultrastructural examination, osteoclasts are devoid of a ruffled perimeter or features of active bone resorption [5,6].

## Differential diagnosis

Osteopetrosis is a disease demonstrating primary bone sclerosis although several conditions may engender secondary osteosclerosis and require a segregation [5,6]. Demarcation is necessitated from

- Myelofibrosis is a condition exhibiting hypo-cellular, diffusely fibrotic bone marrow. Lineage specific immature haematopoietic elements are interspersed with atypical megakaryocytes. Osteosclerotic bone marrow is traversed with irregular, broad bone trabeculae. Marrow sinuses are markedly distended [5,6].

- Osteoblastic bone metastasis wherein tumour cells display diverse morphological configurations. Epithelial neoplasms delineate neoplastic cells articulating acini, sheets, columns, cords, solid or a papillary tumour pattern. Tumour cells depict morphological and functional resemblance to the primary neoplasm and enunciate features of malignant metamorphosis such as loss of polarity, pleomorphism, enhanced nucleo-cytoplasmic ratio, anisonucleosis, anisocytosis, hyperchromasia and significant mitotic activity with atypical mitotic figures. Multinucleated tumour giant cells or enlarged cells with singular, bizarre nuclei are observed [5,6].

- Paget's disease of bone is a condition demonstrating enhanced osteoclastic and osteoblastic activity. Lesions of acute phase are constituted primarily by woven bone, focal mosaic pattern of lamellar bone and numerous osteoclasts incorporated with up to 100 nuclei discernible within the osteolytic phase. Chronic instances are composed of lesions with thickened bony trabeculae and bone marrow traversed by fine fibrotic septa. The condition can be managed with simple observation [5,6].

Additionally, osteopetrosis requires segregation from radiographically similar conditions such as heavy metal poisoning with beryllium, lead or bismuth, fluorosis, malignant lymphoma, melorheostosis, hypervitaminosis D, pyknodysostosis and facial or cranial involvement with fibrous dysplasia [5,6].

## Investigative assay

Pertinent disease discernment and subtyping of osteopetrosis is contingent to occurrence of typical clinical and radiographic features [7,8].

Upon plain radiography, long bones appear shortened. The metaphyseal flare may be absent, thus engendering the "Erlenmeyer flask deformity". Pelvic bones may be uniformly opaque. Peripheral bone sclerosis may alternate with normal bone morphology, thereby enunciating a striped appearance. Osteopetrosis may engender spondylolisthesis of the vertebral column [7,8].

Plain radiographs demonstrate diffuse osteosclerosis with "marble bone" appearance. Generally, elevated cortical thickness is associated with decimated magnitude of medullary canal. Typically, the "Erlenmeyer flask" deformity emerges within metaphysis of long bones, especially the proximal humerus and distal femur. Vertebral column or phalanges of upper extremities depict a "bone-in-bone" or "endobone" appearance. Axial skeleton exhibits a "rugger jersey spine" arising secondary to excessive sclerosis within the vertebral endplates [7,8].

Elevated serum levels of creatinine kinase BB and tartrate-resistant acid phosphatase may also be discerned [7,8].

Cogent genetic evaluation of associated loss of function chromosomal mutations is beneficial [7,8].

Dental evaluation is necessitated in order to circumvent pertinent complications such as dental abscess, cysts and osteomyelitis. Aforesaid complications are frequent due to altered anatomy of the mandible [7,8].

## Therapeutic options

Optimal therapy is tailored pertaining to individual requirements. Cogent treatment is predominantly supportive as specific alleviation of the condition is lacking. Comprehensive surveillance of incriminated subjects is advantageous [9,10].

Treatment of pathological fractures and arthritis accompanying osteopetrosis is necessitated [9,10].

Cranial nerve compression neuropathies, especially optic nerve neuropathy, are frequent. Thus, a comprehensive ophthalmologic evaluation is mandated. Surgical decompression of optic nerve may be beneficially adopted in order to preserve the vision [9,10].

Recommended therapy of osteopetrosis is a comprehensive bone marrow transplant which results in normalized bone production. Bone marrow transplantation of hematopoietic stem cells (HSC) is an optimal treatment strategy for managing malignant, autosomal recessive osteopetrosis. Acceptable bone marrow transplant may engender retroversion of several skeletal anomalies. However, transplant rejection and associated complications may ensue. Haematopoietic stem cell (HSC) therapy of matched donors is associated with an estimated proportion of 73% 5-year disease-free survival [9,10].

Treatment with interferon-gamma (IFN-Ÿ) 1b is beneficial in subjects unamenable to bone marrow transplantation. Also, the molecule can be employed as bridging therapy until haematopoietic stem cell therapy commences. Provision of IFN- Ÿ1b appears beneficial in enhancing immune function and bone resorption. Augmented doses of calcitriol may be employed in order to activate host osteoclasts [9,10].

Along with pathological fractures, increased possibility of repetitive fractures is exemplified on account of brittle, sclerotic bones. Internal mechanical fixation of fractures may be accompanied by device failure [9,10]. Peri-prosthetic fractures occurring adjacent to previously reinforced bone can be challenging to treat. Also, specialized intraoperative tools are required as the hard, brittle bone may not be manageable with pertinent tools such as bone drill, bits and wires. Pathological fractures are frequently associated with complications such as non union, delayed union or osteomyelitis. Bone infections frequently appear secondary to disturbed bone vascularity or mal-union and non-union of pathological fractures [9,10].

Prognostic outcomes of autosomal dominant adult subcategory of osteopetrosis is favourable and life expectancy remains unaltered. The autosomal dominant variant demonstrates minimal impact upon life expectancy and well-being whereas intermediate forms are associated with a life span extending into adulthood [9,10].

Emergence of autosomal recessive infantile subtype may engender a stillbirth or infant death and few individuals achieve middle age.

Malignant, autosomal recessive variant of osteopetrosis may be fatal during childhood in the absence of pertinent bone marrow transplantation. Multiple, although unsuccessful, transplants of haematopoietic stem cells may be required [9,10].

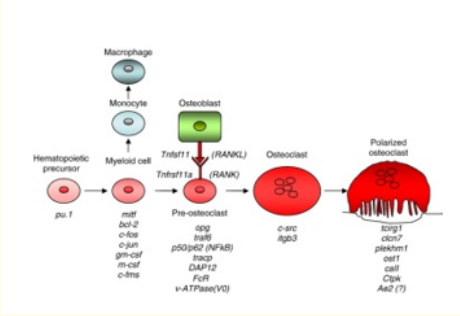


***Figure 1:*** *Osteopetrosis demonstrating diverse genetic events which engender osteoclastic dysfunction [11].*

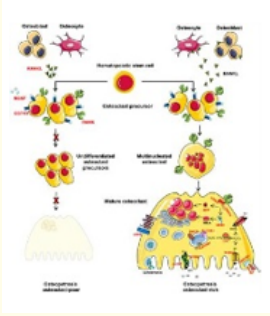

***Figure 2:*** *Osteopetrosis exemplifying divergent pathways and growth factors incriminated in osteoclastic maturation and dysfunction [12].*

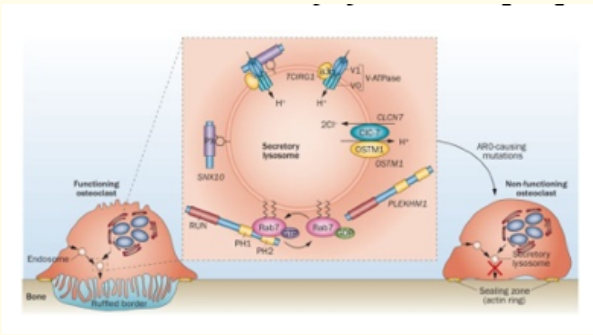


***Figure 3:*** *Osteopetrosis enunciating various genetic pathways involved in appearance of non functioning osteoclasts [13].*

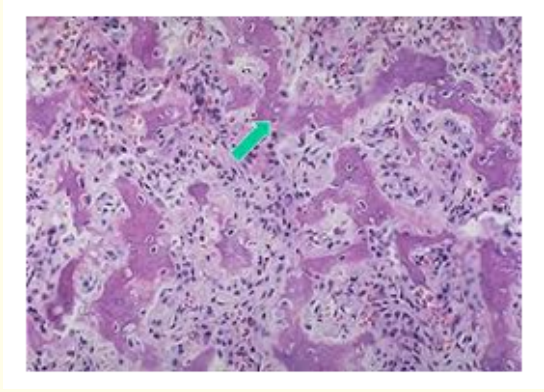

***Figure 4:*** *Osteopetrosis exhibiting thick, bony trabeculae, reduced marrow space and abundant, non functioning osteoclasts [14].*

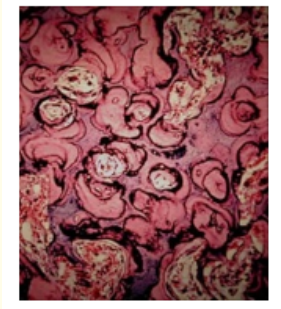

***Figure 5:*** *Osteopetrosis depicting thick trabeculae of woven bone, decimated marrow space, vacant lacunae and occluded Haversian canals [15].*

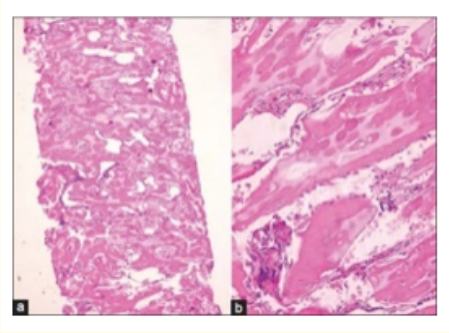

***Figure 6:*** *Osteopetrosis exhibiting thick, dense trabeculae of woven bone, decreased marrow space and aggregates of defective osteoclasts [16].*

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11. Image 1 Courtesy: Science direct.

12. Image 2 Courtesy: Frontiers.com.

13. Image 3 Courtesy: Nature.com.

14. Image 4 Courtesy: 17QQ.com.

15. Image 5Courtesy: Orthobullets.com.

16. Image 6 Courtesy: ijsronline.com.

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