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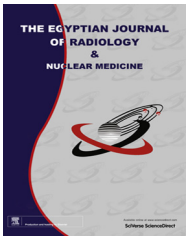

CASE REPORT

# The role of whole-body bone scintigraphy in a case of osteopetrosis

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**Abstract** Male patient, 35 years old, with occasional mild intensity back pain. Lumbosacral spine radiography showed bone structure with increased density, diffusely and symmetrically, conferring to the vertebral bodies "bone-within-bone" aspect, suggesting osteopetrosis (OP). Whole-body bone scintigraphy showed abnormal uptake in proximal epiphysis of both the humeri, tibias and fibulas, distal epiphysis of the femurs and focal in the ribs suggesting old fractures. Conclusions: Nuclear Medicine may provide an important contribution as supporting diagnosis and extensive skeletal evaluation such as fractures and infection. Bone scintigraphy might also be used for baseline assessments, allowing longitudinal monitoring of the disease and patient follow-up.



## 1. Introduction

First described by the German radiologist Albers-Schönberg in 1904 (1), osteopetrosis (OP) is a rare heterogeneous group of inherited hereditary metabolic skeletal disorders, which is usually non-sex-linked, manifested by increased bone mass and density due to impaired bone resorption by osteoclasts, with generalized cortical sclerosis and bone trabeculae remarkably thickened, resulting in marrow space compression with reduced hematopoiesis and skeletal deformity (2). It has been called "marble bone disease" because of the replacement of the trabecular bone with compact bone, resulting in very dense bones radiographically, although they typically have increased susceptibility to fracture (3). The osteoclast activity impedes bone remodeling process, and seriously damages bone formation and structure, with failure of cartilaginous and bone matrix (4). The overall incidence of OP is estimated to be only 1 case per 100,000–500,000 population (5).

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Being biochemically and genetically heterogeneous, there are at least eight human phenotypes (6) and three distinct types of OP: the infantile, "malignant" or "lethal" form, which has precocious onset and is clinically severe, the autosomal recessive or "intermediate" form and the autosomal dominant form (5). Albers-Schönberg disease, which is a relatively mild autosomal dominant form of OP type II, is the most common one and occasionally skips generations (6). There are various forms with the benign ("tarda") variant of OP transmitted as an autosomal dominant trait. Three molecular defects have been identified that compromise the genes encoding carbonic anhydrase II (CA II), chloride channel 7, and a proton-pump subunit; together, these proteins enable osteoclasts to secrete acid (6). The disease is caused by ineffective osteoclastic function resulting from mutations in the chloride channel 7 (ClCN7) gene. Chloride influx into osteoclast by exchange of bicarbonate is important for the formation of HCl-mediated mechanism of bone resorption. Individuals with autosomal dominant OP type II have increased numbers of large ineffective osteoclasts in addition to increased serum total tartrate-resistant acid phosphatase (TRACP) activity (2). Patients with OP have fragile osteosclerotic bone with increased serum levels of the bone formation markers: bone alkaline phosphatase isoenzyme, osteocalcin and N-terminal type I collagen telopeptide/creatinine ratio (2). Following the assignment of the gene causing autosomal dominant osteopetrosis (ADO) type II to chromosome 16p13.3, seven different mutations in the gene encoding the ClCN7 chloride channel have been reported (2). Autosomal recessive, infantile form of OP homozygous for a ClCN7 mutation is a fatal disease without bone marrow transplantation. Its incidence has been underestimated possibly because some cases in the stillborn infant or in those dying soon after birth may go undiagnosed. It is more frequently seen in countries where inbreeding is common such as Costa Rica or Saudi Arabia (7).

There is some variability in the severity of different clinical manifestations in different families. In some families, the symptoms related to the OP dominate the clinical picture. Previous studies suggested that clinical heterogeneity is due to genetic heterogeneity.

Patients with autosomal dominant OP are often asymptomatic, and the diagnosis may be reached by chance. However, by systematic investigations, nearly all patients have manifestations related to the disorder. Symptoms are progressive with age and correlate with osteosclerosis (3).

Although affected individuals can have a normal life expectancy and remain asymptomatic, there is a well-known propensity for fractures, which might not heal satisfactorily (4). Defective skeletal remodeling in patients with OP compromises bone quality, resulting in disorganized bony architecture, because the removal of primary spongiosa and the interconnection of osteons are impaired. When the bones are extensively implicated, it is no longer possible to distinguish between corticalis and spongiosa, and in affected long bones, even the major marrow cavities may no longer be clearly discernible (8). Consequently, spondylolysis (leading to spondylolisthesis) seems more prevalent in such patients, and other fractures are established complications of the disease (6).

Autosomal dominant OP may be a heterogeneous group. Albers-Schonberg disease is characterized by diffuse osteosclerosis with defective tabulation and thickened cortices, predominantly involving the spine (vertebral end-plate thickening, or rugger-jersey spine, similar to that of Pagets disease), pelvis ("bone-within-bone" structures, with iliac wings containing convex arcs of sclerotic bone) (3), and skull base. Affected persons may be relatively asymptomatic, or the disease may be detected because of pathologic fractures, mild anemia, or cranial nerve palsies. The disorder is compatible with a normal life span and is referred to as the adult or benign form of OP (3). Myelophthisic anemia (anemia characterized by the appearance of immature myeloid white cells and nucleated erythrocytes in the peripheral blood) can develop as a result of the overgrowth of sclerotic bone obliterating the marrow cavity, but the severity of anemia, if present, does not necessarily parallel the degree and extent of sclerosis (4). In contrast, in autosomal dominant OP type I, the most striking finding is pronounced sclerosis, which predominantly involves the cranial vault, while the spine is almost unaffected, with less fracture risk (2,3). However, in both types, the disease may have its clinical onset after the arterial and neural foramina have reached their adult size; hence, narrowing of the foramina and canals may not occur. Biochemically, serum phosphate is found to be lower in type I than in type II, and serum acid phosphatase is markedly increased in type II (3). The osteoclasts are found markedly reduced in number and size in type I, but in type II, the osteoclasts are large and highly multinucleated, with increased number (3). In addition, serum carboxy-terminal propeptide of type I collagen (S-PICP) is found to be significantly lower in autosomal dominant OP type II. Serum osteocalcin values in the two types of autosomal dominant OP have been observed to be insignificantly lower than in controls (3).

A more uncommon form of the disease, intermediate OP, also demonstrates autosomal recessive inheritance. However, this variant tends to present later in childhood than the more malignant form. Typically, these patients have short stature and experience some of the more aggressive features of malignant OP (9). Frequently, IOP (intermediate OP) is distinguished from the malignant form only when a milder clinical course evolves with age.

Children affected by more serious forms of the disease, apart from bone deformities, may also suffer from anemia, leukopenia, hepatomegaly, failure to thrive (3), and central nervous system disorders (3,5). Neurological sequel such as cranial nerve compression with blindness (optic atrophy), deafness, or facial nerve paresis is also seen. Other manifestations include stenoses of the petrous internal carotid artery (ICA), jugular veins within narrowed jugular foramina, and cervical vertebral arteries within narrowed transverse foramina (9). Occasionally, these are accompanied by hydrocephalus, convulsions, and mental retardation (7). In children, pancytopenia (malignant OP) occurs due to gradual obliteration of the medullary cavity. Therefore, special attention should be paid to infectious complications. The disease may result in demise usually within the first decade of life, owing to hemorrhage from thrombocytopenia and fatal infection from leukocytopenia (5,10). As a general rule, the earlier the clinical presentation, the more malignant is the disease.

Interestingly, in some patients, symptoms are few. In such cases, relatively benign and asymptomatic conditions are often diagnosed as OP by radiography and other biochemical findings, but complications like osteomyelitis and multiple fractures may be missed by X-ray alone (5). Magnetic Ressonance (MR) or Computed Tomography (CT) is highly