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Case Report

Osteopetrosis complicated by multilevel spondylolysis ☆

William W. Pryor III, MD, Carolina V. Guimaraes, MD, Lane F. Donnelly, MD*

Department of Radiology, University of North Carolina School of Medicine, Chapel Hill, NC, USA

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ABSTRACT

Osteopetrosis is a heterogenous group of inheritable disorders which manifests as increased bone density and brittleness. The most common and mildest variant typically presents in adulthood with bone pain and pathologic fractures, including spondylolysis. We present the case of an otherwise healthy, active 17-year-old male with a history of osteopetrosis and 1 year of chronic back pain, found to have multilevel (L1–L4) spondylolysis in the setting of severe diffuse bony sclerosis consistent with osteopetrosis. While single-level spondylolysis is an uncommon complication of osteopetrosis, multilevel spondylolysis in the pediatric population is extremely rare and the genetics of prior cases studies have not been reported. Spondylolysis should be considered as one of the types of fractures that may occur in patients with osteopetrosis.

Introduction

Spondylolysis is one of the most common causes of lower back pain in adolescents and may lead to spondylolisthesis, defined as anterior subluxation of the affected relative to the unaffected vertebral body [1]. Spondylolysis may be unilateral or bilateral and occurs 85%-95% of the time at L5 vertebrae and 5%-15% of the time at L4 vertebrae [2]. Multilevel spondylolysis is rare [3]. There are several classic radiographic findings of spondylolysis, with MRI providing increased sensitivity for the diagnosis and additional information regarding the anatomic extent of involvement. Most adolescents who present with single-level spondylolysis are otherwise healthy without predisposition for fracture [1]. Repetitive trauma is thought to be the etiology [1,4]. However, metabolic bone diseases, such as renal osteodystrophy, can predispose to fractures, and have been reported to be associated with spondylolysis [5]. We present a case in which an adolescent with mild variant osteopetrosis presented with back pain related to multilevel spondylolysis.

Case report

A 17-year-old male presented with chronic, intermittent low back pain of over 1 year's duration without known injury and

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* Corresponding author.
E-mail address: william_pryor@med.unc.edu (W.W. Pryor III).

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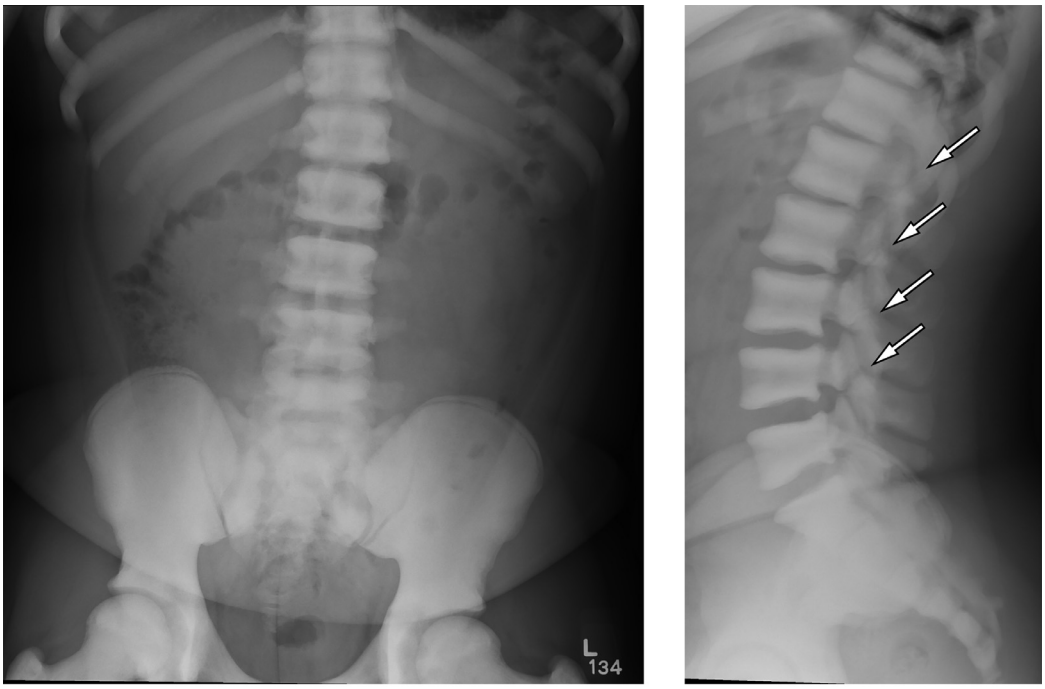

Fig. 1 – Radiographs of lumbar spine in child with osteopetrosis and multilevel spondylolysis. (A) Frontal radiograph shows severe diffuse bony sclerosis and (B) Lateral radiograph again shows severe diffuse bony sclerosis. There is spondylolysis (arrows) demonstrated as linear lucencies through the pars at multiple levels.

a reported history of osteopetrosis. The patient reported significant pain and "tightness" in lower back pain during periods of prolonged sitting and while jumping and playing basketball. Additionally, the patient report that the pain radiated superiorly, although denied any lower extremity weakness, constipation, or urinary incontinence. Physical exam demonstrated no neurologic deficit, however demonstrated generalized mid/lower lumbar tenderness on palpation and with extension and flexion. AP, lateral, and oblique radiographs of the lumbar spine (Fig. 1) demonstrated oblique lucencies through L1, L2, L3, and L4 pars interarticularis consistent with spondylolysis, without evidence of spondylolisthesis. Radiographs also showed severe diffuse bony sclerosis throughout the pelvis and all visualized bones and diffuse peripheral, endplate sclerosis, and lucency of the center of vertebral body, "sandwich vertebrae" resulting in "rugger jersey spine" consistent with osteopetrosis. To further evaluate the anatomic extent of the multilevel spondylolysis, MRI of lumbar spine was obtained (Fig. 2). MRI of the lumbar spine demonstrates bilateral L1, L2, L3, and L4 pars defects without spondylolisthesis with associated right greater than left L4 facet hypertrophy. There was no evidence of spinal canal or neural foraminal stenosis. Images also show diffusely low T1/T2 signal and thickened vertebral body endplates and posterior elements consistent with osteopetrosis. The patient was treated conservatively with an anti-lordotic lumbar-sacral orthosis brace to help alleviate symptoms and promote healing. Genetics work up performed demonstrated a heterozygous frameshift mutation in the CLCN7 (chloride voltage-gated channel 7) gene that codes for the chloride channel 7 (CC7) protein, and which is associated with the type II, autosomal dominant form of osteopetrosis.

Discussion

Osteopetrosis is a heterogeneous group of inheritable disorders due to defective bone resorption secondary to osteoclast dysfunction or abnormal differentiation. As a result, there is increased, abnormal bone density and disorganization leading to increased bone brittleness, which often results in pathologic fractures. Although the process of osteoclast differentiation and bone deposition/resorption are biochemically complex, 4 main types of osteopetrosis have been identified based on molecular pathogenesis and clinical features. These types include the autosomal recessive infantile/malignant form, the intermediate autosomal recessive form, type I autosomal dominant form and type II autosomal dominant form (also called Albert-Schoenberg disease) [6,7]. Type II is overall the most common form and is the genetic diagnosis in this case.

The infantile and intermediate forms most commonly affect children in the first year of life and during the first decade, respectively, with the infantile form often leading to mortality early in childhood. The intermediate form is a milder autosomal recessive form, often presenting with pathologic fractures and cranial nerve compressive neuropathies and is associated with defects in the carbonic anhydrase II protein [6,7]. The autosomal dominant forms (type I and type II) are more in-

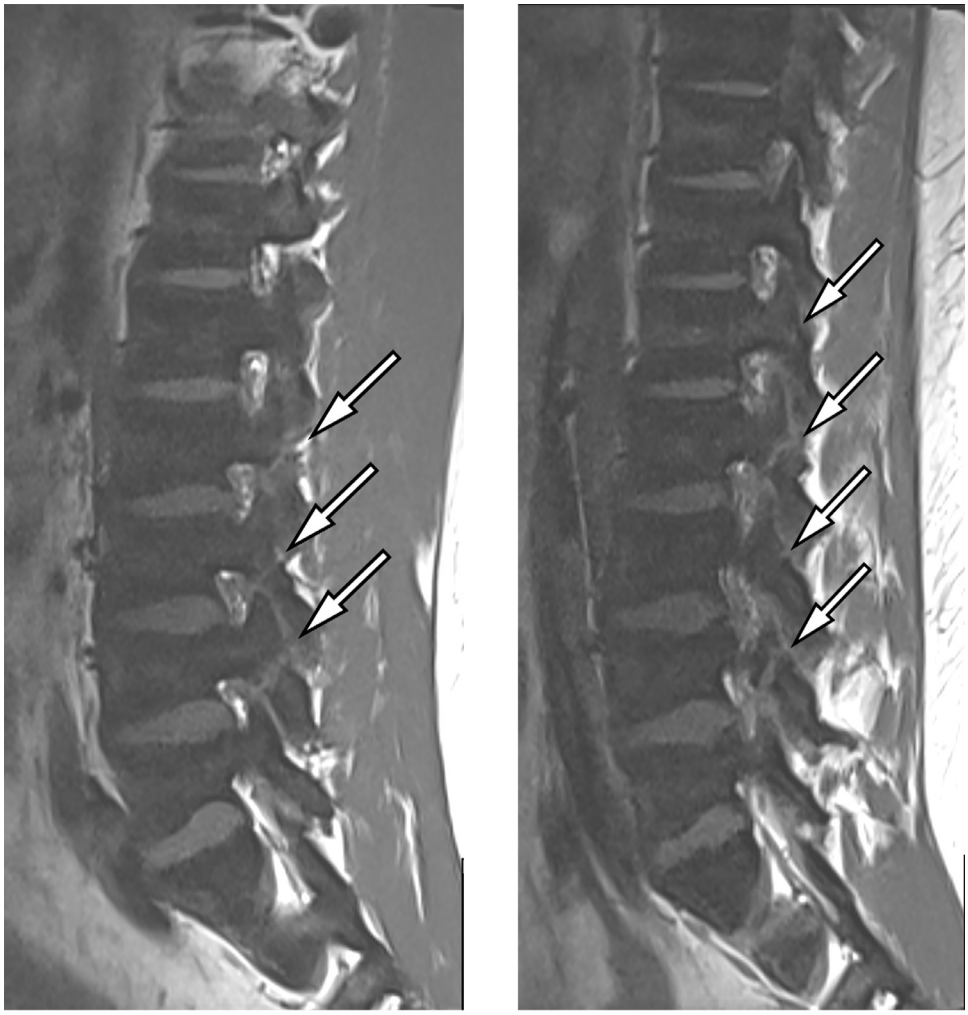

Fig. 2 – T1 weighted MRI images of the lumbar spine at left (A) and right (B) off midline sagittal images shows bilateral pars defects (arrows) at multiple levels of the lumbar spine.

dolent and often asymptomatic, with type II presenting with pathologic fractures, arthritis, bone pain, and/or nerve compression in adulthood. While the infantile autosomal recessive form is associated with multiple gene mutations, the TCIRG1 (T cell immune regulator 1) gene being the most common [8], the autosomal dominant forms are associated with defects in the LRP5 (low-density lipoprotein receptor-related protein 5) gene (type I) and mutation of the CLCN7 gene (type II) [9].

The CLCN7 gene encodes for the CC7 protein, a voltage-gated $2Cl^-/1H^+$ antiporter channel on the membrane of late endosomes and lysosomes and along the ruffled border of resorption lacuna [8,9]. Along with V-ATPase (vacuolar-type ATPase), the CC7 protein is responsible for the acidification of lysosomal vesicles and resorption lacuna, which results in bone resorption [8,9]. Additionally, the CC7 protein is responsible for vesicle trafficking and recycling endosomes by regulating the luminal Cl^- concentration [8]. Biallelic mutations cause a very severe form osteopetrosis, consisting of bone defect and hematologic failure, as well as primary neurodegeneration, cerebral atrophy, spasticity, axial hypotonia, and peripheral hypertonia [8]. The most common defect to the CLCN7 is a heterozygous missense mutation, resulting in abnormal dimerization of the mutant subunits and leading to impaired lysosomal vesicle trafficking and decreased bone resorption from elevated resorption lacuna pH [8].

Classic imaging findings of osteopetrosis include severe diffuse bony sclerosis often with a bone-within-bone appearance. In the spine, the classic imaging appearance is of a "sandwich vertebrae" formed by diffuse endplate (and posterior element) sclerosis and lucency of the center of the vertebral body resulting in a "rugger jersey spine". These findings are similarly translated to MRI as diffusely low signal on T1 and T2 weighted images in the region of sclerosis along the peripheral endplates and relatively increased central signal [6].

In the imaging evaluation of patients with osteopetrosis, some of the potential complications to evaluate in-

clude pathologic fractures, foraminal stenosis impinging on the cranial nerves at the nerve roots, and the potential paradoxical development of rickets secondary to low serum calcium related to sequestration of calcium in the bones [5–7].

The disordered bony matrix and increased bony density of osteopetrosis predisposes patients to pathologic fractures. Most pathologic fractures will be encountered in long bones. However, in categorizing spondylolisthesis, Wiltse *et al.* [10] included osteopetrosis as a pathologic condition which could lead to spondylolysis and associated severe spondylolisthesis. In this case, the patient developed bilateral pars defects at multiple levels. Spondylosis should be one of the fracture types considered when reviewing radiographs of patients with osteopetrosis. On imaging, spondylolysis is seen as an oblique lucency through the pars interarticularis. Oblique positioning may increase the sensitivity, allowing better visualization of the break in the pars interarticularis seen, the classic "Scotty dog" sign. Although in this case, the lateral views better showed the pars defects than the oblique views. Spondylolysis should not be inadvertently overlooked when encountering and potentially being distracted by the striking sclerosis seen with osteopetrosis.

In conclusion, while most cases of spondylolysis occur in otherwise healthy adolescence, underlying bone disease, such as osteopetrosis, can predispose patients to multilevel spondylolysis. We describe a case in which a patient with osteopetrosis (autosomal dominant type II, due to deficient CLCN7 gene) presented with multilevel (L1–L4) bilateral spondylolysis. While cases of multilevel spondylolysis in pediatric osteopetrosis patients have been reported, the genetic basis was not considered [11]. Because of the predisposition of patients with osteopetrosis to pathologic fracture, evaluation of radiographs and other imaging studies performed for the evaluation of these patients should always include intentional review for fractures, including spondylolysis.

Patient consent

The case report was fully explained to the patient. All associated risks and benefits of participating were also explained. The patient's questions were answered to their satisfaction. The patient agreed to participate in the case report. Written informed consent was obtained from the patient by the author.

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