An Unexpected Outcome in an Adolescent With Juvenile Ankylosing Spondylitis

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A 13-year-old boy presented to his pediatrician's office with a 1-day history of left hip pain. The patient reported that he felt a sharp pain in his anterior left hip while running, causing him to limp. He had difficulty getting out of bed, stating it felt like "needles in the (left) hip when putting my foot down."

History. He denied other joint pain, swelling, redness, numbness, fever, rash, or recent illness. He denied sexual activity and recent travel. His medical history was significant for a 7-year history of recurrent right hip pain associated with HLA-B27 juvenile ankylosing spondylitis (JAS), attention deficit hyperactivity disorder (ADHD), vitamin D deficiency, low bone density, and traumatic cervical and thoracic vertebral compression fractures at age 11.

During an annual wellness visit 5 days prior to current presentation, he was noted to have left hip pain on internal rotation. Further questioning revealed that pain onset occurred 2 weeks prior to the routine visit, after being tripped. At that time, his pain had mostly resolved and he followed up with his rheumatologist who increased his indomethacin 25 mg to 3 times daily as needed. The patient's other medications included lisdexamfetamine 30 mg once daily, inconsistent use of over-the-counter vitamin D supplements at 2000 international units (IU) per day, and esomeprazole 20 mg once daily as needed while on prolonged use of nonsteroidal anti-inflammatory drugs (NSAIDs). He denied recent corticosteroid use. Family history was significant for arthritis, lupus, type 2 diabetes mellitus, dental decay, and scoliosis.

The patient was well-nourished in moderate discomfort with vital signs within normal limits. He was at the 49^{th} percentile for height and 58^{th} percentile for weight with a BMI of 19.58 kg/m^2. Dentition was within normal limits. He had difficulty bearing weight and required use of a wheelchair. There was pain to palpation over the anterior femoral head and with internal rotation hip. There was no swelling, redness, increased warmth, bruising, gross deformity, or asymmetry of the lower extremities. His lower extremity sensation and muscle bulk were within normal limits and hips were held in neutral position. There were no skin rashes.

Diagnostic testing. Recent notable laboratory results within normal limits included parathyroid, thyroid, lipids, complete blood count, comprehensive metabolic panel, erythrocyte sedimentation rate, and phosphorus levels. His 25-OH vitamin D was low at 18 ng/mL.

Answer and discussion on the next page.

Answer: B. Fracture

Given the patient's previous vertebral fractures, low bone density, and recent trauma, fracture was suspected. Initial hip X-ray was reported by the radiology team as negative for signs of fracture. However, after review of the X-ray and the patient's clinical condition by the pediatrician, a reread of the hip X-ray was requested. A suspected left femoral neck fracture was noted following the reread and the radiology team recommended magnetic resonance imaging (MRI) for confirmation (Figures 1 and 2), which ultimately confirmed the diagnosis.

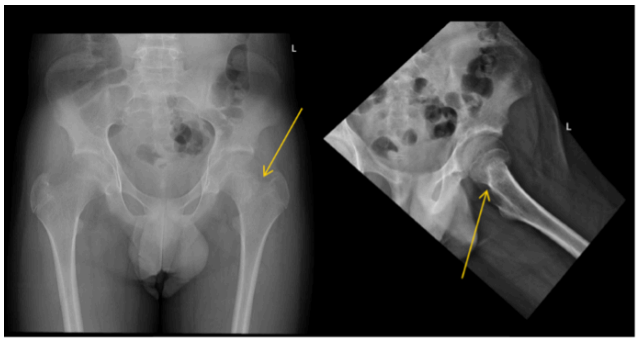

Figure 1. *Bilateral hip X-ray with mildly impacted left femoral neck fracture (yellow arrow).*

Figure 2. *MRI of the left hip with a nondisplaced left femoral neck fracture (yellow arrow), marked marrow edema of the proximal femur (red arrow), and joint effusion with synovitis (white arrow).*

Severe pain with refusal to bear weight is usually caused by acute infections, malignancy, trauma, transient synovitis, or avascular necrosis. His recurrent right hip pain due to JAS put him at increased risk for similar symptoms in the contralateral hip; however, JAS pain is usually less severe with a more insidious onset causing a limp rather than inability to bear weight. He had no evidence of infection or malignancy. SCFE was possible given his age but was less likely since he didn't hold his leg in external rotation and his BMI was within normal range. Transient synovitis could not be ruled out and was a diagnosis of exclusion.

Treatment and management. The patient underwent in situ 3 cannulated screw fixation and was placed on crutches for 6 weeks. He was to continue supplementation with 2000 IU of vitamin D, add a small amount of sun exposure, add 1300 mg of calcium in his diet, and reestablish with an endocrinologist.

Outcome and follow-up. He was mostly consistent with vitamin D supplementation but did not add sun exposure or measure calcium in his diet. The endocrinologist felt that his bones were very fragile and thin for his age, so a dual X-ray absorptiometry (DEXA) scan was completed, which showed a low lumbar spine bone mineral density (BMD) of 0.813 g/cm² and a Z score of -0.6. He was referred to a geneticist for evaluation of bone fragility syndromes.

While awaiting evaluation, he sustained a Salter-Harris II fracture of the distal left tibia after tripping while using crutches (Figure 3).

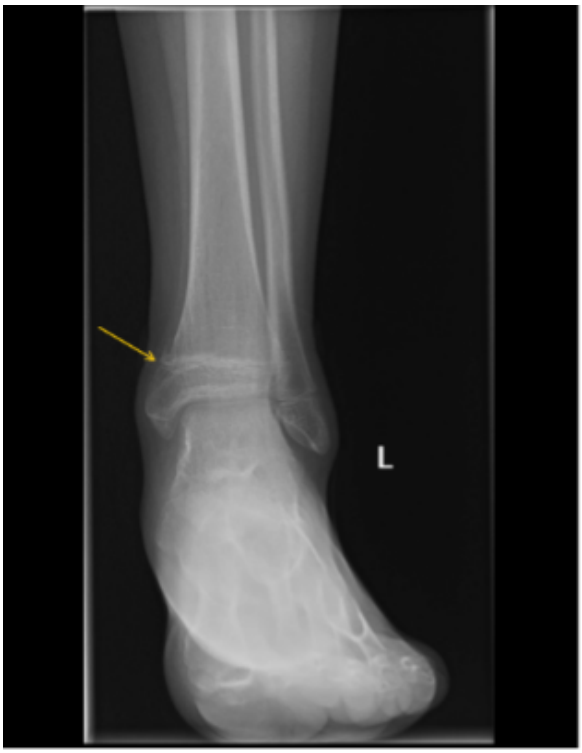

Figure 3. *X-ray of the left ankle with fracture through the medial tibial metaphysis and physis (yellow arrow) with periosteal reaction and osteopenia.*

The genetics team evaluated for hypophosphatasia (HPP), osteogenesis imperfecta (OI), and other bone fragility syndromes. An alkaline phosphatase level within normal limits ruled out HPP. Although he did not have significant findings for OI, a mild form could not be ruled out. A bone fragility gene panel revealed a mutation in *COL1A2* (c.964G>A [p.Gly322Ser]), a pathogenic variant for OI, and *NOTCH2* (c.3467A>G [p.Asn1156Ser]), a variation of unknown significance.

His indomethacin was discontinued, vitamin D supplementation was increased to 4000 IU/day, and pamidronate infusions were started (0.5 mg/kg for initial dose, then 1 mg/kg every 4 months). Additional recommendations included annual DEXA scans and spine X-rays for scoliosis and fractures, hearing evaluation every 3-5 years, cervical X-rays prior

to sports, and MRI of the skull base for basilar impression given any neurologic symptoms.

The patient has been without fractures for the past 8 months. His mom and sister both tested positive for the OI variant.

Discussion. JAS is a seronegative spondyloarthropathy strongly associated with HLA-B27. It is an inflammatory condition affecting the spine and large joints, especially the sacroiliac joints. Clinical features include joint pain, morning stiffness, and uveitis. Numerous studies have shown an increased risk of vertebral fractures in ankylosing spondylitis[1-6]; however, the incidence of nonvertebral fractures is less clear. One case-control study found no significant increased risk of forearm or hip fractures[4], and another population-based cohort study found no increase in the risk of limb fractures.[2]

OI is a rare, heritable connective tissue disorder. Autosomal dominant mutations in the genes encoding type I collagen, *COL1A1,* and *COL1A2*, are the most common causes of OI, but at least 17 other associated genes have been identified.[7] OI has multiple subtypes ranging from premature osteoporosis to perinatal death. Clinical features include low bone mass, bone fragility, blue or grey sclera, hearing impairment, dentinogenesis imperfecta, and spine deformities.[7,8] While vertebral fractures can be associated with OI, evidence suggests that extremity fractures are more common. A retrospective study of pediatric patients diagnosed with OI found that the most common fractures at diagnosis were in the extremities.[9] Another population-based cohort study found that boys with OI aged 0 to 19 years had the highest fracture rates in forearm, femur, lower leg, and ankle.[10]

In patients with multiple or suspicious fractures, genetic testing can be used to confirm the diagnosis. Type I collagen is a protein abundant in bone, skin, and other connective tissue that forms a triple helix with characteristic Gly-X-Y amino acid repeats that are necessary for structure and stability.[11] Our patient had a mutation in the α2(I) chain of type I collagen with the usual glycine residue at position 322 being replaced by serine. This substitution disrupts protein function and is a pathologic variant of OI.[12] He also had a mutation in *NOTCH2,* which encodes a transmembrane receptor protein that regulates gene expression.[13] *NOTCH2* mutations are associated with Hajdu-Cheney syndrome and are characterized by facial anomalies, osteoporosis, and short stature, as well as Alagille syndrome, which presents with severe renal disease, skeletal abnormalities, and hepatic cholestasis.[13,14] The variant identified in our patient's panel has not been found to significantly alter protein function.[15] The lack of dysmorphic facial features, short

stature, and renal or hepatic complications in our patient make the significance of this variant unknown and further support the diagnosis of OI.

Treatment of JAS includes NSAIDS, corticosteroids, and physical therapy.[1,4,16] Conversely, bisphosphonate therapy has long been used to treat children with OI showing increases in BMD, reductions in fractures, and restoration of vertebral size and shape following compression fracture.[7] Bisphosphonates, such as pamidronate and zoledronate, exert their therapeutic effects by inhibiting osteoclast function, thereby inhibiting bone resorption and promoting bone growth and strength.[16] Treatment with pamidronate was chosen for our patient given his BMD within normal limits, mid-puberty status which has natural increases in BMD, and to avoid overtreatment as zoledronate is stronger.

Given overlapping symptoms, it is beneficial to review the features of these conditions. This case exemplifies the importance of obtaining a detailed history and physical examination, the value of continuity of care with a primary care physician, and the increasing utility of multi-gene screening for enhanced diagnostic evaluation.

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