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Case Report

Multiple fractures, pain, and severe disability in a patient with adult-onset hypophosphatasia

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ABSTRACT

Hypophosphatasia (HPP) is a rare, inherited metabolic bone disease resulting from mutations in the gene encoding tissue non-specific alkaline phosphatase. The biochemical hallmark and key diagnostic indicator is low alkaline phosphatase activity, which leads to a variety of clinical manifestations across all ages. The diagnosis is easily missed in adults, who frequently present with nonspecific clinical manifestations such as fractures, osteomalacia, and pain. Here, the pathway to diagnosis and disease course is described in an adult patient presenting with pain. Low serum alkaline phosphatase activity went unnoticed for 2 years until osteomalacia was suspected, during which time he experienced multiple fractures and progressing pain. Currently, accumulated morbidity has rendered the patient unable to work, and treatment is focused on pain management. This case highlights the importance of low alkaline phosphatase in the differential diagnosis of patients with musculoskeletal pain.

1. Introduction

Hypophosphatasia (HPP) is a rare, inherited metabolic bone disease characterized by poor bone mineralization, leading to HPP-related rickets in children and osteomalacia in adults (Rockman-Greenberg, 2013; Whyte, 2013). HPP is caused by loss-of-function mutation(s) in the gene (*ALPL*) that encodes the tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP). Approximately 300 pathogenic mutations in the *ALPL* gene have been identified to date (Mornet, 2015). Inheritance may be either autosomal recessive or autosomal dominant (Rockman-Greenberg, 2013; Mornet, 2015). Reduced TNSALP activity leads to accumulation of its substrates, pyridoxal-5′-phosphate (PLP), phosphoethanolamine (PEA), and inorganic pyrophosphate (PPi). The excess of PPi, a potent inhibitor of bone mineralization, leads to the mineralization defects in bone and teeth characteristic of HPP (Whyte, 2013).

Adult-onset HPP typically manifests during middle age, although some adults recall earlier signs of HPP such as early tooth loss or childhood rickets (Whyte, 2013). Regardless of age at onset of HPP, adults may present with osteopenia, osteomalacia, recurring and/or poorly healing fractures, pseudofractures, bone pain, joint pain caused by chrondrocalcinosis or calcific periarthritis (Whyte, 2013; Coe et al., 1986), and/or proximal muscle weakness (Whyte, 2013; Coe et al., 1986; Berkseth et al., 2013). As many of these symptoms are consistent with diagnosis of other diseases such as osteoporosis, osteoarthritis, and fibromyalgia, the diagnosis of HPP in adults can be challenging and easily missed (Mornet et al., 2014). Although recombinant TNSALP approved for treatment of HPP (asfotase alfa, Alexion Pharmaceuticals, Inc.) currently exists only in Japan, Canada, and the European Union, correct diagnosis of HPP is important as treatments for other disorders may have adverse effects for patients with HPP; for example, treatment with bisphosphonates (structural analogs of PPi) for a presumed diagnosis of osteoporosis in adults may increase fracture risk in patients with HPP (Sutton et al., 2012).

Herein, I describe the pathway to diagnosis, unique features, and the course and current management of a case of adult-onset HPP.

2. Case report

The patient was a 53 year-old, 6 ft tall, 215 lb Caucasian man who was referred to rheumatology in September 2011 for intractable muscle and joint pain. He reported severe diffuse pain at his first rheumatology visit. He had no personal or known family history of metabolic bone disease or dental disease. In August 2011, his primary care physician diagnosed fibromyalgia, based on chronic pain.

The patient first presented in 2009 (Fig. 1) with unexplained back and leg pain. Prior history included hypertension, hypercholesterolemia, and occasional insomnia, but was otherwise unremarkable. In July 2010, he experienced unexplained bilateral swelling of his ankles. In August 2010, he experienced non-traumatic thoracic pain; the first imaging in the patient's chart was a triple phase bone scan that revealed costochondritis and a possible broken rib. A follow-up MRI of the area in November 2010 did not identify a fracture. Pain medications, including

Abbreviations: HPP, hypophosphatasia; PEA, phosphoethanolamine; PLP, pyridoxal-5′-phosphate; PPi, inorganic pyrophosphate; TNSALP, tissue-nonspecific isoenzyme of alkaline phosphatase.

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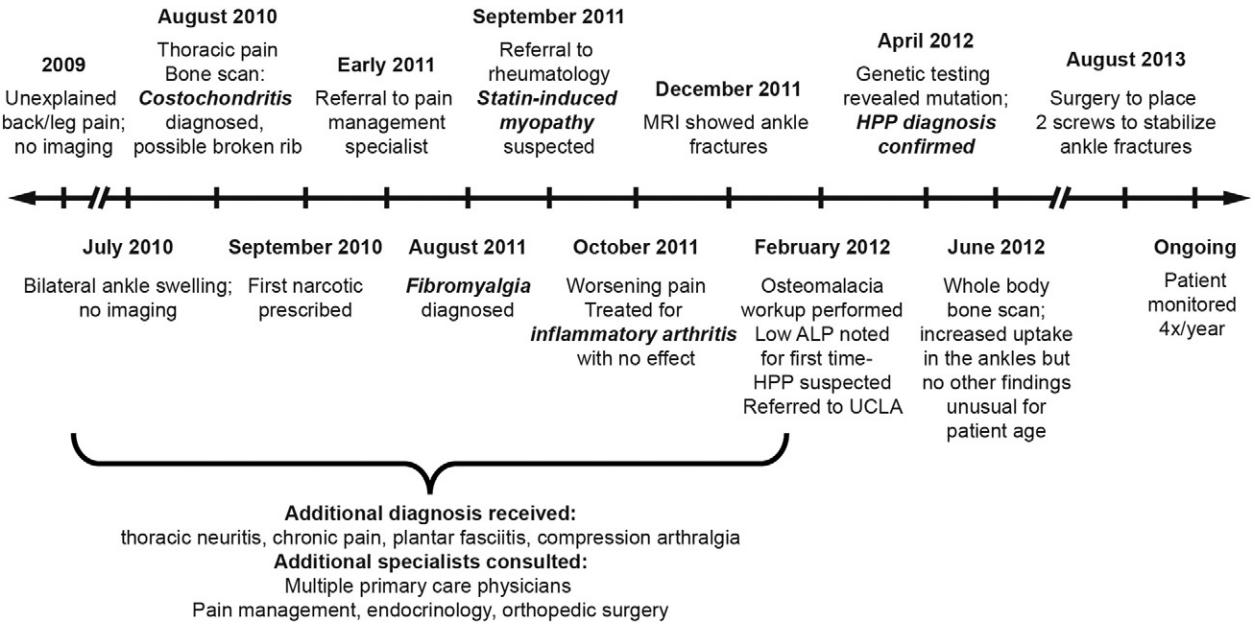

Fig. 1. Timeline illustrating the patient's journey to correct diagnosis of adult-onset HPP.

narcotics, were prescribed without effect, and in early 2011, the patient was referred to a pain management specialist. By the time of his referral to rheumatology in September 2011, the patient had received varying diagnoses, including costochondritis, thoracic neuritis, chronic pain, plantar fasciitis, compression arthralgia, and fibromyalgia.

Rheumatology workup, which included a complete serology panel with muscle enzymes, an autoimmune panel, and a full inflammatory marker panel, returned no abnormal findings. Despite normal levels of liver enzymes and creatine phosphokinase, statin-induced myopathy was considered because his simvastatin dose had recently been increased to 80 mg/day. Simvastatin was discontinued, and corticosteroids and muscle relaxants prescribed. The patient reported a self-estimated 60–70% improvement in symptoms shortly thereafter, but presented again in October 2011 with worsening pain, especially in his ankles. Radiographs of the ankles revealed possible small fractures, prompting an MRI in December 2011, which confirmed bilateral fractures of the medial malleoli and a non-displaced fracture in the left ankle with a torn tendon and joint effusion. The atypical non-traumatic nature of these fractures prompted a workup for osteomalacia in February 2012. Possible diagnoses included HPP, Wilson's disease, and celiac disease. Serum magnesium, phosphorus, copper, zinc, parathyroid hormone, calcium, and celiac markers were within normal limits. Alkaline phosphatase was low on multiple determinations at 27–32 IU/L (normal range: 40–115 IU/L). Upon chart review, serum alkaline phosphatase activity was consistently low, with values below the normal range in December 2011, April 2011, September 2010, and June 2010 (earliest available). Pyridoxal 5′-phosphate (vitamin B_6) was 54 μg/L (normal range: 5–50 μg/L). Vitamin D was insufficient (14 ng/ml, normal range: 30–100 ng/ml) and was normalized with supplementation. A diagnosis of HPP was indicated based on laboratory and clinical evidence. The patient was then referred to the University of California, Los Angeles, for genetic testing, which revealed a heterozygous mutation (c.500C>T) on exon 6 of the *ALPL* gene (Connective Tissue Gene Tests, Allentown, PA, USA), thereby supporting the diagnosis of HPP.

The patient is seen every 3 months to monitor his condition. A whole body bone scan in June 2012 identified increased uptake in the ankles consistent with fracture sites but no other findings unusual for the patient's age. In August 2013, he underwent orthopedic surgery to have two screws placed to stabilize the ankle fractures. He has declined both placement of stabilizer rods and experimental teriparatide treatment. Orthopedists have expressed discomfort with further surgical treatment given the fragility of his bones. As of March 2015, the patient had progressing pain and rib fractures. He fatigues easily and prefers appointments before noon. He regularly wraps his legs for support, and uses a cane or walker to assist ambulation. Decreased mobility has rendered the patient unable to work. Pain is poorly controlled with a 100 μg fentanyl patch/72 h and 20 mg short-acting oxycodone every 4 h. Vitamin D supplementation is provided as needed to maintain serum concentrations within normal ranges. The patient's serum concentration of vitamin D was 48 ng/ml in April 2012 with supplementation, after being 14 ng/ml in March 2012 (normal range: 30–100 ng/ml). Current treatment is focused on pain management due to limited treatment options.

3. Discussion

HPP may present with nonspecific musculoskeletal manifestations, particularly in adults (Berkseth et al., 2013). The patient described here initially presented with pain, and sought help from a variety of medical specialists, including pain management, endocrinology, and orthopedic surgery, before referral to rheumatology. During his 2-year search for the cause of his symptoms, the patient experienced progressive diffuse pain and multiple fractures, which ultimately prompted a workup for osteomalacia and the finding of low serum alkaline phosphatase activity. This case illustrates the difficulty adult patients with HPP may have in obtaining an accurate diagnosis (Girschick et al., 2007; Whyte et al., 2013; Sorensen and Flodgaard, 1975), and highlights the importance of determining and recognizing the clinical significance of low alkaline phosphatase activity level as part of differential diagnosis in patients with musculoskeletal complaints, including undefined pain.

The clinical significance of low serum alkaline phosphatase is underappreciated and may be overlooked (McKiernan et al., 2014). In the present case, the finding of low serum alkaline phosphatase activity, which should prompt consideration of HPP, was repeatedly missed. It was not until osteomalacia was suspected, due to the non-traumatic ankle fractures, that consistently low values of serum alkaline phosphatase were noted in the patient's record, dating back to June 2010 (earliest available, after the initial complaint of leg and back pain). As alkaline phosphatase levels can increase during fracture healing, this finding raised suspicion for HPP and led to examination of PLP levels, a referral for genetic testing, and, ultimately, the correct diagnosis of HPP.