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.

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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 fascitis, 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 2012, September 2010, and June 2010 (earliest available). Pyridoxal 5′-phosphate (vitamin B₆) 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. Hefatigues 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 Floggaard, 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.
Pain is a frequent complaint by patients with HPP (Whyte, 2013; Berkseth et al., 2013), and may result from ectopic calcification in the joints (Berkseth et al., 2013; Guanabens et al., 2014; Metab et al., 2012), inflammation (Beck et al., 2009; Girschick et al., 1999), fractures, and/or pseudofractures (Whyte, 2013; Harper, 1989; Fallon et al., 1984; Whyte et al., 1982). In the present case, there was no indication of ectopic calcification by X-ray or MRI, and neither initial nor continued complaints of generalized severe musculoskeletal pain could be completely attributed to his fractures. Although nonsteroidal anti-inflammatory drugs have been reported to improve pain in some HPP patients (Girschick et al., 1999), they did not provide relief in this patient. Treatment remains focused primarily on pain management with narcotics.

HPP may result from autosomal recessive or autosomal dominant inheritance. The location of the gene mutation influences the level of residual enzymatic activity of the resulting TNSALP protein (Mornet, 2013). In the present case, a single c.500C→T mutation was found on exon 6 of ALPL. This mutation has been determined to result in no residual alkaline phosphatase activity in an in vitro site-directed mutagenesis assay, and it has been identified previously in a single patient with infantile HPP, as part of a compound heterozygous genotype with a c.571G→A mutation (Mornet, 2015). The c.571G→A mutation has been documented in several patients, and to date, appears only to result in symptomatic HPP when part of a compound heterozygote genotype (Henthorn et al., 1992). Thus, the present patient may express autosomal dominant inheritance, consistent with other reports of patients with single mutations and adult onset of HPP symptoms (Whyte, 2012; Fauvert et al., 2009). Although the patient reported no family history of HPP or skeletal or dental disease, it would be of interest to screen close family members for the mutation and possible symptoms. The patient’s chart did not state whether he had siblings or children, which would only have been noted if they had relevant history.

Upon questioning, patients presenting with HPP in adulthood may recall symptoms of HPP in childhood, such as early tooth loss or rickets (Whyte, 2013). In a retrospective study at the Mayo Clinic, 9% of patients diagnosed with HPP as adults recalled earlier symptoms (Berkseth et al., 2013). Despite the presence of a previously reported inactivating mutation (Mornet, 2015), the current patient did not recall any prior symptoms, and he is of normal stature with no periodontal disease. The cause of the sudden onset of his pain and fractures in his 50s is unclear. Epigenetic regulation and dietary mineral intake may influence alkaline phosphatase activity (Whyte, 2013; Mornet, 2013), while bisphosphonate treatment may have precipitated symptoms in other patients with adult-onset HPP (Whyte, 2012; Schalin-Jäntti et al., 2010), while bisphosphonate treatment may have precipitated symptoms in other patients with adult-onset HPP (Sutton et al., 2012), and result in exacerbation of disease (Cundy et al., 2015). Caution is also needed when considering supplemental vitamin D, as vitamin D supplementation in patients with HPP may result in hypercalcemia (Berkseth et al., 2013; Eisenberg and Pimstone, 1967).

The patient presented herein represents one example of the broad spectrum of presentations associated with HPP, including pain, recurrent, non-traumatic, and non-healing fractures, progressive loss of mobility, and diminished quality of life. This case illustrates the challenges of recognizing, diagnosing, and treating HPP, and highlights the need to consider serum alkaline phosphatase activity levels in patients presenting with nonspecific pain.

Authors’ roles
NB managed the patient, collected and interpreted the data, drafted, revised, and approved the final manuscript for submission, and takes responsibility for the integrity of the content.

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Conflict of interest
None.

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