Weaving bone resilience: a case of co-occurrence of osteogenesis imperfecta and hypophosphatasia

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ABSTRACT

This report describes the genetic and clinical findings of a rare case of osteogenesis imperfecta (OI) and hypophosphatasia (HPP) occurring simultaneously in an adult patient.

OI is a rare inherited disease that primarily affects the skeleton, reducing bone mass and causing fractures. About 85% of OI cases are caused by autosomal dominant mutations in either *COL1A1* or *COL1A2*. HPP, also a rare genetic disorder, is caused by pathogenic variants in the *ALPL* gene, leading to deficient activity of tissue-nonspecific alkaline phosphatase and causing defective mineralization of bone.

We describe the case of a 63-year-old female patient with a dual diagnosis of OI and HPP. This patient was initially treated with bisphosphonates with some benefit. However, she presented new fractures, and decreased levels of alkaline phosphatase (ALP) were noted. Two heterozygous variants, in *COL1A1* and *ALPL*, were identified. After the genetic results, we decided to stop bisphosphonate treatment and start her on teriparatide. Since then, no fractures have occurred, and her ALP levels have normalized.

This report details a rare case of a woman co-diagnosed with OI and HPP, illustrating the genetic and clinical manifestations of both conditions. Initially treated with bisphosphonates, the patient experienced new fractures. Following molecular insights, transitioning to teriparatide resulted in no further fractures and normalization of her ALP levels.

KEYWORDS

Osteogenesis imperfecta, hypophosphatasia, osteoporosis, bone fractures.

Introduction

Hereditary and acquired conditions affecting bone and mineral metabolism and resulting in defective bone mineralization and compromised structural integrity of the skeleton [1] include rare diseases like osteopetrosis, hypophosphatemic rickets, osteogenesis imperfecta (OI), and hypophosphatasia (HPP), as well as the most common metabolic bone disease in children, nutritional rickets [1].

OI is a hereditary disorder that mainly impacts the skeleton, decreasing bone mass and leading to fractures. Approximately 85% of OI cases are attributed to autosomal dominant variants in either the *COL1A1* or the *COL1A2* gene, which encode the α1(I) and α2(I) chains of type I collagen, respectively [2]. The remaining cases are linked to dominant, recessive, or X-linked variants in various genes involved in different aspects of collagen synthesis, processing, or crosslinking, as well as in osteoblast differentiation and function [2]. Individuals with OI have low bone mass and fragile bones, making them prone to long bone fractures and vertebral compression fractures. They may also experience varying degrees of deformity in the long bones, ribs, and spine, as well as growth deficiencies. Variable extra-skeletal features can be present, including blue sclera, conductive or sensory hearing loss, and dentinogenesis imperfecta [3].

HPP is a rare genetic disorder caused by pathogenic variants in *ALPL* resulting in reduced activity of tissue-nonspecific alkaline phosphatase (TNAP) [4,5].

The most frequent manifestations include defective mineralization of bones and/or teeth, premature loss of teeth with intact roots, and, most notably, reduced serum alkaline phosphatase (ALP) activity, which is a hallmark of *ALPL* variants [4]. Biallelic variants in the *ALPL* gene are linked to more severe phenotypes, while heterozygous variants in this gene are associated with milder phenotypes and follow an autosomal domi-

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nant inheritance pattern [5].

Combinations of the two diseases can also occur and a few cases have recently been reported [6]. We describe the case of a 63-year-old woman first diagnosed with OI, in whom genetic investigation led to a co-diagnosis of HPP.

Case report

We report the case of a 63-year-old Caucasian female, first observed at our Rheumatology Department in 2005, at the age of 44. At that time, she had a clinical diagnosis of OI type III, with a history of more than 14 bone fractures (namely, of the right femoral neck and the shaft of the left femur) in the absence of major trauma, the first one occurring at the age of 7 years. She had undergone multiple previous orthopedic surgeries. She also complained of easy bruising, myalgia, fatigue, and poor dentition. Her medical history was also notable for anisometropia and dyslipidemia. Menopause occurred at 52 years of age. She had no history of metatarsal fractures, seizures, or nephrocalcinosis, and reported no exacerbation of pain at lower temperatures.

Her daily medications consisted of calcium supplements (1,000 mg) and vitamin D (400 IU). In the past, she had also been treated with calcitonin and alendronate for an unspecified period.

Significant findings of the physical examination included short stature (height of 120 cm, corresponding to -5.7 SD) and weight of 36 kg (-2.4 SD), chest asymmetry with *pectus excavatum*, scoliosis, blue sclera, and long bone deformities.

Initial biochemical investigations showed normal calcium (9.5mg/dl; reference range 8.6–10.2mg/dl) and phosphate (4.0mg/dl; reference range 2.5–4.5mg/dl) with low ALP levels (27U/L; reference range 35–105U/L). Measurement of inorganic pyrophosphate, pyridoxal-5'-phosphate, and phosphoethanolamine was not performed.

At the time of the first consultation (May 2005, 44 years old), dual-energy X-ray absorptiometry (DXA) was used to determine the patient's bone mineral density (BMD) at the lumbar spine (LS), which showed a Z-score of -5.4 SD. The patient started treatment with pamidronate (60 mg every 3 months). Three years later, BMD was re-evaluated, with significant Z-score improvement (a value of -3.2 SD at the LS). In 2012, the patient was re-started on alendronate (70 mg weekly) after suffering a new fracture of the right tibia. In 2015, bilateral tibia fractures were treated conservatively. X-rays showed osteopenia, gracile bone with cortical thinning, long bone and vertebral deformities, signs of previous fracture with hyperplastic callus, intramedullary rods, and calcinosis (Figures 1 and 2). DXA showed worsened T- and Z-scores in the LS (-6.3 SD

Figure 1 Anteroposterior (a) and lateral lumbar (b) spine X-rays showing homogeneous rarefaction of the cortical and trabecular bone, with a "frame-like" pattern of the vertebrae. Note the partial collapse of several vertebral bodies.

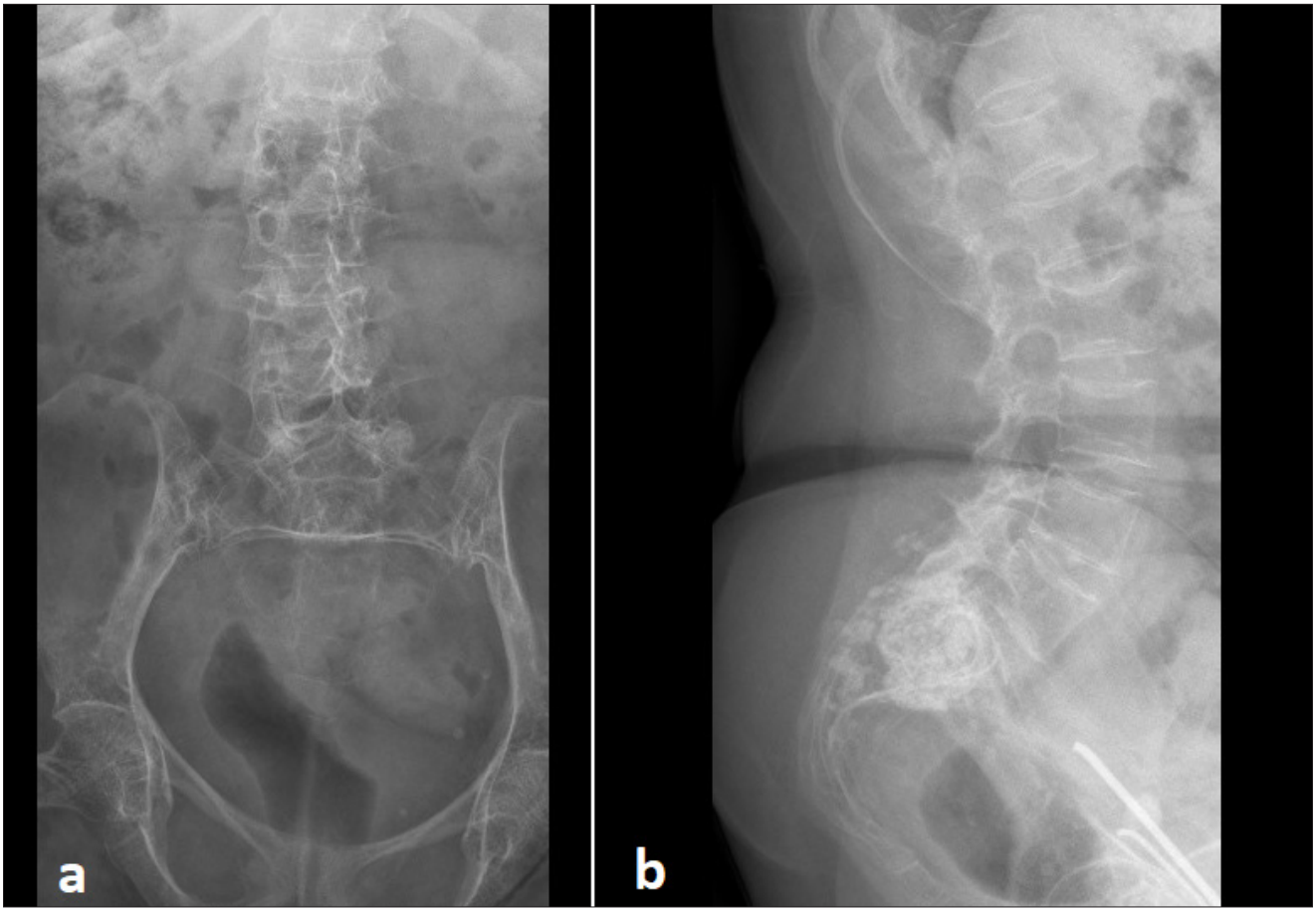
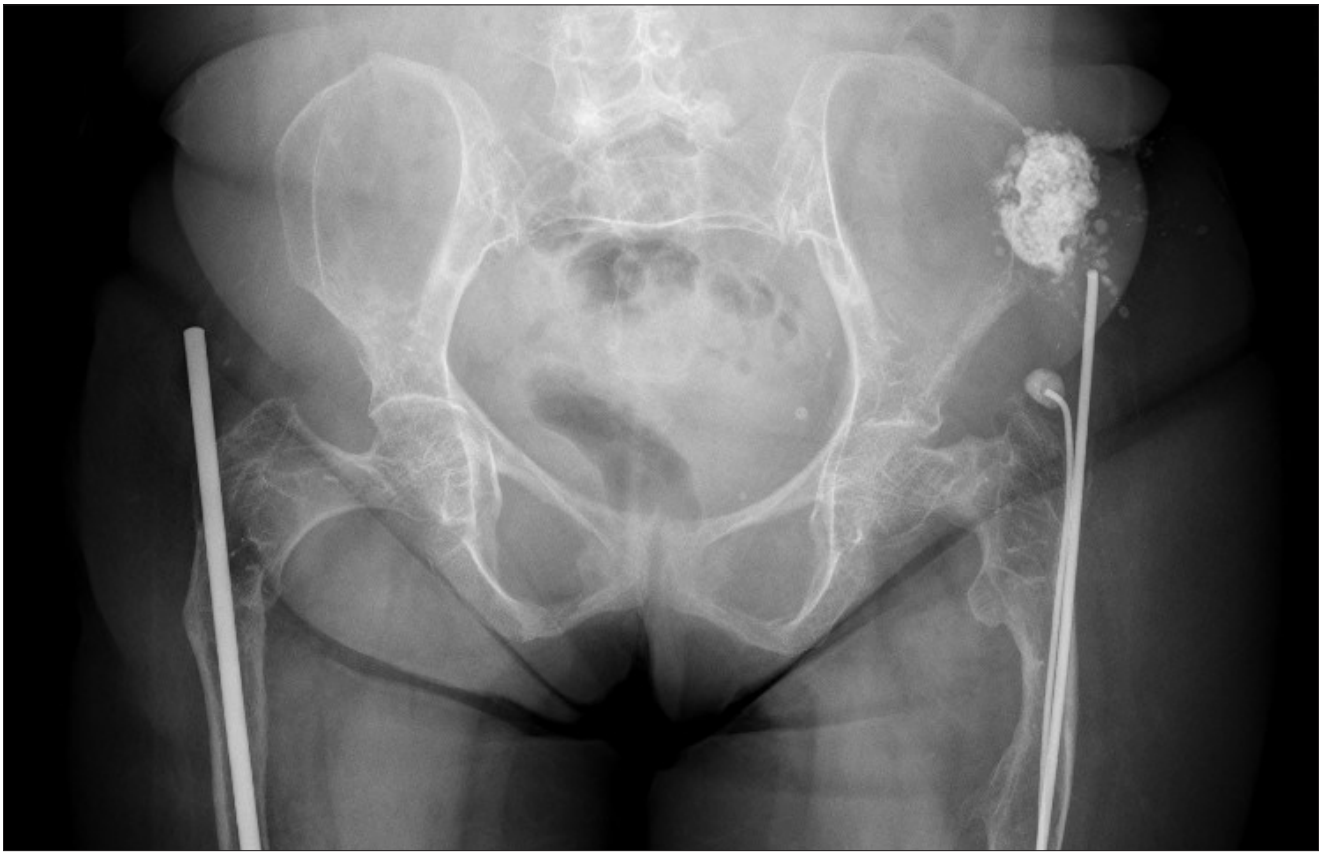


Figure 2 Anteroposterior X-ray of the pelvis showing marked diffuse osteopenia, acetabular dysplasia, a thinning ischiopubic ramus, multiple bilateral femoral deformities and calcinosis on the left.



and -4.6 SD, respectively) and treatment was continued with zoledronate 2.5 mg yearly. In 2018, after four infusions of zoledronate, DXA exhibited a T-score of -5.1 SD and a Z-score of -2.8 SD. In 2019, she sustained two new right lower limb (tibia and fibula) fractures. She had her fifth zoledronate perfusion in October 2019. In summary, five new bone fractures occurred whilst the patient was being treated with bisphosphonates.

In 2020, a large customized skeletal dysplasia Next Generation Sequencing panel was performed. A heterozygous pathogenic variant, NM_000088.4;c.1243C>T p.(Arg415*) in *COL1A1*, was identified, as was a heterozygous pathogenic *ALPL* variant, NM_000478.6:c.1426G>A, p.(Glu476Lys). Functional assays have demonstrated that this latter variant retains only 4.3% residual TNAP activity [7]. It has previously been described in perinatal, juvenile, and adult HPP [7] and in a further Portuguese patient with childhood hypophosphatasia [8]. Subsequently, it was decided to stop zoledronate treatment in our patient.

The patient's follow-up was irregular between 2020 and 2022, due to the disruptions caused by the Covid-19 pandemic. In 2022, DXA exhibited a T-score of -5.6 SD and treatment with teriparatide (parathyroid hormone) was started. The patient completed 24 months of treatment with teriparatide, during which time she did not experience any fractures. Additionally, her serum ALP levels returned to normal (35–40 U/L). Follow-up DXA showed a significant improvement compared with previous values, with an LS T-score of -5.1 SD and a Z-score of -3.4 SD.

Discussion

We here described the case of a woman with a primary clinical diagnosis of OI type III. Genetic investigation revealed an autosomal dominant pathogenic *COL1A1* variant but also a pathogenic variant in *ALPL*, associated with childhood, juvenile- and adult-onset HPP.

Our patient presented a mixed phenotype of the two coexisting diseases, including signs and symptoms seen in both OI and HPP, such as atypical, multiple, and non-traumatic fractures, poor dentition, bone deformities, and bone/muscle pain. She also had typical findings of OI, such as blue sclera, and also of HPP, such as persistent low serum ALP levels and calcinosis. On the other hand, there was no history of pseudogout or metatarsal fractures. In this case, BMD evaluation by DXA revealed very low BMD, which occurs more frequently in OI [9]. Treated with bisphosphonates, our patient showed a temporary improvement in her BMD, as assessed by DXA, although multiple new fractures occurred during the treatment. Antiresorptive therapies must not be used for the chronic management of HPP as they may worsen the underlying osteomalacia [10,11]. This may explain, at least in part, why our patient continued to have fractures while under treatment. Despite her persistently low ALP serum levels, OI was considered the patient's sole diagnosis until the results of the genetic investigation became available. Only after identifying the patient's *ALPL* variant was a dual diagnosis considered, leading to the decision to stop the treatment with zoledronate and to start teriparatide.

A causal enzyme replacement therapy with asfotase-alfa, a human recombinant mineral-targeted form of recombinant TNAP [12], was approved by the Food and Drug Administration in 2015 for the treatment of perinatal, infantile, and juvenile-onset HPP, and in the same year by the European Medicines Agency for the treatment of bone manifestations of childhood or juvenile hypophosphatasia [13]. To date, all asfostase-alfa studies involving HPP patients of different ages have shown a good safety profile [14]. However, data are scarce in adults and trials with asfostase-alfa are limited to adult HPP patients who have been symptomatic since childhood. Thus, there are no formal guidelines for the treatment of adult-onset HPP [15]. Teriparatide is an analog of the first 34 amino acids of parathyroid hormone and is licensed for the treatment of osteoporosis in postmenopausal women and men at risk of fracture, and for glucocorticoid-induced osteoporosis [16]. Teriparatide has been shown in case reports to help fracture healing in adults with HPP [16]. This therapy led to increased ALP levels and accelerated fracture healing in some but not all adult HPP patients [17].

Considering our patient's osteoporosis (her most prominent clinical manifestation) and its consequences, the treatment decision was made mainly with the aim of preventing new non-traumatic fractures. Although HPP treatment with teriparatide remains controversial, we cannot be sure that our patient had a juvenile-onset form of HPP; therefore, considering that asfotase-alfa may not be indicated, we opted for teriparatide. A lifelong continuous multidisciplinary approach, involving rheumatology, medical genetics, orthopedics, and physical rehabilitation specialists, is crucial for this patient's quality of life.

Conclusion

OI and HPP are two rare hereditary conditions that disrupt bone and mineral metabolism, causing defective bone mineralization and impaired structural integrity of the skeleton. Although the diagnosis is mainly clinical, genetic evaluation plays a fundamental role in the classification and management of these diseases. Our patient presented clinical, analytical, and molecular evidence of the two diseases, and thus required therapeutic solutions targeting both conditions, focusing on fracture healing and prevention. After starting treatment with teriparatide, no new fractures occurred. This case should raise awareness of the importance of early and correct diagnosis of OI and/or HPP.

References

1. Charoenngam N, Cevik MB, Holick MF. Diagnosis and management of pediatric metabolic bone diseases associated with skeletal fragility. Curr Opin Pediatr. 2020;32(4):560-73.
2. Morello R. Osteogenesis imperfecta and therapeutics. Matrix Biol. 2018;71-72:294-312.
3. Marini JC, Forlino A, Bächinger HP, et al. Osteogenesis imperfecta. Nat Rev Dis Primers. 2017;3:17052.
4. Mornet E, Taillandier A, Domingues C, et al. Hypophosphatasia: a genetic-based nosology and new insights in genotype-phenotype correlation. Eur J Hum Genet. 2021;29(2):289-99.
5. Martins L, Lessa LF, Ali TM, et al. Childhood hypophosphatasia associated with a novel biallelic ALPL variant at the TNSALP dimer interface. Int J Mol Sci. 2022;24(1):282.
6. Fratzl-Zelman N, Linglart A, Bin K, et al. Combination of osteogenesis imperfecta and hypophosphatasia in three children with multiple fractures, low bone mass and severe osteomalacia, a challenge for therapeutic management. Eur J Med Genet. 2023;66(11):104856.
7. Del Angel G, Reynders J, Negron C, Steinbrecher T, Mornet E. Large-scale in vitro functional testing and novel variant scoring via protein modeling provide insights into alkaline phosphatase activity in hypophosphatasia. Hum Mutat. 2020;41(7):1250-62.
8. Silva I, Castelão W, Mateus M, Branco JC. Childhood hypophosphatasia with myopathy: clinical report with recent update. Acta Reumatol Port. 2012;37(1):92-6.
9. Genest F, Claußen L, Rak D, Seefried L. Bone mineral density and fracture risk in adult patients with hypophosphatasia. Osteoporos Int. 2020;32(2):377-85.
10. Briot K, Roux C. Adult hypophosphatasia. Arch Pediatr. 2017;24 (5S2):5S71-5S73.
11. Salles JP. Hypophosphatasia: biological and clinical aspects, avenues for therapy. Clin Biochem Rev. 2020;41(1):13-27.
12. Simon S, Resch H. Treatment of hypophosphatasia. Wien Med Wochenschr. 2020;170(5-6):112-5.
13. U.S. Food and Drug Administration. Advancing Health through Innovation: New Drug Approvals 2020. Published 2021. Available at: https://fda.report/media/144982/final+FINAL+NewDrugsApprovalReport_Final2020_210108_0948_FINAL.pdf. Accessed April 22, 2024.
14. Whyte MP. Hypophosphatasia: an overview for 2017. Bone. 2017;102:15-25.
15. Fanous N, Barb D. Adult hypophosphatasia manifests in a marathon runner. BMJ Case Rep. 2020;13(9):e234764.
16. Choida V, Bubbear JS. Update on the management of hypophosphatasia. Ther Adv Musculoskelet Dis. 2019;11:1759720X19863997.
17. Simon S, Resch H, Klaushofer K, Roschger P, Zwerina J, Kocijan R. Hypophosphatasia: from diagnosis to treatment. Curr Rheumatol Rep. 2018;20(11):69.

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