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Case Report ACCR-2019-0143

ADULT-ONSET HYPOPHOSPHATASIA: BEFORE AND AFTER TREATMENT WITH ASFOTASE ALFA

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Running Title: Asfotase Alfa Treatment in Adult

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ABSTRACT

Objective: To review the diagnosis and clinical course of a woman with hypophosphatasia who is being treated with newly approved enzyme replacement therapy, asfotase alfa.

Method: Clinical and laboratory data are presented.

Results: This is a unique report of a woman with debilitating adult-onset hypophosphatasia who was successfully diagnosed with low alkaline phosphatase (ALP) levels and elevated vitamin B_6 levels. Treatment with asfotase alfa resolved her chronic bony pain symptoms and quadrupled her daily pedometer step count. Furthermore, whole body scans before and after treatment showed less focal uptake overall, suggesting fracture healing after enzyme replacement therapy.

Conclusion: Improvement in patient reported symptoms, daily pedometer count, and whole body scans was noted after treatment of adult-onset hypophosphatasia with asfotase alfa enzyme replacement therapy. The significance of increased ALP levels after treatment is currently unknown.

Abbreviations:

ALP = alkaline phosphatase; **TNSALP =** tissue-nonspecific alkaline phosphatase; **FDA =**

Federal Drug Administration; **GFR =** glomerular filtration rate; **DEXA =** dual energy x-ray absorptiometry; **PTH =** parathyroid hormone; **SPECT =** single photon emission computerized tomography.

INTRODUCTION

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Hypophosphatasia is a rare inherited bone disease resulting from mutations in the *ALPL* gene that encodes tissue-nonspecific alkaline phosphatase (TNSALP), an enzyme predominant in the skeleton, liver, kidney and development of teeth.[1] Diminished enzymatic activity of TNSALP results in accumulation of its substrates, including pyridoxal 5'-phosphate (a derivative of vitamin B_6), phosphoethanolamine, and inorganic pyrophosphate, an inhibitor of bone mineralization.[2]

There are six forms of the disease based on age of onset and severity: perinatal, infantile, childhood, adult, benign prenatal and odontohypophosphatasia. Estimating prevalence of the adult form has been increasingly difficult due to low rates of diagnosis and variability in clinical manifestations.[3] The adult form typically presents during middle age and is characterized by bone hypomineralization, debilitating bone pain, recurrent non-healing metatarsal stress fractures, and poor dentition.[2] Lab studies reveal low ALP levels, elevated vitamin B_6 levels and elevated inorganic pyrophosphate.[1] Numerous gene mutations related to the disease have been discovered, requiring astute suspicion of this disease in the appropriate clinical setting.[4] Furthermore, each subtype of hypophosphatasia has a variety of manifestations and unique clinical courses, making the development of a successful treatment challenging.

In October 2015, the Federal Drug Administration approved a bone-targeted recombinant TNSALP, asfotase alfa, for use as enzyme replacement therapy for the treatment of perinatal and infantile forms of hypophosphatasia.[1] The clinical trials for the medication were based only on the perinatal and infantile forms of hypophosphatasia, therefore the

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feasibility and efficacy in the other types, including adult-onset, remain unclear at this time.[1] The long-term effects of the medication and resultant elevation of alkaline phosphatase expression are currently unknown.

Few case reports have been published regarding use of asfotase alfa in adults due to the recent FDA approval of the drug. Freitas et al published a case report in 2018 describing the clinical success of using asfotase alfa to treat a 36-year-old male with initially misdiagnosed hypophosphatasia. After 12 months of treatment with asfotase alfa, the patient had improved or stabilized findings on high-resolution peripheral quantitative computed tomography and bone mineral density, as well as improved quality of life.[4] Klidaras et al published two clinical cases wherein asfotase alfa improved fracture healing, clinically and radiographically, in adults with hypophosphatasia.[5]

We present a unique case of adult-onset hypophosphatasia treated with asfotase alfa resulting in improvements on whole body scan and daily pedometer step counts after treatment.

CASE REPORT

In 2014, a 52-year-old female with a history of hypertension, chronic pain and osteoarthritis of hips, knees and spine presented with 10 years of bony pain, poor balance, falls, fractures and recent dental disease of premature tooth loss. She had history of multiple low-trauma fragility fractures including ribs, metatarsals, and an ankle fracture. Pertinent physical exam findings included tenderness of long bones and waddling gait

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with the use of ski poles as assistive walking devices. Blood examination was remarkable for low ALP at 11 U/L (normal 35-120 U/L) and low bone-specific ALP of 3 ug/L (normal 7.0-22.4 ug/L). Without the use of vitamin supplements, Vitamin B_6 level was significantly elevated at greater than 2000 nmol/L (normal 20.0-125.0 nmol/L). Calcium level was 9.8 mg/dL (normal 8.5-10.1 mg/dL) and serum phosphorus was elevated at 5.2 mg/dL (normal 2.3-4.6 mg/dL). Intact parathyroid hormone level was elevated at 114.1 pg/mL (normal 18.5-88.0 pg/mL), with known diagnosis of chronic kidney disease, GFR 27 mL/min (normal >60 mL/min). Her 24-hour urine calcium, 25-OH vitamin D, serum protein electrophoresis, celiac screening test and thyroid hormone studies were all normal. Serum non-fasting N-telopeptide level was elevated at 25.9 nM (normal 6.2 to 19.0 nM). SPECT technetium whole body scan demonstrated increased uptake with multiple fractures of the axial skeleton and proximal femurs, imaging consistent with oncogenic osteomalacia. Due to these imaging findings concerning for oncogenic osteomalacia, further work-up included fibroblast growth factor 23 and indium 111 octreotide scan both resulting without evidence of tumor. DEXA scan showed osteopenia of the left hip and right forearm. Thus, the diagnosis of adult-onset hypophosphatasia was made.

Initially, due to lack of other treatment options at the time and with the hope of lowering bone loss rate to prevent further fractures, she was treated with denosumab. After receiving just three injections, she developed a new atypical femur fracture requiring surgical rod placement; subsequently, denosumab was discontinued.

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In April 2017, she was started on off-label use of asfotase alfa at a dose of 1 mg/kg three times weekly subcutaneously. The off-label use of the medication was justified by the patient's deterioration and the desire for treatment. Furthermore, some of her symptoms, including tooth decay, had begun in childhood, however the majority became pronounced as an adult. Within six months of initiation, the patient noted significant improvements in balance, endurance, and bone pain. Prior to treatment, the patient required an assistive device to walk a maximum of 3000 steps per day. After 10 months of treatment with asfotase alfa, she was able to walk 10,000 to 15,000 steps per day counted by her FitBit and play golf. She had a repeat whole body scan in October 2017 showing less focal uptake overall, consistent with healing fractures. Furthermore, as expected, her ALP level increased to 3140 U/L (normal 35-120 U/L) and bone specific ALP increased to 881.7 ug/L (normal 7.0-22.4 ug/L). Unfortunately, the patient's lab was not able to perform the pyridoxal-5-phosphate level after treatment.

DISCUSSION

Hypophosphatasia is a group of rare inherited systemic diseases that cause debilitating manifestations that appear at varying ages and progress over time. Studies have shown that there is a high burden of symptoms and poor overall quality of life among adults with hypophosphatasia.[3] Unfortunately, due to the low prevalence of disease and lack of awareness, hypophosphatasia is often misdiagnosed as other more common rheumatologic or bone related diseases.

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This case report provides insight into the clinical evaluation of osseous symptoms and highlights the importance of a broad differential diagnosis that includes hypophosphatasia. Diagnostic evaluation should be completed with a thorough history and physical exam along with laboratory studies including ALP, vitamin B_6, calcium, phosphorus and PTH levels. In this case report, the evaluation for oncogenic osteomalacia was undertaken due to the SPECT technetium whole body scan findings, however the scan should have stated that the findings were consistent with osteomalacia; further work-up for oncogenic osteomalacia was unnecessary in the absence of hypophosphatemia. Increased awareness among providers regarding this unique condition will improve disease recognition and avoid improper or delayed diagnoses that could lead to decreased quality of life for patients.

In an attempt to improve our patient's symptoms, she was briefly treated with densoumab; however antiresorptive medications should not be used to treat hypophosphatasia. The treatment of adult-onset hypophosphatasia with asfotase alfa, as presented in this case report, resulted in significant improvements in the patient's subjective symptoms as well as measurable markers of improvement such as imaging and pedometer step counts. Her initial bone scan demonstrated multiple fractures of the axial skeleton and proximal femurs. After just 6 months of enzyme replacement therapy, her bone scan showed less focal uptake overall, correlating with healing fractures. Furthermore, over the same short time period, the patient went from minimal walking with an assistive device to five times the amount of pedometer recorded steps with out

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the use of a supporting assistive device. This unique case exhibits quantifiable improvement in quality of life based on the increased pedometer reading data.

These positive results after treatment are promising for future management of this debilitating disease with use of asfotase alfa. Unfortunately, the long-term risks associated with asfotase alfa treatment are unclear. Additionally, the elevation of alkaline phosphatase levels after treatment with asfotase alfa has unknown long term clinical significance on bone health.

As demonstrated in the clinical case above, asfotase alfa provides significant clinical benefits to patients diagnosed with adult-onset hypophosphatasia, a rare disease with few clinical studies and treatment options. However it is important to note that this is a singular case report of one patient's experience with the use of this medication. Furthermore, a limitation of this case report is that the improvement on bone scan imaging could be due to time-dependent effect of fracture healing, regardless of enzyme replacement therapy. However, this case still highlights important possible future endeavors with this enzyme replacement therapy.

CONCLUSION

We present a distinctive case of adult-onset hypophosphatasia with clinical proof of improvement after treatment with asfotase alfa based on an increased daily step count and improved findings on whole body scan. Asfotase alfa is a newly approved enzyme replacement therapy for hypophosphatasia and therefore long-term outcomes are not yet

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available. However, short-term patient reported subjective findings and clinical data are reassuring for benefits of treatment with this medication. Increased awareness of the disease process will prevent misdiagnosis and inappropriate treatments, thereby preventing complications such as fractures, loss of teeth, chondrocalcinosis and arthritis while improving the overall quality of life.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

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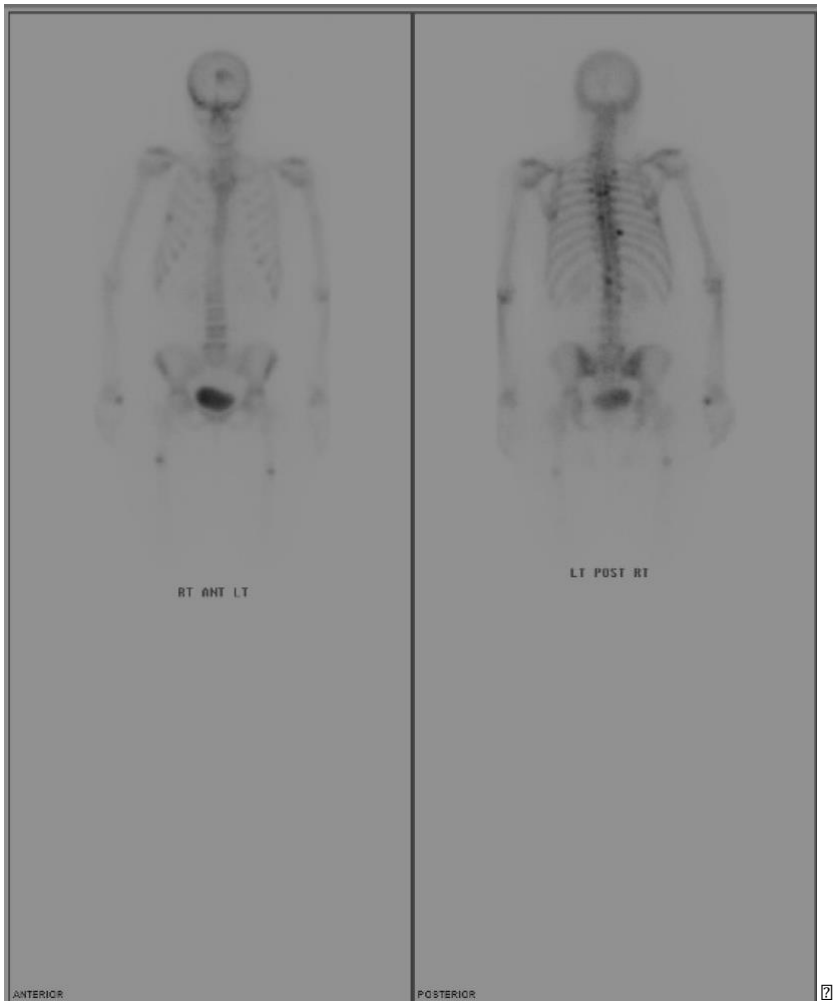

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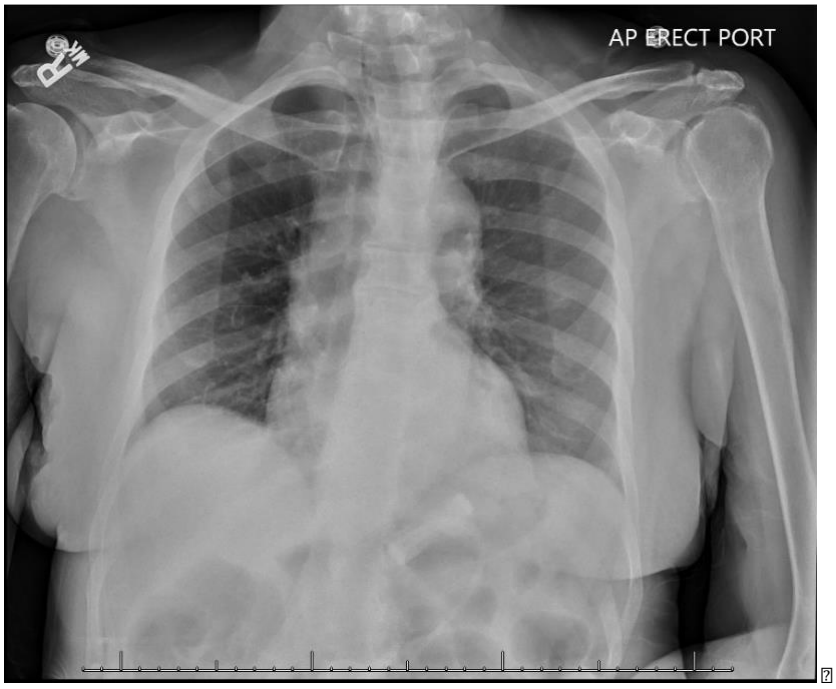

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