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Disproportionate Weakness in Hypophosphatasia Unmasking COL6-Related Muscular Dystrophy: A Case Report

Han-Byeol Choi, M.D.[1], So Jin Kwak, M.D.[1], Duk Hyun Sung, M.D., Ph.D[1], Yoon-Sok Chung, M.D., Ph.D.[2], Yu Jin Im, M.D.[1]

[1]Department of Physical Medicine and Rehabilitation, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea
[2]Departments of Endocrinology and Metabolism, Ajou University Medical Center, Ajou University School of Medicine, Suwon, South Korea

Introduction

- Hypophosphatasia (HPP) is an inherited metabolic disorder caused by loss-of-function variants in the *ALPL* gene, encoding tissue-nonspecific alkaline phosphatase (ALP).
- Beyond skeletal and dental manifestations, proximal muscle weakness and waddling gait have been reported.
- Still, weakness is generally mild, and significant structural muscle pathology is not characteristic.
- Here, we report a case of confirmed HPP presenting with severe progressive proximal muscle weakness, in whom further evaluation revealed a concurrent diagnosis of COL6-related muscular dystrophy (COL6-RD).

Case report

- A 48-year-old premenopausal woman presented with progressive bilateral lower extremity weakness over 20 years—initially difficulty rising from the floor, progressing to requiring hand assistance and bilateral single canes by her early forties.
- She also recalled difficulty running since childhood and early loss of two permanent teeth at age 32.
- Despite no childhood fracture history, she sustained multiple low-trauma fractures in her forties, including the patella, ribs, fibula, and coccygeal bones (Fig. 1).
- Family history was unremarkable.
- Physical examination revealed symmetric proximal girdle muscle weakness (Table 1), waddling gait with excessive lumbar lordosis, intact sensation, bilateral 20-degree ankle flexion contractures, and restricted passive shoulder range of motion.
- Laboratory findings showed persistently low serum ALP (25U/L) and mildly elevated creatine kinase (277IU/L).
- Nerve conduction studies were normal.
- Needle electromyography showed myopathic motor unit action potentials and early recruitment without abnormal spontaneous activity.
- Muscle ultrasonography demonstrated Heckmatt grade 4 echogenicity in the bilateral rectus femoris, biceps brachii, and tibialis anterior.
- HPP was confirmed by *ALPL* gene analysis, identifying a heterozygous likely pathogenic variant, c.1559delT, based on recurrent low-trauma fractures, early tooth loss, and low ALP.
- However, the degree of proximal weakness and fatty muscle degeneration was disproportionate to HPP alone.
- Lower extremity MRI showed characteristic signatures of COL6-RD (Fig. 2), and re-examination revealed additional consistent phenotypic features: a keloid scar on the right hand dorsum, keratosis pilaris on all four extremities, contracture of the distal interphalangeal joints of the fingers, and paradoxical hyperlaxity of the proximal interphalangeal joints.
- *COL6A2* gene testing identified a homozygous intronic variant, c.1771-18_1771-3del, confirming the co-diagnosis.
- Family genetic testing of the proband's son (aged 20) and daughter (aged 16) revealed a heterozygous *COL6A2* variant in both, consistent with carrier status.
- The daughter also carried the *ALPL* variant and was subsequently diagnosed with HPP (Table 1).

Table 1. Summary of clinical characteristics

	Case 1 (Proband)	Case 2 (Daughter)
Age (years)	48	16
Sex	F	F
TALP (U/L)	25	36
PLP (ug/L)	231	60
BMD (g/cm^2), Z-Score	NA	1.093, 0.1
Fractures	Yes (Patella, Ribs, fibula, coccyx)	Yes (Wrist, Ankle)
Teeth Loss	Yes (multiple)	No
Muscle Weakness (MRC scale)	Symmetric proximal girdle muscle weakness (both: grade 2 to 4)	No (all grade 5)
Phenotypic features of COL6-related muscular dystrophy	Yes	No
6-Minute-Walk Test (meter)	NA	422 (62.74% of normal range)
Medications (Treatment)	Calcium + Vitamin D (Conservative)	Calcium + Vitamin D (Efzimfotase alfa clinical trial)

TALP: total alkaline phosphatase (reference range: adult 35~104, adolescent 60~300).
PLP: pyridoxal-5-phosphate (reference range 5~50).
BMD: bone mineral density (Lumbar spine 1~4).
MRC scale: Medical Research Council scale.
DIP joints: distal interphalangeal joints.
PIP: proximal interphalangeal joints.
NA: Not applicable (not tested).

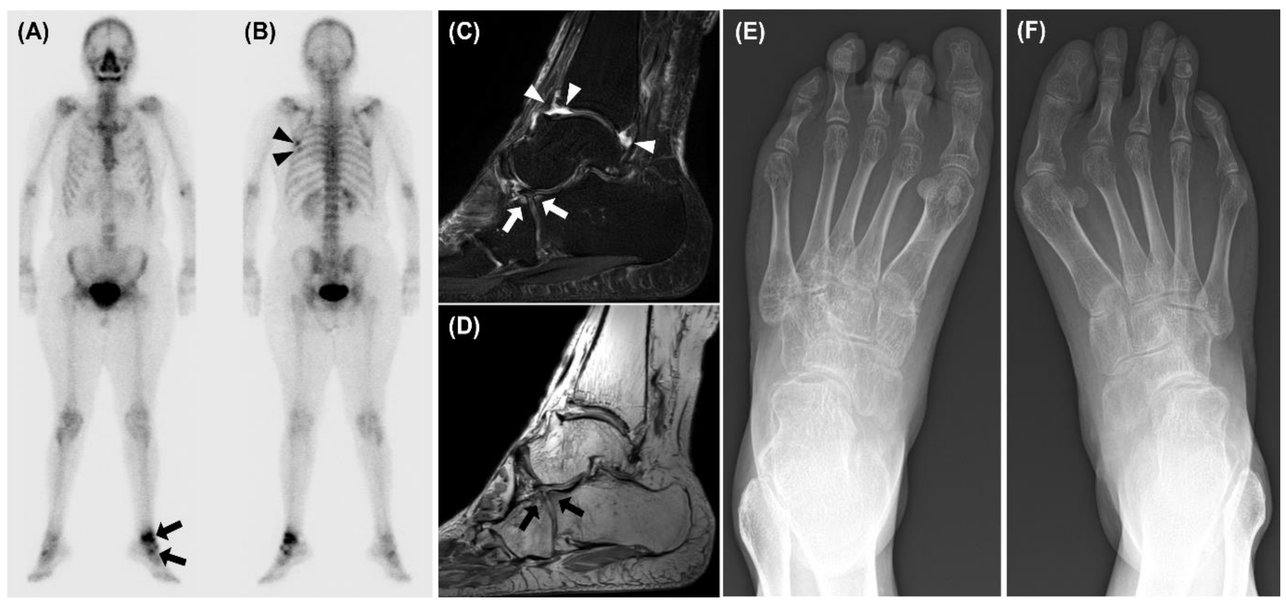

Figure 1. Skeletal imaging findings in Case (proband).
(A, B) Tc-99m bone scintigraphy in anterior (A) and posterior (B) views demonstrates focal increased radiotracer uptake in the posterior arc of the left 5th and 6th ribs (arrowheads), suggestive of fractures, and in the left ankle and tarsal bones (arrows), indicating possible joint pathology or occult fractures.
(C, D) Sagittal T2-weighted fat-suppressed (C) and T1-weighted (D) MRI images of the left ankle reveal arthritis of the talocrural joint (arrowheads) and bone marrow edema in the superior aspect of the calcaneocuboid joint (arrows), indicating joint pathology. These findings correspond to the areas of increased uptake observed on bone scintigraphy. (E, F) Plain radiographs of both feet show no definite evidence of metatarsal fractures.

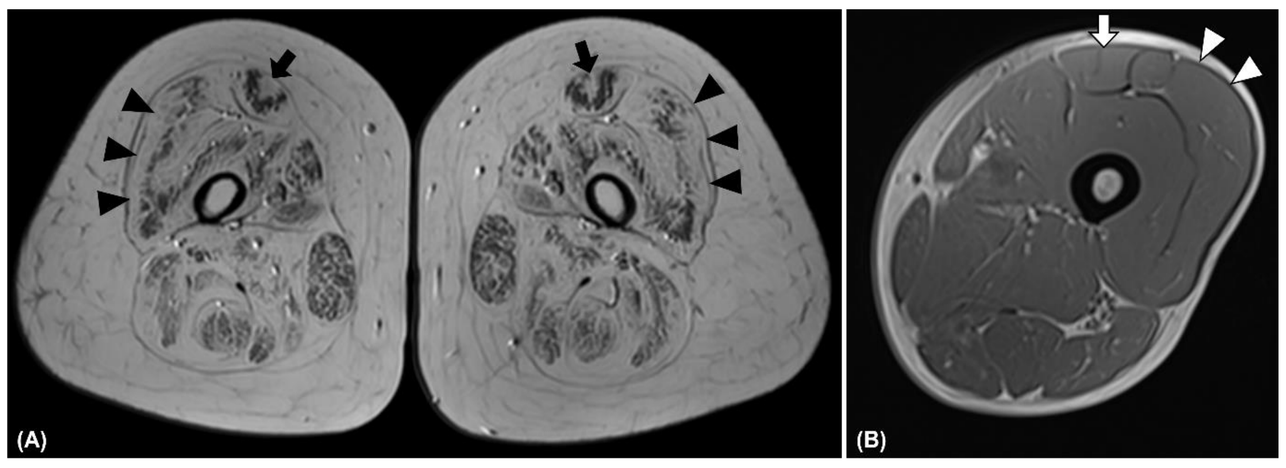

Figure 2. Lower extremity MRI findings of Case (proband).
(A) T1-weighted axial images demonstrate severe fatty infiltration of the thigh muscles. There is centrally predominant involvement of the rectus femoris (arrows) and peripherally predominant involvement of the vastus lateralis (arrowheads), consistent with the characteristic pattern of COL6-related muscular dystrophy. (B) Normal T1-weighted axial image of the left thigh for comparison, showing preserved muscle architecture without fatty infiltration (arrow: rectus femoris; arrowheads: vastus lateralis).

Conclusion

- This case describes a rare dual genetic diagnosis of HPP and COL6-RD.
- Although low-trauma fractures and low ALP initially attributed her gait disturbance to HPP, the severity of proximal weakness and the specific pattern of fatty infiltration on MRI prompted identification of a coexisting structural myopathy.
- Weakness exceeding what HPP alone would explain should raise suspicion for a concurrent neuromuscular disorder.