Adult presentation of hypophosphatasia due to a novel compound heterozygous Tissue Nonspecific Alkaline Phosphatase (ALPL) mutation

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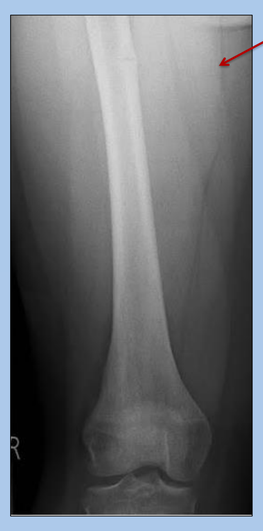
Hypophosphatasia is a rare, and sometimes fatal, genetic metabolic bone disease.

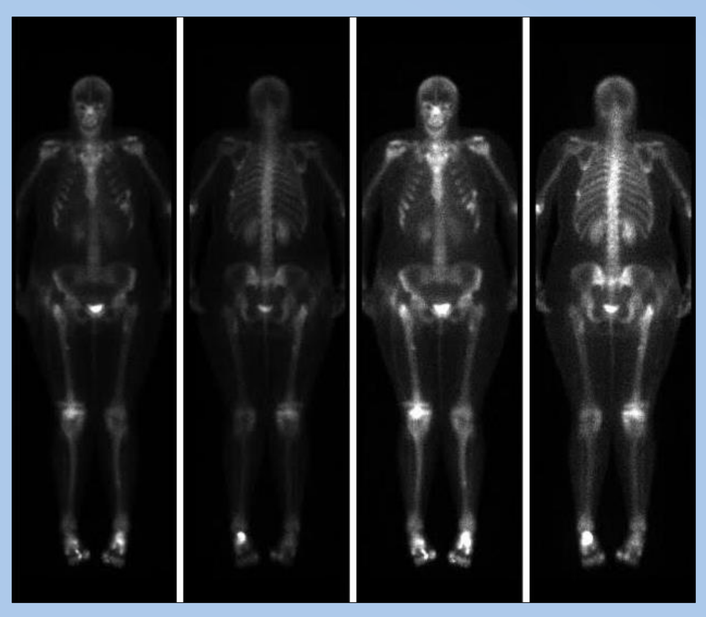
A 27 year old woman with no significant family history presented with atraumatic foot pain.

X-ray's suggestive of healing metatarsal stress fractures with a normal DEXA scan. She was referred to the bone clinic for opinion.

No prior skeletal, joint or dental problems. At time of review complained of right thigh pain.



Plain x-ray revealed right femoral shaft fracture



NM scan : multiple stress fractures

Biochemical analysis demonstrated undetectable serum alkaline phosphatase (ALP) activity, consistent with diagnosis of hypophosphatasia.

Genetic analysis revealed a novel compound heterozygote *ALPL* mutation (p.Tyr101*;Ala176Thr).

The patient required fracture fixation and physiotherapy. She is currently receiving teriparitide with some improvement in pain.

What is hypophosphatasia?

Hypophosphatasia is an autosomal dominant or recessive inborn error of metabolism. Adult hypophosphatasia typically presents in middle age with loss of adult dentition, or recurrent non-healing metatarsal fractures.

Hypophsphatasia is characterised by low ALP activity due to loss of function mutation of *ALPL* gene, encoding for tissue non-specific ALP (TNSALP)

Inorganic pyrophosphate accumulates extracellularly and impairs skeletal mineralisation resulting in fractures.

Treatment is challenging. Teriparitide is reported to stimulate osteoblast synthesis of TNSALP resulting in reduced pain and potential fracture healing[2].

Enzyme replacement therapy with **asfostase alfa** has been approved for paediatric onset hypophosphatase but with limited evidence for adult use.

Key Learning Points

- Hypophosphatasia is a clinical diagnosis with radiographic evidence of fractures and low serum ALP.
- All subtypes have genetic mutations in TNSALP gene.
- Treatment is challenging, options are limited namely aimed at symptom control and fracture prevention.

References:
1. M.Whyte et al, JCEM 92(4):1203-1208

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