An Adult With a Very Low Alkaline Phosphatase

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- 57 y/o male with a hyperlipidemia and hypogonadism
- Alkaline phosphatase of <10 u/l on routine lab

What could this mean?
1. Extremely low liver fat
2. Just another lab error
3. At least it wasn’t high
4. Hypophosphatasia
History follows:

Teeth
- Lost 8 top and bottom front teeth at 18 months. No new front teeth until 8 y/o.
- 10–15 tooth abscesses, requiring root canals and caps. First age 16–17
- Cadaveric bone placed in his gums twice as an adult, the first time at age 40

Bones
- Fractured 5th metacarpals and coccyx between the ages of 8–11 year old with minor trauma. In his 40’s, broke his right 5th metatarsal with minor trauma and three metatarsals on the right (one twice), two metatarsals and a sesamoid bone on the left and two left metacarpals.
- In 2016, a stress fracture left 2nd metatarsal present ~3 years – non-healing and persistent pain in this area.
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Gait and Joints
- Hasn’t jogged for 10 years due to knee pain—limp favoring the R leg
- As a child, he was told that he ran “funny” and, had limited motion in wrists, ankles, and feet—limited range of motion in his hips and neck

Biochemical
- He has had a chronically low alkaline phosphatase (<10 u/L)
- In 12/15, the diagnosis of juvenile onset hypophosphatasia was considered and his relevant labs showed the following:
  - Pyridoxal 5-Phosphate 361 mcg/L (nl 5–50)
  - Phosphoethanolamine 301 nmol/mg Cr (nl <48)
  - Vitamin B6 >400 (nl 20–125)
  - PTH, Ca++, Phos, 25-D, Mg++, Cr all normal

- Hypophosphatasia diagnosed
Family History

- Mother—false teeth “early in life”
- Sister—“known dental issues”
- Brother—“lots of dental bridge work in his 30’s for unknown reasons
- Daughter—scoliosis, 5th metatarsal fracture
Hypophosphatasia

- Rare (~1 case per 100,000 live births)
- Caused by mutations in the gene encoding tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP)
- Leading to low alkaline phosphatase activity levels which in the severe form may lead to rickets, osteomalacia, or both
- TNSALP cleaves phosphate-containing substrates
- Males/females are equally affected
- Clinical presentation from death in utero to cases in which pathologic fractures first present in adulthood.
High extracellular levels of inorganic pyrophosphate block hydroxyapatite crystal growth and may lead to decreased mineralization.
The most severe forms of the disease have an autosomal recessive mode of inheritance.
  ◦ Analysis of the *TNSALP* gene aids prenatal diagnosis.

Compound heterozygosity and autosomal dominant mutations in the *TNSALP* gene may cause childhood and adult hypophosphatasia.
At least 6 clinical forms of hypophosphatasia have been reported
  ◦ Less severe form may be missed for years, until a radiograph is obtained for chronic pain or a pathological fracture.

The types include:
  ◦ Perinatal (lethal)
  ◦ Infantile
  ◦ Childhood
  ◦ Adult– may have had signs of the disease earlier in life
  ◦ Odontohypophosphatasia (no clinical changes in long bones are present, only biochemical and dental manifestations)
  ◦ Pseudohypophosphatasia.
    • Clinically indistinguishable from infantile hypophosphatasia, but serum alkaline phosphatase (ALP) activity is normal
**Adult Form**

- Adult form presents with signs and symptoms during middle age.
  - Premature loss of deciduous teeth due to disturbed cementum formation is common.
  - Mineralization of dentin less likely to influence by the inhibitory action of pyrophosphate than mineralization of cementum

- Diagnosis often made after a low alkaline phosphatase level detected during routine blood work, or when tested after a direct family member was diagnosed with the condition

- Adults may also have a history of foot pain due to stress fractures and joint pain due to deposition of calcium pyrophosphate dihydrate

- Affected adults may manifest osteomalacia, with slowly healing or nonunion stress fractures (commonly metatarsal) and proximal femur pseudofractures.
Low alkaline phosphatase levels

- Measure calcium, phosphorus, magnesium, creatinine, parathyroid hormone (PTH), 25(OH) vitamin D, and 1,25(OH)2 vitamin D.
- Levels of PLP, PPi in plasma, and PEA in urine determine the diagnosis.
  - Patient's intake of vitamins (particularly vitamin B-6) may affect results.
In lethal cases, there is frequently a near absence of skeletal mineralization. Fractures and rachitic changes are often present.

- Pseudo-fractures--hallmarks of hypophosphatasia in adults.
- Increased incidence of poorly healing stress fractures, especially of the metatarsals
- Renal ultrasound may reveal nephrocalcinosis.
Bisphosphonates contra-indicated and teriparatide results inconsistent

The FDA approved asfotase alfa (Strensiq) in 2015 as the first therapy for hypophosphatasia
  ◦ Recombinant, fusion protein comprising the TNSALP ectodomain, the constant region of the human IgG1 Fc domain, and a terminal deca-aspartate motif for bone targeting

Asfotase Alfa is a tissue nonspecific alkaline phosphatase indicated for the treatment of patients with perinatal/infantile- and juvenile-onset hypophosphatasia
Approval–4 prospective, open–label studies–99 patients dx’d with hypophosphatasia in utero, as an infant, or as a juvenile.

- Received the drug up to 6.5 years.
- Patients with either perinatal or infant onset of the disease showed improvement in overall survival, as well as ventilator–free survival.
- 97% receiving the drug were alive at age 1 year compared with 42% of control patients. Ventilator–free survival rates for both groups– same pattern
- Patients with juvenile–onset hypophosphatasia also experienced improved growth and bone health compared with patients in a natural history database.

Given 6–8 months of Forteo in early 2016 without clear bone healing benefit and no change in alkaline phosphatase

Started Asfotase alfa on 12/24/16

Since then, his feet and ankle pains and knee with ambulation have improved 90%

Labs: Alkaline Phosphatase: >6000 (U/L) (04/25/2017) with a normal Ca++ and Cr
Before Rx 1/17

On Rx 7/17