CLINICAL VIGNETTE

Osteoporosis and Celiac Disease

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A 67-year-old man presented with a history of right-sided knee pain and swelling of approximately 8 weeks duration without antecedent trauma or other explanation. MRI revealed insufficiency fractures of the weight bearing portion of the medial femoral condyle and of the non-weight bearing inner lateral femoral condyle as well as tears of the medial meniscus. DEXA revealed osteoporosis of the right femoral neck based on a t-score of -2.5 and t-scores of the remainder of the right femur, the left femur, and lumbar spine, which were otherwise compatible with osteopenia, prompting endocrinology evaluation.

Lab results included: 25-OH Vitamin D 27, 27, TSH 6.6, 4.1, Total Testosterone 451, 393 ng/dL (348-1197), Calcium 9.4, Ionized calcium 1.11, Normalized calcium1.13, Phosphorous 3.7, iPTH 71, 82, 58 (11-51 pg/mL), Alk phosphatase 12.4 mcg/L, 24 urine calcium 28 , total volume 1233 ml. Celiac panel was positive, Endomysial IgA Ab 1:160 (<1:100 positive), Transglutaminase IgA Antibody 156 (<4 U/mL), Gliadin Deamidated Ab, IgA 104.6 (<20), Gliadin Deamidated Ab, and IgG 73.3 (<20).

Gastroenterology recommended an endoscopy with duodenal biopsies to confirm for celiac disease. The patient, however, declined and chose to treat himself with a gluten-free diet.

Four months later, he returned to his primary care physician and repeat studies were as follows: iPTH 43 pg/mL and Calcium 10.1 (9.8).

Discussion

Celiac disease is an autoimmune disease, triggered in response to gluten exposure in wheat, barley, and rye, which causes villous atrophy of the intestinal mucosa accompanied by malabsorption of nutrients. Its prevalence is considered to be about 1% or slightly higher in European populations.[1] It has a marked predilection for females over males in about a 3:1 proportion. Over the last 30 years, the disease has been increasingly recognized not just in its original form presenting with diarrhea but also in atypical forms in which GI symptomatology is not classical or is not identified. Among the subclinical presentations of celiac disease is the presentation with osteoporosis and positive antibodies.

By the 1980's, the association of subclinical forms of the disease with osteoporosis was recognized and in 1999, Bottaro et al[2] characterized the manifestations of 1026 cases of subclinical celiac disease in which osteoporosis was the leading problem in only 3.6% of the adults. Subsequent studies have shown that up to 70% of untreated adults with celiac disease may have bone loss.[3] Much of the loss of bone density is thought to be due to malabsorption of vitamin D and calcium from the injured intestinal mucosa, as well as calcium malabsorption due to saponification associated with fat malabsorption and decreased intake due to associated lactase deficiency. As a consequence of these factors, secondary hyperparathyroidism and accelerated bone remodeling develop. However, there is also an inflammatory state associated with the affected intestinal mucosa, which results in an overproduction of inflammatory cytokines including IL-1, IL-6, and TNF-alpha. IL-6, in particular, is known to play a role in osteoclast recruitment and activation, and in one study baseline IL-6 levels correlated inversely with baseline Z-scores.[4] In addition, inhibitory cytokines such as IL-12 and IL-18, which are decreased in this condition, may also be playing a role since levels of these cytokines may result in a lack of inhibition of osteoclast maturation. Finally, an increase RANKL/OPG found in celiac patients may contribute to accelerating osteoclast function. In additions to these factors, there is a high frequency of hypogonadism in both male and female celiac patients, and the low sex steroid levels may be contributing to osteoporosis.

Numerous studies have looked at the relationship of celiac disease and low bone density as well as fracture rate. Unfortunately, these studies are very inconsistent and difficult to compare because of differences in inclusion criteria and differences in populations studied. Overall, it seems that there is a questionable decrease in bone density and a clearer but nonetheless small increase in fracture rate associated with celiac disease. One study found that a Z-score below -1 was more prevalent in patients who had secondary hyperparathyroidism than those who did not, but there was a wide range of scores in both the euparathyroid and hyperparathyroid group.[5] The scores in these groups overlapped. In a widely cited meta-analysis, individuals with celiac disease were 1.92 more likely to have sustained a fracture at some point in their lives than those who did not have celiac disease.[6] Another review, reported the prevalence of peripheral skeletal fractures was 25% in patients compared to 8% in controls.[7] The same paper included a cohort study of more than 13,000 patients and indicated an increased risk of hip fracture with a hazard ratio of 2.1. Another population-based cohort study also found an increase in fracture (30% any fracture, 90% hip fracture, 77% wrist fracture).[8] However, the absolute increase in fracture rate was very small (3.19 per

1000 patient years for any fracture and 0.97 per 1000 patient years for hip fracture in those over 45 years).

A recent paper examined the microarchitecture measures of skeletal strength in premenopausal celiac patients compared to controls.[9] The patients had lower trabecular density and fewer more widely and irregularly spaced trabeculae. Biomechanical properties of the bone were also tested by microstructure finite element analysis, which correlated with the trabecular abnormalities. Interestingly, cortical abnormalities were less consistent and did not correlate with the functional analysis.

There is a consensus that there is substantial recovery of bone density after the first year on a gluten-free diet.[10,11] However, there is less consistency about whether the bone density can return to normal or the extent of further improvement after the first year. The presence of secondary hyperparathyroidism may also be a poor prognostic indicator.[5]

What should we advise our patient who declined intestinal biopsy? Overall, if he adheres to a gluten-free diet, his prognosis is likely to be good. However in general, adherence to such a restrictive diet is difficult, and there is decreased adherence over time with many patients. In addition, he is a group less likely to respond because of his initial secondary hyperparathyroidism. However, his repeat blood tests suggest that his secondary hyperparathyroidism has resolved with treatment. He should definitely have follow up with further blood tests and with a repeat DEXA after 18 months.

The most important insights to be gained from this case include the idea that when patients present with low impact fragility fractures or have an otherwise unexplained low bone density, one should look for, among other things, celiac disease. If found, the initial intervention of choice is a gluten-free diet, not a bisphosphonate.

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Submitted July 18, 2015