Severe Osteoporosis Secondary to Idiopathic Hypogonadotrophic Hypogonadism (IHH) in a 45-Year Old Male

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Abstract

Synopsis: Male hypogonadism is an important and treatable cause of osteoporosis. Severe osteoporosis leading to multiple osteoporotic fractures from idiopathic hypogonadotrophic hypogonadism (IHH) is rare. The present case illustrates the significance of timely and thorough evaluation of young adult males presenting with a seemingly ordinary complaint of "bone pains."

The Case: I report a case of a 45 year-old male presenting with a 6-year history of progressive bone pains. Most prominent laboratory findings include low total serum testosterone (4.6 nmol/L) in the background of an inappropriately normal serum FSH, LH and sex hormone-binding globulin (SHBG). There is associated elevated urinary N-telopeptide (4x). Sperm analysis showed oligospermia. Scrotal ultrasound revealed normal-sized descended testis with no solid masses. Skeletal survey showed generalized decrease in bone density. Dual energy x-ray absorptiometry (DXA) showed severe osteoporosis. Cranial CT scan with contrast did not show a sellar-suprasellar mass.

Treatment and Outcome: The patient was diagnosed with severe osteoporosis secondary to IHH. The patient received zoledronic acid (Aclasta) 5mg IV infusion. Two months after discharge, the patient reports a significant decrease in bone pains leading to more mobility. He is scheduled for his first dose of a GnRH agonist (Leuprodin acetate 3.75mg IM) to induce testosterone production.

Discussion: The incidence of osteoporosis among males is indirectly correlated to the reduction in circulating testosterone. First-line treatment of osteoporosis in hypogonadal men is with bisphosphonates. Bisphosphonate therapy increase BMD, reduces vertebral fracture risk and is currently considered the standard of care for osteoporotic care for men.

Conclusion: Osteoporosis is fast becoming a common condition among males. Osteoporotic fractures are associated with substantial morbidity and mortality. The present case emphasizes the importance of thorough and timely evaluation among men with low BMD or low-trauma fractures, which should include laboratory assessment to exclude secondary causes such as hypogonadism.

Introduction

Osteoporosis is a frequently underestimated disease among males. There are several etiologies, including vitamin D deficiency, hyperparathyroidism, excessive alcohol consumption, glucocorticoid excess and low serum testosterone levels. Male hypogonadism is an important and treatable cause of osteoporosis.

Case Report

I report a case of a 45 year-old male presenting with a 6-year history of progressive bone pains.

a. Clinical Profile - The patient was a 45 year-old male with progressive bone pains, most prominently over the knee and hip areas, rendering the patient bed-ridden for the past 2 years. Initial work-up of this patient focused on a possible muscle dystrophy which revealed normal laboratory findings including an unremarkable muscle biopsy and negative nerve conduction test. The patient is married with 2 children and claims to have regular sexual intercourse with his wife despite his present condition. There was no note of a decrease in libido or absence of early morning erection. The patient denies previous exposure to potentially toxic chemicals or chronic intake of drugs such as anabolic steroids. The patient is non-alcoholic with no illicit drug use. There was no history of fever, recurrent sinusitis, headache, blurring of vision, and galactorrhea.

b. Physical Examination - The patient came in bed-bound with normal vital signs and does not have eunochoid proportions. The lower extremities were mildly atrophic with no note of fasciculations. He has coarse hair over the axillary and pubic areas with no note of gynecomastia. Both testicles were normal in volume while the penis has an average length in its flaccid state. There were no signs of stigmata of chronic liver disease. Neurologic examination revealed no visual field cuts.

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c. Hormonal Profile - Most prominent laboratory findings of this case include low serum total testosterone (4.6 nmol/L) in the background of an inappropriately normal serum FSH, LH and sex hormone-binding globulin (SHBG). There is associated severe hypophosphatemia, mild hypocalcemia, elevated bone-specific alkaline phosphatase (5x), and elevated urinary N-telopeptide (4x), which is a highly specific measure of increased bone resorption. Serum prolactin, TSH, cortisol, and vitamin D (62.16 nmol/L) were within normal limits. Urine calcium and phosphorus excretion were likewise normal. On further work-up of the hypogonadism, sperm analysis showed oligospermia with normal sperm motility and presence of >90% of sperms with normal morphology. Serum PSA is within normal limits.

d. Imaging Studies - Scrotal ultrasound revealed normally sized descended testis with no solid or cystic masses. KUB ultrasound showed slightly enlarged prostate gland with grade I concretions. Skeletal survey showed generalized decrease in bone density with prominent trabeculations and interspersed linear streaks of lucency in the osseous structures, indicating multiple microfractures (see Figure 1). There is decrease in the vertebral height of vertebral bodies assuming a biconcave configuration (see Figure 2).

Whole body scan revealed abnormal osteoblastic site in the proximal left femoral shaft, signifying a fracture area. Dual energy x-ray absorbiometry (DXA) showed severe osteoporosis with BMD of the spine and hips below the normal range for age and sex (T-score -4.6 for lumbar spine, -5.1 for the right femur, and -5.5 for the left femur) (see Figure 3). Cranial CT scan with contrast did not show a sellar-suprasellar mass.

e. Treatment - The left incomplete femoral neck fracture did not require any surgical intervention. Zoledronic Acid (Aclasta) 5mg IV infusion, a highly potent intravenous bisphosphonate given yearly, was subsequently administered. The patient was also started on a physical therapy program while admitted. He is currently maintained on calcium and vitamin D supplementation.

f. Follow-Up Course - Two months after discharge, the patient reports a significant decrease in bone pains leading to more mobility. He reports being able to sit down with some assistance now, a task he has not able to do for the past 2 years. He is scheduled for his first dose of a GnRH agonist (Leuprodin acetate 3.75mg IM) to be given monthly for the next 3 months, to induce testosterone production.

Discussion

Epidemiology of Male Osteoporosis and Idiopathic Hypogonadotrophic Hypogonadism (IHH)

Local data on the prevalence of osteoporosis among males is limited. Contrary to the present case, most fractures are traumatic in origin and are not caused by osteoporosis prior to the age of 50 years. However, consistent with our patient, the location of osteoporotic fragility fractures is most commonly at the femoral neck and vertebra. Secondary causes for osteoporosis are more common in men than in women. Idiopathic hypogonadotrophic hypogonadism (IHH) is a
heterogenous disorder with a prevalence of approximately 1 in 10,000.4 Severe osteoporosis develops among these patients because the testosterone-mediated increase in bone density of adolescence fails to occur. Only a limited number of reports in the past implicated hypogonadism as the underlying cause of previously undiagnosed osteoporosis among young males presenting as vertebral or spine fractures (12,9).

Relationship of Osteoporosis and Male Hypogonadism

The incidence of osteoporosis among males is indirectly correlated to the reduction in circulating testosterone. Maintenance of bone integrity depends on the action of testosterone which promotes proliferation and differentiation of osteoblasts as well as inhibits osteoclast activity.5 In vitro studies showed that testosterone not only inhibits the activity of isolated osteoclasts but also inhibits the production of interleukin-6 (IL-6), which is a cytokine that promotes resorption in bone marrow stromal and mature osteoblastic cells.6,7 Importantly, testosterone deficiency is associated with deterioration of trabecular architecture as determined by micro-Magnetic Resonance Imaging (MRI).8 This microarchitectural change would be expected to reduce the mechanical strength and increase fracture risk. However, the direct effect of testosterone is likely 25% of its effectiveness whereas its aromatization to estrogen contributes to the remaining 75%.8,9 This was supported by studies showing virilized men with osteoporosis who were found to have mutation in the estrogen receptor gene.10

Diagnostic Approach to Osteoporosis in Men

The International Society for Clinical Densitometry (ISCD) currently recommends the use of a BMD T-score of -2.5 or below to diagnose osteoporosis in men.11 Severe osteoporosis occurs when osteoporotic fractures are present.12 Further laboratory evaluation is indicated to evaluate for potential secondary causes of bone loss. As in this case, serum 25OHD, TSH, PTH, PSA, and M-protein electrophoresis were all within normal limits. Measurement of skeletal turnover markers such as serum bone-specific alkaline phosphatase and urine N-telopeptide of type 1 collagen is not only important to document active bone formation and resorption respectively but also to monitor response to treatment. With the only significant finding of low total testosterone on the background of normal LH, FSH and SHBG, clinically inapparent hypogonadism seems the likely diagnosis. Furthermore, when no clinically evident causes of hypogonadism are noted and the laboratory and imaging evaluation is unrevealing, the diagnosis of idiopathic hypogonadism is appropriate.

Therapeutic Options

Therapies targeting osteoporosis work either by inhibiting bone resorption or by stimulating new bone formation. First-line treatment of osteoporosis in hypogonadal men is with bisphosphonates.13 Bisphosphonate therapy increase BMD, reduces vertebral fracture risk and is currently considered the standard of care for osteoporotic care for men. Zoledronic acid (Aclasta) is a highly potent, once-a-year bisphosphonate administered through the intravenous route. This was the choice for this patient to ensure compliance with the treatment and to avoid the unwanted gastric side effects of oral bisphosphonates since the patient is mostly bed-ridden.

Testosterone replacement therapy may be beneficial because of its action on osteoblast proliferation and osteoclast inhibition. The use of testosterone-replacement therapy for the prevention and treatment of male osteoporosis remains controversial but likely to benefit osteoporotic men with evident hypogonadism such as patients with Kallman Syndrome.14,15 No randomized study exists comparing the effects of different modes of testosterone replacement on bone mineral density (BMD). In primary hypogonadal men, the BMD responds dose dependently to testosterone substitution, whereas in secondary hypogonadism only testosterone enanthate treatment significantly increased the BMD.16

Conclusion

Osteoporosis is fast becoming a common condition among males. Osteoporotic fractures are associated with substantial morbidity and mortality. Since consequent changes due to decreasing testosterone among males are more subtle than among females during menopause, this often leads to delay and neglect of diagnosis. Thus, the need to identify and screen men at a particular risk for osteoporosis has become important. The present case emphasizes the importance of thorough and timely evaluation among men with low BMD or low-trauma fractures, which should include laboratory assessment to exclude secondary causes such as hypogonadism.

References

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