
66-year-old man with hypogonadism

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History of Present Illness

- **History of alcoholic and HCV-related cirrhosis**
- **Orthotopic liver transplant in 1997**
- **Repeat OLT in 2002 for recurrent HCV-related cirrhosis with early evidence of recurrent hepatitis C activity in second graft s/p treatment with pegylated interferon and ribavirin**
- **Presented to Endocrine clinic for opinion regarding fullness in left breast and testosterone levels**

HPI continued

- **Fullness in his left breast**
 - first noticed 6 - 8 months ago with tenderness, no erythema, no milky discharge
 - Evaluation included ultrasound and breast biopsy with report of gynecomastia with no other abnormalities
- **Other symptoms**
 - In the last year he has noticed decreased body hair and that he used to be able to "twist" the hair in his axilla and now there is none
 - He no longer has to shave daily
 - Decreased libido
 - Muscles tiring more easily, can't walk dogs uphill like he used to
 - Feeling sad more often, watching Law and Order reruns all the time

HPI continued

- **One year ago fractured his left first metatarsal while walking down the stairs, missed one stair**
 - PCP ordered BMD: T-score of -3.4 in the spine and -1.9 in the hip
 - Started alendronate, cholecalciferol and calcium
- **With gynecomastia, ordered labs**
 - total testosterone 391 ng/dL (250-1100)
 - free testosterone 17.3 pg/mL (46-224.0)
 - LH 58.22 mIU/mL (adult male ref range 1.7-8.6)
 - FSH 29.70 mIU/mL (adult male ref range 1.50-12.4)

History

■ Past Medical History

- EtOH and HCV-related cirrhosis s/p OLT in 1997 and again in 2002 now with chronic rejection
- Hypothyroidism
- Stage III Chronic Renal Insufficiency (GFR 38 – 44)
- Non-traumatic fracture of metatarsal
- Osteoporosis
- No history of radiation exposure
- H/o basal cell carcinoma

■ Past Surgical History

- R bicep tendon repair, 1990s
- OLT 1997, 2002
- Right knee total arthroplasty 2010

■ Family History

- Negative for breast cancer
- Mother deceased at age 94 years from CHF
- Father deceased at age 90 years from colon cancer
- Brother deceased at age 48 years in motor vehicle collision

■ Social History

- Single
- Report of fathering a child in the past that was adopted, unclear of paternity
- Never smoker
- History of alcohol abuse/dependence, none now
- Illicits: none
- Not currently sexually active

Medications and Allergies

■ Medications

□ Current

- Tacrolimus 1 mg BID
- Sirolimus 1 mg daily
- Imiquimod 5% cream
- Levothyroxine 100 mcg daily
- Tamsulosin 0.4 mg daily
- Tadalafil 20 mg prn
- Calcium 600 mg BID
- Vit D3 400 IU BID

□ Relevant Past

- Prednisone
- Pegylated interferon
- ribavirin

■ Allergies

- Celecoxib , rash
- Meperidine, rash
- Midazolam, cannot recall
- Tetracycline, rash

Review of Systems

General: **Occasional night sweats** Negative for fevers, chills, night sweats, weight change, heat/cold intolerance

HEENT: Negative for headache, blurry vision, double vision, tinnitus, sore throat, rhinorrhea

Neck: Negative for masses, limited movement

Respiratory: Negative for cough, wheezing

Cardiovascular: Negative for chest pain, shortness of breath, palpitation, lightheadedness

Gastrointestinal: Negative for abdominal pain, nausea, vomiting, diarrhea, constipation

Genitourinary: Negative for dysuria, hematuria

Skin: Per HPI; Negative for diaphoresis, new rash

Muskuloskeletal: Negative for myalgias

Neurological: Negative for weakness, numbness, tingling

Psychiatric/Behavioral: Increased sadness as per HPI

Physical Exam

BP 152/82 | Pulse 68 | Ht 177.8 cm (5' 10") | Wt 81.239 kg (179 lb 1.6 oz) | BMI 25.70 kg/m²

Repeat BP: 132/76

Gen: well-nourished, well-developed, white male, comfortable-appearing in no acute distress, does not appear as though his legs are longer than would be expected for his body

HEENT: EOMI, PERRLA

Neck: acanthosis nigricans, thyroid not enlarged, homogenous, with no discrete nodules

Lymphatic: no cervical, supraclavicular or axillary lymphadenopathy

Lungs: clear to auscultation bilaterally

Chest: gynecomastia of L breast, no spontaneous discharge, no expressible discharge

CV: regular rate, no extra heart sounds

GI: bowel sounds present, soft, not distended, non-tender

GU: normal size testes, appropriate pubic hair

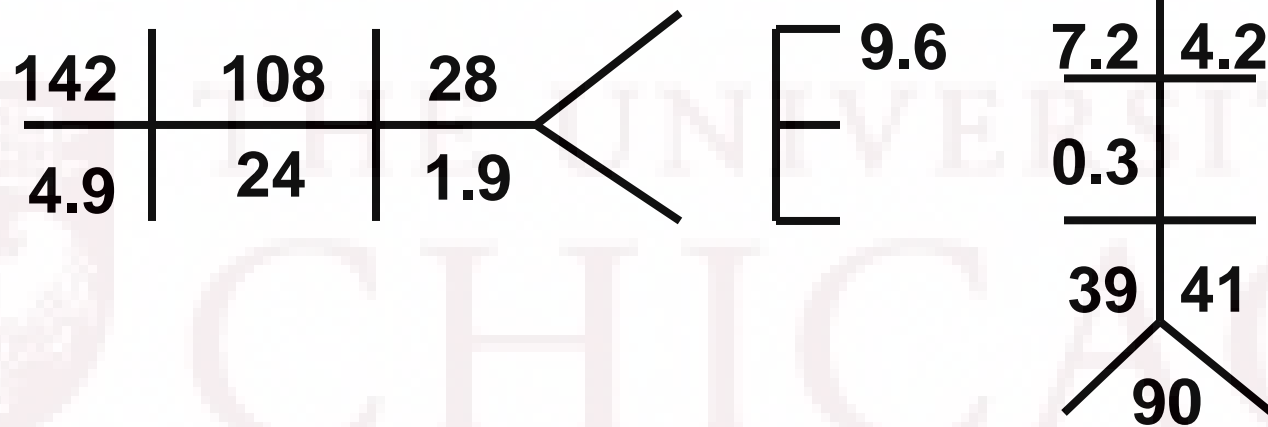
Musculoskeletal: normal gait and station

Neurologic: intact to light touch

Skin: warm, dry



Outside Labs



Total Testosterone 391 ng/dL (250-1100)

Free Testosterone 17.3 pg/mL (46-224.0)

Luteinizing Hormone 58.22 mIU/mL (males reference range 1.7-8.6 mIU/mL)

Follicle Stimulating Hormone 29.70 mIU/mL (males reference range 1.50-12.4)

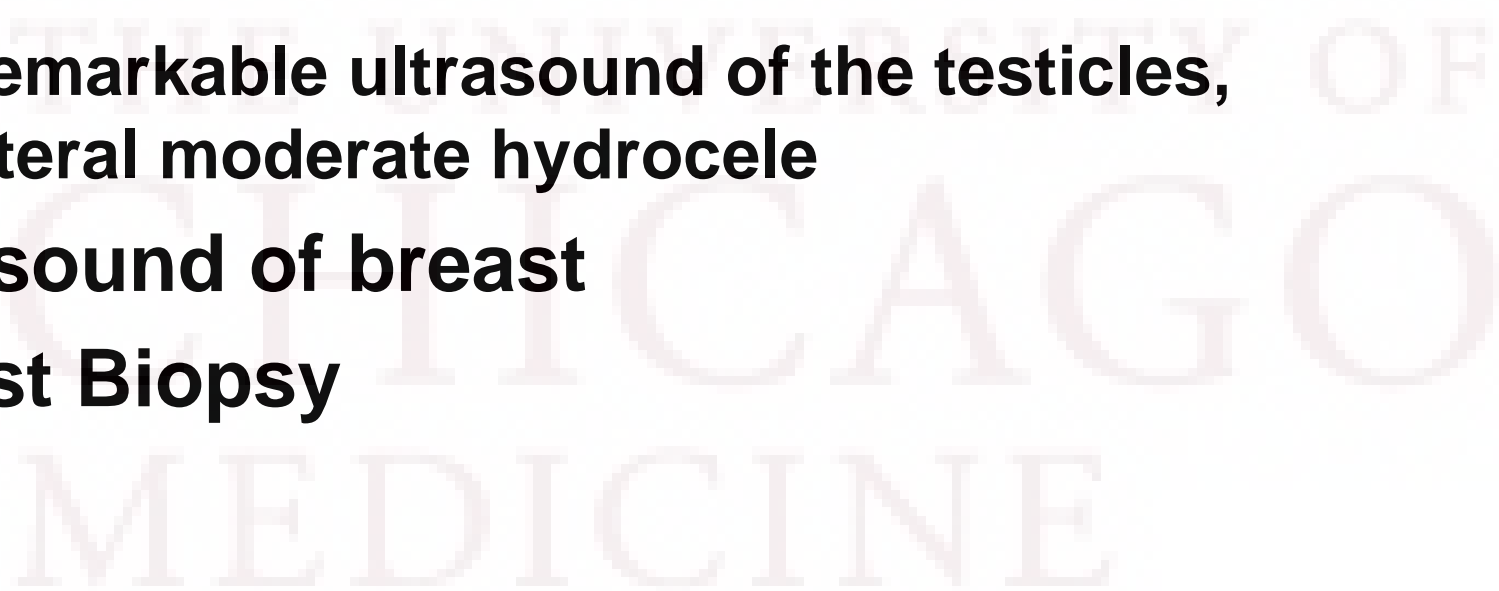
Estradiol 17.76 pg/mL (males reference range 7.63-42.6)

TSH 3.42 uIU/mL (0.4-5.4)

PSA 1.5 ng/mL (0.000-4.1)

Other studies

- **Ultrasound of testicles**
 - unremarkable ultrasound of the testicles, bilateral moderate hydrocele
- **Ultrasound of breast**
- **Breast Biopsy**
- **BMD**



Other questions?

What should we do next?

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Impression and Plan

■ Impression

- Symptoms and biochemical evidence suggest hypergonadotrophic hypogonadism suggestive of primary hypogonadism etiology unclear, but likely contributing to osteoporosis

■ Plan

- Recheck testosterone, free testosterone, sex-hormone binding globulin, gonadotrophs and prolactin
 - Given osteoporosis, start testosterone therapy with Androgel 1.62% 2 pumps once daily
 - Check 25-OH Vitamin D, encourage calcium by diet to achieve 900 – 1200 mg daily, continue Vitamin D supplementation
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Causes of Primary Hypogonadism

■ Congenital

- Klinefelter Syndrome
- Other chromosomal abnormalities (e.g., 46,XY/XO, 47,XYY)
- Mutation in the FSH and LH receptor genes
- Cryptorchidism
- Varicocele
- Disorders of androgen synthesis
- Myotonic dystrophy

■ Acquired

- Infections, especially mumps
- Radiation
- Alkylating agents
- Ketoconazole
- Glucocorticoids
- Trauma
- Testicular torsion
- Autoimmune damage
- Chronic systemic illnesses (e.g., hepatic cirrhosis, chronic renal failure, AIDS)
- Idiopathic



In our Patient

- **Chronic renal failure**
 - **associated with impaired spermatogenesis and testicular damage**
 - **s/p OLT x 2 with chronic rejection**
 - **Case reports of sirolimus associated primary hypogonadism**
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Secondary Osteoporosis*

- **Congenital and genetic conditions**
 - **Structural: osteogenesis imperfecta, Ehlers-Danlos**
 - **Disrupted calcium/phosphate: idiopathic hypercalciuria, hypophosphatemia**
 - **Metabolic/storage disorders: CF, glycogen storage disease**
 - **Hematologic: hemophilia, sickle cell anemia, thalassemia**
- **Hematologic and neoplastic disease: Leukemia, lymphoma, MGUS, MM**
- **Infectious Diseases: HIV**
- **Inflammatory: IBD, RA, SLE**
- **Renal Disease**
- **Liver Disease**

Secondary Osteoporosis*

■ Nutritional deficiencies

- Alcoholism related malnutrition, deficiency of calcium, magnesium, Vitamin D
- Malabsorption: celiac disease, s/p bariatric surgery

Drugs*

- Acid suppression therapies
- Anticoagulants
- Anticonvulsants
- Antidepressants (SSRI)
- Anti-hormonal therapies (aromatase inhibitors)
- Anti-manic therapies (lithium)
- Anti-retroviral drugs (tenofovir)
- Cytotoxic drugs (cyclosporins, tacrolimus)
- Diuretics (furosemide)
- Glucocorticoids
- GnRH analogues (buserelin, goserelin)
- Lipase inhibitors (orlistat)
- TZDs
- Thyroid hormone
- Unfractionated heparins

Post-transplantation Osteoporosis*

- **Renal Transplant**
 - Renal osteodystrophy
 - Metabolic acidosis
 - Hypogonadism
 - Vitamin D deficiency
- **Liver Transplant (11-52% of patients awaiting transplant)****
 - Alcohol abuse (in some)
 - Malnutrition
 - Vitamin D deficiency
 - Cholestasis
 - Hypogonadism
- **Lung Transplant (29-61% of patients awaiting transplant)****
 - Tobacco Use (in some)
 - Glucocorticoids
 - Hypercapnea/Hypoxia
 - Hypogonadism
 - Pancreatic Insufficiency/Malabsorption (CF)
- **Heart Transplant (8-10% of patients awaiting transplant)****
 - Loop diuretics
 - Failure to obtain peak bone mass (in patients with congenital disease)
 - Use of heparins
 - Vitamin D deficiency
 - Hypogonadism

*Arq Bras Endocrinol Metab. 2010;54/2

** Stein et.al Post-Transplantation Osteoporosis. *Endocrinology and Metabolism Clinics of North America* 36 (2007) 937-963

Back to our patient:

Laboratory Studies

LH 49.7 mIU/mL (adult male ref range 2.0 – 6.8)

FSH 28.3 mIU/mL (adult male ref range 1.2 – 8.0)

Total Testosterone 341 ng/dL (180 - 800)

Testosterone Binding Globulin 120 nmol/L (ref range 10 – 80)

Free Testosterone 42 pg/mL (ref range not provided)

Prolactin 5.99 ng/mL (4.0 – 15.2)

Should he be treated?

- **Called patient 2 months after starting therapy, he reports increased energy, improved libido, improved mood but also lower extremity edema**
 - **Mailed prescription for labs to patient's home:**
 - **Total testosterone 1201 ng/dL**
 - **Stopped testosterone, return to clinic in two months, mailed prescription for repeat labs prior to visit**
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Return Visit

- **Feels tired, watching Law and Order reruns again, no energy, edema improved**
 - **Free testosterone 12 ng/dL**
 - **Since last visit stopped alendronate after going to outside hospital for severe pain with swallowing, found to have esophageal ulcer attributed to alendronate**
 - **Restarted Androgel at 1 pump daily**
 - **Repeat labs have been within normal range without increase in lower extremity edema**
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Take Home Points

- **Multiple drugs can contribute to secondary osteoporosis**
 - **Post-transplant patients are at increased risk for underlying low bone mineral density prior to transplant and worsening of metabolic bone disease with the initiation of glucocorticoids and calcineurin inhibitors after transplant**
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