51-year-old woman with autoimmune hypothyroidism

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February 2, 2012
History of Present Illness

- History of relapsing-remitting multiple sclerosis, diagnosed 8 years ago
- Treated with Betaseron (interferon beta-1b) for five years and then Rebif (interferon beta-1a)
- Recently joined study with alemtuzumab, anti CD52 immunotherapy
- One month prior to presentation noticed:
  - Puffiness in her face
  - Stiffness in her back and hands
  - Remarkably dry, cracking skin
  - Swelling in her legs
  - Feeling cold and tired for the last two weeks
  - Depressed mood
  - 5-pound weight gain in the last month
History of Present Illness

- Reported symptoms to her neurologist and was found to have an elevated TSH and referred to endocrinology
- Past Medical History: multiple sclerosis with numbness on her left side since diagnosis
- Past Surgical History: None
- Allergies: NKDA
- Medications: alemtuzumab, no supplements
History contd.

- **Family History**
  - No known autoimmune disease
  - No known thyroid disease
  - Mother is alive at 74 with breast cancer
  - Father is alive at 76 with T2DM and CAD
  - 2 brothers and 3 sisters with no known medical problems

- **Social History**
  - Lives with her husband and three sons 31, 27, and 18 years
  - Originally from Palestine, living in the USA for the last 30 years
  - Tobacco: Never
  - Alcohol: no
  - Illicit Drugs: no
Physical Exam

- Vital signs: BP 130/77, Pulse = 77 bpm, Height = 5’9”, Weight = 194 pounds
- General: well-developed woman moving slowly
- HEENT: face is puffy with slight periorbital edema and infraorbital dark circles, oropharynx is clear
- Neck: no acanthosis nigricans, no thyromegaly
- Pulm: good respiratory effort, lungs clear to auscultation b/l
- CV: regular rate, no extra heart sounds, pretibial edema, DP pulses 2+
- Neurologic: Unable to elicit DTR in Achilles, 1+ in biceps and patellar with delayed relaxation phase b/l
- Skin: yellow-appearing, dry, fissures
- Psychiatric: psychomotor retardation, patient reports recent depressed mood
Laboratory Studies

TSH = 119.4 mcU/mL
Free T4 = <0.10 ng/dL
Total T3: <20 ng/dL
Thyroglobulin Ab = 640  Thyroid Peroxidase Ab = 320
Targeted Therapies and Thyroid Dysfunction

- Tyrosine kinase inhibitors – antineoplastic therapy for several types of carcinoma
  - Toxicity includes thyroid dysfunction
- Sunitinib is an oral multitargeted TKI with activity against vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), KIT and RET (RCC and imatinib-resistant GIST)
  - Retrospective studies suggest the incidence of sunitinib-induced hypothyroidism ranges from 53-85%
  - Prospective studies have found that this problem occurs in 36–71% of patients treated with sunitinib
Proposed Mechanism

- Directly toxic to thyroid cells possibly through inhibition of VEGFR and/or PDGFR. Thyroid follicular cells express VEGF and VEGFR; expression may be regulated in part by TSH. In mice, treatment with VEGF inhibitors resulted in regression in normal capillaries in select organs including thyroid.

- May impair thyroid function via inhibition of thyroid peroxidase (TPO) activity. In vitro studies suggest that sunitinib has anti-TPO activity about 25% the potency of the drug propylthiouracil,

- May induce transient hypothyroidism by blocking iodine uptake. In rat thyroid cells, sunitinib has been shown to inhibit TSH-stimulated iodine uptake

- Little to no biochemical or sonographic evidence of autoimmune thyroid disease
Alemtuzumab

- Monoclonal antibody – binds to CD52 receptor on lymphocytes and monocytes causing complement-mediated lysis of cells and profound lymphopenia
- Under investigation for multiple sclerosis
- In one study 9/27 participants developed TSH receptor Ab-positive Graves’ Disease
- Another study reported hyperthyroidism in 14.8%, hypothyroidism in 6.9% and thyroiditis in 4.2%
Mechanism of thyroid autoimmunity

- Loss of self-tolerance that occurs following profound lymphopenia
- Not clear why thyroid dysfunction has not been described in oncology patients
  - Possibly underlying autoimmunity in patients with MS or use of other immunosuppressive agents in patients with cancer
Back to our patient

- She had no history of CAD and was started on 75 mcg of levothyroxine with repeat TFTs 2 weeks later

**Initial Labs**
- TSH = 119.4 mcU/mL
- Free T4 = <0.10 ng/dL
- Total T3: <20 ng/dL

**After 2 weeks of therapy**
- TSH = 105.8 mcU/mL
- Free T4 = 0.36 ng/dL

- Based on her weight, levothyroxine was increased to 137 mcg daily
Take Home Points

- Multiple antineoplastic and immune modulating agents can cause thyroid dysfunction
- Screening for thyroid disease may be beneficial in these patients
References