51-year-old woman with autoimmune hypothyroidism

Celeste Thomas, MD
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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

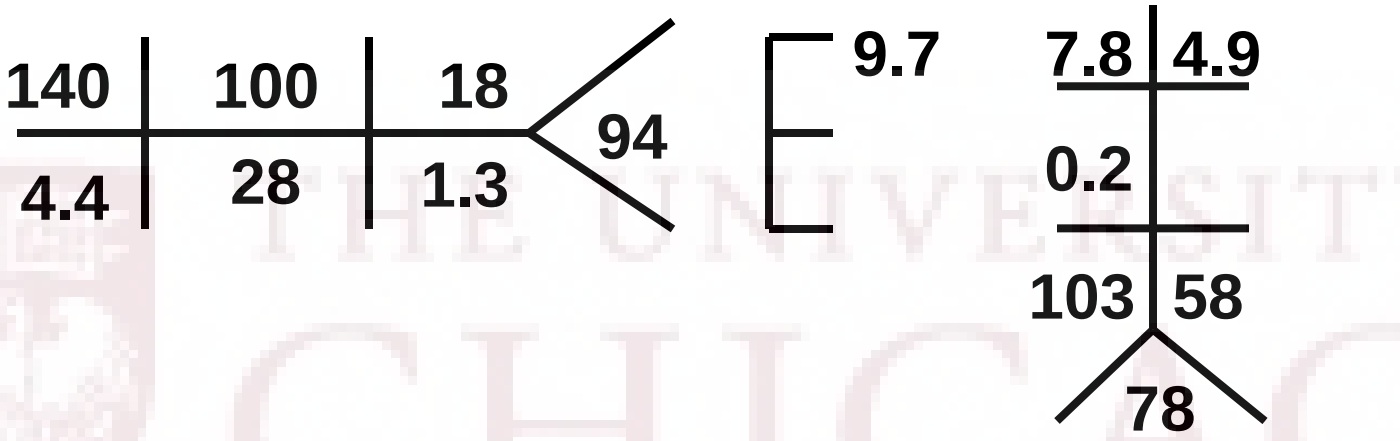
History contd.

- **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, sunitinb 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' Disesae
- 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	After 2 weeks of therapy
TSH= 119.4 mcU/mL	TSH= 105.8 mcU/mL
Free T4 = <0.10 ng/dL	Free T4 = 0.36 ng/dL
Total T3: <20 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

- Brown R. Tyrosine kinase inhibitor-induced hypothyroidism: incidence, etiology, and management. *Targeted Oncology.* 2011;6:217-226
- Ole-Petter H et al. Thyroid Dysfunction from Antineoplastic Agents. *Journal of National Cancer Institute*. 2011;103:1572-1583
- Surks M. Drugs and Thyroid Function. *New England Journal of Medicine*. 1995. 1688-1694