Clinical Approach to Common Thyroid Problems

Lukasz Materek MD FRCPC
Endocrinology and Metabolism
About me

- Medicine at UBC
- Internal Medicine at Western, London ON
- Endocrinology at Western, London ON
Faculty/Presenter Disclosure

• **Presenter:** Lukasz Materek MD FRCPC, Endocrinology and Metabolism

• **Relationships with commercial interests:**
  – **Grants/Research Support:** None
  – **Speakers Bureau/Honoraria:** Novo Nordisk; Eli Lilly, Abbott
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• **Other:** None
Disclosure of Commercial Support

• This program has not received financial support from industry/drug companies

• **Potential for conflict(s) of interest:**
  – None for this presentation
Mitigating Potential Bias

- no financial support from industry
- no significant interest of industry in thyroid disease
- evidence based presentation
Outline

• Thyroid Basics
• Thyroid Nodules in 15 minutes
• Hyperthyroidism in 15 minutes
• Hypothyroidism in 15 minutes
Thyroid Anatomy

• Weight:
  – 15-20g in North America

• Right and Left Lobe Dimensions:
  – ~4 cm Superior to Inferior
  – ~2 cm Lateral to Medial
  – ~2-3 cm Anterior to Posterior (deep)

• Isthmus:
  – ~5 mm Anterior to Posterior (deep)
Thyroid Physiology
Thyroid Nodule(s)

• Case:
  – 28 year old female
  – healthy
  – ? Nodule on clinical exam ~ 1cm; hard, not fixed
  – No obstructive symptoms
  – Clinically euthyroid
  – TSH normal
Best next step?

1. CT
2. Thyroid Uptake/Scan (NM)
3. U/S
4. Reassess clinically in one month
Answer

3. U/S
   – Ultrasound is the best imaging modality to assess thyroid nodule size and characteristics
Epidemiology

• Thyroid nodules are very common
  – Palpable nodules
    • 5% of women
    • 1% of men
  – Ultrasound series
    • 19-67%
  – Autopsy series
    • 37-57%
• The prevalence of nodules increases with age
• Prevalence in women 1.5-1.7 times higher than men
Thyroid Cancer

• Thyroid cancer occurs in 5-15% of thyroid nodules, rate depends on risk factors
• Incidence of thyroid cancer is increasing
  – 1973: 3.6 per 100,000
  – 2009: 8.7 per 100,000
• Rise in incidence mostly attributed to papillary thyroid cancer and tumours < 2cm in size
Thyroid Cancer

• Risk factors
  – Age
    • Thyroid nodules in children are twice as likely to be malignant
    • In adults, higher rate of malignancy if age > 60
  – Sex
    • Malignancy rate 2x higher in men as compared to women (8% versus 4%)
  – History of thyroid irradiation
    • ~25% have thyroid nodules
    • ~33% have of nodules are malignant
    • No evidence that radiation-associated thyroid cancers are more aggressive than other thyroid cancers
Thyroid Cancer

• Risk factors
  – Size
  – Family history of multiple endocrine neoplasia type 2 (MEN2) or medullary thyroid cancer (MTC)
  – Growing nodule
  – Firm or hard nodule consistency
  – Fixed nodule
  – Cervical lymphadenopathy
  – Persistent hoarseness, dysphonia, dysphagia, dyspnea
Thyroid Cancer

• Prognosis
  – Papillary thyroid carcinoma
    • 30-year survival 95%
  – Follicular thyroid carcinoma
    • 30-year survival 85%
  – Medullary thyroid carcinoma
    • 10-year survival 65%
  – Anaplastic thyroid carcinoma
    • 5-year survival 5%
    • Median survival is 8.1 months
Investigations

• Ultrasound
  – Should be performed in patients with:
    • Suspected thyroid nodule
    • Nodular goitre
    • Nodule found on other imaging modality
Thyroid Cancer and Ultrasound

High Risk Features
- Hypoechoic
- Increased central vascularity
- Incomplete halo
- Microcalcifications
- Irregular borders
- Taller than wide (transverse view)
- Suspicious lymph nodes

Low Risk Features
- Hyperechoic
- Peripheral vascularity
- Complete Halo
- Comet-tail
- Large, coarse calcifications
Investigations

• Radionuclide scan (only if low TSH)
  – If TSH low, $^{123}$I or $^{99m}$Tc pertechnetate should be obtained
  – Hyperfunctioning (hot) nodules are rarely malignant
Investigations

• Fine-needle aspiration (FNA)
  – Most accurate and cost effective method for evaluating thyroid nodules
    • Sensitivity 76-98%, specificity 71-100%
  – Prior to FNA, only 15% of resected nodules were malignant
  – With FNA, malignancy rate of resected nodules > 50%
### ATA FNA Indications

**High-risk history:** History of thyroid cancer in first degree relatives; external beam radiation as a child; exposure to ionizing radiation in childhood or adolescence; prior hemithyroidectomy with discovery of thyroid cancer, 18FDG avidity on PET scanning; MEN2=FMTC-associated RET protooncogene mutation, calcitonin >100 pg/mL.

**Suspicious features:** microcalcifications; hypoechoic; increased nodular vascularity; infiltrative margins; taller than wide on transverse view.

<table>
<thead>
<tr>
<th>Nodule sonographic or clinical features</th>
<th>Recommended nodule threshold size for FNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk history&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Nodule WITH suspicious sonographic features&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&gt;5 mm</td>
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<tr>
<td>Nodule WITHOUT suspicious sonographic features&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&gt;5 mm</td>
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<tr>
<td>Abnormal cervical lymph nodes</td>
<td>All&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Microcalcifications present in nodule</td>
<td>≥1 cm</td>
</tr>
<tr>
<td>Solid nodule</td>
<td></td>
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<tr>
<td>AND hypoechoic</td>
<td>&gt;1 cm</td>
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<tr>
<td>AND iso- or hyperechoic</td>
<td>≥1–1.5 cm</td>
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<tr>
<td>Mixed cystic–solid nodule</td>
<td></td>
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<tr>
<td>WITH any suspicious ultrasound features&lt;sup&gt;b&lt;/sup&gt;</td>
<td>≥1.5–2.0 cm</td>
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<tr>
<td>WITHOUT suspicious ultrasound features</td>
<td>≥2.0 cm</td>
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<tr>
<td>Spongiform nodule</td>
<td>≥2.0 cm&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Purely cystic nodule</td>
<td>FNA not indicated&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Fine-needle Aspiration

• Purely cystic nodule
  Any size ➔ No FNA

• Abnormal cervical lymph nodes
  Any size ➔ FNA
Fine-needle Aspiration

• Solid nodule
  >1cm  $\rightarrow$  FNA
Fine-needle Aspiration

- High-risk history
  - > 5mm $\Rightarrow$ FNA
Fine-needle Aspiration

- Mixed cystic-solid
  - Suspicious ultrasound features
    > 1.5-2cm  →  FNA
  - No suspicious sonographic features
    > 2cm  →  FNA

- Spongiform nodule
  > 2cm  →  FNA
Investigations

WORKUP OF THYROID NODULE DETECTED BY PALPATION OR IMAGING

- Low TSH
  - History, Physical, TSH
    - Normal or High TSH
    - Diagnostic US
      - No Nodule on US
      - Elevated TSH
      - Normal TSH
      - FNA not indicated
  - Hyperfunctioning
    - Hyperfunctioning
      - Evaluate and Rx for Hyperthyroidism
      - Nodule on US
        - Do FNA (See R5a–c)
        - RESULTS of FNA
          - Elevated TSH
          - Normal TSH
          - Evaluate and Rx for Hypothyroidism
Hyperthyroidism

• Case:
  – 52 year old Female
  – Presented with sweats
  – No period x 6 months
  – Weight loss and tremors x 4 months
  – Clinically hyperthyroid
  – TSH suppressed
  – fT4 and fT3 high
Next Best Test

1. U/S
2. Repeat Thyroid levels in 4 weeks
3. Thyroid Uptake and Scan
4. No further test required
Answer

3. Thyroid Uptake and Scan

Helps with establishing the diagnosis. Low dose of I-131. This is not an I-131 treatment just diagnostic test
Top 5 Differential of Hyperthyroidism

• Graves’
• Toxic nodular goiter
• Thyroiditis
• Iodine induced
  – Amiodarone, supplements or contrast
• Gestational (HCG driven)
Differential Diagnosis of Thyrotoxicosis by RAIU

- Increased uptake
  - Graves’ disease
  - Toxic multinodular goitre (TMNG)
  - Toxic adenoma (TA)
  - Hydatidiform mole, trophoblastic tumors, choriocarcinoma

- Decreased uptake
  - Thyroiditis (subacute, silent, postpartum, etc)
  - Iodine-induced thyrotoxicosis
  - Amiodarone-induced thyrotoxicosis
  - Thyrotoxicosis factitia
  - Struma ovarii
  - Metastatic thyroid cancer

Adapted from Nuclear Medicine: The Requisites, 4th ed, 2013
Graves’ Disease
Graves’ Disease

• Syndrome consisting of
  – Hyperthyroidism (commonest feature)
  – Goitre
  – Eye disease (orbitopathy)
  – Dermopathy
Graves’ Disease

• TSHR-Abs (TBII)
  – 3 types
    • Stimulatory → Graves’ disease
    • Blocking
    • Neutral
Graves’ Disease

• Antibody Prevalence
  – TSHR-Ab – 80-95%
  – Anti-TG Ab – 50-70%
  – Anti-TPO Ab – 50-80%
Graves’ Ophthalmopathy

• Most patients (90%) with GO are hyperthyroid
  – Can have “euthyroid” Graves’ disease
  – Can have GO in hypothyroid patients with TSHR blocking antibodies

• Timing of GO
  • Before hyperthyroidism – ~20%
  • Concurrently with hyperthyroidism – ~35%
  • 6 months after diagnosis – ~20%
  • After treatment of hyperthyroidism – ~20%

Graves’ Disease – Treatment

• Treatment goals
  – Symptom relief
  – Decrease thyroid hormone production
Graves’ Disease – Treatment

• Symptom relief
  – Beta blockers – improve symptoms caused by increased beta-adrenergic tone
    • ie palpitation, tremors, anxiety, etc
  – Target heart rate < 90
  – Propranolol or Atenolol
Graves’ Disease – Treatment

Decrease thyroid hormone production
  – Medications
  – Radioactive iodine ablation
  – Surgery
Graves’ Disease – Treatment

- Thionamides
  - Methimazole (MMI)
  - Propylthiouracil (PTU)

- Adverse reactions
  - Minor: rash, arthralgias, GI symptoms
  - Major: agranulocytosis, hepatitis, vasculitis

- Relapse may occur in 50-70%
Graves’ Disease – Treatment

• Thionamide dosing
  – If mild hyperthyroidism and small goitre
    ➔ Methimazole 10-15 mg/day
  – If more severe hyperthyroidism or large goitre
    ➔ Methimazole 20-30 mg/day
  – Dose is tapered to maintenance level

• Monitoring
  – TSH, fT4 +/- fT3 q 4-6 weeks until stable
    • TSH may lag
Graves’ Disease – Treatment

• Radioactive iodine (RAI) ablation
  – Most often done in North America
  – Given as a capsule or oral solution of sodium $^{131}$I
    • Concentrates in thyroid tissue
    • Induces tissue damage, resulting ablation within 6-18 weeks
  – Generally well-tolerated
    • May be associated with increased risk of developing/worsening GO
  – Need to follow radiation precautions post-therapy
  – Treatment failure in 10-20% with first RAI treatment
Graves’ Disease – Treatment

• Surgery
  – Indications
    • Large/obstructive goitre
    • Active GO and need for definitive therapy
    • Pregnant women allergic to antithyroid drugs
    • Allergy or poor compliance to antithyroid drugs and refusal of RAI treatment
    • Suspicious/malignant thyroid nodule
  – Risks of surgery
Toxic MNG

- Same 3 options
- Preferred I-131 then surgery
- Rare remission with medications
Hypothyroidism

• Case:
  • 46 year old female
  • Hypothyroid x 10 years, autoimmune
  • on levothyroxine 150 mcg daily
  • TSH 1.1
  • Stops levothyroxine
  • TSH 112
What is the next best step?

1. Restart levothyroxine
2. Check other pituitary hormones
3. Check antibody status
4. Start “thyroid support supplement” from a local health food store
Answer

1. Restart thyroid hormone replacement

Patient is still hypothyroid
Hashimoto’s Thyroiditis

• Hashimoto’s thyroiditis = chronic autoimmune thyroiditis

• Commonest cause of hypothyroidism (in iodine-sufficient areas)

• Caused by cell- and antibody-mediated destruction of thyroid gland
Hashimoto’s Thyroiditis

• Clinical characteristics
  – Gradual thyroid failure and/or
  – Goitre formation

• High levels of serum thyroid autoantibodies and a lymphocytic infiltrate are typically present

• Two forms exist
  – Goitrous
    • Usually asymptomatic, but rarely can be painful
  – Atrophic
Hashimoto’s Thyroiditis

• Antibodies in Hashimoto’s thyroiditis
  – Anti-TPO Ab – 90-100%
  – Anti-Tg Ab – 80-90%
  – Anti-TSHR Ab – 10-20%
Hashimoto’s Thyroiditis – Treatment

• Most often permanent condition
• Requirement for lifelong thyroid hormone replacement
• Goal is euthyroidism
Hashimoto’s Thyroiditis – Treatment

• Indications for treatment include
  – Overt hypothyroidism
  – Subclinical hypothyroidism
    • TSH > 10 mIU/L
    • TSH 5-10 mIU/L
      – Symptomatic and age < 70
      – Patients with goitre
      – anti-TPO Ab
Hashimoto’s Thyroiditis – Treatment

• Levothyroxine adverse events
  – Well tolerated if not under or over replaced
  – Rare reactions to dye or filler used in the tablet
  – White tabs (50 mcg) no color = no dye
Hashimoto’s Thyroiditis – Treatment

• Levothyroxine starting dose
  – Young patient with no medical co-morbidities
    • Full dose – 1.6 mcg/kg (using ideal weight)
  – Older patients or cardiac disease history
    • 12.5-50 mcg daily

• T4 usually improves within 2 weeks

• Check TSH in 4-6 weeks
Hashimoto’s Thyroiditis – Treatment

• T4 treatment target
  – TSH in normal range

  – What is the normal TSH range
    • Usually at lab reported 0.3-5 mU/L
    • I target the lower range 0.3-2.5 mU/L in younger patients
Monitoring

• TSH in 6 weeks (T4 half-life 7 days)
• If TSH still high, increase dose by 12-25 mcg daily and repeat TSH again in 6 weeks
• Once a steady dose is reached TSH should be done q6-12 months
  – Repeat sooner if new symptoms develop
• Dose adjustments required
  – Pregnancy
  – Weight changes
  – Changes in absorption
Hashimoto’s Thyroiditis – Treatment

• T3 treatment
  – T3 is rapidly absorbed in GI tract
  – T3 has a shorter half-life

  ➔ This leads to wide fluctuations of T3 levels in blood
Other Replacement Alternatives

• Combination T4 and T3
  • Metanalysis of 11 trials (1216 patients) showed no benefit as compared to T4
  • Subgroup analysis demonstrated improvement in patients who had a polymorphism in type 2 deiodinase

• Overall conclusion from study is that combination treatment is not recommended due to high hormone level fluctuations
  • But patients preferred combo T4/T3
  • Those who liked more were hyperthyroid

Grozinsky-Glasberg S et al. J Clin Endocrinol Metab. 2006;91(7):2592
Hashimoto’s Thyroiditis – Treatment

• T4 & T3 combination
  – Recent review: Biondi and Wartofsky (2012)
  – Results and conclusions:
    • Previous studies showed no benefit in adding T3 to treatment regimen
    • Studies had poor methodology
    • ? Cardiovascular benefit with T3
    • ? Bad outcomes with T3
    • Further studies are needed

Biondi and Wartofsky, J Clin Endocrinol Metab 2012, (97);2256-2271
Thank You
- **Subclinical Hyperthyroidism**
  - Recent ↑T4 Treatment
  - Drugs (Steroids)
  - NTI

- **Subclinical Hypothyroidism**
  - Poor Adherence/Absorption T4
  - Assay interference
  - NTI Recovery
  - TSH Resistance
  - Central Hypothyroidism

- **Hyperthyroid**
  - TSH ↓
  - FT4/FT3 ↑

- **Hypothyroid**
  - TSH ↑
  - FT4/FT3 ↓

- **Normal**
  - TSH ↔
  - FT4/FT3 ↔

- **Non Thyroidal Illness**
  - Assay Interference
  - Poor L-T4 Adherence
  - Drugs (Amio, heparin)
  - TSHoma
  - RTH

- **Central Hypothyroidism**

TSH ↔ or ↓
FT4/FT3 ↓

TSH ↔ or ↑
FT4/FT3 ↑
FT4

Small reductions in binding proteins should not alter serum free T4 index or direct free T4 values, and these values are usually normal in patients whose illness is not severe.