Benign Thyroid Disease

NAREN VENKATESAN, MD
FACULTY ADVISOR: SUSAN MCCAMMON, MD
The University of Texas Medical Branch
Department of Otolaryngology
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Outline

- History
- Embryology
- Anatomy
- Physiology
- Thyroiditis
- Goiter
- Nodules
- Conclusion
History

- 2700 BC - Emperor ShenNung's prescriptions mentions the use of seaweed for the treatment of goiter
- 300 BC - Ayur Veda, Hindu holy text, discusses goiter.
- 961 - AbulKasim, personal physician to Caliph El-Hakin III of Cordoba, is first to describe thyroidectomy for goiter and to perform a needle biopsy of the thyroid
- 1500 - Leonardo da Vinci is first person to recognize and draw the thyryoid gland
- 1656 - Thomas Wharton names gland "thyroid" after the shape of an ancient Greecian shield
1820 - Jean Francois Coindet concludes that iodine deficiency causes goiter and begins treatment of goiter with iodine.
1829 - LGA Lugol recommends use of aqueous solution of iodine made from KI
1902 - F. de Quervain describes subacute granulomatous thyroiditis
1905 - Robert Abbe treats Graves disease by implanting radium into the patient's goiter
1909 - Kocher received the Nobel Prize for his work on Thyroid Physiology, Pathology, and Surgery
1970 - A. Schally identifies TRH and receives Noble Prize for this work in 1977.
Thyroid Embryology

Derives from:

1. Endoderm – Migrates caudally and becomes the follicular cells

2. Neural Crest cells – Combine with 4th and 5th branchial pouches to form Parafollicular cells and parathyroids
Thyroglossal Duct Cyst

- Arises from persistent foramen cecum
- Sample patient: A child or a young adult presenting with a midline-cystic mass (>1 cm) which moves as the patient swallows
- Picture:
Thyroglossal Duct Cyst Management

1. Imaging – Identify location of functional tissue and evaluate for Thyroglossal Duct Cyst Carcinoma (1% amongst Thyroglossal Duct Cysts)

2. If no Carcinoma, Sistrunk procedure is treatment of choice

3. If Carcinoma, check remainder of thyroid as 1/3 patients will have concurrent thyroid malignancy.
Thyroid Anatomy
Thyroid Physiology

- Controlled by a feedback mechanism through the hypothalamic-pituitary-thyroid axis
- Levels of serum thyroxine (T4) and triiodothyronine (T3) provide a negative feedback to the anterior pituitary, which secretes thyroid stimulating hormone (TSH), and to the hypothalamus which secretes thyrotropin-releasing hormone (TRH), a stimulant of the anterior pituitary for release of TSH.
- Increased TRH or decreased T4/T3 stimulate the release of TSH, which is the major regulator of the thyroid.
- The gland has TSH receptors initiate the production of thyroid hormones by the organification process that attaches iodine to portions of the stored thyroglobulin (TG).
- Serum T3 is formed from conversion of T4 peripherally.
Thyroiditis

- Hashimoto’s
- Reidel
- De Quervain’s
- Post-Partum
Hashimoto’s

- First Described by Dr. Hashimoto Hakaru in Germany in 1912 and also known as Chronic Lymphocytic Thyroiditis
- An autoimmune disease of Antibodies against Thyroid Peroxidase and/or Thyroglobulin
It is also characterized by invasion of the thyroid tissue by Leukocytes, mainly T-Cells.

The left picture shows initially the germinal center starting to form in the thyroid and the right shows the matured germinal center with others around as well. B Cells may also be involved. The patient is thus at an increased risk of non-Hodgkin Lymphoma.
Hashimoto’s, cont.

- Clinical Presentation: Young to Middle-aged woman with a firm, diffuse, bilateral goiter
- High Affiliation with other Autoimmune Diseases with a strong role of Family History
- Implicated genes include HLA-DR5 and CTLA-4
- May be Euthyroid or Hypothyroid when presenting Goiter, and even sometimes, episodic bouts of Hyperthyroidism
Symptoms

- Weight gain
- Depression and sometimes Bipolar Disorder
- Cold Sensitivity
- Fatigue
- Bradycardia
- Infertility and Menorrhagia
- Muscle Weakness
- Hair Loss
Treatment of Hashimoto’s

- Confirm Diagnosis
- Treatment:
  - FNA**
  - Hypothyroidism can be treated with Levothyroxine
  - Frequent Monitoring of Thyroid by physical exam and US if nodule is noted in the Thyroid
  - Thyroidectomy

Order TSH and if low, check for the auto-antibodies. If there is any doubt as to whether the patient has Hashimoto’s or possibly MNG, order an FNA
Reidel’s Thyroiditis

- Clinical Presentation: Middle-age woman with a painless, firm nodule with a normal thyroid function.
- Fibrosis and fixation of adjacent structures can cause compression of trachea and/or esophagus.
- Fibrosclerotic Conditions are simultaneously Retroperitoneal Fibrosis and Sclerosing Cholangitis.
- Management: Surgical Excision if Compressive symptoms are present.

NOTE: As with any nodule, the management would be ordering an FNA. However, due to the fibrosis, these often return indeterminate. Since the nodule can be large, the presentation often can be similar to cancer.
De Quervain’s Thyroiditis

- Also known as Subacute Thyroiditis
- Clinical Presentation: Young adult with a recent history of a URI that presents with an exquisitely tender to palpation Thyroid gland
- Usually resolves on its own in weeks to months at worst after a period of hyper- then hypothyroidism
Post-Partum Thyroiditis

- Classically, a thyroiditis much like Subacute in the sense of having a hyper- and hypothyroid phase
- Onset usually is shortly after delivery
- Many women may only manifest one phase
- Usually most women return to Euthyroid function by 12-18 months
- 20% of those who exhibit the hypothyroid phase will remain with hypothyroidism
- Women with a history of Autoimmune disorders are at higher risk
Robert James Graves

- Irish Surgeon, 1796-1853
- Wrote and Published “Graves’ Clinical Lectures” in 1843 and 1848
- Graves Disease is named in his honor by Dr. Armand Trousseau

NOTES: He was the president of the royal college of physicians of Ireland as well as a fellow of the Royal Society of London. His lectures were published and dispersed serving throughout Europe as a staple of medical education. Two things that he famously began the practice of were measuring a patient’s pulse using a stopwatch and feeding those who had a fever.
NOTES: Armand Trousseau was a French Internist and better known to us for two signs: Trousseau sign of tetany and Trousseau sign of malignancy which ironically he developed prior to succumbing to Gastric Cancer. The Trousseau sign of Tetany which is seen in hypocalcemia when placing a BP cuff around the arm above systolic pressure to occlude the brachial artery causing wrist and MCP joint flexion, PIP and DIP extension, and finger adduction. The Trousseau sign of malignancy is the increase in hypercoagulable state causing DVTs and migratory thrombophlebitis often seen in superficial veins. He was also a significant figure in French ENT history. He performed the first tracheotomy as well as the first intubation in 1851 in French history. More importantly, he coined Graves disease and popularized epitaphs in his many writings.
Graves Disease

- An Autoimmune disease caused by Antibodies towards the TSH receptor which function as positive feedback
- Unregulated, the Thyroid continues to produce T4 and T3 leading to Hyperthyroidism
- In addition to production, the Thyroid also hypertrophies forming a goiter
Graves Disease, cont.

- Most common cause of hyperthyroidism in children and adolescents
- Strong Female Predilection of 5:1 to 10:1
- Three key findings (secondary to autoimmune process)
  - Goiter
  - Ophthalmopathy
  - Pretibial Myxedema
Physical Changes of Graves Disease

NOTES: Graves' ophthalmopathy is characterized by inflammation of the extraocular muscles, orbital fat and connective tissue. It results in the following symptoms, which can be extremely distressing to the patient:[3] Most frequent are symptoms due to conjunctival or corneal irritation: burning, photophobia, tearing, pain, and a gritty or sandy sensation.[3] Protruding eyeballs (known as proptosis and exophthalmos). Diplopia (double vision) is common.[3] Limitation of eye movement (due to impairment of eye muscle function). Periorbital and conjunctival edema (accumulation of fluid beneath the skin around the eyes). Infiltrative dermopathy (pretibial myxedema). In severe cases, the optic nerve may be compressed and acuity of vision impaired.[17] Occasionally loss of vision.
Effects of Hyperthyroidism

- Cardiovascular Changes
  - Hypertension
  - Palpitations
  - Left Ventricular Hypertrophy
- Weight loss
- Heat Intolerance
- Warm/Moist Skin
- Fine Tremor
- Hyperreflexia
- Increased Fatigability
Treatment of Graves’ Disease

- Beta-Blockers combat autonomic hyperactivity
- Propylthiouracil or Methimazole can be used to combat excess Thyroid hormone levels
- If Hyperthyroid symptoms persist, two options exist:
  - 1. Radio Active Iodine Therapy: Cells take up Iodine and are selectively killed over months
  - 2. Thyroidectomy

Cannot do RAI if patient is pregnant, has a solitary nodule, or ophthalmopathy which can be worsened.
Goiter

- A non-specific term used for a swelling in the thyroid
- First described by English and Arabic scientists in 1625
- Goiters can be classified as toxic or nontoxic, diffuse or nodular, and solitary or multiple.
- Prevalence of goiters in the United States remains about 4% to 7%

The high limit of normal for the size of a thyroid is about 20 grams.
Goiter Grading System

- **WHO system to grade goiters:**
  - Grade 0: Non-palpable/Non-visible
  - Grade 1a: Goiter is only palpable
  - Grade 1b: Goiter is palpable and only visible when neck extended
  - Grade 2: Goiter visible when neck is in normal position
  - Grade 3: Large goiter visible from a distance
Multinodular Goiter

- Worldwide, most common endocrine disorder affecting 500 to 600 million people, where iodine deficiency is often the trigger

- Possible causes:
  - In Iodine-deficient areas, increased TSH is implicated
  - In non-deficient areas, genetics is the culprit – examples include MNG-1 gene and codon 727

NOTES: In iodine-deficient areas, resultant hypothyroidism contributes to the etiology of MNG. Through the feedback mechanism, hypothyroidism causes an increase in TSH, which stimulates growth of the thyroid gland. In iodine-replete areas, however, patients are generally euthyroid, with a normal TSH providing evidence that other factors such as genetic influences play a role. More recently, a gene located on chromosome 14q, dubbed “MNG-1,” has been associated with familial nontoxic MNG [5]. In addition, polymorphism of codon 727 has been associated with toxic MNG [6].
Typical Presentation of MNG

**Symptoms**
- Globus Sensation
- Dysphagia
- Recumbent Dyspnea
- Tracheal Deviation
- Hoarseness

**Increased suspicion of Cancer if a patient also has:**
- Fixation to trachea
- Fixation to esophagus
- Vocal Fold Paralysis

Some patients may even exhibit Pemberton’s maneuver where compression at the thoracic inlet causes flushing, neck vein compression, and SOB when patient raises their hands above their head.
Toxic Multinodular Goiter

- Also known as Plummer’s Disease
- Occurs in 5-10%
- Presentation is like Graves’ disease with the absence of ophthalmopathy
- Order Thyroid Studies to work-up
- Management is similar to Graves’ Disease

NOTES: These patients often have a long history of MNG which is suddenly complicated by an acute onset of thyrotoxicosis. Despite having thyrotoxicosis, these patient often have normal to low TSH and usually normal to high normal T4 and T3 levels so have a high index of suspicion for the symptoms and treat appropriately
Substernal Goiter

- Clinical Presentation: A patient in their 40s-50s with complaints of cough, dyspnea, stridor, choking symptoms, and/or dysphagia
- Usually slow, progressive growing goiters
- On CT may show compressive signs such as tracheal deviation
- May be associated with increased risk of cancer - incidence of carcinoma development in goiters at 1.3–3.7 new cases per 1000 patients

NOTES: In the past, the presence alone of substernal goiters warranted surgery. However, now, the thought has been to be more evidence-based and shifting to the idea of only performing surgery if the patient has clinical findings or radiographic signs of compression. Cancer is not common but location often prevents appropriate FNA with bony structures in the way which also cause artifacts when viewing the thyroid with US. Current articles restate that the diagnosis alone of a substernal goiter should be cause for excision as the patient may develop cancer which is hard to diagnose, have compressive symptoms and waiting for their onset in the elderly patients is not advised, and a substernal goiter in the elderly makes surgery much more complicated due to physiological changes.
Management of MNG

Fig. 6. Overview of evaluation and management of a MNG.
Nodules

- Prevalance – Women:Men (5:1)
- Key Objective with a Nodule is to rule out Cancer
- Incidence of Papillary Carcinoma alone has increased 2.9 fold from 1988-2002
- A discrete lesion within thyroid gland that is radiologically distinct from surrounding thyroid parenchyma

NOTES: The prevalence of thyroid nodules in iodine sufficient areas is 5% in women and 1% in men. Cancer is noted to be in 5-15% of nodules. In addition, the incidence of all thyroid cancer has increased greatly, mirroring papillary thyroid cancer with a yearly incidence of 8.7 per 100,000 in 2002 with respect to 3.6 in 1973. Most of this is attributed to the fact that cancers are diagnosed when they are much smaller with recent studies showing 87% of cancers detected at a size of 2 cm or less.
Nodule Criteria

- Size of 1 cm is the main criteria
- Complicating Factors:
  A: History
  - PET Scan Incidentalomas
  - Childhood radiation
  - Family History
  - Rapid growth and Hoarseness

NOTES: Anything less than 1 cm is deemed to be futile for work-up in the sense of balancing cost/benefit ratios. Anything greater than 1 cm requires work-up. Many thyroid nodules are smaller and may harbor cancer. What is the appropriate management for these? The following are factors that prompt a work-up in a patient with a smaller than 1 cm nodule. PET scan is significant as these nodules will light up. Childhood radiation is specific to head and neck region unless it is a transplant patient with whole body radiation. Family history is only pertinent when it is a first degree relative.
Nodule Criteria cont.

B: Physical Exam Findings
- Vocal Cord Paralysis
- Lateral Cervical LAD
- Fixation of Nodule to surrounding tissues
Nodule Evaluation

- Step 1: Thyroid US along with TSH
  A: TSH is subnormal
    - Radionuclide thyroid scan
  B: TSH is elevated
    - Very suspicious for Malignancy

NOTES: Thyroid US is always the first step even in patients where the thyroid nodule is detected on CT, MRI, or PET-CT. Radionuclide scanning will show 3 possibilities. A hot, warm, or cold nodule. A hot nodule means there is increased uptake and therefore making T4 which is a good sign because these are rarely cancer. A warm nodule has the same uptake as the surrounding tissue while a cold nodule has less uptake than the surrounding tissue.
Nodule Evaluation cont.

- Considerations of US:
  - Exact Nodule Size
  - Other Possible Nodules
  - Any Enlarged Cervical Lymph Nodes
  - Cystic component of Nodule
  - Location within Thyroid

NOTES: The key thing to note here is the last two findings because these affect the next step in management. Nodules with over 50% cystic nature and those which are posteriorly located greatly decrease the likelihood of obtaining a successful FNA.
Nodule Evaluation

- **Step 2: Fine Needle Aspiration Biopsy**
  - **Hashimoto’s Thyroiditis**
    - Benign
    - Malignant
    - Indeterminate
    - Nondiagnostic

**NOTES:** The key thing to note here is the last two findings because these affect the next step in management. Nodules with over 50% cystic nature and those which are posteriorly located greatly decrease the likelihood of obtaining a successful FNA.
FNA Characteristics

- **Malignant characteristics**
  - Nodule Hypoechogenicity
  - Increased Intranodular Vascularity
  - Irregular Infiltrative Margins
  - Microcalcifications
  - Absent Halo

NOTES: Something interesting to note is that despite these characteristics being associated with an increased risk of malignancy, not a single one of these characteristics have a high sensitivity or specificity individually.
1. **Follicular Adenoma:**
   - Well-circumscribed, encapsulated lesion
   - Occur secondary to clonal growth
   - Degenerative changes

NOTES: Degenerative changes can include hemorrhage, calcification, and fibrosis. The key here is that the pathologist must make sure that no capsular or vascular invasion is noted because this will change the diagnosis to follicular cancer. Normal thyroid follicles appear at the lower right. The follicular adenoma is at the center to upper left. This adenoma is a well-differentiated neoplasm because it closely resemble normal tissue. The follicles of the adenoma contain colloid, but there is greater variability in size than normal.
2. Hurthle Cell Adenoma:

- Circumscribed and encapsulated lesions
- Appear like Follicular adenoma with key finding of cells rich in Mitochondria

NOTES: Hurthle (oxyphilic) cell tumor, lower half of photomicrograph, with well circumscribed margin established by an intact delicate fibrous capsule. This is a Hurthle cell tumor of low malignant potential (an adenoma).
3. Hyalinizing Trabecular Adenoma

- Cells arranged in trabeculae, clusters, or both with highly granular cytoplasm
- Perivascular Hyaline Fibrosis

NOTES: Microscopically, they were encapsulated or circumscribed and solid, or vaguely lobulated. The polygonal, oval, and elongated tumor cells were arranged in trabeculae, clusters, or both, and were often inserted vertically into capillaries. The sharply outlined cells had finely granular cytoplasm that was either acidophilic, amphophilic, or clear. Typical features included oval and elongated nuclei, perinucleolar vacuoles, acidophilic nuclear inclusions, fine nuclear grooving, and infrequent mitotic figures. Perivascular hyaline fibrosis and cell degeneration mimicked amyloid, but these tumors were Congo red-negative. Occasional trabeculae featured round or irregularly shaped follicles, sometimes with papillary infoldings, that were either empty or contained colloid-like material and psammoma bodies. Immunostaining of tumor cells was positive for thyroglobulin and negative for calcitonin.
4. Nodular Goiter
- Coalescent Nodules of Different Sizes
- Hyperplastic or Dilated with Colloid

NOTES: It has often been thought that multinodular goiter carries the same risk as a solitary nodule. However, this has been challenged with a recent study that found solitary nodules had a higher incidence of cancer than non-solitary nodules (p<0.01).
Management

WORKUP OF THYROID NODULE DETECTED BY PALPATION OR IMAGING

- Low TSH
  - History, Physical, TSH
  - Normal or High TSH
  - $^{123}$I or $^{99m}$Tc Scan
    - Hyperfunctioning
      - Evaluate and Rx for Hyperthyroidism
    - Not Functioning
      - Diagnostic US
      - Nodule on US
        - Do FNA (See RSa–c)
      - No Nodule on US
        - Elevated TSH
          - Evaluate and Rx for Hypothyroidism
        - Normal TSH
          - FNA not Indicated

- Results of FNA
  - Nondiagnostic
    - Repeat US-Guided FNA
  - Malignant PTC
    - Pre-op US
    - Surgery
      - Not Hyperfunctioning
        - Consider $^{123}$I Scan if TSH Low Normal
    - Suspicious for PTC
    - Indeterminate
      - Follicular Neoplasm
        - Hürthle Cell Neoplasm
      - Follow
  - Benign
Management of Nodule

- Long-term management recommendations are follow-up of patients with an initial cytologically benign nodule with ultrasound 6–18 months after biopsy, and further follow-up every 3–5 years.
- If any changes occur, can repeat an FNA or provide option of thyroidectomy.

NOTES: May have to follow up these patients for life or until surgery is performed. All are from ATA 2009 Guidelines on Thyroid Nodules;
Special Considerations: Elderly

- Increasing age associated with an increasing incidence of thyroid disease
- Age over 70 is an independent cardiac risk factor
- Bilateral goiter is overwhelmingly the reason for thyroidectomy
- Despite adequate repletion of Calcium and Vitamin D, nearly 1/3 of patients had temporary hypocalcemia post-thyroidectomy
Special Considerations: Children

- Cretinism
  - Condition of severely stunted physical and mental growth
  - Secondary to Congenital Hypothyroidism
  - Can be treated if noticed at birth or shortly after

NOTES: Similar to other thyroid conditions, it can be triggered by either a lack of iodine intake or secondary to athyrogenesis.
Conclusion

- Importance of the Thyroid gland cannot be underestimated even in Benign Conditions
- Better understanding of the unique role that the Thyroid plays allows Otolaryngologists to better assess a patient appropriately and treat benign conditions as well as those that are cancerous


Cooper DS et al. Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2009: Vol 19 (11)
