

**MECHANISMS OF HUMAN DISEASE: LABORATORY SESSION**  
**ENDOCRINE PATHOLOGY LAB**  
Wednesday, March 24, 2010  
8:30 am – 10:00am

Faculty Copy

**GOALS:**

1. Describe the basic morphologic and pathophysiologic changes which occur in various conditions of the thyroid gland.
2. Correlate structural changes in the thyroid gland with clinical manifestations of the disease.

**OBJECTIVES:**

1. Describe the morphologic changes which characterize thyroid gland adenomas.
2. Describe the morphologic changes which characterize thyroid gland carcinomas.
3. Describe the morphologic changes which characterize diffuse and multinodular goiter.
4. Describe the morphologic changes which characterize Hashimoto's thyroiditis.

**CASE 1:**

Review of normal histology

**CASE 2:**

**CHIEF COMPLAINT:**

"I have a lump in my neck"

**HISTORY:**

The patient is a 42-year-old female who noticed a painless lump in her neck about a month ago. It has not seemed to increase or decrease in size.

She has no chronic medical problems and has had no surgeries.

She takes no medications.

Her father and mother are alive and well. She is an only child.

She has no diarrhea or constipation, no heat or cold intolerance, stable weight, no change in skin or hair texture.

PHYSICAL EXAMINATION:

A painless 3cm mass is palpated in the left neck. The mass moves when the patient swallows and seems contiguous with the thyroid gland. The remainder of the thyroid gland is normal. There is no cervical or supraclavicular lymphadenopathy. The remainder of the physical exam is unremarkable.

1. What is the main clinical problem?

**Thyroid nodule**

2. Develop a clinical differential diagnosis.

**Thyroid adenoma  
Thyroid carcinoma  
Multinodular goiter  
Thyroid cyst**

3. Based on the given data, is the patient clinically euthyroid, hyperthyroid, or hypothyroid?

**Her symptoms and physical exam suggested that she is euthyroid**

LAB DATA

TSH 1.2 (0.4-4.4 uu/mL)

4. How does one differentiate a “follicular adenoma” from a “follicular carcinoma”?

**Follicular carcinomas have**  
**A. evidence of capsular or blood vessel invasion or**  
**B. documented metastases**

**Owing to the need for capsular integrity, the definitive diagnosis of adenomas can only be made after careful histologic examination of a resected specimen (and not from fine needle aspiration biopsy samples)**

5. Identify organ/describe characteristic pathologic in the virtual microscopy slide.

**Thyroid; sections show a discrete nodule compressing adjacent normal thyroid. The capsule is intact. The nodule is composed of small well-differentiated follicles lined by cuboidal cells. Small amount of colloid is seen at the center of some follicles. Nuclear grooves, pseudoinclusions and “Orphan Annie” nuclear changes are absent.**

6. What is your diagnosis?

**Follicular adenoma**

7. Correlate the clinical findings with the pathology

**Scant colloid and hormone production within the adenoma correlates with the status of a “cold nodule”, normal TSH, and euthyroidism**

8. What type of genetic changes have been described in adenomas which produce thyroid hormone autonomously (ie “toxic adenomas”)?

**A small proportion of adenomas do produce thyroid hormones and cause clinically apparent thyrotoxicosis.**

**Gain of function mutations of “TSH receptor signaling pathway” play a role in pathogenesis of toxic adenomas by allowing follicular cells to secrete thyroid hormone independent of TSH stimulation.**

### **CASE 3**

**CHIEF COMPLAINT:** Routine physical.

**HISTORY:**

55-year-old woman presents for an annual physical exam. She feels well and has no concerns except that perhaps her cholesterol might be high due to dietary indiscretion.

She has no chronic medical problems and has had no surgeries.

She takes no medications.

She is adopted and does not know of her family history.

**PHYSICAL EXAMINATION:**

A painless 2.5 cm nodule is palpated in the left thyroid gland. There is an enlarged, nontender 2cm left cervical lymph node. Exam is otherwise unremarkable.

1. What is the clinical problem?

**Nodule in thyroid, enlarged cervical lymph node**

2. Develop a clinical differential diagnosis.

**Thyroid carcinoma**

**Metastatic carcinoma**

**Lymphoma**

**Thyroid adenoma**  
**Thyroid cyst**

Diagnostic work-up:

TSH 2.7 (0.4-4.4 uu/mL)

Cold” thyroid nodule on iodine uptake scan

3. Identify the organ/describe characteristic pathologic changes in the virtual microscopy slide.

**Thyroid; sections of the thyroid show branching papillae with a fibrovascular stalk covered by a single to multiple layers of cuboidal epithelium. The nuclei of the lining epithelium have characteristic changes including nuclear grooves, pseudoinclusions and “Orphan Annie” or a ground glass appearance. Psammoma bodies may be present in some sections as well as hemorrhage and necrosis.**

4. What is your diagnosis?

**Papillary carcinoma; most common thyroid carcinoma, about half of cases will have metastasis to cervical lymph nodes**

5. Name at least two genes involved in the pathogenesis of this lesion. What are clinical implications?

**a) RET protooncogene plays a role in both papillary (and medullary) thyroid carcinomas. RET protooncogene encodes a tyrosine kinase receptor that is not normally expressed by thyroid follicular cells . Rearrangements of chromosome 10 place the tyrosine kinase portion of the RET protooncogene under the transcriptional control of a regulatory region (promoter) of a gene that is constitutively expressed by thyroid epithelial cells. This results in a gene (RET/PTC) that expresses the tyrosine kinase portion of receptor at a high level in the affected cells.**

**b) BRAF gene encodes a signaling intermediary in MAP kinase pathway. 33-50% papillary thyroid cancers have an activating mutation in BRAF gene.**

**The high frequency of Ret/ PTC and BRAF mutations in papillary thyroid cancer and their role in tumor initiation (and ultimately dedifferentiation) make them logical targets for anticancer drug therapy  
Inhibitors of different kinases along the MAP signaling pathway are available and show substantial therapeutic effects in thyroid cells in experimental systems and are currently being tested in clinical trials.**

**Ciampi, R. et al. Endocrinology 2007;148:936-941**

## **CASE 4**

### **CHIEF COMPLAINT:**

“I’ve been feeling tired and cold all the time”

### **HISTORY:**

A 60-year-old previously healthy woman presents with fatigue and cold intolerance. She has had about 10 pound weight gain over the past 6 months which she attributes to inactivity. She is being treated for hypertriglyceridemia with gemfibrozil. She started taking laxatives about 3 months ago for constipation. She does not smoke or drink alcohol.

### **PHYSICAL EXAMINATION:**

Alert and oriented female

Pulse 61, BP 150/90

Thyroid gland is diffusely enlarged. No nodules are palpated. No cervical LAD is present.

Lung, heart, and abdominal exams are unremarkable.

1. Develop a problem list.

**Fatigue**

**Cold intolerance**

**Weight gain**

**Constipation**

**Hx hypertriglyceridemia**

**Elevated blood pressure**

**Bradycardia**

**Diffusely enlarged thyroid gland**

2. What is your clinical differential diagnosis?

**Hypothyroidism**

**Anemia**

**Cancer (ie colon cancer)**

**Depression**

### **Diagnostic Evaluation:**

TSH 21.2 (0.4-4.4 uu/mL)

Free T4 0.4 (0.8-1.7 ng/dL)

3. List etiologies of primary hypothyroidism

**Hashimoto thyroiditis**

**Thyroidectomy**

**Radioactive iodine therapy**

**Drugs (lithium, iodides, amiodarone)**

4. Identify organ/describe characteristic pathologic changes in the virtual microscopy slide.

**Thyroid; sections show that the normal architecture is disrupted by bands of fibrous tissue and an intense infiltrate of lymphocytes and plasma cells. Germinal centers are noted as well as disruption and atrophy of the follicles. Hurthle cell metaplasia is present ((metaplastic response of follicular epithelium undergoing ongoing injury)**

5. What is your diagnosis?

**Hashimoto thyroiditis**

6. What is the primary immunologic defect in this entity?

**In Hashimoto thyroiditis the primary defect is postulated to be in T cells. Activated T cells may interact with B cells and stimulate the secretion of a variety of antithyroid antibodies. Helper T cells may induce the formation of CD8+ cells, which can be cytotoxic to thyroid cells.**

7. Discuss the usual clinical course of this condition.

**Usually hypothyroidism develops gradually, commensurate with atrophy of follicular cells, replacement of thyroid tissue with inflammation and with fibrosis  
Rarely hypothyroidism is preceded by transient thyrotoxicosis cause by disruption of thyroid follicles and secondary release of thyroid hormones**

## **CASE 5**

### **HISTORY**

A 55-year-old female presents for physical exam. She has not seen a physician in many years. he feels well except for some mild dyspnea on exertion. She has no chest pain, no leg edema, no weight loss or weight gain, no heat or cold intolerance, no palpitations, no difficulty swallowing. She has no known chronic medical problems. She had an appendectomy at age 15. She takes no medications.

### **PHYSICAL EXAMINATION:**

Well-developed woman. Pulse 72, BP 112/64. Both lobes of the thyroid gland are enlarged. Several bilateral small, nontender thyroid nodules are palpated. Exam is otherwise unremarkable.

1. What is the clinical problem?

**Enlarged thyroid gland**

2. Based on history and physical, what do you expect serum TSH to be?

**Normal. Clinically the patient is euthyroid.**

3. Identify organ/describe characteristic pathologic changes in the virtual microscopy slide.

**Thyroid; sections of the thyroid show large and small nodules composed of colloid filled follicles of varying size/shape. Some sections may show foci of hemorrhage and necrosis.**

4. What is your diagnosis?

**Multinodular goiter.**

**Most patients with a multinodular goiter are euthyroid, though some goiters may be hyperfunctional and result in hyperthyroidism**

**Large goiters may cause mass effect: Airway obstruction (possible cause of dyspnea on exertion in this patient), dysphagia, compression of large vessels in neck and upper thorax.**